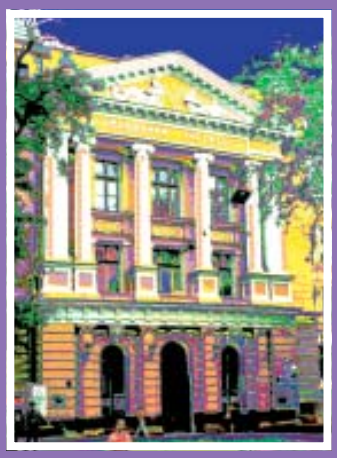

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GENERAL PHARMACOLOGY

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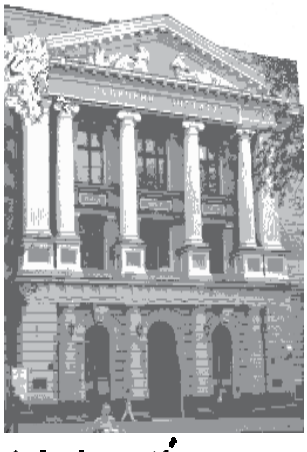

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Medical Student's Library

Initiated in 1999 to mark the Centenary
of the Odessa State Medical University
(1900 — 2000)

Edited and Published by V. M. ZAPOROZHAN,
the State Prize-Winner of Ukraine,
Academician of the Academy of Medical Sciences of Ukraine

The Odessa State
Medical University

Dear Reader,

When in 1999 the lecturers and researchers of the Odessa State Medical University started issuing a series of books united by the collection entitled "Medical Student's Library" they had several aims before them.

Firstly, they wanted to add new books to the Ukrainian library of medical literature that would be written in Ukrainian, the native language of the country. These books should contain both classical information on medicine and the latest information on the state of the art, as well as reflect extensive experience of our best professionals. Secondly, our lecturers and specialists wanted to write such books which reflected the newest subjects and courses that have recently been introduced into the curricula, and in general there have been no textbooks on these subjects and courses at that time.

These two aims have successfully been coped with. Some dozens of textbooks and workbooks published in these years have become a good contribution of their authors and publishers to the development and making of the Ukrainian national educational literature.

The next step that we decided to undertake was to issue a unique series of books in foreign languages. The foreign students taking their medical education in the Ukraine, our University included, are expecting such books to be published. Other countries are also waiting for them as the Odessa State Medical University is a Fellow Member of the International and European Association of Universities. Our Medical University is over a hundred years old and has long since become a center of various original medical schools and trends. These are headed by well-know medical professionals whose competence is acknowledged not only in this country, but abroad as well.

Valery ZAPOROZHAN,
Editor-in-Chief of the Series "Medical Student's Library"
the State Prize-Winner of Ukraine,
Academician of the Academy of Medical Sciences of Ukraine

GENERAL PHARMACOLOGY

COURSE OF LECTURES

Odessa
The Odessa State Medical University
2005

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The lectures are designed according to pharmacological drug groups due to their effects on particular body systems and intended for the 3rd year students of medical faculty. Information is organized according to the sequence used in many International and Ukrainian pharmacology courses. The textbook is intended for students of higher medical institutions.

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Курс лекцій для студентів 3-го курсу медичного факультету складається з розділів, упорядкованих за фармакологічними групами ліків згідно з їх ефектами на специфічні системи органів. Матеріал викладено у послідовності, використовуваній у багатьох міжнародних й українських виданнях з фармакології.

Для студентів вищих навчальних медичних закладів.

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PREFACE

The lectures are designed to provide a complete, up-to-date and readable pharmacology text for the 3rd year students of medical faculty. Planned to be used during the 2 semesters, the text focuses on the major principles of pharmacology with the clinical application of drugs. It also offers special features that make it useful to practicing clinicians.

The content of *Lectures* is organized in 10 sections, primarily by therapeutic drug groups and their effects on particular body systems. This approach helps the student make logical connections between major drug groups and the conditions for which they are used. It also provides a foundation for learning about new drugs, most of which fit into known groups.

Information is organized according to the sequence used in many pharmacology courses: common pharmacology; autonomic drugs; neurotropic agents; cardiovascular drugs; endocrine and vitamin drugs; antimicrobial agents; drugs used to treat diseases of the blood; and special topics. The first lecture contains knowledge required to understand the main principles and rules of medical prescription. Lecture 2 consists of common pharmacological information, including: cellular physiology, drug transport, pharmacokinetic processes, the receptor theory of drug action, types of drug interactions, and factors that influence drug effects on body tissues, dosage forms, routes and methods of accurate drug administration and general principles of drug therapy.

Other lectures within each section emphasize therapeutic classes of drugs and prototypical or commonly used individual drugs, those used to treat common disorders, and those likely to be encountered in clinical practice. Lecture's content is presented in a consistent format and includes a description of a condition for which a drug group is used; a general description of a drug group, including a small historic review, mechanism(s) of action, indications for use, and contraindications; adverse drug effects and descriptions of individual drugs, with recommended dosages and routes of administration. The lectures in these sections include drug names, classifications, prototypes, drug approval processes. Some lectures include initial parts that reviews the physiology of body systems. The reviews are designed to facilitate understanding of drug effects on a body system. Each section includes examination questions with detailed answers to help students test their knowledge of the covered material. Appendices contain information about main international pharmacological abbreviations and examples of combination drugs. All of this made the *Lectures book* comprehensive but not exhaustive, and accurate — a text that supplies both students and university faculties.

These lectures are created at the Department of general and clinical pharmacology of the Odessa State Medical University.

MEDICAL PRESCRIPTION

Lecture 1
INTRODUCTION TO THE MEDICAL PRESCRIPTION RULES OF PRESCRIPTION WRITING

Prescription is a part of pharmacology. It is divided into pharmaceutical prescription, which studies rules of drug's production, and medical prescription that studies rules of prescription writing.

Drug substances have different *sources*. They can be obtained from the plants, animals, minerals, bacteria, and fungi. Drugs, produced from the plants by *simple* processing (drying and mixing), are called simple. They are used seldom. *Composite* drugs are produced from plant origin by more complex processing. For example, *Galen's* and *neo-Galen's drugs*. They are both containing sum of plant's active substances. Galen's drug is obtained by spirit or another kind of extraction from a plant, e.g. tinctures, extracts; usually it contains ballast or non-active substances. However, neo-Galen's drug is subjected to more composite processing; it is more pure and can be used parenterally.

Drug form is a shape that is given to the drug substance. According to their condition drug forms are divided into ***solid***, (powders, capsules, tablets, dragee, granules), ***liquid*** (infusions, decoctions, mixtures, tinctures, fluid extracts, solutions), and ***soft*** (ointments, fluid ointments, pasts, suppositories, plasters). Also drug forms can be dosed, they usually act after reaching the bloodstream, and non-dosed, which as a rule act topically. Drug substance is a chemical compound that provides drug's action. Drug is a drug substance, produced in a concrete drug form.

Pharmacopoeia is a work containing monographs of therapeutic agents, standards for their production strength, purity, and their formulations. Pharmacopoeia includes especial *list A* (agents with high toxicity, poisons, and agents of abuse), *list B* (potent drugs of strict supervision).

Prescription is a written proposition of physician for pharmaceutist to produce and/or to sale a concrete drug. It is a written formula for the preparation and its administration. Also, prescription is a juridical document, because it is observed when the correctness of treatment is doubtful.

PARTS OF PRESCRIPTION

1. **Inscriptio** — tells official data about the hospital (title and address), the physician, who writes prescription (surname, initials), and the patient (surname, initials, age). It is written in national language.

2. **Prepositio** — consisting of the word *recipe*, take, or its sign, *"Rp.:"*

3. **Designatio** materiarum (list of agents) is the main part of the prescription, containing the names and amounts of the drugs ordered. Each drug substance is written in own line from a capital letter, in genitive case, and in Latin. Words can not to be shortened and broken. Doses are written by figures. If ingredient is only one, receipt is *simple*, if many — *complex*.

Drug substances are divided according to their importance.

a. *Remedium cardinale (s.basis)* — a drug substance, which carries the main treating effect.

b. *Remedium adjuvants* are substances with an additive action.

c. *Remedium constituents* — a shape-making substance. A constituent is to be indifferent (non-active).

d. *Remedium corrigens* — substances bettering taste, smell, type. Corrigens are usually sugar, ether oils, syrups.

4. **Subscriptio** — directions for mixing of the ingredients and designation of the form (pill, powder, solution, etc.) in which the drug is to be made, e.g. beginning with the word, misce, mix, or its abbreviation, M., *fiat*, make, or its abbreviation, f., and the name of the drug form (*pulvis*, powder). Also it can include the quantity *Da (D.)*, give; *tales (t.)*, such; *doses (d.)* N, number.

5. **Signatura** — directions to the patient regarding the dose and times of taking the remedy that is preceded by the word signa, designate, or its abbreviation, (S.). It is written in national language.

6. **Nomen medici** — signature and the own stamp of the physician.

Prescription in special cases. It concerns narcotics and other similar substances. Special blanks for

strict calculation are done for this purpose. Those blanks have a serial number. They are covered by pink drawing and are proved by stamp of the hospital and a signature of its head. Prescriptions on poisonous substances including spirit are proved by a special stamp of the hospital. Prescription for privilege using (free of charge for 80%), are proved by stamp of the hospital also. In emergency prescription of a drug we write *"cito!"*, quickly in an upper left corner.

Dose — is a quantity of a drug substance that can be expressed in milliliters, grams, and international units. There are following types of doses — moment, daily, curative, and minimal, medial or maximal therapeutical.

Prescription can indicate a moment dose of an agent (for one time) and its quantity. It is a *distributive way* of prescribing. Tablets, powders, etc. are prescribed in this way. In *dividing way* we prescribe a summary dose and a patient has to divide it only at the moment before using, e.g. mixtures, decoctions. *Magisterial prescription* — prescription that is compiled by physician. *Officinal prescription* — prescription of already produced drug substances.

1.1. SOLID DOSED MEDICINAL FORMS

Powder (pulvis, pulv.) is a homogenous dispersion of finely divided, relatively dry, particulate matter consisting of one *(simple)* or more *(complex)* substances. Its weight is limited — 0.1–1 g, optimal weight — 0.3 g. If basis weight is less than 0.1 g, we add a form-making substance — sugar (**Saccharum**), glucose (**Glucosum**).

Rp.: Platyphyllini hydrotartratis 0.005
Sacchari 0.3
Misce fiat (M.f.) pulvis
Da tales doses (D.t.d.) N 6
Signa (S.) By 1 powder 3 times a day.

If basis weight is enough, we don't add a form-making substance.

Rp.: Amidopyrini 0,3 — ***Simple powder***
D.t.d. N 6
S. By 1 powder during headache.

 # — this sign usually separates two prescriptions.

Rp.: Amidopyrini 0.3
Coffeini natrii-benzoatis 0.1 — ***Complex powder***
M.f. pulv.
D.t.d. N 6
S. By 1 powder during headache.

Capsule (capsula, caps., genitive case — **capsulae**) is a solid dosage form in which the drug is enclosed in either a hard or soft soluble container or "shell" of a suitable form of gelatin. Capsule remove probable unfavorable taste, smell, prevents irritation of the oral cavity and stomach mucosa, and drug's inactivation by the stomach juice. Nowadays capsules are produced at the factories, that's why they are prescribed in a shortened (brief) form:

Rp.: Capsulae Chinini sulfatis 0,2 N 10
D.S. By 1 capsule 5 hours before attack.

Tablet (tabuletta, tab., genitive case — *sing.*, **tabulettae**, *pl.*, **tabulettarum**) is a solid dosage form containing medicinal substances; it may vary in shape, size, and weight. Tablets may be complex and simple according to amount of active substances. They always include nonactive ingredients, but physician doesn't consider them.

A shortened form (for simple prescriptions only):

Rp.: Tabulettarum Reserpini 0,00025 N 50
D.S. By 1 tablet 3 times a day.

A full form (for simple and complex prescriptions):

Rp.: Reserpini 0,00025
D.t.d. N 50 in tabulettis
S. By 1 tablet 3 times a day.
#

Rp.: Acidi acetylsalicylici
Phenacetini $\overline{aa}$ *0,25*
Coffeini natrii-benzoatis 0,1
D.t.d. N 10 in tabulettis
S. By 1 tablet during headache.

Ana, $\overline{aa}$ or both means that ingredients have similar weight.

Patented tablet consists of one or more substances with fixed (determined) weight. It is written without weight. Patented tablet like a sign, under which one or more active agents are present.

Rp.: Tabulettarum "Pentalginum" N 10
D.S. By 1 tablet during headache.

Dragee (dragee, dr.) is a solid dosage form. It is a sugarcoated small globular mass of some coherent but soluble substances, containing a medicinal substance to be swallowed. Consecutive tracing of drug substances produces it. Rules of dragee prescription are the same as tablets'.

Rp.: Dragee Acidi ascorbinici 0,05 N 10
D.S. By 1 dragee 3 times a day.

1.2. LIQUID DOSED MEDICINAL FORMS

Infusion (Inf., in genitive cases — **Infusi**) is a liquid form that contains water extract from the plants. It is produced by steeping of plant origin (leaves — **folium**, *pl.* **folia**, in genitive case — *sing*., **folii**, *pl.*, **foliorum**; grass — **herba**, in genitive case — **herba**e) in water and boiling 15 minutes. **Decoction (Dec.**, in genitive case — **Decocti**) is close to infusion. However, decoction is prepared from more crude and rough plant origin, e.g.

roots — **radix**, in genitive case — **radicis**; bark — **cortex**, in genitive case — **corticis**. That's why decoction boiling is longer (about 20–30 minutes) than infusion.

Infusion and decoction are prescribed in a dividing way. It means that a patient obtains a bottle with a total dose. Then a patient himself selects a moment dose by different spoonfuls. They are a small teaspoonful (for children under 5 years), a teaspoonful (from 6 to 16 years), and tablespoonful (over 17 years).

1 ***small teaspoonful*** *contains* *5 ml*
1 ***teaspoonful*** *contains* *10 ml*
1 ***tablespoonful*** *contains* *15 ml*

Both infusion and decoction are unstable; they loose therapeutic action in a few days. Thus, traditionally they are prescribed for twelve times taking. For prescription of infusion and decoction we have to multiple a moment dose of a plant origin into 12 (amount of its taking), and we'll get the total weight of plant source.

The water volume for infusion and decoction is to be found out as follows:

Spoon volume · Quantity of intake = Total volume

5 ml · 12 = 60 ml *(for children under 5 years)*
10 ml · 12 = 120 ml *(for children from 6 to 16 years)*
15 ml · 12 = 180 ml *(for patients over 17 years)*

For example, prescribe infusion of grass of *Adonis vernalis*, which moment dose (MD) is 0.5 (5 decigram). Take 1 tablespoonful three times a day.

First of all we have to calculate the total weight of grass and total volume of added water.

Total weight of grass: 0.5 · 12 = 6.0
Total volume of water: 15 ml · 12 = 180 ml
Thus

Rp.: Infusi herbae Adonidis vernalis 6.0 — 180 ml
D.S. Take 1 tablespoonful 3 times a day.

Prescription of decoction is similar. For example, prescribe decoction of bark of Frangula, which moment dose is 1.5. Take 1 tablespoonful before sleep.

Rp.: Decocti corticis Frangulae 18.0 — 180 ml
D.S. Take 1 tablespoonful before sleep.

Mixture (**Mixtura**, in genitive case — **Mixturae**) is a liquid medicine that consists of various agents. Water is a liquid solvent that gives form to mixture. If mixture contains decoction or infusion, water can be present in its composition. In the opposite case, water have to be added separately; it is mentioned **Aqua destillata** (**Aq. destill.**, in genitive case — **Aquae destillatae**) on the last line of the agent's list. Mixture as well as infusion and decoction are given by spoonfuls, teaspoonfuls, and small teaspoonfuls. Also, mixture is prescribed for twelve intakes and in a dividing way. All substances in mixture have to be mixed. That's why we write **Misce (M.)**, mix after the list of active agents.

For example, prescribe mixture that contains *potassium (kalium)* and *sodium (natrium)* bromide, a moment dose 0.3 each for adult. Take 1 tablespoonful 3 times per day.

Rp.: Natrii bromidi
Kalii bromidi ana 3.6
Aquae destillatae 180 ml
M.D.S. Take 1 tablespoonful 3 times a day.

Mixture that includes infusions has the next structure. Prescribe mixture that includes infusion of leaves of Digitalis (a moment dose — 0.05) and Themisalum (a moment dose — 0.3). Take 1 tablespoonful 3 times a day.

Rp.: Infusi foliorum Digitalis 0.6 — 180 ml
Themisali 3.6
M.D.S. 1 tablespoonful 3 times a day.

Syrup (**Syrupus**, in genitive case — **Syrupi**) is a highly concentrated aqueous solution of sugar, e.g. sugar syrup (**Syrupus simplex**). That's why it improves mixture test and prevents bacterial growth. Volume of syrup approximately is 20–30% of total mixture volume.

Drops **for enteral usage** are liquid medicines. Water, spirit, and vegetable oils are used as solvents. As usually total volume of drops is 10–30 ml. It is known that 1 ml of spirit solution contains 50 drops and *1 ml of water solution contains 20 drops.* For example, prescribe atropine sulfate (Atropinum sulfas), a moment dose — 0.001. Prescribe 20 drops (1 ml) two times a day during 10 days.

Quantity of intakes = quantity of usage during 1 day · duration of treatment; 2 · 10 = 20. Total weight of atropine = moment dose · quantity of intakes; 0.001 · 20 = 0.02 (g). If it is not mentioned "spirit" or "oil" solution, it is water solution. The moment dose of water is 20 drops or 1 ml. Total volume of water = volume of the moment dose · quantity of intakes; 1 ml · 20 = 20 ml.

Rp.: Atropini sulfatis 0.02
Aquae destillatae20 ml
M.D.S. Take 20 drops 2 times a day.

More often drops for oral intake are prescribed in a shortened form. In this case we begin prescription from characteristics of a medicinal form — the word "solutionis"; then it should be written the name of the agent, its concentration (%) and the total volume of the solution. In general, an expression "1% solution" means that 100 ml of this solution contains 1g of the active substance. That's why, percentage of the solution is a quantity of the active substance (g) in 100 ml of the solution. It can be calculated with the help of the following ratio. For example, we know that it is 0.02 g of atropine sulfate in 20 ml of solution:

In 20 ml of solution — 0.02 of *Atropine sulfate*
In 100 ml of solution — X of *Atropine sulfate*
X = 0.02 · 100 / 20 = 0.01

Thus, it will be 0.01 (g) of *Atropine sulfate* in 100 ml of solution; concentration of solution is 0.01%.

Rp.: Solutionis Atropini sulfatis 0.1% 20 ml
D.S. Take 20 drops 2 times per day.

If a solvent is spirit or vegetable oil, it must be noted **spirituosae** or **oleosae** correspondently after the agent's name.

Rp.: Solutionis Nitroglycerini spirituosae 1% 10 ml
D.S. Take 2 drops on a peace of sugar under the tongue.

Tincture (**Tinctura, T-ra**; in genitive case — **Tincturae, T-rae**) — is an alcoholic, hydroalcoholic, or ether-alcoholic extract of raw plant material. A single medical dosage is 20–25 drops of tincture.

Both infusion and tincture are extracts from the plant origin. However, infusion is a water extract, tincture is an alcoholic extract. Also, tincture is more stable (during a few years) than infusion.

The rule of tincture writing is following: drop's quantity for one intake must be the same as the total volume of tincture in milliliters.

Example:

Rp.: Tincturae Valerianae 25 ml
D.S. Take 25 drops three times per day.

Simple tincture is an alcoholic extract from one plant origin. Complex tincture is composition of two or more tinctures. For instance, prescribe composition of tincture of *Valeriana* and tincture of *Convallaria* in equal volume with addition of tincture of *Grataegus*, volume of which is j of total composition volume. Prescribe 20 drops 3 times per day.

First of all, if we prescribe 20 drops for one intake, the total volume of composition is 20 ml. Then, 1/4 of total composition volume (20 ml) will be 5 ml. So, the total volume of tinctures of *Valeriana* and *Convallaria* is 15 ml. As it mentioned above, tincture of *Valeriana* and tincture of *Convallaria* have equal volume. Thus, volume of both tinctures is 7.5 ml.

Rp.: Tincturae Valerianae
Tincturae Convallaria aa 7.5 ml
Tincturae Crataegi 5 ml
M.D.S. Take 20 drops 3 times per day.

If tincture-including mixture consists of many ingredients, it is prescribed as a patented officinal form. For example, "Corvalolum" includes Valerianic acid, phenobarbital, peppermint oil, alcohol, and water.

Rp.: Corvaloli 15 ml
D.S. Take 15 drops in the evening.

Extract (**Extractum, Extr.,** in genitive case — **Extracti**) is a concentrated preparation obtained from a plant origin by removing of the constituents with suitable solvents. According to its aggregate condition, extract can be dry (**siccum**), thick (**spissum**), and liquid (**fluidum**). A dry extract has less than 5% of moister; thick extract has 5–25% of moister; and a liquid extract has over 25% of moister.

Thick and dry extracts are dosed out in the weight units (gram) and are prescribed in capsules, powders, tablets, and suppositories.

Liquid extract is dosed out in drops and is prescribed in the same way as tincture. It means that the total volume in milliliters must be the same as the quantity of drops for one intake. Also we have to mark that it is liquid (**fluidum**) extract.

Rp.: Extracti Polygoni hydropyperis fluidi 25 ml
D.S. Take 25 drops 4 times per day.

Solution for injection is a liquid officinal form that is formed by dissolving of one or more active substances and is intended for injection using. In general, solution is the incorporation of solid, liquid, or gas in a liquid resulting in a homogeneous single phase.

The solvents are water, spirit, or vegetable oils. Solution for injection differs from tincture, extract with higher degree of purity, sterility, and absence of ballast substances. Also, solution for injection have such advantages as the higher therapeutic activity, quick onset of action, more exact dosage, portability, possibility of their administration to unconscious patients.

A physician begins a prescription from the word solution, sol. (in genitives case — solutionis; in nominative case — solutio) and the agent's name. Then it must be presented the concentration of the solution (in percentage) and volume of one ampoule or bottle. In the next line we have to write **Da tales doses, D.t.d.**, give such doses; amount of ampoules or bottles. Solutions for injections are produced in ampoules (ampullis) with 1, 2, 5, 10, 20 ml capacity or bottles with 5, 10, 50, 200, 400 ml capacity. If they are in ampoules, we have to note after figure **in ampullis, in ampull**. In case of bottle we don't write anything after amount.

Rp.: Solutionis Platyphyllini hydrotartratis 0.2% 1 ml
D.t.d. № 10 in ampullis
S. Inject 1 ml 2 times per day subcutaneously.

If a solvent is spirit or vegetable oil, it must be noted **spirituosae** or **oleosae** correspondingly after the agent's name. For aqueous solutions a solvent isn't indicated.

Rp.: Solutionis Camphorae oleosae 20% 2 ml
D.t.d. № 10 in ampull
S. Inject subcutaneously 2 ml once daily.

#

Rp.: Solutionis Gramicidini spirituosae 2% 5 ml
D.t.d. № 10 in ampull.
S. Before use the ampoule's content is to be diluted of sterile water (500 ml).
Only for external use.

A patented form of solution is prescribed without the word "solution". For instance, 0.15% solution of Cytisinum is known as "Cytitonum". As a rule, we can't write the word "solution" when the

concentration is absent. This agent can be prescribed in both ways.

Rp.: Solutionis Cytisini 0.15% 1 ml
D.t.d. N 10 in ampull.
S. Inject intravenously 1 ml.
#
Rp.: Cytitoni 1 ml
D.t.d. N 10 in ampull.
S. Inject intravenously 1 ml.
#
Rp.: Reopolyglucinum 400 ml
D.t.d. N 2
S. Inject intravenously by drops 200 ml.

Also we don't write the word "solution" for hormones prescription.

Rp.: Pituitrini 1 ml (5 units)
D.t.d. N 6 in ampull.
S. Inject 1 ml subcutaneous per day.
#
Rp.: Insulini 5 ml (1 ml — 40 units)
D.t.d. N 2
S. 20 units subcutaneous per injection (to inject before half hour of the meal).

As it was mentioned above, when the substance is produced in a bottle, the word "bottle" isn't written.

Sometimes we prescribe big bottles, which contain many units of doses of injection solution. In addition, when bottles are produced in the laboratory of the hospital or drug-store, we have to write instruction for its purity — *Sterilizetur*, sterilize.

Rp.: Solutionis Glucosi 5% 400 ml
Sterilizetur!
D.S. For subcutaneous injection.

An agent in the bottle can be produced in a dry form. As a rule, it must be dissolved before using. In signature it have to be marked. The prescription looks like the following:

Rp.: Streptomycini sulfatis 1.0
D.t.d. N 6
S. To dissolve the contents of the bottle in 5 ml of 0.25% novocaine solution. To inject intramuscularly 2.5 ml per 12 hours.

Sometimes the substance is dosed in international (biological) units and produced in bottles:

Rp.: Bicillini — 3,600,000 units
D.t.d. N 5
S. Inject intramuscularly once a week, preliminary dissolving the bottle content in 3 ml of water for injections.

Suspension (**Suspensio, Susp.**, in genitive case — **Suspensionis**) is a class of preparations of finely divided, undissolved drugs (e.g. powders for suspension) dispersed in liquid for oral or parenteral use.

We prescribe it just as solution:

Rp.: Suspensionis Hydrocortisoni acetatis 2.5% 5 ml
D.t.d. N 6
S. To inject 1,5 ml into the cavity of the injured joint 1 time per week.
#
Rp.: Suspensionis Chlorthiazidi 5% 250 ml
D.S. Take orally 10 ml (a teaspoonful) twice per day.

Aerosol (**Aerosolum**; in genitive case — **Aerosoli**) is liquid or particulate matter dispersed in the air in a form of fine mist for therapeutic purposes. It is packaged in bottles under pressure and contains active ingredients intended for inhalation (mostly) and topical application. For example, prescribe aerosol Salbutamolum, in bottles — 10 ml. One inhalation 4 times per day.

Rp.: Aerosoli Salbutamoli 10 ml
D.S. One inhalation 4 times per day.

1.3. SOFT DOSED MEDICINAL FORMS — SUPPOSITORIES

Suppository (**Suppositorium, Supp.**, in genitive case — sing. **Suppositorii**; *pl.* **Suppositoriorum**) is a small solid body shaped for ready introduction into one of the orifices (opening) of the body other than the oral cavity (e.g. rectum, urethra, vagina), made of a substance, which is solid at ordinary temperatures but melts at the body temperature. Usually cacao oil (**Oleum Cacao**) is used as form-making substance suppository.

Rectal and vaginal suppositories are widely spread in medicine. These suppositories (especially rectal) provide both local therapeutical effect and general absorptive effect thanks to absorptive ability of mucous membranes.

Suppositories are used during treatment of rectum (proctitis, paraproctitis) and vagina (vaginitis) diseases. The contraceptive agents are prescribed in globules moreover. Administration of drugs into the rectum has greater importance when the oral using of substances is impossible (vomiting, burn of the gullet and others). During some diseases (decompensation of heart activity, cirrhosis) the absorption from the small intestine is difficult and uncompleted. Drugs absorbed from suppositories in the lower rectum enter vessels that drain into the inferior vena cava, thus bypassing the liver. However, partially drugs achieve superior hemorrhoidal vein that leads to the liver. Also the absorptive ability of the rectum mucosa is lower than of the small intestine. Thus, dose of active substance is in suppository is higher than the dose for oral use.

Rectal suppositories have a conic or a "cigar" form with height of 4 cm and weight of 1.1–4.0 g (average is 3.0 g). Vaginal suppositories have a round or an egg-like form; their weight is 1.5–6.0 (average is 4.0).

Nowadays, suppositories are prepared mostly in industrial route. They can be prescribed in a shortened form.

Rp.: Suppositoriorum Metronidazoli 0.5 N 10
D.S. Use 1 suppository into the vagina, preliminary taking off packing.

The patented suppositories are prescribed as a ready officinal forms.

Rp.: Suppositoriorum Bethioli N 10
D.S. Introduce 1 suppository into the rectum per night.

For prescription of suppositories produced in a drug-store we use a full-form. The "basis" (active substance) is written first of all for the prescription of suppositories. Then the form-making substance follows. In subscription we have to write **Misce fiat suppositorium, M. f. supp.** (mix let it be suppository) **rectale** or **vaginale**. In signature we indicate how to use them.

Rp.: Omnoponi 0.24
Olei Cacao 3.0
M.f. supp. rectale
D.t.d. N 10
S. 1 suppository into the rectum per night.

Instead of oil cacao quantity it is possible to write **quantum satis, q.s.**, that means — as many as it necessary.

Rp.: Metronidazoli 0.5
Ol. Cacao q.s.
M.f. supp. rectale
D.t.d. N 10
S. 1 suppository into the vagina 2 times a day.

1.4. NON-DOSED MEDICINAL FORMS — POWDERS FOR EXTERNAL USE, OINTMENTS, LINIMENTS AND SOLUTIONS FOR EXTERNAL USAGE

Non-dosed medicinal forms are used in external way (application, massage, washing). The preparation's quantity depends on the size of the injured place. The agents that are prescribed in non-dosed forms cause a local action or act in a reflective way. As usually in this route we prescribe different disinfectant remedies. According to aggregate condition non-dosed medicinal forms are divided into solid (powder for external use), liquid (solution for external use), and soft (ointment, pasta).

Powder for external usage (**Aspersio, Aspers**.; in genitive case — **Aspersionis**) is a homogenous dispersion of finely divided, relatively dry, particulate matter consisting of one *(simple)* or more *(complex)* substances for external application on the skin and the mucous membranes. It is used during wetting and maceration of the skin, pyodermititis, micotic lesion of the skin.

Talc (**Talcum**) and starch (**Amylum**) are the form-making substances in powders for external usage.

Powder for external usage can be prescribed in both shortened and complete methods. The shortened method is useful for prescription of patented powder or in case when it consists of only one active substance. When there are two or more compounds in the powder composition, the complete method is used. The shortened method is following:

Rp.: Aspersionis Amycozoli 5% 50.0
D.S. Apply on the injured surface.

Unlike a shortened variant, the quantity of substances in a full one is expressed in grams:

Rp.: Bismuthi subnitratis
Zinci oxydi ana 10.0
Amyli ad 50.0
M. f. aspersio
D.S. Apply on the injured surface.

Smallest powders are used for application on the mucous membranes, e.g. in ophthalmic practice. They are called — **pulvis subtilissimus**.

Rp.: Streptocidi subtilissimi 20.0
D.S. Apply on the injured surface.

Ointment (**Unguentum, Ung.**, in genitive case — **Unguenti**) is a soft non-dosed medicinal form for external usage. Agents, which are prescribed in ointments, usually have astringent, anti-inflammatory, keratolytic (peeling of the skin) or keratoplastic (increasing of keratinization) effects. Vaselin (**Vaselinum**) and lanolin (**Lanolinum**) are used as the form-making substances in ointments.

The ointment that consists of only one compound, is prescribed in a shortened way:

Rp.: Unguenti Resorcini 10% 100,0
D.S. Apply on the injured surface.

Ointment that includes two and more active substances is prescribed by a complete method. Unlike a shortened variant, quantity of substances in a full one is expressed in grams. For example, prescribe 50.0 (grams) of ointment that consists of *Anaesthesinum* (1%) and *Xeroforminum* (10%).

First of all, we have to convert per cents into grams with the help of ratio.

100% of ointment — 50.0 (grams) of ointment
1% of anaesthesinum — X (grams) of anaesthesinum
X = 50,0 · 1 / 100 = 0.5.

Weight of *Xeroforminum*: 50 · 10 / 100 = 5.0

Rp.: Anaesthesini 0.5
Xeroformini 5.0
Vaselini ad 50.0
Misce fiat unguentum
D.S. Apply on the injured skin surfaces.

Paste (**Pasta**, in genitive case — **Pastae**) is a soft semisolid non-dosed medicinal from. It contains more than 25% of solid substances. However, ointment has less than 25% of solid substances. Thus, ointment can be transformed into paste by addition of solid substance (e.g. talc). Paste has the same form-making substances as ointment (e.g. *Vaseline*).

If paste includes only one active substance, or it is produced in a patented form, prescription will have a shortened form:

Rp.: Pastae Resorcini 10% 100.0
D.S. Apply on the injured surface.

In other cases the complete method is used. For example, prescribe 100,0 (grams) paste with the following composition: Acidum salicylicum (5%), Acidum boricum (1%), Zincum oxydum (15%).

The sum of all solid form of this composition is 21%. It is not enough for paste. We have to add talc, e.g. 10%. In this case the sum will be 31% that is enough. Then we have to express the weight of substances in grams.

100% of paste — 100.0 (grams) of paste
5% of Acidum salicylicum — X (grams) of Acidum salicylicum
X = 5 · 100.0 / 100 = 5.0 (grams)

Weight of *Acidum boricum* = 1 · 100.0 / 100 = 1.0 (grams).

Weight of *Zincum oxydum* = 15 · 100.0 / 100 = 15.0.

Rp.: Acidi salicylici 5.0
Acidi borici 1.0
Zinci oxydi 15.0
Talci 10.0
Vaselini ad 100.0
M. f. pasta
D.S. Apply on the injured surface.

Liniment (**Linimentum, Lin.**, in genitive case — **Linimenti**) or fluid ointment is a soft preparation for external application. It is a thick liquid at the room temperature, but melts at the body temperature. Vegetable oils, e.g. sunflower seed oil (**Oleum Helianthi**) are used as a form-making substance for liniment.

The prescription rules are the same as in ointments:

Rp.: Linimenti Synthomycini 10% 20.0
D.S. Apply on the injured surface.
#
Rp.: Chevroformini
Olei Helianthi ana 20.0
M. f. linimentum
D.S. Apply on the injured surface.

An officinal liniment:

Rp.: Linimenti Vipratoxi 50,0
D.S. Apply on the injured surface.

Solution for external usage is a fluid officinal form, which is received during dissolution of solid or fluid medicinal substance in the solvent. The solutions are aqueous, alcoholic, and oil. They are used for washing, irrigation, rinsing, fomentation in the treatment of wounds, ulcers, etc. They are prescribed as already prepared officinal forms:

Rp.: Solutionis Furacilini 0.02% 500 ml
D.S. For irrigation of wound.

In addition, concentration can be expressed in the form of ratio

Rp.: Solutionis Furacilini 1:5000 — 500 ml
D.S. For irrigation of wound.

In cases of spirit or oil solutions we have to write the word "**spirituosae**" or "**oleosae**" correspondingly after the agent's name.

Rp.: Solutionis Iodi spirituosae 5% 50 ml
D.S. For external application.
#
Rp.: Solutionis Camphorae oleosae 10% 10 ml
D.S. For external using.

Usually volume of prescribed solution for irrigation and rinsing of wounds or cavities is about 500 ml, volume for local application is about 50–100 ml, and volume of eye or ear drops is about 10 ml.

Rp.: Solutionis Sulfacili-natrii 30% 10 ml
D.S. Eye drops. Two drops in each eye 4 times per day.

Lecture 2
COMMON PHARMACOLOGY PRINCIPLES

Pharmacology is the science that studies the interaction of substances with living systems through chemical processes. It concerns drugs, their sources, appearance, chemistry, actions, and uses.

The interactions between the drug and the body are conveniently divided into two classes. The actions of the drug on the body are termed ***pharmacodynamic*** processes. These properties play the major role in deciding whether that group is appropriate therapy for a particular symptom or disease. The actions of the body on the drug are called ***pharmacokinetic processes***. Pharmacokinetic processes govern the absorption, distribution, and elimination of drugs. ***Pharmacotoxicodynamic*** is a branch of pharmacology that deals with the undesirable effects of chemicals on living systems, from individual cells to complex ecosystems.

PHARMACOKINETIC PROCESSES

Time, needed for achieving the maximal effect, it's duration and intensity depend on route of administration. So it is necessary to consider peculiarities and principles of different introduction methods, while choosing. They are divided in to enteral (through the digestive tract) and parenteral (omitting the digestive tract).

Enteral routes include oral, sublingual, and rectal administration. The oral way is the most easy, convenient, and widely used way of administration. But a lot of factors influence the absorption and bioavailability of the drug. ***Bioavailability*** is the ratio of the unchanged drug reaching the systemic circulation to the given dose (in per cent). For an intravenous dose of the drug, bioavailability is equal to unity (100%). For example, if bioavailability of a drug is 50%, it means that 50% of the ingested dose reach the serum. For a drug administered orally, bioavailability may be less than 100% for two main reasons — incomplete extent of absorption and ***first-pass elimination***. The latter means that following absorption across the gut wall, the portal blood delivers the drug to the liver prior to entry into the systemic circulation. A drug can be metabolized in the gut wall, but most commonly in the liver that is responsible for metabolism before the drug reaches the systemic circulation.

The hepatic first-pass effect can be avoided to a great extent by use of sublingual route and by use of rectal suppositories. Sublingual absorption provides direct access to systemic — non portal — veins. This route is facile; the onset of action is fast; but the duration of action is short. Drugs absorbed from suppositories in the lower rectum enter vessels that drain into the inferior vena cava, thus bypassing the liver. However, partially drugs achieve superior vena cava that lead to the liver. In addition the absorptive ability of the rectum mucosa is lower than that one of small intestine. Thus, only about 50% of a rectal dose can be assumed to bypass the liver.

Injections (1), *inhalations* (2), and *transdermal route* (3) belong to **parenteral routes**. The first one includes intracutaneous, intravenous, intramuscular and intraarterial infections. The effect appears quickly, especially in case of intravenous injection, and provides precision of dosage. Bioavailability for intravenous route is 100%. After intravenous injection the onset of action is quicker, but duration is shorter than during intramuscular or subcutaneous injection. It is not recommended to use the drugs with strong irritative action subcutaneously and intramuscularly. It is also prohibited to use intravenously insoluble substances and oily solutions because of embolism risk. Lack of these routes is tissue damages, necessity of sterility, and risk of non-specific reactions (shock, collapse, cramps).

Gases and aerosols are introduced using *inhalations*. Therapeutic effect is reached quickly. This route is predominantly desirable for the treatment of diseases of air ways. It causes topical action mainly. Lack of this method is irritation followed by spasm of the larynx, the bronchi.

The oil-solved substances (in the form of ointments and liniments) and electrolytes (by electrophoresis) are introduced through the skin. The transdermal route provides direct access to systemic — nonportal — veins and prolongs the duration of drug absorption.

Drug absorption depends on many factors in the digestive tract. Ionized forms of drugs are poorly dissolved in lipids and poorly absorbed. Salicylates in the stomach (pH 1.0–1.5) are poorly ionized and absorbed

to a great extent in the stomach. Alkaloids are better absorbed in the intestine (pH in duodenum is ~ 6.6), due to poor ionization in alkaline medium. It is necessary to consider, that pH in the stomach is the lowest during and just after meals, and the highest — 1 hour before and 1.5–2 hours after meals. So acid substances are necessary to administrate while or just after eating, alkaline substances — 1 hour before and 1.5–2 hours after eating.

Quantity and character of meals, that can change pH of surrounding, also influence drugs absorption considerably. For example, tetracycline forms stable compounds with calcium, which are not absorbed. That's why simultaneous using of tetracycline and milk that contain calcium can decrease the rate of tetracycline absorption. At the same time, lipids increase the absorption of fat-dissolved drugs (vitamins A, D, K, E, etc.). Alkaline promotes ionization of acid substances and impedes their absorption and vice versa.

Drugs absorption in the intestine depends considerably on motility of the digestive tract too. Substances that decrease motility of the intestine (spasmolytics, cholinolytics, etc.) promote absorption; substances hastening motility (cholinomimetics) impede absorption.

The drug's form has a great meaning during oral administration. The most common rule is that liquid forms are absorbed better, than powders, absorption of which depends on its dispersion; powders are absorbed better than tablets, dragees and granules. So, bioavailability of drugs in case of enteral administration depends on many factors, varies greatly and is hardly predicted.

After parenteral administration drugs absorb into the blood circulation from subcutaneous tissue, muscles and cavities (depending of injection types), from alveoli (during inhalations). A physician can easier predict the serum level of the drug and its effective dose. However, in the case of bloodstream delay the absorption after subcutaneous and intramuscular injections can decrease.

While choosing the route of administration, it is important to consider some basic factors: (1) stability of drug in the digestive tract; (2) possibility of absorption through the walls of the digestive tract and bioavailability; (3) the goal of therapy (in emergency the parenteral route of administration, especially intravenous is preferred).

In the organism drugs permeate through the various barriers that separate different compartments, e.g., the gut, the brain. For a drug given orally to produce an effect in the central nervous system, these barriers include the tissues that comprise the wall of the intestine, the walls of the capillaries that perfuse the gut, and the "blood-brain barrier", the walls of the capillaries that perfuse the brain.

Drug permeation proceeds according to 4 primary mechanisms:

1. ***Passive or lipid diffusion*** occurs due to gradient of the substance concentration. Passive diffusion is the most important limiting factor for drug permeation because of the large number of lipid barriers that separate the compartments of the body. The lipophilic substances are transported by this way. It occurs without energy using.

2. ***Filtration or aqueous diffusion*** appears across epithelial membrane through pores that permit the passage of small molecules. Filtration depends on the concentration gradient of a permeating drug. Small hydrophilic molecules and some ions are transported by this way.

3. ***Active transport*** is provided by special carrier molecules exist for certain substances that are important for cell function and too large or too insoluble in lipid to diffuse passively through membranes (e.g., peptides, amino acids, glucose). Active transport needs energy, which occurs due to decomposition of ATP molecule.

4. ***Pinocytosis*** is the process in which the substance is engulfed by the cell membrane and carried into the cell by pinching off the newly formed vesicle inside the membrane. This process is responsible for the transport of large substances.

There are many biological (blood-histological) barriers in the organism, except the *blood-brain barrier* mentioned above. They are placental, blood-follicular, blood-testicular, and epithelium of the mammary glands. Blood-histological barrier is the capillary wall that consists of endothelium cells, basal membrane, enzymes, and small pores. Lipophilic substances easily pass through cellular membranes, hydrophilic substances pass through the basal membrane and pores. The substances with molecular weight smaller than 5,000–6,000 DA pass easily through the capillary wall too: blood-brain barrier (BBB) consists of cerebral capillaries and astrocytes (neuroglia cells). It possesses selective permeability. Ionized molecules cannot pass trough it. In case of inflammatory process, brain BBB becomes more permeable; and the brain is subjected to harmful influence of different substances. Placental barrier protects fetus from xenobiotics (non endogenous substances). Drugs with molecular weight smaller than 400 DA pass easily trough placenta by the way of passive diffusion. Permeability of placenta depends on many conditions and gradually increases to 33–35 weeks of pregnancy. Thus, it is necessary to care administration of drugs especially in first trimester of pregnancy (a period of fetus' organs appearing). *Blood-follicular* and *blood-testicular barrier* protect sex cells from action of xenobiotics. They consist of lipoprotein membranes and pass easily by lipophilic non-ionized molecules (narcotics, alcohol, etc.). So, genetic material may be damaged (mutagenic effect). The epithelium of the mammary glands is easily passed by lipophilic substances. If drugs used by mother are toxic or may cumulate in breast milk, nursing have to be stopped or the drug have to be changed.

Distribution of drugs in the organism is done by blood and lymph circulation. There are three fractions of substances in the organism: (1) free fraction in serum and tissues; (2) connected with serum proteins; (3) fixed in different tissues.

These fractions are in dynamic balance and constantly remove from one form to another one. Only free fraction is biologically active, because it could transform and excrete. So, the high level of free fraction is associated with strong, quick, but short action. The level of free fraction in blood depends on albumin content. In case of low protein levels (diseases of the liver, the kidneys, starvation) concentration of free frac-

tion considerably increases, that may cause strengthening of the effect.

Some drugs may deposit in tissues, forming extracellular and cellular depots. It occurs due to connection with proteins and phospholipids. Durability of connection is various. Some drugs (e.g., substances for narcosis) form not durable complexes with phospholipids and are quickly deleted from fat depots. Others (sulfanilamides of prolonged action, salts of heavy metals) form durable connections with proteins and for a long time remain in tissues.

Volume of distribution (V_d) relates the amount of drug in the body to the concentration of drug in blood or plasma. Drugs with very high volume of distribution have much higher concentrations in the extravascular tissue than in the vascular compartment. Mostly it is preferable for drugs with high selectivity of action. Serum concentration is sum of free and connected with proteins drug fractions. It shows different phases of pharmacokinetic: absorption, distribution and elimination of the substance. A curve shows the time from the drug administration to appearance of primary effect (latent period of action), the time from first appearance to minimal therapeutic effect (duration of action).

Biotransformation (chemical drug conversion) occurs, basically in the liver, and also in the kidneys, lungs, the wall of the intestines and other organs. The most part of drugs are biotransformed in an organism, except drugs for narcosis and hydrophilic non-ionized substances that are excreted non-transformed. The result of biotransformation is converting of lipid-soluble substances to water-soluble and their excretion. Metabolic products are often less active than the parent drug and may even be inactive. There are two main phases of biotransformation — metabolism and conjugation.

Metabolism (I phase) occurs due activity of oxidizer's systems, basic components of which are cytochrome P-450 and NADP. At this phase reactions usually convert the parent drug to a more polar metabolite by introducing or unmasking a functional group (-OH, -NH2, -SH). Metabolic transformation is done by oxidation, restoration and hydrolysis. For example, *Imipramine, Ephedrine,* and *Aminazine* are subjected to oxidation; *Levomycetin* and *Nitrazepam* are metabolized by restoration; complex ethers (*e.g., Novocain, Atropine*) are hydrolyzed. A major part of substances are metabolized by oxidation for which oxygen is necessary. So, changes of blood circulation, hypoxia sharply lower metabolism of drugs.

An interesting feature of some drugs (e.g., *Barbiturates*, *Rifampicin*) is their ability, on repeated administration, to "induce" cytochrome P-450 by enhancing the rate of its synthesis or reducing its rate of degradation. Induction results in an acceleration of metabolism and usually in a decrease in the pharmacologic action of the inducer and also of coadministered drugs. However, the other drugs (e.g., *Valproic acid, Cimetidine*) inhibit activity of cytochrome P-450 that can result in increasing of coadministered drugs action.

Parent drugs or their phase I metabolites that contain suitable chemical groups often undergo *conjugation* (coupling) reactions with an endogenous substance to yield drug conjugates. For example, histamine and noradrenaline are methylated; sulfanilamides are acetylated; morphine and bilirubin bind with glucuronic acid, etc. In general, conjugates are polar molecules that are readily excreted and often inactive. Conjugate formation involves high-energy intermediates and specific transfer enzymes (transferases).

Excretion of drugs occurs basically via kidneys. Some drugs are excreted with bile into the lumen of the intestine, via the lungs, the mammary glands, sweat and the sebaceous glands. Drugs excrete in changed (metabolites, conjugates) and unchanged (non-transformed) forms. Almost all drugs are filtered at the glomerulus. If a drug is in a lipid-soluble form during its passage down the renal tubule, a significant fraction will be reabsorbed by simple passive diffusion. If the goal is to accelerate excretion of the drug, it is important to prevent its reabsorption from the tubule. This can often be accomplished by adjusting urine to make certain that most of the drug is in the ionized state. As it is mentioned above, acids in acidic medium are poorly ionized and are easily reabsorbed. Alkaloids are better reabsorbed from alkaline urine. Thus, weak acids are usually excreted in alkaline urine; weak bases are better excreted in acidic urine. Also blood circulation in the kidneys (hypotension diminish glomerular filtration), pathological processes in the kidneys play an important role in excretion.

It is necessary to remember that some drugs (e.g., tetracyclines, glycosides), which are excreted with bile, partially are reabsorbed in the intestine. Some substances are excreted through the stomach and the intestine (morphine, salts of heavy metals).

Drugs excretion into breast milk has a special meaning. Most part of the drugs, used by mother, are found in breast milk and may cause side effects in infant. If a drug is excreted into milk and is dangerous for infant, feeding has to be avoided.

Elimination is the process of drug inactivation in result of biotransformation and excretion. It values by half-life of the drug, constant of elimination, and clearance. *Half-life ($T_{1/2}$)* is the time required to change the amount of a drug in the body (usually in blood) by one-half during elimination time. Constant of elimination is the drug quantity (in per cent), that was excreted by the organism during period of time (usually during 1 day). Total clearance of a drug is the ratio of the rate of elimination by all routes to the concentration of drug in serum. Elimination of drug from the body may involve processes occurring in the kidney, the lung, the liver, and other organs. Dividing the rate of elimination at each organ by the concentration of drug presented to it yields the respective clearance at that organ.

PHARMACODYNAMIC PROCESSES

It is a part of pharmacology that studes mechanisms of action, pharmacological, therapeutical and side effects of drugs.

The therapeutical and toxic effects of drugs result from their interactions with molecules in the patient. Most drugs act by associating with specific macromol-

ecules in ways that alter the macromolecules' biochemical or biophysical activities. This idea is embodied in the term receptor. In general, receptor is a structural protein molecule on the cell surface or within the cytoplasm that binds to a specific factor, such as hormone, antigen, or neurotransmitter. This interaction initiates the chain of biochemical events leading to the agent observed effects. The receptor's affinity for binding a drug determines the concentration of drug required to form a significant number of drug-receptor complexes, and the total number of receptors often limits the maximal effect a drug may produce. Many drugs and endogenous chemical signals, such as mediators, regulate the function of receptor macromolecules as ***agonists (mimetics)***; i.e., they change the function of a macromolecule as a more or less direct result of binding to it. They possess affinity and intrinsic activity. Based on the maximal pharmacologic response that occurs when all receptors are occupied, agonists can be divided into two classes. *Partial agonists* produce a lower response, at full receptor occupancy, than do *full agonists.*

Antagonists (lytics, blockers), however, bind to receptors without directly altering their function. Thus, they prevent the binding of agonist molecules and block their biologic actions. The two classes of receptor antagonism are known. In the presence of a fixed concentration of agonist, increasing concentrations of a *competitive antagonist* progressively inhibit the agonist response. Conversely, sufficiently high concentrations of agonist can completely surmount the effect of a given concentration of the antagonist. Some receptor antagonists bind to the receptor in an *irreversible* fashion, i.e., not competitive. The antagonist's affinity for the receptor may be so high that for practical purposes the receptor is unavailable for binding of agonist.

Mechanisms of drugs action may be connected with *enzymes inhibition*. For example, *Proserine*, which inhibits acetylcholinesterase, preserves acetylcholine from enzymatic decomposition, as a result — tonus of cholinergic system increases. Mechanism of action of some drugs is connected with blockade of ionic channels in cellular membranes, e.g., antagonists of calcium channels. The other drugs cause the exhaustion of mediator reserves in neural fibers in result of synthesis breach or reverse neuronal seizure (e.g., tricyclic antidepressants).

Types of the drugs action. There are local, reflective, and resorptive action. Under *local action* one can understand the drug action at the place of administration. It is used seldom. *Reflective action* appears as a result of irritation of neural fibers that transmitted through the CNS or by axon-reflexes. It may appear both: during local and resorptive action (e.g., reflective action of mustard plaster and *Cytitone*). *Resorptive action* is observed after the drug reaching the blood.

There are some types of resorptive action: direct and indirect, basic and side, selective and general, convertible and non-convertible. *Direct action* occurs at the place of drug contact with tissues, e.g., cardiotonic action of cardiac glycosides. *Indirect action* appears as a result of function changes, e.g., increased diuresis during administration of cardiac glycosides. Basic action is the main goal of the drug administration, e.g., lowering of blood pressure during administration of *Octadine*. *Side action* is an additional effect to basic action. As a rule, side effect is unfavorable. For example, *Octadine* can cause dyspeptic disorders.

Selective action alters function of a certain organ and a system. Usually it relates to the action on functionally determined cytoreceptors (e.g., *Salbutamol, Pilocarpine*). *General action* is non-specific action in different organs and tissues (action of narcotic substances and alcohol). *Convertible (reversible) action* disappears just after drug elimination. Non-convertible (irreversible) action appears as a result of strong connection of a drug with a receptor (usually covalent) that cause irreversible breaking off its functions (e.g., *Proserine* cause convertible inhibition of acetylcholinesterase, *Phosphacol* causes non-convertible inhibition of acetylcholinesterase).

Factors that influence the drug action.
They may be divided into 3 groups:
1. Features of drugs.
2. Factors related to the whole organism.
3. Environmental factors.

The first group includes the drug, its physical and chemical features, pharmaceutical form, and doze. *Chemical structure* of a drug determines its mechanism of action and toxicity. The molecular size, shape, and electrical charge of a drug determine whether it will bind to a particular receptor among the vast array of chemically different binding sites available in a cell, an animal, or a patient. Accordingly, changes in the chemical structure of a drug can dramatically increase or decrease the new drug affinities for different classes of receptors, with resulting alterations in therapeutic and toxic effects. The drug dissociation, solubility in lipids and water, permeation through biological barriers and membranes as well as pharmaceutical form and way of administration determine the drug action also. Strength and duration of effect, possibility of toxic action depends on the doze of the drug. There is direct correlation between the doze and the drug level in serum.

As it was said above, the dose is the quantity of a drug to be taken. It can be expressed in milliliters, grams, and international unites. There are the *moment dose* (for one time use), the *daily dose* (the total amount of a remedy that is to be taken within 24 hours), the *curative dose* (quantity of any substance required to effect the cure of disease). *The minimal (threshold) therapeutical dose* is the smallest amount of a drug that will produce a desired therapeutic effect in an adult; *the maximal therapeutical dose* is the largest amount of a drug that an adult can take with safety; *the median therapeutical dose* is the dose that produces a desired therapeutical effect in majority of patients. *The initial (loading) dose* is a comparatively large dose given at the beginning of treatment to get the patient under the influence of the drug; *the maintenance dose* supports the effect of drug therapy.

Therapeutical index is used for evaluation of activity and safety of drugs. It is a ratio of the dose that causes death in 50% of laboratory animals to the dose that cause a desirable effect in 50% of animals. It can

be also expressed as a ratio of the dose, which evokes a toxic effect in 50% of patients to the dose which evokes a favorable effect in 50% of patients. Another data of a drug safety is *wideness of therapeutical action* — difference between threshold and maximal therapeutical doses. That drug is safer, which has large wideness of therapeutical action.

The factors concerning the whole organism of the patient are age, sex, genetic features, condition of the patient, and biological rhythms. *The age of the patient* influences considerably on the drug action. This factor is especially important in the children and old patients. Most part of protective mechanisms in a child's organism is poorly developed. It is necessary to refer possibility of cramps, allergic reactions, slow biotransformation and excretion of the drugs, unripeness of biological barriers, high absorptive ability of the skin and mucosa coats. In children of first 3 years drugs connection with serum proteins is lowered and level of free fraction is increased. In addition, children possess higher sensitiveness to drugs.

Old patients, especially over 75 years are characterized by higher sensitiveness to drugs, which suppress the CNS and lower sensitiveness that cause an opposite effect. Tonus of the vegetative nervous system, the endocrine gland lowers. Susceptibility to thrombus formation increases, and it is dangerous to use coagulants. Level of serum albumins is lower and level of free fraction is higher. Biotransformation in the liver and excretion by the kidneys are delayed. So, the dose is smaller and administration is more careful in old patients.

It is necessary to consider *condition of the patient* as well. Weakened and exhausted patients need for lowering the dose. During shock and bleeding the sensitiveness for oppressing drugs increases (narcotics, neuroleptics, etc.). It is necessary to consider the additive diseases. For example, hepatic disease has been shown to reduce the clearance and prolong the half-life of many drugs.

The biological rhythm is alternation activity of processes through a determined interval of time. Dependence of the drug action on the biological rhythm and the influence on each other are studied by *chronopharmacology*. Biorhythms may have a seasonal, monthly, and daily (circadian) character. Knowledge of the rhythm is necessary for choosing the drug optimal regimen. For example, it is ascertained that maximal production of hormones in adrenal cortex occurs in the morning and sensitiveness of tissues for those hormones increases that time too. So, using of corticosteroids in the morning increases efficacy of therapy and lowers a risk of complications.

Some effects of drugs concern genetic factors. These problems are studied by *pharmacogenetics*, part of medical genetics. For instance, metabolism of isoniazid and apressin occur due to their acetylation in the liver. People are divided into "slow acetylators" with slow drugs acetylation and "quick acetylators". One of genetically determined reactions is *idiosyncrasy*, which appears as an abnormal reaction to a drug. It is characterized by redness, edema of the skin and mucous, disorders of breathing and blood pressure, fever, and other disorders up to shock. Usually these reactions are related to congenital insufficiency of enzymes (enzymopathies). For example, in case of glucose-6-phosphate dehydrogenase of erythrocytes insufficiency sulfanilamides and derivatives of nitrofuran cause hemolytic anemia and jaundice.

Pharmacogenetics is also studying mutagenic effects of drugs. It has great significance for individualization of treatment and prognoses efficacy and safety of pharmacotherapy.

Factors of environment also have a determined influence on the drugs action. They are social conditions that may cause psycho-emotional strain, strong noises, vibration, radiation, ecological problems, fluctuation of temperature, etc. Prolonged and excessive influence of these factors increases the drugs action on the CNS especially of narcosis substances, soporifics and neuroleptics. Some drugs (sulfanilamides) increase sensitivity of the skin to sunlight that named as *photosensitization.*

Changes in the drugs action while repeated administration. In many cases drugs are used for prolonged therapy that can strengthen or weaken their action. Strengthening of effect may be stipulated by its cumulation both material and functional. ***Material cumulation*** is the accumulation of drugs (e.g., digitoxine, strychnine) that are slowly excreted from the organism. ***Functional cumulation*** is the accumulation of the drugs effect (alcohol, caffeine, etc.). It means that after the drugs excretion their effects are still present. As a result, toxic effects may appear.

Tolerance (accustoming, adaptation) is an ability to endure or be less responsive to the drug, especially over a period of continued exposure. Tolerance can be explained by accelerated biotransformation and excretion, and lowered of receptors sensitiveness. For overcoming the tolerance you need to increase the dose of the drug that sometimes cause intoxication. Usually tolerance to one drug is accompanied by developed tolerance to pharmacologically similar compounds.

Tachyphylaxis is a rapid appearance of progressive decrease in response of constantly repeted administration of pharmacologically or physiologically active substances (e.g., while using ephedrine).

Dependence (drug abuse, addiction) is characterized by constant and repeated wish of drug using. Usually it is indicated by *withdrawal symptoms (abstinence)* that develop when the use of the substance is terminated. *Psychologic dependence* is manifested by compulsive drug-seeking behavior in which the individual uses the drug repeatedly for personal satisfaction. Cigarette smoking is an example. Abstinence is characterized by mental depression that includes depressed or irritable mood, loss of interest in usually pleasurable activities, sleep and appetite disturbance, fatigue, suicidal thoughts, hopelessness, and guilt. *Physiologic dependence* is present when withdrawal of the drug produces symptoms and signs that are frequently the opposite of those sought by the user. It has been suggested that the body adjusts to a new level of homeostasis during the period of drug use and reacts in the opposite fashion when a new equilibrium is disturbed. For example, symptoms of opioid withdrawal include lacrimation, sweating, weakness, chills, nausea and vomiting, muscle aches, hyper- or hypotension.

Drugs interaction. Combined therapy is used for the treatment of majority of diseases. Thus, it is necessary to know more about drugs interaction. There are two types of interaction: pharmaceutical and pharmacological. *Pharmaceutical interaction* may appear between incompatible drugs while their production, storing or mixing in solution. It can lower components activity and increase their toxicity. For example, it is not recommended to mix in one-syringe vitamins B_1, B_6, and B_{12}.

Pharmacological interaction occurs on the level of pharmacodynamic and pharmacokinetic processes.

Interaction on the level of *pharmacokinetic processes* can be observed during absorption, transport, biotransformation, and excretion of drugs. For example, activated carbon, which has adsorbent properties, decreases the extent of the intestine absorption of the concomitant drug. Competition for binding with serum proteins may develop between drugs, e.g., *Salicylates* replace *Butamide*, which decrease the blood glucose concentration, that may cause hypoglycemic coma. Drugs interaction on the biotransformation level may appear due to inducing or inhibiting effects on microsomal enzymes of the liver. As it is mentioned above barbiturates increase the enzymes activity that is accompanied by hastened biotransformation of other drugs. Cimetidine has an opposite effect. Interaction on the stage of excretion may cause hastening and slowing of drugs excretion from the organism. So, alkaline drugs (sodium bicarbonate) hasten excretion of the acid substances (salicylates) and on the contrary. This interaction may be used during poisoning, e.g., administration of sodium bicarbonate during poisoning by salicylates and barbiturates.

Drugs interaction on the pharmacodynamic level appears in the form of synergism or antagonism. *Synergism* is a coordinated or correlated action of two or more agents so that the combined action is greater than the effect of each one acting separately. It has two forms: *summation (additive)* and *potentiation*. The former one is a simple sum (addition) of effects, e.g., combination of agents for narcosis. Potentiation is an interaction between two or more drugs or agents resulting in a pharmacologic response greater than the sum of individual responses to each drug or agent, e.g. combination of sedative drugs with alcohol. Synergism may be *direct*, when drugs act on the same substrate, and indirect, when drugs act on different substrates.

Antagonism is the situation in which the combined effect of two or more agents is smaller than the solitary effect of any of the factors. It can be physiological, chemical, physico-chemical and physical. *Physiological antagonism* appears on the level of a biological substrate. It may be *direct* and *indirect*. Interaction of cholinomimetic and cholinolytic is an example of direct antagonism. *Indirect antagonism* is stipulated by interaction of drugs with different mechanism of action. For example, *Pilocarpine* narrows the pupil through the stimulation of M-cholinoreceptors of the pupil's sphincter; adrenaline widens the pupil due to stimulation of adrenoreceptors of pupil's radial muscle. *Chemical antagonism* is a type of chemical reaction that results in loosing of initial pharmacological activity of agents and in formation of a non-active substance (e.g., binding of unithiol with metals). Example of *physico-chemical antagonism* is neutralization of heparin (anticoagulant) by *Protamine sulfate*, as a result of electrostatic interaction. Physical antagonism is stipulated by physical features of the drug, e.g., activated carbon adsorbs molecules of many substances on its own surface.

Types of drug therapy. Basic types of pharmacotherapy are prophylactic, etiotropic, pathogenic, and symptomatic. *Prophylactic* drug is an agent that acts to prevent a disease, e.g., *Chloridine* for malaria prevention. *Etiotropic therapy* is directed against the cause; etiotropic agent is a remedy that attenuates or destroys the causal factor of a disease, e.g., antimicrobial drugs. *Pathogenic therapy* is directed on the pathologic, physiologic, or biochemical mechanism resulting in the development of a disease or morbid process, e.g., uses of cardiac glycosides in heart insufficiency. Finally, *symptomatic therapy* is directed on removing of symptoms of a disease (analgesics, stimulators of breathing, etc.).

Complications of drug therapy. Together with therapeutically action drugs may cause *unfavorable side (adverse) effects.* There are different types of side effects.

It may be complications related to *the absolute drug overdose* — exceed of the maximal therapeutical dose. *A comparative overdose* can appear as a result of fast intravenous injection of a drug, in severe diseases of the liver, kidneys that delay drug elimination and increase drug concentration in the blood. Unfortunately many drugs possess a *toxic action* on human's organs and tissues. For example, aminoglycosides are ototoxic (vestibular and auditory damage) and nephrotoxic, *Chloramphenicol* commonly causes bone marrow depression (anemia, leukopenia).

Mutagenic, teratogenic, embryotoxic, and carcinogenic effects of the drugs engage prominent place in nowadays medicine. *Mutagenic effect* is a promoting of the changes in the chemistry of a gene that is perpetuated in subsequent divisions of the cell in which it occurs. It may be a result of the drug action on sex cells (e.g., anticancer drugs). Mutagenic action may lead to congenital diseases like the Daune's syndrome. *Teratogenic action* of the drugs appears after its administration during pregnancy. It is characterized by the disturbed growth processes of fetus that lead to the formation of growth anomalies and malformed neonate. The most dangerous period is the first trimester of pregnancy (2–3 months) during formation of organs and systems. That's why, administration of drugs in this period of pregnancy must be especially careful. In 60-s years of XX century it was so-called "thalidomide catastrophe". Using of thalidomide during pregnancy was accompanied by development of numerous congenital defects in fetus. Nowadays, any drug cannot be proposed for sale and using without observing on teratogenic features.

Negative action on fetus can appear in growth retardation as well. If this effect appears during first 12 weeks of pregnancy, it is named *embryotoxic*, if later — *fetotoxic*.

Allergic reactions are the most spread complications of pharmacotherapy. They are stipulated by formation of antibodies to the drugs that possess antigen features or to their metabolites. Increasing of organism's sensitivity to drugs is named sensitization. Hypersensitivity can be classified as immediate or delayed depending on the time required for clinical symptoms to become manifest following exposure of the host to the sensitizing antigen. The most dangerous is anaphylactic shock.

EXAMINATION QUESTIONS

1. Receptors are macromolecules that
   (A). Are designed to attract drugs.
   (B). Are resistant to antagonists.
   (C). Exist as targets for physiological neurotransmitters and hormones.
   (D). Are only on the outer surface of cells.
   (E). Are only inside of cells.

2. All of the following are capable of initiating a signal transduction process EXCEPT:
   (A). Combination of an agonist with its receptor.
   (B). Combination of an antagonist with its receptor.
   (C). Combination of a neurotransmitter with its receptor.
   (D). Combination of a hormone with its receptor.

3. Which of the following chemical bonds would create an irreversible combination of an antagonist with its receptor?
   (A). Ionic bond.
   (B). Hydrogen bond.
   (C). Van der Waals bond.
   (D). Covalent bond.

4. Potency is determined by
   (A). Affinity alone.
   (B). Efficacy alone.
   (C). Affinity and efficacy.
   (D). Affinity and intrinsic activity.
   (E). Efficacy and intrinsic activity.

5. Following oral administration, a drug is absorbed into the body, wherein it can exert its action. For a drug given orally, the primary site of drug absorption is:
   (A). The esophagus.
   (B). The stomach.
   (C). The upper portion of the small intestine.
   (D). The large intestine.

6. Patients can exhibit alterations in the rate and extent of drug absorption because of various factors. All of the following factors might affect the rate and/or extent of drug absorption EXCEPT:
   (A). Gastric emptying time.
   (B). Intestinal motility.
   (C). The presence of food.
   (D). The formulation of the drug.
   (E). A generic form of the drug.

7. The body has developed defense mechanisms that reduce the amount of foreign chemicals, such as drugs, that enter the body. One of the more prominent of these mechanisms is an efflux transport system that pumps some drugs back into the intestinal lumen following absorption into the enterocytes and that is responsible for the lack of complete absorption of some drugs. This efflux transport system is:
   (A). Facilitated diffusion.
   (B). P glycoprotein.
   (C). Cytochrome P450 3A.
   (D). Pinocytosis.

8. All of the following statements concerning the blood-brain barrier and the passage of drugs from the systemic circulation into the cerebrospinal fluid are true EXCEPT:
   (A). Ionized drugs are more likely to cross into the CSF than unionized drugs.
   (B). The higher the lipid solubility of a drug, the more likely it will cross into the CSF.
   (C). Inflammation of the meninges improves the likelihood that drugs will cross the blood-brain barrier as compared to the uninflamed state (i.e., normal condition).
   (D). P glycoprotein serves to pump drugs back into the systemic circulation from endothelial cells lining the blood-brain barrier.

9. Which of the following organs or tissues is a potential site for drug accumulation of lead that has been ingested?
   (A). Eyes.
   (B). Fat.
   (C). Bone.
   (D). Lungs.
   (E). Blood.

10. Concerning regulation of CYP-mediated drug metabolism, all of the following statements are true EXCEPT:
   (A). Drugs that competitively inhibit CYP enzymes cause a decrease in concentrations of the object (original) drug.
   (B). Induction of drug-metabolizing enzymes results in a decrease in concentrations of the object (original) drug, thus potentially reducing efficacy.
   (C). Induction of drug-metabolizing enzymes frequently requires the synthesis of new enzyme protein and thus may not occur immediately upon introduction of the inducing agent.
   (D). Mechanism-based inactivation results in irreversible inactivation of the enzyme that lasts for the duration of the enzyme molecule.

11. Conjugation of a drug with glucuronic acid via the glucuronosyl transferases will result in all of the following EXCEPT:
   (A). Production of a more water-soluble moiety that is more easily excreted.
   (B). A new compound that may also possess pharmacological activity.
   (C). A drug molecule that may be more susceptible to biliary elimination.

(D). A drug molecule that may undergo enterohepatic recirculation and reintroduction into the bloodstream.
(E). A drug with a different pharmacological mechanism of action.

12. Concerning the renal excretion of drugs:
(A). Drugs that are ionized in the renal tubule are more likely to undergo passive reabsorption than those that are unionized.
(B). Low-molecular-weight drugs are much more likely to be actively secreted than filtered.
(C). Only drug that is not bound to plasma proteins (i.e., free drug) is filtered by the glomerulus.
(D). Decreasing renal tubular fluid pH will increase elimination of weakly acidic drugs.

13. Drug presence in breast milk is most likely for:
(A). Drugs highly bound to plasma proteins.
(B). Lipid-soluble molecules.
(C). Large ionized water-soluble molecules.
(D). Acidic compounds.

14. Frequently it is useful to consider the overall exposure of a person to a drug during the dosing interval. Which of the following pharmacokinetic parameters defines the exposure of a person to a drug?
(A). C_{max}.
(B). T_{max}.
(C). AUC (area under the curve).
(D). Half-life.
(E). Clearance.

15. Organs such as the liver remove exogenous chemicals, such as drugs, from the body. For drugs such as phenytoin, for which the difference between the minimum effective concentration and the minimum toxic concentration is small, clinicians must calculate the rate at which a given individual removes drug from the body. The volume of fluid from which drug can be completely removed per unit of time (rate of drug removal) is termed:
(A). Distribution.
(B). Clearance.
(C). Metabolism.
(D). Excretion.

16. For a drug such as *Piroxicam* with a 40-hour half-life and being dosed once daily (i.e., every 24 hours), steady state will be reached shortly following which DOSE (not which half-life)?
(A). 1st dose.
(B). 3rd dose.
(C). 5th dose.
(D). 8th dose.
(E). 12th dose.

17. Volume of distribution (Vd), though not a physiological volume, helps a clinician to estimate drug distribution in the body. Drugs distribute throughout the body to differing degrees depending on a number of factors. Which of the following factors is TRUE concerning drug distribution?
(A). In general, a drug with a higher degree of plasma protein binding will have a lower volume of distribution.
(B). All drugs distribute to the same degree in all tissues.
(C). The binding of drugs to tissues has no relationship to the distribution of drug in the body.
(D). In general, lipophilic drugs distribute to a lesser extent than hydrophilic drugs.

18. A clinician must concern the amount of a drug dose that reaches the systemic circulation, since this will affect the plasma concentration and therapeutic effects observed. The fraction of a dose reaching the systemic circulation as unchanged drug (i.e., intact) is defined as:
(A). Theoretical dose.
(B). C_{max}.
(C). Bioavailability.
(D). Ideal dose.

19. A dental technician begins to display symptoms, including tremor, depression, and insomnia. Which of the following chemicals present in the workplace may be responsible for the symptoms?
(A). Solvents used in dental adhesives.
(B). Fluoride used in oral rinses.
(C). Mercury used in the preparation of amalgams.
(D). Lidocaine used as an anesthetic.

20. A patient has learned recently that she is about 5 weeks pregnant, but as she has been suffering from depression, she asks her physician for a drug to treat this problem. Her physician refused to prescribe a drug that time because he was concerned that the fetus was at risk for toxicity from in utero exposure to the drug. What is the most likely adverse outcome if the woman began taking the drug that time?
(A). The fetus would die.
(B). A teratogenic response would occur in the fetus.
(C). The growth of the fetus would be retarded.

21. Exposure to air pollutants can have adverse effects on human health. Which can result of the following conditions an exposure to one such pollutant — carbon monoxide?
(A). Irritation of the deep lungs because of damage to the epithelium.
(B). An increased susceptibility to respiratory infection due to impairment in phagocyte function.
(C). Exacerbation of asthmatic episodes because of bronchoconstriction.
(D). Hypoxia due to displacing oxygen from hemoglobin.

22. A 4-year-old boy is taken to the emergency department by his parents in the afternoon the first Saturday in June. The family is moving into the house. They found the boy almost unconscious in the corner of the garage, having difficulty of breathing. He was surrounded by chemical containers left by the previ-

ous owners. The labels had deteriorated and couldn't be read. On examination you noted bronchoconstriction and profuse airway secretion, weakness of the muscles, difficulty of breathing, and CNS depression. Which of the following chemicals do you suspect was involved?

(A). Compound 1080.
(B). Pyrethrin.
(C). Parathion.
(D). Diquat.

23. You are a staff physician at a major chemical manufacturing company. A worker on the maintenance crew has complained of being light-headed and tired occasionally at work and that if it occurs, it clears up after he leaves for the day. He was asked to write down where he had worked on the days this occurred; these are listed below. In which of these areas is he most likely to have exposures that would cause these symptoms?

(A). Herbicide production area.
(B). Insecticide packaging area.
(C). Label printing area.
(D). Kitchen area of the cafeteria.

24. You have been told there has been a large spill at the chemical company but in the confusion you weren't told where it occurred. The exposed workers were agitated and irritable and said to be having difficulty of walking in a coordinated manner. Some feel quite hot as if they are burning up, and one had a seizure. Which area do you suspect had the spill?

(A). Herbicide production area.
(B). Insecticide packaging area.
(C). Label printing area.
(D). Kitchen area of the cafeteria.

ANSWERS

1. **(C)**. There are a large number of receptors in the body. Although many drugs are attracted to receptors, the receptors are not designed for that purpose. Antagonists are also attracted to receptors. Some receptors are on the cell surface, while others are found inside the cell.

2. **(B)**. An antagonist binds to a receptor and prevents the action of an agonist. Choice **(A)** is wrong because this combination does initiate a signal transduction process. **(C)** and **(D)** are incorrect because both neuro-transmitters and hormones work through their appropriate receptor to initiate signal transduction.

3. **(D)**. A covalent bond is a strong and stable bond that is essentially irreversibly formed at normal body temperature. The other bonds are much weaker.

4. **(C)**. Potency is a useful measure of the comparison between two or more drugs. It does not equate to therapeutic superiority but rather is a measure of the size of the dose required to produce a particular level of response.

5. **(C)**. The primary site of absorption is the small intestine. Because of its large surface area and high blood perfusion rate, the small intestine is optimal for absorbing drugs. Some drug absorption occurs in the stomach and large intestine, but because of their reduced surface area in relative terms and for some drugs less than optimal physicochemical conditions, these tissues play a lesser role in drug absorption. Because of the tissue type, very little drug absorption occurs through the esophagus.

6. **(E)**. To be approved, generic formulations must exhibit the same rate and extent of absorption as the trademark compound. All of the other choices can affect drug absorption. For example, slowing gastric emptying time may increase the absorption of a drug absorbed in the stomach. Alterations in gastric motility may affect the amount of time a drug spends in the region of the gastrointestinal tract, where it undergoes the most extensive absorption. The presence of food may cause decreased absorption through binding to the drug or may increase absorption through making a better local environment for absorption of particular drugs. Finally, changes in drug formulation can alter absorption by changing dissolution rates.

7. **(B)**. P-glycoprotein transporters in the intestinal lumen serve as an efflux transporter for many drugs. This transporter pumps drugs out of the enterocytes into which they were absorbed and back into the intestinal lumen, reducing absorption. Facilitated diffusion and pinocytosis generally result in drug influx (absorption). The cytochrome P450 3A enzymes metabolize drugs; therefore, even though they may reduce the amount of drug absorbed, the reduction is due to drug metabolism, not efflux transport back into the intestinal lumen.

8. **(A)**. Un-ionized drugs cross into the cerebrospinal fluid more readily than ionized drugs. All of the other choices are correct.

9. **(C)**. Lead can substitute for calcium in the bone crystal lattice, resulting in bone brittleness. Bone may become a reservoir for other substances as well. Several drugs, such as chlorpromazine, may accumulate in the eye. Drugs with extremely high lipid-water partition coefficients tend to accumulate in fat, while basic amines tend to accumulate in the lungs. Many agents bind avidly to albumin in the blood.

10. **(A)**. When one inhibits the action of a drug-metabolizing enzyme **(A)**, one would expect an increase instead of a decrease in drug concentrations, since less is being metabolized. Induction of an enzyme **(B)** would have the opposite effect, since there would be more enzyme available to metabolize the drug. **(C)** is correct, since the most common mechanism of enzyme induction is through synthesis of new enzyme protein, which does not occur immediately. Finally, mechanism-based inactivation **(D)** is also correct, since this is irreversible, leaving the enzyme inactive and eventually it is degraded by the body.

11. **(E)**. Most glucuronic acid conjugates are less effective than the parent drug. The conjugate, however, usually maintains the same pharmacological mechanism of action, although frequently of a lesser magnitude. Conjugation with glucuronic acid makes a drug molecule more water soluble **(A)**, and glucuronic acid conjugates are more likely to be eliminated by secretion into the bile **(C)** than are unconjugated compounds. These glucuronide conjugates, once secreted into the bile, may be cleaved by β-glucuronidases to liberate the parent compound, which can then be reabsorbed **(D)**. Several glucuronic acid conjugates of drugs (e.g., morphine 6-glucuronide) possess pharmacological activity **(B)**.

12. **(C)**. Plasma proteins are too large to be filtered by the glomerulus, so that any drug molecules bound to these plasma proteins will not undergo filtration. A is not correct: ionized drugs are less likely to undergo reabsorption, since this is generally thought to be a passive process. B is also not correct: low-molecular-weight drugs are more likely to be filtered, since they can easily pass through the glomerulus filter. Finally, weakly acidic drugs will be un-ionized at a low (acidic) pH, hence more

likely to undergo reabsorption, thus reducing the net elimination **(D)**.

13. **(B)**. Lipid-soluble molecules are more likely to be excreted in breast milk because it is primarily a passive diffusion process. **(A)**, **(C)**, and **(D)** are not correct because they are opposite of the typical characteristics of drugs excreted into breast milk.

14. **(C)**. The AUC (area under the curve) best describes the overall exposure of a person to a given drug over the course of the dosing interval. It describes the concentration of drug integrated over the period assessed, usually the dosing interval. **(A)** (C_{max}) is not correct, as C_{max} gives the maximum concentration achieved but does not reveal how long measurable concentrations of the drug were present or how long until this concentration was achieved. **(B)** (T_{max}) only refers to the time until the maximum concentration is achieved, again not giving a reference to overall exposure over time. **(D)** (half-life) simply describes how much time is required for the concentration to decrease by one-half. Finally, clearance **(E)** is the volume of fluid (usually plasma) from which drug can be removed per unit of time and as such does not define exposure.

15. **(B).** Clearance is defined as the volume of fluid from which drug is completely removed per unit of time and as such is a measure of the body's ability to remove drug by whatever manner (e.g., elimination, metabolism, excretion). Distribution is the theoretical volume to which the drug distributes and metabolism and excretion are simply methods of clearing drug.

16. **(D)**. Approximately five half-lives are required for a drug to reach steady-state concentrations. Since *Piroxicam* has a half-life of 40 hours, it will require approximately 200 hours before steady state is reached. If given every 24 hours, shortly after the 8th dose (192 hours at exactly the 8th dose) steady state will be reached.

17. **(A)**. Drugs with a higher degree of plasma protein binding in general have a lower volume of distribution, since the plasma proteins (and thus the drug bound to the plasma protein) tend to stay in the plasma and not distribute to the extravascular tissues. Different drugs can have widely disparate volumes of distribution, so **(B)** is incorrect. Tissue binding of drugs is extremely important to drug distribution and can override plasma protein binding, so **(C)** is incorrect. Finally, **(D)** is incorrect, since in general the more lipophilic a drug is, the greater volume of distribution it has.

18. **(C)**. Bioavailability describes the portion of the drug that reaches the systemic circulation without being metabolized or eliminated. Bioavailability is highly dependent on the drug and the route of administration. C_{max} **(B)** is incorrect, since this is only the maximum concentration reached following a dose and gives no measure of the amount reaching the circulation. The other terms (ideal dose and theoretical dose) are fabricated.

19. **(C)**. The symptoms are characteristic of a person chronically exposed to vapors released from elemental mercury. Since the dental technician may handle elemental mercury, including mishandling, the symptoms presented may occur. While the technician may be exposed to solvent vapors released from dental adhesives, the symptoms are not characteristic of this type of exposure. Fluoride toxicity would not be expected because these are not symptoms associated with fluoride ingestion, and the patient and not the technician would be most likely exposed to quantities high enough to cause any symptoms. The technician has little exposure to lidocaine, and the symptoms are not typical of lidocaine toxicity.

20. **(B)**. The fetus is particularly vulnerable to teratogens between days 25 and 40 of gestation, and this patient is within this window of time. The fetus is at much greater risk for death if exposure occurs during the first 2 weeks of gestation. Growth retardation of the fetus is the principal outcome if exposure to drugs occurs during the last 6 months of gestation.

21. **(D)**. Carbon monoxide can cause hypoxia because it reduces the oxygen carrying capacity of the blood by displacing oxygen from hemoglobin as well as impairing the erythrocyte's ability to release oxygen. Particulate air pollutants and reactive air pollutant gases, such as ozone and nitrogen dioxide, can damage the lungs, including increasing susceptibility to respiratory infection and irritation of the deep lungs, while exposure to sulfur dioxide can exacerbate asthmatic episodes.

22. **(C)**. Bronchoconstriction and secretion and muscular weaknesses occur from acetylcholine accumulation after inhibition of acetylcholinesterase. Parathion is an organophosphate insecticide that inhibits acetylcholinesterase, and it is readily available. Poisoning with compound 1080 (fluorocitrate) inhibits mitochondrial respiration and causes seizures and cardiac arrhythmias. Pyrethrin and pyrethroids are generally low in toxicity and few poisonings have been reported; however, seizures are a symptom. Diquat causes gastrointestinal disturbances.

23. **(C)**. Symptoms that occur during the working day and clear up after the work are often due to inhalation exposure of volatile or aerosol materials. The solvents used in printing inks cause light-headedness and sedation. The symptoms are not those of herbicide exposure and insecticide exposure.

24. **(B)**. Spills cause acute high-dose exposures. The symptoms are referable to an acute high exposure to an organochlorine or pyrethroid insecticide. While organochlorine pesticides are not used in this country, they are manufactured for export. An acute high exposure to herbicide would be primarily irritation of the skin and mucous membranes. The solvents in printing ink would cause the CNS depression.

DRUGS AFFECTING EFFERENT INNERVATION

The nervous system is divided into two anatomical divisions, the central nervous system (CNS), which is composed of the brain and spinal cord, and the peripheral nervous system, which includes neurons located outside the brain and spinal cord, that is, any nerves that enter or leave the CNS (Fig. 1).

The peripheral nervous system can be further divided into the efferent division, whose neurons carry signals away from the brain and spinal cord to the peripheral tissues, and the afferent division, whose neurons bring information from the periphery to the CNS.

The efferent portion of the peripheral nervous system can be further divided into two major functional subdivisions, the somatic and autonomic systems. The somatic efferents are involved in voluntarily controlled functions such as contraction of the skeletal muscles in locomotion. The autonomic system functions involuntarily to regulate the everyday needs and requirements of the body without the conscious participation of the mind. It is composed primarily of visceral motor (efferent) neurons that innervate smooth muscle of the viscera, cardiac muscle, vasculature and the exocrine glands.

ANATOMY OF THE AUTONOMIC NERVOUS SYSTEM

Efferent neurons. The autonomic nervous system carries nerve impulses from the CNS to the effector organs by way of two types of efferent neurons. The first nerve cell is called a **preganglionic neuron** and its cell body is located within the CNS. Preganglionic neurons emerge from the brain stem or spinal cord and make a synaptic connection in ganglia. These ganglia function as relay stations between the preganglionic neuron and the second nerve cell, the **postganglionic neuron**. The latter neuron has a cell body originating in the ganglion. It is generally non-myelinated and terminates on effector organs such as smooth muscle of the viscera, cardiac muscle, and the exocrine glands.

Afferent neurons. The afferent neurons (fibers) of the autonomic nervous system are important in the reflex regulation of this system, for example, by sensing pressure in the carotid sinus and aortic arch and signaling the CNS to influence the efferent branch of the system to respond.

Sympathetic neurons. The efferent autonomic nervous system is divided into the sympathetic and the parasympathetic nervous systems. The preganglionic neuron of the sympathetic system comes from thoracic and lumbar region of the spinal cord and synapse in two cord-like chains of ganglia that run in parallel on each side of the spinal cord. Axons of the postganglionic neurons extend from these ganglia to the glands and viscera. [Note: The adrenal medulla, like the sympathetic ganglia, receives preganglionic fibers from the sympathetic system. Lacking axons, the adrenal medulla in response to stimulation, influences other organs by secreting the hormone adrenaline, also known as epinephrine (and lesser amounts of noradrenaline) into the blood.]

Parasympathetic neuron. The parasympathetic preganglionic fibers arise from the cranial and sacral areas of the spinal cord and synapse in ganglia near or on the effector organs. In both the sympathetic and parasympathetic systems, postganglionic fibers extend from the ganglia to effector organs.

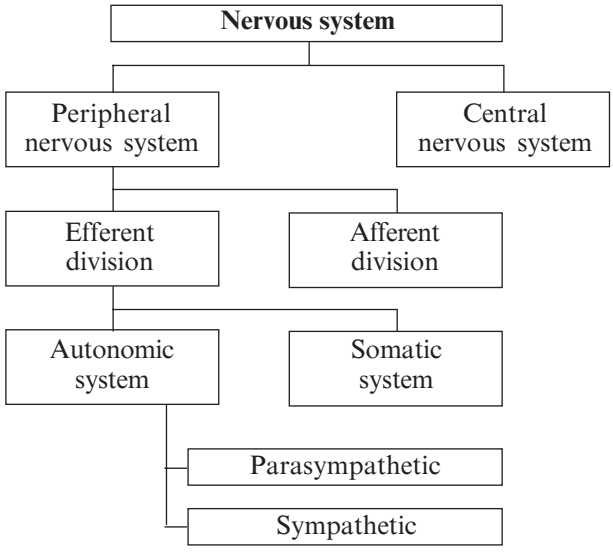


Fig. 1. Structure of the autonomic nervous system

FUNCTIONS OF THE SYMPATHETIC SYSTEM

The sympathetic division has the property of adjusting in response to stressful situations, such as trauma, fear, hypoglycemia, cold, or exercise (Table 1).

The effect of sympathetic output is to increase heart rate and blood pressure, to mobilize energy stores, and to increase blood flow to skeletal muscle and heart while diverting flow from the skin and internal organs. Sympathetic stimulation also results in dilation of the pupils and the bronchioles. The changes experienced by the body during emergencies have been referred to as the "fight or flight" response. These reactions are triggered both by direct sympathetic activation of the effector organs and by stimulation of the adrenal medulla to release adrenaline which enters the blood stream. The sympathetic nervous system tends to function as a unit and often discharges as a complete system.

The parasympathetic division maintains essential bodily functions, such as digestive processes and elimination of wastes. It usually acts to oppose or balance the action of the sympathetic division and is generally dominant over the sympathetic system in "rest and digest" situation. The parasympathetic system is not a functional entity as such and never discharges as a complete system. If it did, it would produce massive and undesirable symptoms. Instead, discrete parasympathetic fibers are activated separately, and the system functions to affect specific organs, such as the stomach or eye.

INNERVATION BY THE AUTONOMIC NERVOUS SYSTEM

Dual innervation. Most organs in the body are innervated by both divisions of the autonomic nervous system. Thus, the heart has vagal parasympathetic innervation that slows rate of contraction, and sympathetic innervation that speeds contraction. Despite this dual innervation, one system usually predominates in controlling the activity of a given organ. E.g., in the heart, the vagus is the predominant controlling factor for rate.

Organs receiving only sympathetic innervation. Although most tissues receive dual innervation, some effector organs, such as the adrenal medulla, kidney, pilomotor muscles, and sweat glands, receive innervation only from the sympathetic system. The control of blood pressure is also mainly a sympathetic activity, with essentially no participation by the parasympathetic system.

Somatic nervous system. The efferent somatic nervous system differs from the autonomic system in that a single myelinated motor neuron, originating in the CNS, travels directly to skeletal muscle without the mediation of ganglia. As noted earlier, the somatic nervous system is under voluntary control, whereas the autonomic is an involuntary system.

Neurotransmitters. Each neuron is a distinct anatomic unit. Communication between nerve cells — and between nerve cells and effector organs — occurs through the release of specific chemical signals, called neurotransmitters, from the nerve terminals. This release depends on processes that are triggered by Ca++ uptake and regulated by phosphorylation of synaptic proteins. The neurotransmitters rapidly diffuse across the synaptic cleft or gap (synapse) between nerve endings and combine with specific receptor on the postsynaptic (target) cell.

Membrane receptors. All neurotransmitters (and most hormones and local mediators) are too hydrophilic to penetrate the lipid bilayer of cell membranes; instead, their signal is mediated by binding to specific receptors on the cell surface of target organs. [Note: A receptor is defined as a recognition site for a substance. It shows a binding specificity and is cou-

Table 1. **Action of sympathetic and parasympathetic nervous systems on effector organs**

Organ	Sympathetic	Parasympathetic
Eye	Contraction of iris radial muscle (pupil dilates)	Contraction of iris sphincter muscle (pupil contracts) Contraction of ciliary muscle (lens accommodates for near vision)
Lacrimal glands		Stimulates tears
Salivary glands	Thick, viscid secretion	Copious, water secretion
Trachea and bronchioles	Dilates	Constricts, increases secretions
Heart	Increased rate and contractility	Decreased rate and contractility
Blood vessels (skeletal muscle, skin, mucus membranes and splanchnic area)	Dilatation Constriction	
Gastrointestinal	Decreased in muscle motility and tone; contraction of sphincters	Increased muscle motility and tone
Ureters and bladder	Relaxes detrusor; contraction of trigone and sphincter	Contraction of detrusor Relaxation of trigone and sphincter
Genitalia-male	Stimulates ejaculation	Stimulates erection
Genitalia-female	Relaxation of uterus	

pled to processes that eventually evoke a response. Most receptors are proteins.]

Types of neurotransmitters. Although over 50 chemical signal molecules in the nervous system have tentatively been identified, 6 signal compounds — norepinephrine (and closely related epinephrine), acetylcholine, dopamine, serotonin, histamine, and γ-amino butyric acid — are most commonly involved in the actions of therapeutically useful drugs. Each of these chemical signals binds to a specific family of receptors. Cholinergic and adrenergic neurotransmitters are the primary chemical signals in the autonomic nervous system, whereas a wide variety of neurotransmitters function in the CNS (Fig. 2).

Acetylcholine. The autonomic nerve fibers can be classified into two groups based on the chemical nature of the neurotransmitter released. If transmission is mediated by acetylcholine, the neuron is termed **cholinergic**. Acetylcholine mediates the transmission of nerve impulses across autonomic ganglia in both the sympathetic and parasympathetic nervous systems. It is the neurotransmitter at the adrenal medulla.

Transmission from the autonomic postganglionic nerves to the effector organs in the parasympathetic system also involves the release of acetylcholine. In the somatic nervous system, transmission at the neuromuscular junction (that is, between nerve fibers and voluntary muscles) is also cholinergic.

Noradrenaline and adrenaline. If noradrenaline or adrenaline is the transmitter, the fiber is called **adrenegic** (epinephrine being another name for adrenaline). In the sympathetic system, noradrenaline mediates the transmission of impulses from post-ganglionic nerves to effector organs. A summary of the neuromediators released and the type of receptors within the peripheral nervous system is shown in figure above. [Note: A few sympathetic fibers, such as those involved in sweating, are cholinergic; for simplicity, they are not shown on the figure.]

Lecture 3
CHOLINERGIC AGONISTS

Drugs affecting the autonomic nervous system are divided into two subgroups according to the type of neurons involved in their mechanism of action. The cholinergic drugs act on receptors that are activated by acetylcholine. The second group — the adrenergic drugs — act on receptors that are stimulated by noradrenaline or adrenaline. Both the cholinergic and adrenergic drugs act either by stimulating or blocking neurons of the autonomic nervous system.

THE CHOLINERGIC NEURON

The preganglionic fibers terminating in the adrenal medulla, the autonomic ganglia (both parasympathetic and sympathetic), and the postganglionic fibers of the parasympathetic division use acetylcholine as a neurotransmitter. Cholinergic neurons innervate voluntary muscles of the somatic system and are also found in the CNS.

Neurotransmission at cholinergic neurons. Neurotransmission in cholinergic neurons involves six steps. The first four, synthesis, storage, release and binding of acetylcholine to a receptor, are followed by the fifth step, degradation of the neurotransmitter in the synaptic gap, and the sixth step, the recycling of choline.

1. *Synthesis of acetylcholine.* Choline is transported from the extracellular fluid into the cytoplasm of the cholinergic neuron by a carrier system that cotransports Na+ and can be inhibited by the drug Hemicholinium. Choline acetyltransferase (CAT) catalyzes the reaction of choline with acetyl CoA to form acetylcholine in cytosol.

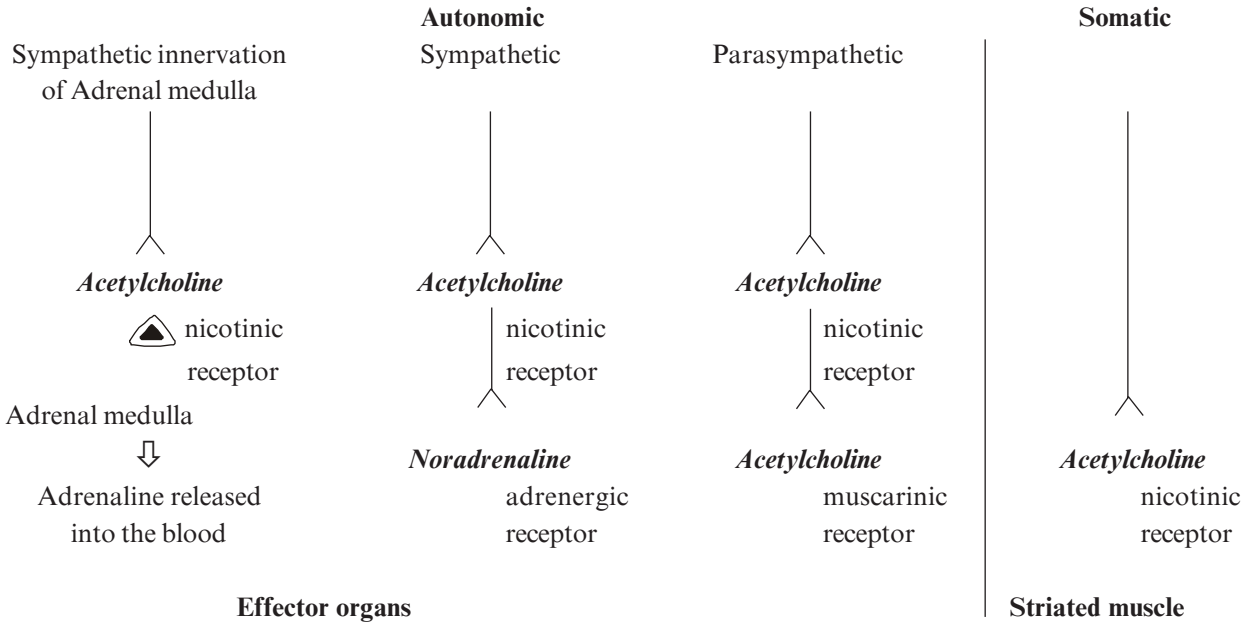


Fig. 2. Neurotransmitters of the efferent innervation

2. *Storage of acetylcholine in vesicles.* The acetylcholine (AC) is packaged into vesicles by an active transport process. The mature vesicle not only contains AC but also adenosine triphosphate (ATP) and proteoglycan. The function of the latter substances in the nerve terminal is unknown.

3. *Release of AC (Acetylcholine).* When an action potential arrives at a nerve ending, voltage-sensitive Ca++ channels in the presynaptic membrane open, causing an increase in the concentration of intracellular Ca++. Elevated Ca++ levels promote the fusion of synaptic vesicles with the cell membrane and release of AC into the synapse. This release is blocked by Botulinum toxin. By contrast, black widow spider venom causes all of the cellular AC stored in synaptic vesicles to spill into the synaptic gap.

4. *Binding to receptor.* AC released from the synaptic vesicles diffuses across the synaptic space and binds to either postsynaptic receptors on the target cell or to presynaptic receptors in the membrane of the neuron that released the AC. Binding to the receptor leads to a biological response within the cell such as the initiation of a nerve impulse in a postganglionic fiber or activation of specific enzymes in effector cell as mediated by second messenger molecules.

5. *Degradation of AC.* The signal at the postjunctional effector site is rapidly terminated. This occurs in the synaptic cleft where acetylcholinesterase cleaves AC to choline and acetate.

6. *Recycling of AC.* Choline may be recaptured by a sodium-coupled high affinity uptake system that transports the molecule back into the neuron, where it is acetylated and stored until released by a subsequent action potential.

CHOLINERGIC RECEPTORS

Two families of cholinergic receptors (cholinoreceptors), designated muscarinic and nicotinic receptors, can be distinguished from each other on the basis of their different affinities for agents that mimic the action of acetylcholine (cholinomimetic agents).

Muscarinic receptors. These receptors, in addition to binding AC, also recognize muscarine, an alkaloid that is present in certain poisonous mushrooms. By contrast, the muscarinic receptors show only a weak affinity for nicotine. Using binding studies and specific inhibitors, several subclasses of muscarinic receptors have been pharmacologically distinguished as M_1, M_2, M_3, M_4, and M_5.

Locations of muscarinic receptors. The most important sites of location of the muscarinic receptors are (1) neuroeffector endings of the parasympathetic system. They have been also found (2) sweating glands innervated by sympathetic fibers, and (3) in the CNS. M_1 receptors are found on gastric parietal cells, M_2 receptors on cardiac cells and smooth muscle, and M_3 receptors on exocrine glands and smooth muscle.

Muscarinic agonists and antagonists. Attempts are currently underway to develop muscarinic agonists and antagonists that are directed against specific receptor subtypes. For example, pirenzepine, a tricyclic anticholinergic drug, selectively inhibits M_1 muscarinic receptors, such as in gastric mucosa. At therapeutic doses, *Pirenzepine* does not cause many of the side effects seen with the non-subtype-specific drugs. Therefore, *Pirenzepine* may be useful in the treatment of gastric and duodenal ulcers. [Note: At present there are no clinically important agents that interact with the M_4 and M_5 receptors.]

Nicotinic receptors. These receptors, in addition to binding AC, also recognize nicotine but show only a weak affinity for muscarine. Nicotine initially stimulates and then blocks the receptor. Nicotinic receptors are located in the (1) CNS, (2) adrenal medulla, (3) autonomic ganglia, (4) neuromuscular junctions, and (5) in the carotid sinuses. The nicotinic receptors of autonomic ganglia differ from those of the neuromuscular junction. For example, ganglionic receptors are selectively blocked by *Benzohexonium*, whereas neuromuscular junction receptors are specifically blocked by *Tubocurarine*.

DIRECT-ACTING CHOLINERGIC AGONISTS

Cholinergic agonists mimic the effects of acetylcholine (AC) by binding directly to cholinoreceptors. These agents are synthetic esters of choline, such as *Carbachol*, or naturally occurring alkaloids, such as *Pilocarpine*. All of the direct acting cholinergic drugs have longer duration of action than AC. [Note: Muscarinic receptors are located primarily, but not exclusively, at the neuroeffector junction of the parasympathetic nervous system.] However, as a group, the direct acting agonists show little specificity in their action, which limits their clinical usefulness.

Acetylcholine

Acetylcholine is a quaternary ammonium compound that cannot penetrate membranes. Although it is the neurotransmitter of parasympathetic and cholinergic nerves, it is therapeutically of no importance because of its multiplicity of action and its rapid inactivation by acetylcholinesterase. AC has both muscarinic and nicotinic activity. Its action include:

a) **decrease in heart rate and cardiac output**: The action of AC on the heart mimic the effects of vagal stimulation. E.g., acetylcholine, if injected intravenously, produces a brief decrease in cardiac rate and stroke volume as a result of a reduction in the rate of firing at the sinoatrial (SA) node. [Note: It should be remembered that normal vagal activity regulates the heart by the release of AC at the SA node.]

b) **decrease in blood pressure**: Although no innervation of vasculature by the parasympathetic system exists, there are cholinergic receptors on the blood vessels that respond by causing vasodilation. Vasodilation is due to an acetylcholine-induced rise in intracellular Ca++ — caused by the phosphatidylinositol system — that results in the formation of nitric oxide (NO) from arginine in endothelial cells. [Note: NO is also known as endothelium-derived relaxing factor (EDRF).] In the absence of administered cholinergic agents, the vascular receptors have no known function, since AC is never released into the blood in any significant quantities. *Atropine* (see next lecture) blocks

these muscarinic receptors and prevents AC from producing vasodilation.

c) **other actions:** In the gastrointestinal tract, AC increases salivary secretion, and stimulates intestinal secretion and motility. Bronchiolar secretion is also stimulated. In the urogenital tract, the tone of the uterine detrusor muscle is increased. In the eye, AC is involved in stimulating ciliary muscle contraction for near vision and in the constriction of the pupillae sphincter muscle, causing miosis (marked constriction of the pupil).

Carbachol

Carbachol has both muscarinic and nicotinic actions. Carbachol is an ester and a poor substrate for acetylcholinesterase. It is biotransformed by other esterases but at a much slow rate. A single administration can last as long as one hour.

Actions. *Carbachol* has a profound influence on both cardiovascular system and the GI tract because of its ganglion-stimulating activity and may first stimulate and then depress these systems. It can cause release of *epinephrine* from the adrenal medulla by its nicotinic action. Locally instilled into the eye, it mimics the effects of AC, causing miosis.

Therapeutic uses. Because of its high potency and relatively long duration of action, *Carbachol* is rarely used therapeutically, except in the eye as a miotic agent to cause contraction of the pupil and decrease in intraocular pressure.

Adverse effects. At doses used ophthalmologically, there are little to no side effects.

Pilocarpine

The alkaloid *Pilocarpine* is a tertiary amine and is stable to hydrolysis by acetyl-cholinesterase. Compared with AC and its derivatives, it is far less potent. *Pilocarpine* exhibits muscarinic activity and is primarily used in ophthalmology.

Actions. Applied topically to the cornea, *Pilocarpine* produces a rapid miosis and contraction of the ciliary muscle. The eye undergoes a spasm of accommodation, and vision is fixed at some particular distance, making it impossible to focus. *Pilocarpine* is one of the most potent stimulators of secretions such as sweat, tears, and saliva, but it is not used for this purpose.

Therapeutic uses. *Pilocarpine* is a drug of choice in the emergency lowering of intraocular pressure of both narrow-angle (also called closed-angle) and wide-angle (also called open-angle) glaucoma. *Pilocarpine* is extremely effective in opening the trabecular meshwork around Schlemm's canal, causing an immediate drop in intraocular pressure as a result of the increased drainage of aqueous humor. This action lasts up to 1 day and can be repeated. Cholinesterase inhibitors, such as *Phosphacol*, have longer duration of action. [Note: Carbonic anhydrase inhibitor Acetazolamide, the β-adrenergic blocker, timolol, and adrenaline are effective in treating glaucoma chronically but are not used for the emergency lowering of intraocular pressure.]

Adverse effects. *Pilocarpine* can enter the brain and cause CNS disturbances. It stimulates profuse sweating and salivation.

ANTICHOLINESTERASES (REVERSIBLE)

Acetylcholinesterase is an enzyme that specifically cleaves acetylcholine (AC) to acetate and choline. It is located in the nerve terminal, where it is membrane bound. Inhibitors of acetylcholinesterase indirectly provide cholinergic action by prolonging the lifetime of AC. This results in accumulation of AC in the synaptic space. These drugs can thus provoke a response at all cholinoreceptors in the body, including both muscarinic and nicotinic receptors of the autonomic nervous system as well as the neuromuscular junction and the brain.

Physostigmine

Physostigmine is an alkaloid (a nitrogenous compound found in plants) and a tertiary amine. It is a substrate for acetylcholinesterase, and forms a relatively stable enzyme-substrate intermediate that reversibly inactivates acetylcholinesterase. The result is potentiation of cholinergic activity throughout the body.

Action: *Physostigmine* has a wide range of actions because it stimulates not only muscarinic and nicotinic sites of the autonomic nervous system but also the nicotinic receptors of the neuromuscular junction. Its duration of action is about 2-4 hours. *Physostigmine* can enter and stimulate the CNS.

Therapeutic uses: The drug increases intestinal and bladder motility, which serve as its therapeutic action in atony of either organ. Placed topically in the eye, it produces miosis and spasm of accommodation and a lowering of intraocular pressure. It is used to treat glaucoma, but *Pilocarpine* is more effective. *Physostigmine* is also used in the treatment of overdoses of drugs with anticholinergic actions such as *Atropine, Phenothiazine*, and tricyclic antidepressants.

Adverse effects: The effects of *Physostigmine* on the CNS may lead to convulsions when high doses are used. Bradycardia may also occur. Inhibition of acetylcholinesterase at the skeletal neuromuscular junction causes the accumulation of AC and ultimately results in paralysis of skeletal muscle. However, these effects are rarely seen with therapeutic doses.

Neostigmine

Neostigmine is a synthetic compound that reversibly inhibits acetylcholinesterase as does *physostigmine.* Unlike *Physostigmine*, *Neostigmine* is more polar and therefore does not enter the CNS. Its effect on skeletal muscle is greater than that of Physostigmine, and it can stimulate contractility before it paralyzes. Neostigmine has a moderate duration of action, usually 2–4 hours. It is used to stimulate the bladder and the GI tract, and is also used as antidote for *Tubocurarine* and other competitive neuromuscular blocking agents. *Neostigmine* has found use in symptomatic treatment of myasthenia gravis, an autoimmune disease caused by antibodies to the nicotinic receptors that bind to the AC receptors of neuromuscular junctions. This causes their degradation, and thus makes fewer receptors available for interaction with neurotransmitter. Adverse effects of *Neostigmine* include the actions of generalized cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, and bronchospasm.

Pyridostigmine

Pyridostigmine is another cholinesterase inhibitor that is used in the chronic management of myasthenia gravis. Its duration of action (3–6 hours) is longer than that of *Neostigmine*.

ANTICHOLINESTERASES (IRREVERSIBLE)

A number of synthetic organophosphate compounds have the capacity to bind covalently to acetylcholinesterase. The result is a long lasting increase in AC at all sites where it is released. Many of these drugs are extremely toxic and were developed by the military as nerve agents. Related compounds such as *Parathion, Chlorophos* are insecticides.

Armine

Mechanism of action. *Armine* is an organophosphate that covalently binds to the active site of acetylcholinesterase. Once this occur, the enzyme is permanently inactivated, and restoration of acetylcholinesterase activity requires the synthesis of new enzyme molecules. Following covalent modification of acetylcholinesterase, the phosphorylated enzyme slowly release one of its alkyl groups. The loss of an alkyl group, which is called aging, makes it impossible for chemical reactivators, such as *Pralidoxime or Dipiroxime* (see below), to break the bond between the remaining drug and the enzyme. Newer nerve agents, available to the military, age in minutes or seconds. *Armine* ages in several hours.

Actions: Actions include generalized cholinergic stimulation, paralysis of motor function (causing breathing difficulties), and convulsions. Armine produces intense miosis and thus has found therapeutic use. Atropine in high dosage can reverse many of the muscarinic and central effects of organophosphate compounds.

Therapeutic uses: An ophthalmic solution of the drug is used topically in the eye for the chronic treatment of open-angle glaucoma. The effect can last for up to one week after a single administration.

Reactivation of acetylcholinesterase. *Dipiroxime, Pralidoxime* (PAM) are synthetic compounds that can reactivate inhibited acetylcholinesterase. The presence of a charged group allows it to approach an anionic site on the enzyme where it is essentially displaces the organophosphate and regenerates the enzyme. If given before aging of the alkylated enzyme occurs, it can reverse the effects of armine except for those for the CNS. With the newer nerve agents, which produce aging within seconds, reactivators are less effective.

Available forms:

Aceclidine — in ampoules 0.2% solution 1 and 2 ml each

Arminum — in bottles 0.01% solution 10 ml each

Dipiroxime — in ampoules 15% solution 1 ml each

Neostigmine — in tablets 0.015 each; in ampoules 0.05% solution 1 ml each

Physostigmine — in bottles 0.25% solution 5 ml each

Pilocarpine — in bottles 1% and 2% solution 5 and 10 ml each

Lecture 4
CHOLINERGIC ANTAGONISTS

The cholinergic antagonists (also called cholinergic blockers or anticholinergic drugs) bind to cholinoreceptors but do not trigger the usual receptormediated intracellular effects. The most useful of these agents selectively the muscarinic synapses of the parasympathetic nerves. The effects of parasympathetic innervation are thus interrupted, and the actions of sympathetic stimulation are left unopposed. A second group of drugs interfere with cholinergic transmission primary in the CNS and are used in Parkinson's disease. A third group, the ganglionic blockers, show a preference for the nicotinic receptors of the sympathetic and parasympathetic ganglia. A fourth family of compounds, the neuromuscular blocking agents, interfere with transmission of efferent impulses to skeletal muscles.

ANTIMUSCARINIC AGENTS

These agents, for example, atropine and scopolamine, block muscarinic receptors causing inhibition of all muscarinic function. In addition, these drugs block the few exceptional sympathetic neurons that are cholinergic, such as those innervating sweat glands. In contrast to cholinergic agonists, which have limited usefulness therapeutically, the cholinergic blockers are beneficial in a variety of clinical situations. Because they do not block nicotinic receptors, the antimuscarinic drugs have little or no action at skeletal neuromuscular junctions or autonomic ganglia.

Atropine

Atropine, a belladonna alkaloid, has a high affinity for muscarinic receptors, where it binds competitively, preventing acetylcholine (AC) from binding to that site. *Atropine* is both a central and peripheral muscarinic blocker. Its general actions last about 4 hours except when placed topically in the eye, where the action may last for days.

Actions:

Ophthalmic: *Atropine* blocks all cholinergic activity on the eye (Fig. 3), resulting in mydriasis (dilation of the pupil), unresponsiveness to light and cycloplegia (inability to focus for near vision). In patients with glaucoma, intraocular pressure may rise dangerously. Locally applied *Atropine* produces ocular effects of considerable duration; accommodation and papillary reflexes may not fully recover for 7 to 12 days.

Gastrointestinal (GI): *Atropine* can be used as an antispasmodic to reduce activity of the GI tract. *Atropine* and *Scopolamine* are probably the most potent drugs available that produce that effect. Although gastric motility is reduced, hydrochloric acid production is not significantly affected. Thus, the drug is not effective in promoting healing of peptic ulcer. [Note: *Pyrenzipine*, an M_1-muscarinic antagonist, does reduce gastric acid secretion at doses that do not antagonize other systems.]

Urinary system: *Atropine* is also employed to reduce hypermotility states of the urinary bladder. It is

still occasionally used in enuresis (involuntary voiding of urine) among children but α-adrenergic agonists may be more effective with fewer side effects.

Cardiovascular: *Atropine* produces divergent effects on the cardiovascular system, depending on the dose. At low doses the predominant effect is a decreased cardiac rate (bradycardia). Originally thought to be due to central activation of vagal efferent outflow, newer data indicate that the effect results from blockade of the M_1 receptors on the inhibitory prejunctional neurons, thus permitting increased AC release. With higher doses of *Atropine*, the cardiac receptors on the SA node are blocked, and the cardiac rate increases modestly (tachycardia). This generally requires at least 1 mg of *Atropine*, which is a higher dose than ordinary given. Arterial blood pressure is unaffected.

Secretions: *Atropine* blocks the salivary glands to produce a drying effect on the oral mucous membranes (xerostomia). The salivary glands are exquisitely sensitive to atropine. Sweat and lacrimal glands are also affected. Inhibition of secretions by the former can cause elevated body temperature.

Therapeutic uses:

Ophthalmic: In the eye, topical *Atropine* exerts both mydriatic and cycloplegic effects and permits the measurement of refractive errors without interference by the accommodative capacity of the eye. Atropine may induce an attack in individuals with narrow angle glaucoma.

Antispasmodic agent: *Atropine* is used as antispasmodic agent to relax the GI tract and bladder.

As antidote for cholinergic agonists: *Atropine* is used for the treatment of organophosphate (contained in certain insecticides) and some types of mushroom poisoning (certain mushrooms contain cholinergic substances). Its ability to enter the CNS is of particular importance. *Atropine* blocks the effects of excess acetylcholine (AC) that results from inhibition of acetylcholinesterase by drugs such as *Physostigmine*.

Anti-secretory agent: The drug is sometimes used to block secretions in the upper and lower respiratory tracts prior to surgery.

Pharmacokinetics: *Atropine* is readily absorbed, partially metabolized in the liver, and is eliminated primarily in the urine. It has a half-life of about 4 hours.

Adverse effects: Depending on the dose, *Atropine* may cause dry mouth, blurred vision, "sandy eyes", tachycardia, and constipation. Effects on the CNS include restlessness, confusion, hallucination, and delirium, which may progress to depression, collapse of the circulatory and respiratory systems and death (see Fig. 3). In older individuals, the use of *Atropine* to induce mydriasis and cycloplegia is considered too risky since it may exacerbate an attack of glaucoma in someone with a latent condition.

Scopolamine

Scopolamine, another belladonna alkaloid, produces peripheral effects similar to those of Atropine. However, *Scopolamine* has greater action on the CNS and a longer duration of action in comparison to those of *Atropine*. It has some special actions indicated below.

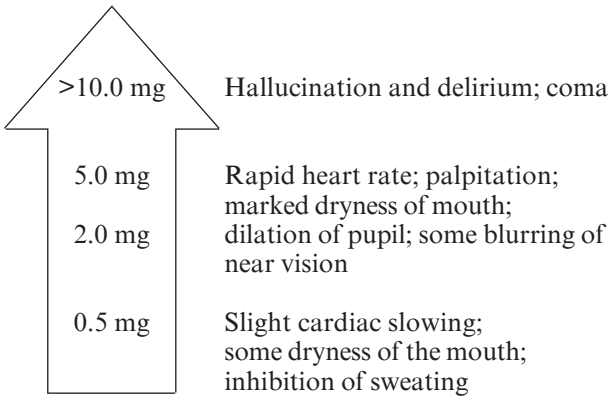


Fig. 3. Dose-dependent effects of *Atropine*

Actions: *Scopolamine* is one of the most effective anti-motion sickness drug available. *Scopolamine* also has the unusual effect of blocking short-term memory. In contrast to *Atropine, Scopolamine* produces sedation, but at higher doses can instead produce excitement.

Therapeutic uses: Though similar to *Atropine*, its therapeutic use is limited to prevention of motion sickness (for which *Scopolamine* is particularly effective) and blocking of short-term memory. [Note: As with all such drugs used for this condition, it is much more effective prophylactically than for treating motion sickness after it occurs. The amnesic action of *Scopolamine* is sometimes made use of in anesthetic procedures.]

Pharmacokinetics and adverse effects. These aspects are similar to those of *Atropine*.

Other compounds

An alkaloid *Platyphylline* is a naturally occurring tertiary amine found in plants. *Platyphylline* is less potent than *Atropine*. Its use has been limited chiefly to gastrointestinal diseases where it is administered as antispasmodic agent.

Homatropine, a quaternary ammonium compound, is available in an ophthalmic solution. Applied topically in the eye, *Homatropine* produces ocular effects similar to those of *Atropine* (pupillary dilation and loss of accommodation). Compared with *Atropine*, its duration of action is shorter (15–20 H).

Methacine is a quaternary ammonium derivative and therefore lacks the central actions. Other pharmacological properties are similar to those of *Atropine*. Methacine is used parenterally and enterally.

Ipratropium bromide, a quaternary derivative of *Atropine*, produces effects that are similar to those of *Atropine* when each agent is administered parenterally. These include bronchodilation, tachycardia, and inhibition of salivary secretion. Although *Ipratropium* lacks appreciable effect on the CNS. When *Ipratropium* is inhaled, the actions are confined almost exclusively to the airways. Even when administered in amounts many times the recommended dosage, little or no change occurs in heart rate, blood pressure, bladder function, intraocular pressure, or pupillary diameter. This selectively results from the very inefficient absorption of the drug from the lungs or the GI tract. *Ipratropium* is useful in treating asthma and chronic obstructive pulmonary disease in patients unable to take adrenergic agonists.

Pyrenzipine hydrochloride is a tricyclic drug, similar in structure to *Imipramine*. In contrast to the classic anticholinergics, *Pirenzepine* has selectivity for M_1-receptors and was initially shown to have greater gastrointestinal selectivity than other muscarinic antagonists. *Pirenzepine* suppresses basal and stimulated gastric acid secretion at doses having a minimal effect on the salivary glands, the heart and the eyes.

CENTRALLY ACTING ANTIMUSCARINIC DRUGS

The belladonna alkaloids and related antimuscarinic agents have long been used in the treatment of Parkinson's disease. Parkinson's disease is a progressive neurologic disorder of muscle movement, characterized by tremor, muscular rigidity, and bradykinesia (slowness in initiating and carrying out voluntary movements). The disease is correlated with a reduction in the activity of dopaminergic neurons in the substantia nigra and corpus striatum — parts of the brain basal ganglia system that are responsible for motor control. The substantia nigra, part of the extrapyramidal system, is the source of dopaminergic neurons that terminate in the striatum. Dopaminergic system serves as a tonic, sustaining influence on motor activity, rather than participating in specific movements. Cells of the substantia nigra sends neurons to the striatum, secreting the inhibitory transmitter dopamine at their termini (Fig. 4).

In turn, the striatum is connected to the substantia nigra by neurons that secrete the inhibitory transmitter GABA at their termini in the substantia nigra. This mutual inhibitory pathway normally maintains a degree of the two separate areas. Nerve fibers from the cerebral cortex and thalamus secrete acetylcholine (AC) in the neostriatum, causing excitatory effects. In Parkinson's disease, destruction of cells in the substantia nigra results in the degeneration of neurons responsible for the secreting dopamine in the neostriatum.

Consequently, the decrease in dopaminergic activity results in a relative excess of cholinergic influence. The symptoms of parkinsonism reflect an imbalance between the excitatory cholinergic neurons and the greatly diminished number of inhibitory dopaminergic neurons. Strategy for the treatment is aim to restore dopamine in the basal ganglia and antagonizing the excitatory effect of cholinergic neurons, thus reestablishing the correct dopamine/acetylcholine balance.

Anticholinergic drugs play only an adjuvant role in antiparkinsonian therapy (they are much less efficacious than dopaminergic agonists). Currently available antiparkinsonian muscarinic antagonists *(Cyclodolum, Amizylum etc.)* qualitatively resemble the belladonna alkaloids in its pharmacological action and side effects.

POISONING BY BELLADONNA ALKALOIDS

The deliberate or accidental ingestion of belladonna alkaloids or other classes of drugs with atropinic properties is a major cause of poisonings. Infants and young children are especially susceptible to the toxic effects of atropinic drugs. Indeed, many cases of intoxication in children have resulted from conjunctival instillation of atropine eye-drops. Serious intoxication may occur in children who ingest berries or seeds containing belladonna alkaloids. The diagnosis of atropine poisoning is suggested by the wide-spread paralysis of parasympathetic innervation — dry mouth, mydriasis, blurred vision, hot dry skin, and, in addition, hyperreflexia, excitement, hallucinations, delirium and later, cerebral depression and coma. As it was described with characteristic American verbal felicity — "hot as a hare, blind as a bat, dry as a bone, red as a beet and mad as a hen".

The treatment of atropine (and other anticholinergic drugs) poisoning is on general lines. Measures to limit intestinal absorption should be initiated without delay if the poison has been taken orally. For symptomatic treatment, anticholinesterase drug (physostigmine) is the rational therapy. This agent enters the central nervous system and reverses both the central and peripheral effects. *Physostigmine* 1–4 mg i.v. or i.m. is effective, though it may need repeating, as its action (1–2 hours) is shorter than that of *Atropine*. If marked excitement is present, diazepam is the most suitable agent for sedation and for control of convulsion. Ice bags and alcohol sponges help to reduce fever, especially in children.

AGENTS ACTING ON THE NICOTINIC RECEPTORS

Several drugs have their major action the interruption of transmission of the nerve impulses at the skeletal neuromuscular junction and/or autonomic ganglia. These agents can be classified together, since they interact with a common family of receptors; these receptors are called *nicotinic cholinergic*, since they are stimulated by both the natural transmitter acetylcholine and the alkaloid nicotine. Distinct subtypes of nic-

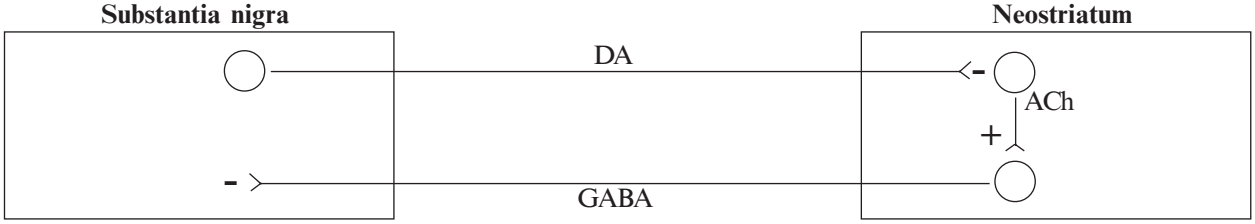


Fig. 4. Relations of synapses of the extrapyramidal system

otinic receptors exist at the neuromuscular junction and the ganglia, and two groups of pharmacological agents discriminate between them (ganglionic blockers and neuromuscular blocking agents).

GANGLIONIC BLOCKERS

Ganglionic blockers specifically act on the nicotinic receptors of the autonomic ganglia. These drugs show no selectivity towards the parasympathetic or sympathetic ganglia and are not effective as neuromuscular antagonists. Thus, these drugs block the entire output of the autonomic nervous system at the nicotinic receptor. The responses observed are complex and can be anticipated by knowing which division of the autonomic nervous system exercises dominant control of various organs (Table 2).

Actions:

Cardiovascular system: Blockade of sympathetic ganglia interrupts adrenergic control of arterioles and results in vasodilation, improved peripheral blood flow, and a fall in blood pressure. Venous return decreases resulting from venous dilation and peripheral pooling of blood. In patients with cardiac failure, ganglionic blockade results in increased cardiac output due to a reduction in peripheral resistance. Blood flow to the hands and feet may increase and skin temperature in the limbs is elevated.

Other effects: Generalized ganglionic blockade may result also in atony of the bladder and the GI tract, cycloplegia, xerostomia, diminished perspiration. These changes represent the generally undesirable feature, which limits the therapeutic use of the ganglionic blockers.

Pharmacokinetics. Ganglionic blocking agents are divided chemically into bisquaternary and tertiary amines. The absorption of quaternary ammonium compounds from the enteric tract is incomplete and unpredictable *(Benzohexonium, Pentamine)*. Therefore, they are administered parenterally. According to the duration of action, ganglionic blockers are classified into:

— short-acting drugs — 15 to 20 minutes *(Trimethaphan (Arfonad), Hygronium)*

— intermediate-acting drug — up to 6 hours *(Benzohexonium, Pentamine, Pachycarpine)*

— long-acting drug — 6 to 12 hours *(Pirilen)*

Therapeutic uses:

Trimethaphan (Arfonad) is a short-acting ganglionic blocker that must be given by i.v. infusion. Today, the drug is used for the emergency lowering of blood pressure, for example, in hypertension caused by pulmonary edema or dissecting aortic aneurysm. Also it is used to produce controlled (moment-to-moment) hypotension in anesthesia.

Benzohexonium and *Pentamine* act longer and are generally used in the treatment of moderately severe to severe hypertension.

Pirilen is useful for the long-term treatment of severe hypertension and peripheral vascular disease.

Pachycarpine has an additional specific property to stimulate myometrium and accelerate parturition.

NEUROMUSCULAR BLOCKING DRUGS

These drugs block cholinergic transmission between motor nerve ending and the nicotinic receptors on the neuromuscular end-plate of the skeletal muscle. These neuromuscular blockers are structural analogs of acetylcholine and act either as antagonists (non-depolarizing type) or agonists (depolarizing type) at the receptors on the end-plate of the neuromuscular junction. Neuromuscular blockers are clinically useful during surgery to produce complete muscle relaxation, without having to employ higher anesthetic doses to achieve comparable muscular relaxation. A second group of muscle relaxants, the central muscle relaxants, are used to control spastic muscle tone. These drugs include *Diazepam* (which binds at GABA receptors in the CNS), *Dantrolene* (which act directly on muscles by interfering with the release of Ca++ from the sarcoplasmic reticulum), and *Baclofen* (which probably acts at GABA receptors in the CNS).

NONDEPOLARIZING (COMPETITIVE) BLOCKERS

The first drug that was found capable of blocking the skeletal neuromuscular junction was curare, which the native hunters of the Amazon in South America used to paralyze game. The drug *Tubocurarine* was ultimate-

Table 2. **Usual predominance of adrenergic or cholinergic tone at various effector sites, with consequent effects of autonomic ganglionic blockade**

Site	Predominant tone	Effect
Arterioles	Sympathetic (adrenergic)	Vasodilation; increased peripheral blood flow; hypotension
Veins	Sympathetic (adrenergic)	Dilation; peripheral pooling of blood; decreased venous return; decreased cardiac output
Heart	Parasympathetic (cholinergic)	Tachycardia
Iris	Parasympathetic (cholinergic)	Mydriasis
Ciliary muscle	Parasympathetic (cholinergic)	Cycloplegia
GI tract	Parasympathetic (cholinergic)	Reduced tone and motility; constipation
Urinary bladder	Parasympathetic (cholinergic)	Urinary retention
Salivary glands	Parasympathetic (cholinergic)	Xerostomia
Sweat glands	Sympathetic (adrenergic)	Anhidrosis

ly purified and introduced into clinical practice in the early 1940s. The neuromuscular blocking agents have significantly increased the safety of anesthesia, since less anesthetic is required to produce muscle relaxation.

Mechanism of action: Nondepolarizing neuromuscular blocking drugs combine with the nicotinic receptor and prevent the binding of ACh. These drugs prevent depolarization of the muscle cell membrane and inhibit muscular contraction. Because these agents compete with ACh at the receptors, they are called competitive blockers. Their action can be overcome by increasing the concentration of ACh in the synaptic gap, e.g. by administration of cholinesterase inhibitors such as *Neostigmine*. Anesthesiologists often employ this strategy to shorten the duration of the neuromuscular blockade.

Actions. Not all muscles are equally sensitive to blockade by competitive blockers. Small, rapidly contracting muscles of the face and eye are most susceptible and are paralyzed first, followed by the fingers. Thereafter the limbs, neck, and trunk muscles are paralyzed, then the intercostal muscles are affected, and lastly, the diaphragm muscles are paralyzed.

Therapeutic uses. These blockers are used therapeutically as adjuvant drugs in anes-thesia during surgery to relax skeletal muscle.

Pharmacokinetics. All neuromuscular blocking agents are injected i.v. since their uptake via oral absorption is minimal. They penetrate membranes very poorly and do not enter cells or cross the blood-brain barrier. Many of the drugs are not metabolized; their actions are terminated by redistribution. For example, tubocurarine and pancuronium are excreted in the urine unchanged. Atracurium is degraded spontaneously in the plasma and by ester hydrolysis. The aminosteroid drug vecuronium is deacetylated in the liver, and their clearance may be prolonged in patients with hepatic disease.

Drug interaction:

a) **Cholinesterase inhibitors**. Drugs such as *Neostigmine* and *Physostigmine* can over-come the action of nondepolarizing neuromuscular blockers, but with increased dosage, can cause a depolarizing block as a result of elevated ACh concentration at the end-plate membrane.

b) **Halogenated hydrocarbon anesthetics**. Drugs such as *Halothane* act to enhance neuromuscular blockade by exerting a stabilizing action at the neuromuscular junction.

c) **Aminoglycoside antibiotics**. Drugs like *Gentamicin* or *Tobramycin* inhibit acetylcholine release from cholinergic nerves by competing with calcium ions. They synergize with tubocurarine and other competitive blockers, enhancing the blockade.

d) **Calcium channel blockers**. These agents may increase the neuromuscular block of competitive blockers as well as depolarizing blockers.

DEPOLARIZING BLOCKERS

Mechanism of action. The depolarizing neuromuscular blocking drug, *Succinylcholine (Dithyline)*, attaches to the nicotinic receptor and acts like ACh to depolarize the junction. Unlike acetylcholine, which is instantly destroyed by acetylcholinesterase, the depolarizing agent persists at high concentrations in the synaptic cleft, remaining attached to the receptor for a relatively long time, and providing a constant stimulation of the receptor. The depolarizing agent first causes the opening of the sodium channel associated with the nicotinic receptor, which results in depolarization (Phase I). This leads to a transient twitching of the muscle (fasciculations). The continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses. With time, the continuous depolarization gives way to gradual repolarization as the sodium channel closes or is blocked. This causes a resistance to depolarization (Phase II) and a flaccid paralysis.

Actions. The sequence of paralysis may be slightly different, but as is seen with the competitive blockers, the respiratory muscles are paralyzed last. *Succinylcholine* initially produces short-lasting muscle fasciculations, followed within a few minutes by paralysis. Normally, the duration of action of *succinylcholine* is extremely short, since this drug is rapidly broken down by plasma cholinesterase.

Therapeutic uses. Because of its rapid onset and short duration of action, *Succinylcholine* is useful when rapid endotracheal intubation is required during the induction of anesthesia (a rapid action is essential if aspiration of gastric contents is to be avoided during intubation). It is also employed during electroconvulsive shock treatment.

Pharmacokinetics. *Succinylcholine* is injected i.v. Its brief duration of action (several minutes) results from rapid hydrolysis by plasma cholinesterase.

Adverse effects:

Hyperthermia: When *Halothane* is used as anesthetic, administration of *Succinylcholine* may occasionally cause malignant hyperthermia (with muscular rigidity and hyperpyrexia) in genetically susceptible people. This is treated by rapid cooling of the patient and by administration of *Dantrolene*, which blocks release of Ca++ from the sarcoplasmic reticulum of muscle cells, thus reducing heat production and relaxing muscle tone.

Apnea: A genetically related deficiency of plasma cholinesterase or presence of an atypical form of the enzyme can lead to apnea due to paralysis of the diaphragm.

Available forms:

Atropine sulfate — in ampoules 0.1% solution 1 ml each; in tablets 0.0005

Benzohexonium — in tablets 0.1 and 0.25 each; in ampoules 2.5% solution

Diplacini dichloridum — in ampoules 2% solution 5 ml each

Dithylinum — in ampoules 2% solution 5 and 10 ml each

Hygronium — in bottles and ampoules 0.1 each (to dilute in physiologic solution)

Ipratropium bromide — in aerosol 15 ml each

Pachycarpini hydroiodidum — in tablets 0.1 each; in ampoules 3% solution 2 ml each

Platyphyllinum — in tablets 0.005 each; in ampoules 0.2% solution 1 ml

Pyrenzipine — in tablets 0.025 and 0.05 each

Scopolamine — in ampoules 0.05% solution 1 ml each

Tubocurarine chloride — in ampoules 1% solution 1.5 ml each

Lecture 5
ADRENERGIC AGONISTS

The adrenergic drugs affect receptors that are stimulated by *Noradrenaline (Norepinephrine)* or *Adrenaline (Epinephrine)*. This lecture describes agents that either directly or indirectly stimulate the adrenoreceptors.

The adrenergic neuron. Adrenergic neurons release *Noradrenaline* as the neurotransmitter. These neurons are found in the CNS, and also in the sympathetic nervous system where they serve as links between ganglia and effector organs. The adrenergic receptors located either pre-synaptically on the neuron or postsynaptically on the effector organ are the sites of action of the adrenergic drugs.

Neurotransmission at adrenergic neurons. *Neurotransmission* in adrenergic neurons closely resembles that already described for the cholinergic neurons, except that *Noradrenaline* is the neurotransmitter instead of *Acetylcholine*. Neurotransmission takes place at numerous beadlike enlargements called varicosities; the process involves five steps: the synthesis, storage, release, and receptor binding of the *Noradrenaline*, followed by removal of the neurotransmitter from the synaptic gap (Fig. 5).

Synthesis of Noradrenaline. Tyrosine is transported by Na+-linked carrier into the axoplasm of the adrenergic neuron, where it is hydroxylated to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase. This is the rate-limiting step in the formation of *Noradrenaline*. DOPA is decarboxylated to form *Dopamine*.

Storage of Noradrenaline in Vesicles. Dopamine is transported into synaptic vesicles by an amine transporter system. This carrier system is blocked by *Reserpine*. In vesicles, *Dopamine* is hydroxylated to form *Noradrenaline* by the enzyme, dopamine β-hydroxylase. In the adrenal medulla, *Noradrenaline* is methylated to yield *Adrenaline*. On stimulation, the adrenal medulla release about 85% *Adrenaline* and 15% *Noradrenaline*.

Release of Noradrenaline. An action potential arriving at the nerve junction triggers an influx of Ca++ from the extracellular fluid into the sarcoplasm of the neuron. This causes vesicles to fuse with cell membrane and expel their content into the synapse. This release is blocked by drugs such as *Guanethidine*.

Binding by receptor. *Noradrenaline* released from the synaptic vesicles diffuses across the synaptic space and binds to either postsynaptic receptors on the effector organ or to presynaptic receptors on the nerve ending. The recognition of *Noradrenaline* by the mem-

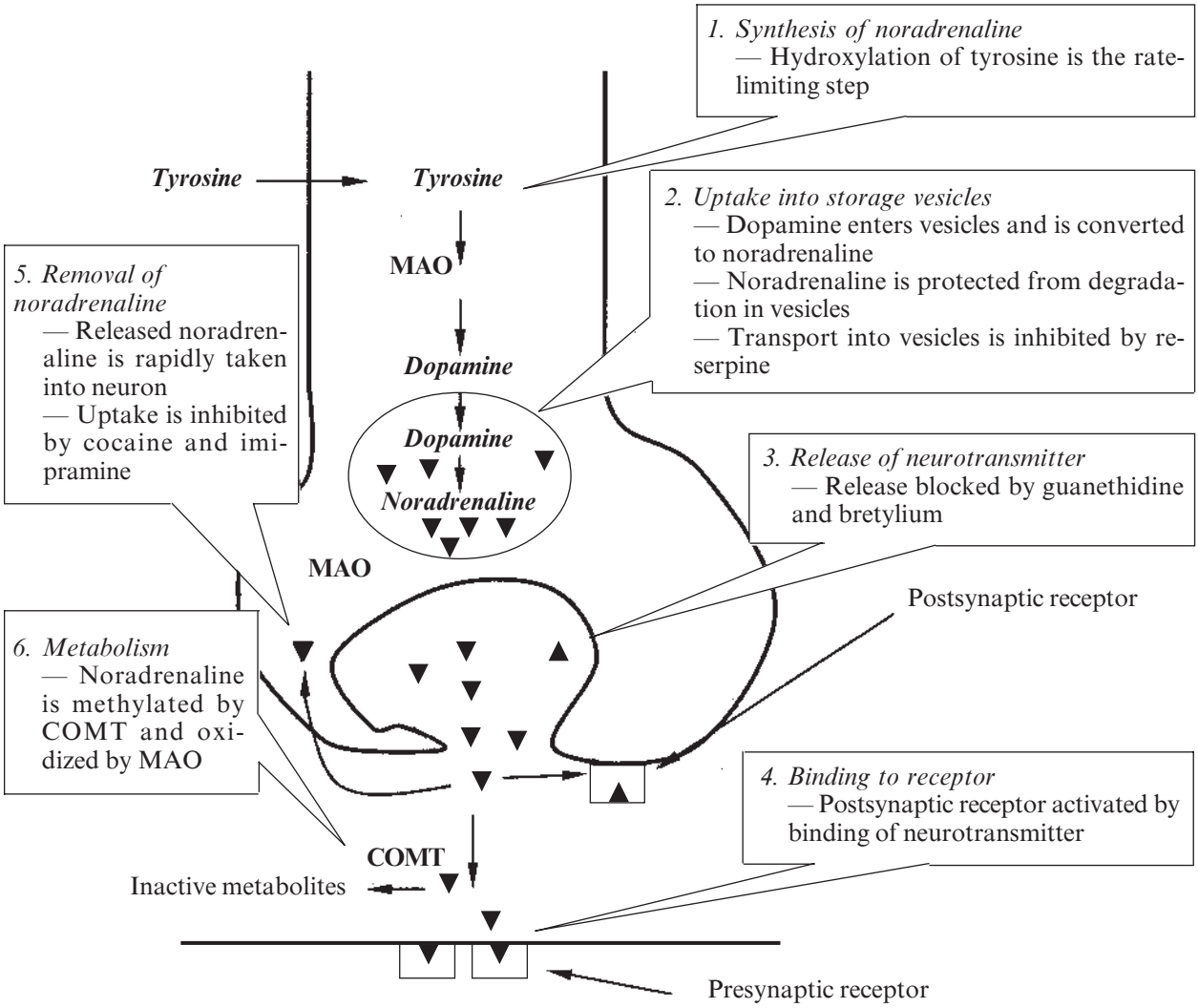


Fig. 5. Neurotransmission at adrenergic neurons

brane receptors triggers a cascade of events with in the cell, resulting in the formation of intracellular second messengers that act as links (transducers) in the communication between the neurotransmitter and the action generated within the effector cell. Adrenergic receptors use both the cyclic adenosine monophosphate (cAMP) second messenger system and the phosphoinositide cycle.

Removal of Noradrenaline. *Noradrenaline* may (1) diffuse out of the synaptic space and enter the general circulation, (2) be metabolized to O-methylated derivatives by post-synaptic cell membrane-associated catechol O-methyltransferase (COMT) in the synaptic space, or (3) be recaptured by an uptake system that pulls the *Noradrenaline* back into the neuron. The uptake by the neuronal membrane involves a Na+-K+ activated ATPase that can be inhibited by tricyclic antidepressants such as *Imipramine*, or by *Cocaine*.

Potential fates of recaptured Noradrenaline. Once the *Noradrenaline* reenters the cytoplasm it may be taken up into vesicles via the amine transporter system and be sequestered for release by another action potential. Alternatively, *Noradrenaline* can be oxidized by monoamine oxidase (MAO) present in neuronal mitochondria. The inactive products of *Noradrenaline* metabolism are excreted in the urine as vanillylmandelic acid (VMA), *Metanephrine* and *Normetanephrine*.

Adrenergic receptors. In the sympathetic nervous system, several classes of adrenoreceptors can be distinguished pharmacologically. Two families of receptors, designated 'α' and 'β', were initially identified on the basis of their responses to the adrenergic agonists, *Adrenaline*, *Noradrenaline*, and *Isoproterenol*. The use of the specific blocking drugs and the cloning of genes have revealed the molecular identities of a number of subtypes. Alteration in the primary structure of the receptors influence their affinity for various agents.

α_1- and α_2-receptors. The a receptors show a weak response to the synthetic agonist *Isoproterenol*, but are responsive to the naturally occurring catecholamines, *Adrenaline*, and *Noradrenaline*. For a receptors the rank order of potency is:

Adrenaline ≥ Noradrenaline >> Isoproterenol

The α-adrenoreceptors are subdivided into two groups, α_1 and α_2 , based on their affinities for α-agonists and blocking drugs. For example, the α_1-receptors have a higher affinity for Phenylephrine than do the α_2-receptors. Conversely, the drug Clonidine selectively binds to α_2-receptors, and has less effect on α_1-receptors:

a) α_1-receptors are present on the postsynaptic membrane of the effector organs and mediate many of the classic effects, originally designated as α-adrenergic, involving constriction of smooth muscle.

b) *α_2-receptors* located primarily on presynaptic nerve ending and on other cells, such as the β-cells of the pancreas, control adrenergic neuro-mediator and insulin output, respectively. When a sympathetic adrenergic nerve is stimulated, the released *Noradrenaline* traverses the synaptic cleft and interacts with the α_1-receptor. A portion of released *Noradrenaline* "circles back" and reacts with the α_2-receptors on the presynaptic membrane. The stimulation of the α_2-receptors causes feedback inhibition of the ongoing release of *Noradrenaline* from the stimulated neuron. This inhibitory action decreases further output from the adrenergic neuron and serves as a local modulating mechanism for reducing sympathetic neuro-mediator output when there is high sympathetic activity.

β-Receptors exhibit a set responses different from those of the α-receptors. These are characterized by a strong response to *Isoproterenol*, with less sensitivity to *Adrenaline* and *Noradrenaline*. For β-receptors, the rank order of potency is:

Isoproterenol > Adrenaline > Noradrenaline

The β receptors can be subdivided into two major groups, β_1 and β_2 based on their affinities for adrenergic agonists and antagonists. β_1 receptors have approximately equal affinities for *Adrenaline* and *Noradrenaline*, whereas β_2-receptors have a higher affinity for *Adrenaline* than for *Noradrenaline*. Thus, tissues with a predominance of β_2-receptors (such as the vasculature of skeletal muscle) are particularly responsive to the hormonal effects of circulating *Adrenaline* released by the adrenal medulla.

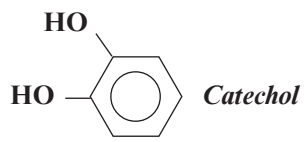
Distribution of receptors. Adrenergic innervated organs and tissues tend to have a predominance of one type of receptor. For example, tissues such as vasculature to skeletal muscle have both α_1- and β_2-receptors, but β_2 receptors predominate. Other tissues may have one type of receptors exclusively, with practically no significant numbers of other type of adrenergic receptors. For example, the heart contains predominantly β_1-receptors.

Characteristic responses mediated by adrenoreceptors. It is useful to organize the physiologic responses according to the receptor type, since many drugs preferentially stimulate or block one type of receptor. As a generalization, stimulation of α_1-receptors characteristically produces vasoconstriction (particularly in the skin and abdominal viscera) and an increase in total peripheral resistance and blood pressure (Table 3).

Conversely, stimulation of β_1-receptors characteristically causes cardiac stimulation, while β_2-produces vasodilation (in skeletal vascular beds), and bronchiolar relaxation.

ADRENERGIC AGONISTS

Most of adrenergic drugs are derivatives of β-phenylethylamine. Substitutions on the benzene ring or on the ethylamine side chains produce a great variety of compounds with varying abilities to differentiate between α- and β-receptors and to penetrate the CNS. Two important structural features of these drugs are the number and location of OH substitutions on the benzene ring and the nature of the substituent on the amino nitrogen.



Catechol

Table 3. **Effects of adrenoreceptors stimulation**

	Type of receptor			
	α_1	α_2	β_1	β_2
Effects	**V**asoconstriction **I**ncreased peripheral resistance **I**ncreased blood pressure **B**ronchodilation **M**ydriasis **I**ncreased closure of internal sphincter of the bladder	**I**nhibition of noradrenaline release **I**nhibition of insulin release	**T**achycardia **I**ncreased lipolysis **I**ncreased myocardial contractility	**V**asodilation **S**lightly decreased peripheral resistance **I**ncreased glycogenolysis **I**ncreased release of glucagon **R**elaxed uterine smooth muscle

Catecholamines. Sympathomimetic amines that contain the 3,4-dihydrobenzene group (such as, *Adrenaline, Noradrenaline, Isoproterenol*, and *Dopamine*) are called catecholamines. [Note: 1,2-dihydrobenzene is catechol.] These compound share the following properties:

High potency. Drugs that are catechol derivatives show the highest potency in activation α- or β-receptors.

Rapid inactivation. Not only the catecholamines are metabolized by COMT postsynaptically and by MAO intraneuronally, but they are also metabolized in other tissues. For example, COMT is in the gut wall and MAO is in the liver and gut wall. Thus catecholamines have only a brief period of action when given parenterally, and are ineffective when administered orally.

Poor penetration into the CNS. Catecholamines are polar and therefore do not readily penetrate into the CNS. Nevertheless, most of these drugs have some clinical effects (anxiety, tremor, headaches) that are attributable to action on the CNS.

Non-catecholamines. Compounds lacking the catechol hydroxyl groups have longer half-lives, since they are not inactivated by COMT. These include *Phenylephrine (Mesaton), Ephedrine*, and *Amphetamine*. Increased lipid solubility of many of the non-catecholamines permits greater access to the CNS. These compounds may act indirectly by causing the release of stored catecholamines.

Substitution on amine nitrogen. The nature of the substituent on the amine nitrogen is important in determining the β selectivity of the adrenergic agonist. For example, *Adrenaline* with a $-CH_3$ substituent is more potent at β-receptors than *Noradrenaline*. Similarly, *Isoproterenol* with an isopropyl substituent $-CH(CH_3)_2$ on the amine nitrogen, is a strong β-agonist with little α activity.

Mechanism of action.

Direct-acting agonists. These drugs act directly on α- or β-receptors, producing effects similar to those that occur following stimulation of sympathetic nerves or release of the hormone *Adrenaline* from the adrenal medulla. Examples of direct acting agonists include *Adrenaline, Noradrenaline, Isoproterenol*, and *Phenylephrine*.

Indirect-acting agonists. These agents (e.g. *Amphetamine*) are taken up into the presynaptic neuron and cause the release of *Noradrenaline* from the cytoplasmic pools or vesicles. As with neuronal stimulation, the *Noradrenaline* traverses the synapse and binds to the α or β receptors.

Mixed-acting agonists. Some agonists, such as *Ephedrine*, have the capacity both to direct stimulate adrenoreceptors and to release *Noradrenaline* from the adrenergic neuron.

DIRECT-ACTING AGONISTS

Direct-acting agonists bind to adrenoreceptors without interacting with the presynaptic neuron. The activated receptor initiates synthesis of second messengers and subsequent intracellular signals. As a group these agents are widely used clinically.

Adrenaline

Adrenaline is one of five catecholamines — *Adrenaline, Noradrenaline, Dopamine, Dobutamine*, and *Isoproterenol* — commonly used in therapy. The first three catecholamines occur naturally, the latter two are synthetic compounds. *Adrenaline* is synthesized in the adrenal medulla and released into the blood stream. *Adrenaline* interacts with both α- and β-receptors. At low doses, β-effects (vasodilatation) on the vascular system predominate, whereas at high doses, α effects (vasoconstriction) are strongest.

Actions:

Cardiovascular: the major actions of *Adrenaline* are on the cardiovascular system. *Adrenaline* strengthens the contractility of the myocardium (positive inotropic: β_1-action) and increases its rate of contraction (positive chronotropic: β_1-action). Cardiac output therefore increases. With these effects comes increased oxygen demands on the myocardium. *Adrenaline* constricts arterioles in the skin, mucous membranes, and viscera (α-effects) and dilates vessels going to the liver and skeletal muscle (β_2-effects). Renal blood flow is decreased. The cumulative effect, therefore, is an increase in systolic blood pressure, coupled with a slight decrease in diastolic pressure.

Respiratory: *Adrenaline* causes powerful bronchodilation by acting directly on bronchial smooth muscle (β_2-action). This action relieves all known allergic- or histamine-induced bronchoconstriction. In

the case of anaphylactic shock, this can be life-saving.

Hyperglycemia: *Adrenaline* has a significant hyperglycemic effect because of increased glycogenolysis in the liver (β_2-effect), increased release of glucagon (β_2-effect), and decreased release of insulin (α_2-effect).

Lipolysis: *Adrenaline* initiates lipolysis through its agonist activity on the β-receptors of adipose tissue, which activate a hormone-sensitive lipase, which hydrolyzes triacylglycerols to free fatty acids and glycerol.

Biotransformations. *Adrenaline*, like other catecholamines, is metabolized by two enzymatic pathways: COMT, and MAO. The final metabolites found in the urine are metanephrine and vanillylmandelic acid. [Note: Urine also contains normetanephrine, a product of *Noradrenaline* metabolism.]

Therapeutic uses:

Bronchospasm: *Adrenaline* is the primary drug used in the emergency treatment or any condition of the respiratory tract where the presence of bronchoconstriction has resulted in diminished respiratory exchange. Thus, in the treatment of acute asthma and anaphylactic shock, *Adrenaline* is the drug of choice; within a few minutes after subcutaneous administration, greatly improved respiratory exchange is observed. Administration may be repeated after a few hours. However, selective β_2-agonists, such as *Terbutaline*, are presently favored in the chronic treatment of asthma because of a longer duration of action and minimal cardiac stimulatory effect.

Glaucoma: In ophthalmology, a 2% *Adrenaline* solution may be used topically to reduce intraocular pressure in open-angle glaucoma. It is reduces the production of aqueous humor by vasoconstriction of the ciliary's body blood vessels.

Anaphylactic shock: *Adrenaline* is the drug of choice for the treatment of Type I hypersensitivity reactions in response to allergens.

In anesthetics: Local anesthetic solutions usually contain 1:100,000 parts of *Adrenaline*. The effect of the drug is to greatly increase the duration of the local anesthesia. It does this by producing vasoconstriction at the site of injection, thereby allowing the local anesthetic to persist at the site before being absorbed into the circulation and metabolized. Very weak solutions of *Adrenaline* (1:100,000) can also be used topically to vasoconstriction mucous membranes to control oozing of capillary blood.

Pharmacokinetics. *Adrenaline* has a rapid onset but brief duration of action. In emergency situation *Adrenaline* is given intravenously for the most rapid onset of action; it may also be given subcutaneously, by endotracheal tube, by inhalation, or topically to the eye. Oral administration is ineffective.

Adverse effects. Adrenaline can produce adverse CNS effects that include anxiety, fear, tension, headache, and tremor. The drug may induce cerebral hemorrhage as a result of a marked elevation of blood pressure. *Adrenaline* can trigger cardiac arrhythmias, particularly if the patient is receiving *digitalis*. *Adrenaline* can induce pulmonary edema in predisposing patients with left ventricular failure.

Noradrenaline

Since *Noradrenaline* is the neuromediator of adrenergic nerves, it should theoretically stimulate all types of adrenergic receptors. In practice, when the drug is given in therapeutic doses, the α-receptors are most affected.

Cardiovascular actions:

Vasoconstriction: *Noradrenaline* causes a rise in peripheral resistance due to intense vasoconstriction of most vascular beds, including the kidney (an α_1-receptor effect). Both systolic and diastolic blood pressure increase.

Baroreceptor reflex: In isolated cardiac tissue *Noradrenaline* stimulates cardiac contractility; however, *in vivo*, little if any cardiac stimulation is noted. This is due to the increased blood pressure that induces the reflex rise in vagal activity by stimulating the baroreceptors. This bradycardia is sufficient to counteract the local action of *Noradrenaline* on the heart.

If *atropine* (which blocks the transmission of vagal effects) is given before *Noradrenaline*, *Noradrenaline* stimulation of the heart is evident as tachycardia.

Therapeutic uses. *Noradrenaline* is used to treat shock because it increases vascular resistance and, therefore, increases blood pressure; however, *Dopamine* is better, because it does not reduce blood flow to the kidney as does *Noradrenaline*. Other actions of *Noradrenaline* are not considered clinically significant. It is never used for asthma.

Isoproterenol (Isadrinum)

Isoproterenol is a direct-acting synthetic catecholamine that predominantly stimulates both β_1 and β_2 adrenergic receptors. Its non-selectivity is one of its drawbacks. Its action on α-receptors is insignificant.

Actions:

Cardiovascular: *Isoproterenol* produces intense stimulation of the heart to increase its rate and force of contraction, causing increased cardiac output. It is as active as *Adrenaline* and is therefore useful in the treatment of atrioventricular (AV) block or cardiac arrest. *Isoproterenol* also dilates the arterioles of skeletal muscle (β_2). Because of its cardiac stimulatory action, it may increase systolic blood pressure slightly, but it greatly reduces mean arterial and diastolic blood pressure.

Pulmonary: A profound and rapid bronchodilatation is produced by the drug (β_2-action). *Isoproterenol* is as active as *Adrenaline* and rapidly alleviates an acute attack of asthma, when taken by inhalation (which is the recommended route). This action lasts about one hour and may be repeated by subsequent doses.

Therapeutic uses. *Isoproterenol* is now rarely used as a bronchodilator in asthma. It can be employed to stimulate the heart in emergency situations.

Pharmacokinetics. *Isoproterenol* can be absorbed systemically by the sublingual mucosa but is more reliably absorbed when given parenterally or as inhaled aerosol. It is a marginal substrate for COMT and is stable to MAO action.

Adverse effects. *Isoproterenole's* adverse effects are similar to those of *Adrenaline*.

Dopamine

Dopamine, the immediate metabolic precursor of *Noradrenaline*, occurs naturally in the CNS in the basal ganglia where it functions as a neurotransmitter as well as in the adrenal medulla. *Dopamine* can activate α- and β-receptors. At higher doses it causes vasoconstriction by activating α-receptors, whereas at lower doses, it stimulates β_1 cardiac receptors. In addition, D_1 and D_2 dopaminergic receptors, distinct from the α and β adrenergic receptors, occur in the peripheral mesenteric and renal vascular beds, where binding of *Dopamine* produces vasodilatation. D_2 receptors are also found on presynaptic adrenergic neurons, where their activation interferes with *Noradrenaline* release.

Actions:

Cardiovascular: *Dopamine* exerts a stimulatory effect on the β_1 receptors of the heart, having both inotropic and chronotropic effects. At very high doses, dopamine activates α-receptors on the vasculature, resulting in vasoconstriction.

Renal and visceral: *Dopamine* dilates renal and splanchnic arterioles by activating dopaminergic receptors, thus increasing blood flow to the kidney and other viscera. These receptors are not affected by α- or β-blocking drugs. Therefore, *Dopamine* is clinically useful in the treatment of shock, in which significant increases in sympathetic activity might compromise renal function.

Therapeutic uses. *Dopamine* is the drug of choice for shock and is given by continuous infusion. It raises the blood pressure by stimulating the heart (β_1 action). In addition, it enhances perfusion to the kidney and splanchnic areas, as described above. An increased blood flow to the kidney enhances the glomerular filtration rate and causes sodium diuresis. In this regard, *Dopamine* is far superior to *Noradrenaline*, which diminishes the blood supply to the kidney and may cause kidney shutdown.

Adverse effects. An overdose of *Dopamine* produces the same effects as sympathetic stimulation. *Dopamine* is rapidly metabolized to homovanilic acid, and its adverse effects (nausea, hypertension, arrhythmias) are therefore short-lived.

Dobutamine

Dobutamine is a synthetic, direct-acting catecholamine that is a β_1-receptor agonist. The drug increases cardiac output with little change in the heart rate and with few vascular effects. It does not significantly elevate oxygen demands of the myocardium — a major advantage over other sympathomimetic drugs. *Dobutamine* is used in congestive heart failure. *Dobutamine* should be used with caution in atrial fibrillation, since the drug increases atrioventricular conduction. Other adverse effects are the same as those for *Adrenaline*.

Phenylephrine (Mesatonum)

Phenylephrine is a direct-acting, synthetic adrenergic agonist that bind primarily to a receptors and favors α_1-receptors over α_2-receptors. It is not a catechol derivative and therefore not a substrate for COMT. *Phenylephrine* is a vasoconstrictor that raises both systolic and diastolic blood pressures. It has no effect on the heart itself but induces reflex bradycardia when given parenterally. It is often used topically on the nasal mucous membranes and in ophthalmic solutions for mydriasis. The drug is used to raise blood pressure and to terminate episodes of supraventricular tachycardia. Large doses can cause hypertensive headache.

Clonidine (Clophelinum)

Clonidine is an α_2-agonist that is used in essential hypertension to lower blood pressure because of its action in the CNS. It can be used to minimize the symptoms that accompany withdrawal from opiates or benzodiazepines. *Clonidine* acts centrally (α_2) to produce inhibition of the sympathetic vasomotor centers.

Metaproterenol (Alupent, Orciprenaline)

Metaproterenol, although chemically similar to *Isoproterenol*, is not a catecholamine and is resistant to COMT. It can be administered orally or by inhalation. The drug acts primarily at β_2-receptors, producing little effect on the heart (β_1). *Metaproterenol* is used to dilate bronchioles and improve airway function.

Terbutaline (Bricanyl)

Terbutaline is a β_2-agonist with more selective properties than Metaproterenol and a longer duration of action. *Terbutaline* can be administered either orally or subcutaneously. It is used as a bronchodilator and to reduce uterine contractions in premature labor.

INDIRECT-ACTING ADRENERGIC AGONISTS

Indirect-acting adrenergic agonists cause *Noradrenaline* release from presynaptic terminals. These agents do not directly affect postsynaptic receptors. For example, the central and peripheral actions of *Amphetamine* are mediated primarily through the cellular release of stored catecholamines. The actions and uses of *Amphetamine* are discussed under stimulants of the CNS.

MIXED-ACTING ADRENERGIC AGONISTS

Mixed-action drugs induce the release of *Noradrenaline* from the presynaptic terminals and activate adrenergic receptors on the postsynaptic membrane.

Ephedrine

Ephedrine, a plant alkaloid, is now made synthetically. The drug is mixed-action adrenergic agent. It not only releases stored *Noradrenaline* from the nerve endings but also stimulates both α- and β-receptors. Thus, a wide variety of adrenergic actions ensue that are similar to those of *Adrenaline*, although less potent. *Ephedrine* is not a catechol and is a poor substrate for MAO

and COMT; thus, the drug has a long duration of action. *Ephedrine* has excellent absorption orally and penetrates into the CNS. It is eliminated unchanged in the urine. *Ephedrine* raises systolic and diastolic blood pressures by vasoconstriction and cardiac stimulation. *Ephedrine* produces bronchodilatation, but less potent and more slowly than *Adrenaline* or *Isoproterenol*. It is therefore sometimes used prophylactically in chronic treatment of asthma to prevent attacks, rather than to treat acute attack. *Ephedrine* enhances contractility and improves motor function in myasthenia gravis, particularly when used in conjunction with anti-cholinesterase. *Ephedrine* produces mild stimulation of the CNS. This increases alertness, decreases fatigue, and prevents sleep. It also improves athletic performance. *Ephedrine* has been used to treat asthma, as a nasal decongestant (due to its local vasoconstrictor action), and to raise blood pressure. [Note: The clinical use of *Ephedrine* is declining due to the availability of better, more potent agents which cause fewer adverse effects.]

Available forms:

Adrenaline hydrochloride — in bottles 0.1% solution 10 ml each; in ampoules 0.1% solution 1 ml each

Ephedrine — in tablets 0.025 (for adults) and 0.001; 0.002 and 0.003 each; in ampoules 5% solution 1 ml each; in bottles 2% and 3% solution 10 ml each

Isoproterenol (Isadrinum) — in tablets 0.005 each; in bottles 0.5% and 1% solution 25 ml and 100 ml (for inhalation)

Naphthyzinum — in bottles 0.05% and 0.1% solution 10 ml each

Phenylephrine (Mesatonum) — in ampoules 1% solution 1 ml each

Terbutaline (Bricanyl) — in aerosol; in tablets 0.0025 each; in ampoules 0.05% solution 1 ml each

Lecture 6
ADRENERGIC ANTAGONISTS

The adrenergic antagonists (also called blockers) bind to adrenoreceptors but do not trigger the usual receptor-mediated intracellular effect. These drugs act by either reversibly or irreversibly attaching to the receptors, thus preventing its activation by endogenous catecholamines. Like the agonists, the adrenergic antagonists are classified according to their relative affinity for α- or β-receptors in the peripheral nervous system. [Note: Antagonists that block dopamine receptors are most important in the CNS and will be considered in that section.]

α-ADRENERGIC BLOCKING AGENTS

Drugs that block α-adrenoreceptors profoundly affect blood pressure. Since normal sympathetic control of the vasculature occurs in large part through agonist action on α-receptors, blockade of these receptors reduces the sympathetic tone of the blood vessels, resulting in decreased peripheral vascular resistance. This induces a reflex tachycardia resulting from the lowered blood pressure. [Note: β-receptors, including β_1-adrenoreceptors on the heart, are not affected by α-blockade].

Phentolamine

Phentolamine produces a competitive block of α_1- and α_2-receptors. The drug's action lasts for approximately 4 hours after a single administration.

Cardiovascular effects: By blocking α-receptors, *Phentolamine* prevents vasoconstriction of peripheral blood vessels by endogenous catecholamines. The decreased peripheral resistance provokes a reflex tachycardia. Furthermore, the ability to block presynaptic α_2 receptors in the heart can contribute to an increased cardiac output.

Adrenaline reversal: All α-adrenergic blockers reverse the α-agonist actions of *Adrenaline*. For example, the vasoconstrictive action of *Adrenaline* is interrupted, but vasodilatation of other vascular beds caused by stimulation of β-receptors is not blocked. Therefore, the systemic blood pressure decreases in response to *Adrenaline* given in the presence of *Phentolamine*. [Note: The action of *Noradrenaline* is not reversed but diminished, since *Noradrenaline* lacks significant β-agonist action on the vasculature.] *Phentolamine* has no effect on the actions of *Isoproterenol*, which is a pure β-agonist.

Therapeutic uses: *Phentolamine* is used in the diagnosis and treatment of pheochromocytoma, a catecholamine-secreting tumor of cells derived from the adrenal medulla. Prior to surgical removal of the tumor, patients are treated with *Phentolamine* to preclude hypertensive crisis that can result from manipulation on the tissue. This drug also finds use in the chronic management of these tumors, particularly when the Catecholamine cells are diffuse and therefore inoperable. *Phentolamine* is sometimes effective in treating Raynaud's disease.

Adverse effects: *Phentolamine*-induces reflex cardiac stimulation and tachycardia are mediated by the baroreceptor reflex and by blocking the α_2- receptors of the cardiac sympathetic nerves. The drug can also trigger arrhythmias and anginal pain and is contraindicated in patients with decreased coronary perfusion. It can inhibit ejaculation.

Prazosin, Terazosin and Doxazosin

Prazosin, Terazosin and *Doxazosin* are selective competitive blockers of α_1-receptor. In contrast to Phentolamine, these drugs are useful in the treatment of hypertension. Metabolism leads to inactive products that are excreted in the urine, except for those of *Doxazosin* which appear in the feces. *Doxazosin* is longest acting.

Cardiovascular effects: *Prazosin* and *Terazosin* decrease peripheral vascular resistance and lower arterial blood pressure by causing the relaxation of both arterial and venous smooth muscle. These drugs, unlike *Phentolamine*, cause minimal changes in cardiac output, renal blood flow, and glomerular filtration rate.

Therapeutic uses: Individuals with elevated blood pressure who have been treated with *Prazosin* or *Terazosin* do not become tolerant to its action. However, the first dose of these drugs produces an exaggerated hypotensive response that can result in syncope (faint-

ing). This action, termed as a "first-dose" effect, may be minimized by adjusting the first dose to one third or one fourth of the normal dose, and by giving the drug at bed time. The α_1-antagonists have been used as an alternative to surgery in patients with symptomatic benign prostatic hypertrophy. Blockade of the α-receptors decreases tone in the smooth muscle of the bladder neck and prostate and improves the urine flow. [Note: *Fenestrate*, which inhibits dihydrotestosterone synthesis, has been approved for treatment of benign prostatic hypertrophy, but its effects are not evident for several weeks.]

Adverse effects: Prazosin and terazosin may cause dizziness, lack of energy, nasal congestion, headache, drowsiness, and orthostatic hypotension (although to a lesser degree than that observed with phentolamine). An additive antihypertensive effect occurs when *Prazosin* is given with either a diuretic or a β-blocker, thereby necessitating a reduction in its dose. Due to a tendency to retain sodium and fluid, *Prazosin* is frequently used along with a diuretic. Male sexual function is not as severely affected by these drugs as it is by *Phentolamine.*

β-ADRENERGIC BLOCKING AGENTS

All the clinically available β-blockers are competitive antagonists. Nonselective β-blockers act at both β_1- and β_2-receptors, whereas cardioselective β-antagonists primarily block β_1-receptors. These drugs also differ in intrinsic sympathomimetic activity, in CNS effects, and in pharmacokinetics. Although all β-blockers lower blood pressure in hypertension, they do not induce postural hypotension because the α-adrenoreceptors remain functional; therefore, normal sympathetic control of the vasculature is maintained. β-blockers are also effective in treating angina, cardiac arrhythmias, myocardial infarction, and glaucoma, as well as serving in prophylaxis of migraine headaches. [The names of all β-blockers end in ***"-olol"***, except for *Labetalol*, which has a component of α_1-blocking action.]

Propranolol

Propranolol is a prototype β-adrenergic antagonist and blocks both β_1- and β_2-receptors.

Actions:

Cardiovascular: *Propranolol* diminishes cardiac output, having both negative inotropic and chronotropic effects. It directly depresses sino-auricular and atrioventricular activity. Cardiac output, work, and oxygen consumption are decreased; these effects are useful in the treatment of angina. The β-blockers are effective in attenuating supraventricular cardiac arrhythmias but are generally not effective against ventricular arrhythmias (except those induced by exercise).

Peripheral vasoconstriction: Blockade of β-receptors prevents β_2-mediated vasodilatation. The reduction in cardiac output leads to decreased blood pressure. This hypotension triggers a reflex peripheral vasoconstriction, which is reflected in reduced blood flow to the periphery. On balance, there is a gradual of both systolic and diastolic blood pressures in hypertensive patients. No postural hypotension occurs, since the α_1-receptors that control vascular resistance are unaffected.

Bronchoconstriction: Blocking β_2-receptors in the lungs of susceptible patients causes contraction of the bronchiolar smooth muscle. This can precipitate a respiratory crisis in patients with chronic obstructive pulmonary disease or asthma. β-blockers are thus contraindicated in patients with asthma.

Increased Na^+ retention: Reduced blood pressure causes decease in renal perfusion, resulting in an increase in Na^+ retention and plasma volume. In some cases this compensatory response tends to elevate the blood pressure. For these patients, β-blockers are often combined with a diuretic to prevent Na^+ retention.

Disturbances in glucose metabolism: β-blockade leads to decreased glyco-genolysis and decreased glucagon secretion. Therefore, if an insulin-dependent diabetic is to be given *Propranolol*, very careful monitoring of blood glucose is essential, since pronounced hypoglycemia may occur after *Insulin* injection. β-blockers also attenuate the normal physiologic response to hypoglycemia.

Blocks action of *Isoproterenol*: All β-blockers, including *Propranolol*, have the ability to block the actions of *Isoproterenol* on the cardiovascular system. Thus, in the presence of β-blocker, *Isoproterenol* does not produce either the typical reductions in mean arterial pressure and diastolic pressure, nor cardiac stimulation. [In the presence of β-blocker, *Adrenaline* no longer lowers diastolic blood pressure nor stimulates the heart, but its vasoconstrictive action (mediated by α-receptors) remains unimpaired. The actions of *Noradrenaline* on the cardiovascular system are primarily mediated by α-receptors and are, therefore, unaffected.]

Therapeutic uses:

Hypertension: *Propranolol* lowers blood pressure in hypertension by decreasing cardiac output.

Glaucoma: *Propranolol* and other β-blockers, particularly *Timolol*, are effective in diminishing intraocular pressure in glaucoma. This occurs by decreasing the secretion of aqueous humor by the ciliary body. Many patients with glaucoma have been maintained with these drugs for years. They neither affect the ability of the eye to focus for near vision, nor change pupil size, as do the cholinergic drugs. However, in an acute attack of glaucoma, *Pilocarpine* is still the drug of choice. The β-blockers are only used to treat this disease chronically.

Migraine: *Propranolol* is also effective in reducing migraine episodes. The value of the β-blockers is in the treatment of chronic migraine in which the drug decreases the incidence and severity of the attacks. The mechanism may depend on the blockade of catecholamine-induced vasodilation in the brain vasculature. [Note: During an attack, the usual therapy with *Sumatriptan* or other drugs is used.]

Hyperthyroidism: *Propranolol* and other β-blockers are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism. In acute hyperthyroidism (thyroid storm), β-blockers may be lifesaving in protecting against serious cardiac arrhythmias.

Angina pectoris: *Propranolol* decreases the oxygen requirement of heart muscle and therefore is effective in reducing the chest pain on exertion that is common in angina. *Propranolol* is therefore useful in the chronic management of stable angina (not for acute treat-

ment). Tolerance to moderate exercise is increased and this is noticeable by improvement in the ECG. However, treatment with *Propranolol* does not allow strenuous physical exercise, such as tennis.

Myocardial infarction: *Propranolol* and other β-blockers have a protective effect on the myocardium. Thus, patients who have had one myocardial infarction appear to be protected against a second heart attack by prophylactic use of β-blockers. In addition, administration of a β-blocker immediately following a myocardial infarction reduces infarct size and hastens recovery. The mechanisms for these effects may be blocking of the actions of circulating catecholamines, which would increase the oxygen demand in an already ischemic heart muscle. *Propranolol* also reduces the incidence of sudden arrhythmic death after myocardial infarction.

Adverse effects:

Bronchoconstriction: *Propranolol* has a serious and potentially lethal side effect when administered to an asthmatic. An immediate contraction of the bronchiolar smooth muscle prevents air from entering the lungs. Death by asphyxiation have been reported for asthmatics who were inadvertently administered the drug. Therefore, *Propranolol* must never be used in treating any individual with obstructive pulmonary disease.

Arrhythmias: Treatment with β-blockers must never be stopped quickly because of the risk of precipitating cardiac arrhythmias, which may be severe. The β-blockers must be tapered off gradually for a week. Long-term treatment with a β-antagonist leads to up-regulation of the β-receptor. On suspension of therapy, the increased receptors can worsen angina or hypertension.

Sexual impairment: Since sexual function in the male occurs through α-adrenergic activation, β-blockers do not affect normal ejaculation nor the internal bladder sphincter function. On the other hand, some men do complain of impaired sexual activity. The reasons for this are not clear and may be independent of β-receptor blockade.

Disturbances in metabolism: β-Blockade leads to decreased glycogenolysis and decreased glucagon secretion. Fasting hypoglycemia may occur. [Note: Cardioselective β-blockers are preferred in treating *Insulin*-dependent asthmatics.]

Drug interactions: Drugs that interfere with the metabolism of *Propranolol*, such as *Cimetidine, Furosemide*, and Chlorpromazine, may potentiate its anti-hypotensive effects. Conversely, those that stimulate its metabolism, such as barbiturates, *Phenytoin* and *Rifampin*, can mitigate its effects.

Timolol and Nadolol: Nonselective β-Antagonists

Timolol and *Nadolol* also block β_1- and β_2-receptors and are more potent than *Propranolol. Nadolol* has a very long duration of action. *Timolol* reduces the production of aqueous humor in the eye and is used topically in the treatment of chronic open-angle glaucoma, and occasionally for systemic treatment of hypertension (Table 4).

Atenolol, Metoprolol, Acebutolol and Esmolol

Drugs preferentially block the β_1-receptors have been developed to eliminate the unwanted bronchoconstrictor effect (β_2) of *Propranolol* seen among asthmatic patients. Cardioselective β-blockers antagonize β_1-receptors at doses 50 to 100 times less than those required to block β_2-receptors. This cardioselectivity is thus most pronounced at low doses and is lost in high drug doses. In contrast to *Propranolol*, the cardiospecific blockers have relatively little effect on pulmonary function, peripheral resistance, and carbohydrate metabolism. Nevertheless, asthmatics must be carefully monitored to make certain that respiratory activity is not compromised. *Esmolol* has a very short lifetime. It is only given i.v. if required during surgery.

Pindolol and Acebutolol: Antagonists with Partial Agonist Activity

Acebutolol and *Pindolol* are not pure blockers; instead they have the ability to weakly stimulate both β_1- and β_2-receptors and are said to have intrinsic sympathomimetic activity (ISA). These partial agonists stimulate the β-receptor to which they are bound, yet they inhibit stimulation by the more potent endogenous catecholamines, *Adrenaline* and *Noradrenaline*. The result of these opposing actions is a much diminished effect on cardiac rate and cardiac output, compared to β-blockers without ISA. Blockers with ISA minimize the disturbances of lipid and carbohydrate metabolism seen with other β-blockers.

β-Blockers with ISA are used in hypertensive patients with moderate bradycardia, since a further decrease in heart rate is less pronounced with these drugs. Carbohydrate metabolism is less affected with *Acebutolol* and *Pindolol*, making them valuable in the treatment of diabetics.

Labetalol: an α- and β-Blocker

Actions: *Labetalol* is a β-blocker with concurrent α_1-blocking actions that produce peripheral vasodilation, thereby reducing blood pressure. *Labetalol* thus contrasts with the other β-blockers that produce peripheral vasoconstriction. *Labetalol* does not alter serum lipid or blood glucose levels.

Table 4. **Uses of β-adrenoblockers**

Propranolol	β_1, β_2	Hypertension Glaucoma Migraine Hyperthyroidism Angina pectoris Myocardial infarction
Timolol	β_1, β_2	Glaucoma Hypertension
Atenolol Metoprolol Acebutolol	β_1	Hypertension
Pindolol	β_1, β_2	Hypertension
Labetalol	α_1, β_1, β_2	Hypertension

Therapeutic uses in hypertension: *Labetalol* is useful for treating the elderly or black patients in whom increased peripheral resistance is undesirable. [Note: In general black hypertensive patients are not well controlled with β-blockers.] *Labetalol* may be employed as an alternative to *Hydralazine* in the treatment of pregnancy-induced hypertension (PIH).

SYMPATHOLYTICS

Sympatholytic drugs do not act directly on the adrenoreceptors. Instead, they exert their effects by either interfere in neurotransmitter release or alter the uptake of the neurotransmitter into the adrenergic nerve.

Reserpine

Reserpine, a plant alkaloid, blocks the transport of biogenic amines *Noradrenaline, Dopamine*, and *Serotonin* from the cytoplasm into storage vesicles in the adrenergic nerves of all body tissues. This cause an ultimate depletion of *Noradrenaline* levels in the adrenergic neuron, since monoamine oxidase (MAO) degrade the *Noradrenaline* in cytoplasm. Sympathetic function, in general, is impaired because of decreased release of *Noradrenaline*. Hypertensive patients taking the drug show a gradual decline in blood pressure with a concomitant slowing in the cardiac rate. The drug has a slow onset of action. When one stops taking the drug, the action persists for many days.

Guanethidine (Octadinum)

Guanethidine acts by blocking the release of stored *Noradrenaline*. *Guanethidine* also displaces *Noradrenaline* from storage vesicles. This leads to depletion of the neurotransmitter in nerve endings except those in the CNS. *Guanethidine* is now rarely used in the treatment of hypertension.

Available forms:
Atenolol — in tablets 0.1 each
Guanethidine (Octadinum) — in tablets 0.025 each
Phentolamine — in tablets 0.025 each
Pindolol — in tablets 0.005; 0.01 and 0.015 each; in ampoules 0.004% solution 2 ml each
Prazosin — in tablets 0.001 and 0.005 each
Propranolol (Anaprilinum) — in tablets 0.01 and 0.04 each

EXAMINATION QUESTIONS

1. Selective β_2-agonists, such as terbutaline
   (A). Have shorter durations of action than catecholamines when taken orally.
   (B). Have stronger cardiac stimulant effects than *Epinephrine*.
   (C). Can be taken orally because these agents are not degraded by COMT.
   (D). Are definitely no better than methylxanthines for asthmatic patients who are hypertensive.

2. Which drug does not induce mydriasis?
   (A). *Phenylephrine*.
   (B). *Cocaine*.
   (C). *Phentolamine*.
   (D). *Norepinephrine*.
   (E). *Ephedrine*.

3. Epinephrine given in small therapeutic doses
   (A). Increases systolic blood pressure through β_2-receptor stimulation in the left ventricle.
   (B). Decreases heart rate reflexively.
   (C). Decreases peripheral resistance through stimulation of β_2-receptors on the vascular smooth muscle cells.
   (D). Decreases peripheral resistance through β_2-adrenoceptor stimulation predominantly in skeletal muscle vascular beds.

4. The pressor response to amphetamine is
   (A). Decreased in the presence of a monoamine oxidase (MAO) inhibitor.
   (B). Potentiated by a reuptake inhibitor, such as cocaine.
   (C). Associated with marked tolerance (tachyphylaxis).
   (D). Potentiated by pretreatment with *Reserpine*.

5. Which of the following actions of epinephrine would be antagonized by prazosin but not by propranolol?
   (A). Increase in heart rate.
   (B). Mydriasis.
   (C). Release of renin.
   (D). Bronchiolar dilation.
   (E). Glycogenolysis.

6. Which of the following adrenoceptor antagonists will reduce responses mediated by both α- and β-receptors?
   (A). *Propranolol*.
   (B). *Prazosin.*
   (C). *Phenoxybenzamine.*
   (D). *Labetalol*.
   (E). *Metoprolol.*

7. A young patient is being treated for myasthenia gravis, which requires frequent adjustment of the optimal dose of neostigmine. The patient is challenged with edrophonium to evaluate the effectiveness of the cholinesterase inhibition. Optimal dosing will be indicated by
   (A). An increase in muscle strength.
   (B). A decrease in muscle strength.
   (C). No change in muscle strength.

8. A young man broke his leg in a skiing accident, causing severe muscular spasm that necessitated relaxation of the muscle with a competitive nicotinic receptor antagonist before the fracture could be set. At the end of the orthopaedic procedure, the doctor restored neuromuscular transmission by administering:
   (A). *Succinylcholine.*
   (B). *Carbachol*.
   (C). *Physostigmine.*
   (D). *Neostigmine*.

9. A patient has developed glaucoma that is refractory to noncholinergic therapies. You decide to prescribe eyedrops containing *Pilocarpine*, but you are concerned about the patient's ability to self-administer the drops. The most sensitive indicator of excessive administration of pilocarpine is

(A). An increased heart rate.
(B). A decreased heart rate.
(C). Mental confusion.
(D). Constriction of the pupil.

10. An 80-year-old man is increasingly forgetful, and his wife is afraid he is developing Alzheimer's disease. You are considering prescribing an anti-AChE drug to see if this will decrease his forgetfulness. Before making this prescription, you want to be sure that these drugs are suitable given the patient's medical history. Of the possible preexisting conditions listed below, you should be least concerned about

(A). Asthma.
(B). Weak atrioventricular conduction.
(C). Glaucoma.
(D). Obstruction of the GI tract.

11. The choice of route of administration plays an important role in the actions of directly acting cholinomimetics. An adverse effect of choline esters that may be avoided by selection of an appropriate route of administration is

(A). Bradycardia.
(B). Hypotension.
(C). Delirium.
(D). Sweating.

12. Which of the responses to atropine listed below is most likely to be different in an elderly versus a young patient?

(A). Inhibition of sweating.
(B). Tachycardia.
(C). Mydriasis.
(D). Drowsiness.

13. You have successfully prescribed *Neostigmine* to a young patient with myasthenia gravis, and her muscle strength has improved markedly. However, she also exhibits cardiovascular and gastrointestinal signs of excessive vagal tone, which you would like to block with atropine. Which of the following risk factors in prescribing *Atropine* is most important to you?

(A). Dry mouth.
(B). Ocular disturbances.
(C). Paralysis of the respiratory muscles.
(D). Tachycardia.

14. Antimuscarinic mydriatics, such as tropicamide, are useful in ophthalmological examinations. Prior to administering tropicamide, it would be most important to know

(A). If the patient has angle-closure glaucoma.
(B). If the patient has open-angle glaucoma.
(C). If the patient is taking a cholinomimetic miotic drug.

15. In which of the following conditions would atropine be the least likely to increase blood pressure?

(A). A healthy young medical student.
(B). A patient being treated with an AChE inhibitor.
(C). A patient being treated with *Bethanechol*.

16. A patient has come to you complaining of feeling drowsy and finding it hard to concentrate. The patient tells you that he is taking a medication, but he cannot remember the name of the medication. You proceed to ask questions that might provide a clue to the source of his problems. Which of the following questions would be *least* likely to be helpful?

(A). Has the patient had problems with hay fever and stuffiness?
(B). Is the patient being treated for glaucoma?
(C). Has the patient had back spasms?
(D). Is the patient being treated for mood disorders?

17. During a laboratory demonstration to depict the complexity of neurotransmission in autonomic ganglia, Professor Smith sets up an anesthetized mammalian preparation in which she is recording postsynaptic events following the electrical stimulation of preganglionic sympathetic nerves. This demonstrates a complex action potential that consists of a fast EPSP followed by a slow IPSP followed by a slow EPSP and finally by a late very slow EPSP. L In Professor Smith's demonstration, the mediator of the fast EPSP is

(A). Dopamine.
(B). Neuropeptide Y.
(C). Serotonin.
(D). Angiotensin.
(E). Acetylcholine.

18. In Professor Smith's demonstration, the slow EPSP and slow IPSP can both be blocked by prior administration of

(A). *Prazosin.*
(B). *Sumatriptan*.
(C). *Atropine*.
(D). *Losartan.*
(E). *Chlorpromazine*.

19. In Professor Smith's demonstration, the receptor most likely mediating the slow EPSP is

(A). Nicotinic cholinergic.
(B). Muscarinic cholinergic.
(C). α-Adrenergic.
(D). P_{2X} Purinergic.
(E). β-Adrenergic.

20. A patient you are treating in the hospital has a hypertensive emergency, with blood pressure of 210/140 mm Hg. Of the following drugs, which would be most effective intravenously?

(A). *Hydralazine*.
(B). *Hydrochlorothiazide.*
(C). *Trimethaphan*.
(D). *Methyldopa.*
(E). *Spironolactone.*

21. Ganglionic blocking agents are rarely used because of the numerous side effects they may produce. One such side effect is

(A). Increased stimulation of the genital tract.
(B). Urinary hesitation or urgency.
(C). Vasoconstriction.
(D). Increased cardiac output.
(E). Mydriasis.

ANSWERS

1. **(C)**. Structural modification by placing the hydroxy groups at positions 3 and 5 of the phenyl ring has resulted in compounds that are not substrates for COMT, resulting in lower rates of metabolism and enhanced oral bioavailability compared to catecholamines.

2. **(C)**. α-Adrenoceptors mediate contraction of the radial muscle of the iris. The shortening of the radial muscle cells opens the pupil. *Phentolamine* blocks α-adrenoceptors, allowing parasympathetic nerves innervating the sphincter muscle to take over. This leads to a less opposed contraction of the sphincter muscle induced by transmitter acetylcholine and a constriction of the pupil or miosis.

3. **(D)**. A small dose of *Epinephrine* (0.1 mcg/kg) given by intravenous route may cause the blood pressure to fall, decreasing peripheral resistance. The depressor effect of small doses is due to greater sensitivity to epinephrine of vasodilator β_2-adrenoceptors than of constrictor α-adrenoceptors and a dominant action on β_2-adrenoceptors of vessels in skeletal muscle. Consequently, diastolic blood pressure usually falls. The mean blood pressure in general, however, is not greatly elevated. The compensatory baroreceptor reflexes do not appreciably antagonize the direct cardiac actions.

4. **(C)**. *Amphetamine* is an indirectly acting adrenomimetic amine that depends on the release of norepinephrine from noradrenergic nerves for its action. Thus, its effect depends on neuronal uptake (blocked by cocaine) to displace norepinephrine from the vesicles and the availability of norepinephrine (depleted by reserpine). The substitution on the α-carbon atom blocks oxidation by monoamine oxidase. With no substitution on its benzene ring, amphetamine resists metabolism by COMT.

5. **(B)**. The adrenoceptors that epinephrine acts on to affect heart rate, renin release, bronchiolar tone, and glycogenolysis are β-receptors. *Prazosin* is an β-antagonist so would not antagonize epinephrine at those receptors. The radial smooth muscle in the iris has α-receptors that when activated, contract the radial muscle which dilates the pupil. This action is antagonized by prazosin.

6. **(D)**. Propranolol and metoprolol are selective for β-receptors, whereas *Prazosin* and *Phenoxybenzamine* are selective for α-receptors. Labetalol is the only antagonist in this list that has the ability to reduce responses mediated by both α- and β-receptors.

7. **(C)**. At an optimal dose of neostigmine, there should be no change in muscle strength with administration of *Edrophonium*. If *Edrophonium* increases muscle strength, the inhibition of AChE is insufficient and the maximum therapeutic benefit is not being achieved. If edrophonium decreases muscle strength, the dose of neostigmine is too high, bordering on the production of a depolarizing block of neuromuscular transmission.

8. **(D)**. *Neostigmine* will inhibit AChE and increase the ACh available to compete with the antagonist at the neuromuscular junction, overcoming the block of neurotransmission. Succinylcholine, a nicotinic agonist, will only very transiently increase the strength of the muscle, after which it will produce a depolarizing block. Carbachol is a nonselective cholinoreceptor agonist that will stimulate nicotinic and muscarinic receptors without therapeutic benefit. Physostigmine will increase the strength of the muscle by the same mechanism as *Neostigmine*, but it will also enter the CNS, producing undesirable side effects.

9. **(A)**. Excessive administration of pilocarpine can cause it to enter the circulatory system, activate endothelial muscarinic receptors, and produce a fall in blood pressure. This will activate sympathetic reflexes that increase the heart rate. Higher levels of pilocarpine would be required to stimulate muscarinic receptors on the heart that can decrease the heart rate. Although pilocarpine can enter the CNS and produce confusion in older patients, this also requires higher doses. Pilocarpine will constrict the pupil at therapeutically appropriate doses.

10. **(C)**. Glaucoma as a preexisting condition does not contraindicate an AChE inhibitor. The other preexisting conditions preclude the administration of AChE inhibitors. Potentiation of parasympathetic stimulation can constrict airway smooth muscle and aggravate asthma, further weaken A-V conduction, and risk perforation of the bowel if an obstruction is present.

11. **(B)**. Hypotension, which can be life threatening, can be avoided by preventing the entry of directly acting cholinomimetics into the circulatory system. Bradycardia and sweating are also avoided by the same precaution, but they are less significant. Delirium is not an issue for choline esters, since they do not enter the CNS.

12. **(B)**. The resting level of vagal stimulation of the heart decreases with age, which is typically accompanied by a gradual increase in heart rate with age. Therefore, the tachycardia produced by atropine is greater in young patients with strong vagal tone, and the response decreases with age in parallel with the decrease in vagal tone.

13. **(C)**. *Atropine* will not directly paralyze the respiratory muscles. However, it can prevent the detection of early signs of an overdose of neostigmine, which can quickly progress to a depolarizing block of skeletal muscle and paralysis of the respiratory muscles. Dry mouth, ocular disturbances, and tachycardia are common side effects of atropine given alone, but these effects are less likely to occur with competition between atropine and the increase in the synaptic ACh produced by inhibition of AChE by neostigmine.

14. **(A)**. Application of tropicamide to the eye of a patient with narrow-angle (angle-closure) glaucoma is a very serious risk, because the peripheral movement of the relaxed iris can block the outflow of fluid and trigger a rapid rise in intraocular pressure. Open-angle glaucoma does not present the same risk for the application of a short-acting mydriatic such as *Tropicamide*. If the patient is taking a cholinomimetic miotic for open-angle glaucoma, there is even less risk of applying tropicamide, although potential competition between the miotic and the antagonist may have to be considered.

15. **(A)**. *Atropine* has little effect on blood pressure in the absence of a circulating muscarinic agonist because the muscarinic receptors on endothelial cells do not receive synaptic input. Therefore, the blood pressure of a healthy patient will not change with treatment with atropine. In contrast, patients being treated with an AChE inhibitor may have slightly elevated plasma ACh levels, and patients being treated with bethanechol may be hypotensive because of its direct actions on the muscarinic receptors on endothelial cells.

16. **(B)**. The symptoms are suggestive of central antimuscarinic effects of a drug. Glaucoma is treated with muscarinic agonists or noncholinergic drugs. Although

the entry of pilocarpine into the CNS can disturb CNS function, it is not as likely as an antimuscarinic drug to produce drowsiness and loss of concentration. The other questions would all be useful. A patient who has hay fever or stuffiness may be taking an antihistamine. A patient with back spasms may be taking a muscle relaxant, such as cyclobenzaprine. One who is being treated for mood disorders may be taking antipsychotic medication. All of these treatments can produce significant central antimuscarinic side effects.

17. **(E)**. The principal neurotransmitter released from preganglionic nerve terminals in all autonomic ganglia is acetylcholine. It acts on the postganglionic cell body to activate a nicotinic-cholinergic receptor resulting in a fast EPSP. *Dopamine* or *Norepinephrine* or both are the mediators released from SIF cells or interneurons. Neuropeptide Y is a peptide neurotransmitter. Angiotensin and serotonin are modulatory mediators. These last three contribute to the late very slow EPSP.

18. **(C)**. The slow EPSP results from activation of muscarinic-cholinergic receptors on SIF cells or interneurons, which release norepinephrine or dopamine from their terminals. These catecholamines then cause a slow IPSP in the ganglionic cell body. Therefore, both the slow EPSP and subsequent slow IPSP would be prevented by the muscarinic antagonist atropine. *Prazosin* is an ar adrenergic antagonist; *Sumatriptan* is a serotonin $5HT_{1D}$ agonist; losartan is an angiotensin receptor antagonist; and *Chlorpromazine* is a *Dopamine* antagonist. Only atropine would block both the slow EPSP and the slow IPSP.

19. **(B)**. The receptor contributing to the slow EPSP is a muscarinic-cholinergic receptor and is activated by ACh. The nicotinic-cholinergic receptor mediates the fast EPSP, an α-receptor may mediate the slow IPSP, and a P_{2X} receptor and a β-adrenergic receptor do not appear to be involved in the complex action potentials seen at autonomic ganglia.

20. **(C)**. *Trimethaphan* is a ganglionic blocking agent that will lower blood pressure very rapidly. Hydralazine is a vasodilator; hydrochlorothiazide and spironolactone are diuretics; and methyldopa is a sympatholytic acting in the central nervous system. All of these drugs are used clinically as antihypertensive agents. None works as rapidly as *Trimethaphan*. Clinically, however, either nitroprusside or clonidine is used much more commonly than trimethaphan in this situation.

21. **(E)**. The effect of ganglionic blockade depends upon the predominant autonomic tone exerted within various organ systems. Since the activity of the parasympathetic nervous system predominates in the eye, the effect of ganglionic blockade is mydriasis, not miosis. Similarly, stimulation of the genital tract and urinary retention would be decreased. Since sympathetic nervous system activity predominates in blood vessels and the ventricles, vasodilation and a decreased cardiac output would follow ganglionic blockade.

DRUGS AFFECTING AFFERENT INNERVATION

Lecture 7
DRUGS THAT IRRITATE RECEPTORS

Irritants stimulate sensory nerve endings at the site of application and induce local and reflex responses. Depending on their nature, concentration and sensitiveness of the site, they produce cooling sensation or warmth, pricking and tingling, hyperaesthesia or numbness and local hyperemia. Local vasodilation improves blood circulation and tissue nutrition.

Certain irritants also produce a remote effect which tends to relief pain and inflammation in deeper organs — called *counter-irritants*. Cutaneous sensations are precisely localized. Deeper sensations from muscles, joints and viscera are perceived more diffusely. A spinal segment receives afferent impulses from the surface as well as from deeper organs. According to a spinal segment, a determined region of the skin corresponds a determined internal organ (called Zakharin-Ged's zones). Irritation of afferent nerve endings from the surface modulates pain impulses coming from deeper organs. This, through segmental association of afferents, results in decrease of pain afferentation, vasodilation in the corresponding deeper organ. Increased blood supply helps to fight the cause of pain and inflammation in the deeper organ.

Counter-irritants are generally massaged to relieve headache, muscular pain, joint pain, colica etc. **The drugs are**:

— Volatile oils: Turpentine oil, Eucalyptus oil
— Stearoptenes: Camphor, Thymol, Menthol
— Mustard seeds
— Capsicum
— Ammonia etc.

Volatile oils (essential oils) are terpene hydrocarbons of plant origin having a characteristic odor. They have variable properties, but all are irritants. Stearoptenes are solid volatile oils.

Turpentine oil obtained by distilling Pinus oleoresin; used as counterirritant in the form of liniment.

Eucalyptus oil used in pain balms.

Camphor obtained from bark of *Cinnamomum camphora* or produced synthetically. Produces cooling sensation on the skin and is mildly anesthetic relieves itching. It is added in liniments and pain balms. Taken internally small doses produce a warm and comforting sensation in epigastria; large doses are emetic. Systemically it produces excitement and convulsions (specially in children). *Menthol* from mint or prepared synthetically, has cooling and soothing action. It is added to pain balms, throat paints and inhalers for relief of nasal congestion. *Menthol* is included in *Validol* — tablets used sublingually in angina pectoris.

Mustard seeds contain a glycoside *Sinirgin* and enzyme *Myrosin*. When ground seeds are soaked in water, *Myrosin* hydrolyses *Sinirgin* to release *Allyl isothiocyanate* which is strong irritant. Mustard plasters has been used as counter-irritant. As a suspension in water 4–8 g, it is emetic.

CAUSTICS AND ESCHAROTICS

Caustic means corrosive and *escharotic* means cauterize. These chemicals cause local tissue destruction and sloughing. An escharotic, in addition, precipitates proteins that exude to form a scarb. They are used to remove moles, warts, condylomata, papillomas and on keratotic lesions. Care is needed in their application to avoid ulceration. It is believed that all microorganisms are killed during cauterization, but it is not always so.

Podophyllum resin as 10–25% alcoholic solution or suspension in mineral water;

Silver nitrate as toughened silver nitrate sticks or pencils;

Phenol as 80% solution;

Trichloracetic acid as crystals or 10–20% solution.

KERATOLYTICS

Keratolytics dissolve the intracellular substance in the horny layer of the skin. The epidermal cells swell, soften and then desquamate. They are used on hyperkeratotic lesions like corns, warts, psoriasis, chronic dermatitis, ring warm, athletes foot.

Salicylic acid as 10–20% solution in alcohol or propylene glycol for dissolving corns;

Benzoic acid is antifungal with mild keratolytic action.

Bitters, emetic drugs, purgatives, and bile-drive drugs are described in lecture "Drugs used in gastrointestinal diseases".

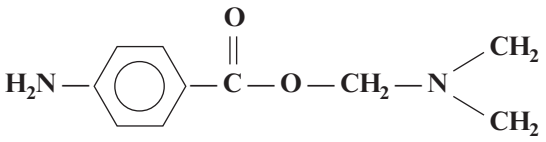
Available forms:

Menthol — in bottles 1% and 2% spirit solution 10 ml each

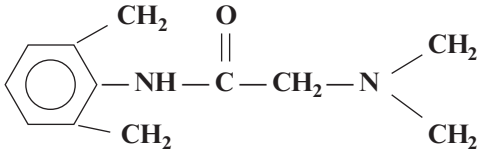
Validolum — in bottles 10 ml each; in capsules 0.05 and 0.1 each

Camphor — ointment (Unguentum Camphoratum) 10% 100.0

Salicylic acid — in bottles 1% and 2% spirit solution



Procaine



Lidocaine

Lecture 8
DRUGS THAT PROTECT RECEPTORS

LOCAL ANESTHETICS

Local anesthetics (LAs) are drugs which upon topical application or local injection cause reversible loss of sensory perception, specially of pain, in a restricted area of the body. They block generation and conduction of nerve impulse at all parts of the neuron where they came in contact, without causing any structural damage. Thus, not only sensory but also motor impulses are interrupted when a LA is applied to a mixed nerve, resulting in muscular paralysis and loss of autonomic control as well.

The first local anesthetic to be discovered was *Cocaine*, an alkaloid contained in the leaves of *Erythroxylon coca*, a shrub growing in the Andes Mountains. The pure alkaloid was first isolated in 1860 by Niemann. A russian scientist Von Anrep in 1880 observed that the skin became insensitive to the prick of a pin when *Cocaine* was infiltrated subcutaneously. He recommended the alkaloid to be used clinically as a local anesthetic. A chemical search for synthetic substitutes for *Cocaine* started in 1892 with the work of Einhorn. This resulted in 1905 in the synthesis of *procaine* which became the prototype for local anesthetic drugs for half a century. The most widely used agents today are *Lidocaine, Bupivacaine,* and *Tetracaine.*

Properties Desirable in LA. A Good LA should combine several properties. It should not be irritating to the tissue to which it is applied, nor should it cause any permanent damage to nerve structure. Its systemic toxicity should be low because it eventually absorbed from its site of application. The ideal LA must be effective regardless of whether it is injected or applied locally to mucous membranes. It is usually important that the time required for the onset of anesthesia should be as short as possible. Furthermore, the action must last long enough.

Chemistry. The clinically useful LAs are weak bases with amphiphilic property. A hydrophilic secondary or tertiary amine on one side and a lipophilic aromatic residue on the other are joined by an alkyl chain through an ester or amide linkage.

The nature of this bond determines certain of the pharmacological properties of these agents. The ester link is important because this bond is readily hydrolyzed during metabolic degradation in the body. According to the chemical structure LAs are classified into:

— **Ester linked LAs** *Procaine, Tetracaine, Anaesthesin* (paraaminobenzoic acid derivatives), and *Cocaine*.

— **Amide linked LAs** *Lidocaine, Trimecaine, Bupivacaine* (xylidine derivatives). They differ from the ester linked LAs in that they are not hydrolyzed by plasma esterases; are generally longer acting and less frequently produce hypersensitivity reactions; no cross sensitivity with ester linked LAs.

Mechanism of action: The LAs block the nerve conduction by decreasing the entry of Na^+ ions during upstroke of action potential. The LAs directly interact with voltage-sensitive Na^+ channels. As the anaesthetic action progressively develops in a nerve, the threshold for electrical excitability gradually increases, the rate of rise of the action potential declines, impulse conduction slows and fails. As a general rule, small nerve fibers seem to be more susceptible to the action of LAs than are large fibers. This may explain why the LAs affect the functions of a nerve in predictable order. Autonomic fibers are generally more susceptible than somatic fibers. Among the somatic afferents order of blockade is: ***pain — temperature sense — touch — deep pressure sense***.

In clinical practice the preparation of LA often contains a vasoconstrictor, usually *Adrenaline* (1: 50,000 to 1: 200,000). The vasoconstrictor decreases the rate of absorption of a LA into the circulation. This performs a dual service: (1) prolongs duration of action of a LA, and (2) reduces systemic toxicity of a LA.

Actions: The danger of such adverse reactions is proportional to the concentration of LA in the circulation.

CNS: Following absorption, LAs may cause stimulation of the CNS, producing restlessness and tremor that may proceed to clonic convulsions followed by depression with respiratory failure.

CVS (usually seen after high systemic concentrations): The primary site of action is the myocardium, where decreases in electrical excitability, conduction rate, and force of contraction occur. In addition, most LAs cause arteriolar dilation. *Lidocaine* has little effect on contractility and atrioventricular conductivi-

ty; it may serve as an antiarrhythmic. *Procaine* is not used as antiarrhythmic, but its amide derivative *Procainamide* is a classical antiarrhythmic.

Pharmacokinetics: Surface anesthetics are rapidly absorbed from mucous membranes, but absorption from intact skin is poor. Procaine does not significantly penetrate mucous membranes. Rate of absorption depends on the blood flow to the area of application or injection. Esters linked LAs *(procaine etc.)* are rapidly hydrolyzed by plasma pseudocholinesterase and the remaining by esterases in the liver. Amide linked LAs *(lidocaine etc.)* are metabolized only in the liver microsomes.

Adverse effects: Systemic toxicity is related to the intrinsic anesthetic potency of the LA. However, toxicity is influenced by relative rates of absorption and metabolism. CNS effects are mental confusion, tremors and finally convulsions and respiratory arrest. CVS toxicity is manifested as bradycardia, hypotension, cardiac arrhythmias and vascular collapse. Hypersensitivity reactions like rashes, dermatitis, asthma, and rarely anaphylaxis occur. These are more common with ester type LAs and cross reactivity is frequent among them, but not with amide linked LAs.

Therapeutic uses: Local anesthesia is the loss of sensation without the loss of consciousness. The choice of a LA and the technique of its use are the determinants of the properties and toxicity of the LA.

Surface anesthesia: It is produced by topical application of surface anaesthetics to mucous membranes (nose, mouth, throat, tracheobronchial tree, esophagus, urogenital tract) and abraded skin. *Tetracaine* (2%), *Lidocaine* (2 to10%), and *Cocaine* (1 to 4%) are most often used. *Procaine* and other more polar LAs are clinically unsatisfactory; they penetrate mucous membranes too poorly. *Cocaine* has the unique advantage of producing vasoconstriction as well as anaesthesia.

Infiltration anaesthesia: Dilute solution of LA is injected under the skin in the area of operation — blocks sensory nerve endings. It is used for minor operations. The LAs most frequently used for infiltration anaesthesia are *Lidocaine* (0.5 to 1.0%), *Procaine* (0.25 to 1.0%), and *Bupivacaine* (0.125 to 0.25%).

Conduction block: The LA is injected around nerve trunks so that area distal to injection is anesthetized and paralyzed. It is frequently used for tooth extraction, operation on eye, limbs, abdominal wall, fracture setting etc.

Spinal anesthesia: The LA is injected into the lumbar subarachnoid space between L_{II-III} or L_{III-IV} below the lower end of spinal cord. The primary site of action is the nerve root in the cauda eqina rather than the spinal cord. Lower abdomen and lower limbs are anesthetized and paralyzed. Spinal anesthesia is used for operations on the lower abdomen, pelvis, lower limbs, prostatectomy, obstetric procedures, caesarian section etc. Its advantage over general anesthesia are — (1) it is safer; (2) produces good analgesia and muscle relaxation without loss of consciousness; (3) cardiac, pulmonary, renal disease and diabetes pose less problem.

Epidural anesthesia: The spinal epidural space is filled with semiliquid fat through which nerve roots travel. The LA injected in this space acts primarily on nerve roots (in the epidural as well as subarachnoid spaces to which it diffuses). It is a popular form of regional anaesthesia.

ASTRINGENTS

Astringents are substances that precipitate proteins, but do not penetrate cells, thus affecting the superficial layer only. They toughen the surface making it mechanically stronger and decrease exudation and inflammation.

These drugs are divided into:

— **Organic:** Tannins, Tanalbine, Decoctions of bark of Oak-Tree, Camomile, etc.

— **Non-organic:** weak solutions of zinc, aluminum, cooper and bismuth salts. They form tough albuminates on the surface, thus serve as protective coat

Astringents are used for the treatment of skin diseases, inflammatory diseases of oral, nasal cavities. *Tannic acid* and *Tannin* are used in alkaloid poisonings — precipitate ingested alkaloids (morphine, atropine, etc.) as tannates.

COATING DEMULCENTS

They are, in general, high molecule weight substances and are applied as thick colloidal solutions in water. They form viscous film over the sooth inflamed mucosa, preventing contact with irritants in the surroundings.

ADSORBENTS

Adsorbents are finely powdered, inert and insoluble solids with great adsorptive surface *(activated charcoal, starch, kaolin)*. They are capable to bind to their surface noxious and irritant substances, preventing mucosa from irritation and absorption from mucous membrane. These agents are used in case of poisoning, inflammatory disease of GIT, meteorism, etc.

EMOLLIENTS

Emollients are brand oily substances which sooth and soften the skin and mucosa. They form an occlusive film over the skin, preventing evaporation, thus restoring elasticity of cracked and dry skin. They are also used as vehicles for topically applied medicaments. They are (1) vegetable oils *(Olive oil, Cocoa butter, Linseed oil)*; (2) animal products *(Wool fat (Lanolin), Spermaceti (from the head of sperm whale), Bees wax)*; (3) petroleum products (*Soft and hard paraffin, Liquid paraffin*). Cocoa butter, wool fat and paraffin are commonly employed as ointment bases. Bees wax and spermaceti are used to harden ointment bases. Wool fat may cause allergy in some patients.

ANTACIDS

Antacids are described in lecture "Drugs used in gastrointestinal diseases".

Available forms:

Tetracaine — in bottles 0.5% and 1% solution 10 ml each

Novocain (Procaine) — in ampoules 0.25%; 0.5%; 1% and 2% solution 1; 2; 5 and 10 ml each

Anaesthesinum — in tablets 0.3 each; 5% ointment

Lidocaine hydrochloride (Propoxycaine) — in ampoules 1% solution 10 ml each; in ampoules 2% solution 2 and 10 ml each

EXAMINATION QUESTIONS

1. With the movement of which ion as a fundamental basis for their action do the local anesthetics interfere?
   (A). Calcium.
   (B). Sodium.
   (C). Potassium.
   (D). Hydrogen.
   (E). Oxygen.

2. Sympathetic block is one use of local anaesthetics. What is the best location to apply the local anesthetic?
   (A). Nerve cell ending.
   (B). Neuromuscular junction.
   (C). Sympathetic ganglia.
   (D). Spinal cord.

3. Frequently vasoconstrictors are combined with local anesthetics to delay absorption of the anesthetic from its injection site. What is the most widely employed agent?
   (A). *Dopamine*.
   (B). *Phenylephrine*.
   (C). *Levonordefrin*.
   (D). *Epinephrine*.
   (E). *Cocaine*.

4. What is the most commonly used local anesthetic?
   (A). *Bupivacaine*.
   (B). *Procaine*.
   (C). *Lidocaine*.
   (D). *Etidocaine*.

5. A 25-year-old woman visits your office with red and itchy eczematoid dermatitis. She had a dental procedure earlier in the day, and the dentist administered a local anesthetic. There were no other findings, although she indicated that she had a history of allergic reactions. Which of the following drugs is most likely involved?
   (A). *Cocaine*.
   (B). *Procaine*.
   (C). *Lidocaine*.
   (D). *Bupivacaine*.
   (E). *Etidocaine*.

ANSWERS

1. **(B)** Inhibition of inward migration of Na^+ can result in complete block of conduction and therefore abolition of pain transmission. This block of conduction is not a feature of alteration of any of the other ions.

2. **(C)** A block at this level will affect only the sympathetic nerves, not parasympathetic activity. Application to the nerve cell ending would result only in topical anesthesia, and blockade of the neuromuscular junction could produce respiratory failure. Administration to the spinal cord is too general an answer. The injection must be near a nerve or nerve plexus proximal to the surgical site.

3. **(D)** Epinephrine is by far the most commonly employed vasoconstrictor. *Phenylephrine* is occasionally used with procaine for dental procedures. Levonordefrin is also used rarely in dental procedures. Dopamine has no vasoconstrictor activity. Cocaine is itself a local anesthetic with some vasoconstrictor properties. However, cocaine, because of its abuse potential and toxicity, is seldom used. Its only use is topical.

4. **(C)** *Lidocaine* is well tolerated and has a rapid onset and an adequate duration of action for most procedures. Bupivacaine has a particularly long duration of action. This may be advantageous in certain procedures, but not in most. Procaine has a relatively slow onset of action as well as a short duration of action. Etidocaine shows a preference for motor rather than sensory block; this limits its effectiveness in obstetrics.

5. **(B)** Allergic reactions occur only to the ester type of local anesthetics. This is because the metabolism of all ester-linked local anesthetics leads to the formation of PABA, which is known to be allergenic to some individuals. Both *Cocaine* and *Procaine* are esters. However, cocaine is not employed in dental procedures. Therefore, the best choice is *Procaine*.

DRUGS AFFECTING THE CENTRAL NERVOUS SYSTEM

Introduction to the CNS. Most drugs that affect the central nervous system (CNS) act by altering some step in the neurotransmission process. Drugs may act presynaptically by influencing the production, storage, or termination of action of neurotransmitters. Other agents may activate or block postsynaptic receptors.

In many ways, the basic functioning of neurons in the CNS is similar to that of the autonomic nervous system. E.g. transmission of information in the CNS and in the periphery both involve the release of neurotransmitters that diffuse across the synaptic space to bind to specific receptors on the postsynaptic neuron. In both systems, the recognition of the transmitter by the membrane receptor of the postsynaptic neuron triggers intracellular changes. Several major differences exist between neurons in the peripheral autonomic nervous system and those of the CNS. The circuitry of the CNS is much more complex than the autonomic nervous system, and the number of synapses in the CNS is far greater. The CNS, unlike the peripheral nervous system, contain powerful networks of inhibitory neurons that are constantly active in modulating the rate of neuronal transmission. In addition, the CNS communicates through the use of more than 50 different neurotransmitters. In contrast, the autonomic system uses only two primary neurotransmitters, acetylcholine and noradrenaline.

Lecture 9
GENERAL ANAESTHETICS

General anaesthesia is essential to surgical practice because it renders patients (1) analgesics, (2) amnesic, and (3) unconscious while causing (4) muscle relaxation and (5) suppression of undesirable reflexes. No single drug is capable of achieving these effects rapidly and safely. Rather, several different categories of drugs are utilized to produce "balanced anaesthesia". E.g. adjuncts to anaesthesia consist of preanaesthetic medication and skeletal muscle relaxants. Preanaesthetic medication serves to calm the patient, relieve pain, and protect against undesirable effects of the subsequently administered anaesthetic. Skeletal muscle relaxants facilitate intubation and suppress muscle tone to the degree required for surgery. Potent general anaesthetics are delivered via inhalation or intravenous injection. With the exception of *nitrous oxide*, modern inhaled anaesthetics are all volatile, halogenated hydrocarbons that derive early research and clinical experience with *Diethyl ether* and *Chloroform*. On the other hand, intravenous general anaesthetics consist of a number of chemically unrelated drug types that are commonly used for the rapid induction of anaesthesia.

Concominant use of drugs. Quite often, surgical patients receive one or more of the following preanaesthetic medications: benzodiazepines (e.g. *Diazepam*) to relieve anxiety and facilitate amnesia; barbiturates (e.g. *Pentobarbital*) for sedation; antihistamines for prevention of allergic reactions (e.g. *Dimedrol*); antiemetics (e.g. *Droperidol*); opioids (e.g. *Fentanyl*) for analgesia; anticholinergics (e.g. *Scopolamine*) to prevent bradycardia and secretion of fluids into the respiratory tract. These agents facilitate smooth induction of anaesthesia, and lower the dose of anaesthetic required to maintain the desired level of surgical (Stage III) anaesthesia.

Induction, maintenance and recovery. Anaesthesia can be divided into three stages: induction, maintenance, and recovery. Induction is defined as the period of time from onset of administration of the anaesthetic to the development of effective surgical anaesthesia in the patient. Maintenance provides a sustained surgical anaesthesia. Recovery is the time from discontinuation of administration of anaesthesia until consciousness is regained. Induction of anaesthesia depends on how fast effective concentration of anaesthetic drug reach the brain; recovery is the reverse of induction and depends on how fast the anaesthetic drug is removed from the brain.

Depth of anaesthesia. The depth of anaesthesia can be divided into a series of four sequential stages; each is characterized by increased CNS depression that is caused by accumulation of the anaesthetic drug in the brain. With *ether*, which produce a slow onset of anaesthesia, all the stages are discernible. However, with *Halothane* and many other commonly used anaesthetics, the stages are difficult to clearly characterize because of the rapidity of onset of anaesthesia.

Stage I — ***analgesia***: Loss of pain sensation results from interference with sensory transmission in the spi-

nothalamic tract. The patient is conscious and conversational. A reduced awareness of pain occurs as Stage II approaches.

Stage II — excitement: The patient experiences delirium and violent combative behaviour. There is a rise and irregularity in blood pressure. The respiratory rate may be increased. To avoid this stage of anaesthesia, a short acting barbiturate, such as *sodium thiopental*, is given i.v. before inhalation anaesthesia is administered.

Stage III — surgical anaesthesia: Regular respiration and relaxation of the skeletal muscle occur in this stage. Eye reflexes decrease progressively, until the eye movements cease and the pupil is fixed. Surgery may proceed during this stage.

Stage IV — medullary paralysis: Severe depression of the respiratory center and vasomotor center occur during this stage. Death can rapidly occur.

INHALATION ANAESTHETICS

Inhaled gases are the mainstay of anaesthesia and are primarily used for the maintenance of anaesthesia after administration of an intravenous agent. Inhalation anaesthetics have a benefit that is not available with intravenous agents, since the depth of anaesthesia can be rapidly altered by changing the concentration of the inhaled anaesthetic. Because most of these agents are rapidly eliminated from the body, they do not cause postoperative respiratory depression.

Common features of inhaled anaesthetics. Modern inhalation anaesthetics are non-explosive agents that include the gas *nitrous oxide* as well as a number of volatile halogenated hydrocarbons. As a group, these agents decrease cerebrovascular resistance, resulting in increased perfusion of the brain. They cause bronchodilation and decrease minute ventilation. Their clinical potency cannot be predicted by their chemical structure, but potency does correlate with their solubility in lipid. The movement of these agents from the lungs to the different body compartments depends upon their solubility in blood and various tissues. Recovery from their effects is due to their redistribution from the brain.

Potency. The potency of inhaled anaesthetics is defined quantitatively as the minimum alveolar concentration (MAC), which is the concentration of anaesthetic gas needed to eliminate movement among 50% of patients challenged by standardized skin incision. The MAC is usually expressed as the per cent of gas in a mixture required to achieve the effect. Numerically, is small for potent anaesthetics, such as *Halothane*, and large for less potent agents, such as *Nitrous oxide* (Fig. 6). The MAC values are useful in comparing pharmacologic effects of different anaesthetics. The more lipid-soluble an anaesthetic, the lower the concentration of anaesthetic needed to produce anaesthesia.

Uptake and Distribution. The partial of an anaesthetic gas at the origin of the respiratory pathway is the driving force that moves the anaesthetic into the alveolar space and hence into the blood, which delivers the drug to the brain and various other body compartments. Since gases move from one compartment to another within the body according to partial pressure gradients, a steady state is achieved when the partial pressure in each of these compartments is equivalent to that in the inspired mixture. The time course for attaining this steady state is determined by the following three factors:

1. Alveolar wash in: This term refers to the replacement of the normal lung gases with the inspired anaesthetic mixture. The time required for this process is directly proportional to the functional residual capacity of the lung, and inversely proportional to the ventilatory rate; it is independent to the physical properties of the gas. Once the partial pressure builds within the lung, anaesthetic uptake from the lung begins.

2. Solubility in the blood: The first compartment that the anaesthetic gas encounters the blood. Solubility in blood is determined by a physical property of the anaesthetic molecule called the blood/gas portion coefficient, which is the ratio of the total amount of gas in the blood relative to the gas equilibrium phase. Drugs with low versus high solubility in blood differ in their speed of induction of anaesthesia. E.g. when an anaesthetic gas with low blood solubility, such as *Nitrous oxide,* diffuses from the alveoli into the circulation, little of the anaesthetic dissolves in the blood. Therefore, the equilibrium between the inhaled anaesthetic and arterial blood occur rapidly, and relative few additional molecules of anaesthetic are required to raise arterial tension (that is, steady state is rapidly achieved). In contrast, an anaesthetic gas with high blood solubility, such as *Halothane*, dissolves more completely in the blood, and greater amount of the anaesthetic and longer periods of time are required to raise arterial tension. This results in increased time of induction and recovery, and slower changes in the depth of anaesthesia in response to changes in the concentration of the inhaled drug.

3. Tissue uptake: The arterial circulation distributes the anaesthetic to various tissues, and the pressure gradient drives free anaesthetic gas into tissues. The time required for a particular tissue to achieve a steady-state is inversely proportional to the blood flow to that tissue (faster flow results in a more rapidly achieved steady-state), and directly proportional to the capacity to store

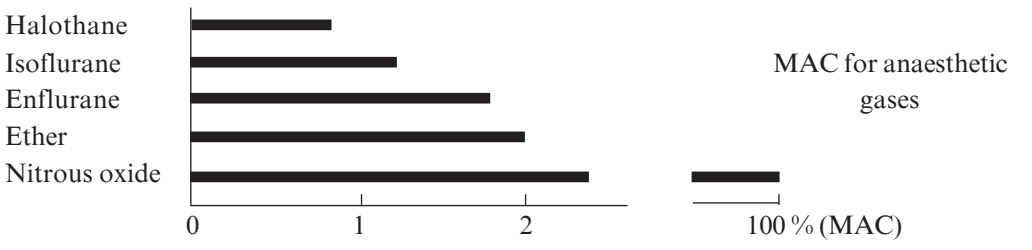


Fig. 6. Comparative potency of inhalation anaesthetics

anaesthetic (larger capacity results in a longer time to achieve steady-state). Capacity, in turn, is directly proportional to the tissue's volume, and the tissue/blood solubility coefficient of the anaesthetic. On the basis of these considerations, four major compartments determine the time course of anaesthetic uptake:

a) **Brain, heart, liver, kidney, endocrine glands:** These highly perfused tissues rapidly attain a steady-state with the partial pressure of the anaesthetic in blood.

b) **Skeletal muscles:** These are poorly perfused during anaesthesia. This fact prolongs the time required to achieve steady-state.

c) **Fat:** This tissue is also poorly perfused. However, potent general anaesthetics are very lipid soluble. Therefore, fat has a large capacity to store anaesthetic. This combination of slow delivery to a high capacity prolongs the time required to achieve steady state.

d) **Bone, ligaments, and cartilage:** These are poorly perfused and have a relatively low capacity to store anaesthetic. Therefore, these tissues have only a slight impact on the time course of anaesthetic distribution in the body.

4. **Washout.** When the administration of an inhalation anaesthetic is discontinued, the body now becomes the "source" that drives the anaesthetic into the alveolar space. The same factors that influence attainment of steady-state with an inspired anaesthetic determine the time course of clearance of the drug from the body.

Specific inhalation anaesthetics. Each of the halogenated gases has characteristics beneficial for selected clinical applications. No one anaesthetic is superior to another under all circumstances. [Note: In a very small population of patients, all of the halogenated hydrocarbon anaesthetics have the potential to induce malignant hyperthermia. While the etiology of this condition is unknown, it appears to be inherited. Should a patient exhibit the hyperthermia and muscle rigidity characteristic to malignant hyperthermia, *Dantrolene* is given as the anaesthetic mixture is withdrawn.]

Halothane (Ftorotan)

This agent is the prototype to which newer agents in this series of anaesthetics are compared. While *Halothane* is a potent anaesthetic, it is a relatively weak analgesic. Thus, *Halothane* is usually co-administered with *Nitrous oxide*, opioids, or local anaesthetics. Like other halogenated hydrocarbons, *Halothane* is vagomimetic and will cause *atropine*-sensitive bradycardia. In addition, *Halothane* has the undesirable property of causing cardiac arrhythmias. *Halothane* is oxidatively metabolized in the body to tissue-toxic hydrocarbons (e.g. trifluoroethanol) and bromide ion. These substances may be responsible for the toxic reactions that some patients (especially females) develop after *Halothane* anaesthesia. This reaction begins as fever, anorexia, nausea, and vomiting, and patients may exhibit signs of hepatitis. Although the incidence of this reaction is low — approximately 1 in 10,000 individuals — 50% of such patients will die of hepatic necrosis. [Note: *Halothane* is not hepatotoxic in pediatric patients and that, combined with its pleasant odor, make it the agent of choice in children.] *Halothane* anaesthesia is not repeated at intervals less than 2 to 3 weeks.

Enflurane

This gas is less potent than *Halothane* but it produces rapid induction and recovery. About 2% of the agent is metabolized to fluoride ion, which is excreted by the kidney. Therefore, *Enflurane* is contraindicated in patients with kidney failure. *Enflurane* anaesthesia exhibits the following differences from *Halothane*: fewer arrhythmias, less sensitization of the heart catecholamines, and greater potentiation of muscle relaxants. A disadvantage of *Enflurane* is that it causes CNS excitation at twice the MAC and at lower doses if hyperventilation reduces the PCO_2.

Isoflurane

This is a newer halogenated anaesthetic that has low biotransformation and low organ toxicity. Unlike the other halogenated anaesthetic gases, *Isoflurane* does not induce cardiac arrhythmias and does not sensitize the heart to the action of catecholamines. *Isoflurane* is a very stable molecule that undergoes little metabolism, as a result of which, less fluoride is produced. *Isoflurane* is not currently believed to be tissue toxic.

Methoxyflurane

The agent is the most potent inhalation anaesthetic because of its high solubility in lipid. Prolonged administration of *Methoxyflurane* is associated with metabolic release of fluoride, which is toxic to the kidneys. Therefore, *Methoxyflurane* is rarely used outside obstetric practice. It finds use in child-birth because it does not relax the uterus when briefly inhaled.

Nitrous oxide

Whereas *Nitrous oxide* (N_2O or "laughing gas") is a potent analgesic, it is a weak general anaesthetic. Thus, it is frequently combined with other more potent agents. Because it moves very rapidly into and out of the body, *Nitrous oxide* can increase the volume (pneumothorax) or pressure (sinuses) within closed body compartments. Furthermore, its speed of movement allows *Nitrous oxide* to retard oxygen uptake during recovery, thus causing diffusion hypoxia. This anaesthetic does not depress respiration nor does it produce muscle relaxation. It also has the least effect on cardiovascular system and on increasing cerebral blood flow, and is the least hepatotoxic of the inhalation anaesthetics. It is therefore probably the safest of these anaesthetics, provided that at least 20% of oxygen is always administered at the same time. [Note: *Nitrous oxide* at 80% (without other adjunct agents) cannot produce surgical anaesthesia.] *Nitrous oxide* is often employed of 30% in combination with oxygen for analgesia, particularly in dental surgery.

INTRAVENOUS ANAESTHETICS

Intravenous anaesthetics are often used for the rapid induction of anaesthesia, which is then maintained with an appropriate inhalation agent. They rapidly induce anaesthesia, and must therefore be injected slowly. Recovery from intravenous anaesthetics is due to redistribution from sites in the CNS.

BARBITURATES

Thiopental is a potent anaesthetic and a weak analgesic. It is the most widely used intravenously administered general anaesthetic. It is an ultra-short-acting barbiturate and has a high lipid solubility. When *Thiopental* is administered intravenously, it quickly enters the CNS and depresses function, often in less than 1 minute. However, diffusion out of the brain can occur very rapidly as well, because of redistribution of the drug to other body tissues, including skeletal muscle and ultimately adipose tissue. This latter site serves as a reservoir of drug from which the agent slowly leaks out and is metabolized and excreted. The short duration of action is due to the decrease of its concentration in the brain. Thus, metabolism of *Thiopental* is much slower than tissue redistribution. The barbiturates are not significantly analgesic and require some type of supplementary analgesic administration during anaesthesia. *Thiopental* has minor effects on the cardiovascular system, but it may contribute to severe hypotension in hypovolemic or shock patients. All barbiturates can cause apnea, coughing, chest wall spasm, laryngospasm, and bronchospasm. Barbiturates are contraindicated in patients with acute intermittent or variegate porphyria.

BENZODIAZEPINES

Although *Diazepam* is the prototype benzodiazepine, *Lorazepam* and *Midazolam* are more potent. All three facilitate amnesia while causing sedation. *Midazolam* has become popular because of its combination of water solubility, rapid onset and short duration of action. It produces amnesia with few side effects. Mental function returns to normal within 4 hours, making it popular choice for ambulatory surgery and during regional anaesthesia.

OPIOIDS

Because of their analgesic property, opioids are frequently used together with other anaesthetics; e.g. the combination of *Morphine* and *Nitrous oxide* provide good anaesthesia for cardiac surgery. However, opioids are not good amnesiacs and they can cause hypotension, respiratory depression, and muscle rigidity as well as post-anaesthetic nausea and vomiting. *Fentanyl* is more frequently used than *Morphine*.

The combination of *Droperidol* and *Fentanyl* is a fixed ration preparation called *Thalamonal (Innovar®)*. Since *Droperidol* is a neuroleptic substance, *Thalamonal* is said to produce neurolept analgesia. A neuroleptic has adrenergic blocking as well as sedative, antiemetic properties.

OTHER ANAESTHETICS

Ketamine, a short-acting nonbarbiturate anaesthetic, induces a dissociated state in which the patient appears awake but is unconscious and does not feel pain. This dissociative anaesthesia provides sedation, amnesia, and immobility. *Ketamine* stimulates the central sympathetic outflow, which in turn, causes stimulation of the heart and increases blood pressure and cardiac output. *Ketamine* is therefore used when circulatory depression is undesirable. On the other hand, these effects mitigate against the use of *Ketamine* in hypertensive or stroke patients. The drug is lipophilic and enters the brain very quickly, but like the barbiturates, it can redistribute to other organs and tissues. It is metabolized in the liver. *Ketamine* is employed mainly in children and young adults for short procedures. It is not widely used because it increases cerebral blood flow and induces postoperative hallucinations (nightmares).

Propanidid

Propanidid (Sombrevin) is an ultra-short-acting intravenous anaesthetic. Onset is smooth and occurs within about 40 seconds of administration. The emergence from anaesthesia from *Propanidid* is more rapid than that from *Thiopental* and is characterized by minimal postoperative confusion.

Sodium oxybutyrate

Sodium oxybutyrate is a derivative of γ-aminobutyric acid (GABA). GABA is an inhibitory neurotransmitter in the CNS. In contrast to GABA, *Sodium oxybutyrate* readily crosses the blood-brain barrier and produces sedative, hypnotic, anaesthetic, anticonvulsive, and antihypoxic effects. However, *Sodium oxybutyrate is not good analgesic.* The onset of action is slow (in 30–40 minutes after i.v. injection). It must be used with other anaesthetics for surgical anaesthesia.

Available forms:

Thiopental-sodium — in bottles 0.5; 1.0 each (to dilute in 20 ml of physiological solution)

Midazolam — in ampoules 0.5% solution 3 ml

Lecture 10
ETHYL ALCOHOL (ETHANOL)

Pharmacology of alcohol is important for its presence in beverages (which have been used since recorded history) and for alcohol intoxication, rather than as a drug. Alcohol is manufactured by fermentation of sugar:

$$C_6H_{12}O_6 \longrightarrow 2CO_2 + 2C_2H_5OH$$

Fermentation proceeds till alcohol content reaches 15%. Then reaction is inhibited by alcohol itself.

Local action. Rubbed on skin *Ethanol* dissolves fat, precipitate surface proteins and harden skin. By precipitation bacterial proteins it acts as an antiseptic. The antiseptic action increases with concentration from 20 to 70%, remains constant from 70 to 90% and decreases above that. 100% *Ethanol* is more dehydrating but poorer antiseptic than 90% *Ethanol*. Applied to delicate skin or mucous membrane *Ethanol* produces irritation and burning sensation. Injected s.c. it causes intense pain, inflammation and necrosis followed by

fibrosis. Injected round a nerve it produces permanent damage.

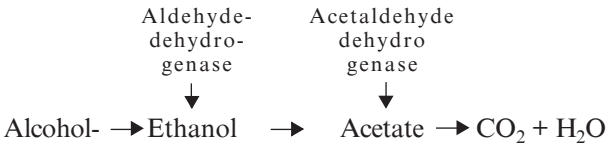
Resorptive action. *Ethanol* is a neuronal depressant. However, as highest areas are most sensitive to alcohol (these are primarily inhibitory), — excitation and euphoria are experienced at lower plasma concentrations (30-100 mg/dl). Caution, self criticism and restraint are lost first. With the increasing concentration (100–150 mg/dl) mental clouding, disorganization of thought and drowsiness occur. At 150–200 mg/dl the person is sloppy, ataxic and drunk; 200–300 mg/dl results in stupor and above this unconsciousness prevails, medullary centers are paralyzed and death may occur. Though, *Ethanol* can produce anaesthesia, margin of safety is narrow. Effects of alcohol are more marked when the concentration is rising than when it is falling.

Small doses of alcohol produce cutaneous and gastric vasodilation, a sense of warmth, but heat lost is increased in cold surroundings.

Alcoholic beverages have variable effect on gastric secretion depending on beverage itself and whether the individual likes it. Dilute alcohol (optimum 10%) is a strong stimulant of gastric secretion. Higher concentrations (above 20%) inhibit gastric secretion.

Regular intake of small amounts of alcohol has been found to raise high density lipids and diminish low density lipids levels in plasma. This may be responsible for the somewhat lower incidence of coronary artery disease.

Pharmacokinetics. Rate of alcohol absorption from the stomach is dependant on its concentration, presence of food, and other factors. Absorption from the intestines is very fast. Thus, gastric emptying determines rate of absorption. Alcohol distributes widely in the body, crosses blood-brain barrier (concentration in the brain is very near to blood concentration); it also crosses placenta freely. It is oxidized in the liver.



Metabolism of alcohol follows *zero order* kinetics, i.e. a constant amount is degraded in unit time, irrespective to blood concentration (8-10 ml of absolute alcohol/hour). Small amounts are excreted through kidney and lungs.

Acute Alcoholic Intoxication. Nausea, vomiting, hypotension, hypoglycemia, collapse, respiratory depression, coma and death.

Treatment. Gastric lavage, maintain patent airway and aspiration of vomitus. Most patients will recover with supportive treatment and maintenance of fluid and electrolyte balance. *Insulin+Fructose* has been found to accelerate alcohol metabolism.

Disulfiram (Teturamum) has found some use in the patients seriously desiring to stop alcohol ingestion. The drug blocks the oxidation of acetaldehyde to acetic acid by inhibiting aldehyde dehydrogenase. This results in accumulation of acetaldehyde in the blood, causing flushing, tachycardia, hyperventilation, and nausea.

Lecture 11
HYPNOTIC DRUGS

Sleep is an active, circadian, physiological depression of consciousness. It is characterized by cyclical electroencephalographic (EEG) and eye movement changes. Normal sleep (categorized by eye movement) is of two kinds:

NREM (non-rapid eye movement), orthodox, forebrain or slow-wave EEG sleep. Heart rate, blood pressure and respiration are steady or decline and muscles are relaxed; growth hormone secretion is maximal.

REM (rapid eye movement), paradoxical, hindbrain of fast-wave EEG sleep; awakened subjects state they were 'dreaming'. Heart rate, blood pressure and respiration are increased, skeletal muscles are profoundly relaxed.

Cycles of NREM sleep (about 90 min) alternate with REM sleep (about 20 min). Thus, normal sleep contains 4–6 cycles (NREM+REM).

Classification of insomnias (sleep disorders):

1. Difficulty in getting to sleep, *onset insomnia*; this was associated with neurotic personality disorder. People who lie awake in bed for hours unable to relax, and then sleep well.
2. Difficulty in staying asleep, repeated awakenings.
3. Early waking in which sleep is shorter.

In general, a short-acting hypnotic drug is prescribed for patients who have prolonged sleep latency but who sleep well once sleep ensues; and a drug with a longer duration of action for those who awaken early and have difficulty in returning to sleep. Insomnia has many causes, and an accurate differential diagnosis is required before treatment should be considered. Prescription of a hypnotic without regard to the underlying disturbance subjects the patient to the risk of abuse, may mask the signs and symptoms of a pernicious disease etc.

BARBITURATES

Barbital was introduced in 1903 and *Phenobarbital* in 1912. The barbiturates were formerly the mainstay of treatment used to sedate the patient or to induce and maintain sleep. Today, they have been largely replaced by the benzodiazepines, mainly because barbiturates induce tolerance, drug-metabolizing enzymes, physical dependence, and very severe withdrawal symptoms. Foremost is their ability to cause coma in toxic doses. Certain barbiturates, such as the very short-acting *Thiopental*, are still used to induce anaesthesia.

Mechanism of action. Barbiturates are thought to interfere with Na^+ and K^+ transport across cell membrane. This leads to inhibition of the mesencephalic reticular activation system. Polysynaptic transmission is inhibited in all areas of the CNS. Barbiturates also potentiate GABA action on chloride entry into the neuron, although they do not bind at the benzodiazepine receptor.

Actions.

Depression of the CNS: The barbiturates can produce all degrees of depression of the CNS. Low doses produce sedation (calming effect, reducing excitement). At high doses, the drugs cause hypnosis, followed by anaesthesia (loss of feeling or sensation), and finally coma and death. Thus, any degree of depression of the CNS is possible, depending on the dose. Barbiturates do not raise the pain threshold and have no analgesic properties. They may even exacerbate pain.

Respiratory depression: Barbiturates suppress the hypoxic and chemoreceptor response to CO_2, and overdosage is followed by respiratory depression and death.

Enzyme induction: Barbiturates induce P-450 microsomal enzymes in the liver. Therefore, chronic barbiturate administration diminishes the action of many drugs that are dependant on P-450 metabolism (including barbiturates themselves).

Barbiturates are classified according to their duration of action:

1. Long-acting *(Phenobarbital, Barbital, Barbital-sodium)*, which have a duration of action greater than a day; *Phenobarbital* is useful in the treatment of seizures.
2. Intermediate-acting *(Pentobarbital, Cyclobarbital, Secobarbital)*, which are effective as sedative and hypnotic (but not antianxiety) agents.
3. Short-acting *(Hexobarbital)*.
4. Ultra short-acting *(Thiopental, Hexenal)*, which act within seconds and have a duration of action of about 30 min, are used in the intravenous induction of anaesthesia.

Therapeutic uses:

Anaesthesia: Selection of a barbiturate is strongly influenced by the desired duration of action. The ultra-short-acting barbiturates, such as *Thiopental*, are used intravenously to induce anaesthesia.

Anticonvulsant: *Phenobarbital* is used in long-term management of tonic-clonic seizures, status epilepticus, and eclampsia. *Phenobarbital* has been regarded as the drug of choice for treatment of young children with recurrent febrile seizures. However, *Phenobarbital* can depress cognitive performance in children, and the drug should be used cautiously. *Phenobarbital* has specific anticonvulsant activity that is distinguished from the nonspecific CNS depression.

Sedation-hypnosis: Barbiturates have been used as mild sedative to relieve nervous tension, and insomnia. Most have been replaced by benzodiazepines.

Pharmacokinetics. Barbiturates are absorbed orally and distributed widely throughout the body. All barbiturates redistribute from the brain to the splanchnic areas, to skeletal muscle, adipose tissue. This movement is important in causing the short duration of action of *thiopental*. Barbiturates are metabolized in the liver, and inactive metabolites are excreted in the urine.

Adverse effects:

CNS: Barbiturates cause drowsiness, impaired concentration, and mental and physical sluggishness.

Drug hangover: Hypnotic doses of barbiturates produces feeling of tiredness well after the patient awakes. This drug hangover leads to impaired ability to function normally for many hours after waking.

Addiction: Abrupt withdrawal from barbiturates may cause tremor, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium, and cardiac arrest. Withdrawal is much more severe than that associated with opiates and can result in death.

Precautions: As noted previously, barbiturates induce the P-450 system and therefore may decrease the effect of drugs that are metabolized by these hepatic enzymes. Barbiturates increase porphyrin synthesis, and are contraindicated in patients with acute intermittent porphyria.

Poisoning. Barbiturate poisoning has been a leading cause of death among drug overdoses for many decades. Severe depression of respiration is coupled with central cardiovascular depression, and results in a shock-like condition with shallow, infrequent breathing. Treatment includes artificial respiration and purging the stomach of its contents if the drug has been recently taken. Hemodialysis may be necessary if large quantities have been taken. Alkalinization of the urine often aids in the elimination of *Phenobarbital*. Analeptics *(Bemegride, Corazole)* may be useful if respiration is not depressed completely to restore breathing.

BENZODIAZEPINES

Chlordiazepoxide was synthesized in 1957 by Sternbach. Randall discovered its unique pattern of actions. With its introduction into clinical medicine in 1961, more than 3,000 benzodiazepines have been synthesized, over 120 have been tested for biological activity, and about 35 are in clinical use in various parts of the world. They have largely replaced barbiturates and *Meprobamate* as sedative-hypnotic agents mainly because of remarkably low capacity to produce fatal CNS depression.

Although the benzodiazepines exert qualitatively similar effects, important quantitative differences in their pharmacodynamic spectra and pharmacokinetic properties have led to varying patterns of therapeutic application. Benzodiazepines vary in the degrees of sedative-hypnotic, muscle relaxant, anxiolytic, and anticonvulsant effects.

Mechanism of action. Binding of GABA to its receptor on the cell membrane triggers an opening of a chloride channel, which leads to an increase in chloride conductance (Fig. 7).

The influx of chloride ions causes a small hyperpolarization that moves the postsynaptic potential away from its firing threshold and thus inhibits the formation of action potentials. Benzodiazepines bind to specific, high affinity sites on the cell membrane, which are separate from but adjacent to the receptor of GABA. The benzodiazepine receptors are found only in the CNS, and their location parallels that of GABA neurons. The binding of benzodiazepines enhances the affinity of GABA receptors for its neurotransmitter, resulting in a more frequent opening of adjacent chloride channels. This in turn results in enhanced hyperpolarization and further inhibition of neuronal firing.

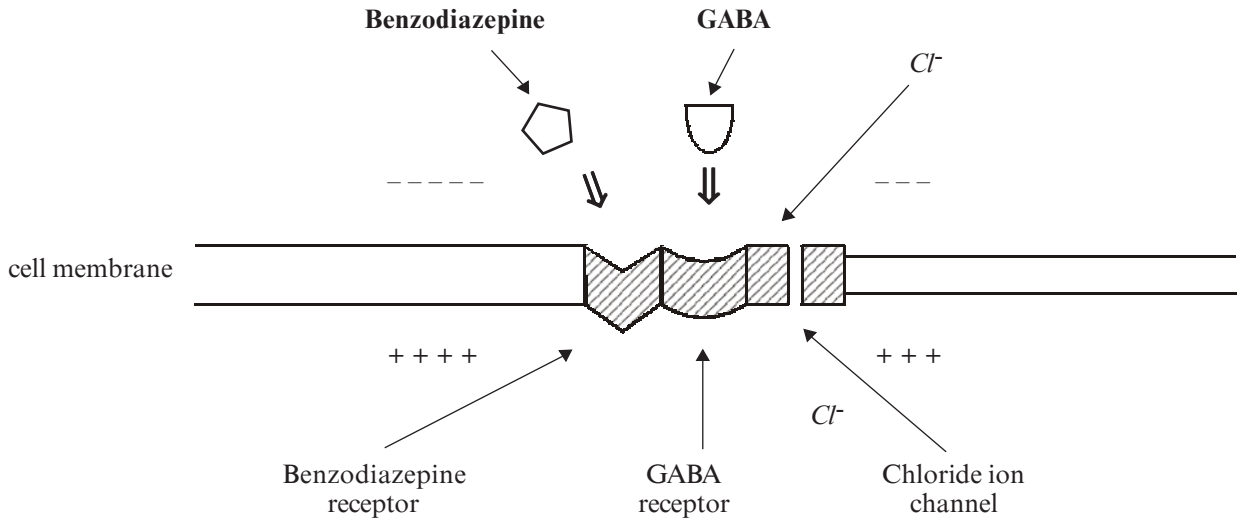


Fig. 7. Mode of action of benzodiazepines

Actions. The benzodiazepines are not general neuronal depressants, as are the barbiturates. All the benzodiazepines have quite similar pharmacological profiles. The most prominent of these effects are sedation, hypnosis, decreased anxiety, muscle relaxation, anterograde amnesia, and anticonvulsant activity. Nevertheless, the drugs differ in selectivity, and the clinical usefulness of individual benzodiazepines varies considerably.

Uses in sleep disorders. This lecture describes the benzodiazepines used primarily as hypnotic and anticonvulsant agents. Other applications will be discussed in details in a following lecture (see tranquilizers). Not all of the benzodiazepines are useful as hypnotic agents, although all have sedative or calming effects. The three most commonly prescribed benzodiazepines for sleep disorders are long-acting *Flurazepam*, intermediate-acting *Temazepam*, and short-acting *Triazolam*. The principal factors that determine selection are pharmacokinetics.

Flurazepam

This long-acting benzodiazepine significantly reduces both sleep-induction time and the number of awakening, and increases the duration of sleep. With continued use, the drug has been shown to maintain its effectiveness for up to 4 weeks. *Flurazepam* has a half-life of approximately 85 hours, which may result in daytime sedation and accumulation of drug.

Temazepam

This drug is useful in patients who experience frequent awakening. However, the peak sedative effect occurs two to three hours after an oral dose, and therefore it may be given several hours before bedtime.

Triazolam

This benzodiazepine has a relatively short duration of action and is therefore used to induce sleep in patients with recurring insomnia. Whereas *Temazepam* is useful for insomnia caused by the inability to stay asleep, *Triazolam* is effective in treating individuals who have difficulty in going to sleep. Tolerance frequently develops within a few days, and withdrawal of the drug often results in rebound insomnia, leading the patient to demand another prescription. Therefore, this drug is best used intermittently rather than daily. In general, hypnotics should be given for only a limited time, usually less than 2 to 4 weeks.

Pharmacokinetics. The benzodiazepines are lipophilic and are rapidly and completely absorbed after oral administration and are distributed throughout the body. The half-lives of the benzodiazepines are very important clinically, since the duration of action may determine the therapeutic usefulness. The benzodiazepines can be roughly divided into short-, intermediate- and long-acting groups. The long-acting agents form active metabolites with long half-lives. Most benzodiazepines, including *Chlordiazepoxide* and *Diazepam,* are metabolized by the hepatic microsomal metabolizing system to compounds that are also active. For these benzodiazepines, the apparent half-life of the drug represents the combined actions of the parent drug and its metabolites. The benzodiazepines are excreted in urine as glucuronides or oxidized metabolites.

Dependence. Psychological and physical dependence on benzodiazepines can develop if high doses of the drug are given over a prolonged period. Abrupt discontinuation of the benzodiazepines results in withdrawal symptoms, including confusion, anxiety, agitation, restlessness, insomnia, and tension. Because of the long half-lives of some of the benzodiazepines, withdrawal symptoms may not occur until a number of days after discontinuation. Benzodiazepines with a short elimination half-life, such as *Triazolam*, induce more abrupt and severe withdrawal reactions.

Adverse Effects. Drowsiness and confusion are the two most common side effect of the benzo-diazepines. Ataxia occurs at high doses and precludes activities that require motor coordination, such as driving an automobile. Cognitive impairment (decreased long-term recall and acquisition of new knowledge) can occur. *Triazolam,* the benzodiazepine with most rapid elimination, often show a rapid development of tolerance, early morning in-

somnia and daytime anxiety, along with amnesia and confusion. Benzodiazepines potentiate alcohol and other CNS depressants. However, they are considerably less dangerous than other anxiolytic and hypnotic drugs. As a result, a drug overdose is seldom lethal, unless other central depressants, such as alcohol, are taken concurrently.

Benzodiazepine antagonists. Flumazenil is a GABA receptor antagonist that can rapidly reverse the effects of benzodiazepines. The drug is available by i.v. administration only. Onset is rapid but duration is short, with a half-life of about one hour. Frequent administration may be necessary to maintain reversal of benzodiazepines.

OTHER HYPNOTIC AGENTS

Although the hypnotic *Zopiclone (Imovan)* is not a benzodiazepine, it acts on a subset of the benzodiazepine receptor family. *Zopiclone* has no anticonvulsive or muscle relaxing properties. It shows no withdrawal effects, exhibits minimal rebound insomnia and little or no tolerance occurs with prolonged use. *Zopiclone* has a rapid onset of action and short elimination. Although *zopiclone* potentially has advantage over the benzodiazepines, clinical experience with the drug is still limited.

Chloral hydrate is a trichlorinated derivative of acetaldehyde that is converted to trichloroethanol in the body. The drug is an effective sedative and hypnotic that induces sleep in about 30 minutes and lasts about 6 hours. *Chloral hydrate* is irritating to the gastrointestinal tract and causes epigastric distress. It also produces an unusual, unpleasant taste sensation.

Available forms:

Thiopental-sodium — in bottles 0.5; 1.0 each (to dilute in 20 ml of physiological solution)

Midazolam — in ampoules 0.5% solution 3 ml

Lecture 12
ANTICONVULSANTS

ANTIEPILEPTIC DRUGS

Epilepsy is widespread among the general population. Epilepsy is not a single entity; it is a family of different recurrent seizure disorders that have in common the sudden and excessive discharge of cerebral neurons. This results in abnormal movements or perceptions that are of short duration but that tend to recur. The site of electrical discharge determines the symptoms that are produced. E.g. epileptic seizures may cause convulsions if the motor cortex is involved. The seizures may include visual, auditory, or olfactory hallucinations if the parietal or occipital cortex plays a role. Drug therapy is the most widely effective mode of treatment for epilepsy. Seizures can be controlled completely in approximately 50% of epileptic patients, and meaningful improvement may be achieved in at least one half of the remaining patients.

Etiology. The neuronal discharge in epilepsy results from the firing of a small population of neurons in some specific area of the brain, referred to as the primary focus. These focal areas may be triggered into activity by changes in any of a variety of environmental factors, including alteration in blood gases, pH, electrolytes, or glucose availability.

Classification of epilepsy:

Primary epilepsy: When no specific anatomic cause for the seizure, such as trauma or neoplasm, is evident the syndrome called primary epilepsy. These seizures may be produced by an inherited abnormality in the CNS. Patients are treated chronically with antiepileptic drugs, often for life.

Secondary epilepsy: A number of reversible disturbances, such as tumors, head injury, hypoglycemia, meningeal infection, or rapid withdrawal of alcohol can precipitate seizures. Antiepileptic drugs are given until the primary cause can be corrected.

Seizures have been classified into two broad groups, partial (or focal), and generalized (Fig. 8). Choice of drug treatment is based on the classification.

Partial: The symptoms of each seizure type depend on the site of neuronal discharge and on the extent to which the electrical activity spreads to other neurons in brain. Partial seizures may progress, becoming generalized tonic-clonic seizures.

Simple partial. These seizures are caused by a group of hyperactive neurons and are confined to a single locus in the brain; the abnormal activity does not spread. The patient does not lose consciousness and often exhibits abnormal activity of a single limb or muscle group that is controlled by the region the brain experiencing the disturbance. The patient may also show sensory distortions. Simple partial seizures may occur at any age.

Complex partial. These seizures exhibit complex sensory hallucinations, mental distortion, and loss of consciousness. Motor dysfunction may involve chewing movements, diarrhea, urination. Most (80%) of individuals experience their initial seizures before 20 years of age.

Generalized: These seizures begin locally, but they rapidly spread, producing abnormal electrical discharge throughout both hemispheres of the brain. Generalized seizures may be convulsive or nonconvulsive; the patient usually has an immediate loss of consciousness.

Tonic-clonic (grand mal). This is the most commonly encountered and the most dramatic form of epilepsy. Seizures result in loss of consciousness, followed by tonic, then clonic phases. The seizure is fol-

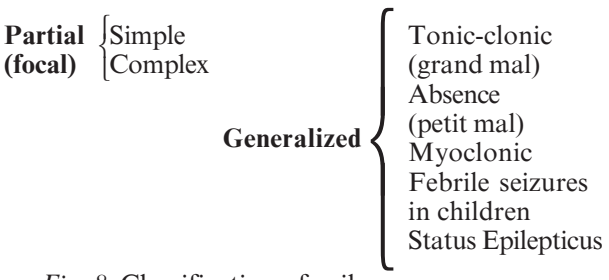


Fig. 8. Classification of epilepsy

lowed by a postictal period of confusion and exhaustion.

Absence (petit mal). These seizures involve a brief, abrupt, and self-limiting loss of consciousness. The onset occurs in patients at the age of 3 to 5 years and lasts until puberty. The patient stares and exhibits rapid eye blinking, which lasts for 3 to 5 seconds.

Myoclonic. These seizures consist of short episodes of muscle contractions that may reoccur for several minutes. Myoclonic seizures are rare, occur at any age, and are often a result of hypoxia, uremia, encephalitis, or drug poisoning.

Febrile seizures. Young children (3 month to 5 years of age) frequently develop seizures with illness accompanied by high fever. The febrile consist of generalized tonic-clonic convulsions of short duration. Although febrile seizures may be frighten-ing, they are benign and do not cause death, neurologic damage, injury, or learning disorders, and they rarely require medication.

Status Epilepticus. Seizures are rapidly recurrent.

Mechanism of action. Drugs that are effective in seizure reduction can either block the initiation of the electrical discharge from the focal area or, more commonly, prevent the spread of the abnormal electrical discharge to adjacent brain areas.

Initial drug treatment is based on the specific type of seizures (Fig. 9). Thus, tonic-clonic (grand mal) seizures are treated differently than absence (petit mal). Several drugs may be equally effective, and the toxicity of the agent is often a major consideration in drug selection.

Diphenin *(Phenytoin)* is effective in suppressing tonic-clonic and partial seizures, and is a drug of choice for initial therapy, particularly in treating adults.

Mechanism of action. *Diphenin* stabilizes neuronal membranes to depolarization by decreasing the flux of sodium ions in neurons in the resting state or during depolarization and suppresses repetitive firing of neurons.

Actions. *Diphenin* is not a generalized CNS depressant like the barbiturates, but it does produce some degree of drowsiness and lethargy. *Diphenin* reduces the propagation of abnormal impulses in the brain.

Therapeutic uses. *Diphenin* is highly effective for all partial seizures (simple and complex), for tonic-clonic seizures, and in status epilepticus. *Diphenin* is not effective for absence seizures, which often may worsen if such a patient is treated with this drug.

Carbamazepine

Action. *Carbamazepine* reduces the propagation of abnormal impulses in the brain by blocking sodium channels, thereby inhibiting the generation of repetitive action potentials in the epileptic focus.

Therapeutic uses. *Carbamazepine* is highly effective for all partial seizures and is often the drug of first choice. In addition the drug is highly effective for tonic-clonic seizures and is used to treat trigeminal neuralgia. It has occasionally been used in manic-depressive patients to ameliorate the symptoms.

Phenobarbital

Phenobarbital provides a 50% favorable response rate for simple partial seizures, but it is not very effective for complex partial seizures. The drug has been regarded as the first choice in treating recurrent seizures in children, including febrile seizures. The drug is also used to treat tonic-clonic seizures, especially in patients who do not respond to *Diazepam* plus *Diphenin.* Doses required for antiepileptic action are lower than those that cause pronounced CNS depression. *Phenobarbital* is also used as a mild sedative to relieve anxiety, nervous tension and insomnia, although benzodiazepines are superior.

Hexamidine *(Primidone)* is structurally related to *phenobarbital,* and resembles *Phenobarbital* in its anticonvulsive activity. *Hexamidine* is an alternative choice in partial seizures and tonic-clonic seizures. Much of *Hexamidin's* efficacy comes from its metabolites *Phenobarbital* and Phenylethylmalonamide.

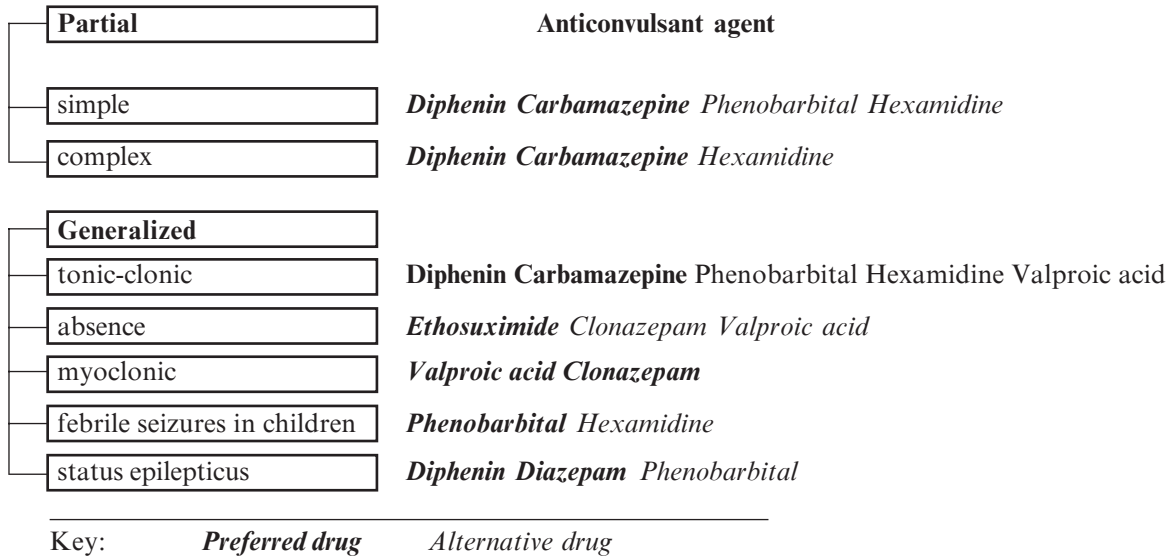


Fig. 9. Choice of antiepileptic drug

Valproic acid is the most effective agent available for treatment myoclonic seizures. The drug diminishes absence seizures but is a second choice because of its hepatotoxic potential. *Valproic acid* also reduces the incidence and severity of tonic-clonic seizures.

Ethosuximide reduces propagation of abnormal electrical activity in the brain, and is the first choice in absence seizures.

Several of the benzodiazepines show antiepileptic activity. *Clonazepam* and *Clorazepate* are used for chronic treatment, whereas *Diazepam* is the drug of choice in the acute treatment of status epilepticus. Of all the anti-epileptics, the benzodiazepines are the safest.

DRUGS USED IN PARKINSON'S DISEASE

Parkinsonism is a progressive neurologic disorder of muscle movement, characterized by tremors, muscular rigidity, and bradykinesia (slowness in initiating and carrying out voluntary movements). Parkinson's disease is the fourth most common neurologic disorder among the elderly. Most cases involve people over the age of 65 among whom the incidence is about 1:100 individuals.

Etiology. The cause of Parkinson's disease is unknown for most patients. The disease is correlated with a reduction in the activity of inhibitory dopaminergic neurons in the substantia nigra and corpus striatum — parts of the brain's basal ganglia system that are responsible for motor control. Genetic factors do not play a dominant role in the etiology.

Substantia nigra. The substantia nigra, part of the extrapyramidal system, is the source of dopaminergic neurons that terminate in the striatum. Each neuron makes thousands synaptic contacts within the striatum and modulates the activity of a large number of cells. These dopaminergic projections from the substantia nigra fire tonically, rather than in response to specific muscular movements or sensory input. Thus, dopaminergic system appears to serve as a tonic, sustaining influence on motor activity, rather than participating on specific movements.

Striatum. Normally, the striatum is connected to the substantia nigra by neurons that secrete the inhibitory transmitter GABA at their termini in the substantia nigra. In turn, cells of the substantia nigra sends neurons back to the striatum secreting the inhibitory transmitter dopamine. This mutual inhibitory pathway normally maintains a degree of inhibition of the two separate areas. Nerve fibers from the cerebral cortex and thalamus secrete acetylcholine in the neostriatum, causing excitatory effects that initiate and regulate gross intentional movements of the body. In Parkinson's disease, destruction of cells in the substantia nigra results in the degeneration of neurons responsible for secreting dopamine in the neostriatum. Thus the normal modulating inhibitory influence of dopamine on the neostriatum is significantly diminished, resulting in the parkinsonian degeneration of the control of muscle movement.

Secondary parkinsonism. Parkinsonian symptoms infrequently follow viral encephalitis or multiple small vascular lesions. Drugs such as *Phenothiazines* and *Haloperidol*, whose major pharmacologic action is blockade of dopamine receptors in the brain, may also produce parkinsonian symptoms. These drugs should not be used in parkinsonian patients.

Strategy of treatment. In addition to an abundance of inhibitory dopaminergic neurons, the neostriatum is also rich in excitatory cholinergic neurons that oppose the action of *Dopamine*. Many of the symptoms reflect an imbalance between the excitatory cholinergic neurons and the greatly diminished number of inhibitory dopaminergic neurons. Therapy is aimed at restoring *Dopamine* in the basal ganglia and antagonizing the excitatory effect of cholinergic neurons, thus reestablishing the correct *Dopamine/Acetylcholine* balance.

Currently available drugs offer temporary relief from the symptoms of the disorder, but do not arrest or reverse the neuronal degeneration caused by the disease.

Levodopa

Levodopa is a metabolic precursor of *Dopamine*. It restores dopamine level in the extrapyramidal centers (substantia nigra) that atrophy in parkinsonism. In patients with early disease, the number of residual dopaminergic neurons (about 20% of normal) is adequate for conversion of *Levodopa* to *Dopamine*. *Levodopa* decreases the rigidity, tremor, and other symptoms of parkinsonism. Unfortunately, with time the number of neurons decreases and the drug effects "wear off".

Dopamine itself does not cross the blood-brain barrier, but its immediate precursor *Levodopa* is readily transported into the CNS and is converted to *Dopamine* in the brain. Large doses of *Levodopa* are required because much of the drug is decarboxylated to *Dopamine* in the periphery, resulting in peripheral side effects (nausea, vomiting, cardiac arrhythmias, hypotension).

The effects of *Levodopa* on the CNS can be greatly enhanced by coadministration *Carbidopa*, a *Dopamine* decarboxylase inhibitor that does not cross the blood-brain barrier. *Carbidopa* diminishes the metabolism of *Levodopa* in the GI tract and peripheral tissues. The addition of *Carbidopa* lowers the dose of *Levodopa* needed by 4- to 5-fold and, consequently, decreases the severity of the side effects of peripherally formed dopamine.

Bromocriptine

Bromocriptine, en ergotamine (an alkaloid with vasoconstrictor action) derivative, is a dopamine receptor agonist. The drug produces little response in patients who does not react to *Levodopa*, but it is often used with *Levodopa* in patients responding to drug therapy.

It was accidentally discovered that the antiviral drug, *Amantadine*, effective in the treatment of influenza, has Antiparkinsonian action. It appears to enhance the synthesis, release, or reuptake of *Dopamine* from the surviving neurons. *Amantadine* is less efficacious than *Levodopa*, but it has fewer side effects. The drug has little effect on tremor but is more effective than the *Anticholinergics* against rigidity and bradykinesia.

The antimuscarinic agents (*Cyclodol, Noracin* etc.) are much less efficacious than *Levodopa* and play only

adjuvant role in the antiparkinsonian therapy. Blockage of the cholinergic transmission produces similar to augmentation of dopaminergic transmission (again, because of the creation of an imbalance in the *Dopamine/Acetylcholine* ratio). All these drugs can induce mood changes and produce xerostomia (dryness of the mouth) and visual problems, as do all muscarinic blockers. They interfere with gastrointestinal peristaltic, may cause urinary retention and increase in intraocular pressure.

Available forms:

Phenobarbital — powder; tablets 0.005 each (for children) and 0.05; 0.1 (for adults)

Phenytoin (Dipheninum) — in patented tablets

Carbamazepine — in tablets 0.2 each

Valproate sodium (Acediprolum) — in tablets 0.3 each

Clonazepam — in tablets 0.001 each

Diazepam (Sibazonum) — in tablets 0.005 (for adult) and 0.001 (for children) each; in ampoules 0.5% solution 2 ml each

Baclofen — in tablets 0.01 or 0.025 each

Levodopa — in tablets and capsules 0.25; 0.5 each

Nakom (composition of *Levodopa* with *Carbidopa*) — in patented tablets

Cyclodolum — in tablets 0.001; 0.002 or 0.005 each

Lecture 13
NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

In this lecture drugs that are anti-inflammatory, analgesics, and antipyretics will be considered; their mechanism of action differ from those of the anti-inflammatory steroids and opioid analgesics. The anti-inflammatory, analgesic, and antipyretic drugs are a heterogeneous group of compounds, often chemically unrelated (although most of them are organic acids), which share certain therapeutic actions and side effects. The prototype is *aspirin*; hence these compounds are often referred to as *aspirin-like drugs*. They are also frequently designated as *nonsteroidal anti-inflammatory drugs* (NSAIDs).

The medicinal effect of the bark of willow has been known to several cultures for centuries. The active ingredient in the willow bark (called salicin) was first isolated in a pure form in 1829 by Leroux. The latter compound can be converted into *salicylic acid. Sodium salicylate* was first used for the treatment of rheumatoid fever and as an antipyretic in 1875. The enormous success of this drug prompted Hoffman, a chemist employed by Bayer, to prepare *acetylsalicylic acid.* This compound was introduced into medicine in 1899 by Dresser under the name of *Aspirin*.

Inflammation. Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or microbiologic agents. Inflammation is the body's effort to inactivate or destroy invading organisms, remove irritants, and set the stage for tissue repair. However, inflammation is sometimes inappropriately triggered by an innocuous agent, such as pollen, or by an autoimmune response, as in asthma or rheumatoid arthritis. In such cases, the defense reactions themselves may cause injury, and anti-inflammatory drugs may be required to modulate the inflammatory process. Inflammation is triggered by the release of chemical mediators from injured tissues and migrating cells. The specific mediators vary with the type of inflammation and include amines, such as histamine and 5-hydroxytryptamine; lipids, such as prostaglandins; small peptides, such as bradykinin; and larger peptides, such as interleukin-1. Discovery of the wide variation among chemical mediators has clarified the apparent paradox that an anti-inflammatory drugs may interfere with the action of a particular mediator important in one type of inflammation but be without effect in process not involving the drug's target mediator.

Prostaglandins. Many of the NSAIDs act by inhibiting the synthesis of prostaglandins. Thus, an understanding of NSAIDs requires a comprehension of the actions and biosynthesis of prostaglandins — unsaturated fatty acid derivatives containing 20 carbons that include a cyclic ring structure. [Note: These compounds are sometimes referred to as eicosanoids; "eicosa" refers to the 20 carbon atoms.]

Role of prostaglandins. Prostaglandins and related compounds are produced in minute quantities by virtually all tissues. They generally act locally on the tissues in which they are synthesized, and are rapidly metabolized to inactive products. Therefore, the prostaglandins do not circulate in the blood in significant concentration. Thromboxanes, leukotrienes, and the hydroperoxyeicosateraenoic and hydroxyeicosatetraenoic acids (HPETEs and HETEs) are related lipid, synthesized from the same precursors as are the prostaglandins, using interrelated pathways.

Synthesis of prostaglandins. Arachidonic acid, a 20-carbon fatty acid, is the primary precursor of the prostaglandins. Arachidonic acid is present as a component of the phospholipids of cell membranes. Free arachidonic acid is released from tissue phospholipids by the action of phospholipase A_2. There are two major pathways in the synthesis of the eicosanoids from arachidonic acid (Fig. 10).

Cyclooxygenase pathway. All eicosanoids with ring structures, that is, the prostaglandins, thromboxanes, and prostacyclins, are synthesized via the cyclooxygenase pathway. Two cyclooxygenases have been identified: COX-1 and COX-2. The former is ubiquitous and constitutive, whereas the latter is induced in response to inflammatory stimuli.

Lipoxygenase pathway. Alternatively, several lipoxygenases can act on arachidonic acid to form 5-HPETE, 12-HPETE and 15-HPETE, which are unstable peroxidated derivatives that are converted to the corresponding hydroxylated derivatives (HEPEs), or to leukotrienes or lipoxins, depending on the tissue.

Function in the body. Prostaglandins act as local signals that fine-tune the response of a specific cell type. Their functions vary widely depending on the tissue. For example, the release of TXA_2 from platelets triggers the recruitment of new platelets for aggrega-

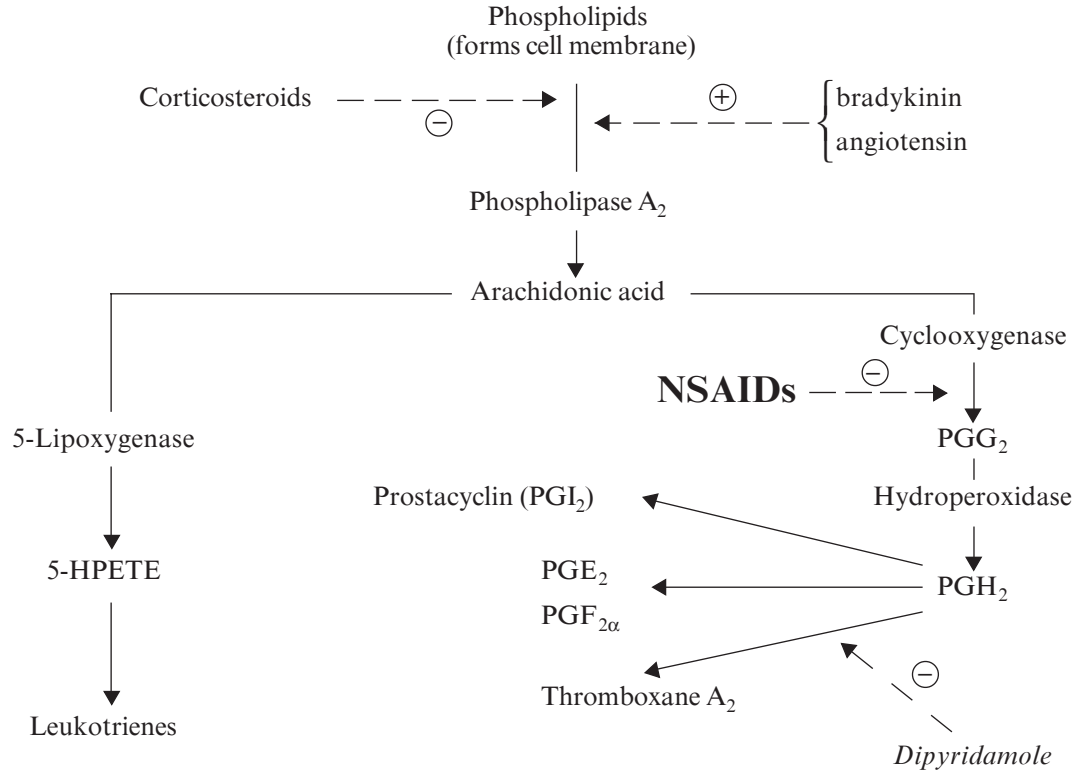


Fig. 10. Mechanism of action of nonsteroidal anti-inflammatory drugs

tion (the first step in clot formation). However, in other tissues, elevated levels of TXA_2 convey a different signals; e.g. in certain smooth muscle, this compound induces contraction. Prostaglandins are one of the chemical mediators that are released in allergic and inflammatory processes.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

NSAIDs are group of chemically dissimilar agents that differ in their antipyretic, analgesic and anti-inflammatory activities. They act primarily by inhibiting the cyclooxygenase enzymes but not the lipoxygenase enzymes. *Aspirin* is the prototype of this group; it is the most commonly used and the drug to which all other anti-inflammatory agents are compared. Some of the newer NSAIDs are marginally superior to *aspirin* in certain patients, because they have greater anti-inflammatory activity and/or cause less gastric irritation, or can be taken less frequently. However, the newer NSAIDs are considerably more expensive than *aspirin*, and some have proved to be more toxic in other ways.

ASPIRIN AND OTHER SALICYLATES

Aspirin is a weak organic acid that is unique among the NSAIDs in irreversibly acetylating (and thus inactivating) cyclooxygenase. The other NSAIDs, including salicylate, are all reversible inhibitors of cyclooxygenase. *Aspirin* is rapidly deacetylated by esterases in the body, producing salicylate, which has anti-inflammatory, antipyretic, and analgesic effects.

Mechanism of action. The antipyretic and anti-inflammatory effects of the salicylates are due primarily to the blockade of prostaglandin synthesis at the thermoregulatory centers in the hypothalamus and at the peripheral target sites. By decreasing prostaglandin synthesis, the salicylates also prevent the sensitization of pain receptors to both mechanical and chemical stimuli. *Aspirin* may also depress pain stimuli at subcortical sites (that is, the thalamus and hypothalamus).

Actions. The NSAIDs have three major therapeutic actions, namely they reduce inflammation (anti-inflammatory), pain (analgesia), and fever (antipyresis). However, not all of the NSAIDs are equally potent in each of these actions.

Anti-inflammatory action: *Aspirin* modulates those aspects of inflammation in which prostaglandins act as mediators. *Aspirin* inhibits inflammation in arthritis, but it neither arrest the progress of the disease nor does it induce remission.

Analgesic action: Prostaglandin E_2 is thought to sensitize nerve endings to the action of bradykinin, histamine, and other chemicals mediators released locally by the inflammatory process. Thus, by decreasing PGE_2 synthesis, *aspirin* and other NSAIDs repress the sensation of pain. The salicylates are used mainly for the management of pain of low to moderate intensity arising from integumental structures rather than that arising from the viscera. NSAIDs are superior to opioids in the management of pain in which inflammation is involved; combination of opioids and NSAIDs are effective in treating pain in malignancy.

Antipyretic action: Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated. This can be caused by PGE_2 synthesis, stimulated when an endogenous fever-producing agents

(pyrogen) such as a cytokine is released from white cells that are activated by infection, hypersensitivity, malignancy, or inflammation. The salicylates lower body temperature in patients with fever by impeding PGE_2 synthesis. *Aspirin* resets the "thermostat" towards normal and lowers the body temperature by increasing heat dissipation as a result of peripheral vasodilation and sweating. *Aspirin* has no effect on normal body temperature.

Gastrointestinal effects: Normally, prostacyclin (PGI_2) inhibits gastric acid secretion, whereas PGE_2 and $PGF_{2\alpha}$ stimulate synthesis of protective mucus in both the stomach and small intestine. In presence of *Aspirin*, these prostanoids are not formed, resulting in increased gastric acid secretion and diminished mucous protection. This may cause epigastric distress, ulceration, and/or hemorrhage. At ordinary *aspirin* doses, as much as 3 to 8 ml of blood may be lost in feces per day. [Note: Buffered and enteric-coated preparations are only marginally helpful in dealing with this problem. The PGE_1 derivative, *Misoprostol*, is used in the treatment of gastric damage induced by NSAIDs.]

Effect on platelets: TXA_2 enhances platelet aggregation, whereas PGI_2 decreases it. Low doses (60 to 80 mg daily) of *Aspirin* can irreversibly inhibit thromboxane production platelets without markedly affecting PGI_2 production in the endothelial cells of the blood vessel. [Note: The acetylation of cyclooxygenase is irreversible. Because platelets lack nuclei, they cannot synthesize new enzyme, and the lack of thromboxane persist for the lifetime of the platelet (3 to 7 days). This contrasts with endothelial cells, which have nuclei and therefore can produce new cyclooxygenase.]

Action on the kidney: Cyclooxygenase inhibitors prevent the synthesis of PGE_2 and PGI_2 — prostaglandins that are responsible for maintaining renal blood flow. Decreased synthesis of prostaglandins can result in intrarenal vasoconstriction, retention of sodium and water in some patients. Interstitial nephritis can also occur with all of the NSAIDs except *Aspirin*.

Therapeutic uses:

Antipyretics and analgesics: *Sodium salicylate* and *aspirin* are used as antipyretics and analgesics in the treatment of gout, rheumatic fever, and rheumatoid arthritis. Commonly treated conditions requiring analgesia include headache, arthralgia, and myalgia.

External applications: *Salicylic acid* is used topically to treat corns, calluses, and epidermophytosis (eruption caused by fungi). *Methyl salicylate* is used externally as a cutaneous counterirritant in liniments.

Cardiovascular applications: *Aspirin* inhibits platelet aggregation. Low doses are used prophylactically to decrease the incidence of transient ischemic attack and unstable angina as well as that of coronary artery thrombosis.

Colon cancer: There is evidence that chronic use of *Aspirin* reduces the incidence of colorectal cancer.

Pharmacokinetics. Salicylates, especially *methyl salicylate*, are absorbed through intact skin. After oral administration, the unionized salicylates are passively absorbed from the stomach and small intestine. Rectal absorption is slow and unreliable, but it is a useful route to vomiting children. Salicylates cross both the blood-brain barrier and placenta.

The salicylates exhibit analgesic activity at low doses (Fig. 11); only at higher doses these drugs show anti-inflammatory activity. E.g. two 300 mg *Aspirin* tablets administered 4 times a day produce analgesia, whereas 12 to 20 tablets per day produce both analgesic and anti-inflammatory activity. Low doses of *Aspirin* (160 mg every other day) have been shown to reduce the incidence of recurrent myocardial infarction and to reduce mortality in postmyocardial infarction patients. Further, *Aspirin* 160 to 325 mg/day appears to be beneficial in the prevention of a first myocardial infarction, at least in men over the age of 50 years. Thus, prophylactic *Aspirin* therapy is advocated in patients with clinical manifestations of coronary disease if no specific contraindications are present.

At normal low doses (600 mg/day), *aspirin* is hydrolyzed to salicylate and acetic acid by esterases

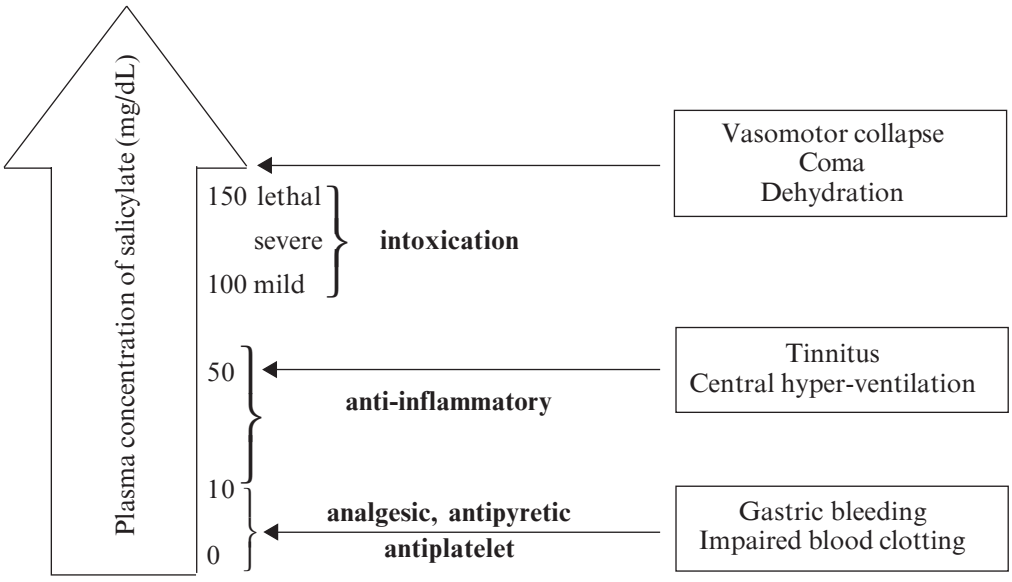


Fig. 11. Dose-dependent effects of *Aspirin*

present in tissues and blood. Salicylate is converted by the liver to water-soluble conjugates that are rapidly cleared by the kidney, resulting in elimination with first-order kinetics and a serum half-life of 3.5 hours. At anti-inflammatory dosages (>4 g/day), the hepatic metabolic pathway becomes saturated, and zero-order kinetics are observed, with the drug having a half-life of 15 hours or more. Saturation of the hepatic enzymes requires treatment for several days to 1 week. Being an organic acid, salicylate is secreted into the urine and can affect uric acid secretion. At low doses of *aspirin,* uric acid secretion is decreased; at high doses, it is increased. [Note: Alkalinization of the urine promotes excretion.]

Adverse effects:

GI. The most common GI effects of the salicylates are epigastric distress, nausea, and vomiting. Microscopic GI bleeding is almost universal in patients treated with salicylates. [Note: *Aspirin* is an acid. At stomach pH, *Aspirin* is uncharged; consequently it readily crosses into the mucosal cells where it ionizes and becomes trapped. *Aspirin* should be taken with food and large volumes of fluids to diminish GI disturbances. Alternatively, *Misoprostol* may be taken concurrently.

Blood. The irreversible acetylation of platelet cyclooxygenase reduces the level of platelet TXA_2, resulting in inhibition of platelet aggregation and prolonged bleeding time. For this reason *Aspirin* should not be taken at least 1 week prior to surgery.

Respiration. In toxic doses, salicylates cause respiratory depression and a combination of uncompensated respiratory and metabolic acidosis.

Metabolic processes. Large doses of salicylates uncouple oxidative phosphorylation. The energy normally used for the production of ATP is dissipated as heat, which explains the hyperthermia caused by salicylates when taken in toxic quantities.

Hypersensitivity. Approximately 15% of patients taking *Aspirin* experience hypersensitivity reactions. Symptoms of true allergy include urticaria, bronchoconstriction, or angioneurotic edema. Fatal anaphylactic shock is rare.

Reye's syndrome. *Aspirin* given during viral infections has been associated with an increased incidence of Reye's syndrome, an often fatal, fulminating hepatitis with cerebral edema. This is especially encountered in children, who therefore should be given *Paracetamol* instead of *Aspirin*.

Salicylate intoxication may be mild or severe. The mild form is called salicylism and is characterized by nausea, vomiting, marked hyperventilation, headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears). When large doses are administered, severe salicylate intoxication may result. The symptoms listed above are followed by restlessness, delirium, hallucinations, convulsions, coma, respiratory and metabolic acidosis, and death from respiratory failure. Children are particularly prone to salicylate intoxication. Ingestion of as little as 10 g of *Aspirin* can cause death in children. Treatment of salicylism should include measurement of serum salicylate concentrations and of pH to determine the best form of therapy. In mild cases, symptomatic treatment is usually sufficient. Increasing the urinary pH enhances the elimination of salicylates. In serious cases, mandatory measures include the intravenous administration of fluid, dialysis, and correction of acid-base and electrolyte balances.

PROPIONIC ACID DERIVATIVES

Ibuprofen was first in this class of agents to become available. It has been joined by *Naproxen, Ketoprofen, Flurbiprofen*, and others. All of these drugs possess anti-inflammatory, analgesic and antipyretic activity and have gained wide acceptance in the chronic treatment of rheumatoid and osteoarthritis because their GI effects are generally less intense than that of *Aspirin*. These drugs are reversible inhibitors of the cyclooxygenase and thus, like *Aspirin*, inhibit the synthesis of prostaglandins but not that of leukotrienes. All are well absorbed on oral administration and are almost totally bound to serum albumin. They undergo hepatic metabolism and are excreted by the kidney. The most common adverse effect is gastrointestinal, ranging from dyspepsia to bleeding. Side effects involving the CNS, such as headache, tinnitus and dizziness, have also been reported.

INDOLEACETIC ACIDS

This group includes *Indomethacin, Sulindac* and *Etodolac*. All have anti-inflammatory, analgesic and antipyretic activity. They act by reversibly inhibiting cyclooxygenase. They are generally not used to lower fever.

Indomethacin. This NSAID is more potent than *Aspirin* as an anti-inflammatory agent, but it is inferior to the salicylates at doses tolerated by rheumatoid arthritic patients. In certain instances (acute gouty arthritis, ankylosing spondylitis, and osteoarthritis of the hip) *Indomethacin* is more effective than *Aspirin* is or any of the other NSAIDs. It is also effective in treating patent ductus arteriosus. Like *Aspirin*, *Indomethacin* can delay labor by suppressing uterine contractions. *Indomethacin's* toxicity limits its use. Adverse effects occur in up to 50% of patients; approximately 20% find the adverse effects to be intolerable and discontinue use of the drug. Most adverse effects are dose-related. GI complaints consist of nausea, vomiting, anorexia, diarrhea, and abdominal pain. Ulceration of the upper GI tract can occur, sometimes with perforation and hemorrhage. The most severe and frequent CNS effect is frontal headache, which occurs in 25 to 50% of patients who chronically use *Indomethacin*. Other CNS effects are dizziness, vertigo, and mental confusion. Concurrent administration of *Indomethacin* may decrease the antihypertensive effects of *Furosemide*, the thiazide diuretics, β-blockers and ACE inhibitors.

Sulindac. This inactive pro-drug is closely related to *Indomethacin*. Metabolism of hepatic microsomal enzymes produces the active form (a sulfide) of the drug, which has a long duration of action. Although the drug is less potent than *Indomethacin*, it is useful in the treatment of rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and acute gout. The adverse

reactions are similar to but less severe than those of the other NSAIDs, including *Indomethacin*.

PYRAZOLON DERIVATIVES

This group of drugs includes *Butadion, Analgin, Antipyrine, Amidopyrine*. All these drugs have been in clinical use for many years. Although not a first-line drug, *Butadion (Phenylbutazone)* is the most important from the therapeutic viewpoint. *Antipyrine* and *Amidopyrine* are seldom used today. *Analgin (metamizole)* is not yet available in certain countries.

Butadion *(Phenylbutazone)*. *Butadion* has powerful anti-inflammatory effects but weak analgesic and antipyretic activities. *Butadion* is prescribed chiefly in short-term therapy when other NSAIDs have failed. The usefulness of *Butadion* is limited by its toxicity. The most serious adverse effects are agranulocytosis and aplastic anemia. However, the most common adverse effects are nausea, vomiting, skin rashes, and epigastric discomfort. Other side effects include fluid and electrolyte retention, diarrhea, vertigo, insomnia. *Butadion* reduces the uptake of iodine by thyroid gland, sometimes resulting in goiter and myxedema. Because of all these potential side-effects, the drug should be given for short period of time — up to 1 week only.

OTHER AGENTS

Diclofenac. A cyclooxygenase inhibitor, *Diclofenac* is approved for long-term treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondilitis. It is more potent than *Indomethacin*. *Diclofenac* accumulates in synovial fluid. The urine is the primary route of excretion. Its toxicities are similar to those of the other NSAIDs, e.g. GI problems are common, and the drug can also give rise to elevated hepatic enzyme levels.

Mefenamic acid has no advantages over the other NSAIDs as anti-inflammatory agent. Its side effects, such as diarrhea, can be severe and associated with inflammation of the bowel. Cases of hemolytic anemia have been reported.

Piroxicam is one of the oxicam derivatives that possesses anti-inflammatory, analgesic, and antipyretic activity. In recommended doses, *Piroxicam* appears to be equivalent to *Aspirin, Indomethacin,* or *Naproxen* for the long-term treatment of rheumatoid arthritis or osteoarthritis. It may be tolerated better than *Aspirin* or *Indomethacin*. The principal advantage of *Piroxicam* is its long half-life (50 hours), which permits the administration of a single daily dose. GI disturbances are encountered in approximately 20% of patients.

Ketorolac. This drug acts like other NSAIDs. In addition to the oral rout, *Ketorolac* can be administered intramuscularly in the treatment of postoperative pain, and topically for allergic conjunctivitis. *Ketorolac* undergoes hepatic metabolism; the drug and its metabolites are eliminated via the urine. It causes the same side effects as the other NSAIDs.

NON-NARCOTIC ANALGESICS

Non-narcotic analgesics, unlike the NSAIDs, have little or no anti-inflammatory activity. They have a therapeutic advantage of narcotic analgesics in that they do not cause physical dependence or tolerance.

Paracetamol *(Acetaminophen)* and *Phenacetin* act by inhibiting prostaglandin synthesis in the CNS. This explains their antipyretic and analgesic properties. They have less effects on cyclooxygenase in peripheral tissues, which accounts for their weak anti-inflammatory activity. *Paracetamol* and *Phenacetin* do not affect platelet function or increase blood clotting time, and they lack many of the side-effects of *Aspirin*. [Note: *Phenacetin* can no longer be prescribed in many countries because of its renal toxicity. However, it is present in some proprietary preparations.]

Therapeutic uses. *Paracetamol* is a suitable substitute for the analgesic and antipyretic effects of *Aspirin* in those patients with gastric complaints and in those for whom prolongation of bleeding time would be a disadvantage or who do not require the anti-inflammatory action of *Aspirin*. *Paracetamol* is the analgesic-antipyretic of choice for children with viral infections or chicken pox (recall that *Aspirin* increases the risk of Reye's syndrome).

Pharmacokinetics. *Paracetamol* is rapidly absorbed from the GI tract. A significant first-pass metabolism occurs in the luminal cells of the intestine and in the hepatocytes. *Phenacetin* is largely converted to *Paracetamol* within 3 hours of administration. Under normal circumstances, *paracetamol* is conjugated in the liver to form inactive glucuronidated or sulfated metabolites. A portion of *paracetamol* is hydroxylated to form N-acetyl-benzoquinoneimine — a highly reactive and potentially dangerous metabolite that reacts with sulfhydryl groups. At normal doses of *Paracetamol,* the N-acetyl-benzoquinoneimine reacts with groups of glutathione, forming a nontoxic substance. *Paracetamol* and its metabolites are excreted in the urine.

Adverse effects. With normal therapeutic doses, *Paracetamol* is virtually free of any significant adverse effects. Skin rash and minor allergic reactions occur infrequently. Renal tubular necrosis and hypoglycemic coma are rare complications of prolonged large-dose therapy. With large doses of *Paracetamol,* the available glutathione in the liver becomes depleted and N-acetyl-benzoquinoneimine reacts with the sulfhydryl groups of hepatic proteins, forming covalent bounds. Hepatic necrosis, a very serious and potentially life-threatening condition, can result. Renal tubular necrosis may also occur. [Note: Administration of N-acetylcysteine, which contains sulfhydryl groups to which the toxic metabolite can bind, can be life-saving if administered within 10 hours of the overdose.]

Available forms:

Paracetamol — in tablets 0.2 each

Acetylsalicylic acid — in tablets 0.25; 0.5 (for adult) and 0.1 (for children)

Phenylbutazone (Butadionum) — in tablets 0.15 (for adult) and 0.03; 0.05 (for children); 5% ointment 20.0

Ortophenum — in tablets 0.025 (for adult) and 0.015 (for children) each; in ampoules 2.5% solution 3 ml each

Sulindac — in tablets 0.1; 0.2; 0.4 each

Piroxicam — in tablets 0.01 each; in capsules 0.02 each

Lecture 14
NARCOTIC ANALGESICS

This lecture presents the pharmacological properties of the opioids (opioid agonists) and the opioid antagonists. Opioids are natural or synthetic compounds that produce morphine-like effects. The term opiates is reserved for drugs, such as *Morphine* and *Codeine*, obtained from the juice of the opium poppy. All drugs of this category act by binding to specific opioid receptors in the CNS to produce effects that mimic the action of endogenous peptide neurotransmitters, the opiates (e.g. endorphins, and enkephalins). Although the opioids have a broad range of effects, their primary use is to relieve intense pain and the anxiety that accompanies it, whether it be form surgery or as a result of injury or a disease, such as cancer. However, their widespread availability has led to abuse of these opioids with euphoric properties. Antagonists that can reverse the action of opioids are also very important clinically in cases of overdose.

Opioid receptors. Opioids interact with protein receptors on the membranes of certain cells in the CNS, on nerve terminals on the periphery, and on cells of the GI tract. The major effects of the opioids are mediated by 4 families of receptors, designated by the Greek letters, μ, κ, σ and δ, each of which exhibits a different specificity for the drug(s) it binds. In general, binding potency correlates with analgesia (Fig. 12). The analgesic properties of the opioids are primarily by the μ-receptors; however, the k receptors on the dorsal horn also contribute. The enkephalins interact more selectively with the d receptors in the periphery. The s receptors are less specific (e.g. the σ-receptor also binds nonopioid agents, such as the hallucinogen *Phencyclidine*). The s receptor may be responsible for the hallucinations and dysphoria sometimes associated with opioids.

Distribution of receptors. High densities of opioid receptors are present in five general areas of the CNS known to be involved in integrating information about pain. These pathways descend from the periaqueductal gray (PAG) through the dorsal horn of the spinal cord. They have also been identified in the periphery.

Brainstem. Opioid receptors mediate respiration, cough, nausea and vomiting, maintenance of blood pressure, pupillary diameter, and control of stomach secretions.

Medial thalamus. This area mediates deep pain that is poorly localized and emotionally influenced.

Spinal cord. Receptors in substantia gelatinosa are involved with the receipt and integration of incoming sensory information.

Hypothalamus. Receptors here affect neuroendocrine secretion.

Limbic system. These receptors probably do not exert analgesic action, but they may influence emotional behavior.

Periphery. Opioids also bind to peripheral sensory nerve fibers and their terminals. As in the CNS, they inhibit Ca^{++}-dependent release of excitatory, pro-inflammatory substances (e.g. substance P) from these nerve endings.

Immune cells. The role of these receptors has not been determined.

Opioids are classified according to its affinity for opioid receptors (Fig. 13).

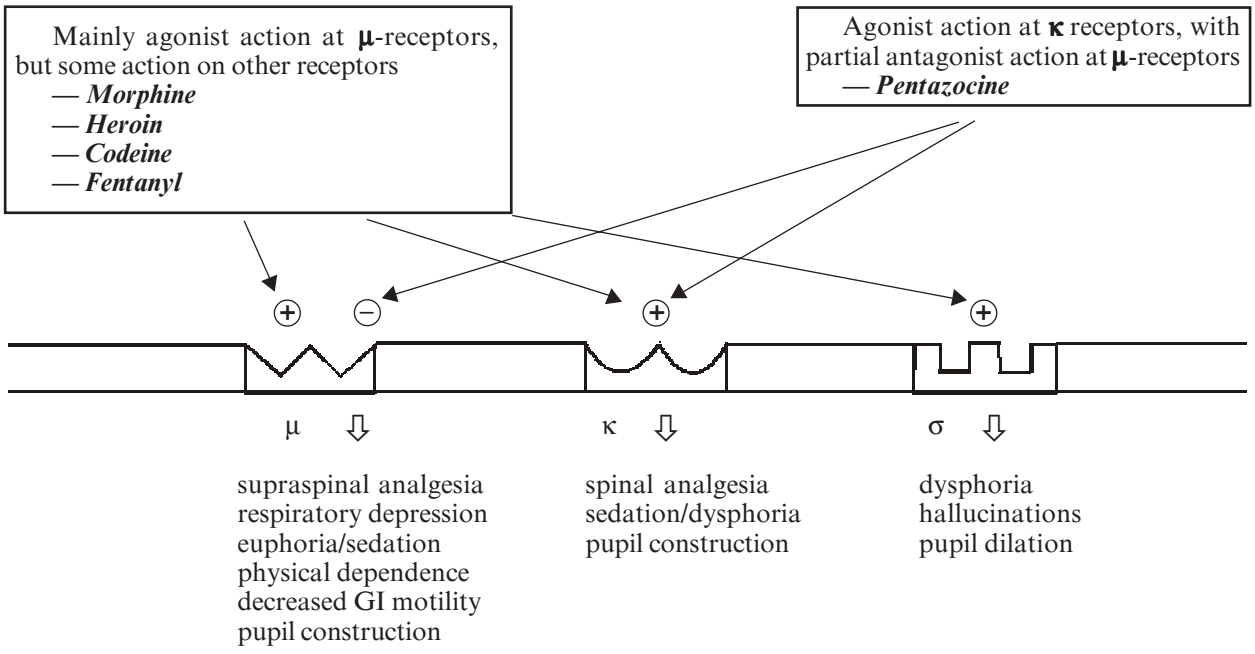


Fig. 12. Opioid receptors and effects of drugs

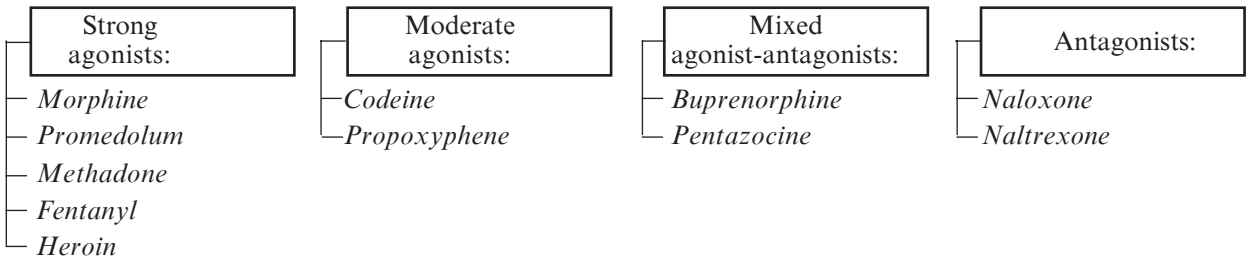


Fig. 13. Classification of opioids according to its affinity for opioid receptors

STRONG AGONISTS

Morphine is the major analgesic drug contained in crude opium and is the prototype agonist. *Codeine* is present in lower concentrations and is inherently less potent. These drugs show a high affinity for μ-receptors, varying affinities for δ- and κ-receptors, and low affinity for σ-receptors.

Morphine

Mechanism of action. Opioids exert their major effects by interacting with opioid receptors in the CNS and the GI tract. Opioids cause hyperpolarization of nerve cells, inhibiting the nerve firing, and presynaptic inhibition of transmitter release. *Morphine* inhibits the release of many excitatory transmitters from nerve terminals carrying nociceptive (painful) stimuli; it also decreases the release of substance P, which modulates pain perception in the spinal cord.

Actions:

Analgesia. *Morphine* causes analgesia (relief of pain without loss of consciousness). Opioids relieve pain both by raising the threshold at the spinal cord level, and more importantly, by altering the brain's perception of pain. Patients treated with *Morphine* are still aware of the presence of pain, but the sensation is not unpleasant.

Euphoria. *Morphine* produces a powerful sense of contentment and well-being. Euphoria may be caused by stimulation of the ventral tegmentum.

Respiration. *Morphine* causes respiratory depression by reduction of the sensitivity of respiratory center to carbon dioxide. This occurs with ordinary doses of *Morphine* and is accentuated as the dose increases until, ultimately, respiration ceases. Respiratory depression is the most cause of death in acute opioid overdose.

Depression of cough reflex. *Morphine* and *Codeine* have antitussive properties. In general, cough suppression does not correlate closely with analgesic and respiratory depressant properties of opioid drugs. The receptors involved in the antitussive action appear to be different than those involved in analgesia.

Miosis. The pinpoint pupil, characteristic of *Morphine* use, results from stimulation of μ- and κ-receptors. *Morphine* excites the Edinger-Westphal nucleus of the oculomotor nerve, which causes enhanced parasympathetic stimulation of the eye. There is little tolerance to the effect, and all addicts demonstrate pinpoint pupils. This is important diagnostically, because most other causes of coma and respiratory depression produce dilation of the pupil.

Emesis. *Morphine* directly stimulates the chemoreceptor trigger zone in the area postrema that causes vomiting. However, the emesis does not produce unpleasant sensation.

GI tract. *Morphine* relieves diarrhea. It decreases motility of smooth muscle and increases tone. It increases pressure in the biliary tract. *Morphine* also increases tone of the anal sphincter. Overall, *Morphine* produces constipation, with little tolerance developing.

Cardiovascular. *Morphine* has no major effect on the blood pressure or heart rate except at large doses, when hypotension and bradycardia may develop. Because of respiratory depression and carbon dioxide retention, cerebral vessels dilate and increase cerebrospinal fluid (CSF) pressure. Therefore, *Morphine* is usually contraindicated in individuals with severe brain injury.

Histamine release. *Morphine* releases histamine from mast cells, causing urticaria, sweating, and vasodilation. Because it can cause bronchoconstriction, asthmatics should not receive the drug.

Hormonal actions. *Morphine* inhibits release of gonadotropin-releasing hormone and decreases the concentration of luteinizing hormone, follicle-stimulating hormone, adrenocorticotropic hormone, and β-endorphin. Testosterone and cortisol levels decrease. *Morphine* increases prolactin and growth hormone release by diminishing dopaminergic inhibition. It increases antidiuretic hormone (ADH) and thus leads to fluid retention.

Therapeutic uses:

Analgesia. Despite intensive research, few other drugs have been developed that are as effective in the treatment of pain (postoperative pain, pain of terminal illness and cancer pain, etc.). Opioids induce sleep, and in clinical situations when pain is present and sleep is necessary, opiates may be used to supplement the sleep-inducing properties of benzodiazepines. [Note: The sedative-hypnotic drugs are not usually analgesic, and may have diminished sedative effect in the presence of pain.]

Relief of cough. *Morphine* suppresses the cough reflex; however, *Codeine* is more widely used. *Codeine* has greater antitussive action than *Morphine*.

Pulmonary edema. *Morphine* is used to alleviate the dyspnea of acute left ventricular failure and pulmonary edema, in which to i.v. *Morphine* may be dramatic. The mechanism underlying this relief is still not clear. It may involve an alteration of the patient's reaction to impaired respiratory function and indirect of the work of the heart due to reduced fear.

Treatment of diarrhea. *Morphine* decreases the motility of smooth muscle and increases tone. Synthet-

ic opioids also produce a decrease in bowel motility; several of these, such as *Loperamide* are used exclusively for this purpose.

Pharmacokinetics. Absorption of *morphine* from the GI tract is slow and erratic, and the drug is usually not given orally. *Codeine*, by contrast, is well absorbed when given by mouth. Significant first pass metabolism occurs in the liver; therefore, i.m., s.c., or i.v. injections produce more reliable responses. Opiates have been commonly taken for nonmedical purposes by inhalation of the smoke from burning crude opium, which provides a rapid onset of action.

Morphine rapidly enters all body tissues, including the fetuses of pregnant women, and should not be used for analgesia during labor. Infants born of addicted mothers show physical dependence on opiates and exhibit withdrawal symptoms. Only a small percentage of *Morphine* crosses the blood-brain barrier, since *Morphine* is the least lipophilic of the common opioids. This contrasts with the more fat-soluble opioids, such as *fentanyl* and *heroin*, which readily penetrate into the brain and rapidly produce an intense "rush" of euphoria.

Morphine is metabolized in the liver to glucuronides. Morphine-6-glucuronide is a very potent analgesic, whereas the conjugate at the 3-position is inactive. The conjugates are excreted primarily in the urine. The duration of action of *Morphine* is 4 to 6 hours in naïve individuals. [Due to the low conjugation capacity in neonates, they should not receive *Morphine*.]

Adverse effects. Severe respiratory depression occurs. Other effects include vomiting, dysphoria, and allergy-enhanced hypotensive effects. The elevation of intracranial pressure, particularly in head injury, can be serious. *Morphine* enhances cerebral and spinal ischemia. In prostatic hypertrophy, *Morphine* may cause acute urinary retention. A serious action is stoppage of respiratory exchange in emphysema or cor pulmonale patients. If employed in such individuals, respiration must be carefully watched.

Tolerance and physical dependence. Repeated use produces tolerance to the respiratory depressant, analgesic, euphoric, and sedative effects of *Morphine*. However, tolerance usually does not develop to the pupil-constricting and constipating effects of the drug. Physical and psychologic dependence readily occur with *Morphine* and with some other agonists. Withdrawal produces a series of autonomic, motor and psychological responses that causes serious, almost unbearable symptoms. However, it is very rare that the effects are so profound as to cause death.

Methadone

Methadone is a synthetic, orally effective opioid that is approximately equal in potency to *Morphine*, but induces less euphoria and has a longer duration of action. *Methadone* has its greatest action on μ-receptors. The analgesic activity is equivalent to that of *Morphine*. The drug is well absorbed when administered orally. The miotic and respiratory depressant actions of *Methadone* have average half-lives of 24 hours.

Methadone is used in the controlled withdrawal of addicts from *Heroin* and *Morphine*. Orally administered, *Methadone* is substituted for the injected opioid. The patient then slowly weaned from *Methadone*. *Methadone* causes a milder withdrawal syndrome, which also develops more slowly than that seen during withdrawal from *Morphine*. Readily absorbed following oral administration, *Methadone* has a longer duration of action than does *Morphine*. *Methadone* can produce dependence like that of *Morphine*. The withdrawal syndrome is much milder but is more protracted (days to weeks) than with opiates.

Fentanyl

Fentanyl has 80 times the analgesic potency of *Morphine*, and is used in anaesthesia. It has a rapid onset and short duration of action (15 to 30 minutes). When combined with *Droperidol* it produces a dissociative anaesthesia (neuroleptanalgesia). *Sufentanil*, a related drug, is even more potent than *Fentanyl*.

Heroin

Heroin does not occur naturally but is produced by acetylation of *Morphine*, which leads to a tree-fold increase in its potency. Its greater lipid solubility allows it to cross blood-brain barrier more rapidly than *Morphine*, causing a more exaggerated euphoria when the drug is taken by injection. *Heroin* is converted to *Morphine* in the body, but lasts about half as long. It has no accepted medical use.

Omnoponum

Omnoponum is a mixture of purified opium alkaloids that contains 48–50% of *Morphine* and 32–35% of other alkaloids. *Omnoponum* produces a pattern of effects quite similar to that of *Morphine*. Sometimes it is better tolerated than *Morphine* and appears to be less spasmogenic.

Trimeperidine (Promedolum)

Promedolum is a synthetic opioid with a structure unrelated to *Morphine*. The pharmacological effects of *Promedolum* closely parallel but not identical those of *Morphine*. *Promedolum* causes a depression of respiration. On i.v. administration, the drug produces a decrease in peripheral resistance and an increase in peripheral blood flow. As with *Morphine, Promedolum* dilates cerebral vessels, increases cerebrospinal fluid pressure, and contracts smooth muscle (the latter to a lesser extent than does *Morphine*). In GI tract, *Promedolum* impedes motility, and chronic use results in constipation. *Promedolum* does not cause pinpoint pupils, but rather causes pupil to dilate because of an atropine-like activity. *Promedolum* provides analgesia for any type of severe pain. Unlike *Morphine*, it is not clinically useful in the treatment of diarrhea or cough. *Promedolum* produces less of an increase in urinary retention than does *Morphine*.

MODERATE AGONISTS

Codeine

Codeine is a much less potent analgesic than *Morphine*, but it has a higher oral efficacy. *Codeine* shows good antitussive activity at doses that do not cause

analgesia. The drug has a lower abuse potential than *Morphine* and rarely produces dependence. *Codeine* produces less euphoria than *Morphine*. *Codeine* is often used in combination with *Aspirin* or *Paracetamol*. [Note: In most nonprescription cough preparations, *codeine* has been replaced by newer drug, such as *Dextromethorphan*, a synthetic cough depressant that has no analgesic action and a low potential for abuse.]

MIXED AGONIST-ANTAGONISTS

Drugs that stimulate one receptor but block another are termed mixed agonist-antagonists. The effects of the drugs depend on previous exposure to opioids. In individuals who have not recently received opioids, mixed agonist-antagonists show agonist activity and are used to relieve pain. In the patient with opioid dependence, the agonist-antagonist drugs may show primarily blocking effects, that is, produce withdrawal symptoms. Most of the drugs in this group cause dysphoria, rather than euphoria, mediated by activation of σ-receptors.

Pentazocine

Pentazocine acts as an agonist on κ-receptors and is a weak antagonist at μ- and δ-receptors. It also binds to σ-receptors, which may account for its dysphoric properties. *Pentazocine* promotes analgesia by activating receptors in the spinal cord, and is used to relieve moderate pain. In higher doses, the drug causes respiratory depression. High doses increase blood pressure and can cause hallucination, nightmares, tachycardia, and dizziness. In angina, *Pentazocine* increases the mean aortic pressure and pulmonary arterial pressure and thus increases the work of the heart. The drug decreases renal blood flow. Despite its antagonist action, *Pentazocine* does not antagonize the respiratory depression of *Morphine*, but it can precipitate a withdrawal syndrome in a *Morphine* abuser. *Pentazocine* should not be used with agonists such *Morphine*, since the antagonist action may block the analgesic effect of *Morphine*. Tolerance and dependence develop on repeated use.

Buprenorphine

Although *Buprenorphine* is classified as a partial agonist acting on the μ-receptors, it behaves like *Morphine* in naïve patients. However, it can also antagonize *Morphine. Buprenorphine* has a long duration of action because of its tight binding to the receptor. It is metabolized by the liver and excreted in the bile and urine. Adverse effects include respiratory depression, decrease (or, rarely, increase) in blood pressure, nausea and dizziness.

ANTAGONISTS

The opioid antagonists bind with high affinity to opioid receptors but fail to activate the receptor-mediated response. Administration of opioid antagonists produces no profound effects in normal individuals. However, in patients addicted to opioids, antagonists rapidly reverse the effect of agonists, such as *Heroin*, and precipitate the symptoms of opiate withdrawal.

Naloxone

Naloxone is used to reverse the coma and respiratory depression of opioid overdose. It rapidly displaces all receptor-bound opioid molecules and therefore is able to reverse the effect of a *Heroin* overdose. Within 30 seconds of intravenous injection of *Naloxone*, the respiratory depression and coma characteristic of high doses of *heroin* are reversed, causing the patient to be revived and alert. *Naloxone* has a half-life of 60 to 100 minutes. *Naloxone* is a competitive antagonist at μ, κ and δ-receptors, with a 10-fold higher affinity for μ-receptors than for κ. This may explain why *Naloxone* readily reverses respiratory depression with only minimal reversal of analgesia that results from agonist stimulation of κ-receptors in the spinal cord. *Naloxone* produces no pharmacological effects in normal individuals, but it precipitate withdrawal symptoms in *Morphine* and *Heroin* abusers.

Naltrexone

Naltrexone has action similar to those of *Naloxone*. This drug has a longer duration of action than *Naloxone*, and a single oral dose blocks the effects of injected *Heroin* for up to 48 hours. *Naltrexone* is used in opiate-dependence maintenance programs and may also be beneficial in treating chronic alcoholism.

Available forms:

Morphine hydrochloride — in tablets 0.01 each; in ampoules 1% solution 1 ml each

Codeine — in tablets 0.015 each

Pentazocine — in tablets 0.05 each; in ampoules 1 ml (contain 0.03 of pentazocine) each

Trimeperidine (Promedolum) — in tablets 0.025 each; in ampoules 1% or 2% solution 1 ml

Fentanyl — in ampoules 0.005% solution 2 or 5 ml each

Naloxone hydrochloride — in ampoules 1 ml (contain 0.0004 of naloxone)

Naltrexone — in tablets 0.05 each

Lecture 15
NEUROLEPTICS

The use of drugs with well-demonstrated efficacy in psychiatric disorders has become widespread since the mid 1950s. In 1950, *Chlorpromazine* was synthesized in France. The recognition of its unique effects by Laborit and its use in psychiatric patients by Deley and Deniker (1952) marked the beginnings of modern psychopharmacology. A report on *Meprobamate* by Berger (1954) marked the beginning of investigation of modern sedatives with useful antianxiety properties. An antitubercular drug, *Iproniazid*, was introduced in the early 1950s and was

soon recognized as a MAO inhibitor and antidepressant. In 1958, Kuhn recognized the antidepressant effect of *imipramine*. The first of antianxiety benzodiazepines, *Chlordiazepoxide*, was developed by Sternbach in 1957. During the 1960s the expansion of psychopharmacological research was rapid, and many theories of psychoactive drug effects were introduced. The clinical efficacy of many of these agents was firmly established during that decade. Today, about 10–20% of prescriptions are for medications intended to affect mental processes, namely, to sedate, stimulate, or otherwise change mood, thinking, or behavior.

Neuroleptic drugs (also called **antischizophrenic drugs, antipsychotic drugs,** or **major tranquilizers**) are used primarily to treat schizophrenia but also effective in other psychotic states, such as manic states and delirium. The traditional neuroleptic drugs are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blocking of dopamine receptors. The drugs vary in their potency, but no one drug is clinically more effective than another. In contrast, the newer "atypical" antipsychotic drugs appear to owe their unique activity to blockade serotonin receptors. Neuroleptics are not curative and do not eliminate the fundamental thinking disorders, but often do permit the psychotic patient to function in a supportive environment.

Schizophrenia is a particular type of psychosis, that is, a mental disorder caused by some inherent dysfunction of the brain. It is characterized by delusions, hallucinations (often in the form of voices), and thinking or speech disturbances. This mental disorder is a common affliction, occurring among about 1% of the population, or at about the same incidence as diabetes mellitus. Schizophrenia has a strong genetic component and probably reflects some fundamental biochemical abnormality, possibly an overactivity of the mesolimbic dopaminergic neurons.

The **neuroleptic drugs** can be divided into five major classes based on the structure of the drugs (Fig. 14). This classification is of modest importance, because within each chemical group, different side chains have profound effects on the potencies of the drugs. The management of psychotic disorders can typically be achieved by familiarity within the effects of one or two drugs in each class.

Mechanism of action:

Dopamine receptor-blocking activity in brain. All of the neuroleptics block dopamine receptors in the brain and in the periphery. Five types of dopamine receptors have been identified. The clinical efficacy of the traditional neuroleptic drugs correlates closely with their ability to block D_2 receptors in the mesolimbic system. The action of the neuroleptic drugs are antagonized by agents that raise dopamine concentration, e.g. *L-dopa* and *Amphetamines*.

Serotonin receptor-blocking activity in the brain. The newer "atypical" agents appear to exert part of their unique action through inhibition of serotonin (S) receptors. Thus, *Clozapine* has high affinity for D_1 and D_4, S_2, muscarinic and α-adrenoreceptors, but it is also a dopamine D_2-receptor antagonist. Another new agent, *Risperidone*, blocks S_2-receptor to a greater extent than it does D_2-receptors. Both of these drugs exhibit a low incidence of extrapyramidal side effects.

Actions. The antipsychotic actions of neuroleptic drugs reflect blockade at dopamine/serotonin receptors. However, many of these agents also block cholinergic, adrenergic, and histamine receptors, causing a variety of side effects.

Antipsychotic actions. The neuroleptic drugs reduce the hallucinations and agitation associated with schizophrenia by blocking dopamine receptors in the mesolimbic system of the brain. These drugs also have a calming effect and reduce spontaneous physical movement. In contrast to the CNS depressants, such as barbiturates, the neuroleptics do not depress intellectual function of the patient, and motor incoordination is minimal. The antipsychotic effects usually take several weeks to occur.

Extrapyramidal effects. Parkinsonian symptoms, akathisia (motor restlessness), and tardy dyskinesia (inappropriate postures of the neck, trunk, and limbs) occur with chronic treatment. Blocking of dopamine receptors in the nigrostriatal pathway probably causes these unwanted parkinsonian symptoms. *Clozapine* and *Risperidone* exhibit a low incidence of these symptoms.

Antiemetic effect. With the exception of *Thioridazine*, most of the neuroleptic drugs have antiemetic effects that are mediated by blocking D_2 receptors of the chemoreceptor trigger zone of the medulla.

Antimuscarinic effect. All of the neuroleptics, particularly *Thioridazine* and *Aminazine*, cause anticholinergic effect, including blurred vision, dry mouth, sedation, and inhibition of gastrointestinal and urinary smooth muscle, leading to constipation and urinary retention.

Other effects. Blockade of α-adrenegic receptors causes orthostatic hypotension and lightheadedness. The neuroleptics also alter temperature-regulating

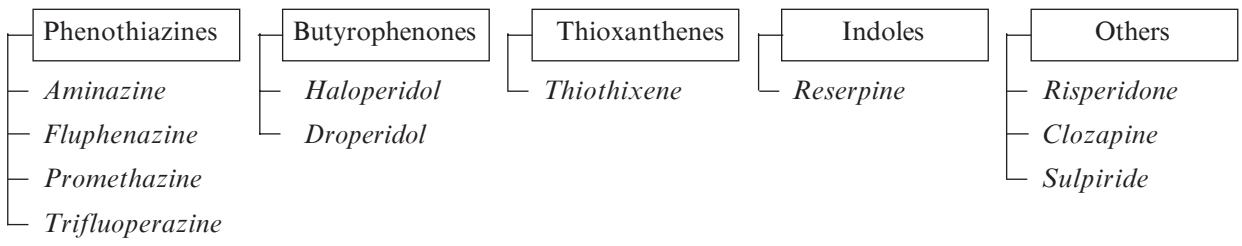


Fig. 14. Classification of neuroleptics

mechanism and can produce poikilothermy (body temperature varies with the environment). In the pituitary, the neuroleptics block D_2 receptors, leading to an increase in prolactin release.

Therapeutic uses:

Treatment of schizophrenia. The neuroleptics are the only efficacious treatment of schizophrenia. Not all patients respond, and complete normalization of behavior is seldom achieved. The traditional neuroleptics are most effective in treating positive symptoms (delusions, hallucinations and thought disorders). The newer agents with serotonin blocking activity are effective in many patients resistant to the traditional agents, especially in treating negative symptoms of schizophrenia (withdrawal, blunted emotions, reduced ability to relate to people).

Prevention of severe nausea and vomiting. The neuroleptics are useful in the treatment of drug-induced nausea. (*Scopolamine*, a muscarinic antagonist, is the drug of choice for the treatment of motion sickness.

Other use. The neuroleptic drugs may be used as tranquilizers to manage agitated and disruptive behavior. Neuroleptics are used in combination with narcotic analgesics for treatment of chronic pain with severe anxiety. *Aminazine* is used to treat intractable hiccups. *Droperidol* is a component of neuroleptanaesthesia. *Promethazine* is not a good antipsychotic drug, but the agent is used in treating pruritus because of its antihistaminic properties.

Adverse effects. Adverse effects of the neuroleptic drugs occur in practically all patients and are significant in about 80%. Although antipsychotic drugs have an array of adverse effects, their therapeutic index is high.

Parkinsonian effects. The inhibitory effects of dopaminergic neurons are normally balanced by the excitatory actions of cholinergic neurons. Blocking dopamine receptors alter this balance, causing a relative excess of cholinergic influence and resulting in extrapyramidal motor effects. A new, nearly normal balance can be achieved by administration of an anticholinergic drug, such as *Cyclodolum*.

Other effects. Drowsiness occurs due to CNS depression, usually during the first 2 weeks of treatment. Confusion is sometimes encountered. The neuroleptics produce dry mouth, urinary retention, constipation, and loss of accommodation. They block α-adrenergic receptors, resulting in lowered blood pressure and orthostatic hypotension. The neuroleptics depress the hypothalamus, causing amenorrhea, infertility, and impotence.

Available forms:

Chlorpromazine hydrochloride (Aminazinum) — in dragee 0.025; 0.05 or 0.1 each; in ampoules 2.5% solution 1; 2; 5 or 10 ml

Trifluoperazine (Triftazinum) — in tablets 0.001; 0.005 or 0.01 each; in ampoules 0.2% solution 1 ml each

Haloperidol — in tablets 0.0015 or 0.005 each; in ampoules 0.5% solution 1 ml each

Clozapine (Azaleptinum) — in tablets 0.025; 0.1 each; in ampoules 2.5% solution 2 ml each

Lecture 16
TRANQUILIZERS (ANXIOLYTICS)

Anxiety is an unpleasant state of tension, apprehension, or uneasiness — a fear that seems to arise from an unknown source. Disorders involving anxiety are the most common mental disturbances. The symptoms of severe anxiety are similar to those of fear (such as, tachycardia, sweating, trembling, palpitations) and involve sympathetic activation. Episodes of mild anxiety are common life experiences and do not warrant treatment. However, the symptoms of severe, chronic, debilitating anxiety may be treated with antianxiety drugs (sometimes called anxiolytic or minor tranquilizers), and/or some form of psycho- or behavioral therapy. Since all of the antianxiety drugs also cause sedation, the same drugs often function clinically as both anxiolytic and hypnotic agents.

In the XIX century, bromide salts and compounds similar in effects to *alcohol*, including *Paraldehyde* and *Chloral hydrate*, were introduced in medical practice as sedatives. These were followed in the early 1900s by the introduction of barbiturates. The barbiturates were the dominant antianxiety agents throughout the first half of this century. However, by the 1950s concern had arisen about their propensity to induce tolerance, physical dependence, and potentially lethal reactions during withdrawal, and this encouraged the search for safer agents. Compounds such as *Meprobamate* were the initial result. But they also shared many of the undesirable properties of barbiturates. These properties included an unclear separation between their useful antianxiety effect and excessive sedation. This set the scene for the discovery of *Chlordiazepoxide* in the late 1950s and introduction more than a dozen benzodiazepines since that time. This class of sedatives has come to dominate the market and medical practice.

BENZODIAZEPINES

Benzodiazepines are the most widely used anxiolytic drugs. They have largely replace barbiturates and *Meprobamate* in the treatment of anxiety, since the benzodiazepines are most effective and safer. Approximately 20 benzodiazepines are currently available.

Mechanism of action. The mechanism of action of benzodiazepine derivatives has already been discussed in details in the previous lecture (see hypnotics). They bind to specific receptors in the CNS. The result is to enhance the effects of gamma-aminobutyric acid (GABA); an important inhibitory neurotransmitter that acts by opening chloride ion channels into cells).

Actions. The benzodiazepines have no antipsychotic activity, nor any analgesic action and do not affect the autonomic nervous system. All of the benzodiazepines exhibit the following actions to a greater or lesser extent:

Reduction of anxiety. At low doses, the benzodiazepines are anxiolytic. They are thought to reduce anxiety by selectively inhibiting neuronal circuits in the limbic system of the brain.

Sedative and hypnotic actions: All of the benzodiazepines used to treat anxiety have some sedative properties. At higher doses, certain benzodiazepines produce hypnosis (artificially-produced sleep).

Anticonvulsant: Several of the benzodiazepines have anticonvulsant activity and are used to treat epilepsy and other seizure disorders.

Muscle relaxant: The benzodiazepines relax the spasticity of sceletal muscle, probably by increasing presynaptic inhibition in the spinal cord.

Therapeutic uses:

Anxiety disorders. Currently, the most useful antianxiety drugs are the benzodiazepines. These drugs should not be used to alleviate the normal stress of everyday life, but should be reserved for continued severe anxiety, and then should only be used for short periods of time because of addiction potential. The longer acting agents such as *Diazepam*, are often preferred in those patients with anxiety that may require treatment for prolonged periods of time. The antianxiety effects of the benzodiazepines are less subject to tolerance than the sedative and hypnotic effects. For panic disorders, *Alprazolam* is effective for short- and long-term treatment, although it may cause withdrawal reactions in about 30% of sufferers.

Sleep disorders. Not all of the benzodiazepines are useful as hypnotic agents, although all have sedative and calming effects. The most commonly prescribed benzodiazepines for sleep disorders are long-acting *Nitrazepam, Phenazepam,* and *Flurazepam,* intermediate-acting *temazepam,* and short-acting *Triazolam.*

Seizures. *Diazepam* is the drug of choice in terminating status epilepticus and grand mal seizures. *Clonazepam* is useful in the chronic treatment of epilepsy.

Muscular disorder. *Diazepam* is useful in the treatment of skeletal muscle spasms such as occur in muscle strain, and in treating spasticity from degenerative disorders, such as multiple sclerosis and cerebral palsy.

Pharmacokinetics. The benzodiazepines are lipophilic and are rapidly and completely absorbed after oral administration and are distributed throughout the body. *Diazepam* reaches peak concentration in about an hour in adults, and as quickly as 15 to 30 minutes in children. *Alprazolam, Chlordiazepoxide*, and *Lorazepam* have intermediate rates of absorption. Most of the benzodiazepines are bound to plasma protein to a great extent (85 to 95%) — a factor that limits the efficacy of dialysis in the treatment of acute poisonings. The apparent volumes of distribution for most benzodiazepines are about 1 to 3 liters per kilogram.

The pharmacokinetic parameters for these agents can often be misleading because active metabolites with long half-lives can markedly alter the duration of effects. For example, the formation of *Nordiazepam* from *Diazepam* can extend the duration of effect by two-fold or three-fold. The benzodiazepines can be roughly divided into short-, intermediate- and long-acting groups (Table 5).

Most benzodiazepines, including *Chlordiazepoxide* and *Diazepam,* are metabolized by the hepatic microsomal metabolizing system to compounds that are also active. For these benzodiazepines, the apparent half-life of the drug represents the combined actions of the parent drug and its metabolites. The benzodiazepines are excreted in urine as glucuronides or oxidized metabolites.

Dependence. Psychological and physical dependence on benzodiazepines can develop if high doses of the drug are given over a prolonged period. Abrupt discontinuation of the benzodiazepines results in withdrawal symptoms, including confusion, anxiety, agitation, restlessness, insomnia, and tension. Because of the long half-lives of some of the benzodiazepines, withdrawal symptoms may not occur until a number of days after discontinuation. Benzodiazepines with a short elimination half-life, such as *Triazolam*, induce more abrupt and severe withdrawal reactions.

Adverse effects. Drowsiness and confusion are the two most common side effect of the benzodiazepines. Ataxia occurs at high doses and precludes activities that require motor coordination, such as driving an automobile. Cognitive impairment (decreased long-term recall and acquisition of new knowledge) can occur. *Triazolam,* the benzodiazepine with most rapid elimination, often show a rapid development of tolerance, early morning insomnia and daytime anxiety, along with amnesia and confusion. Benzodiazepines potentiate alcohol and other CNS depressants. However, they are considerably less dangerous than other anxiolytic and hypnotic drugs. As a result, a drug overdose is seldom lethal, unless other central depressants, such as alcohol, are taken concurrently.

Precautions. Use benzodiazepines cautiously in treating patients with liver diseases. They potentiate alcohol and other CNS depressants. Benzodiazepines are, however, considerably less dangerous than other anxiolytic and hypnotic drugs. As a result, a drug overdose is seldom lethal, unless other central depressants, such as alcohol, are taken concurrently.

Benzodiazepine antagonist. Flumazenil is a GABA receptor antagonist that can rapidly reverse the effects

Table 5. **Groups of benzodiazepines according to the duration of action**

Long-acting	Intermediate-acting	Short-acting
1–3 days	10–20 hours	3–8 hours
Diazepam	Alprazolam	Triazolam
Chlordiazepoxide	Lorazepam	Oxazepam
Fenazepam	Temazepam	
Flurazepam		

of benzodiazepines. The drug is available by i.v. administration only. The onset is rapid but duration is short, with a half-life of about one hour. Frequent administration may be necessary to maintain reversal of benzodiazepines.

OTHER ANXIOLYTIC AGENTS

Other drugs that have been used in the treatment of anxiety include the propanediol carbamates (*Meprobamate*), certain anticholinergic agents (*Amizil*), antihistamines, etc. Many of these uses are now virtually obsolete.

Meprobamate. The properties of *Meprobamate* resemble those of the benzodiazepines (anxiolytic, sedative-hypnotic, muscle relaxant, and anticonvulsive actions). However, *Meprobamate* present additional problems, particularly its liability to produce tolerance, physical dependence, severe withdrawal reactions, and life-threatening toxicity with overdosage.

Amizylum. *Amizytlum* is a centrally acting muscarinic antagonist with anxiolytic effect. Its side effects qualitatively resemble the belladonna alkaloids.

Buspirone. *Buspirone* represents an entirely new class of drugs useful in the treatment of generalized anxiety disorders. It has an efficacy comparable to the benzodiazepines. The action of *Buspirone* appear to be mediated by serotonin ($5\text{-}HT_{1A}$) receptors, although other receptors could be involved, since *Buspirone* displays some affinity for DA_2 dopamine receptors and $5\text{-}HT_2$ serotonin receptors. The mode of action thus differs from that of benzodiazepines. Further, *Buspirone* lacks anticonvulsant and muscle-relaxant properties. The frequency of adverse effects is low. Sedation and psychomotor and cognitive dysfunction are minimal, and dependence is unlikely. *Buspirone* has the disadvantage of a slow onset of action.

Available forms:
Diazepam — in tablets 0.01 each
Alprazolam — in tablets 0.25 or 0.5 each
Oxazepam — in tablets 0.1
Amizylum — in tablets 0.001 or 0.002 each.

Lecture 17
PSYCHOSEDATIVE AGENTS

A sedative drug (or dose of a drug) produces decrease in psychomotor activity and calms the recipient. In contrast to anxiolytics, this group of agents depresses the central nervous system in a relatively nonselective fashion. Many drugs share central depressant action.

Traditionally, the following drugs (or doses of drugs) used as sedatives:

— long-acting and intermediate-acting *barbiturates* in low doses (1/5–1/10 of a hypnotic dose);

— sodium bromide or potassium bromide;

— plant extracts (Valeriana officinalis, Leonurus cardiaca);

— complex mixtures containing sedative agents.

Available forms:
Tincture of *Valerian* — in bottles 30 ml each

Lecture 18
ANTIDEPRESSANT DRUGS

Affective disorders — *major depression* and *mania* (or *bipolar manic-depressive illness*) — are characterized by changes in mood as the primary clinical manifestation. Depression is different from schizophrenia, which produces disturbances in thought. The symptoms of depression are intense feeling of sadness, hopelessness, despair, and inability to experience pleasure in usual activities. Mania is characterized by the opposite behavior, that is, enthusiasm, rapid thought and speech patterns, and extreme self-confidence and impaired judgment. All clinically useful antidepressant drugs (also called thymoleptics) potentiate, either directly or indirectly, the action of noradrenaline, dopamine, and/or serotonin in the brain. This, along with other evidence, led to biogenic amine theory, which proposes that depression is due to a deficiency of monoamines such as noradrenaline and serotonin in certain key sites in the brain. Conversely, mania is envisioned as caused by overproduction of these neurotransmitters.

Classification of antidepressants:
— Inhibitors of neuronal reuptake:
a) nonselective (tricyclic/polycyclic antidepressants): *Amitriptyline, Imizine (Imipramine), Maprotiline, Amoxapine;*
b) selective serotonin reuptake inhibitors: *Fluoxetine, Paroxetine, Trazodone.*
— Monoamine oxidase inhibitors: *Nialamide, phenelzine, Tranylcypromine*
— Drugs used to treat mania: lithium salts

TRICYCLIC/POLYCYCLIC ANTIDEPRESSANTS

Mechanism of action:
Inhibition of neurotransmitter uptake. Tricyclic antidepressants (TCAs) inhibit the neuronal reuptake of noradrenaline and serotonin into presynaptic nerve terminals. This leads to increased concentration of monoamines in the synaptic cleft, resulting in antidepressant effect. This theory has been discounted by some because of several observations. E.g. the potency in blocking neurotransmitter uptake often does not correlate with antidepressant effects. Further, blockade of reuptake occurs immediately after administration of the drug, but the antidepressant effect of the TCA requires several weeks of continued treatment. It has been suggested that monoamine receptor densities in the brain may change over a 2 to 4 week period with drug use and may be important in the onset of activity.

Blocking of receptors. The TCAs also block serotoninergic, α-adrenergic, histamine, and muscarinic receptors. It is not known which, if any, of these accounts for the therapeutic benefit.

Actions. TCAs elevate mood, improve mental alertness, increase physical activity, and reduce morbid preoccupation in 50 to 70% of individuals with major depression. The onset of the mood-elevation is slow, requiring 2 weeks or longer. These drugs do not produce

stimulation or mood elevation in normal individuals. Drugs can be used for prolonged treatment of depression without loss of effectiveness.

Therapeutic uses. The TCAs are effective in treating severe major depression. Some panic disorders also respond to TCAs. *Imipramine* has been used to control bed-wetting in children (older than 6 years) by causing contraction of the internal sphincter of the bladder. At present it used cautiously, because of the inducement of cardiac arrhythmias and other serious cardiovascular problems.

Pharmacokinetics. The TCAs are well absorbed upon oral administration, and because of their lipophilic nature, are widely distributed and readily penetrate into the CNS. This lipid solubility also causes these drugs to have long half-lives, for example, 4 to 17 hours for *Imipramine*. The initial treatment period is typically 4 to 8 weeks. These drugs are metabolized by the hepatic microsomal system and conjugated with glucuronic acid. Ultimately, the TCAs are excreted as inactive metabolites via the kidney.

Adverse effects:

Antimuscarinic effects. Blockade of acetylcholine receptors leads to blurred vision, xerostomia (dry mouth), urinary retention, constipation, and aggravation of glaucoma and epilepsy.

Cardiovascular. Increased catecholamine activity results in cardiac overstimulation, which can be life-threatening in case of overdoses. Blockade of α-adrenergic receptors may cause orthostatic hypotension and reflex tachycardia. In clinical practice this is the most serious problem in the elderly.

Sedation. Sedation may be prominent, especially during the first several weeks of the treatment.

Precautions. The tricyclic antidepressant should be used with caution in manic-depressive patients, since they may unmask manic behavior. The TCAs have a narrow therapeutic index; e.g. 5 to 6 times the maximal daily dose of *Imipramine* can be lethal. Depressed patients who are suicidal should be given only limited quantities of these drugs.

SELECTIVE SEROTONIN-REUPTAKE INHIBITORS

The selective serotonin-reuptake inhibitors (SSRI) are a new group of chemically unique antidepressant drugs that specifically inhibit serotonin reuptake. Compared with tricyclic antidepressant, the SSRIs cause fewer anticholinergic effects and lower cardiotoxicity. However, the newer SSRIs should be used cautiously until their long-term effects have been evaluated.

Fluoxetine

Actions. *Fluoxetine* is the prototype of antidepressant drugs that selectively inhibit serotonin reuptake. *Fluoxetine* is as effective as tricyclic antidepressants in the treatment major depression. The drug is free of most of the troubling side effects of TCAs, including anticholinergic effects, orthostatic hypotension, and weight gain. *Fluoxetine* is preferred over TCAs by non-specialists who write most of the prescriptions for antidepressant drugs. As a result, *Fluoxetine* is now the most widely prescribed antidepressant in many countries.

Therapeutic uses. The primary indication for *Fluoxetine* is depression, where it is as effective as the tricyclic antidepressants. *Fluoxetine* is effective in treating bulimia nervosa and obsessive-compulsive disorder. The drug has been used for a variety of other indications, including anorexia nervosa, panic disorder, pain associated with diabetic neuropathy, and for premenstrual syndrome.

Pharmacokinetics. *Fluoxetine* is slowly cleared from the body, with a 1 to 10-day half-life for the parent compound, and 3 to 30-day for the active metabolites. *Fluoxetine* is administered orally; with a constant dose, a steady-state plasma concentration of the drug is achieved after several weeks of treatment. *Fluoxetine* is a potent inhibitor of a hepatic cytochrome P-450 isoenzyme responsible for the elimination of tricyclic antidepressants, neuroleptics, some antiarrhythmic and β-blockers. [Note: About 7% of the population lack this P-450 enzyme and therefore metabolize *Fluoxetine* very slowly.]

Adverse effects. Commonly observed adverse effects are nausea, insomnia, anorexia, weight loss, sexual dysfunction. Loss of libido, delayed ejaculation and anorgasmia are probably under-reported side effects often noted by clinicians, but are not prominently featured in the list of standard side effects. Overdoses of *Fluoxetine* do not cause cardiac arrhythmias but can cause seizures. [In a report of patients who took an overdose of *Fluoxetine* (up to 1200 mg compared with 20 mg/day as a therapeutic dose) about half of the patients had no symptoms.]

Other SSRIs

Other antidepressant drugs that primarily affect serotonin reuptake include *Trazodone, Fluvoxamine, Paroxetine* and others. These SSRIs differ from *Fluoxetine* in their relative effects on the reuptake of serotonin and noradrenaline. They do not seem to be more efficacious than *Fluoxetine*, but their profiles of side effects are somewhat different. There is a high variability among patients in the rate of elimination of these drugs (including *Fluoxetine*), and failure to tolerate one drug should not preclude a trial of another SSRI.

MONOAMINE OXIDASE INHIBITORS

Monoamine oxidase (MAO) is a mitochondrial enzyme found in neuronal and other tissues, such as the gut and liver. In the neuron, MAO functions as a "safety valve" to inactivate any excess neurotransmitter molecules *(Noradrenaline, Dopamine, and Serotonin)* that may leak out of synaptic vesicles when the neuron is at rest. The MAO inhibitors inactivate the enzyme, permitting neurotransmitter molecules to escape degradation and therefore to accumulate within the presynaptic neuron. First generation of MAO inhibitors *(Nialamide)* blocks MAO irreversibly; in contrast, second generation is reversible MAO inhibitors (*Pirlindole, Incazanum)*. Use of MAO inhibitors is now limited because of the complicated dietary restrictions required of patients taking these drugs.

Mechanism of action. MAO inhibitors form complexes with the enzyme, causing irreversible *(Nialamide)* or reversible *(Pirlindole, Incazanum)* inactiva-

tion. This results in increased stores of *Noradrenaline, Serotonin* and *Dopamine* within the neuron, and subsequent potentiation of their actions. These drugs inhibit not only MAO in brain, but oxidases that catalyze oxidative deamination of drugs and potentially toxic substances, such as tyramine, which is found in certain foods. The MAO inhibitors therefore show a high incidence of drug-drug and drug-food interactions.

Although MAO is fully inhibited after several days of treatment, the antidepressant action is delayed several weeks. Most MAO inhibitors have a mild amphetamine-like stimulant effect (Table 6).

Therapeutic uses. MAO inhibitors are indicated for depressant patients who are unresponsive or allergic to tricyclic antidepressants. Patients with low psychomotor activity may benefit from the stimulant properties MAO inhibitors. These drugs are also useful in the treatment of phobic states.

Pharmacokinetics. These drugs are well absorbed on oral administration. Antidepressant effect requires 2 to 4 weeks of treatment. Enzyme regeneration, when irreversibly inactivated, usually occurs several weeks after termination of the drug. Thus, when switching antidepressant agents, a minimum of 2 weeks delay must be allowed after termination of MAO-inhibitor therapy.

Adverse effects. Severe and often unpredictable side effects limit the widespread use of MAO inhibitors. For example, tyramine, contained in certain foods, such as aged cheeses, chicken liver, beer, and red wines, is normally inactivated by MAO in the gut. Individuals, receiving a MAO inhibitor are unable to degrade tyramine obtained from the diet. Tyramine causes the release of large amount of stored catecholamines from the nerve terminals, resulting in hypertension, tachycardia, cardiac arrhythmias, headache, nausea, and stroke. Patients must therefore be educated to avoid tyramine-containing foods. *Phentolamine* or *Prazosin* are helpful in the management of tyramine-induced hypertension. Other possible side effects of treatment with MAO inhibitors include drowsiness, orthostatic hypotension, blurred vision, dryness of the mouth, dysuria, and constipation. MAO inhibitors and SSRIs should not be coadministered due to the risk of life-threatening "serotonin-syndrome". Both drugs required washout periods of 6 weeks before administering the other.

LITHIUM SALTS

Lithium salts are used prophylactically in treating manic-depressive patients and in the treatment manic episodes. They are also effective in treating 60 to 80% of patients exhibiting mania and hypomania. Although many cellular processes are altered by treatment with lithium salts, the mode of action is unknown. Lithium is given orally, and the ion is excreted by the kidney. Lithium salts are very toxic. Their safety factor and therapeutic index are extremely low comparable to those of digitalis. Adverse effects include ataxia, tremor, confusion, and convulsions. Lithium causes no noticeable effect on normal individuals. It is not a sedative, euphoriant or depressant.

Available forms:

Pirlindole — in tablets 0.025 or 0.05 each

Imipramine — in tablets 0.025 each; in ampoules 1.25% solution 2 ml

Fluoxetine — in capsules 0.02 each

Lecture 19
PSYCHOSTIMULANTS. NOOTROPIC DRUGS

This section describes two groups of drugs. The first group, the genuine psychostimulants, cause excitement and euphoria, decrease feelings of fatigue, and increase motor activity. The second group includes drugs with some psychostimulant effects.

According to this psychostimulants are classified into

— Genuine psychostimulants:

a) methylxanthines — *Caffeine*, *Caffeine-benzoate sodium*;

b) benzoylmethylecgoine — *Cocaine*;

c) phenylalkilamines — *Amphetamine (Phenaminum)*;

d) phenylalkylsydnonimes — *Mesocarb*.

— Cerebroactive drugs (cerebral activators):

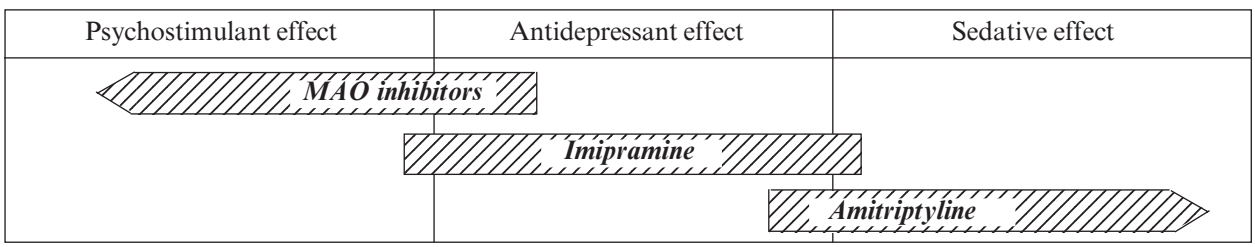
a) nootropic and GABA-ergic agents — *Piracetam (Nootropil)*, *Pyritinol*, *Aminalon (Gamma-aminobutyric acid)*, *Pantohamum (Hopantenic acid)*;

b) adaptogenes and miscellaneous agents with stimulant activity — preparations of *Ginseng*, *Eleutherococcus*, etc.

METHYLXANTHINES

Methylxanthines include *Theophylline* found in tea, *Theobromine* found in cocoa, and *Caffeine*. *Caffeine*, the most widely consumed stimulant in the world, is

Table 6. **Psychotropic spectra of action of the antidepressant drugs**



found in highest concentration in coffee but is also present in tea, cola drinks, chocolate candy, and cocoa.

Mechanism of action. The methylxanthines may act by several mechanisms, including increase in cAMP and cGMP caused by inhibition of phosphodiesterase, and blockade of adenosine receptors.

Actions:

CNS. The caffeine contained in 1 to 2 cups of coffee (100 to 200 mg) cause a decrease in fatigue and increased mental alertness as a result of stimulating the cortex and other areas of the brain. Consumption of 1.5 g of caffeine (12 to 15 cups of coffee) produces anxiety and tremors. The spinal cord is stimulated only by very high doses (2 to 5 g) of caffeine.

Cardiovascular system. A high dose of caffeine has positive inotropic and chronotropic effects on the heart. [Note: Increased contractility can be harmful to patients with angina pectoris. Accelerated heart rate can trigger premature ventricular contractions in others.]

Diuretic action. Caffeine has a mild diuretic action that increases urinary output of sodium, chloride, and potassium.

Gastric mucosa. Since all methylxanthines stimulate secretion of hydrochloric acid (HCl) from the gastric mucosa, individuals with peptic ulcers should avoid beverages containing methylxanthines.

Pharmacokinetics. The methylxanthines are well absorbed orally. *Caffeine* distributes throughout the body, including brain. The drugs cross the placenta to the fetus and are secreted into the mother's milk. All the methylxanthines are metabolized in the liver, and the metabolites are then excreted in the urine.

Adverse effects. Moderate doses of *Caffeine* cause insomnia, anxiety, and agitation. A high dosage is required to show toxicity, which is manifested by emesis and convulsions. The lethal dose is about 10 g for *Caffeine* (about 100 cups of coffee), which induces cardiac arrhythmias. Death from *Caffeine* is thus highly unlikely. Lethargy, irritability, and headache occur in users who have routinely consumed more than 600 mg of *Caffeine* per day (roughly 6 cups of coffee) and then suddenly stop.

Cocaine

Cocaine is an inexpensive, widely available, and highly addictive drug (e.g. as it has been estimated, *Cocaine* is currently abused daily by over 3 million people in the United States).

Mechanism of action. The primary mechanism of action is blockade of noradrenaline, serotonin, and dopamine reuptake into the presynaptic terminals from which these transmitters are released. This block potentiates and prolongs the CNS and peripheral actions of these catecholamines. In particular, the prolongation of dopaminergic effects in the brain's pleasure system (limbic system), produces the intense euphoria that *Cocaine* initially causes. Chronic intake of *Cocaine* depletes *Dopamine*. This depletion triggers the vicious cycle of craving for *Cocaine* that temporarily relieves severe depression.

Actions. The behavioral effects of *Cocaine* result from powerful stimulation of the cortex and brainstem. *Cocaine* acutely increases mental awareness and produces a feeling of well-being and euphoria that is similar to that caused by *Amphetamine*. Like *Amphetamine*, *Cocaine* can produce hallucinations, delusions, and paranoia. *Cocaine* increases motor activity, and at high doses cause tremors and convulsions, followed by respiratory and vasomotor depression.

Peripherally, *Cocaine* potentiates the action of noradrenaline and produces the "fight or flight" syndrome characteristic of adrenergic stimulation. This is associated with tachycardia, hypertension, pupillary dilation, and peripheral vasoconstriction.

Therapeutic uses. *Cocaine* has a local anaesthetic action that represents the only current rationale for the therapeutic use of *Cocaine*; *Cocaine* is applied topically as a local anaesthetic during eye, ear, nose, and throat surgery. The local anaesthetic action of *Cocaine* is due to a block of voltage-activated sodium channels. [Note: *Cocaine* is the only local anaesthetic that causes vasoconstriction. This effect is responsible for the necrosis and perforation of the nasal septum seen in association with chronic inhalation of *cocaine* powder.]

Pharmacokinetics. *Cocaine* is self-administered by chewing, intranasal snorting, smoking, and intravenous injection. Peak effect occurs at 15 to 20 min after nasal intake of *Cocaine* powder, and the high disappears in 1 to 1.5 hours. Rapid but short effects are achieved following i.v. injection of *Cocaine*, or by smoking the free base form of the drug ("crack"). Because the onset of action is most rapid, the potential for overdosage and dependence is greatest with i.v. injection and crack smoking.

Adverse effects. The toxic response to acute *cocaine* ingestion can precipitate an anxiety reaction that includes hypertension, tachycardia, sweating, and paranoia. Like all stimulant drugs, *Cocaine* stimulation of the CNS is followed by a period of mental depression. Addicts withdrawing exhibit physical and emotional depression as well as agitation. These symptoms can be treated with benzodiazepines or phenothiazines.

Cocaine can induce seizures as well as fatal cardiac arrhythmias. Intravenous *Diazepam* and *Propranolol* may be required to control *Cocaine*-induced seizures and arrhythmias, respectively.

Amphetamine

Amphetamine shows neurologic and clinical effects that are quite similar to those of *Cocaine*.

Mechanism of action. As with *Cocaine*, the effects of *Amphetamine* on the CNS and peripheral nervous system are indirect; that is, they depend upon an elevation of the level of catecholamine transmitters in synaptic spaces. *Amphetamine*, however, achieves this effect by releasing intracellular stores of catecholamines. Since *Amphetamine* also blocks MAO, high level of catecholamines are readily released into synaptic spaces. Despite different mechanisms of action, the behavioral effects of *Amphetamine* are similar to those of *Cocaine*.

Actions. The major cause of the behavioral effects of *Amphetamine* is probably due to release of dopamine rather than release of noradrenaline. *Amphetamine* stimulates the entire cerebrospinal axis, cortex, brain stem, and medulla. This leads to increased alert-

ness, decreased fatigue, depressed appetite, and insomnia. In high doses, convulsions can ensue. These CNS stimulant effects of *Amphetamine* and its derivatives have led to their use in the therapy of depression, hyperactivity in children, narcolepsy, and appetite control.

In addition to its marked action on the CNS, *Amphetamine* acts on the adrenergic system, indirectly stimulating the receptors through noradrenaline release.

Therapeutic uses. Factors that limit the therapeutic usefulness of *amphetamine* include psychological and physiological dependence similar to those with *Cocaine*, and the development of tolerance to the euphoric and anorectic effects with chronic use. [Note: Less tolerance to the toxic CNS effects (e.g. convulsions) develops.]

Attention deficit syndrome. Some young children are hyperkinetic and lack the ability to be involved in any one activity for longer than a few minutes. *Amphetamine* and more recently *Amphetamine* derivative *Methylphenidate* alleviate many of the behavior problems associated with this syndrome, and reduce the hyperkinesia that the children demonstrate. Their attention is thus prolonged, allowing them to function better in a school atmosphere.

Narcolepsy. *Methylphenidate* and *Amphetamine* are used to treat narcolepsy, a disorder marked by an uncontrollable desire for sleep.

Pharmacokinetics. *Amphetamines* are completely absorbed from the GI tract, metabolized by the liver, and excreted in the urine. *Amphetamine* abusers often administer the drugs by i.v. injection and by smoking. The euphoria caused by *amphetamine* lasts 4 to 6 hours, or 4 to 8 times longer than the effects of *cocaine*. The *Amphetamines* produce addiction — dependence, tolerance and drug-seeking behavior.

Adverse effects. Undesirable side effects of *amphetamine* usage include insomnia, irritability, weakness, dizziness, tremor, and hyperactive reflexes. *Amphetamine* can also cause confusion, delirium, panic states, and suicidal tendencies, especially in mentally ill patients. Chronic *Amphetamine* use produces a state of "*Amphetamine* psychosis" that resembles an acute schizophrenic attack. Overdoses of *Amphetamine* are treated with *Aminazine*, which relieves the CNS symptoms as well as the hypertension because of its α-blocking effects.

In addition to its CNS effects, *Amphetamine* causes palpitations, cardiac arrhythmias, hypertension, anginal pain, and circulatory collapse. Headache, chills, and excessive sweating may also occur. *Amphetamine* should not be given to patients receiving MAO inhibitors. *Amphetamine* acts on the GI tract, causing anorexia, nausea, vomiting, and abdominal cramps, and diarrhea.

NOOTROPIC DRUGS

"Nootropic" means a drug that selectively improves higher telencephalic integrative activities (cognitive function, learning, memory etc.). They are thought to bring about their effects by improvement in cerebral circulation, activation of neuronal metabolism, neurotransmitter modulation, improvement of neuronal integration, etc.

Piracetam. It is a cyclic GABA derivative, but has no GABA like activity. *Piracetam* has been claimed to improve ATP/ADP ratio in telencephalon, stimulate synaptic transmission. It is believed also to act by protecting altered brain metabolism.

Pyritinol. It consists of two pyridoxine (vit. B_6) molecules, joined through a disulfide bridge, but has no vitamin B_6 activity. It is claimed to improve regional blood flow in ischemic brain areas, activate cerebral metabolism, increase glucose uptake in brain, etc.

Clinical indication for *Piracetam, Pyritinol* and other nootropic agents include:

— transient ischemic attacks, cerebrovascular accidents — stroke;

— mental retardation in children;

— sequelae of head injury, brain surgery;

— organic psycho-syndromes;

— senile dementia and confusional states of old age;

— concentration and memory defects.

The above therapeutic field is commercially highly profitable. Cerebroactive drugs have been briskly promoted by manufacturers and wishfully prescribed by physicians. However, precise trails have been shown that in many cases the initial enthusiasm about "cerebroactive drugs" was merely wishful thinking. But they continue to be prescribed in the absence of any thing better.

Available forms:

Caffeine-sodium-benzoate — in tablets 0.1; 0.2 (for adult) and 0.075 (for children); in ampoules 10% or 20% solution 1 or 2 ml

Mesocarb — in tablets 0.005 or 0.025 each

Piracetam — in capsules 0.4 each; in tablets 0.2 each; in ampoules 20% solution 5 ml each

Phenibut-anvi — in tablets 0.25 each

Lecture 20
ANALEPTICS

These are drugs which stimulate respiratory and cardiovascular centers. They have resuscitative value in coma or fainting. Analeptics do stimulate respiration in subconvulsive doses, but margin of safety is narrow; the patient may get convulsions while still in coma. Mechanical support to respiration and other measures to improve circulation are more effective and safe. They are not dependable for long term support. Situations in which they may employed are: hypnotic drug poisoning; failure to ventilate spontaneously after general anaesthesia; apnoea in premature infant, etc. More information about analeptics see in lecture "Drugs used in respiratory diseases".

Available forms:

Sulfocamphocainum — in ampoules 10% solution 2 ml each

EXAMINATION QUESTIONS

1. A patient whose anaesthesia is being managed only with isoflurane *(Forane)* delivered at an inspired concentration near the MAC occasionally moves and exhibits facial grimacing, apparently in response to surgical manipulation of the bowel. These responses are

(A). Natural consequences of physical manipulations that induce noxious sensory input to the CNS.
(B). An indication that neuromuscular blocking agents should be administered without delay.
(C). Not likely to be blocked by coadministering an analgesic drug such as morphine.
(D). Signs suggesting that the patient should be given twice the MAC of isoflurane.
(E). Not avoidable because the bowel is unusually sensitive to physical manipulation.

2. A hypotensive patient suspected of having internal bleeding is given a dose lower than the usual amount of an intravenous anaesthetic. An acceptable level of anaesthesia occurs. How is it possible to achieve anaesthesia in this patient with a dose of anaesthetic that may be inadequate in a normotensive patient with adequate blood volume?

(A). Enzymatic activity of hepatic enzymes is compromised when blood pressure is low.
(B). More anaesthetic appears in the brain and redistribution of the intravenous drug to tissues with reduced blood flow is compromised when hemorrhagic shock occurs.
(C). The diffusion of lipid-soluble drugs through the blood-brain barrier is enhanced.
(D). Tissues with a characteristically high blood flow per unit mass receive less blood and less anaesthetic when blood volume is low.
(E). Anaesthetics bind more readily to tissue receptors when hypotension and poor oxygenation occur.

3. With which hypothetical anaesthetic would you expect anaesthetic partial pressure to be achieved relatively quickly?

(A). An agent that is highly soluble in blood and other body tissues.
(B). An agent with a low MAC (in range less than 1% in the inspired air).
(C). An agent with a high Ostwald solubility coefficient.
(D). An agent whose rate of rise of partial pressure in the lung is influenced minimally by uptake into the blood.
(E). An agent supplied as a gas rather than one supplied as a volatile liquid.

4. *Remifentanil (Ultiva)* has recently gained popularity as a high-dose opioid anaesthesia because

(A). It induces anaesthesia in patients faster than any other drug.
(B). Phenylpiperidine-type opioids releases histamine from mast cells.
(C). It is metabolized by nonspecific esterases in red blood cells and other tissues.
(D). It has a long duration of action following intravenous infusion.
(E). It does not produce chest wall rigidity.

5. Patients with coronary artery disease are particularly challenging for anaesthesia, since alterations in vascular responsiveness and myocardial function may put them at risk. In this respect, which statement correctly describes the cardiovascular action of an agent or agents that should be taken into account when planning anaesthesia for such patients?

(A). All halogenated hydrocarbon inhalational anaesthetics sensitize the myocardium to catecholamine-induced cardiac arrhythmias.
(B). Halogenated hydrocarbon inhalational agents reduce cardiac output equally well.
(C). Sevoflurane (Ultane) directly stimulates sympathetic function.
(D). Reflex sympathetic stimulation is a major component of halothane's (Fluothane) cardiovascular profile.
(E). Several halogenated hydrocarbons produce vascular relaxation to reduce blood pressure.

6. The mechanism of anaesthesia remains an active area of research. Which statement best describes significant developments in this area of scientific investigation?

(A). Anaesthetics are physically attracted to the aqueous phase of neuronal membranes.
(B). Anaesthesia is associated with interactions of the agents with a single unique site on the $GABA_A$ receptor.
(C). Anaesthesia ultimately occurs as Cl moves out of neuronal cells, an action that makes the cells less excitable.
(D). Although some exceptions occur, a correlation between anaesthetic potency and their oil-water partition coefficient suggested a unitary hypothesis for the production of anaesthesia.
(E). Enantiomers of inhalational agents provide support for the Meyer Overton rule.

7. Which of the following opioids has an analgesically active metabolite?

(A). *Naloxone.*
(B). *Meperidine.*
(C). *Propoxyphene.*
(D). *Codeine.*
(E). *Nalmefene.*

8. Which of the following statements about *Celecoxib* is true?

(A). It irreversibly acetylates the COX-2 enzyme.
(B). It inhibits both the inducible and constitutive COX-2 enzyme.
(C). It produces no GI bleeding.
(D). It is indicated only for the disease, osteoarthritis.
(E). It increases healing of GI ulcers.

9. Morphine produces an analgesic effect due to

(A). A block of potassium efflux from the neuron.
(B). An increase in c-AMP accumulation in the neuron.

(C). A decrease in intracellular calcium in the neuron.
(D). Interaction with a G_s protein in the neuron.
(E). An increase in calcium channel phosphorylation in the neuron.

10. κ-Opioid receptor activation is required to observe
(A). Respiratory depression.
(B). Bradycardia.
(C). Miosis.
(D). Mydriasis.
(E). Hypocapnia.

11. Which of the following statements about fentanyl patches is true?
(A). They produce no respiratory depression.
(B). They produce anaesthesia and analgesia.
(C). They produce no constipation.
(D). They can be used during pregnancy.
(E). They cannot be used in nonambulatory patients.

12. A man aged 74 has moderate hypertension controlled with *Hydrochlorothiazide* 12.5 mg once daily and losartan 50 mg once daily. He is prescribed rofecoxib 50 mg once daily to control osteoarthritis pain. After 3 months of this therapy, his blood pressure begins to rise. This increase in blood pressure is most likely due to
(A). Inhibition of COX-2 by *Rofecoxib*, which leads to decreased renal blood flow.
(B). Increased metabolism of *Losartan* due to induction of CYP2C9 by rofecoxib.
(C). Increased excretion of *Hydrochlorothiazide* due to increased renal blood flow (caused by rofecoxib).
(D). Arteriolar contraction in the peripheral circulation caused by inhibition of COX-1 by rofecoxib.
(E). Weight gain caused by rofecoxib's ability to decrease basal metabolic rate.

13. The use of low-dose methotrexate in the treatment of rheumatoid arthritis is most frequently
(A). Reserved for cases in which NSAIDs no longer adequately control pain and stiffness.
(B). Initiated only after significant joint destruction.
(C). Contraindicated in individuals being treated with NSAIDs.
(D). Used for pregnant women, since it is the DMARD with the least fetal toxicity.
(E). Initiated early in the course of moderate to severe forms of the disease.

14. A 52-year-old woman with a history of eczema and heavy alcohol use begins taking *Ibuprofen* to control hip and knee pain due to osteoarthritis. Over the course of 6 months, as the pain worsens, she increases her dosage to a high level (600 mg four times daily). What toxicity is most likely to occur, and why?
(A). Abnormal heart rhythms; alcohol induces cytochrome P450 isozymes that convert *Ibuprofen* to a cardiotoxic free radical metabolite.
(B). Necrotizing fasciitis; eczema predisposes an individual to this toxicity of *Ibuprofen*.
(C). Gastric ulceration; heavy alcohol use increases the susceptibility of an individual to ibuprofen-induced GI toxicity.
(D). Confusion and ataxia; these CNS toxicities of ibuprofen are additive with those of ethanol.
(E). Eosinophilia; this rare complication of ibuprofen therapy is exacerbated by the immunosuppression frequently seen in alcoholics.

15. Etanercept produces its antirheumatic effects by direct
(A). Inhibition of cAMP phosphodiesterase in monocytic lineage leukocytes.
(B). Selective inhibition of COX-2.
(C). Enhancement of leukotriene synthesis at the expense of prostaglandin synthesis.
(D). Reduction of circulating active TNF-a levels.
(E). Inhibition of the production of autoantibodies.

16. An advantage of celecoxib over most other NSAIDs is
(A). Less inhibition of PGE_2 effects on the gastric mucosal.
(B). Less risk of bronchospasm and hypersensitivity reactions. Once-daily dosing allows the patient convenience.
(C). Less risk of harm to the developing fetus in the third trimester.
(D). Greater degree of efficacy in the treatment of rheumatoid arthritis.

17. Opisthotonos is a convulsive condition that is often associated with the ingestion of strychnine. This condition is associated with all of the following EXCEPT
(A). Antagonism of the inhibitory amino acid neurotransmitter glycine.
(B). The predominance of glycine as an inhibitory amino acid transmitter in the spinal cord.
(C). Antagonism of the inhibitory amino acid neurotransmitter GABA.
(D). The convulsions lead to tonic extension of the body and all limbs.

18. Which of the following classes of agents is useful in the treatment of attention deficit hyperkinetic disorder?
(A). Analeptic stimulants.
(B). Benzodiazepines.
(C). Xanthines.
(D). Psychomotor stimulants.
(E). Phosphodiesterase inhibitors.

19. Which of the following mechanisms of action account for the effects of all analeptic stimulants except strychnine?
(A). Antagonism of chloride ion influx at the GABA receptor-chloride channel complex.
(B). Increased release of catecholamines from CNS neurons.
(C). Inhibition of cholinesterase leading to increased acetylcholine levels.

(D). Antagonism of CNS adrenoceptors to reduce inhibition produced by catecholamines.
(E). Antagonism of nicotinic receptors that inhibit motor neuron activity.

20. The CNS stimulation produced by methylxanthines, such as caffeine, is most likely due to the antagonism of which of the following receptors?
(A). Glycine receptors.
(B). Adenosine receptors.
(C). Glutamate receptors.
(D). GABA receptors.
(E). Cholinergic muscarinic receptors.

21. Cardiac stimulation is an adverse effect associated with the use of the psychomotor stimulants, such as amphetamine. Which of the following mechanisms is most likely responsible for this peripheral effect?
(A). Inhibition of vagal tone through an action in the CNS.
(B). Indirect sympathomimetic effects in the periphery due to release of norepinephrine.
(C). Inhibition of a GABA-mediated negative chronotropic effect at the heart.
(D). Antagonism of muscarinic receptors in the heart.
(E). Blockade of ganglionic transmission at sympathetic ganglia in the periphery.

22. A 21-year-old man is a full-time college student who also works 25 hours per week. Over the past 3 months he has become increasingly anxious. He says he is tired most of the time and has trouble concentrating on his studies. Which of the following drugs would be the most appropriate initial pharmacologic treatment for his anxiety?
(A). *Phenobarbital.*
(B). *Alprazolam.*
(C). *Zolpidem.*
(D). *Hydroxyzine.*
(E). *Propranolol.*

23. A 33-year-old woman has recently undergone a divorce. She reports that although she is exhausted, it usually takes her 2 or more hours to fall asleep at night. Which of the following drugs would help relieve her sleep disturbance while being least disruptive to REM sleep?
(A). *Triazolam.*
(B). *Chloral hydrate.*
(C). *Zolpidem.*
(D). *Amobarbital.*
(E). *Hydroxyzine.*

24. A 54-year-old man is scheduled for an elective colonoscopy that will take approximately 20 minutes. Which of the following drugs would be most likely to produce the desired anaesthesia and antero-grade amnesia?
(A). *Buspirone.*
(B). *Zephalon.*
(C). *Midazolam.*
(D). *Chlordiazepoxide.*
(E). *Hydroxyzine.*

25. A 33-year-old woman has a 15-year history of alcohol abuse. She comes to the emergency department for treatment of injuries received in a fall. She says she has been drinking heavily and almost continuously for 2 weeks, and she wants to stop. Which of the following drugs would most effectively and safely lessen the intensity of her withdrawal syndrome?
(A). *Buspirone.*
(B). *Chlordiazepoxide.*
(C). *Chloral hydrate.*
(D). *Midazolam.*
(E). *Zolpidem.*

26. A 23-year-old medical student has to make a presentation before his classmates. He is very anxious about this presentation and reports that on one previous occasion the sweating and palpitations that accompany his stage fright were so intense that he was unable to complete his presentation. Pretreatment with which of the following drugs would relieve his symptoms without making him drowsy?
(A). *Alprazolam.*
(B). *Zephalon.*
(C). *Chloral hydrate.*
(D). *Propranolol.*
(E). *Diazepam.*

27. A 10-year-old boy with generalized tonic seizures is seen by his dentist at a routine checkup. The dentist observes that the patient has an overgrowth of gum tissue. The patient was most likely receiving which of the following agents?
(A). *Ethosuximide.*
(B). *Clonazepam.*
(C). *Primidone.*
(D). *Phenytoin.*
(E). *Zonisamide.*

28. The metabolism of which AED frequently displays zero-order kinetics following moderate to high therapeutic doses?
(A). *Carbamazepine.*
(B). *Phenytoin.*
(C). *Valproic acid.*
(D). *Ethosuximide.*
(E). *Zonisamide.*

29. Many anticonvulsant drugs, as a major part of their mechanism of action, block the sodium channel, but other effective agents do not use this mechanism. Which of the following anticonvulsants has the ability to block T-calcium currents as its primary mechanism of action?
(A). *Ethosuximide.*
(B). *Phenytoin.*
(C). *Topiramate.*
(D). *Carbamazepine.*
(E). *Lamotrigine.*

30. A 14-year-old patient is diagnosed with absence epilepsy. Any of the following drugs could be considered a reasonable choice to prescribe EXCEPT
(A). *Ethosuximide.*
(B). *Phenobarbital.*
(C). *Carbamazepine.*
(D). *Valproic acid.*

31. Which of the following agents has the capacity to inhibit the reuptake of GABA into neurons and glia?
(A). *Zonisamide.*
(B). *Vigabatrin.*
(C). *Tiagabine.*
(D). *Ethosuximide.*
(E). *Gabapentin.*

32. Which of the following antidepressants is most selective for inhibition of neuronal reuptake of serotonin?
(A). Mirtazapine *(Remeron).*
(B). Venlafaxine *(Effexor).*
(C). Bupropion *(Wellbutrin).*
(D). Sertraline *(Zoloft).*
(E). Imipramine *(Tofranil).*

33. In a patient with a seizure disorder, which antidepressant is contraindicated?
(A). Nefazodone *(Serzone).*
(B). Fluoxetine *(Prozac).*
(C). Venlafaxine *(Effexor).*
(D). Mirtazapine *(Remeron).*
(E). Bupropion *(Wellbutrin).*

34. Mr. Smith is 28 years old and has no active medical problems. He has been treated with Li^+ for manic-depressive illness for 1 year, and his mood has been stable. He now reports the gradual onset of fatigue, weight gain, and cold intolerance. Which single laboratory test is most likely to lead to the correct diagnosis?
(A). TSH (thyroid-stimulating hormone).
(B). Hepatic function panel.
(C). Glucose tolerance test.
(D). Hematocrit.
(E). Serum prolactin level.

35. Which of the following antidepressants requires therapeutic blood monitoring for safe use?
(A). Paroxetine *(Paxil).*
(B). Phenelzine *(Nardil).*
(C). Nortriptyline *(Pamelor).*
(D). Venlafaxine *(Effexor).*
(E). Bupropion *(Wellbutrin).*

36. Which of the following statements about antidepressant medications is most appropriate?
(A). They all have a delay of approximately 48 hours for onset of benefit.
(B). There are large differences in efficacy among individual agents.
(C). Some benefit is expected in 65 to 80% of patients treated with an antidepressant for major depression.
(D). The major contribution of the newer antidepressants lies in the marked improvement in duration of action.

37. Which of the following agents possesses pharmacological actions characterized by high antipsychotic potency, high potential for extrapyramidal toxicity, and a low likelihood of causing sedation?
(A). *Thioridazine.*
(B). *Haloperidol.*
(C). *Flumazenil.*
(D). *Clozapine.*
(E). *Carbamazepine.*

38. Tardive dyskinesia after long-term antipsychotic administration is thought to be due to
(A). A decrease in dopamine synthesis.
(B). Enhanced stimulation of D_2 dopamine autoreceptors.
(C). Loss of cholinergic neurons in striatum.
(D). Up-regulation of striatal dopamine receptors.
(E). Increased tolerance to antipsychotic agents.

39. Which neuroleptic agent has the lowest likelihood of producing tardive dyskinesia?
(A). *Imipramine.*
(B). *Chlorpromazine.*
(C). *Clozapine.*
(D). *Fluoxetine.*
(E). *Thiothixene.*

40. Which clinical condition poses the greatest concern to a patient on antipsychotic therapy?
(A). Epilepsy.
(B). Nausea associated with motion sickness.
(C). Manic phase of bipolar disorder.
(D). Hallucinogen-induced psychosis.
(E). Tourette's syndrome.

41. Mr. James began haloperidol therapy for schizophrenia and within several weeks developed bradykinesia, rigidity, and tremor. Though his psychoses were well controlled, he was switched to another agent, thioridazine, which proved to be as effective as haloperidol in managing his primary condition and did not result in the undesirable symptoms. The most likely explanation for these observations is that
(A). *Haloperidol* acts presynaptically to block dopamine release.
(B). *Haloperidol* activates GABA-ergic neurons in the striatum.
(C). *Haloperidol* has a low affinity for D_2-receptors.
(D). *Thioridazine* has greater α-adrenergic blocking activity than haloperidol.
(E). *Thioridazine* has greater muscarinic blocking activity in brain than haloperidol.

42. Which drug may be useful in the management of the neuroleptic malignant syndrome, although it can worsen the symptoms of schizophrenia?
(A). *Risperidone.*
(B). *Thiothixene.*
(C). *Haloperidol.*
(D). *Bromocriptine.*
(E). *Valproic acid.*

ANSWERS

1. **(A).** Unless supplemented with strong analgesic drugs such as opioids, most general anaesthetics allow reflex reactions to painful stimuli, which may include movement and autonomic reflex changes. Even though these reflex changes occur, if adequately anaesthetized, patients will not experience the noxious stimulus. To give this patient a neuro-muscular blocking agent without in-

itially evaluating the adequacy of anaesthesia would be a mistake. A lawsuit is almost certain, should the patient be inadequately anaesthetized and complain postoperatively of being aware but paralyzed. If it is determined that the patient is receiving adequate anaesthesia (i.e. evaluate the delivery of gas, and check other reflexes such as corneal), the use of a neuromuscular blocking drug may be acceptable if movement is interfering with the procedure. *Morphine* may be a reasonable supplement to anaesthetic management to inhibit reflex reactions to noxious stimuli. Raising the inspired concentration of isoflurane may further blunt reflex reactions to noxious stimuli. However, it may not be a wise choice, since multiples of MAC may cause greater instability of physiological functions (i.e. cardiovascular function). Use a balanced anaesthetic approach with adjunctive agents. The gut is quite responsive to noxious insult, but the reflex responses are still inhibited with proper analgesics, so muscular movement is avoidable.

2. **(B).** Perfusion of the brain is preserved when hemorrhage occurs. Thus, a greater proportion of the initial dose of anaesthetic should appear in the brain, and a dose smaller than what is needed for a normovolemic patient is all that is required. Also, since flow to tissues associated with redistribution of the drug and termination of anaesthesia is compromised, anaesthesia should be deep and extended. Titrate this patient to a safe level of effect. While poor perfusion of the liver may reduce the exposure of drugs to metabolic enzymes, most intravenous anaesthetics rely very little on hepatic clearance to terminate the anaesthetic effect when a single bolus is administered. Furthermore, the question implies a direct influence of blood pressure on the efficiency of hepatic enzymes, and there is no evidence to support such a contention. Option **(C)** is not true. The opposite of option **(D)** is true. No evidence exists that binding of anaesthetics is altered by these conditions.

3. **(D).** Anaesthetics with low blood and tissue solubility require minimal uptake from the lung, as alveolar partial pressure equilibrates with tissue. Remember, alveolar partial pressure is the driving force to establish tension gradients throughout the body. Thus, when uptake is low and alveolar tension rises quickly, blood and brain (which receives a high blood flow) equilibrate with gaseous agents quickly, and anaesthesia is induced relatively rapidly. A gas that is highly soluble in tissues requires a greater accumulation from the lung before partial pressure equilibria are attained, since with greater uptake the rate of rise of the alveolar tension to the inspired level is slower. Although a relationship exists between MAC and blood solubility with respect to anaesthetic concentration in the tissues, the association suggested by choice **(B)** is opposite the expectation. Consider the implications of the Meyer Overton rule. An agent with a high Ostwald solubility coefficient is one of the more soluble agents in tissue, so the explanation of option **(A)** applies. Option **(E)** has no apparent bearing on the rate of rise of the alveolar partial pressure in brain, alveolus, or any other tissue.

4. **(C).** *Remifentanil* has become popular as a component drug in the technique of total intravenous anaesthesia as a consequence of this feature. It is distribution of blood to the brain, not specific pharmacological properties, that primarily controls the rate of induction of anaesthesia with IV agents. Phenylpiperidines as a class of opioids are less likely to produce histamine release. Moreover, histamine release may complicate anaesthetic management (e.g. bronchoconstriction and hypotension), so if it were an action of remifentanil it would be a negative feature. *Remifentanil's* duration of action is short because it is rapidly metabolized. Chest wall rigidity is associated with high doses of phenylpiperidine opioids in particular, and no evidence suggests that remifentanil would be any less likely to cause such an effect.

5. **(E).** Reduced peripheral vascular resistance occurs with most halogenated hydrocarbons, and reflex tachycardia may be a concern. Halothane may be the clearest exception, since there appears to be a balance between relaxation and constrictor influences in various vascular beds with this agent so that total peripheral resistance changes very little. Halothane is the agent of concern when sensitization of the myocardium to catecholamine-induced arrhythmias may be important, such as during incidences of hypercapnia. Sevoflurane does not directly influence sympathetic function. However, reflex tachycardia can occur. Reflex sympathetic stimulation is blocked by halothane. In fact, this may be an advantage of the drug in physiologically risky patients when swings in blood pressure are likely to be frequent.

6. **(D).** Although few contend that a unitary hypothesis will explain anaesthesia, the Meyer Overton rule was among the first explanations provided by the scientific community. The correlation remains significant, as it suggests that sites of action for various anaesthetics may reside near (or the agent must pass though) hydrophobic tissue components. Also, physical disruption of membrane function may yet be found to play a role for at least some agents. Option **(A)** is the reverse of the true interaction. Several sites on the GABA receptor complex may be involved. Cl moves inward to cause cells to become less excitable. Enantiomers, which have nearly identical physical properties but different potencies, challenge the Meyer Overton rule.

7. **(D).** The purpose of this question is to identify first opioids that produce analgesia and then those with a metabolite that compounds the analgesic effects of the drug by being an active analgesic. *Naloxone* and nalmefene are not analgesics but opioid antagonists. Codeine is metabolized to an active analgesic metabolite, morphine. Meperidine and propoxyphene have nonanalgesic, excitatory, and proconvulsant metabolites.

8. **(B).** The purpose of this question is to clarify the uses and limitations of use of the COX-2 selective inhibitor celecoxib. *Celecoxib*, by inhibiting COX-2 reversibly, will block the activity of both injury inducible COX-2 and the small amount of constitutive COX-2. COX-2 inhibition has been shown to produce some GI bleeding, albeit less than with the nonselective COX inhibitors. If a patient has ulcerations and bleeding, COX-2 inhibitors will prolong healing by blocking the protective effects of COX-2 in the GI tract. Celecoxib is indicated for both osteoarthritis and rheumatoid arthritis.

9. **(C).** The purpose of this question is to clarify the cellular mechanism of analgesia produced by morphine. First, morphine blocks the transmission of nociceptive impulses. In that case, the relevant question is how nociceptive impulses are transmitted via the release of pronociceptive neurotransmitters. The question then is to determine which intracellular process favors a block of release of neurotransmitters. The correct answer is **(C)** because calcium is required for neurotransmitter release. Blocking potassium efflux and increasing calcium channel phosphorylation produce functional depolarization and neurotransmitter release. Opioids are coupled to Gi (inhibitory proteins) that decrease cAMP.

10. **(C).** The purpose of this question is to clarify the functional significance of the activation of opioid receptor types. Respiratory depression and bradycardia are associated with the μ_2-opioid receptor. Mydriasis is associated with the σ-receptor, which is no longer thought of as opioid. Opioids, via respiratory depression, induce

hypercapnia, a build-up of carbon dioxide. The clinically relevant sign of opioid overdose and opioid use is miosis, pinpoint pupils, mediated by κ-receptor activation.

11. **(E).** Fentanyl patches have the same effect as fentanyl, only in a time-release manner. Thus, the purpose of the question is delineation of opioid effects — respiratory depression and constipation. The respiratory depression is life-threatening when the patch is used in nonambulatory patients, and it is therefore contraindicated for that purpose. Similarly, fentanyl is a teratogenic drug contraindicated for use during pregnancy. The fentanyl patch does not induce anaesthesia (loss of consciousness) but does produce analgesia.

12. **(A).** By blocking renal prostaglandin synthesis, COX-2 inhibitors, such as rofecoxib, decrease the blood flow to the juxtaglomerular apparatus, thus stimulating the release of renin and subsequent Na^+ retention and blood pressure elevation. Rofecoxib is neither metabolized nor induced by CYP2C9. It decreases rather than increases renal blood flow and does not increase the excretion of hydrochlorothiazide. Item **(D)** is incorrect because rofecoxib has very little effect on COX-1 and prostaglandins are not a major controlling factor of peripheral vascular tone. Rofecoxib does not decrease basal metabolic rate.

13. **(E).** Treatment guidelines suggest the use of DMARDs early in the course of rheumatoid arthritis to slow the joint deterioration associated with the disease. Methotrexate is the DMARD of choice for people with moderate to severe forms of rheumatoid arthritis. Although NSAIDs can decrease methotrexate clearance, NSAIDs can be safely used with the low doses of methotrexate used in the therapy of rheumatoid arthritis. Methotrexate is highly teratogenic and should not be used by women who are or may become pregnant.

14. **(C).** The likelihood of gastric ulceration and GI bleeding is increased by heavy alcohol use, poor health, advanced age, long-term NSAID use, and use of drugs such as corticosteroids and anticoagulants. Ibuprofen is not converted to a cardiotoxic metabolite. Dermal toxicities, such as epidermal necrolysis, are rare complications of ibuprofen therapy, but necrotizing fasciitis is not one of them. Confusion and ataxia are not side effects associated with ibuprofen, nor is eosinophilia.

15. **(D).** Etanercept is a recombinant fusion protein consisting of two TNF receptor domains linked to one IgG Fc molecule. It binds to soluble TNF-α and TNF-β and forms inactive complexes. It does not directly affect cAMP phosphodiesterase, leukotriene synthesis, or autoantibody production.

16. **(A).** Celecoxib selectively inhibits COX-2, so it does not inhibit the constitutive activity of COX-1 in the regulation of gastric acid secretion. When prostaglandin synthesis by COX-1 or COX-2 is blocked, eicosanoids are shifted into the leukotriene pathway, so bronchospasm and hypersensitivity reactions are favored. The shorter half-life of celecoxib does not allow once-daily dosing. This drug is no less able than other NSAIDs to close the ductus arteriosus during the third trimester. None of the NSAIDs is empirically more efficacious than the others; a patient's own response and side effects determine the best drug for him or her.

17. **(C).** Glycine is the major inhibitory amino acid transmitter in the spinal cord, and strychnine is a relatively selective antagonist of glycine. Strychnine has very little if any action at the GABA receptor-chloride channel complex.

18. **(D).** Attention deficit-hyperkinetic disorder and attention deficit disorder are among only a few approved uses of the psychomotor stimulants of the amphetamine type.

19. **(A).** Analeptic stimulants, such as pentylenetetrazol and picrotoxin, act by inhibiting chloride influx at the $GABA_A$ receptor-chloride channel complex. This antagonism can occur through interaction with one of several binding sites or allosteric modifiers of receptor-channel function.

20. **(B).** Methylxanthines have been proposed to be inhibitors of phosphodiesterase, which would elevate intracellular levels of cAMP. However, the concentration of cAMP that is required for such action is above the threshold of CNS stimulation. Since the methylxanthines are relatively potent antagonists of adenosine and since adenosine has been shown to be a reasonably potent inhibitor of both central and peripheral neurons, the most likely mechanism by which CNS stimulation occurs is through antagonism of adenosine receptors.

21. **(B).** Psychomotor stimulants such as amphetamine are also indirectly acting sympathomimetics that increase the release of catecholamines from sympathetic nerve terminals. While amphetamine and other congeners possess additional actions on peripheral sympathetic nerves, this is the most likely explanation for the cardiac stimulation observed following the administration of these agents.

22. **(B).** The young man's anxiety is probably caused by the stress induced by a full college curriculum along with working 25 hours per week. A benzodiazepine antianxiety agent would help relieve his symptoms.

23. **(C).** *Zolpidem* is effective at relieving sleep-onset insomnia. The other agents listed could also induce sleep, although each would be expected to produce more disruption of sleep rhythm than would zolpidem.

24. **(C).** *Midazolam*, like all benzodiazepines given in sufficient dose, has the capacity to produce anterograde amnesia. It is also available in an injectable form and frequently is used as an anaesthetic agent during short procedures.

25. **(B).** *Chlordiazepoxide*, through its metabolites, has a relatively long biological half-life. It will prevent many of the severe symptoms of acute alcohol withdrawal. *Buspirone* is not a sedative and will not suppress alcohol withdrawal. The other agents have sedative properties and could potentially suppress alcohol withdrawal but each has a much shorter biological half-life than chlordiazepoxide.

26. **(D).** As a β-adrenoceptor blocker, *Propranolol* can relieve many of the symptoms of stage fright. For this use it can be taken once a few hours before the performance. Chronic dosing is usually not necessary. The other agents produce sedation.

27. **(D).** This is a rather specific effect of phenytoin. Although the gum tissue can be cut back and in some cases overgrowth prevented with good oral hygiene, this is a source of embarrassment to the patient and constitutes a deterrent to the use of this agent.

28. **(B).** *Phenytoin* is one of a handful of drugs that demonstrates zero-order (or saturation) kinetics. If a patient is showing signs of toxicity to phenytoin, it is important to measure blood levels, since the likelihood that phenytoin is demonstrating zero-order kinetics is very high.

29. **(A).** *Ethosuximide* has no effect on blocking the sodium channel at therapeutics doses; however, it is very effective in blocking the T-calcium current in the therapeutic dose range. All other choices block the sodium channel at therapeutic doses, and it is acknowledged that this is their sole (or major) mechanism of action.

30. **(C).** The only drug listed that would be expected to offer no benefit to a patient with absence seizures is carbamazepine. In fact, there is clinical evidence that it may actually increase the incidence of absence seizure episodes.

31. **(C).** *Tiagabine* is the first agent that has been shown to elevate GABA levels by inhibiting the reuptake of this neurotransmitter at neuronal and glial sites in the brain. Vigabatrin can also elevate GABA levels, but it does so by inhibiting the metabolism of GABA.

32. **(D).** *Mirtazapine* acts at serotonin and adrenergic receptors and does not effect reuptake of neurotransmitters. Venlafaxine is a mixed serotonin-norepinephrine reuptake inhibitor. Bupropion inhibits norepinephrine and dopamine reuptake. Imipramine is a TCA with mixed serotonin and norepinephrine properties. Sertraline belongs to the class of antidepressants know as the SSRIs and selectively blocks neuronal reuptake of serotonin.

33. **(E).** *Nefazodone*, *Fluoxetine*, *Mirtazapine*, and *Venlafaxine* have minimal effects on seizure threshold. Bupropion in its original formulation caused seizures in 4 in 1,000 patients. Although this has been reduced with the slow release form of the medication *(Wellbutrin SR),* it remains a contraindication to prescribe this medication to patients with a history of seizures.

34. **(A)**. Approximately 5% of patients taking lithium over the long term develop hypothyroidism, and thyroid status should be followed as routine care for these patients. Mr. Smith's symptoms are classic for hypothyroidism. Impairment in glucose metabolism, hepatic function, red blood cell production, and prolactin secretion are not typical complications of lithium therapy.

35. **(C).** *Nortriptyline (Pamelor)* is a TCA, and as a class these drugs require at least one steady-state blood level to safely and effectively use the medication. Paroxetine, venlafaxine, and bupropion have not had blood levels correlated to response, and their relatively low toxicity does not require therapeutic blood monitoring. Nardil is a MAOI, which can be lethal in overdose, but blood levels are not used to monitor for efficacy or toxicity.

36. **(C).** All agents have a delay of approximately 48 hours. There are no significant differences in efficacy among the individual agents. The major contribution of the newer antidepressants is in their improved safety and tolerability.

37. **(B).** The question describes the pharmacological profile of a high-potency classical antipsychotic agent, most likely of the butyrophenone or phenothiazine class. Thioridazine is a low-potency piperidine phenothiazine agent with significant affinity for α_1-adrenergic and muscarinic receptors, having a high potential for sedation as a side effect. *Haloperidol* is a high-potency butyrophenone with its primary action at the D_2 dopaminergic receptor, so it produces a significant incidence of extrapyramidal toxicity and little sedation. Clozapine is a low-potency atypical antipsychotic that binds primarily to D_4, 5-HT_2, and a_1-receptors and possesses very little extrapyramidal toxicity but significant sedative and autonomic side effects. *Flumazenil* is a benzodiazepine antagonist, and carbamazepine is an anticonvulsant; neither possesses significant antipsychotic properties.

38. **(D).** This question concerns the most important extrapyramidal reaction to long-term antipsychotic administration tardive dyskinesia and its generally accepted basis. Although some tolerance to the sedative effects of antipsychotics can occur, there is no evidence linking this to tardive dyskinesia. Antipsychotic agents enhance dopamine synthesis acutely by blocking D_2-autoreceptors by which the transmitter normally inhibits dopamine cell firing and synthesis. Long-term treatment with a D_2-receptor antagonist causes depolarization inactivation of dopamine neurons with diminished transmitter production and release. However, a decrease in dopamine synthesis has not been linked with tardive dyskinesia. On the contrary, lower dopamine tone would more resemble a parkinsonian state, whereas in tardive dyskinesia, antidopaminergic drugs tend to suppress the dyskinetic symptoms, and dopaminergic agonists worsen the condition. Therefore, it is generally accepted that up-regulated dopamine receptors underlie tardive dyskinesia. There is no evidence that the antipsychotics lead to loss of striatal cholinergic neurons.

39. **(C).** Tardive dyskinesia is an extrapyramidal reaction that occurs most commonly after long-term administration of high-potency butyrophenone, thioxanthene, or phenothiazine. Thus, thiothixene is not a good choice. *Chlorpromazine* is a low-potency phenothiazine agent with moderate potential to cause extrapyramidal signs. *Clozapine* is well known to have the lowest potential for producing tardive dyskinesia during chronic therapy. It has other undesirable side effects, but clinical experience with other newer atypical antipsychotics is not sufficient to establish their potential for causing this disorder. Imipramine and fluoxetine are antidepressants.

40. **(A).** The question concerns actions of antipsychotic agents that may have untoward consequences when combined with other coincident or preexisting medical conditions. These drugs have an activating effect on the EEG in epileptic patients and thus may worsen that condition. Generally, the antipsychotics have antiemetic properties but generally are more potent than is necessary to treat motion sickness. The other three conditions listed **(C)**, **(D)**, and **(E)** are indications for the use of antipsychotic agents.

41. **(E)**. The question concerns the emergence of parkinsonian signs relatively early in a patient's therapy for schizophrenia and their elimination by switching treatment to a second agent, thioridazine. Haloperidol has high affinity for D_2-dopaminergic receptors and is well known to have a high potential for causing these kinds of extrapyramidal signs. The drug has no direct action on GABAergic neurons and does not act presynaptically to affect dopamine release. While thioridazine binds to D_2-dopaminergic receptors with an affinity similar to that of haloperidol, it also has much greater antimuscarinic activity. This latter action can compensate for dopamine receptor blockade in the nigrostriatal tract, so that extrapyramidal function is more appropriately maintained. *Thioridazine* has greater α-adrenergic blocking activity than *Haloperidol*, but this is not thought to play a role in elimination of the parkinsonian signs.

42. **(D)**. The neuroleptic malignant syndrome is an infrequent extrapyramidal reaction with a relatively high rate of lethality. It is marked by muscle rigidity, high fever, and autonomic instability. It may result from too-rapid block of dopaminergic receptors in individuals who are highly sensitive to the extrapyramidal effects of antipsychotic drugs. Management consists of control of fever, use of muscle relaxants, and administration of the dopamine agonist *Bromocriptine*, which is likely to worsen the psychotic symptoms. Choices **(A)** to **(C)** are antipsychotics and would likely worsen neuroleptic malignant syndrome. Valproic acid has antimanic, antimigraine, and anticonvulsant properties, but it is not used to treat the syndrome in question.

DRUGS AFFECTING THE CARDIOVASCULAR SYSTEM

Lecture 21
CARDIAC GLYCOSIDES

The cardiac glycosides are a group of chemically similar compounds that can increase the contractility of the myocardium and are therefore widely used in treating heart failure.

A large number of plats extracts containing cardiac glycosides have been used by native in various parts of the world as arrow and ordeal poisons. *Squill* was known as a medicine to the ancient Egyptians.

The Romans employed it as a diuretic, heart tonic, emetic, and rat poison. The dried skin of the common toad has been used for centuries as a drug by Chinese. Digitalis or foxglove was mentioned in 1250 in the writings of Welsh physicians.

In 1775, Dr. William Withering was making a routine journey from Birmingham (England) to see patients at the Stafford Infirmary. While the carriage horses were being changed half way, he was asked to see an old dropsical woman. He thought she would die and so some weeks later, when he heard of her recovery, was interested enough into the cause. Recovery was attributed to an herb tea containing foxglove as an ingredient. He began to investigate its properties, trying it on the poor of Birmingham, whom he used to see without fee each day. Withering found that foxglove extracts caused diuresis in some edematous patients. He defined the type of patients who might benefit from it, and equally important he standardized his foxglove leaf preparations and was able to lay down accurate dosage schedules. Crude foxglove preparations are called 'digitalis'. In 1785, William Withering published his famous book entitled *An Account of the Foxglove and Some of Its Medical Use: With Practical Remarks on Dropsy and Other Diseases.* Apparently Withering did not associate digitalis effectiveness in dropsy (edema) with cardiac action of the drug. Probably, John Ferrier in 1799 was the first to ascribe to digitalis a primary action on the heart and to relegate the diuretic effect to a position of secondary importance. Only subsequently was it established that digitalis is valuable for the therapy of congestive heart failure.

Sources. Official digitalis is the dried leaf of the foxglove plant, *Digitalis purpurea. Digitalis lanata* leaves are used in Europe and are the source of certain purified preparations. Strophanthus is obtained from the seeds of the *Strophanthus Kombe* or *Hispidus;* ouabain is derived from *Strophanthus gratus*.

Chemical nature. Each glycoside molecule consists of aglycone (or genin) attached to glycone (from one to four molecules of sugar). The particular sugars modify water and lipid solubility, potency, and the pharmacokinetic properties, while pharmacologic activity resides in the aglycone. Basic structure of the aglycone is a cyclopentaneperhydrophen nucleus to which is attached an unsaturated lactone ring. The aglycones are chemically related to bile acids, sterols, and steroid hormones.

Congestive heart failure (CHF). CHF is a condition in which the heart is unable to transfer venous return into adequate cardiac output. CHF can be caused by an impaired ability of the cardiac muscle to contract or by an increased workload imposed on the heart. CHF is accompanied by abnormal increases in blood volume and interstitial fluid; the heart, vein, and capillaries are therefore generally dilated with blood. Hence the term "congestive" since the symptoms include pulmonary congestion with left heart failure and peripheral edema with right heart failure. Underlying causes of CHF include arteriosclerotic heart disease, valvular heart disease, dilated cardiomyopathy, and congenital heart disease. The most common cause of heart failure is left systolic dysfunction secondary to coronary artery disease.

The therapeutic goal for CHF is to increase cardiac output. Three classes of drugs have been shown to be clinically effective in reducing symptoms and prolonging life: 1) vasodilators that reduce the load on the myocardium; 2) diuretic agents that decrease extracellular fluid volume; 3) inotropic agents that increase the strength of contraction of cardiac muscle. [Note: These agents relieve the symptoms of cardiac insufficiency but do not reverse the underlying condition.]

Knowledge of the physiology of cardiac muscle contraction is clearly essential to an understanding of the compensatory responses evoked by the failing heart, as well as the action of drugs used to treat CHF.

PHYSIOLOGY OF MUSCLE CONTRACTION

The myocardium, like smooth and skeletal muscle, responds to stimulation by depolarization of the membrane; this is followed by shortening of the contractile proteins and ends with relaxation and return to the resting state. However, unlike skeletal muscle, which shows graded contractions depending on the number of muscle cells stimulated, the cardiac muscle cells are interconnected in groups that respond to stimuli as a unit, contracting together whenever a single cell is stimulated.

Action potential. Cardiac muscle cells are electrically excitable. However, unlike the cells of other muscles and nerves, the cells of cardiac muscles show a spontaneous, intrinsic rhythm generated by specialized "pacemaker" cells located in the sinoatrial (SA), and atrioventricular (AV) nodes. The cardiac cells also have an unusually long action potential, which can be divided into five phases (0 to 4; Fig. 15). Na^+, K^+, Ca^{++} are the major ions contributing to depolarization and polarization of cardiac cells. These ions pass through channels in the sarcolemmal membrane and thus create a current. The channels open and close at different times during the action potential; some respond primarily to changes in ion concentration, whereas other are either adenosine triphosphate (ATP)- or voltage-sensitive.

Cardiac contraction. The contractile machinery of the myocardial cell is essentially the same as in a striated muscle. The force of contraction of the cardiac muscle is directly related to the concentration of free (unbound) cytosolic calcium. Therefore agents that increase these calcium levels (or increase the sensitivity of the contractile machinery to calcium) result in the force of contraction (inotropic effect). [Note: The inotropic agents increase the contractility of the heart by directly or indirectly altering the mechanisms that control the concentration of intracellular calcium.]

1. Sources of free intracellular calcium: Ca^{++} comes from two sources. The first is from outside the cell, where opening of voltage-sensitive Ca^{++} channels causes an immediate rise in free cytosolic Ca^{++}. The second source is the release of calcium from the sarcoplasmic reticulum and mitochondria, which further increases the cytosolic level of calcium.

2. Removal of free cytosolic Ca^{++}: If free cytosolic level were to remain high, the cardiac muscle would be in a constant state of contraction, rather than showing a periodic contraction. Mechanisms of removal include two alternatives.

a. Sodium-calcium exchange: Ca^+ is removed by a sodium-calcium exchange reaction that reversibly exchanges calcium ions across the cell membrane. This interaction between the movement of Ca^{2+} and Na^+ is significant, since changes in intracellular Na^+ can affect cellular levels of Ca^{++}.

b. Uptake of Ca^{++} by the sarcoplasmic reticulum and mitochondria: Ca^{++} is also recaptured by the sarcoplasmic reticulum and the mitochondria. More than 99% of the intracellular calcium is located in these or-

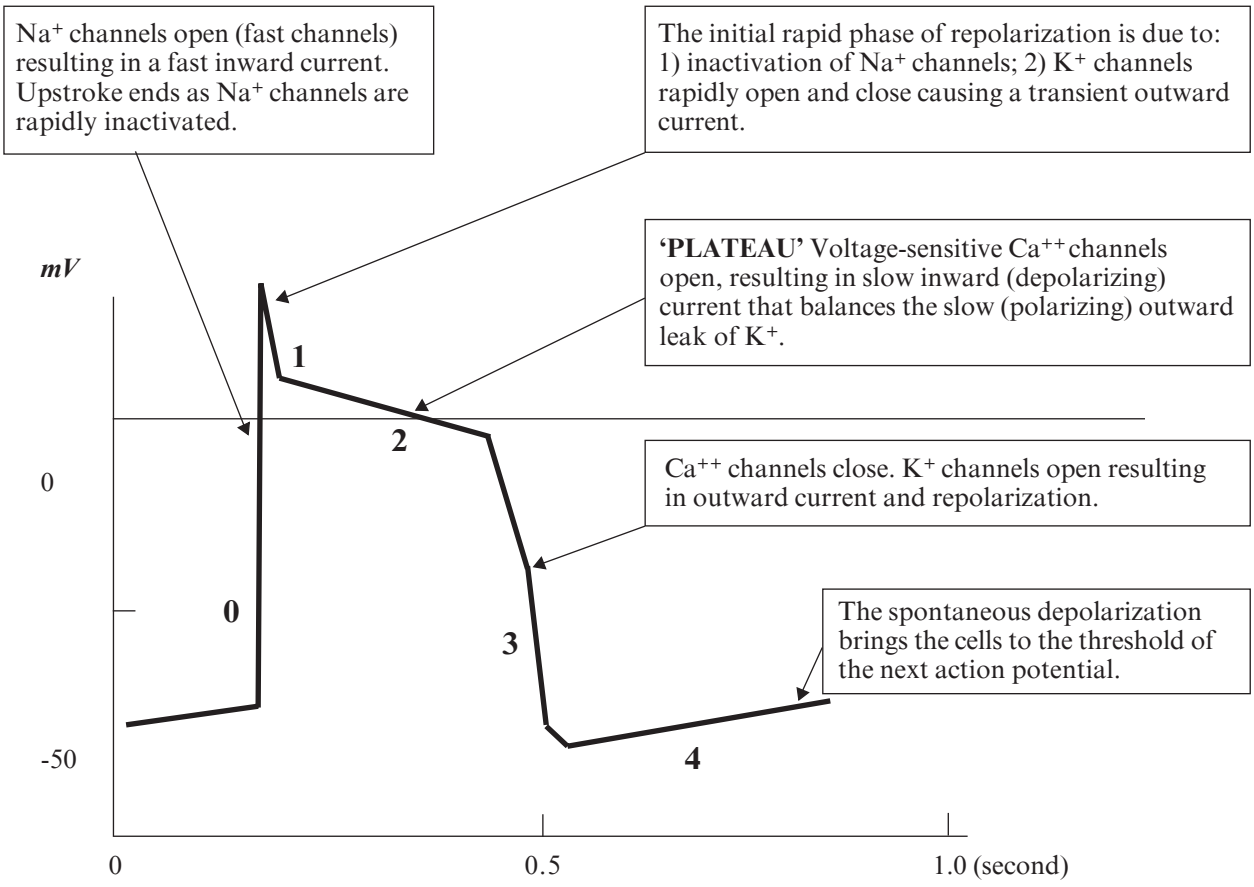


Fig. 15. Action potential

ganelles, and even a modest shift between these stores and free calcium can lead to the large changes in the concentration of free cytosolic calcium.

COMPENSATORY PHYSIOLOGICAL RESPONSES IN CHF

The failing heart evokes three major compensatory mechanisms to enhance cardiac output (Fig. 16).

Increased sympathetic activity. Baroreceptors sense a decrease in blood pressure, and trigger activation of β-adrenergic receptors in the heart. This results in an increase in heart rate and a grater force of contraction of the heart muscle. In addition, vasoconstriction (a_1-mediated) enhances venous return and increases cardiac preload. These compensatory responses increase the work of the heart and, therefore, can contribute to the further decline in cardiac function.

Fluid retention. A fall in cardiac output decrease blood flow to the kidney, prompting the release of renin, with a resulting increase in the synthesis of angiotensin II and aldosterone. This result in increased peripheral resistance and retention of sodium and water. Blood volume increases and more blood is returned to the heart. If the heart is unable to pump this extra volume, venous pressure increases and peripheral edema and pulmonary edema occur. These compensatory responses increase the work of the heart and, therefore, can contribute to the further decline in cardiac function.

Myocardial hypertrophy. The heart increases in size, and the chambers dilate. Initially, stretching of the heart muscle leads to a stronger contraction of the heart. However, excessive elongation of the fibers results in weaker contraction. This type of failure is termed systolic failure and is a result of a ventricle unable to pump effectively. Less commonly, patients with CHF may have diastolic dysfunction — a term applied when the ventricles' ability to relax and accept blood is impaired by structural changes, such as hypertrophy. The thickening of the ventricular wall and subsequent decrease in ventricular volume decreases the ability of heart muscle to relax. In this case, the ventricle does not fill adequately, and the inadequacy of cardiac output is termed diastolic heart failure.

DECOMPENSATED HEART FAILURE

If the mechanisms listed above adequately restore cardiac output, then the heart failure is said to be compensated. However, these compensations increase the work of the heart and contribute to further decline in cardiac performance. If the adaptive mechanisms fail to maintain cardiac output, the heart failure is termed decompensated.

THERAPEUTIC STRATEGIES IN CHF

Chronic heart failure is typically managed by reduction in physical activity, low dietary intake of sodium (less than 1,500 mg sodium per day), and treatment with vasodilators, diuretics and inotropic agents. Patients with CHF complain of dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and dependent edema. Positive inotropic agents enhance cardiac muscle contractility, and thus increase cardiac output.

DIGITALIS

The cardiac glycosides are often called digitalis glycosides because most of the drugs come from the dig-

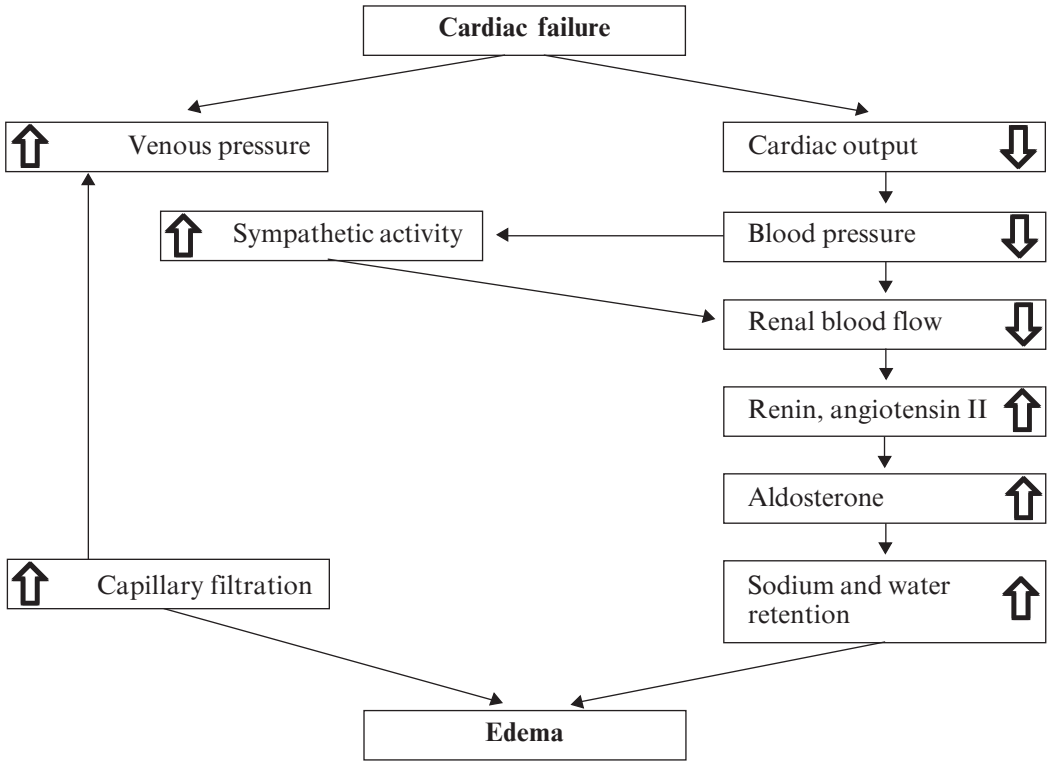


Fig. 16. Compensatory physiological responses in congestive heart failure

italis (foxglove) plant. The cardiac glycosides increase cytoplasmic calcium concentration in the cardiac muscle, thereby enhancing contraction of the atrial and ventricular myocardium (positive inotropic effect). The digitalis glycosides show only a small difference between a therapeutically effective dose and doses that are toxic or even fatal. Therefore, the drugs have a low therapeutic index. The digitalis glycosides include *digitoxin* and the most widely used agent, *Digoxin.*

Mechanism of action:

Regulation of cytosolic calcium concentration. Cardiac glycosides combine reversibly with the sodium-potassium ATPase of the cardiac cell membrane, resulting in an inhibition of pump activity (Fig. 17). This causes an increase in the intracellular sodium concentration, which favors the transport of calcium into the cell via the Na^+/Ca^{++} exchange mechanism. The elevated intracellular Ca^{++} levels result in an increase in the systolic force of contraction.

Increased contractility of the cardiac muscle. An increased myocardial contraction leads to a decrease in end systolic volume, thus increasing the efficiency of contraction (increased ejection fraction). The resulting improved circulation leads to reduced sympathetic activity, which then reduces peripheral resistance. Together, these effects cause a reduction in heart rate. Vagal tone is also enhanced so the heart rate decreases and myocardial oxygen demand is diminished. [Note: In the normal heart, the positive inotropic effect of digitalis is counteracted by compensatory autonomic reflexes.]

Basic effects of cardiac glycosides include:

a. Positive inotropic effect (increased force of contraction).

b. Negative chronotropic effect (reduction in heart rate).

c. Negative dromotropic effect (decreased or blocked atrioventricular conduction).

d. Positive bathmotropic effect (increased myocardial excitability).

The ECG effects of cardiac glycosides. PR interval is prolonged (delayed conduction); QT interval is shortened (increased contractility); T wave becomes smaller or inverted.

Therapeutic uses. *Digoxin* therapy is indicated in patients with severe left ventricular systolic dysfunction after initiation of diuretic and vasodilator therapy. *Digoxin* is not indicated in patients with diastolic or right-sided heart failure. *Dobutamine*, another inotropic agent (β_1-adrenergic agonist), can be given intravenously in the hospital, but at present no good oral inotropic agents exist other than *Digoxin*. Patients with mild to moderate heart failure will often respond to treatment with ACE inhibitors and diuretics and do not require *Digoxin.* Digitalis is also used to slow ventricular rate in patients with atrial fibrillation or flatter (decreased conduction in AV node protects the ventricles from excessive bombardment in atrial dysrhythmias).

Pharmacokinetics. All cardiac glycosides possess the same pharmacologic actions, but they vary in potency and pharmacokinetics (Table 7). *Digoxin* and *Digitoxin* are absorbed after oral administration. Note that *Digitoxin* binds strongly to proteins in the extravascular space, resulting in a large volume of distribution. *Digoxin* has the advantage of a relatively short half-life, which allows better treatment of toxic reactions. *Digoxin* also has a more rapid onset of action, making it useful in emergency situations. *Digoxin* is eliminated largely unchanged in the urine. *Digitoxin* is extensively metabolized by the liver before excretion in the feces.

Adverse effects. Digitalis toxicity is one of the most commonly encountered adverse drug reactions. Side effects can be often managed by discontinuing glycoside therapy, determining serum potassium levels, and if indicated, by giving potassium supplements. In general, decreased serum levels of potassium predispose a patient to glycoside toxicity. Severe toxicity resulting in ventricular tachycardia may require administration of antiarrhythmic drugs, and the use of antibodies (FAB fragments) to the glycoside, which bind and inactivate the drug.

Types of adverse effects include:

Cardiac effects. The major effect is progressively more severe dysrhythmia, moving from decreased or blocked atrioventricular nodal conduction, paroxysmal supraventricular tachycardia, premature ventricular depolarization, ventricular fibrillation, and finally, to complete heart block. A decrease in intracellular potassium is the primary predisposing factor in these effects.

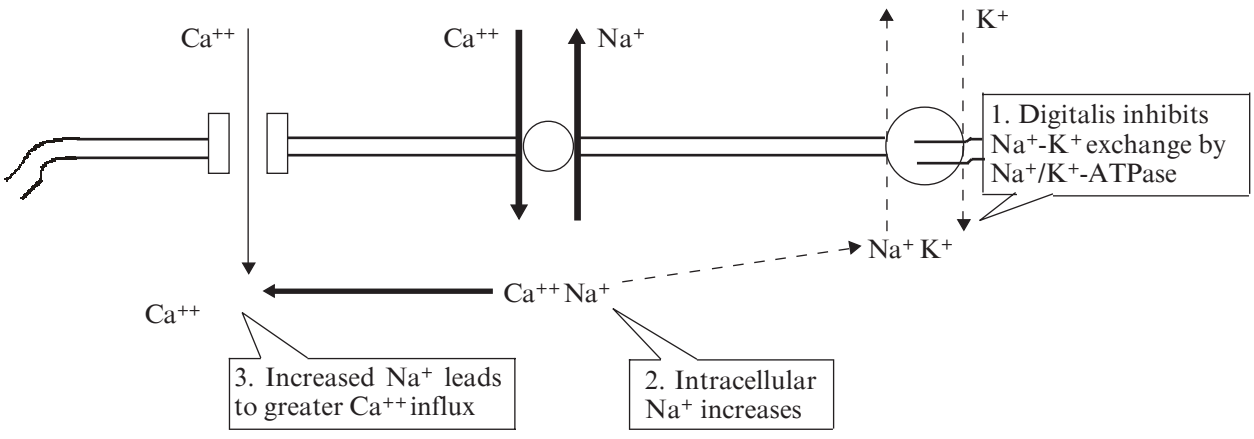


Fig. 17. Mechanism of action of cardiac glycosides

Table 7. **Pharmacokinetic of cardiac glycosides**

	Digoxin	Digitoxin	Strophanthin
Lipid solubility	Medium	High	Low
Oral availability (% absorbed)	75	>90	0
Half-life in body (hours)	40	168	21
Plasma protein binding (% bound)	20–40	>90	0
% metabolized	<20	>80	0
Volume of distribution (L/kg)	6,3	0,6	18
Average digitalizing dose Oral i. v.	 0.75–1.25 mg 0.5–1.0 mg	 0.8–1.2 mg	
Average daily maintenance dose Oral i. v.	 0.125–0.5 mg 0.25 mg	 0.05–0.3 mg	

Gastrointestinal effects. Anorexia, nausea, and vomiting are commonly encountered adverse effects.

CNS effects. These include headache, fatigue, confusion, blurred vision, alteration of color perception, and haloes on dark objects.

Dosage and administration. If there is no urgent need for an immediate effect, a maintenance dose can be given daily by mouth and its effect evaluated after appropriate intervals. A maximal effect will be achieved in approximately four elimination half-lives. On the other hand, if it is desired to achieve a full therapeutic effect fairly rapidly, it is necessary to give a large initial dose because of the relatively long half-time for elimination.

By tradition, the initial loading dose is called the *digitalizing dose.* The size of this dose may be difficult to estimate. In theory, it is the steady-state total body store sufficient to cause the desired therapeutic effect. In practice, the digitalizing dose is selected from prior estimates (see table 7). The maintenance dose must be equal to the daily loss. For digoxin, this is approximately 35% of the total body store; for digitoxin, approximately 10%.

Available forms:

Digitoxin — in tablets 0.0001 each; in suppositories 0.00015 each

Digoxin — in tablets 0.00025 (for adults) and 0.0001 (for children) each; in ampoules 0,025% solution 1 ml each

Celanidum (Lanatoside C) — in tablets 0.00025 each; in ampoules 0.02% solution 1 ml each

Strophanthin — in ampoules 0.025% solution 1 ml each

Corglyconum — in ampoules 0.06% solution 1 ml each

Panangin® — in patented dragee; in ampoules 10 ml each

Unithiol — in ampoules 5% solution 5 ml each

Lecture 22
ANTIANGINAL DRUGS

Angina pectoris is the principal symptom of ischemic heart disease. Both the typical and variant forms of angina may be manifested by sudden, severe, pressing substernal pain that often radiates to the left shoulder and arm. The pain of typical angina is commonly induced by exercise, emotion, and is often associated with depression of the S-T segment of the ECG. The underlying pathological process is usually advanced atherosclerosis of the coronary vasculature. In contrast, variant (Prinzmetal's) angina is caused by vasospasm of the coronary vessels and may not by associated with severe atherosclerosis.

Anginal attacks result from temporary ischemia of the myocardium, such that blood flow is insufficient to maintain adequate oxygenation. This can be due to a decrease in myocardial blood flow, an increase in the requirement of the myocardium for oxygen, or both.

Three classes of drugs are effective, either alone or in combination, in treating patients with stable angina: **nitrates, β-blockers,** and **calcium channel blockers**.

All three of the drug groups useful in angina *decrease myocardial oxygen requirement* by decreasing peripheral vascular resistance, by decreasing cardiac output, or in both ways. In some patients, a redistribution of coronary flow may increase oxygen delivery to ischemic tissue. In variant angina, the nitrates and the calcium channel blockers may also *increase myocardial oxygen delivery* by reversing coronary arterial spasm.

ORGANIC NITRATES

Organic nitrates (and nitrites) are simple nitric and nitrous acid esters of alcohols. They differ in their volatility; for example, *isosorbide dinitrate* is solid at room temperature, *nitroglycerin* is moderately volatile, whereas *amyl nitrate* is extremely volatile. These com-

pounds cause a rapid reduction in myocardial oxygen demand followed by rapid relief of symptoms. They are effective in stable and unstable angina, as well as Prinzmetal's or variant angina pectoris.

Nitroglycerin

Nitrates, β-blockers, and calcium channel blockers are equally effective for relief of anginal symptoms. However, for prompt relief of an ongoing attack of angina precipitated by exercise or emotional stress, sublingual (or spray form) *nitroglycerin* is the drug of choice.

Mechanism of action. The organic nitrates, such as *Nitroglycerin*, are thought to relax vascular smooth muscle by their intracellular conversion to nitrite ions and to nitric oxide (NO), which in turn activates guanylate cyclase and increases the cells' cyclic GMF. Elevated cGMP ultimately leads to dephosphorylation of the myosin light chain, resulting in vascular smooth muscle relaxation (Fig. 18).

Actions on cardiovascular system. At therapeutic doses, *Nitroglycerin* has two major effects. First, it causes dilation of the large veins, resulting in pooling of blood in the veins. This diminishes preload (venous return to the heart), and reduces the work of the heart. Second, *nitroglycerin* dilates the coronary vasculature, providing increased blood supply to the heart muscle. *Nitroglycerin* causes a decrease in myocardial oxygen consumption because of decreased cardiac work.

Pharmacokinetics. The time to onset of action varies from one minute for *nitroglycerin* to more than one hour for *isosorbide mononitrate*. Significant first pass metabolism of *nitroglycerin* occurs in the liver. Therefore, it is common to give the drug either sublingually or via a transdermal patch.

Adverse effects. The most common adverse effect of *Nitroglycerin,* as well as other nitrates, is headache.

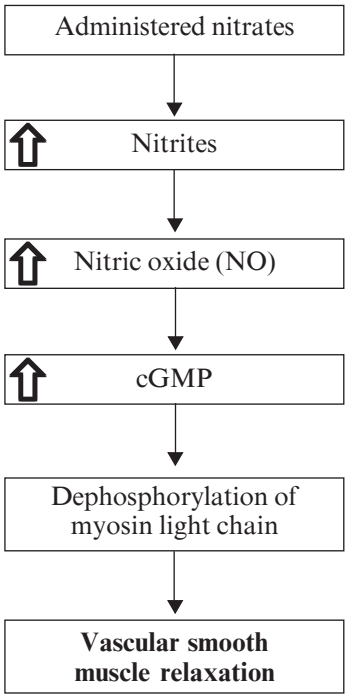


Fig. 18. Mechanism of action of nitrates

Thirty to sixty percent of patients receiving intermittent nitrate therapy with long-acting agents develop headaches. High doses of organic nitrates can also cause postural hypotension, facial flushing, and tachycardia.

Tolerance. Tolerance to the action of nitrates develops rapidly. It can be overcome by provision of a daily "nitrate-free interval" to restore sensitivity to the drug. This interval is typically 6 to 8 hours, usually at night because there is decreased demand on the heart at that time. *Nitroglycerin* patches are worn for 12 hours and removed for 12 hours. However, Prinzmetal's or variant angina worsens early in the morning, perhaps due to circadian catecholamine surges. These patients' nitrate-free interval should be late afternoon.

Isosorbide dinitrate

Isosorbide dinitrate is an orally active nitrate. The drug is not readily metabolized by the liver or smooth muscle and has a lower potency than *Nitroglycerin* in relaxing vascular smooth muscle.

β-ADRENERGIC BLOCKERS

The β-adrenergic blocking agents suppress the activation of the heart by blocking β_1-receptors. They also reduce the work of the heart by decreasing cardiac output and causing a slight decrease in blood pressure. *Propranolol* is the prototype of this class of compounds, but other β-blockers, such as *Metoprolol* and *Atenolol* are equally effective. However, agents with intrinsic sympathomimetic activity (for example, *Pindolol*, and *Acebutolol*) are less effective in angina and should be avoided. The β-blockers reduce the frequency and severity of angina attacks. These agents are particularly useful in the treatment of patients with myocardial infarction. The β-blockers can be used with nitrates to increase exercise duration and tolerance. They are, however, contraindicated in patients with diabetes, peripheral vascular disease, or chronic obstructive pulmonary disease.

CALCIUM CHANNELS BLOCKERS

The calcium channels blockers inhibit the entrance of calcium into cardiac and smooth muscle cells of the coronary and systemic arterial beds. All calcium channels blockers are therefore vasodilators that cause a decrease in smooth muscle tone and vascular resistance. At clinical doses, these agents affect primarily the resistance of vascular smooth muscle and the myocardium. [Note: *Verapamil* mainly affects the myocardium, whereas *Nifedipine* exerts a greater effect on smooth muscle in the peripheral vasculature. *Diltiazem* is intermediate in its actions.]

Nifedipine

Nifedipine functions mainly as an arteriolar vasodilator. This drug has minimal effect on cardiac conduction or heart rate. *Nifedipine* is administered orally and has a short half-life (about 4 hours) requiring multiple dosing. The vasodilation effect of *Nifedipine* is useful in the treatment of variant angina caused by

spontaneous coronary spasm. *Nifedipine* can cause flushing, headache, hypotension, and peripheral edema as side effects of its vasodilation activity. The drug may cause reflex tachycardia if peripheral vasodilation is marked resulting in a substantial decrease in blood pressure.

Verapamil

Verapamil slows cardiac conduction directly and thus decreases heart rate and oxygen demand. *Verapamil* causes greater negative inotropic effects than does *nifedipine*, but it is a weaker vasodilator. *Verapamil* is contraindicated in patients with preexisting depressed cardiac function or AV conduction abnormalities. It also causes constipation. *Verapamil* should be used with caution in digitalized patients, since it increases *Digoxin* levels.

Diltiazem

Diltiazem has cardiovascular effects that are similar to those of *Verapamil.* It reduces the heart rate, although to a lesser extent than *Verapamil*, and also decreases blood pressure. In addition, *Diltiazem* can relieve coronary artery spasm and is therefore particularly useful in patients with variant angina. The incidence of adverse side effects is low.

Available forms:

Nitroglycerine — in bottles 1% spirit solution 5 ml each; in tablets 0.0005

Sustac-mite and ***Sustac-forte —*** in tablets 0.0026 and 0.0064 correspondingly each

Nitroderm® — transdermal patch (contains 0.05 of nitroglycerin each)

Isosorbide mononitrate — in tablets 0.02 or 0.04 each; in ampoules 1% solution 1 ml each

Metoprolol — in tablets 0.1 each

Nifedipine — in tablets 0.01 each

Riboxinum — in tablets 0.2 each; in ampoules 2% solution 10 ml each

Lecture 23
ANTIARRHYTHMIC DRUGS

Drug therapy for cardiac arrhythmias is based on knowledge of the mechanism, consequences, and natural history of the arrhythmia to be treated and on a clear understanding of the pharmacology of the drugs to be used. The latter includes knowledge of drug action on the electrophysiological properties of normal and abnormal cardiac tissues, of their effects on the mechanical properties of the heart and vasculature, and their effects on other organ systems. Optimal therapy of arrhythmias requires an appreciation of the pharmacokinetic properties of antiarrhythmic drugs and how they are affected by disease. Finally, a broad knowledge of adverse effects of the agents and their potential interactions with other drugs is necessary to monitor the course of therapy.

Introduction to the arrhythmias. The heart contains specialized cells that exhibit automaticity, that is, they can intrinsically generate rhythmic action potential in the absence of external stimuli. These "pacemaker" cells differ from other myocardial cells in showing a slow, spontaneous depolarization during diastole (Phase 4) caused by an inward positive current carried by sodium and calcium currents. This depolarization is fastest in the SA node (the normal initiation site of the action potential) and decreases throughout the normal conduction pathway through the AV node to the bundle of His and the Purkinje system. Dysfunction of the impulse generation or conduction at any of a number of sites in the heart can cause an abnormality in cardiac rhythm.

The arrhythmias are conceptually simple — dysfunctions cause abnormalities in impulse formation and conduction in the myocardium. However, in the clinic, arrhythmias present as a complex family of disorders that show a variety of symptoms. For example, cardiac arrhythmias may cause the heart (1) to beat too slowly (sinus bradycardia); (2) to beat too rapidly (sinus tachycardia, atrial or ventricular premature depolarization, atrial flutter); (3) to respond to impulses originating from sites other than the SA node; or (4) to respond to impulses traveling along accessory (extra) pathways that lead to deviant depolarization (A-V reentry, Wolf-Parkinson-White syndrome). In order to make sense of this large group of disorders, it is useful to organize the arrhythmias into groups according to the anatomic site of the abnormality — the atria, AV node, or the ventricles. Several commonly occurring arrhythmias are summarized in the following figure. (Each of these abnormalities can be further divided into subgroups depending on the ECG findings).

Causes of arrhythmias. Most arrhythmias arise either from aberrations in impulse generation (abnormal automaticity) or from a defect in impulse conduction.

Abnormal automaticity. The SA node shows the fastest rate of Phase 4 depolarization and therefore, exhibits a higher rate of discharge than that occurring in the pacemaker cells exhibiting automaticity. The SA thus normally sets the pace of contraction of the myocardium, and latent pacemakers are depolarized by impulses coming from the SA node. However, if cardiac sites other than the SA node show enhanced automaticity, they may generate competing stimuli, and arrhythmia may arise. Abnormal automaticity may also occur if the myocardial cells are damaged, for example, by hypoxia or potassium imbalance. These cells may remain partially depolarized during diastole and therefore can reach the firing threshold earlier than normal cells.

Effect of drug on automaticity. Most of the antiarrhythmic agents suppress automaticity (1) by decreasing the slope of Phase 4 (diastolic) depolarization and/or (2) by raising the threshold of discharge to a less negative voltage. Such drugs cause the frequency of discharge to decrease, an effect that is more pronounced in cells with ectopic pacemaker activity than in normal cells.

Abnormalities in impulse conduction. Impulses from higher pacemaker centers are normally conducted down pathways that bifurcate to activate the entire

ventricular surface. A phenomenon called reentry can occur if a uni-directorial block caused by myocardial injury or a prolonged refractory period results in an abnormal conduction pathway (Fig. 18). Reentry is the most common cause of arrhythmias and can occur at any level of the cardiac conduction system. For example, consider a single Purkinje fiber with two conduction pathways to ventricular muscle. An impulse normally travels down both limbs of the conduction path. However, if myocardial injury results in a uni-directorial block, the impulse may only be conducted down path #1. If the block in pathway #2 is in the forward direction only, the impulse may travel in a retrograde fashion through pathway #2 and reenter the point of bifurcation. This short-circuit pathway results in reexcitation of the ventricular muscle, causing premature contraction or sustained ventricular arrhythmia.

Effects of drugs on conduction abnormalities. Antiarrhythmic agents prevent reentry by slowing conduction and/or increasing the refractory period required to convert a uni-directorial block into a bi-directorial block.

ANTIARRHYTHMIC DRUGS

As noted above, the antiarrhythmic drugs can modify impulse generation or conduction. More than a dozen such drugs that are potentially useful in treating arrhythmias are currently available. However, only a limited number of these agents are clinically beneficial in the treatment of selected arrhythmias.

For example, the acute termination of ventricular tachycardia by *Lidocaine* or supraventricular tachycardia by *Adenosine* or *Verapamil* are examples in which antiarrhythmic therapy results in decreased morbidity. In contrast, many of the antiarrhythmic agents are now known to have lethal proarrhythmic actions (*Flecainide, Encainide, Moricizine)*, that is, to cause arrhythmias.

CLASS I ANTIARRHYTHMIC DRUGS

The antiarrhythmic drugs can be classified according to their predominant effects on the action potential (Table 8). Although this classification is convenient, it is not entirely clear-cut, because many of the drugs have action relating to more than one class. Class I antiarrhythmic drugs act by blocking voltage-sensitive sodium channels. The decrease rate of enter of sodium slows the rate of rise of Phase 0 of the action potential. Class I therefore generally causes a decrease in excitability and conduction velocity.

The class I drugs have been subdivided into three groups according to their effects on the duration of the action potential. Class IA agents slow the rate of rise of the action potential, thus slowing conduction, and prolong the action potential and increase the ventricular effective refractory period. Class IB drugs have little effect on the rate of depolarization, but rather they decrease the duration of the action potential by shortening repolarization. Class IC agents markedly depress the rate of rise of the membrane action potential, and therefore they cause marked conduction slowing but have little effect on the duration of the membrane action potential or the ventricular effective period. Class I drugs show a greater degree of blockade in tissues that are frequently depolarizing (for example, during tachycardia). This property is called "use-dependence" and enables these drugs to block cells that are discharging at an abnormally high frequency without interfering with the normal low-frequency beating of the heart.

Quinidine

Quinidine is the prototype Class IA drug.

Mechanism of action. *Quinidine* binds to sodium channels and prevents sodium influx, thus slowing the rapid upstroke during Phase 0. It also decreases the slope of Phase 4 spontaneous depolarization.

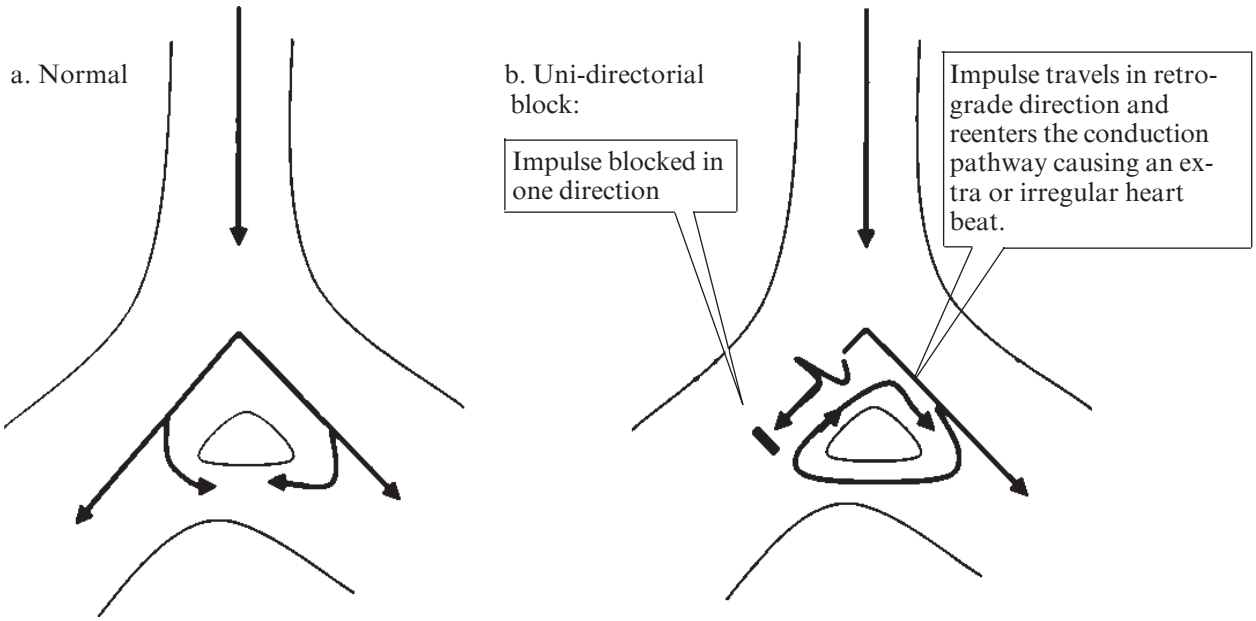


Fig. 18. Phenomenon of reentry

Table 8. **Mechanism of action of antiarrhythmic drugs**

Classification of drug	Mechanism of action	Comment
IA	Na^+ channel blocker	Slows Phase 0 depolarization
IB	Na^+ channel blocker	Shortens Phase 3 repolarization
IC	Na^+ channel blocker	Markedly slows Phase 0 depolarization
II	β-Adrenoreceptor blocker	Suppresses Phase 4 depolarization
III	K^+ channel blocker	Prolongs Phase 3 repolarization
IV	Ca^{2+} channel blocker	Shortens action potential

Actions. *Quinidine* inhibits ectopic arrhythmias and ventricular arrhythmias caused by increased automaticity. *Quinidine* also prevents reentry arrhythmias by producing bi-directorial block through prolonging the effective refractory period. The drug has little effect on normal automaticity.

Therapeutic uses. *Quinidine* is used in the treatment of a wide variety of arrhythmias, including atrial, AV junctional, and ventricular tachyarrhythmias. *Quinidine* is used to maintain sinus rhythm after direct current cardioversion of atrial flutter or fibrillation and to prevent frequent ventricular tachycardia.

Pharmacokinetics. *Quinidine sulfate* is rapidly and almost completely absorbed after oral administration.

Adverse effects. A potential adverse effect of *quinidine* (or any antiarrhythmic drug) is exacerbation of the arrhythmia. *Quinidine* may cause SA and AV block, asystole, and ventricular tachycardia. Cardiotoxic effects are exacerbated by hyperkalemia. Nausea, vomiting, and diarrhea are commonly observed. Large doses may induce the symptoms of cinchonism, for example, blurred vision, tinnitus, headache, disorientation, and psychosis. The drug has a mild α-adrenergic blocking action as well as an atropine-like effect.

Procainamide (Novocainamide)

Actions. This Class A drug, a derivative of the local anaesthetic *Procaine (Novocain)*, shows action similar to those of *Quinidine*.

Pharmacokinetics. *Procainamide* is absorbed following oral administration. [Note: The intravenous route is associated with hypotension occurs if the drug is too rapidly infused.] *Procainamide* has a relatively short half-life of 2–3 hours. A portion of drug is acetylated in the liver to N-acetylprocainamide (NAPA), which is eliminated via the kidney.

Adverse effects. With chronic use, *Procainamide* causes a high incidence of side effects, including a reversible lupus erythematosus-like syndrome that develops in 25 to 30% of patients. Toxic concentrations of *Procainamide* may cause asystole or induction of ventricular arrhythmias. CNS side effects include depression, hallucination and psychosis.

Disopyramide (Rythmilen, Rythmodan)

Actions. This class IA drug shows actions to those of *Quinidine. Disopyramide* produces a negative inotropic effect that is greater than the weak effect exerted by *Quinidine* and *Procainamide*, and unlike the latter drugs, *Disopyramide* causes peripheral vasoconstriction. The drug may produce a clinically important decrease in myocardial contractility in patients with preexisting impairment of left ventricular function. *Disopyramide* is used for treatment of ventricular arrhythmias as an alternative to *Procainamide* or *Quinidine*.

Pharmacokinetics. Approximately one half of the orally ingested drug is excreted unchanged by the kidneys. About 30% of the drug is converted by the liver to the less active mono-N-dealkylated metabolite.

Adverse effects. *Disopyramide* shows effects of anticholinergic activity, for example, dry mouth, urinary retention, blurred vision, and constipation.

Lidocaine

Lidocaine is a Class IB drug. The IB agents rapidly associate and dissociate from sodium channels. Thus the actions of Class IB agents are manifested when the cardiac cell is depolarized or firing rapidly. Class IB drugs are particularly useful in treating ventricular arrhythmias. *Lidocaine* is the drug of choice for emergency treatment of cardiac arrhythmias.

Actions. *Lidocaine*, a local anaesthetic, shortens phase 3 repolarization and decreases the duration of the action potential. Unlike *Quinidine*, which suppresses arrhythmias caused by increased normal automaticity, *Lidocaine* suppresses arrhythmias caused by abnormal automaticity. *Lidocaine*, like *Quinidine*, abolishes ventricular reentry.

Therapeutic uses. *Lidocaine* is useful in treating ventricular arrhythmias arising during myocardial ischemia, such as that experienced during a myocardial infarction. The drug does not markedly slow conduction and thus has little effect on atrial or AV junction arrhythmias.

Pharmacokinetics. *Lidocaine* is given intravenously. The drug is dealkylated and eliminated almost entirely by the liver.

Adverse effects. *Lidocaine* has a fairly wide toxic-to-therapeutic ratio; it shows little impairment of left ventricular function, and has no negative inotropic effect. The CNS effects include drowsiness, slurred speech, paresthesia, agitation, confusion, and convulsions; cardiac arrhythmias may also occur.

Flecainide

Flecainide is a Class IC drug. These drugs slowly dissociate from resting sodium channels and show prominent effects, even at normal heart rates. These drugs are approved only for refractory ventricular arrhythmias. However, recent data have cast serious doubts on the safety of the Class IC drugs.

CLASS II ANTIARRHYTHMIC DRUGS

The Class II agents include the β-adrenergic antagonists. These drugs diminish Phase 4 depolarization, thus depressing automaticity, prolonging AV conduction, and decreasing heart rate and contractility. Class II agents are useful in treating tachyarrhythmias caused by increased sympathetic activity. They are also used for atrial flutter and fibrillation, and for AV nodal reentrant tachycardia.

Propranolol (Anaprilinum)

Propranolol reduces the incidence of sudden arrhythmic death after myocardial infarction (the most common cause of death in this group of patients). The mortality rate in the first year after a heart attack is significantly reduced by *Propranolol*, partly because of its ability to prevent ventricular arrhythmias.

Metoprolol and Pindolol

Propranolol is the β-adrenergic antagonist most widely used in the treatment of cardiac arrhythmias. However, β_1-specific drugs, such as *Metoprolol* reduce the risk of bronchospasm, and drugs with partial agonist activity, such as *Pindolol* may decrease the frequency of cardiac failure.

CLASS III ANTIARRHYTHMIC DRAGS

Class III agents block potassium channels and thus diminish the outward potassium current during repolarization of cardiac cells. These agents prolong the duration of action potential without altering Phase 0 of depolarization or the resting potential. Instead, they prolong the effective refractory period.

Sotalol

Actions. *Sotalol*, although a class III antiarrhythmic agent, also has potent β-blocker activity. *Sotalol* block a rapid outward potassium current. This blockade prolongs both repolarization and the duration of the action potential, thus lengthening the effective refractory period.

Therapeutic uses. β-Blockers are used for the long-term therapy to decrease the rate of sudden death following an acute myocardial infarction. β-Blockers have modest ability to suppress ectopic beats and reduce myocardial oxygen demand. They have strong anti-fibrillar effects, particularly in the ischemic myocardium.

Adverse effects. This drug also has the lowest rate of acute or long-term adverse effects. As with all drugs that prolong the QT interval, the syndrome of torsade de pointes is a serious potential adverse effect, typically seen in 3 to 4% of patients.

Amiodarone

Actions. *Amiodarone* contains iodine and is related structurally to thyroxine. It has complex effects showing Class I, II, III and IV actions. Its dominant effect is prolongation of the action potential duration and the refractory period. *Amiodarone* has antianginal as well as antiarrhythmic activity.

Therapeutic uses. *Amiodarone* is effective in the treatment of severe refractory supraventricular tachyarrhythmia. Its clinical usefulness is limited by its toxicity.

Pharmacokinetics. *Amiodarone* is incompletely absorbed after oral administration. The drug is unusual in having a prolonged half-life of several weeks. Full clinical effects may not be achieved until 6 weeks after initiation of treatment.

Adverse effects. *Amiodarone* shows a variety of toxic effects. After long-term use, more than one half of the patients receiving the drug show side effects sufficiently severe to prompt its discontinuation. Some of the more common effects include interstitial pulmonary fibrosis, GI tract intolerance, tremor, ataxia, dizziness, hyper- or hypothyroidism, liver toxicity, photosensitivity, neuropathy, muscle weakness, and blue skin discoloration caused by iodine accumulation in the skin. [Recent clinical trials have shown that *Amiodarone* did not reduce incidence of sudden death or prolong survival in patients with congestive heart failure.]

CLASS IV ANTIARRHYTHMIC DRUGS

The Class IV drugs are calcium channel blockers. They decrease the inward current carried by calcium, resulting in a decrease in the rate of Phase 4 spontaneous depolarization and slowed conduction in tissues dependant on calcium currents, such as the AV node. Although voltage-sensitive calcium channels occur in many different tissues, the major effect of calcium-channels blockers is on vascular smooth muscle and the heart.

Verapamil and Diltiazem

Verapamil shows greater action on the heart than on vascular smooth muscle, whereas *nifedipine*, a calcium channel-blocker used to treat hypertension exerts a stronger effect on vascular smooth muscle than on the heart. *Diltiazem* is intermediate in its actions.

Actions. Calcium enters cells by voltage-sensitive channels and by receptor-operated channels that are controlled by the binding of agonists, such as catecholamines, to membrane receptors. Calcium channels blockers, such as *Verapamil* and *Diltiazem*, are more effective against the voltage-sensitive channels, causing a decrease in the slow inward current that triggers cardiac contraction. *Verapamil* and *Diltiazem* bind only to open, depolarized channels. These drugs are therefore use-dependant, that is, they block most effectively when the heart is beating rapidly, since in a nor-

mally paced heart, the calcium channels have time to repolarize, and the bound drug dissociates from the channel before the next conduction pulse. *Verapamil* and *Diltiazem* are effective in treating arrhythmias that must traverse calcium-dependant cardiac tissues, such as AV node.

Therapeutic uses. *Verapamil* and *Diltiazem* are more effective against atrial than ventricular dysrhythmias (Fig. 19). They are useful in treating reentrant supraventricular tachycardia and reducing ventricular rate in atrial flutter and fibrillation. In addition, these drugs are used to treat hypertension and angina.

Pharmacokinetics. *Verapamil* and *Diltiazem* are absorbed after oral administration. *Verapamil* is extensively metabolized by the liver; thus, care should be taken in administration of this drug to patients with hepatic dysfunction.

Adverse effects. *Verapamil* and *Diltiazem* have negative inotropic properties and therefore may be contraindicated in patients with preexisting depressed cardiac function. Both drugs can also cause a decrease in blood pressure caused by peripheral vasodilation.

OTHER ANTIARRHYTHMIC DRUGS (CLASS V)

Digoxin

Digoxin shortens the refractory period in atrial and ventricular cells while prolonging the effective refractory period and diminishing conduction velocity in Purkinje fibers. *Digoxin* is used to control the ventricular response rate in atrial fibrillation and flutter. At toxic concentrations, *Digoxin* causes ectopic ventricular beats that may result in ventricular tachycardia and fibrillation. [Note: This arrhythmia is usually treated with *Lidocaine* or *Phenytoin.*]

Adenosine

Adenosine naturally occurs in nucleoside, but at high doses the drug decreases conduction velocity, prolongs the refractory period, and decreases automaticity in the AV node. Intravenous *Adenosine* is the drug of choice for abolishing acute supraventricular tachy-

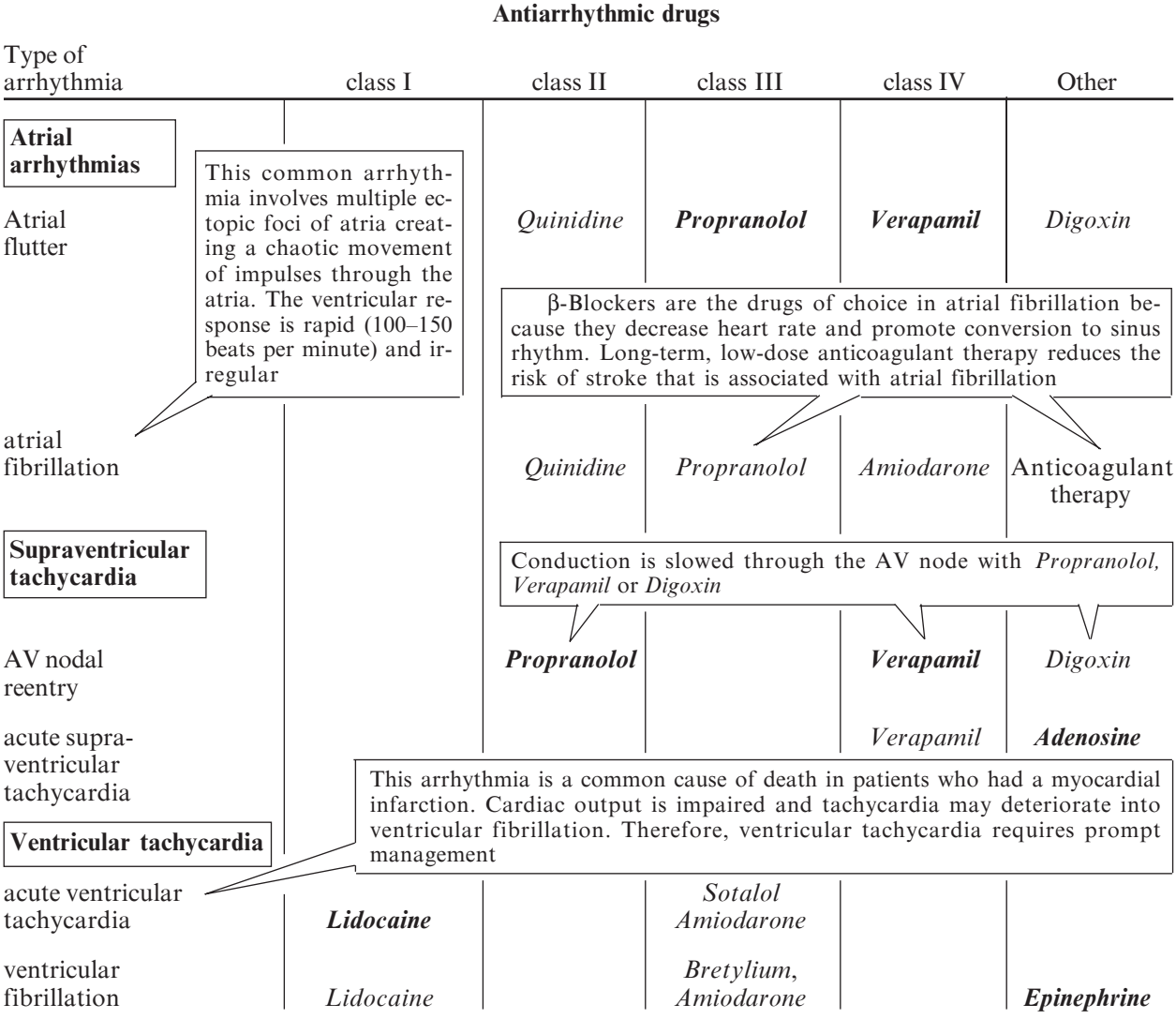


Fig. 19. Uses of antiarrhythmic drugs

cardia. It has low toxicity, but causes flushing, chest pain and hypotension. *Adenosine* has an extremely short duration of action.

Available forms:

Quinidine — in tablets 0.1 and 0.2 each

Mexiletine hydrochloride — in capsules 0.05 and 0.2 each; in ampoules 2.5% solution 10 ml each

Pindolol — in tablets 0.005; 0.01 and 0.015 each; in ampoules 0.004% solution 2 ml each

Amiodarone — in tablets 0.2 each; in ampoules 5% solution 3 ml each

Verapamil — in tablets 0.04, 0.12 each; in ampoules 0.25% solution 2 ml

Lecture 24
DIURETIC DRUGS

Diuretics are agents that increase the rate of urine formation. Except for the osmotic diuretics, these agents are ion transport inhibitors that decrease the reabsorption of Na^+ at different sites in the nephron. As a result, Na^+ and other ions such as Cl^- enter the urine in greater amounts than normal along with water, which is carried passively to maintain osmotic equilibrium. Diuretics thus increase the volume of the urine and often change its pH as well as the ionic composition of the urine and blood. The efficacy of the different classes of diuretics varies considerably, with the increase in secretion of Na^+ varying from less than 2% for the weak, potassium-sparing diuretics, to over 20% for the potent loop diuretics. Their major clinical use are in managing disorders involving abnormal fluid retention (edema) or in treating hypertension in which their diuretic action causes a decreased blood volume, leading to a reduction in blood pressure. Except for the osmotic diuretics, the diuretic drugs act directly on the tubular epithelia. For the most part, these direct actions are site, i.e., a drug will act on one or another tubular segment, but not on all of them. However, sites that are not attacked directly may well be affected indirectly; a change in the behavior of one segment will alter conditions for the downstream segments. In this lecture, the diuretic drugs are discussed in the order of their site of action along the nephron.

Normal regulation of fluid and electrolytes by the kidneys. Approximately 16–20% of the blood plasma entering the kidneys is filtrated from the glomerular capillaries into Bowman's capsule. The filtrate, although normally free of proteins and blood cells, does contain most low molecular weight plasma components in approximately the same concentration as are found in the plasma. These include glucose, sodium bicarbonate, amino acids, and other organic solutes, plus electrolytes, such as Na^+, K^+, and Cl^-. The kidney regulates the ionic composition and volume of the urine by the reabsorption or secretion of ions and/or water at five functional zones along the nephron, namely the proximal convoluted tubule, the descending loop of Henle, the ascending loop of Henle, the distal convoluted tubule, and the collecting duct.

Proximal convoluted tubule. In the extensively convoluted proximal tubule located in the cortex of the kidney, almost all of the glucose, bicarbonate, amino acids, and other metabolites are reabsorbed. Approximately two third of the Na^+ is also reabsorbed in the proximal tubule; chloride and water follow passively to maintain electrical and osmolar equality. If it were not for the extensive reabsorption of solutes and water in the proximal tubule, the mammalian organism would rapidly become dehydrated and lose its normal osmolarity.

Acid secretory system. The proximal tubule is the site of the organic acid and base secretory system. The organic acid secretory system secretes a variety of organic acids (such as uric acid, some antibiotics, and diuretics) from the bloodstream into the proximal tubule's lumen. Most diuretic drugs are delivered to the tubular fluid via this system. The organic acid secretory system is saturable, and diuretic drugs in the bloodstream compete for transfer with endogenous organic acids, such as uric acid. This explains the hyperuricemia seen with certain of the diuretic drugs, such as *Furosemide* and *Chlorothiazide*.

Descending loop of Henle. The remaining filtrate, which is isotonic, next enters the descending limb of Henle and passes into the medulla of the kidney. The osmolarity increases along the descending portion of the loop of Henle because of the countercurrent mechanism. This results in a tubular fluid with a three-fold increase in salt concentration.

Ascending loop of Henle. The cells of the ascending tubular epithelium are unique in being impermeable to water. Active reabsorption of Na^+, K^+ and Cl^- is mediated by a $Na^+/K^+/2Cl^-$ cotransporter. Mg^{++} and Ca^{++} enter the interstitial fluid via the paracellular pathway.

The ascending loop is thus a diluting region of the nephron. Approximately 25–30% of the tubular sodium chloride returns to the interstitial fluid, thus helping to maintain the fluid's high osmolarity. Since the loop of Henle is a major site of salt reabsorption, drugs affecting this site, such as loop diuretics, are the most efficacious of all the diuretic classes.

Distal convoluted tubule. The cells of the distal convoluted tubule are also impermeable to water. About 10% of the filtrated sodium chloride is reabsorbed via a Na^+/Cl^- transporter, which is sensitive to thiazide diuretics. Additionally, Ca^{++} excretion is regulated by parathyroid hormone in this portion of tubule.

Collecting tubule and duct. The principal and intercalated cells of the collecting tubule are responsible for Na^+-K^+ exchange and for H^+ secretion and K^+ reabsorption, respectively. Stimulation of aldosterone receptors in the principal cells results in Na^+ reabsorption and K^+ secretion. Antidiuretic hormone (ADH, vasopressin) receptors promote the reabsorption of water from the collecting tubules and ducts.

Kidney function in disease. In many diseases the amount of NaCl reabsorbed by the kidney tubules is abnormally high. This leads to the retention of water, an increase in blood volume, and expansion of the extravascular fluid compartment, resulting in the edema of the tissues. Several commonly encountered causes of edema include:

Congestive heart failure. The decreased ability of the failing heart to sustain adequate cardiac output causes the kidney to respond as if there were a decrease in blood volume. The kidney, as part of the normal compensatory mechanism, retains more salt and water as a means of raising blood volume and increasing the amount of blood that is returned to the heart. However, the diseased heart cannot increase its output, and increased vascular volume results in edema.

Hepatic ascites. Ascites, the accumulation of fluid in the abdominal cavity, is a common complication of cirrhosis of the liver.

Increased portal blood pressure. Blood flow in the portal system is often obstructed in cirrhosis, resulting in an increased portal blood pressure. Further, colloidal osmotic presser of the blood is decreased as a result of impaired synthesis of plasma proteins by the liver. Increased portal blood pressure and low osmolarity of the blood cause fluid to escape from the portal vascular system and collect in the abdomen.

Secondary hyperaldosteronism. Fluid retention is promoted by elevated levels of circulating aldosterone. This secondary hyperaldosteronism results from the decreased ability of the liver to inactivate the steroid hormone and leads to increased Na^+ and water reabsorption, and exacerbation of fluid accumulation.

Nephrotic syndrome. When damaged by disease, the glomerular membranes allow plasma proteins to enter the glomerular ultrafiltrate. The loss of protein from the plasma reduces the colloidal osmotic pressure resulting in edema. The low plasma volume stimulates aldosterone secretion through the renin — angiotensin — aldosterone system. This leads to retention of Na^+ and fluids, further aggravation of the edema.

Premenstrual edema. Edema associated with menstruation is the result of imbalances in hormones such as estrogen excess, which facilitates the loss of fluid into the extracellular space. Diuretics can reduce the edema.

CARBONIC ANHYDRASE INHIBITORS

Acetazolamide (Diacarb) is a sulfanilamide without antibacterial activity. Its main action is to inhibit the enzyme carbonic anhydrase in the proximal tubule epithelial cells. However, carbonic anhydrase inhibitors are more often used for their other pharmacologic action rather than for their diuretic effect, because these agents are much less efficacious than thiazides or loop diuretics.

Mechanism of action. *Acetazolamide* inhibits carbonic anhydrase, located intracellularly and on the apical membrane of the proximal tubule epithelium (Fig. 20). [Carbonic anhydrase catalyzes the reaction of CO_2 and H_2O leading to H^+ and HCO_3^- (bicarbonate).] The decreased ability to exchange Na^+ for H^+ in the presence of *Acetazolamide* results in a mild diuresis. Additionally, HCO_3^- is retained in the lumen with marked elevation in urinary pH. The loss of HCO_3^- causes a hyperchloremic metabolic acidosis and decreased diuretic efficacy following several days of therapy.

Therapeutic uses:

Treatment of glaucoma. The most common use of *Acetazolamide* is to reduce the elevated intraocular pressure of open-angle glaucoma. *Acetazolamide* decreases the production of aqueous humor, probably by

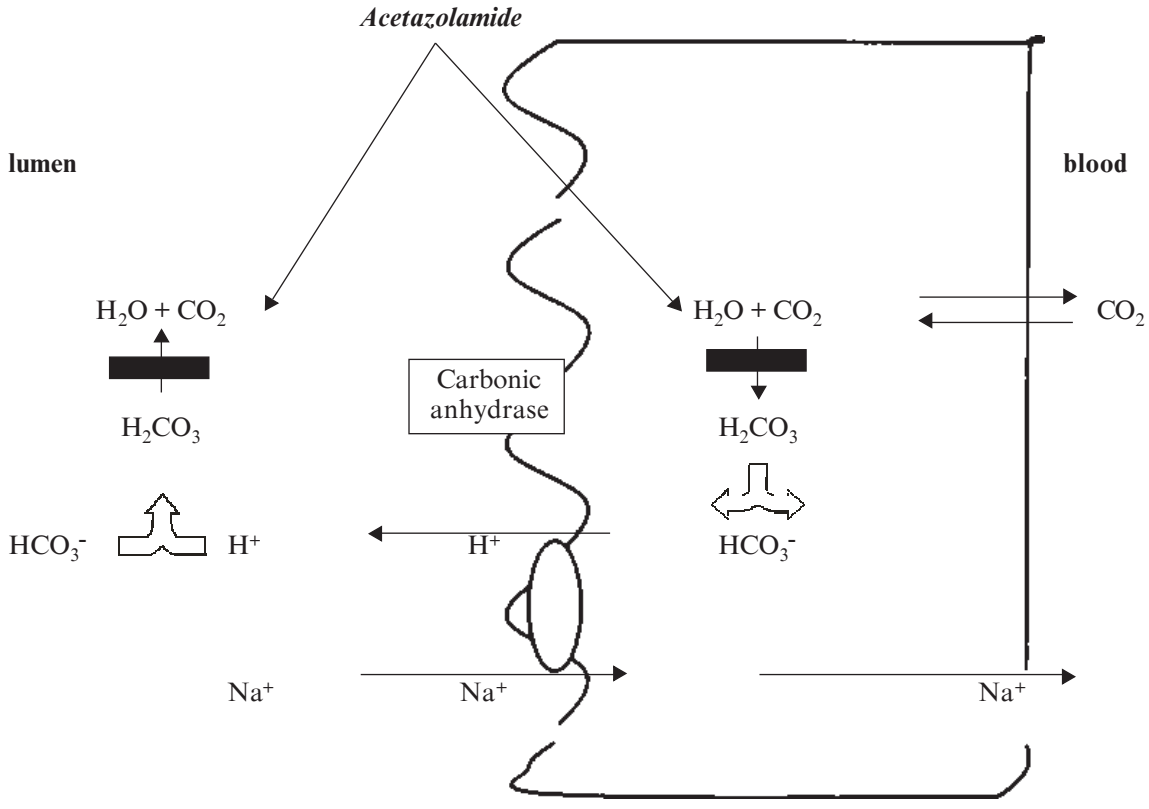


Fig. 20. Mechanism of action of *Acetazolamide*

blocking carbonic anhydrase in the ciliary body of the eye. It is useful in the chronic treatment of glaucoma but should not be used for an acute attack; *Pilocarpine* is preferred for an acute attack because of its immediate action.

Epilepsy. *Acetazolamide* is sometimes used in the treatment of epilepsy — both generalized and partial. It reduces the severity and magnitude of the seizures. Often *Acetazolamide* is used chronically in conjunction with antiepileptic medication to enhance the action of these other drugs.

Mountain sickness. Less commonly *Acetazolamide* can be used in the prophylaxis of acute mountain sickness among healthy, physically active individuals who rapidly ascend above 10,000 feet. *Acetazolamide* given nightly for 5 days before the ascent prevents the weakness, breathlessness, dizziness, nausea, and cerebral and pulmonary edema characteristic of the syndrome.

Pharmacokinetics. *Acetazolamide* is given orally once a day.

Adverse effects. Metabolic acidosis (mild), potassium depletion, renal stone formation, drowsiness, and paresthesia may occur.

LOOP (OR HIGH-CEILING) DIURETICS

The term *high ceiling* has been used to denote a group of diuretics that have a distinctive action on renal tubular function. *Furosemide, Bumetanide, Torsemide and Ethacrynic acid* are four diuretics that have their major action on the ascending limb of the loop of Henle. Compared to all other classes of diuretics, these drugs have the highest efficacy in mobilizing Na^+ and Cl^- from the body. *Ethacrynic acid* has a steeper dose-response curve than *Furosemide*; it shows greater side effects than those seen with the other loop diuretics and is not as widely used. *Bumetanide* is much more potent than *Furosemide*, and its use is increasing.

Mechanism of action. Loop diuretics inhibit the $Na^+/K^+/Cl^-$cotransport of the luminal membrane in the ascending limb of the loop of Henle. Therefore reabsorption of Na^+, K^+, and Cl^- is decreased. The loop diuretics are the most efficacious of the diuretic drugs, because the ascending limb accounts for the reabsorption of 25–30% of filtered NaCl and downstream sites are not able to compensate for this increased Na^+ load.

Actions. The loop diuretics act promptly, even among patients who have poor renal function or who have not responded to thiazides or other diuretics. [Note: Loop diuretics increase the calcium content, while thiazide diuretics decrease the Ca^{++} concentration of the urine.] The loop diuretics cause decreased renal vascular resistance and increased renal blood flow.

Therapeutic uses. The loop diuretics are the drug of choice for reducing the acute pulmonary edema of congestive heart failure because of their rapid onset of action. The high-ceiling diuretics are effective for the treatment of edema of cardiac, hepatic, or renal origin. In the management of refractory edema, the high-ceiling agents may be used in conjunction with other types of diuretics, such as a thiazide or K^+-sparing drug, but there is no rationale for administering two loop diuretics concomitantly. High-ceiling diuretics (along with hydration) are also useful in treating symptomatic hypercalcemia because they increase Ca^{++} urinary excretion.

Pharmacokinetics. Loop diuretics are administered orally or parenterally (i.v. or i.v.). Their duration of action is relatively brief, 1 to 4 hours.

Adverse effects:

Ototoxicity. Hearing can be affected adversely by the loop diuretics, particularly when used in conjunction with the aminoglycoside antibiotics. Vestibular function is less likely to be disturbed, but it may be affected too.

Hyperuricemia. *Furosemide* and *Ethacrynic acid* compete with uric acid for the renal and biliary secretory systems, thus blocking its secretion and thereby causing or exacerbating gouty attacks.

Acute hypovolemia. Loop diuretics can cause a severe and rapid reduction of blood volume, with the possibility of hypotension.

Potassium depletion. The heavy load of Na^+ presented in the collecting tubule results in increased exchange of tubular Na^+ for K^+, with the possibility of inducing hypokalemia. The loss of K^+ from cells in exchange for H^+ leads to hypokalemic alkalosis. Potassium depletion can be averted by use of potassium-sparing diuretics or dietary supplementation with K^+.

THIAZIDES AND RELATED AGENTS

The thiazides are the most widely used of the diuretic drugs. They are related in structure to the carbonic anhydrase inhibitors. The thiazides have significantly greater diuretic activity than *acetazolamide*, and they act on the kidney by different mechanisms. All thiazides affect the distal tubule, and all have equal maximum diuretic effect, differing only in potency, expressed on a per-milligram basis.

Chlorothiazide

Chlorothiazide, the prototype thiazide diuretic, was the first modern diuretic that was active orally and was capable of affecting the severe edema of cirrhosis and congestive heart failure with a minimum of side effects. Its properties are representative of the thiazide group, although newer derivatives such as *Hydrochlorothiazide* or *Chlorthalidone* are now used more commonly.

Mechanism of action. The thiazide derivatives act manly in the distal tubule to decrease the reabsorption of Na^+ by inhibition of a Na^+/Cl^- cotransporter on the luminal membrane. They have a lesser effect in the proximal tubule. As a result, these drugs increase the concentration of Na^+ and Cl^- in the tubular fluid. The acid-base balance is not usually affected. [Note: Because the site of action of the thiazides is on the luminal membrane, these drugs must be excreted into the tubular lumen to be effective. Therefore, with decreased renal function, thiazide diuretics lose efficacy.]

Actions:

Increased excretion of Na^+ and Cl^-. *Chlorothiazide* causes diuresis with increased Na^+ and Cl^- excretion,

which can result in the excretion of a very hyperosmolar urine. This latter effect is unique among the other diuretic classes, which are unlikely to produce a hyperosmolar urine. The diuretic action is not affected by the acid-base status of the body, nor does *Chlorothiazide* use change the acid-base status of the blood.

Loss of K^+. Because thiazides increase the filtrate arriving at the distal tubule, more K^+ is also exchanged for Na^+. Thus, prolonged use of these drugs results in continual loss of the K^+ from the body. Therefore, it is imperative to measure serum K^+ once a month (more frequently at the beginning of therapy). Often, K^+ can be supplemented by diet along, such as by increasing the intake of citrus fruits, bananas, and prunes. In some cases, K^+ salt supplementation may be necessary.

Decreased urinary calcium excretion. Thiazides decrease the Ca^{++}content of the urine by promoting the reabsorption of Ca^{++}. This contrasts with the loop diuretics, which increase the Ca^{++} concentration of the urine.

Reduced peripheral vascular resistance. An initial reduction in blood pressure results from a decrease in blood volume and therefore a decrease in cardiac output. With continued therapy, volume recovery occurs. However, there are continued hypotensive effects, results from reduced peripheral vascular resistance caused by relaxation of arteriolar smooth muscle. This usually occurs prior to the diuretic effect.

Therapeutic uses:

Hypertension. Clinically, the thiazides have long been the mainstay of antihypertensive medication, since they are inexpensive, convenient to administer, and well tolerated. They are effective in reducing systolic and diastolic blood pressure for extended periods in the majority of patients with mild to moderate essential hypertension. After 3–7 days of treatment, the blood pressure stabilizes at a lower level and can be maintained indefinitely by a daily dosage of the drug, which causes lower peripheral resistance without having a major diuretic effect. Many patients can be continued for years on the thiazides alone, although a small percentage of patients require additional medication, such as β-adrenergic blockers.

Congestive heart failure. Thiazides can be the diuretic of choice in reducing extracellular volume in mild to moderate congestive heart failure. If the thiazide fails, loop diuretics may be useful.

Renal impairment. Patients with nephrotic syndrome accompanied by edema are initially treated with loop diuretics; only if this treatment fails, they are given *Metolazone* in conjunction with loop diuretic.

Hypercalciuria. The thiazides can be useful in treating idiopathic hypercalciuria because they inhibit urinary Ca^{++} excretion. This is particularly beneficial for patients with calcium oxalate stones in the urinary tract.

Diabetes insipidus. Thiazides have a unique ability to produce a hyperosmolar urine. Thiazides can be substitute for the antidiuretic hormone in the treatment of nephrogenic diabetes insipidus. The urine volume of such individuals may drop from 11 L/day to about 3 L/day.

Pharmacokinetics. The drugs are effective orally. Most thiazides take 1 to 3 weeks to produce a stable reduction in blood pressure, and they exhibit a prolonged biological half-life (40 hours). All thiazides are secreted by the organic acid secretory system of the kidney.

Adverse effects:

Potassium depletion. Hypokalemia is the most frequent problem encountered with the thiazide diuretics and can predispose patients on *Digitalis* to ventricular arrhythmias. Activation of the renin-angiotensin-aldosterone system by the decrease in intravascular volume contributes significantly to urinary K^+ losses. The K^+ deficiency can be overcome by *Spironolactone* or by *Triamterene*. Low sodium diets blunt the potassium depletion caused by thiazide diuretics.

Hyperuricemia. Thiazides increase serum uric acid by decreasing the amount of acid excreted by the organic acid secretory system. Being insoluble, the uric acid deposits in the joints, and an attack of gout may result in individuals predisposed to gouty attack. It is important, therefore, to perform periodic blood tests for uric acid levels.

Hyperglycemia. Patients with diabetes mellitus, who are taking thiazides, may become hyperglycemic and have difficulty in maintaining appropriate blood sugar levels.

Hydrochlorothiazide is a thiazide derivative that has proven to be more popular than the parent drug. This is because it has far less ability to inhibit carbonic anhydrase as compared to *Chlorothiazide*. It is also more potent, so that the required dose is considerably less than that of *Chlorothiazide.* On the other hand, the efficacy is the same as that of the parent drug.

Chlorthalidone is a thiazide derivative that behaves like *Hydrochlorothiazide*. It has a very long duration of action and therefore is often used to treat hypertension. It is given once per day for this indication.

THIAZIDE ANALOGS

Metolazone is more potent than the thiazides and, unlike the thiazides, causes Na^+ excretion in advanced renal failure.

Indapamide is a lipid soluble, nonthiazide diuretic that has a long duration of action. At low doses, it shows significant antihypertensive action with minimal diuretic effects. *Indapamide* is often used in advanced renal failure to stimulate additional diuresis on top of that achieved by loop diuretics. *Indapamide* is metabolized and excreted by the GI tract and kidneys; it therefore is less likely to accumulate in patients with renal failure and may be useful in their treatment.

POTASSIUM-SPARING DIURETICS

These agents act in the collecting tubule to inhibit Na^+ reabsorption, K^+ secretion, and H^+ secretion. Potassium-sparing diuretics are used primarily when aldosterone is present in excess. The major use of potassium-sparing agents is in the treatment of hypertension, most often in combination with a thiazide. It is extremely important that patients treated with any potassium-sparing diuretic be closely monitored for potassium levels. Exogenous potassium supplementation is usually discontinued when potassium-sparing diuretic therapy is instituted.

Spironolactone

Mechanism of action. *Spironolactone* is a synthetic aldosterone antagonist that competes with aldosterone for intracellular cytoplasmic receptor sites. The *spironolactone*-receptor complex is inactive, that is, it prevents translocation of the receptor complex into the nucleus of the target cell, and thus does not bind to DNA. This results in a failure to produce proteins that are normally synthesized in response to aldosterone. These mediator proteins normally stimulate the Na^+-K^+ exchange sites of the collecting tubule.

Actions. In most edematous states, blood levels of aldosterone are high, which is instrumental in retaining Na^+. When *Spironolactone* is given to a patient with elevated circulating levels of aldosterone, the drug antagonizes the activity of the hormone, resulting in retention of K^+ and excretion of Na^+. Where there are no significant circulating levels of aldosterone, such as in Addison's disease (primary adrenal insufficiency), no diuretic effect of the drug occurs.

Therapeutic uses:

Diuretic. Although *spironolactone* has the low efficacy in mobilizing Na^+ from the body in comparison with the other drugs, it has the useful property of causing the retention of K^+. Because of this latter action, *Spironolactone* is often given in conjunction with a thiazide or loop diuretic to prevent K^+ excretion.

Secondary hyperaldosteronism. *Spironolactone* is the only potassium sparing diuretic that is routinely used alone to induce net negative salt balance. It is particularly effective in clinical situations associated with secondary hyperaldosteronism.

Pharmacokinetics. *Spironolactone* is completely absorbed orally and is strongly bound to proteins. It is rapidly converted to an active metabolite, *canrenone*. The action of *spironolactone* is largely due to the effect of *Canrenone*, which has mineralocorticoid-blocking activity. *Spironolactone* induces hepatic cytochrome P-450.

Adverse effects. Because *Spironolactone* chemically resembles some of the sex steroids, it does have minimal hormonal activity and may induce gynecomastia in males and menstrual irregularities in females. Because of this, the drug should not be given in high doses on a chronic basis. It is most effectively employed in mild edematous state where it is given for a few days at a time. At low doses, *spironolactone* can be used chronically with few side effects. Hyperkalemia, nausea, lethargy, and mental confusion can occur.

Triamterene and Amiloride

Triamterene and *Amiloride* block Na^+ transport channels resulting in a decrease in Na^+-K^+ exchange; they have K^+-sparing diuretic action similar to that of *Spironolactone.* However, the ability of these drugs to block Na^+-K^+ exchange site in the collecting tubule does not depend on the presence of aldosterone. Thus, they have diuretic activity even in individuals with Addison's disease. They, like *Spironolactone*, are not very efficacious diuretics. Both *Triamterene* and *amiloride* are frequently used in combination with other diuretics, usually for their potassium-sparing properties. For example, much like *Spironolactone*, they prevent K^+ loss that occurs with thiazides and *Furosemide.* The side effects of *Triamterene* are leg cramps and the possibility of increased blood urea nitrogen (BUN) as well as uric acid and K^+ retention.

OSMOTIC DIURETICS

The term osmotic diuretic is used for certain solutes that have the following attributes in common: (1) they are freely filterable at the glomerulus; (2) they undergoes little or no reabsorption and (3) they are relatively inert by conventional pharmacological criteria. These agents are administered in sufficiently large quantities to contribute significantly to the osmolarity of the plasma, the glomerular filtrate, and the tubular fluid. *Mannitol* is the most frequently used of the osmotic diuretics. Other agents include *urea, glycerin,* and *isosorbide*. Increase in diuresis is due to their ability to carry water with them into the tubular fluid. Only a small amount of additional salt may also be excreted. Because osmotic diuretics are used to effect increased water excretion, they are not useful in treating conditions in which Na^+ retention occurs. They are used to maintain urine flow following acute toxic ingestion of substances capable of producing acute renal failure. Osmotic diuretics are a mainstay of treatment for patients with increased intracranial pressure, or acute renal failure due to shock, drug toxicities, severe traumatic injury, and management of hemolytic transfusion reactions. Maintaining urine flow preserves long-term kidney function and may save the patient from dialysis. [Note:*Mannitol* is not absorbed when given orally; the agent can only be given intravenously.]

METHYLXANTHINES

The *Methylxanthines* have long been known for their additional diuretic action. Of the *Methylxanthines*, *Theophylline* has the greatest action on kidney. Although there is some controversy, theophylline-induced diuresis probably result from an increase in renal blood flow and glomerular filtration rate. This is most obvious in conditions that produce reductions in these parameters, such as hypotension or cardiac insufficiency. The methylxanthines are rarely employed as primary diuretics. However, when used for other purposes, particularly as bronchodilators, the coexistence of their diuretic action should be kept in mind.

Available forms:

Hydrochlorothiazide — in tablets 0.025 and 0.1 each

Furosemide — in tablets 0.04 each; in ampoules 1% solution 2 ml each

Acetazolamide (Diacarbum) — in tablets 0.25 each

Triamterene — in capsules 0.05 each

Triampur — in patented tablets (each contains *Triamterene* and *Hydrochlorothiazide*)

Spironolactone — in tablets 0.025 each

Mannite — in ampoules 15% solution 200, 400 and 500 ml each

Lecture 25
DRUGS USED IN ARTERIAL HYPERTENSION

Hypertension is defined as a sustained diastolic blood pressure greater than 90 mm Hg accompanied by an elevated systolic blood pressure (>140 mm Hg). Hypertension results from increased peripheral vascular muscle tone, which leads to increased arteriolar resistance and reduced capacitance of the venous system. Elevated blood pressure is an extremely common disorder, affecting approximately 15% of the population in developed countries. Although many of these individuals have no symptoms, chronic hypertension — either systolic or diastolic — can lead to congestive heart failure, myocardial infarction, renal damage, and cerebrovascular accidents. The incidence of morbidity and mortality significantly decreases when hypertension is diagnosed early and is properly treated.

Etiology of hypertension. Although hypertension may occur secondary to other disease processes, more than 90% of patients have essential hypertension, a disorder of unknown origin affecting the blood pressure-regulating mechanism. A family history of hypertension increases the likelihood that an individual will develop hypertensive disease. Essential hypertension occurs four times more frequently among blacks than whites, and it occurs more often among middle-aged males than among middle-aged females. Environmental factor such as a stressful lifestyle, high dietary intake of sodium, obesity, and smoking all further predispose an individual to the occurrence of hypertension.

Mechanisms for controlling blood pressure. Arterial blood pressure is regulated within a narrow range to provide adequate perfusion of the tissues without causing damage of the arterial intima. Arterial blood pressure is directly proportional to the product of the cardiac output and the peripheral vascular resistance:

Arterial blood ≈ **Cardiac output** × **Peripheral pressure resistance**

In both normal and hypertensive individuals, cardiac output and peripheral resistance are controlled mainly by two overlapping control mechanisms: the baroreflexes mediated by the sympathetic nervous system, and the renin — angiotensin — aldosterone system. Most antihypertensive drugs lower blood pressure by reducing cardiac output and/or decreasing peripheral resistance.

Baroreceptors and the sympathetic nervous system. Baroreflexes involving the sympathetic nervous system are responsible for the rapid moment-to-moment regulation of the blood pressure. A fall in blood pressure causes pressure-sensitive neurons (baroreceptors in the aortic arch and carotid sinuses) to send fewer impulses to the cardiovascular centers in the CNS. This prompts a reflex response of increased sympathetic and decreased parasympathetic output to the heart and vasculature, resulting in vasoconstriction and increased cardiac output (Fig. 21). These changes result in a compensatory rise in blood pressure.

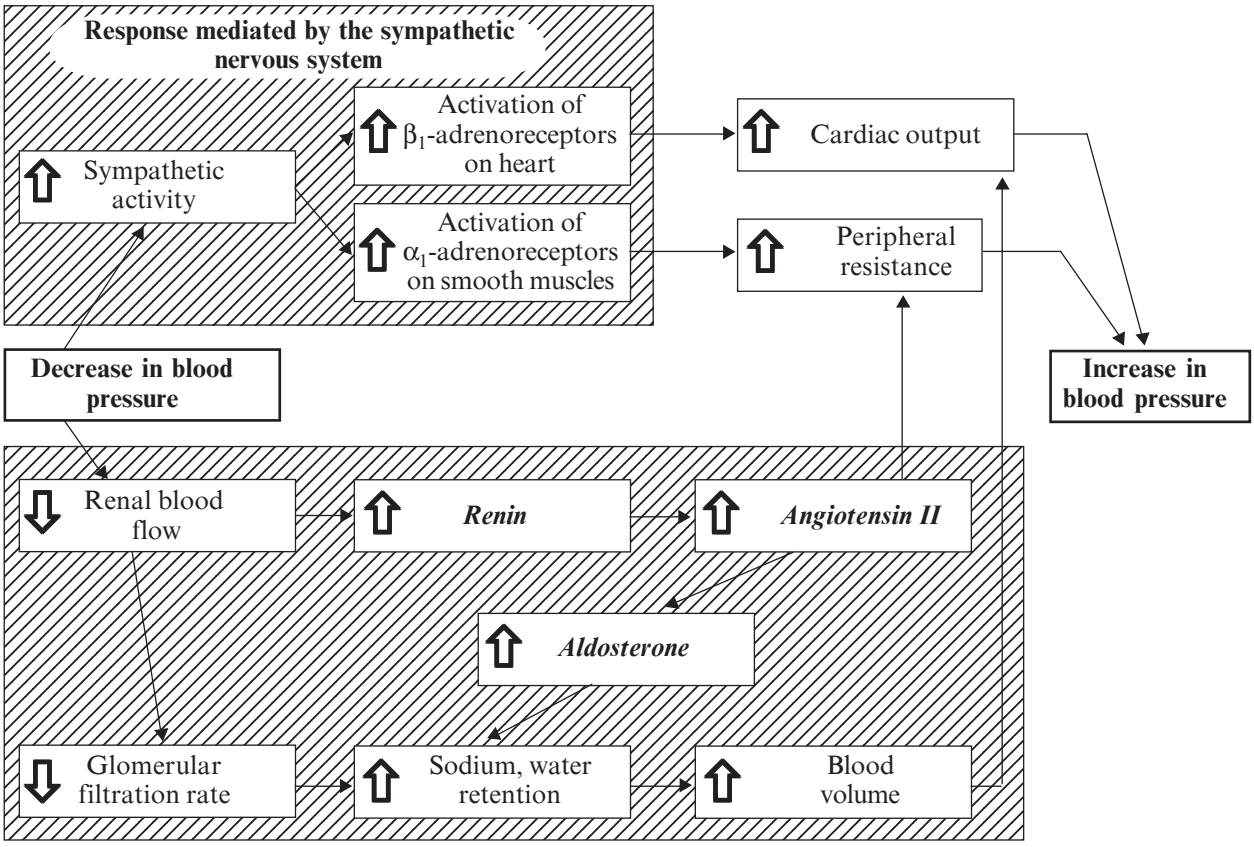


Fig. 21. Mechanisms increasing blood pressure

Renin — angiotensin — aldosterone system. The kidney provides for the long-term control of blood pressure by altering the blood volume. Baroreceptors in the kidney respond to reduced arterial pressure (and to sympathetic stimulation of β-adrenoreceptors) by releasing the enzyme renin.

This peptidase converts angiotensinogen to angiotensin I, which is in turn converted to angiotensin II in the presence of angiotensin converting enzyme (ACE).

Angiotensin II is the body's most potent circulating vasoconstrictor, causing an increase in blood pressure. Furthermore, angiotensin stimulates aldosterone secretion, leading to increased renal sodium reabsorption and an increase in blood volume, which contribute to a further increase in blood pressure.

Classification of drugs

Antihypertensive drugs can be classified according to their sites of action. There is a variety of mechanisms of action and some drugs appear under more than one heading.

1. Neurotropic: sedatives, anxiolytics, neuroleptics, and hypnotic drugs in low doses;

2. Drugs acting at synaptic transmission:

a) centrally-acting adrenergic drugs (*Clonidine,* α-*Methyldopa*);

b) adrenergic antagonists:

— sympatholytics

— α-adrenergic blockers: 1) α_1-blockers (*Prazosin*); 2) α_1- and α_2-blockers (*Phentolamine*);

— β-adenergic blockers: 1) nonselective β_1- and β_2-blockers (*Propranolol, Pindolol, Timolol*); 2) selective β_1-blockers (*Atenolol, Acebutolol, Metoprolol*);

— an α + β-blocker: *Labetalol*;

c) cholinergic (ganglionic blockers): *Benzohexonium, Pentaminum*;

3. Myotropic:

a) calcium channels blockers: *Verapamil, Diltiazem, Nifedipine*;

b) phosphodiesterase inhibitors: *Aminophylline, Papaverine*;

c) imidazole derivatives: *Dibazole*;

d) peripheral vasodilators: *Hydralazine, Minoxidil, Diazoxide, Sodium nitroprusside, ganglionic blockers*;

4. Drugs affecting blood volume and plasma enzymes:

a) angiotensin converting enzyme inhibitors: *Captopril, Enalapril;*

b) diuretics.

Treatment strategies. Mild hypertension can be controlled with a single drug. More severe hypertension may require treatment with several drugs that are selected to minimize adverse effects of the combined regimen. Treatment is initiated with any of four drugs depending on the individual patient: a diuretic, a β-blocker, an ACE inhibitor, or a calcium channel blocker. If blood pressure is inadequately controlled, a second drug is added. A β-blocker is usually added if the initial drug was a diuretic, or a diuretic is added if the first drug was a β-blocker. A vasodilator can be added as a third step for those patients who still fail to respond.

Individualized care. Certain subsets of the hypertensive population respond better to one class of drug than another. For example, black patients respond well to diuretics and calcium channel blockers, but therapy with β-blockers or ACE inhibitors is often less effective. Similarly, calcium channels blockers, ACE inhibitors, and diuretics are favored for treatment of hypertension in the elderly, whereas β-blockers and α-antagonists are less well tolerated. Furthermore, hypertension may coexist with other diseases that can be aggravated by some of the antihypertensive drugs. For example, the Table 9 shows the preferred therapy in hypertensive patients with various concomitant diseases. In such cases, it is important to match antihypertensive drugs to the particular patient.

The hypertensive patient is usually asymptomatic and is diagnosed by routine screening before the occurrence of overt end-organ damage. Thus, therapy is directed at preventing disease sequelae (that occur in the future), rather than in relieving present discomfort of the patient. The adverse effects associated with the hypertensive therapy may influence the patient more the future benefits. Thus, it is important to enhance compliance by carefully selecting a drug regimen that both reduces adverse effects and minimizes the number of doses required daily.

DIURETICS

Diuretics and/or β-blockers are currently recommended as the first-line drug therapy for hypertension. Low-dose diuretic therapy is safe and effective in preventing stroke, myocardial infarction, congestive heart failure and total mortality. Recent data suggest that diuretics are superior to β-blockers in older adults.

THIAZIDE DIURETICS

All oral diuretic drugs are effective in the treatment of hypertension, but the thiazides have found the most widespread use.

Actions. Thiazide diuretics, such as *Hydrochlorothiazide*, lower blood pressure, initially by increasing sodium and water excretion. This causes a decrease in extracellular volume, resulting in a decrease in cardiac output and renal blood flow. With long-term treatment, plasma volume approaches a normal value, but peripheral resistance decreases. *Spironolactone*, a potassium-sparing diuretic, is often used with thiazides.

Therapeutic use. Thiazide diuretics decrease blood pressure in both the supine and standing positions; postural hypotension is rarely observed, except in elderly, volume-depleted patients. These agents counteract the sodium and water retention observed with other agents (for example, *Hydralazine*). Thiazides are therefore useful in combination therapy with variety of other antihypertensive agents including β-blockers and ACE inhibitors. Thiazide diuretics are particularly useful in the treatment of black and elderly patients, and in those with chronic renal disease. Thiazide diuretics are not effective in patients with in-

Table 9. **Individualized care of hypertension according to concomitant disease**

Concomitant disease	Drugs commonly used in treating hypertension			
Angina pectoris	Diuretics	***β-Blockers***	ACE	***Ca^{++}blockers***
Diabetes (insulin-dependant)			***ACE***	***Ca^{++}blockers***
Hyperlipidemia			***ACE***	***Ca^{++}blockers***
Congestive heart failure	Diuretics		***ACE***	avoid verapamil
Previous myo-cardial infarction	Diuretics	***β-Blockers***	***ACE***	Ca^{++}blockers
Chronic renal disease	***Diuretics***	β-Blockers	ACE	***Ca^{++}blockers***
Asthma, chronic pulmonary disease	***Diuretics***		ACE	***Ca^{++}blockers***

KEY. ***drug*** — commonly used drug; drug — alternative drug

adequate kidney function (creatinine clearance less than 50 mls/min). Loop diuretics may be required in these patients.

Pharmacokinetics. Thiazide diuretics can be administered orally. They induce considerable disturbances in electrolyte balance. For example, blood levels of K^+ and Mg^{++} are reduced, and Ca^{++} is retained by the body.

Adverse effects. Thiazide diuretics induce hypokalemia and hyperuricemia in 70% of patients, and hyperglycemia in 10% of patients. Serum potassium level should be monitored closely in patients who are predisposed to cardiac arrhythmias and who are concurrently being treated with both thiazide diuretics and digitalis glycosides. Diuretics should be avoided in the treatment of hypertensive diabetics or patients with hyperlipidemia.

LOOP DIURETICS

The loop diuretics act promptly, even in patients who have poor renal function or who have not responded to thiazides. The loop diuretics cause decreased renal vascular resistance and increase renal blood flow. [Note: Loop diuretics increase the Ca^{++} content of the urine, whereas thiazides decrease the Ca^{++} concentration of the urine.

β-ADRENORECEPTOR BLOCKING AGENTS

β-Blockers and/or diuretics are currently recommended as first-line drug therapy for hypertension. These drugs are efficacious but have some contraindications.

Actions. The β-blockers reduce blood pressure primarily by decreasing cardiac output. They may also decrease sympathetic outflow from the CNS and inhibit the release of renin from the kidneys, thus decreasing the formation of angiotensin II and secretion of aldosterone. The prototype β-blocker is *Propranolol*, which acts at both β_1- and β_2-receptors. Newer agents, such as *Atenolol* and *Metoprolol*, are selective for β_1 receptors. These agents may be used in disease states such as asthma, in which *Propranolol* is contraindicated due to its β_2-mediated bronchoconstriction.

Therapeutic uses:

Subsets of the hypertensive population. The β-blockers are more effective for treating hypertension in white than in black patients, and in young patients compared to the elderly. [Note: Conditions that discourage the use of β-blockers (for example, severe chronic obstructive lung disease, congestive heart failure, occlusive peripheral vascular disease) are more commonly found in the elderly and in diabetics.]

Hypertensive patients with concomitant diseases. The β-blockers are useful in treating conditions that may coexist with hypertension, such as supraventricular tachyarrhythmia, previous myocardial infarction, glaucoma (applied topically), and migraine headache.

Pharmacokinetics. The β-blockers are orally active. *Propranolol* undergoes extensive first-pass metabolism. The β-blocker may take several weeks to develop their full effects.

Adverse effects:

Common effects. The β-blockers may cause CNS side effects such as fatigue, lethargy, insomnia, and hallucinations; these drugs can also cause hypotension. The β-blockers may decrease libido and cause impotence; drug-induced sexual dysfunction can severely reduce patient compliance.

Alteration in serum lipid patterns. The β-blockers may disturb lipid metabolism, decreasing high-density lipoproteins (HDL) and increasing plasma triacylglycerol.

Drug withdrawal. Abrupt withdrawal may cause rebound hypertension, probably as a result of up-regulation of β-receptors. Patients should be tapered off of β-blocker therapy in order to avoid precipitation of arrhythmias. The β-blokers should be avoided in treat-

ing patients with asthma, congestive heart failure, and peripheral vascular diseases.

ACE INHIBITORS

The ACE inhibitors *(Captopril, Enalapril)* are recommended when the preferred first-line agents (diuretics or β-blockers) are contraindicated or ineffective. Despite their wide-spread use, it is not clear if ACE inhibitors increase the risk of other major diseases.

Actions. The ACE inhibitors lower blood pressure by reducing peripheral vascular resistance without reflex increasing cardiac output, rate, or contractility (Fig. 22). These drugs block the angiotensin converting enzyme that cleaves angiotensin I to form the potent vasoconstrictor, angiotensin II. These inhibitors also diminish the rate of bradykinin inactivation. Vasodilation occurs as a result of the combined effects of lower vasoconstriction caused by diminished levels of angiotensin II and the potent vasodilating effect of increased bradykinin. By reducing circulating angiotensin II levels, ACE inhibitors also decrease the secretion of aldosterone, resulting in decreased sodium and water retention.

Therapeutic uses. Like β-blockers, ACE inhibitors are most effective in hypertensive patients who are white and young. However, when used in combination with a diuretic, the effectiveness of ACE inhibitors is similar in white and black hypertensive patients. Unlike β-blockers, ACE inhibitors are effective in the management of patients with chronic congestive heart failure. ACE inhibitors are now a standard in the care of a patient following a myocardial infarction.

Adverse effects. Common side effects include dry cough, rashes, fever, altered taste, hypotension (in hypovolemic states), and hyperkalemia. Potassium supplements or *Spironolactone* are contraindicated. Angioedema is a rare but potentially life-threatening reaction. Because of the risk of angioedema and first dose syncope, ACE inhibitors are first administered in the physician's office with close observation. Reversible renal failure can occur in patients with severe renal artery stenosis. ACE inhibitors are fetotoxic and should not be used in pregnant women.

ANGIOTENSIN II ANTAGONISTS

The nanopeptide *Losartan*, a highly selective angiotensin II receptor blocker, has recently been approved for antihypertensive therapy. Its pharmacologic effects are similar to ACE inhibitors in that it produces vasodilation and blocks aldosterone secretion. Its adverse effects profile is improved over the ACE inhibitors, although it is fetotoxic.

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers are recommended when the preferred first-line agents are contraindicated or ineffective. Despite their wide-spread use, it is not clear what effects antihypertensive therapy with these drugs has on major disease. One retrospective study suggests that use of short-acting calcium channel blockers, especially in high doses, is associated with an increased risk of myocardial infarction. If confirmed in more rigorous randomized trials, these finding will reinforce the importance of diuretics and β-blockers as first-line agents.

The calcium channel blockers are divided into three chemical classes, each with different pharmacokinetic properties and clinical indications:

1. Diphenylalkylamines. *Verapamil* is the only member of this class that is currently in clinical practice. *Verapamil* is the least selective of any calcium channel blocker, and has significant effects on both cardiac and vascular musculature. It is used to treat angina, supraventricular tachyarrhythmias, and migraine headache.

2. Benzothiazepines. *Diltiazem* is the only member of this class. Like *Verapamil*, *Diltiazem* affects both cardiac and vascular smooth muscle cells; however, it has a less pronounced negative inotropic effect on the heart than does *Verapamil*. *Diltiazem* has a favorable side-effect profile.

3. Dihydropyridines. This rapidly expanding class of calcium channel blockers includes the first-generation *Nifedipine*, and newer agents *Amlodipine, Felodipine, Isradipine, Nicardipine,* and *Nisoldipine.* These second-generation calcium channel blockers differ in pharmacokinetics, approved uses, and drug interactions. All the dihydropyridines have a much

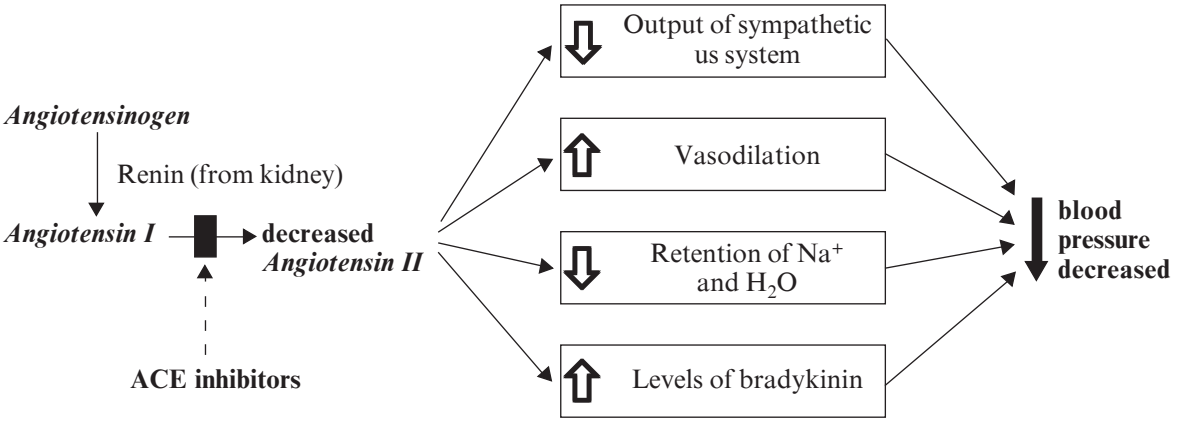


Fig. 22. Action of renin — angiotensin system

greater affinity for vascular calcium channels than for calcium channels in the heart. They are therefore particularly attractive in treating hypertension. Some of the newer agents, such as *Amlodipine* and *Nicardipine*, have the advantage that they show little interaction with other cardiovascular drugs, such as *Digoxin* or *Warfarin.*

Actions. The intracellular concentration of calcium plays an important role in maintaining the tone of smooth muscle and in the contraction of the myocardium. Calcium enters muscle cells through special voltage-sensitive calcium channels. This triggers release of calcium from the sarcoplasmic reticulum and mitochondria, which further increases the cytosolic level of calcium. Calcium channel antagonists block the inward movement of calcium by binding to L-type calcium channels in the heart and in smooth muscle of the coronary and peripheral vasculature. This causes vascular smooth muscle to relax, dilating mainly arterioles.

Therapeutic uses. Calcium channel blockers have an intrinsic natriuretic effect; therefore, they do not usually require the addition of a diuretic. These agents are useful in the treatment of hypertensive patients who also have asthma, diabetes, angina, and/or peripheral vascular disease.

Pharmacokinetics. Most of these agents have short half-lives ($T_{1/2}$=3 to 8 hours) following an oral dose. Treatment is required three times a day to maintain good control of hypertension. Sustained release preparations permit less frequent dosing.

Adverse effects. Although infrequent, side effects include constipation in 10% of patients, dizziness, headache, and a feeling of fatigue caused by a decrease in blood pressure. *Verapamil* should be avoided in patients with congestive heart failure due to its negative inotropic effects.

α-ADRENERGIC BLOCKING AGENTS

Prazosin, Oxazosin and *Terazosin* produce a competitive block of α_1-adrenoreceptors. They decrease peripheral vascular resistance and lower arterial blood pressure by causing the relaxation of both arterial and venous smooth muscle. These drugs cause only minimal changes in cardiac output, renal blood flow, and glomerular filtration rate.

Therefore, long-term tachycardia and increased renin release do not occur. Postural hypotension may occur in some individuals. *Prazosin is* used to treat mild to moderate hypertension and is prescribed in combination with *Propranolol* or a diuretic for additive effects. Reflex tachycardia and first dose syncope are almost universal adverse effects. Concomitant use of a β-blocker may be necessary to blunt the short-term effect of reflex tachycardia.

CENTRALLY-ACTING ADRENERGIC DRUGS

Clonidine (Clophelinum)

This α_2-agonist diminishes central adrenergic outflow. *Clonidine* is used primarily for the treatment of mild to moderate hypertension that has not responded adequately to treatment with diuretics alone. *Clonidine* does not decrease renal blood flow or glomerular filtration and therefore is useful in the treatment of hypertension complicated by renal disease. *Clonidine* is absorbed well after oral administration and is excreted by the kidney. Because it causes sodium and water retention, *Clonidine* is usually administered in combination with a diuretic. Adverse effects are generally mild, but the drug can produce sedation and drying of nasal mucosa. Rebound hypertension occurs following abrupt withdrawal of *Clonidine.* The drug should therefore be withdrawn slowly if the clinician wishes to change agents.

α-Methyldopa

This α-adrenergic agonist diminishes the adrenergic outflow from the CNS, leading to reduced total peripheral resistance. Cardiac output is not decreased and blood flow to vital organs is not diminished. Because blood flow to the kidney is not diminished, α-*Methyldopa* is especially valuable in treating hypertensive patients with renal insufficiency. The most common side effects are sedation and drowsiness.

VASODILATORS

The direct-acting smooth muscle relaxants, such as *Hydralazine* and *Minoxidil*, have traditionally not been used as primary drugs to treat hypertension. Vasodilators act by producing relaxation of vascular smooth muscle, which decreases resistance and therefore decreases blood pressure. These agents produce reflex stimulation of the heart, resulting in the competing symptoms of increased myocardial contractility, heart rate, and oxygen consumption. These actions may prompt angina pectoris, myocardial infarction. Vasodilators also increase plasma renin concentration, resulting in sodium and water retention. These undesirable side effects can be blocked by concomitant use of a diuretic and a β-blocker.

Hydralazine

This drug causes vasodilation, acting primarily on arteries and arterioles. This results in a decreased peripheral resistance, which in turn prompts a reflex elevation in heart rate and cardiac output. *Hydralazine* is used to treat moderately severe hypertension. It is almost always administered in combination with a β-blocker (to balance the reflex tachycardia) and a diuretic (to decrease sodium retention). Together, the three drugs decrease cardiac output, plasma volume, and peripheral vascular resistance. Adverse effects of hydralazine therapy include headache, nausea, sweating, arrhythmia, and precipitation of angina. A lupus-like syndrome can occur with high dosage, but it is reversible on discontinuation of the drug.

Minoxidil

This drug causes dilation of resistance vessels (arterioles) but not of capacitance vessels (venules). *Minoxidil* is administered orally for treatment of severe to malignant hypertension that is refractory to other drugs. Reflex tachycardia may be severe and may re-

quire the concomitant use of a diuretic and a β-blocker. *Minoxidil* causes serious sodium and water retention, leading to volume overload, edema, and congestive heart failure. [Note: *Minoxidil* treatment also causes hypertrichosis (the growth of the body hair). This drug is now used topically to treat male pattern baldness.]

HYPERTENSIVE EMERGENCY

Hypertensive emergency is a rare, but life-threatening situation in which the diastolic blood pressure is either over 150 mm Hg (with systolic blood pressure greater than 210 mm Hg) in an otherwise healthy person, or 130 mm Hg in an individual with preexisting complications, such as encephalopathy, cerebral hemorrhage, left ventricular failure, or aortic stenosis. The therapeutic goal is to rapidly reduce blood pressure.

Sodium Nitroprusside

Nitroprusside is administered intravenously, and causes prompt vasodilation, with reflex tachycardia. It is capable of reducing blood pressure in all patients, regardless of the cause of hypertension. The drug has little effect outside the vascular system, acting equally on arterial and venous smooth muscle. [Note: Because *Nitroprusside* also acts on the veins, it can reduce cardiac preload.] *Nitroprusside* is metabolized rapidly ($t_{1/2}$ of minutes) and requires continuous infusion to maintain its hypotensive action. *Sodium nitroprusside* exerts few adverse effects except for those of hypotension caused by overdose. *Nitroprusside* metabolism results in cyanide ion production, although cyanide toxicity is rare and can be effectively treated with an infusion of *sodium thiosulfate* to produce thiocyanate, which is less toxic and eliminated by the kidneys. [Note: *Nitroprusside* is poisonous if given orally because of its hydrolysis to cyanide.]

Diazoxide

Diazoxide is a direct acting arteriolar vasodilator. It has vascular effects like those of hydralazine. For patients with coronary insufficiency, *Diazoxide* is administered i.v. with a β-blocker, which diminishes reflex activation of the heart. *Diazoxide* is useful in the treatment of hypertensive emergencies, hypertensive encephalopathy, and eclampsia. Excessive hypotension is the most serious toxicity.

Labetalol

Labetalol is both an α- and β-blocker that has been successfully used in hypertensive emergencies. *Labetalol* does not cause the reflex tachycardia that may be associated with *Diazoxide*. *Labetalol* carries the contraindications of a nonselective β-blocker.

Available forms:

Captopril — in tablets 0.025; 0.05 and 0,1 each

Ethacrynic acid — in tablets 0.05 each; in ampoules 0.05 each (to dilute in physiologic solution before using)

Clonidine (Clophelinum) — in tablets 0.000075 and 0.00015 each; in ampoules 0.01% solution 1 ml each

Reserpine — in tablets 0.0001 and 0.00025 each

Atenolol — in tablets 0.1 each

Prazosin — in tablets 0.001 and 0.005 each

Diltiazem — in tablets 0.03 and 0.06 each

Papaverine hydrochloride — in tablets 0.04 each; in ampoules 2% solution 2 ml each

Nitroprusside sodium — in ampoules 0.025 and 0.05 each (to dilute in 500 ml of 5% solution of glucose)

Hydralazine (Apressinum) — in tablets 0.01 and 0.25 each

Lecture 26
DRUGS USED IN HYPOTENSION

Shock is a state of inadequate capillary perfusion (oxygen deficiency) of vital tissues to an extent that adversely affects cellular metabolism (capillary endothelium and organs) causing malfunction including release of enzymes and vasoactive substances, i.e. it is a low flow or hypoperfusion state.

The essential element, hypoperfusion of vital organs, is present whatever the cause, whether the pump failure (myocardial infarction), maldistribution of the blood (septic shock) or loss of total intravascular volume (bleeding, or increased permeability of vessels damaged by bacterial cell wall substances, by burns or by anoxia). Function of vital organs, brain (consciousness) and kidney (urine formation) are critical indicators of adequacy of perfusion of these organs.

Treatment may be summarized:

1. Treatment of the cause: pain, wounds, infections, adrenocortical deficiency.
2. Replacement of any fluid lost from the circulation; but extra fluid is dangerous when the primary fault is in the heart or pulmonary circulation.
3. Maintenance of the diastolic blood pressure and perfusion of vital organs (brain, heart, kidneys).

Blood flow rather than blood pressure is of the greatest immediate importance for the function of vital organs. Hypotension due to low peripheral resistance is of little importance if the patient is horizontal or tilted head down, for venous return to the heart, and so the cardiac output, are then maintained, and blood flow to brain, myocardium and kidneys remains adequate until the diastolic blood pressure falls below about 40 mm Hg. But low cardiac output is always serious even though compensatory vasoconstriction maintains the arterial pressure, for blood flow is reduced.

The decision how to treat shock depends on assessment in the individual patient of the pathophysiology, whether cardiac output, and so peripheral blood flow, is inadequate (low pulse volume, cold constricted periphery), or whether cardiac output is normal and peripheral blood flow is adequate (good pulse volume and warm dilated periphery) whether the patient is hypov-

olemic or not, or needs a cardiac inotropic agent, a vasoconstrictor or a vasodilator.

In poisoning by cerebral depressant the principal cause of hypotension is low peripheral resistance due to sympathetic block. The cardiac output can be restored by tilting the patient head down and by increasing the venous filling pressure by cautiously expanding the blood volume with plasma. Use of vascular drugs is unnecessary and may be harmful. They do not reproduce the pattern of the missing sympathetic (neurogenic) vasoconstriction.

In central circulatory failure (e.g. myocardial infarction) the cardiac output and blood pressure are low due to loss of pumping power. Venous return (central venous pressure) is normal or high. Not surprisingly, the use of drugs in low output due to acute myocardial damage is disappointing. Vasoconstriction (by α-adrenoreceptor agonist), by increasing peripheral resistance, may raise the blood pressure by increasing afterload, but this can further reduce cardiac output. Cardiac stimulation with β_1-adrenoreceptor agonist may increase myocardial oxygen consumption and may cause a dysrhythmia. *Dopamine* and *Dobutamine* offer a reasonable choice. However, if there is bradycardia, output can be increased by vagal block with *Atropine*. Digitalis is not useful in cardiogenic shock. Vasodilators may be needed to treat severe heart failure.

In septic shock (caused by endotoxins from gram-negative organisms and other cell products from gram-positive organisms), the cardiac output may be low or high, but vital organs are underperfused. First there is a peripheral vasodilation with eventual fall in arterial pressure. Blood is sequestrated in the periphery.

The immediate aim of treatment is to restore cardiac output by increasing venous return to the heart. This can be done by increasing intravascular volume (plasma transfusion), keeping a close watch on central venous pressure to avoid overload the heart. In addition a vasodilator drug may allow the release of the sequestered blood, and α-adrenoreceptor blockers (e.g. phentolamine) have been used for this. Administration of a vasodilator to a patient with a low blood volume is, of course, disastrous.

Drugs that increase peripheral resistance (sympathomimetics with α-effect and no β_1-effect) are likely only to make matters worse by further reducing blood flow to vital organs. *Noradrenaline* does have some cardiac inotropic (β_1) effect and may be used if substantial vasoconstriction is judged necessary. But *Dopamine* provides a "mix" of actions that is least likely to do harm and even may do good (α + β-effect + renal vasodilation).

Adrenocortical steroids in enormous (and costly) doses (e.g. *Dexamethasone* 2–6 mg/kg i.v. as a single injection, repeated in 2–6 hours and after that as clinical judgment counsels for a maximum of 2–3 days) may benefit by reducing the consequences of damage of cellular membranes by toxins or anoxia and so preventing the release of biologically active damaging substances. The effect probably has nothing to do with the ordinary actions of corticosteroids. Ordinary replacement doses are useless.

Choice of drug in shock. On present knowledge the best drug would be one that stimulates the myocardium as well as selectively modifying peripheral resistance increase flow to vital organs.

Dopamine meets these requirements best. Where high doses are being used and vasoconstriction predominates it may sometimes be useful to add a vasodilator, e.g. an α-adrenoreceptor blocking drug. As well as reducing peripheral blood flow, prolonged vasoconstriction reduces blood volume due to passage of fluid into the extravascular space. Thus cessation of use may be followed by a drop in cardiac output.

Dobutamine is used when cardiac inotropic effect is the primary requirement.

Noradrenaline is used when vasoconstriction is the first priority, plus some slight cardiac inotropic effect.

Restoration of intravascular volume. Ideally the transfusion should be similar to that which has been lost blood for hemorrhage, plasma for burns, saline for gastrointestinal loss. However, in an emergency, speed of replacement is more important than its nature. Note on **dextrans** (polysaccharides): *Dextran 150, 110* or *70* (these are the molecular weights in thousands; albumin MW is 69,000) can be used as plasma substitutes to restore volume; they are retained in the circulation and largely eliminated by catabolism (*Dextran 60* is also called *Polyglucin*). *Dextran 40 (Reopolyglucin)* should not be used for this purpose; its small molecule means that it is rapidly (few hours) excreted by renal glomerular filtration; it is concentrated in the urine and, especially if there is oliguria, this results in a highly viscous urine that blocks renal tubules causing acute renal failure. It is used to improve peripheral blood flow by decreasing plasma sludging of cells, e.g. peripheral vascular disease and postsurgical thromboembolism. Large volume of all dextrans (above 1.5 L) can interfere with platelet function. They also interfere with blood group cross-matching and clinical biochemical measurements. *Gelatin* (MW approx. 30,000) are alternatives to dextrans.

Available forms:

Dobutamine — in ampoules 5% solution 5 ml each

Dopamine — in ampoules 0.5% or 4% solution 5 ml each

Noradrenaline hydrotartrate — in ampoules 0.2% solution 1 ml each

Prednisolone hemisuccinate — in ampoules 0.025 each (to dilute before using in 5 ml of sterile water)

Dextran 60 (Polyglucinum) — in bottles 100; 200 and 400 ml each

EXAMINATION QUESTIONS

1. A 40-year-old man goes to the emergency department because of an intractable cough for the past few days. No one else in his household has any cough, fever, upper respiratory infection, and so on. He was released from the hospital a week ago with the diagnosis of idiopathic dilated cardiomyopathy following an extensive evaluation that revealed normal coronary anatomy and a left ventricular EF of 38%. He was discharged with prescriptions for *Digitalis, Furosemide, Captopril,* and *Carvedilol*. He has been more active and has noted improvement in his dyspnea and fatigue

that prompted his initial presentation 10 days ago. He appreciates all of the care that he received and apologizes for making a fuss over the cough. He states that his wife made him come in because she was concerned that it might be his heart. He states that the cough is different from the congested feeling he had 10 days ago. On examination, he was afebrile; his heart rate was 60 beats per minute; blood pressure, 100/60. Neck veins were flat; carotid upstrokes were normal. Chest and lungs were clear. Heart revealed a regular rate and rhythm without murmurs, gallops, or rubs. Abdomen was soft and not tender. Bowel sounds were present without organomegaly. Extremities revealed no cyanosis, clubbing, or edema. Chest radiograph and electrocardiogram revealed no acute changes and no active disease. The physician was satisfied that he was hemodynamically stable and the cough was not resulting from worsening heart failure. What is a reasonable next step?

(A). Admit to the hospital to exclude (rule out) a myocardial infarction.
(B). Apply a PPD skin test to exclude tuberculosis.
(C). Substitute an angiotensin II receptor blocker for the ACE inhibitor.
(D). Provide reassurance and continue with current medications.
(E). Immediately stop the (β-adrenergic blocker, *Carvedilol*.

2. A 67-year-old woman has had fatigue and shortness of breath over the past few months. She has diabetes and hypertension for which she has been treated for 25 years with appropriate medications. She is status post three myocardial infarctions (MI X3) and has known inoperable coronary artery disease and CHF. She has been very compliant with her complicated medical regimen, which includes *Digitalis*, an ACE inhibitor *(Fosinopril)*, loop diuretic *(Furosemide)*, (3-adrenergic receptor blocker *(Carvedilol)* and aldosterone antagonist *(Spironolactone)*. On examination she was noted to be in acute respiratory distress with a respiratory rate of 24, a heart rate of 60, and blood pressure of 110/60. She was anxious and uncomfortable but polite and cooperative. Neck veins were elevated to 8 cm with the patient partially supine. Lungs revealed rales to the angles of the scapulae bilaterally. Heart revealed a third heart sound and a high pitched holosystolic murmur at the apex consistent with mitral regurgitation. Abdomen was protuberant with a fluid shift consistent with ascites. Extremities revealed 2 to 3 + pretibial pitting edema bilaterally. What can the physician offer this woman?

(A). Intravenous (cAMP elevating) positive inotropic agents.
(B). Vasodilator therapy with *Hydralazine*.
(C). α-Adrenergic blockade with *Prazosin*.
(D). Stop the diuretic, *Furosemide.*
(E). Stop the ACE inhibitor, *Fosinopril.*

3. Digitalis functions to improve congestive heart failure by

(A). Induction of emesis.
(B). Activation of β-adrenergic receptors.
(C). Improving survival in patients of heart failure.
(D). Binding to and inhibiting the Na-K ATPase enzyme in cardiac myocytes.
(E). Deactivation of the angiotensin receptor.

4. The combination of hydralazine and nitrates has been shown to improve survival in patients of heart failure. All of the following statements about this combination are true except:

(A). The combination serves to decrease both afterload and preload.
(B). *Prazosin* is as effective as the combination in treatment of congestive heart failure.
(C). The concept of afterload reduction is principally derived from patients of significant mitral regurgitation.
(D). The VA cooperative study was a landmark trial demonstrating the beneficial effect of hydralazine and nitrate combination in patients of heart failure.

5. β-Blockers have been effective in the treatment of heart failure. They primarily exert their effect by

(A). Binding to the receptor that binds *Norepinephrine*.
(B). Inducing a prominent diuretic effect.
(C). Increasing contractility.
(D). Improving asthma control.
(E). Increasing heart rate to meet the additional demands placed upon the heart in CHF.

6. A 45-year-old woman has had recurrent episodes of atrial fibrillation. She is receiving *Phenytoin* and *Quinidine* to control the atrial fibrillation. She is also taking a low dose of diazepam for insomnia and estrogen replacement therapy. You learn today that she has been receiving *Ciprofloxacin* for a urinary track infection. The reason for her appointment today is that she has been having ringing in the ears, headache, nausea, and blurred vision. She tells you that she is also having trouble hearing the television. You suspect drug toxicity. The most likely agent is

(A). *Ciprofloxacin.*
(B). *Estrogen.*
(C). *Phenytoin.*
(D). *Diazepam.*
(E). *Quinidine.*

7. You are asked to treat a 55-year-old patient for continuing ventricular arrhythmias. The patient is receiving *Timolol* drops for glaucoma, daily insulin injections for diabetes mellitus, and an ACE inhibitor for hypertension. What pharmacological effect of *Procainamide* made you to decide to use *Phenytoin* instead of *Procainamide*?

(A). The local anaesthetic effect of *Procainamide* would potentiate diabetes.
(B). The anticholinergic effect of *Procainamide* would aggravate glaucoma.
(C). The hypertensive effects of *Procainamide* would aggravate the hypertension.
(D). The local anaesthetic effect of procainamide would aggravate the hypertension.
(E). The cholinergic effects of *Procainamide* would aggravate the diabetes.

8. Exercise-induced ventricular tachycardia in persons without overt cardiac disease is an example of delayed after-depolarizations and is characterized by an increase in intracellular ionized calcium. This type of arrhythmia is known to often respond well to which of the following combinations?

(A). β-Blocker and ACE inhibitor.
(B). Calcium channel antagonist and ACE inhibitor.
(C). α-Blocker and ACE inhibitor.
(D). β-Blocker and calcium channel antagonist.
(E). α-Blocker and calcium channel antagonist.

9. Antiarrhythmic drugs are classified in four main groups based on their predominant mechanism of action. Antiarrhythmic agents in which class suppress abnormal automaticity and permit the sinoatrial node to again assume the role of the dominant pacemaker?

(A). Class I.
(B). Class II.
(C). Class III.
(D). Class IV.

10. Although most antiarrhythmic drugs (and indeed most drugs) are chemically synthesized, some compounds that occur endogenously in humans are useful. Indicate which of the following agents occurs endogenously and is a useful antiarrhythmic agent.

(A). *Phenytoin.*
(B). *Digoxin.*
(C). *Adenosine.*
(D). *Quinine.*
(E). *Lidocaine.*

11. A patient comes to your office with effort-induced angina and resting tachycardia. You choose the following drug to treat the patient because it slows heart rate by blocking L-type calcium channels in the SA node:

(A). *Verapamil.*
(B). *Propranolol.*
(C). *Nitroglycerin.*
(D). *Isosorbide dinitrate.*
(E). *Metoprolol.*

12. Which of the following hemodynamic effects of *Nitroglycerin* are primarily responsible for the beneficial results observed in patients with secondary angina?

(A). Reduction in the force of myocardial contraction.
(B). Reduction in systemic vascular resistance (afterload).
(C). Increased heart rate.
(D). Reduction in venous capacitance (preload).
(E). Increased blood flow to the subepicardium.

13. A woman is prescribed a combination of drugs consisting of a nitroglycerin patch and a β-blocker, such as *Propranolol*, to treat her attacks of secondary angina. Which effect of *Propranolol* would counteract an adverse effect of *Nitroglycerin*?

(A). A decrease in preload.
(B). A decrease in afterload.
(C). A decrease in heart rate.
(D). An increase in myocardial contractile force.
(E). A reduction in coronary vasospasm.

14. A patient who has been taking propranolol for a long period for secondary angina comes to your office complaining of increased frequency of chest pains on exertion. You decide to stop the *Propranolol* and give him *Diltiazem* because you suspect he has a mixture of secondary and primary angina. Why would *Diltiazem* be more likely to relieve the angina if your new diagnosis is accurate?

(A). *Diltiazem* produces a decrease in heart rate.
(B). *Diltiazem* dilates coronary blood vessels in spasm.
(C). *Diltiazem* produces AV blockade.
(D). *Diltiazem* reduces myocardial contractility.
(E). *Diltiazem* reduces afterload.

15. *Metoprolol* would produce which beneficial effect in a patient with secondary angina?

(A). A decrease in preload.
(B). An increase in collateral blood flow.
(C). An increase in afterload.
(D). An increase in diastolic filling time.
(E). An increase in blood flow through a concentric stenosis.

16. Which of the following statements most accurately characterize the cellular action of the calcium channel blockers?

(A). Their interaction with membrane phospholipids results in a nonselective decrease of ion transport.
(B). They inhibit the Na^{+}-Ca^{++} exchanger in cardiac and smooth muscle.
(C). They interact at three distinct sites at the L-type voltage-gated calcium channels.
(D). Their interaction with the sodium pump results in an inhibition of calcium transport.

17. Which of the following calcium channel blockers would be most likely to suppress atrial tachyarrhythmias involving the A-V node?

(A). *Nifedipine.*
(B). *Verapamil.*
(C). *Nicardipine.*
(D). *Amlodipine.*

18. All of the following statements are applicable with regard to the systemic effects caused by *Nifedipine* EXCEPT:

(A). It typically causes peripheral vasodilation.
(B). It often elicits reflex tachycardia.
(C). It causes coronary vasodilatation and an increase in coronary blood flow.
(D). Its benefit in the management of angina is related to the reduction in preload that it induces.

19. All of the following statements regarding the pharmacokinetics of calcium channel blockers are correct EXCEPT

(A). They are characterized by significant amount (~ 90%) of protein binding.
(B). They undergo significant first-pass metabolism.
(C). Their half-life is not altered by hepatic cirrhosis.
(D). They can be administered orally.

20. All of the following adverse effects are likely to occur with long-term use of calcium channel blockers EXCEPT
(A). Skeletal muscle weakness.
(B). Flushing.
(C). Dizziness.
(D). Headache.

21. A 55-year-old patient has been referred to you. She complains about a skin rash and a cough. In the course of history taking, she tells you that she takes high blood pressure medication but she doesn't remember the name. You suspect a drug toxicity. Which of the following antihypertensive agents is the patient most likely taking?
(A). *Captopril.*
(B). *Nifedipine.*
(C). *Prazosin.*
(D). *Propanolol.*
(E). *Clonidine.*

22. Which of the following compounds depends least upon the release of EDRF (nitric oxide) from endothelial cells to cause vasodilation?
(A). Bradykinin.
(B). Histamine.
(C). Minoxidil.
(D). Hydralazine.
(E). Acetylcholine.

23. Which of the following antihypertensive drugs is contraindicated in a hypertensive patient with a pheochromocytoma?
(A). *Metyrosine.*
(B). *Labetalol.*
(C). *Prazosin.*
(D). *Phenoxybenzamine.*
(E). *Guanethidine.*

24. Which of the following antihypertensive agents would decrease renin release?
(A). *Prazosin.*
(B). *Clonidine.*
(C). *Captopril.*
(D). *Nitroprusside.*
(E). *Diazoxide.*

25. An accurate statement regarding the actions of both ACE inhibitors and AT1 receptor antagonists is that
(A). Both classes of drugs increase bradykinin.
(B). Angiotensin II can act at the AT2 receptor with both classes of drugs.
(C). Both classes of drugs reduce total peripheral resistance.
(D). Both classes of drugs decrease circulating angiotensin II levels.
(E). Both classes of drugs are first-choice treatments for congestive heart failure.

26. Angiotensin II can
(A). Increase the synthesis and release of aldosterone.
(B). Reduce the activity of the sympathetic nervous system.
(C). Be a potent positive inotropic at the heart.
(D). Relax vascular smooth muscle.
(E). Reduce the growth of cardiovascular cell types.

27. The most potent vasoconstrictor known is
(A). Bradykinin.
(B). Angiotensin II.
(C). Angiotensin IV.
(D). Natriuretic peptide.
(E). Endothelin.

28. The mechanism of action of *Captopril* is
(A). Angiotensin receptor antagonist.
(B). ACE inhibitor.
(C). Aldosterone receptor antagonist.
(D). Bradykinin antagonist.

29. L-Argenine serves as a precursor for
(A). Bradykinin.
(B). L-Citrulline.
(C). Nitrous oxide.
(D). Atrial natriuretic peptide.

30. When a patient is treated with a thiazide diuretic for hypertension, all of the following are likely EXCEPT:
(A). The fall of blood pressure that occurs in the first 2 weeks of therapy results from a decrease of extracellular volume.
(B). The sustained fall in blood pressure that occurs after several weeks of therapy is due to a decrease of intravascular resistance.
(C). After the blood pressure is reduced, hypokalemia remains a complication.
(D). Hyperuricemia may occur.
(E). Hypoglycemia may occur.

31. *Furosemide* increases the excretion of all of the following EXCEPT:
(A). Na^+.
(B). K+.
(C). Ca^{++} and Mg^{++}.
(D). Uric acid.

32. Which of the following drugs is an appropriate initial antihypertensive therapy in an otherwise healthy adult with mild hypertension?
(A). *Bumetanide.*
(B). *Triamterene.*
(C). *Hydrochlorothiazide.*
(D). *Aldactone.*

33. When *Furosemide* is administered to a patient with pulmonary edema, there is often symptomatic relief within 5 minutes of starting treatment. This relief is primarily due to:
(A). A rapid diuretic effect.
(B). An increase in venous capacitance.
(C). A direct effect on myocardial contractility.
(D). Psychological effects.

ANSWERS

1. **(C)**. The most likely diagnosis is ACE inhibitor-induced cough. A reasonable approach is to substitute an ARB (angiotensin II receptor blocker) such as valsartan or losartan for the ACE inhibitor, *Captopril*. Reassure and encourage the patient and spouse that you think the cough will resolve a few days after stopping the ACE inhibitor. There is generally no benefit to trying any other ACE inhibitor, as the side effect is a class effect resulting from enhanced kinin activity from ACE inhibition. Myocardial infarction is extremely unlikely in this patient based on the catheterization data showing normal coronary anatomy. Abrupt withdrawal of a 3-blocker may precipitate tachycardia and hypertension and should be avoided.

2. **(A)**. This woman with CHF has obviously decompensated despite compliance with standard care. She is symptomatic and may benefit from a short course of high-intensity intravenous therapy with a cAMP-elevating agent (e.g. *Dobutamine, Milrinone, Amrinone*). This may be a reversible event or part of the inevitable decline of the disease process. Approximately 45% of CHF patients die suddenly of a presumed electrical event (e.g. ventricular tachycardia, asystole). The others die slowly of progressive deterioration. Many patients at the end stages of CHF prefer to try repeated outpatient in-otropic (cAMP elevating) therapy for symptomatic relief even though it may be associated with a higher incidence of sudden death.

3. **(D)**. Inhibition of Na-K ATPase leads to an elevation of intracellular Na^+. This results in an increase in intracellular Ca^{++} and an enhanced myocardial contractibility. There is no definitive evidence that Digitalis improves survival of patients in heart failure, but it clearly improves the symptoms of this condition.

4. **(B)**. Prazosin has been shown not to be as effective as the combination of hydralazine and nitrates.

5. **(A)**. The salutary effect of β-blockers appears to be due solely to its binding to the β-receptor, which prevents norepinephrine binding and stimulates cAMP formation. The other choices do not occur.

6. **(E)**. *Quinidine.* These are the classic signs of cinchonism and are adverse effects of *Quinidine* and *Quinine*, constituents of the cinchona tree. Some of these effects could be seen as toxic effects of phenytoin. However, auditory acuity is associated with cinchonism and not with phenytoin toxicity. Nausea but not the other effects could be associated with ciprofloxacin. Excessive drowsiness would be expected if diazepam were involved. These effects would not be expected with the estrogen replacement therapy.

7. **(B)**. Anticholinergic agents, such as *Procainamide* and *Disopyramide*, are relatively contraindicated in patients with glaucoma. Procainamide is hypotensive rather than hypertensive. The local anaesthetic activity of *Procainamide* would have no adverse interaction with the diabetes mellitus.

8. **(B)**. Each of these approaches would reduce the tissue calcium concentration and prevent arrhythmias. Agents with α-blocking capacity would have no effect on calcium. Agents with ACE inhibitory activity would likewise have no effect on calcium.

9. **(A)**. Class I agents suppress both normal Purkinje fiber and His bundle automaticity in addition to abnormal automaticity resulting from myocardial damage. Class II drugs block β-adrenoceptors; class III drugs prolong the membrane action potential by delaying repolarization; and class IV drugs block the slow inward movement of calcium ions.

10. **(C)**. *Adenosine* is a product of the metabolism of adenosine triphosphate. *Phenytoin* and *Lidocaine* are totally synthetic, while *Digoxin* occurs naturally in plants and *Quinine* occurs in the cinchona tree.

11. **(A)**. Verapamil is an L-type calcium channel blocker. *Nitroglycerin* and Isosorbide are both organic nitrates and have no direct effect on L-type calcium channels at the SA node, while *Propranolol* and *Metoprolol* are β-adrenoceptor blockers and will slow heart rate by blocking the actions of norepinephrine and epinephrine on β-receptors at the SA node.

12. **(D)**. *Nitroglycerin* can reduce preload, which in turn reduces wall tension and increases subendocardial blood flow. *Nitroglycerin* also reduces afterload, but this is a small effect compared to the reduction in preload. Its effects on heart rate and contractility are minimal, and if anything reflex tachycardia and increase in contractility would be detrimental effects of too much *Nitroglycerin.*

13. **(C)**. *Nitroglycerin* can increase heart rate via an increase in sympathetic tone to the heart due to an excessive decrease in blood pressure; *Propranolol* would block the β-receptors responsible for the tachycardia. *Propranolol* does not decrease preload, and its effect to decrease afterload would exacerbate the decrease in afterload produced by nitroglycerin. *Propranolol* does not increase myocardial contractile force and could actually increase the incidence of vasospasm by unmasking α-adrenoceptors in the coronary blood vessels.

14. **(B)**. Both diltiazem and propranolol would produce the effects listed in **(A)**, **(C)**, **(D)**, and **(E)**. Only *Diltiazem* would dilate vessels in spasm. *Propranolol* would tend to produce vasoconstriction, not vasodilation.

15. **(D)**. An increase in time spent in diastole would increase subendocardial blood flow. *Metoprolol* does not decrease preload or increase afterload; in fact the opposite is likely to occur. *Metoprolol* does not affect collateral blood flow or flow through a concentric stenosis.

16. **(C)**. The available blockers act primarily at voltagegated calcium channels of the L type. The three prototypes, *Verapamil, Nifedipine,* and *Diltiazem*, act at three discrete sites at this channel.

17. **(B)**. The other three drugs (dihydropyridines) are characterized by relatively selective vasodilator effects with little if any cardiac effects at doses employed clinically for hypertension or angina.

18. **(D)**. The vasodilatory effects of *Nifedipine* are largely restricted to arteries (and consequently the afterload). It does not alter venous tone (and thus preload) significantly.

19. **(C)**. Since they are metabolized in the liver, hepatic cirrhosis can be expected to alter their half-life.

20. **(A)**. Skeletal muscles depend on the mobilization of intracellular stores of calcium for their contractile responses rather than transmembrane flux of calcium through the calcium channels. Therefore, skeletal muscle weakness is not likely to occur.

21. **(A)**. Although many drugs can evoke a reaction such as a rash, a rash and a dry cough are well-recognized side effects of angiotensin converting enzyme (ACE) inhibitors, such as *Captopril*. Up to 20% of these patients may develop a cough with ACE inhibitors. The cause is not known for certain, but it may be related to the accumulation in the lungs of bradykinin or other inflammatory mediators. Inhibiting ACE leads to an increase in bradykinin, which is normally broken down by this enzyme. The rash was originally attributed to a sulfhydryl group in *Captopril* but is known to occur with other non-sulfhydryl-containing ACE-inhibitors.

22. **(C)**. The vasodilation caused by bradykinin, histamine, hydralazine, and acetylcholine depends in part upon nitric oxide release from the endothelium. Minoxidil activates K^+ channels, which results in vascular smooth muscle hyperpolarization and thereby relaxation.

23. **(E)**. *Guanethidine* does not normally cause release of catecholamines from the adrenal medulla. However, it may provoke the release of catecholamines from pheochromocytoma. This action plus its ability to antagonize neuronal uptake of catecholamines could trigger a hypertensive crisis. The other drugs are good choices to lower blood pressure in a patient with pheochromocytoma: *Metyrosine*, by decreasing synthesis; *Labetalol*, by blocking both the α- and β-effects of the catecholamines; *Prazosin* and especially *Phenoxybenzamine*, by introducing a fairly long α-blockade.

24. **(B)**. *Clonidine* is an antihypertensive because it decreases sympathetic outflow from the CNS to the periphery and therefore reduces the sympathetically induced stimulation of renin release. The sympathetic effect on renin release is mediated by β-receptors, so prazosin, an α-blocker would not decrease release. *Captopril* is an ACE inhibitor and is likely to enhance renin release, although it would prevent the effects of renin by reducing the formation of angiotensin II. *Nitroprusside* and *Diazoxide* are directly acting vasodilators and will promote renin release reflexively.

25. **(C)**. ACE inhibitors increase circulating bradykinin levels, while AT1 receptor antagonists have no effect on circulating bradykinin. The ability of converting enzyme inhibitors to increase bradykinin levels is thought to contribute to the benefits of this class of drugs in the treatment of hypertension and heart failure. With an ACE inhibitor, the actions of angiotensin II at both the AT1 and the AT2 receptor is decreased; however, with an AT1 receptor antagonist, angiotensin II can act at the AT2 receptor. Only ACE inhibitors decrease circulating angiotensin II levels; the level of angiotensin II may actually increase with an AT1 receptor antagonist because of removal of the endocrine feedback loop. ACE inhibitors have proven benefits in the treatment of congestive heart failure, while AT1 receptor antagonists are reserved for therapy of patients who have significant adverse effects from converting enzyme inhibition.

26. **(A)**. Angiotensin II has diverse physiological effects, including stimulating the synthesis and release of aldosterone from the adrenal cortex. This effect of angiotensin II results in fluid and water retention. The other answers are incorrect in that angiotensin II stimulates the sympathetic nervous system, is a weak inotropic, contracts vascular smooth muscle, and increases the growth status of cardiovascular cell types.

27. **(E)**. Bradykinin and natriuretic peptide are vasodilators. Both angiotensin II and angiotensin IV are vasoconstrictors but not nearly as potent as any endothelin peptide.

28. **(B)**. Compounds that act as ACE inhibitors are particularly useful for the treatment of hypertension and congestive heart failure.

29. **(C)**. Nitric oxide is an important compound that acts as a biological messenger in many physiological responses. L-Citrulline is a product of the oxidation of L-argenine in the formation of nitric oxide. Bradykinin is formed from a precursor kininogen.

30. **(E)**. There is no evidence that the thiazides have any effect on blood sugar. Initial reductions of blood pressure are due to decreased extracellular volume and cardiac output. The beneficial effect of the sustained reduction of blood pressure is due to reduced vascular resistance. Extracellular volume remains modestly reduced and cardiac output returns to pretreatment levels. Hypokalemia does not ameliorate over time and is associated with an increased risk of ventricular fibrillation and malignant arrhythmias. The magnitude of hypokalemia produced by thiazide and thiazide-like diuretics is dose dependent. However, the degree to which individual patients are affected varies, though chronic administration of even small doses causes some K^+ depletion. Hyperuricemia is thought to have two causes. One is competition of the thiazide class of diuretics, which are weak organic acids, with uric acid for secretion by proximal tubules. This leads to diminished uric acid excretion. Serum concentrations of uric acid are further elevated by the reduced extracellular volume. Diuretic-induced hyperuricemia may cause acute gouty attacks.

31. **(D)**. Increased Na^+ excretion is a direct consequence of diuretic treatment. In thick ascending limbs, the site of furosemide action, calcium and magnesium transport is largely determined by the magnitude of sodium absorption. Decreases of Na^+ absorption are accompanied by diminished Ca^{++} and Mg^{++} absorption. K^+ wasting is due to increased K^+ secretion by late distal tubules and collecting ducts. Uric acid excretion decreases as a consequence of competition for the proximal tubule organic acid secretory mechanism.

32. **(C)**. Although still highly controversial, the initial use of a thiazide diuretic for monotherapy has been recommended by the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. *Triamterene* and *Aldactone* are rarely used alone and exhibit no antihypertensive activity. A recent study found that the loop diuretics Bumetanide and Furosemide effectively reduced blood pressure. Serum lipid levels were less affected than with thiazide diuretics or *Chlorthalidone*. However, thiazide diuretics are a more conservative and approved approach for the initial treatment of hypertension that avoid the more dramatic fluid and electrolyte shifts that occur with loop diuretics.

33. **(B)**. Intravenous *Furosemide* causes a significant decrease in pulmonary capillary wedge pressure and right atrial pressure, concomitantly decreasing stroke volume and increasing vascular resistance. This effect in many cases occurs before diuresis begins.

Lecture 27
DRUGS AFFECTING THE ENDOCRINE SYSTEM

Hormones are the biological active substances that are produced by endocrine glands. They possess high activity being present in small doses. Hormones regulate processes of reproduction, growth, development of organism and model it's protective reactions.

By chemical structure hormone drugs are divided into next groups:

— **Substances of protein or peptide structure** (drugs of hypothalamus, pituitary, parathyroid and pancreatic hormones, and calcitonin)

— **Derivatives of aminoacids** (agents of thyroid hormones)

— **Steroid substances** (drugs of adrenal cortex and gonadal hormones)

Hormones interact with specific receptors, located on cellular membranes or intracellularly. Hormones of protein structure predominantly bind with receptors on cellular membranes. Mostly these receptors are cooperated with adenylate cyclase system, which stimulating leads to increasing of cAMP forming, and it's through protein kinases influence on intracellular processes. Adenylatecyclase, cAMP and calcium-ions are mediators among receptors and intercellular processes. Steroid hormones enter cells of target tissues and binds to an intracellular specific receptor. The hormone receptor complex translocates into the nucleus and binds to nucleotides on various genes and regulate their transcription and proteins synthesis.

Hormonal drugs are received from **different sources**. Some agents are extracted from correspondent animal gland (thyreoidine, bovine insulin), the other ones are synthesized (L-thyroxine, triiodothyronine). Also, hormones can be produced by recombinant DNA techniques (human insulin) by inserting the human proinsulin gene into *E coli* or yeast.

Hormonal drugs are used for the *treatment of endocrine diseases* (substitutive, stimulating, and inhibiting therapy) and *nonendocrine diseases* (allergic disorders, cancer). It is necessary to remember, that during prolonged using of high doses of hormonal substances, the atrophy of endocrine glands is possible, in result of which during sudden cessation of the treatment "syndrome of breaking" (withdraw) may develop. It is characterized by symptoms of acute endocrine insufficiency.

HORMONES OF PROTEIN AND AMINOACID STRUCTURE

Hypothalamic and Pituitary Hormones

Neuroendocrine control of metabolism, growth, and certain aspects of reproduction is mediated by a combination of neural and endocrine systems located in the hypothalamus and pituitary gland (hypophysis). The pituitary gland consists of anterior and intermediate lobes (adenohypophysis), and a posterior lobe (neurohypophysis), which release a number of hormones that either control the secretion of other endocrine glands or affect the metabolic actions of target tissues directly. The secretion of anterior lobe hormones is regulated by hormones formed in the hypothalamus. These hormones are small peptides that function as releasing or inhibiting hormones. The posterior lobe hormones are synthesized in the hypothalamus and transported to the pituitary posterior lobe, from which they are released into the circulation.

Six anterior pituitary hormones are recognized: ***Somatotropin*** (growth hormone), ***Thyrotropin*** (TSH), ***Adrenocorticotropin*** (ACTH), ***Follicle-stimulating Hormone*** (FSH), ***Luteinizing Hormone*** (LH), and ***Prolactin*** (PRL).

Somatotropin (growth hormone) is a peptide hormone. It's deficiency leads to short stature. Somatotropin for pharmacologic use is produced with recombinant DNA technology. Somatotropin can be administered intramuscularly. Pharmacologic doses of growth hormone cause longitudinal growth indirectly via another class of peptide hormones, the somatomedins, or insulin-like growth factors that are synthesized predominantly in the liver. Also somatotropin stimulates growing of skeletal muscle and organs. It increases protein synthesis, which results in nitrogen retention. Somatotropin cause the retention of phosphorus, sodium, and potassium through promotion of cellular growth. The metabolic action of growth hormone is an initial insulin-like effect with increased tissue uptake

of both glucose and amino acids and decreased lipolysis. Within a few hours, there is a peripheral insulin antagonistic effect with impaired glucose uptake and increased lipolysis. Somatotropin is indicated for long-term treatment of growth failure in children caused by pituitary growth hormone deficiency (pituitary dwarfism). Adverse effects often include arthralgia and fluid retention.

Somatostatin is found in the hypothalamus. It has been synthesized. Somatostatin has been shown to inhibit the release of growth hormone, glucagon, insulin, and gastrin. Somatostatin has limited therapeutic usefulness because of its short duration of action (half-life 2–3 minutes) and its multiple effects on many secretory systems. *Octreotide* is synthetic analogous of somatostatin. It is more potent than somatostatin in inhibiting growth hormone release. Because of this relatively reduced effect on pancreatic β-cells, octreotide has been particularly useful in treating acromegaly and carcinoid tumors (gastrinoma, glucagonoma) without provoking hyperglycemia. The serum half-life of octreotide is about 80 minutes. Adverse effects of therapy include biliary sludge and steatorrhea.

Thyrotropin is normally secreted as part of a feedback system of thyroid hormone level regulation. It stimulates each step of thyroid hormone synthesis, including iodine uptake. In hyperthyroidism, the serum thyrotropin level is suppressed. Therapeutic thyrotropin is prepared from bovine anterior pituitaries. Thyrotropin is used diagnostically to differentiate between primary and secondary hypothyroidism. Thyroid tenderness and symptoms of hyperthyroidism may occur. *Thyrotropin-releasing hormone* that is found in the hypothalamus stimulates the pituitary to produce thyrotropin. Thyrotropin-releasing hormone stimulation of thyrotropin is blocked by thyroxine and potentiated by lack of thyroxine. *Protirelin* is a synthetic analogous of thyrotropin-releasing hormone. Protirelin is indicated as an adjunct for distinguishes between secondary (pituitary) and tertiary (hypothalamic) hypothyroidism.

Adrenocorticotropin primary endocrine function is to stimulate synthesis and release of cortisol by the adrenal cortex. *Corticotropin* is an ACTH that is obtained from porcine or bovine pituitary glands. Synthetic human ACTH is known as *cosyntropin*. Both animal and synthetic corticotropin are well absorbed by the intramuscular route. Cosyntropin is preferred because it is less antigenic. The biologic half-live of agents is under 20 minutes. The effects of long-acting repository forms of corticotropin persist for up to several days with a zinc hydroxide complex. Corticotropin shares many actions of the corticosteroids due to its ability to increase endogenous corticosteroid synthesis. Corticotropin is indicated as an aid in diagnosing adrenocortical insufficiency and after prolonged using of glucocorticoids for restoring of adrenal's cortex functioning. But it may also cause depression of ACTH production. The toxicity of therapeutic doses of ACTH resembles that of the glucocorticoids with the added mild virilism (hyperandrogenism) in women.

FSH stimulates gametogenesis and follicular development in women and spermatogenesis in men. It is needed for proper ovarian estrogenesis. *Human menopausal gonadotropins* (HMG) are a mixture of partially catabolized human FSH and LH extracted from the urine of postmenopausal women. They are used in states of infertility to stimulate ovarian follicle development in women and spermatogenesis in men and for pituitary or hypothalamic hypogonadism with infertility. In both sexes, they must be used in conjunction with a luteinizing hormone. Overstimulation of the ovary with HMG can lead to ovarian enlargement.

Luteinizing hormone acts on testicular Leydig cells to stimulate testosterone production. In the ovary, LH acts on the mature follicle to induce ovulation, and it stimulates the corpus luteum in the luteal phase of the menstrual cycle to produce progesterone. *Human chorionic gonadotropin* is a hormone produced by the human placenta and excreted into the urine, whence it can be extracted and purified. It is very similar to LH in structure. HCG can be used in combination with human menotropins to induce ovulation in women and for stimulation of testosterone secretion by the testes of men with hypogonadotropic hypogonadism. HMG and HCG are administered intramuscularly. Androgen-dependent neoplasia and precocious puberty are contraindications to HCG use.

Gonadotropin-releasing hormone (GnRH) is produced by hypothalamus and controls the release of gonadotropins (FSH, LH). Pharmaceutical GnRH is synthetic. Analogs (e.g. *Leuprolide, Nafarelin*) are more potent and longer-lasting than native GnRH. GnRH and its analogs are administered parenterally. Pulsatile intravenous administration stimulates FSH and LH secretion. Thus, GnRH is used to treat infertility caused by hypothalamic hypogonadism in both sexes. In contrast, GnRH administered continuously or GnRH analogs administered in depot formulations inhibit gonadotropin release and induce hypogonadism. *Leuprolide*, *Nafarelin* are used to treat prostate cancer, uterine fibroids, and endometriosis. *Danazol* is gonadotropin inhibitor. It suppresses the output of pituitary gonadotropins (FSH, LH). As a result, anovulation and associated amenorrhea occur. Danazol is being used to treat gynecomastia, endometriosis, and menorrhagia.

Prolactin is the principal hormone that stimulates the development of mammary glands and lactation. Its preparation — *Lactin* is obtained from bovine pituitary glands. Lactin is available for use in lactation-deficient women in period following birth. For patients with symptomatic hyperprolactinemia, inhibition of prolactin secretion can be achieved with *Bromocriptine* and other dopamine agonists. Also bromocriptine may be used to treat acromegaly and Parkinson's disease.

The hormones of the intermediate lobe have melanocyte-stimulating properties. Its preparation — *Intermedin* that is obtained from bovine pituitary gland is used for the treatment of degenerative processes in retina and hemeralopia (impairment of vision in reduced illumination) in eye-drops form.

Two posterior pituitary hormones are known: *Vasopressin* and *Oxytocin.* Their structures are very similar. Pharmaceutical vasopressin and oxytocin are synthetics.

In pharmacologic doses, *Oxytocin* can be used to induce uterine contractions and maintain labor. It can also be used for control of postpartum uterine hemor-

rhage. *Oxytocin* elicits milk ejection in lactating women. Oxytocin is administered intravenously or intramuscularly. It's circulating half-life is 5 minutes. Contraindications include fetal distress, prematurity, abnormal fetal presentation, cephalopelvic disproportion, and other predispositions for uterine rupture. *Desaminooxytocin* is a synthetic analog of oxytocin. It acts longer than parental agent and is used subglossal.

Vasopressin (antidiuretic hormone, ADH) possesses antidiuretic and vasopressor properties. A deficiency of this hormone results in diabetes insipidus. Vasopressin interacts with two types of receptors. V_1-receptors are found on vascular smooth muscle cells and mediate vasoconstriction. V_2-receptors are found on renal tubule cells and mediate antidiuresis through increased water permeability and water resorption in the collecting tubules. Vasopressin is administered by intravenous, intramuscular, or intranasal routes. The half-life of circulating ADH is approximately 20 minutes. *Desmopressin* is a long-acting synthetic analog of vasopressin with an antidiuretic-to-pressor ratio 4,000 times that of vasopressin. Vasopressin and desmopressin are the alternative treatments of choice for pituitary diabetes insipidus. Vasopressin (but not desmopressin) can cause vasoconstriction and should be used cautiously in patients with coronary artery disease.

THYROID AND ANTITHYROID DRUGS

The normal thyroid gland secretes the thyroid hormones — **triiodothyronine (T_3)** and **tetraiodothyronine (T_4, thyroxine)**. These hormones contain iodine as an essential part of the molecule. Nearly all of the iodide intake is via the gastrointestinal tract from food, water, or medication. Once taken up by the thyroid gland, iodide undergoes a series of enzymatic reactions that convert it into active thyroid hormone. First of all iodide is oxidized to iodine, in which form it rapidly iodinates tyrosine residues within the thyroglobulin molecule to form *Monoiodotyrosine* (MIT) and *Diiodotyrosine* (DIT). This process is called **iodide organification**. Two molecules of DIT combine within the thyroglobulin molecule to form *L-thyroxine* (T_4). One molecule of MIT and one molecule of DIT combine to form T_3. Thyroid hormones are released from thyroglobulin by proteolysis of thyroglobulin. T_4 and T_3 in plasma are reversibly bound to globulin. *Thyrotropin* (pituitary) stimulates the synthesis and release of T_4 and T_3. These thyroid hormones, in a negative feedback fashion, act in the pituitary to block the action of thyrotropin-releasing hormone and in the hypothalamus to inhibit it's synthesis and secretion.

The free forms of thyroid hormones, T_4 and T_3 enter the cell. Within the cell, T_4 is converted to T_3, which is more potent than T_4, and the T_3 enters the nucleus, where it binds to a specific receptor. Most of the effects of thyroid on metabolic processes appear to be mediated by activation of nuclear receptors that lead to increased formation of RNA and subsequent protein synthesis.

Thyroid hormones have both **catabolic (calorigenic)** and **anabolic effects**. Thyroid hormones increase basal metabolism and consequent increase oxygen consumption of tissues and body temperature. They speed up the catabolism of carbohydrates, fats, and proteins. However, it potentiates the secretion and action of growth hormone. Many of the manifestations of thyroid hyperactivity resemble sympathetic nervous system overactivity (tachycardia, cardiac arrhythmia, tremor, excessive sweating, and nervousness). The secretion and degradation rates of hormones, including catecholamines, cortisol, estrogens, testosterone, and insulin, are affected by thyroid status. Diminished production of thyroid hormone (hypothyroidism, myxedema) leads to clinical manifestations of thyroid insufficiency, including low metabolic rate, tendency to weight gain, somnolence and edema of subcutaneous tissue. Thyroid deprivation in early life results in cretinism (mental retardation, dwarfism).

Thyroid preparations may be synthetic *(L-Thyroxine, Triiodothyronine)* or of animal origin *(Thyreoidine)*.

Synthetic *L-thyroxine* is the preparation of choice for thyroid replacement because of its stability, lack of allergenic foreign protein, and long half-life (7 days), which permits once-daily administration. Oral absorption of current preparations of *L-Thyroxine* is averaging 80%. Although *Triiodothyronine (Liothyronine)* is 3–4 times more active than *L-Thyroxine*, it is not recommended for routine replacement therapy because of its shorter half-life (24 hours), which requires multiple daily doses. Furthermore, because of its greater hormone activity and consequent greater risk of cardiotoxicity, T_3 should be avoided in patients with cardiac disease. T_3 is almost completely absorbed (95%) and minimally interfered with by intraluminal binding proteins. *Thyreoidine (Thyroid)* is the preparation of bovine desiccated thyroid gland. It contains the combination of thyroid hormones. *Thyreoidine* has variable hormone concentrations and high protein antigenicity.

Thyroid hormones are indicated as replacement therapy in the treatment of hypothyroidism. In general, *L-thyroxine* is the preferred thyroid hormone because of the absence of variability. *Triiodothyronine* is recommended because of its short half-life and readily reversible effects for initial therapy in myxedema and myxedema coma. It may also be preferred when gastrointestinal absorption processes are impaired.

Antithyroid drugs are used in case of hyperthyroidism.

The thioamides *Mercazolil (Methimazole)* and *Propylthiouracil* are major drugs for treatment of thyrotoxicosis. *Mercazolil* is about ten times more active than *Propylthiouracil. Mercazolil* and *Propylthiouracil* are rapidly absorbed. They are readily accumulated by the thyroid gland. The major action is to prevent thyroid hormones synthesis by inhibiting iodine organification. A single dose of *Mercazolil* exerts an antithyroid effect for longer than 24 hours; thus it can be used one time a day. Since the synthesis rather than the release of hormones is affected, the onset of these agents is slow, often requiring 3–4 weeks before stores of T_4 are depleted. The adverse effects are rash, leukopenia, and goiter. It can be explained by decreasing of thyroid hormones

level in blood that leads to increasing of thyrotropin synthesis. The last one stimulates thyroid gland hypertrophy and hyperplasia. For preventing of goitrogenic effect iodine drugs are used.

Potassium perchlorate ($KClO_4$) can block uptake of iodide by the gland. Since these effects can be overcome by large doses of iodides, their effectiveness is somewhat unpredictable. Potassium perchlorate is rarely used clinically because it's mild antithyroid activity and adverse effects (leukopenia, anemia).

Iodides — Potassium iodide, Sodium iodide — have multiple effects on the thyroid gland. They decrease the thyrotropin synthesis. Also iodides inhibit hormone's release and decrease the size and vascularity of the hyperplastic gland that make these drugs valuable as preoperative preparation for surgery. Disadvantages of iodide therapy include an increase in intraglandular stores of iodine, which may delay onset of thioamide therapy or prevent use of radioactive iodine therapy for several weeks. Iodide should not be used alone, because the gland will "escape" from the iodide block in 2–8 weeks. Adverse reactions include acneiform rash (similar to that of bromism), swollen salivary glands, conjunctivitis, and rhinorrhea.

Radioactive iodine (I^{131}) is used for treatment of thyrotoxicosis. It is concentrated by the thyroid gland. Its therapeutic effect depends on emission of β-rays with an effective half-life of 5–8 days. Within a few weeks after administration, destruction of the thyroid parenchyma is evidenced by epithelial necrosis and follicular disruption.

The *Calcitonin* secreted by the thyroid gland. The principal effects of *Calcitonin* are to lower serum calcium and phosphate by actions on bone and kidney. *Calcitonin* inhibits osteoclastic bone resorption. In the kidney, *Calcitonin* reduces both calcium and phosphate reabsorption. Also it decreases gastrin secretion and reduces gastric acid output. Human *Calcitonin* monomer has a half-life of about 10 minutes. Salmon *Calcitonin (Miacalcin)* has a longer half-life. Both human calcitonin and *Miacalcin* are synthesized. In addition, *Calcitonin* is present in *Calcitrin* that is obtained from porcine thyroid gland. The ability of calcitonin to block bone resorption and lower serum calcium makes it a useful drug for the treatment of hypercalcemia and osteoporosis.

Parathormone (parathyroid hormone, PTH) is produced by the parathyroid gland. PTH enhances calcium and phosphate absorption in the intestine. In bone, PTH increases the activity and number of osteoclasts, the cells responsible for bone resorption. It increases bone remodeling, a specific sequence of cellular events initiated by osteoclastic bone resorption and followed by osteoblastic bone formation. In the kidney, PTH increases the ability of the nephron to reabsorb calcium but reduces its ability to reabsorb phosphate. Another important action of PTH on the kidney is its stimulation of 1.25-dihydroxyvitamin D production. All these effects result in increasing serum calcium.

Parathyreoidine is produced from bovine parathyroid gland. It is injected intramuscularly or subcutaneous. Its action starts in 4 hours and lasts for 24 hours. *Parathyreoidine* is used for hypothyroid tetany treatment.

PANCREATIC HORMONES AND ANTIDIABETIC DRUGS

Insulin is synthesized in β-cells islets of Langerhans, which interspersed throughout the pancreatic gland. Insulin is a small protein that contains 51 amino acids arranged in two chains linked by disulfide bridges. Within the β-cell, insulin precursor is produced and then proinsulin is hydrolyzed into insulin. Insulin releasing from pancreatic β-cells is stimulated in response to a glucose, mannose, certain amino acids (e.g. leucine, arginine), and vagal activity. Hyperglycemia results in increased intracellular ATP levels, which close the ATP-dependent potassium channels, and results in depolarization of the β-cell and opening of voltage-gated calcium channels. The resulting increased intracellular calcium triggers secretion of the hormone. The liver and kidney remove insulin from the circulation, presumably by hydrolysis of the disulfide connections through the action of insulinase. The half-life of circulating insulin is 3–5 minutes.

Once insulin has entered the circulation, it is bound by specialized receptors that are found on the membranes of most tissues. The full insulin receptor consists of β-subunit, which is entirely extracellular and constitutes the recognition site, and a β-subunit that spans the membrane. The β-subunit contains a tyrosine kinase. When insulin binds to the β-subunit at the outside surface of the cell, tyrosine kinase activity is stimulated in the β-portion that leads to the series of phosphorylation within the cell. Finally, the insulin-receptor complex is internalized where insulin acts.

Insulin promotes uptake of carbohydrates, proteins, and fats in most tissues. Also, insulin stimulates protein and free fatty acid synthesis, and inhibits release of free fatty acid from adipose cells. Insulin increases active glucose transport through liver, muscle and adipose cellular membranes, and promotes conversion of intracellular glucose and free fatty acid to the appropriate storage forms (glycogen and triglyceride, respectively). In the liver and muscles it inhibits glycogenolysis and gluconeogenesis. In addition, insulin decreases protein catabolism and ketogenesis.

Administered insulin substitutes for the lack of endogenous insulin secretion and partially corrects the disordered metabolism and inappropriate hyperglycemia of diabetes mellitus. They're two types of diabetes mellitus. Type I diabetes (IDDM, insulin-dependent diabetes mellitus) is a catabolic disorder in which circulating insulin is virtually absent. Exogenous insulin is therefore required. Type II diabetes (NIDDM, non-insulin-dependent diabetes mellitus) represents a group comprising milder forms of diabetes that occur predominantly in obese. Circulating endogenous insulin is relatively inadequate because of tissue insensitivity. When dietary treatment fails to correct hyperglycemia, sulfonylurea drugs are usually prescribed. Insulin therapy may be required to achieve satisfactory glycemic control.

Three principal types of insulins are available (1) short-acting — *Insulin*, (2) intermediate-acting — *Insulin-Semilente, Insulin-Lente*, (3) long-acting — *Insulin-Ultralente* (Table 10).

Table 10. **Pharmacokinetic of insulins**

Insulin type	Onset of action, h	Time to peak	Duration of action
Regular insulin	0.5–1	2–4	5–7
Insulin-Semilente	1–3	2–8	12–16
Insulin-Lente	1–3	8–12	18–28
Insulin-Ultralente	4–6	18–24	36

Short-acting insulin is dispensed as solutions and contains small amounts of zinc to improve their stability and shelf-life. Other insulins have been modified to provide prolonged action and are dispensed as suspensions with varying concentrations of zinc in acetate buffer (*Ultralente* and *Lente* insulins). Conventional subcutaneous insulin therapy presently consists of split-dose injections of mixtures of short-acting and intermediate-acting insulins or multiple doses of short-acting insulin preprandial in association with any of insulin suspensions (*Lente*, or *Ultralente*) whose prolonged duration of action provides overnight basal insulin levels. Clinical trials have demonstrated that optimal time of pre-prandial subcutaneous injection of regular human insulin is 30 minutes before the meal. Short-acting soluble insulin is the only type that should be administered intravenously and it is particularly useful when the insulin requirement is changing rapidly, such as diabetic ketoacidosis or after surgery.

According to the sources insulins are divided into **beef, pork,** and **human**. The beef hormone is slightly more antigenic than pork insulin. Human insulin, which is less expensive and immunogenic than pork insulin, has generally supplanted it. Currently, all insulins in Ukraine are available in a concentration of 40 units/ml.

Hypoglycemic reactions are the most common complication of insulin therapy. They may result from a delay in taking a meal or an overdosing of insulin. The symptoms of hypoglycemia are tachycardia, palpitations, sweating, tremulousness, nausea, and hunger. They may progress to convulsions and coma if untreated. In a case of mild hypoglycemia orange juice, glucose, or any sugar-containing beverage or food may be given. In case of unconsciousness the treatment of choice is to give 20 ml of 40% glucose solution by intravenous infusion or solutions of adrenaline or glucagon injected either subcutaneously or intramuscularly.

Because sensitivity is often to non-insulin protein contaminants, the new highly purified insulins have markedly reduced the incidence of insulin allergy, especially local reactions. Some diabetic patients have a high titer of circulating anti-insulin antibodies. This results in extremely high insulin requirements — often more than 200 units daily. Atrophy or hypertrophy of subcutaneous fatty tissue may occur at the site of injection.

Oral hypoglycemic drugs. The major oral medications currently available for treating hyperglycemia in non-insulin-dependent diabetics are the class of compounds known as sulfonylureas.

Sulfonylureas release insulin from β-cells and potentiate the action of insulin on its target tissues. Sulfonylureas inhibit the efflux of potassium ion through the channel and results in depolarization. Depolarization, in turn, opens a voltage-gated calcium channel and results in calcium influx and the release of preformed insulin. Sulfonylurea drugs might restore peripheral tissue sensitivity to insulin.

Sulfonylureas are absorbed from gastrointestinal tract readily and completely. Mostly they bind with blood proteins (70–99%). Sulfonylureas are metabolized in liver and excreted mainly via kidneys. The most serious adverse effect is hypoglycemia. Also disulfiram-like reaction (flushing of the face, neck, and arms) may occur with any of the sulfonylureas when alcohol is ingested concurrently.

There are two generations of sulfonylureas: **first generation** are *Butamide*, *Chlorpropamide*; **second generation** are *Glibenclamide*, *Glipizide*.

Butamide (Tolbutamide) is well absorbed but rapidly oxidized in the liver. Its duration of effect is relatively short (6–10 hours). It is administered before each meal and at bedtime. *Chlorpropamide* has a long duration of effect (24–48 hours) and is slowly metabolized in the liver. The maintenance dose is given in the morning. Potential for serious adverse effects is high because of *Chlorpropamide* prolonged action. Also *Chlorpropamide* can cause antidiuretic effect. Diabetes patients who have not responded to *Tolbutamide* or *Chlorpropamide* may respond to the more potent second-generation sulfonylureas.

Duration of action of *Glipizide* and *Glibenclamide (Glibutide)* is approximately 24 hours. These agents should be ingested 30 minutes before breakfast, since rapid absorption is delayed when the drug is taken with food. The dose is given once a day. Serious adverse effect occurs more often with glibenclamide than with *Chlorpropamide* and *Glipizide*, because of prolonged action of *Glibenclamide*. *Gliclazide* has the same serum half-life and duration of action as *Glibenclamide*. In addition, it reduces platelet adhesiveness and aggregation and has fibrinolytic activity — hence *Gliclazide* has prevent possible disorders of microcirculation during diabetes mellitus.

Second group of oral hypoglycemic compounds consists of the **Biguanides**. These agents reduce blood glucose even in the absence of pancreatic β-cell function. Currently proposed mechanisms of action include direct stimulation of glycolysis in tissues, with increased glucose removal from blood, and slowing of glucose absorption from the gastrointestinal tract. Biguanides cause the accumulation of lactic acid in muscles (probably due to stimulation of anaerobic glycolysis). Bigua-

nides have been most often prescribed for patients with refractory obesity. *Buformin (Glibutide)* and *Metformin* belong to this group. They are well absorbed from the gastrointestinal tract. The onset of maximal hypoglycemic effect is 5 hours and duration of effect is 14 hours. A common schedule would be to begin with a single daily tablet given for several days. If this is well tolerated, to add a second tablet if hyperglycemia persists. The toxic effects of biguanides are gastrointestinal upset (nausea, vomiting, and diarrhea) and lactic acidosis. Biguanides does not provoke hypoglycemia.

Glucagon is synthesized in α-cells of Langerhans islets. The pharmacologic result of glucagon infusion is to raise blood glucose at the expense of stored hepatic glycogen. *Glucagon* has a potent inotropic and chronotropic effect on the heart. Thus, it produces an effect very similar to that of β-adrenoreceptor agonists without requiring functioning β-receptors. The major use of *Glucagon* is for emergency treatment of severe hypoglycemic reactions in insulin-dependent patients when unconsciousness precludes oral feedings and use of intravenous glucose is not possible.

Available forms:

Somatotropin — in bottles 5 ml (2 or 4 unites)

Octreotide — in ampoules 0.00005; 0.0001 or 0.0005 each

Gonadotropin chorionic — in bottles 500; 1000; 1,500 or 2,000 unites each (to dilute in 1 ml solution, for i.m. injection)

Danazol — capsules 0.1 or 0.2 each

Oxytocin — in ampoules 1 ml (5 unites) each

Pituitrinum — in ampoules 1 ml (5 unites) each

Triiodothyronine hydrochloride — tablets 0.00002 or 0.000005 each

L-Thyroxine — tablets 0.05 or 0,1 each

Mercazolilum — tablets 0.005 each

Calcitonin — in ampoules 1 ml (50 or 100 unites) each

Parathyroidinum — in ampoules 1 ml (20 unites) each

Insulin — in bottles 5 or 10 ml (1 ml contains 40 unites) each

Tolbutamide (Butamidum) — tablets 0.25 or 0.5 each

Glibenclamide — tablets 0.005 each

Buformin — tablets 0.5 each

HORMONES OF STEROID STRUCTURE

Adrenocorticosteroids

The adrenal cortex releases a large number of steroids that may be classified as those having important effects on intermediary metabolism **(glucocorticoids)**, those having principally salt-retaining activity **(mineralocorticoids)**, and those having **androgenic** or **estrogenic activity**.

The **glucocorticoids (corticosteroids)** in humans are *cortisol* (major) and *cortisone*. They are synthesized from cholesterol. The rate of their secretion changes in a circadian rhythm governed by irregular pulses of adrenocorticotropin (ACTH) that peak in the early morning hours and after meals. In plasma, they are bound to plasma proteins. Free hormone diffuses across cell membranes and complex with specific cytoplasmic receptors. These complexes then enter the cell nucleus, bind to DNA, and stimulate transcription of messenger RNA (mRNA) and subsequent protein synthesis. Glucocorticoids in rapid feedback way suppress the synthesis of pituitary ACTH. Most of the glucocorticoids are inactivated in the liver by reduction and conjugation with glucuronic acid or sulfate, and are excreted into the urine.

Effects of glucocorticoids. The glucocorticoids have important dose-related effects on carbohydrate, protein, and fat metabolism. In the liver, glucocorticoids increase glycogen deposition by stimulating glycogen synthase activity and increasing glucose production from protein (gluconeogenesis). Glucocorticoids inhibit the peripheral glucose uptake and lead to hyperglycemia. Glucocorticoids have catabolic effects in lymphoid and connective tissue, muscle, fat, and skin. In children, the catabolic effects of excessive amounts of glucocorticoid reduce growth. Glucocorticoids increase lipolysis and mobilize fatty acids from adipose tissues, leading to increased plasma fatty acid concentrations. Glucocorticoids increase bone resorption and calcium excretion, and decrease gastrointestinal absorption of calcium. These actions may lead to inhibition of bone growth in children and adolescents and the development of osteoporosis at any age.

Glucocorticoids have **immunodepressive** and **anti-inflammation activities**. Glucocorticoids decrease or prevent tissue responses to inflammatory processes, thereby reducing development of symptoms of inflammation without affecting the underlying cause. Glucocorticoids inhibit accumulation of inflammatory cells, including macrophages and leukocytes, at sites of inflammation. They also inhibit phagocytosis, lysosomal enzyme release, and release of several chemical mediators of inflammation. They reduce the permeability of inflamed capillaries and reduce leukocyte adherence to the capillary endothelium, leading to inhibition of both leukocyte migration and edema formation; and diminish the activity of the phospholipase A_2 with subsequent inhibition of the inflammation mediators synthesis (prostaglandins, thromboxanes, and leukotrienes) from arachidonic acid.

Mechanisms of immunosuppressant action may involve prevention or suppression of cell-mediated (delayed hypersensitivity) immune reactions as well as more specific actions affecting the immune response. Glucocorticoids reduce the concentration of thymus-dependent lymphocytes (T-lymphocytes), monocytes, and eosinophils. They also decrease binding of immunoglobulin to cell surface receptors and inhibit the synthesis, and release of interleukins, thereby decreasing T-lymphocyte blastogenesis and reducing expansion of the primary immune response. Glucocorticoids may also decrease concentrations of complement components and immunoglobulins.

The structural and functional changes in the lungs near term, including the production of pulmonary surfactant required for air breathing, are stimulated by glucocorticoids. Treatment of the mother with large doses of glucocorticoid reduces the incidence of respiratory distress syndrome in infants delivered prematurely.

Steroids having glucocorticoid activity have become important agents for use in the treatment of many inflammatory and allergic disorders (Table 11).

Table 11. **Main glucocorticoids and their biological activity**

Glucocorticoids	Relative potency		Biological (tissue) half-life, h
	Glucocorticoid activity*	Mineralocorticoid activity**	
Short-acting			
Cortisone	0.8	++	8-12
Hydrocortisone	1	++	8-12
Intermediate-acting			
Methylprednisolone	5	0	18-36
Prednisolone	4	+	18-36
Triamcinolone	5	0	18-36
Long-acting			
Dexamethasone	20-30	0	36-54
Betamethasone	20-30	0	36-54

Note: *anti-inflammatory, immunosuppressant, metabolic effects; **sodium and water retention, potassium depletion.

Indications. Glucocorticoids are indicated for their anti-inflammatory and immunosuppressant effects in the treatment of allergic disorders (allergic rhinitis, angioedema, anaphylactic reactions, bronchial asthma, transfusion reactions), collagen disorders (dermatomyositis, vasculitis, lupus erythematosus, rheumatic fever), dermatitis, autoimmune anemia, chronic hepatitis, leukemia, ophthalmic disorders (iridocyclitis, keratitis). For most indications, glucocorticoid administration provides symptomatic relief but has no effect on the underlying disease processes. Use of these medications does not eliminate the need for other therapies that may be required.

Glucocorticoids are indicated (in physiologic doses) as replacement therapy in the treatment of adrenal insufficiency states. *Cortisone, Hydrocortisone (Cortisol)*, and *Fludrocortisone* are indicated for this purpose because of their significant mineralocorticoid activity (see table 11). *Cortisone* is transformed in the organism to *Hydrocortisone*. It is used orally (tablets) or intramuscularly (suspension). *Hydrocortisone* can be injected intraarticulate (suspension) for the treatment of arthritis or can be applied topically (ointment) for dermatitis treatment. *Fludrocortisone*, a synthetic corticosteroid, is the most commonly prescribed salt-retaining hormone.

Natural glucocorticoids are used mostly in those cases, when their mineralocorticoid activity is desirable (adrenal insufficiency). However, agents having minimal mineralocorticoid activity are preferred in all other cases. This group includes *Prednisolone, Methylprednisolone*, fluorinated glucocorticoids *(Triamcinolone, Dexamethasone, Betamethasone)*, and bis-fluorinated glucocorticoids *(Flumethasone, Fluocinolone)*. It is considered, that presence of the *Fluor* atom in glucocorticoids molecule has decrease its mineralocorticoid activity and its absorption from the skin. *Prednisolone* is used orally, topically. It must be injected intramuscularly or intravenously for emerge states (anaphylactic reaction, bronchial asthma attack, shock states of different etiology). In general, *Triamcinolone* and *Dexamethasone* are produced as tablets. Thanks to their bad absorption from the skin (that diminish their systemic effects) *Flumethasone, Fluocinolone* are prescribed in ointment form for the treatment of dermatitis of different etiology.

Adverse effects. When the glucocorticoids are used less than 1 week, it is unusual to see serious adverse effects. The major undesirable effects of the glucocorticoids are the result of their hormonal actions and lead to the clinical picture of iatrogenic Cushing's syndrome. The appearance of the face is altered by rounding. Fat tends to be redistributed from the extremities to the trunk and face. Over a period of time there can appear such adverse effects as weight gain, thinning of the skin (with striae), hyperglycemia, osteoporosis, and hypertension. Wound healing is also impaired. Other serious complications include the development of peptic ulcers, bacterial and mycotic infections. Glucocorticoids (especially, cortisone and hydrocortisone) cause some sodium and fluid retention and loss of potassium.

Nowadays antagonists of the synthesis or action of the glucocorticoids are well-known. They can be used in the treatment of Cushing's syndrome. *Mifepristone* is a glucocorticoid antagonist that binds to glucocorticoid as well as to progesterone receptors. *Metyrapone* is an inhibitor of glucocorticoids and mineralocorticoids synthesis.

The most important mineralocorticoid in humans is *Aldosterone*. However, small amounts of *Desoxycorticosterone* (DOC) are also formed and released. Its actions, effects, and metabolism are similar to aldosterone. ACTH and angiotensin produce a stimulation of aldosterone release. Also its secretion is enhanced by dietary sodium restriction. Mineralocorticoids act by binding to the receptor in the cytoplasm of cells of the kidneys collecting tubules. Aldosterone promotes the reabsorption of sodium from urine by the distal renal tubules, loosely coupled to the secretion of potassium ion. Excessive levels of aldosterone lead to hypernatremia, hypokalemia, increased plasma volume, and hypertension. *Desoxycorticosterone acetate* (DOCSA) is used in practice. It is prescribed in case of chronic adrenal

glands insufficiency, myasthenia and adynamia. Adverse effects of DOCSA are edema, hypertension.

Spironolactone is steroid that competes with aldosterone for binding sites and decrease its effect peripherally. It is used as diuretic drug (the lecture "Diuretic drugs") and for the treatment of hyperaldosteronism.

THE GONADAL HORMONES. ESTROGENS AND PROGESTINS

The ovary has important gametogenic and hormonal functions. First of all hypothalamic produce *Gonadotropin-releasing hormone* (GnRH) which stimulates the release of *Follicle-stimulating hormone* (FSH) and *Luteinizing hormone* (LH) (see "Hypothalamic and pituitary hormones"). At the beginning of each cycle, a variable number of follicles, each containing an ovum, begin to enlarge in response to FSH. After 5 or 6 days, one of the follicles begins to develop more rapidly. The granulosa cells of this follicle synthesize estrogens. When ovum is matured, follicle ruptures and ovulation is appearing. Following the above events, the cavity of the ruptured follicle fills is transformed to the corpus luteum. The cells of this structure produce estrogens and progesterone for the remainder of the cycle, or longer if pregnancy occurs. If pregnancy does not occur, the corpus luteum begins to degenerate and ceases hormone production. The endometrium, which proliferated during the follicular phase and developed its glandular structure during the luteal phase, is shed in the process of menstruation.

The major **estrogens** produced by women are *Estradiol*, *Estrone*, and *Estriol*. Estradiol appears to be the major secretory product of the ovary. Most estrone and estriol are formed in the liver from estradiol. As noted above, estrogens are produced in the ovarian follicle and in corpus luteum. During pregnancy, the fetoplacental unit synthesizes a large amount of estrogen. When released into the circulation, estradiol binds strongly to a sex hormone-binding globulin. Estrogens are metabolized in the liver and their conjugated metabolites excreted in the bile. However, the conjugates may be hydrolyzed in the intestine to active, reabsorbable compounds.

Physiologic effects. Free plasma estrogens enter the cell and bind to their receptor. The receptor-hormone complex binds to nucleotides on various genes and regulates their transcription and proteins synthesis.

Estrogens stimulate the development of the vagina, uterus, and uterine tubes as well as the growth of the axillary and pubic hair. They stimulate stromal development and ductal growth in the breast and are responsible for the accelerated growth phase and the closing of the epiphyses of the long bones that occur at puberty. Estrogen also plays an important role in the development of the endometrial lining (proliferation). Estrogens decrease the rate of resorption of bone. Estrogens increase high-density lipoproteins level, slightly reduce low-density lipoproteins and cholesterol levels. Estrogens enhance the coagulability of blood. They are responsible for estrous behavior in animals and influence libido in humans. They facilitate the loss of intravascular fluid into the extracellular space, producing edema.

Many agents of steroid estrogens are used in medicine. They are *Estrone, Estradiol dipropionate, and ethinyl Estradiol*. Estrone and estradiol are produced as oil solutions and are injected intramuscularly. Estrone acts during 24 hours, however estradiol — 2–4 days. Ethinyl estradiol is a semisynthetic estrogen. It's 50 times as much potent than estrone. Furthermore, ethinyl estradiol is available for ingestion. In addition to the steroid estrogens, a variety of nonsteroidal compounds with estrogenic activity have been synthesized and used clinically. These include *Hexestrol (Synoestrolum), Diethylstilbestrol. Hexestrol* is the synthetic analogue of estradiol. It is taken orally and injected intramuscularly.

Indications. Estrogens are indicated for replacement therapy in estrogen-deficient patients (upset of menstrual cycle — dysmenorrhea, amenorrhea, castration, or menopause). They are indicated for complex treatment of breast carcinoma in postmenopausal women and prostatic carcinoma in men. Estrogens alone or combined with progestins can be used for contraception. They have been used extensively to replace estrogen in the treatment of vasomotor symptoms, and osteoporosis associated with menopause. For this purpose patients can use estrogens or their combination with gestagens: *Proginova* (contains *estradiol valerate*; 21 dragee for month), *Clinorm* (two-phase agent; 9 dragee that contain *estradiol valerate*; 12 dragee — *estradiol valerate* + *levonorgestrel* (gestagen)).

Adverse effects. Estrogen therapy may cause menorrhagia, endometrial hyperplasia. They can be prevented by administration of a progestin agent with estrogen in each cycle. Nausea and breast tenderness are common and can be minimized by using the smallest effective dose of estrogen. Estrogen can lead to cholestasis, thrombophlebitis, peripheral edema, and hypertension. Diethylstilbestrol should be avoided during pregnancy.

Nowadays **antiestrogen** agents are well known. *Tamoxifen* is a competitive inhibitor of estrogen receptors and is extensively used in the palliative treatment of breast cancer. It is a nonsteroidal agent that is given orally.

Progesterone is the most important progestin in humans. It is synthesized in the ovary (corpus luteum), testis, adrenal, and in placenta during pregnancy. The level of progesterone in the female is higher the luteal phase than during the follicular phase of the cycle. Progestins enter the cell and bind to progesterone receptors. The ligand-receptor complex binds to a response element to activate gene transcription, resulting in an increase in protein synthesis. Progesterone causes the maturation and secretory changes in the endometrium that are seen following ovulation. Also it leads to relaxation of uterine smooth muscle and stimulation of mammary alveolar tissue growth. Progesterone is responsible for pregnancy preservation. It also has depressant and hypnotic effects on the brain.

Progesterone is rapidly absorbed following administration by any route. It is almost completely metabolized in one passage through the liver, and for that reason it is quite ineffective when administered orally. In the liver, progesterone is metabolized and conjugated with glucuronic acid. It is excreted into the urine. A variety of progestin compounds have been synthe-

sized. In general, such compounds as *Hydroxyprogesterone (Oxyprogesterone)* and *Medroxyprogesterone* are the most closely related, pharmacologically as well as chemically, to progesterone. *Hydroxyprogesterone* and *Medroxyprogesterone* have a long duration of action. They are used in oil solution intramuscularly once in 7-14 days. *Pregnine* is 5 times weaker than progesterone. However, *Pregnine* is available for oral and subglossal (sublingual) route of using.

A group of testosterone-derivatives with progestin activity — *Levonorgestrel, Norethisterone (Norethindrone)* — has been introduced, principally as components of oral contraceptives. They do not support pregnancy in test animals, are more effective gonadotropin inhibitors, and may have minimal androgenic or anabolic activity.

Progestins have been used in the first trimester of pregnancy to prevent habitual abortion or to treat threatened abortion, however their usefulness is doubtful. Progestins are used for the treatment of amenorrhea in the presence of estrogen. They are useful in producing long-term ovarian suppression for the treatment of dysmenorrhea, endometriosis, and for contraception. Progestins may cause changes in menstrual flow, edema, and hypertension.

It is already synthesized antiprogestin agent — *Mifepristone.* It binds strongly to the progesterone receptor and inhibits the activity of progesterone. *Mifepristone* is used for termination of early pregnancies.

CONTRACEPTIVES

A large number of oral contraceptives containing estrogens or progestins (or both) are now available for clinical use. Two types of preparations are used for oral contraception: (1) **combinations of estrogens and progestins** and (2) **continuous progestin therapy**. The estrogenic component of commercially oral contraceptive combinations is *Ethinyl estradiol.* The progestin component is *Levonorgestrel, Norethisterone (Norethindrone),* or *Norgestrel*. The combinations of estrogens and progestins exert their contraceptive effect largely through selective inhibition of pituitary function that results in inhibition of ovulation. The combination agents also produce a change in the cervical mucus, endometrium, and uterine tubes, which decrease the likelihood of conception and implantation.

Estrogen-progestin oral contraceptives are usually classified according to their formulation. **Monophasic preparations** contain fixed-combination of estrogen and progestin *(Nonovlon, Rigevidon, and Microgynon)*. **Biphasic** *(Anteovin)* and **triphasic** *(Trisiston, Tri-regol)* **preparations** consist of 2 or 3 sequentially administered fixed combinations of estrogen and progestin. Bi- and triphasic contraceptives are more physiological, because differences of estrogen-progestin correlation imitate normal fluctuation of female sex hormones.

Most combinations are available as 21-day dosage preparations. In establishing an oral contraceptive dosage cycle, the menstrual cycle is usually considered to be 28 days. The first day of bleeding is counted as the first day of the cycle. Administration of oral contraceptives usually begins on the fifth day of the menstrual cycle and is usually administered once daily for 21 consecutive days.

The pregnancy rate with combination agents is estimated to be about 0.5–1 per 100 woman years at risk. About 97% of patients will ovulate by the third post-treatment cycle. Progestins and estrogens are also useful in the treatment of endometriosis. It is now clear that these compounds reduce the risk of endometrial and ovarian cancer.

Adverse effects. Minor adverse effects are frequent, but most are mild and many are transient. Mild adverse effects are headache, nausea, mastalgia, breakthrough bleeding, weight gain, and edema. Severe adverse effects are rare and include increasing coagulability of blood (risk of thromboembolic disease), hypertension, reduction of glucose tolerance, cholestatic jaundice, depression. These drugs should be avoided in patients with estrogen-dependent neoplasm. These agents are contraindicated in adolescents in whom epiphysial closure has not yet been completed.

Small doses of progestins can be used for contraception also. **Progestin-only contraceptives** alter cervical mucus and endometrium so that sperm migration into the uterus and probable implantation is inhibited. In addition, continuous administration of the drugs decreases the ovum transport by altering motility in fallopian tubes. Although progestin-only oral contraceptives are less effective than estrogen-progestin combinations, they are particularly suited for use in patients for whom estrogen administration is undesirable. Orally can be taken *Continuin, Microlut*. Unlike estrogen-progestin combinations, progestin-only oral contraceptives must be taken daily, without interruption, to be effective. The main adverse effect is incidences of abnormal bleeding.

Pregnancy can be prevented following coitus by the administration of large doses of estrogens or progestins **(postcoital contraceptives)**. For example *Postinor* (contain *L-norgestrel*). When treatment is begun within 72 hours, it is effective 99% of the time. Postcoital contraceptives can be used no more than 4 times a month.

ANDROGENS, ANABOLIC STEROIDS AND ANTIANDROGENS

The testis, like the ovary, has both gametogenic and endocrine functions. In humans, the most important androgen secreted by the testis (in the interstitial or Leydig cells) is *Testosterone*. Endogenous plasma testosterone is maintained and regulated by gonadotropins within a normal range by a negative feedback system involving the hypothalamus and pituitary. In blood circulating testosterone is bound to sex hormone-binding globulin. In many target tissues (for example in prostate), *Testosterone* is converted to dihydrotestosterone. Androgens are highly lipid-soluble and enter cells of target tissues by passive diffusion. *Testosterone* or dihydrotestosterone binds to an intracellular androgen receptor. The hormone-receptor complex translocates into the nucleus and initiates or suppresses transcription, and protein synthesis. In the liver testosterone is transformed into non-active substances such as androsterone that is then conjugated and excreted into the urine.

Physiologic effects. Androgens stimulate spermatogenesis, development of male sexual organs (seminal vesicles, penis, and scrotum) and secondary sexual characteristics (male hair, enlargement of the larynx, and thickening of vocal cords). Androgens increase linear bone growth and bone density, and help fuse the epiphysial growth centers. They cause nitrogen retention that indicates an increasing of protein synthesis within the body (anabolic effect). That leads to growing of skeletal muscles and parenchymal organs. They also stimulate erythrocyte production.

The ethers of testosterone have been used extensively in clinics (*Testosterone propionate* and *Testosterone enanthate*). They are injected intramuscularly one time in 2 days or in 3–4 weeks correspondently. These derivatives are hydrolyzed to release free *Testosterone* at the site of injection. *Methyltestosterone* is *Testosterone* derivative that is active when given by mouth (subglossal).

Indications. Androgens are used to replace or augment endogenous androgen secretion in hypogonadal men. Androgens have also been used in the treatment of breast cancer as a supplement to chemotherapy in women until 60 years. Androgens are sometimes given for the therapy of dysmenorrhea, postmenopausal syndrome. In women, the administration of testosterone is associated with masculinize actions (virilism): hirsutism, acne, depression of menses, and deepening of the voice. Sodium retention and edema may appear also.

Anabolic steroids are synthetic derivatives of testosterone. Chemical changes result in reduction of their androgenic properties comparatively with testosterone and retention of their anabolic features. Many anabolic steroids are used in clinics: *Methandrostenolone, Phenoboline (Nandrolone phenylpropionate)*, *Retabolil (Nandrolone decanoate)*. *Phenoboline* and *Retabolil* are used intramuscularly. Duration of action is 2–3 weeks. *Methandrostenolone* is used orally daily. Anabolic steroids have been used for reversing of protein loss after trauma, surgery, or prolonged immobilization and in patients with debilitating diseases. Anabolic agents are indicated for the treatment of osteoporosis. These agents have been used to stimulate growth in boys with delayed puberty.

Since complete dissociation of anabolic and androgenic effects is not possible, anabolic steroids produce slight masculinize actions. In addition, anabolic steroids can cause nausea, edema, hypercalcemia, and upset of liver function.

The potential usefulness of **antiandrogens** for the treatment of patients producing excessive amounts of testosterone has led to the search for effective drugs that can be used for this purpose. Since dihydrotestosterone appears to be the essential androgen in the prostate, androgen effects in this tissues can be reduced by an inhibitor of 5α-reductase. *Finasteride*, an inhibitor of this enzyme, produces a reduction in dihydrotestosterone levels. It has been reported to be moderately effective in reducing prostate size in men with benign prostatic hyperplasia. *Cyproterone acetate* is effective antiandrogen that inhibits the action of androgens at the target organ. These compounds have been used in women for the treatment of hirsutism and in men to decrease excessive sexual drive. *Flutamide*, is a competitive antagonist at the androgen receptor that has been used in the treatment of prostatic carcinoma. *Spironolactone*, a competitive inhibitor of aldosterone (see "Diuretic drugs") also competes for the androgen receptors in target tissues. It also reduces the synthesis of testosterone. It is used for the treatment of hirsutism in women.

Available forms:

Cortisone — tablets 0.025 or 0.05; in bottles 10 ml (1 ml contains 0.025 g *Cortisone acetate*)

Prednisolone — tablets 0.001 or 0.005 each

Prednisolone hemisuccinate — in ampoules 0.025 each (to dilute in 5 ml solution, for i.v. or i.m. injections)

Dexamethasone — tablets 0.0005 each

Fluocinolone acetonide (Sinaflan) — 0.025% ointment 10.0 or 15.0

Desoxycorticosterone acetate — in ampoules 0,5% oil solution 1 ml each; tablets 0.005 each (subglossal usage)

Oestradiol dipropionate — in ampoules 0.1% oil solution 1 ml each

Ethinylestradiol — tablets 0.01 or 0.05 each

Synoestrolum — in ampoules 0.1% or 2% oil solution 1 ml each; tablets 0.001 each

Tamoxifen — tablets 0.01; 0.02 or 0.04 each

Oxyprogesterone caproate — in ampoules 12.5% or 25% oil solution 1 ml

Non-Ovlon (Ethinylestradiol + Norethisterone) — patented tablets (21 tablets in package)

Continuin — patented tablets (42 tablets in package)

Testosterone propionate — in ampoules 1% or 5% oil solution 1 ml each

Methyltestosterone — tablets 0.005 or 0.01 each

Nandrolone (Retabolil) — in ampoules 5% oil solution 1 ml each

Finasteride — tablets 0.005 each

Lecture 28
VITAMINS

Vitamins (lat. *vita,* life, + amine) are the organic substances, present in minute amounts in natural foodstuffs, that are essential to normal metabolism, usually as coenzymes; insufficient amounts in the diet may cause deficiency diseases.

Vitamins are usually divided into water-soluble and fat-soluble vitamins. Vitamins B_1 *(Thiamine)*, B_2 *(Riboflavin)*, PP *(Nicotinic acid)*, B_5 *(Pantothenic acid)*, B_6 (*Pyridoxine*), B_{12} *(Cyanocobalamin)*, B_{15} *(Pangamic acid)*, B_c *(Folic acid)*, C *(Ascorbic acid)*, P (group of bioflavonoids) are water-soluble. Vitamins A *(Retinol)*, E *(Tocopherol)*, K *(Phylloquinone)* belong to fat-soluble.

The organism's needs in vitamins change in dependence on age, work, climate, character of feeding, etc. The hard work, neuro-psychical stress, pregnancy, and breast-feeding, hard climate conditions lead to the higher vitamin demands. Also it is higher in children than in adults. Hypovitaminosis and avitaminosis appear during the vitamin deficiency.

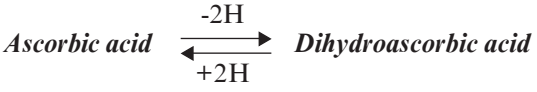
Nowadays avitaminosis is observed comparatively seldom. Hypovitaminosis is more often observed. It is characterized by not determined symptoms (fatigue, headache, weakness, lowering of capacity for work, lowering of resistance for infections and other diseases, etc.). Avitaminosis is the brightest appearance of vitamin insufficiency. It is characterized by clearly expressed specific symptomatology and is stipulated by full absence or prolonged vitamin deficiency. Reasons of vitamin's deficiency in the organism include low content of vitamins in meals *("alimentary" hypovitaminosis)*, disorders of vitamin's absorption from intestine that evoked by diseases of the GI and liver *("secondary" or "endogenic" hypovitaminosis)*, and considerable increasing of dietary requirements. However, prolonged overdosing of vitamins, usually fat-soluble (vitamins A, D), can cause development of *hypervitaminosis*.

Vitamin drugs are used in substitutive, adaptive and pharmacodynamic therapy. Substitutive vitamin therapy is used during treatment of avitaminosis and hypovitaminosis. Adaptive vitamin therapy is used for bettering of organism's adaptation for quickly changing conditions of environment (spring-autumn) and in hard conditions (polar or tropical climate, climbing, work under surface of water, during flying by plains, etc.). Doses for substitutive and adaptive therapy are 2–3 times higher than physiologic dietary requirements and are used for course therapy.

Pharmacodynamic vitamin therapy is used during treatment of diseases that are not caused by vitamin's deficiency. It's basic difference from substitutive therapy is in using of higher vitamin's doses, which dozens and hundreds times exceed daily requirements. Example is using of vitamin D_2 *(Ergocalciferol)* by 100,000 IU per day for treating of tubercular lupus of the skin.

WATER-SOLUBLE VITAMINS

Ascorbic acid (vitamin C, antiscorbutic vitamin) is a water-soluble vitamin, which is present in fresh fruit, vegetables, berries (wild rose). Citrus fruit are a particularly good source of vitamin C. *Ascorbic acid* is synthesized for use as a drug. Ascorbic acid is reversibly oxidized to dehydroascorbic acid in the body. These two forms of the vitamin are believed to be important in oxidation-reduction reactions:



Ascorbic acid is required for collagen formation, tissue repair and preservation of blood vessel integrity. The vitamin is involved in tyrosine metabolism, conversion of *Folic acid* to *Folinic acid*, carbohydrate metabolism, synthesis of lipids and proteins, resistance to infections, and cellular respiration. In addition, *Ascorbic acid* enhances the absorption of nonheme iron.

Ascorbic acid deficiency results in scurvy. Collagenous structures are primarily affected, and lesions develop in bones and blood vessels: ulceration of the gums hemorrhages into the skin and from the mucous membranes, debility, and immunity impairment.

Vitamin C is readily absorbed after oral administration. *Ascorbic acid* is widely distributed in body tissues. Large concentrations of the vitamin are found in the liver, leukocytes, and adrenal glands. Mostly *Ascorbic acid* is metabolized to oxalates, which are excreted in the urine. Large doses of ascorbic acid may cause acidification of the urine, occasionally leading to precipitation of urate, oxalate stones, or drugs in the urinary tract. *Ascorbic acid* is used to prevent and to treat scurvy. It has been prescribed for hemorrhagic states, fever, infection, and trauma, poisoning by different substances, anemia, atherosclerosis, peptic ulcer, and the common cold. *Ascorbic acid* may be useful to treat idiopathic methemoglobinemia. *Ascorbic acid* injection has been reported to be incompatible with many drugs.

Thiamine (vitamin B_1, antineuritic vitamin) is a water-soluble vitamin, which is present in many foods including yeast, cereal grains, nuts, and meat. *Thiamine* combines with *Adenosine triphosphate* (ATP) in the liver, kidneys, and leukocytes to form thiamine diphosphate *(Thiamine pyrophosphate)* which is a coenzyme in carbohydrate metabolism (in the decarboxylation of pyruvic and alpha-ketoglutaric acids). Thiamine diphosphate is also a coenzyme of transketolase in the utilization of glucose in the pentose phosphate pathway.

Thiamine deficiency leads to increased pyruvic and lactic acids concentration in the blood (acidosis). The organ systems principally affected by *Thiamine* deficiency are the peripheral nervous system (polyneuritis), cardiovascular system (heart failure), and the GI tract. In severe cases *Thiamine* deficiency results in beriberi (paresis, paralysis) and encephalopathy syndrome. Administration of Thiamine completely reverses the cardiovascular and GI symptoms of *Thiamin* deficiency; however, the degree of improvement in neurologic symptoms depends on the duration and severity of the lesions.

Following oral administration *Thiamine* is readily absorbed; however, the total amount absorbed following oral administration of a large dose is limited. GI absorption of *Thiamine* is decreased in alcoholics and in patients with cirrhosis or malabsorption. *Thiamine* is rapidly and completely absorbed following intramuscular administration.

Thiamine is used to prevent and to treat *Thiamin* deficiency syndromes including beriberi, encephalopathy syndrome, and peripheral neuritis. It is also used for the treatment of paresis, neuritis, heart failure, arrhythmia, and ketoacidosis. *Thiamine* commercially is available in the form of *Thiamin bromide* or *Thiamin chloride* for oral and intramuscular administration. The probable adverse effect is hypersensitivity.

Riboflavin (vitamin B_2) is a water-soluble vitamin, which is present in many foods including milk, meat, eggs, nuts, cereal grains, and yeast. In humans, an exogenous source of *Riboflavin* is required for tissue respiration. *Riboflavin* is converted to the coenzyme, *Flavin mononucleotide* (FMN) and *Flavin adenine dinucleotide* (FAD). These coenzymes act as hydrogen-carrier molecules for several enzymes (flavoproteins) involved in oxidation-reduction reactions of organic substrates and in intermediary metabolism. *Ribofla-*

vin is also indirectly involved in maintaining erythrocyte integrity.

Riboflavin deficiency (ariboflavinosis) results in cheilosis (angular stomatitis), glossitis, keratitis, ocular changes (photophobia, hemeralopia), and anemia.

Riboflavin is readily absorbed from the upper GI tract. FAD and FMN are widely distributed into body tissues, including GI mucosal cells, erythrocytes, and the liver. Free *Riboflavin* is present in the retina. *Vitamin B_2* is used to prevent *Riboflavin* deficiency and to treat ariboflavinosis. *Riboflavin* may be useful in treating keratitis, iritis, skin and infection diseases. Commercially available is *Riboflavin* (oral, topical), *Riboflavin mononucleotide* (injection). *Riboflavin* is nontoxic.

Vitamin PP (B_3) has two forms: *Nicotinic acid (Niacin) and Nicotinamide (Niacinamide). Nicotinic acid* and Tryptophan (that is converted to *Nicotinamide*) present in many stufts including yeast, meat, fish, milk, eggs, green vegetables, and cereal grains. Commercially available *Nicotinic acid* and *Nicotinamide* are prepared synthetically. *Nicotinic acid* is incorporated into 2 coenzymes: *Nicotinamide adenine dinucleotide* (NAD) and *Nicotinamide adenine dinucleotide phosphate* (NADP). They act as hydrogen-carrier molecules in glycogenolysis, tissue respiration, and lipid metabolism (more than 150 reactions). In large doses, *Nicotinic acid* (not nicotinamide) produces peripheral vasodilatation, predominantly of cutaneous vessels in the face, neck, and chest; decreases serum low-density lipoprotein concentrations; activates the fibrinolytic system. *Nicotinic acid* reportedly increases gastric acid secretion. *Vitamin PP* deficiency results in pellagra that accompanied by dermatitis, diarrhea, and dementia (loss of cognitive functions).

Vitamin PP is readily absorbed from the GI tract following oral administration, as well as from subcutaneous and i.m. injection site. It is widely distributed into body tissues. Metabolites of *Vitamin PP* are excreted in urine.

Vitamin PP is used to prevent and to treat nicotinic acid deficiency. Large doses of *Nicotinic acid* are used for the treatment of atherosclerosis (antilipemic agent); conditions associated with deficient circulation (e.g. peripheral vascular disease and vascular spasm), gastritis, and liver diseases.

Large doses of *Nicotinic acid* can cause flushing (face, neck), pruritus, heartburn, hypotension, and headache. Long-term using of *Nicotinic acid* may impair glucose tolerance and lead to lipid dystrophy of the liver (*Methionine* can prevent liver damage).

Nowadays some drugs include *Nicotinic acid*. For example, *Nicoverin* (*Nicotinic acid* + *Papaverine*), *Nicoshpan* (*Nicotinic acid* + *No-Spa*). *Papaverine* and *No-Spa* relieve smooth muscle spasm (spasmolytics) and *Nicotinic acid* enhances their action, especially vasodilatation. Thus, *Nicoverine* and *Nicospan* are used for the treatment of hypertonia. *Litonit* (*Lithium salt* of *Nicotinic acid*) is known as tranquilizer. The head of the pharmacology department of the Odessa Medical University prof. V. Y. Kresyun investigated it. Nowadays *Litonit* is used for alcoholism treatment. Current work of the OGMU pharmacology department is based on the study of neurotropic and hepatotropic activities of newly synthesized compounds of *Germanium* and *Nicotinic* acid as well as *Nicotinamide*. These substances possess tranquilizer and hepatoprotective effects, that opens perspective of their purpose investigation.

Vitamin B_6 (as pyridoxine, pyridoxal, and pyridoxamine) is a water-soluble vitamin, which is present in many foods including cereal grains, vegetables, liver, meat, and eggs. *Pyridoxine, Pyridoxal*, and *Pyridoxamine* are converted to the active forms of the vitamin, *Pyridoxal phosphate* and *Pyridoxamine phosphate*, which act as coenzymes in a wide variety of reactions in nitrogenous metabolism. They are involved in transamination, deamidation, and decarboxylation of amino acids, in the conversion of *Tryptophan* to *Nicotinamide*. *Pyridoxine* appears to be essential in the synthesis of GABA within the CNS and in the synthesis of heme. The vitamin is also involved in lipid metabolism.

Deficiency of the vitamin has rarely been identified in humans. Artificial *Pyridoxine* deficiency affects the peripheral nerves (neuritis), CNS (seizure), skin (dermatitis), and the hematopoietic system (leukopenia). *Pyridoxine* deficient state can occur during treatment of tuberculosis with *Ioniazid* that inhibits the conversion of *Vitamin B_6* to the *Pyridoxal phosphate*.

Vitamin B_6 is readily absorbed from the GI tract following oral administration. It is stored mainly in the liver. *Pyridoxine* is used to prevent and to treat *Vitamin B_6* deficiency. Also it is indicated for the treatment of hematopoietic upset (leukopenia, anemia), disorders of nervous system (neuritis, parkinsonism, and vertigo), and hepatitis.

Commercially available form is *Pyridoxine hydrochloride* (oral, injection). Long-term administration of megadose of *Pyridoxine* can cause sensory neuropathy.

Pantothenic acid (*Vitamin B_5*) is a water-soluble vitamin, which is widely distributed in plant and animal tissues. Rich sources of *Pantothenic acid* include meat, vegetables, cereal grains, eggs, and milk. Also it is synthesized in bowel by *E. coli*. In humans, an exogenous source of pantothenic acid is required for intermediary metabolism of carbohydrates, proteins, and lipids. *Pantothenic acid* is a precursor of coenzyme A which is required for acetylation reactions in gluconeogenesis, in the release of energy from carbohydrates, in the synthesis and degradation of fatty acids, and in the synthesis of steroid hormones, acetylcholine, and other compounds.

Dietary deficiency of *Pantothenic acid* has not been clinically identified in humans. Experimentally produced *Pantothenic acid* deficiency resulted in drowsiness, fatigue, headache, paresthesia of legs, and GI complaints.

Pantothenic acid is readily absorbed from the GI tract following oral administration. It is widely distributed into body tissues, mainly as coenzyme A. Highest concentrations are found in the liver and adrenal glands. *Pantothenic acid* is excreted unchanged.

The vitamin is commercially available as the calcium salt (*Calcium pantothenate*). It has been used orally and parenterally. *Calcium pantothenate* is indicated for the treatment of peripheral neuritis, toxicosis during pregnancy, hepatitis, atony of the intestine, *Streptomycin* neurotoxicity, and catarrhal respiratory disorders. *Pantothenic acid* is usually nontoxic

even in large doses. Allergic reactions to it have been reported occasionally.

Pangamic acid Vitamin B_{15} is considered to vitamin-like substances. It is donator of methyl groups and possesses anti-hypoxanthic action. It is used in a form of *Calcium pangamate* during dystrophy of myocardium, angina pectoris, atherosclerosis, diseases of the liver, and during treatment of alcoholism.

Rutin (Vitamin P) unites group of bioflavonoids, which are present in green tea, citruses, wild rose, etc. Together with *Ascorbic* acid it takes part in oxidizing-restoring processes and prevents forming of lipid's peroxides. It increases firmness and lowers penetrability of capillaries. So, it is used in combination with *Ascorbic acid Ascorutin* for the treatment of increased penetrability of vessels (capillary toxicosis, hemorrhagic diathesis), allergy, and polyarthritis.

Vitamin U is contained in cabbage, asparagus, and fresh tomato. It is donator of methyl groups and takes part in oxidizing-restoring processes. It is used enterally during ulcerative disease of stomach and duodenum, gastritis, and colitis.

Vitamin B_{12} (Cyanocobalamin) and *Folic acid (Vitamin B_c, Pteroylglutamic acid)* are discussed in lecture "Drugs influencing the erythropoiesis".

Multivitamins. When a single vitamin deficiency is evident, other vitamin deficiencies (clinical or subclinical) often accompany it. Therapeutic multivitamin preparations may, therefore, be useful in these patients. Therapeutic multivitamins may also be indicated in pathologic conditions in which nutritional requirements are greatly increased (e.g. alcoholism, hyperthyroidism, severe illness or injury, cachexia) or in conditions in which absorption, utilization, or excretion of vitamins is abnormal (including malabsorption syndromes).

The vitamin combination chosen should fit the needs of the individual patient. It should be remembered that some vitamins (especially *Vitamins A* and *D*) and many minerals may be toxic in large doses, and dosage of multivitamin preparations containing these agents should take the patients dietary intake into account. Vitamins are usually administered orally; however, the drugs may be given parenterally in patients in whom oral administration is not feasible, including those receiving total parenteral nutrition. Multivitamin injections are reportedly incompatible with i.v. solutions containing various drugs. Multivitamin preparations are tablets or dragee "*Hexavit*", "*Pangexavit*", "*Decamevit*", "*Aerovit*", "*Glytamevit*", "*Unicap*", etc. For instance, dragee "*Hexavit*" includes *Vitamin A, B_1, B_2, PP, B_6, C*.

Available forms:

Ascorbic acid — powder; tablets 0.05 or 0.1 each (for adults); tablets 0.025 each (for children); in ampoules 5% or 10% solution 1 or 2 ml

Thiamine chloride — tablets 0.002; 0.005 or 0.01 each; in ampoules 2.5% or 5% solution 1 ml each

Riboflavin — powder; tablets 0.002 each (for prophylaxis); tablets 0.005; 0.01 each (for treatment)

Nicotinic acid — powder; 0.05 each; in ampoules 1% solution 1 ml

Nicotinamide — powder; tablets 0.005 each (for prophylaxis); tablets 0.025 each (for treatment)

Pyridoxine — powder; tablets 0.002; 0.005 or 0.01 each; in ampoules 1% or 5% solution 1 ml each

Potassium pantothenate — tablets 0.1 each; in ampoules 10% solution 2 or 5 ml

Rutin — powder; tablets 0.02 each

Hexavit — patented dragee

FAT-SOLUBLE VITAMINS

Vitamin A is a fat-soluble vitamin that is present in foods in a variety of forms: *Retinol (Vitamin A_1)*, *Dehydroretinol (Vitamin A_2)*, and *Retinoic acid*. *Vitamin A* is present in esterified form in eggs, milk, butter, and oily salt-water fish. Provitamin A carotenoid pigments (including α-, β-, and γ-carotene), the most active of which is β-carotene, are present in green and yellow vegetables and fruit and are converted to retinol in humans.

In humans, an exogenous source of *Vitamin A* is required for growth, vision, reproduction, and the integrity of mucosal and epithelial surfaces. *Vitamin A* has been reported to act as a cofactor in mucopolysaccharide synthesis. In the retina, *Retinol* is converted to the *Aldehyde* (retinal), which combines with *Opsin* to form *Rhodopsin*, the visual pigment. Under the influence of light rhodopsin is split into retinal and opsin that accompanied with perceiving of light. In darkness the resynthesis of *Rhodopsin* occurs. Thus, *Rhodopsin* is necessary for visual adaptation for darkness (Fig. 23).

Vitamin A deficiency leads to night blindness (nyctalopia or hemeralopia — impairment of vision in reduced illumination), xerophthalmia (dryness of the cornea) and keratomalacia (ulceration of the cornea), hyperkeratosis of the skin, immunodeficiency, and epithelial metaplasia of mucous membranes that decrease resistance to infections. That's why, *Vitamin A* is known also as "anti-infection agent".

Vitamin A is readily and completely absorbed if fat absorption is normal. Retinol esters are hydrolyzed in the GI lumen by pancreatic enzymes and in presence of bile. *Retinol* is absorbed and then reesterified, mainly to *Retinyl palmitate*. It is stored in the liver. Normal body stores of *Vitamin A* are sufficient to meet the body's requirements for several months. *Retinol* is released from the liver bound to the plasma proteins. *Vitamin A* metabolites are excreted in the urine and feces.

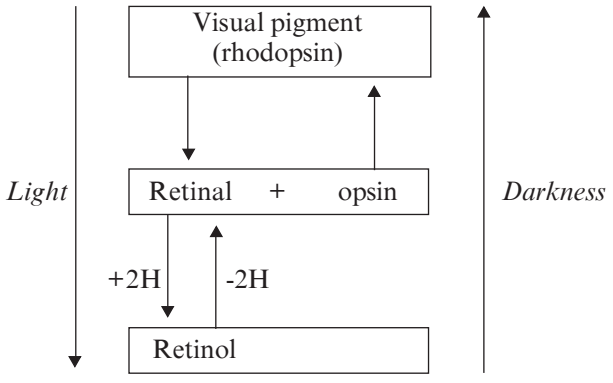


Fig. 23. Synthesis and breaking of *Vitamin A*

Vitamin A is used to prevent and to treat symptoms of *Vitamin A* deficiency such as xerophthalmia and night blindness. Oral administration of water-miscible *Vitamin A* preparations may be useful in preventing deficiency in patients with malabsorption. *Vitamin A* may be useful in infections, skin disorders (burns, ichthyosis, and psoriasis), and however, other retinoids (e.g. *Etretinate, Isotretinoin*) are currently being investigated for use in the treatment of these dermatological disorders. *Vitamin A* has been studied in animals as an anticarcinogen; further study in humans is needed to determine efficacy. For clinical use, *Vitamin A* is available as *Retinol* (*Vitamin A* alcohol) or *esters of Retinol* formed from acetic and palmitic acids. *Vitamin A* activity is preferably expressed in International Units (IU).

Doses of *Vitamin A* that do not exceed the physiologic requirement are usually nontoxic. Effects of acute overdosing are vomiting, diarrhea, confusion or unusual excitement. Chronic overdosing includes bone or joint pain, painful hyperostosis of the bones (thickening of bones), drying or cracking of skin, loss of hair, unusual tiredness. Large doses of *Vitamin A* are teratogenic in animals. Treatment of hypervitaminosis A consists of discontinuance of *Vitamin A* and symptomatic therapy as indicated.

Group of *Vitamin D* (antirachitic vitamins) includes fat-soluble vitamins that possess antirachitic and hypercalcemia activity. Because they are activated in the body and have regulatory effects, they are sometimes considered hormones. *Vitamin D* analogs include *Cholecalciferol Vitamin* D_3 and *Ergocalciferol Vitamin* D_2. *Vitamin D* is present in fish oil, liver of aquatic mammals (e.g. seals, polar bears), eggs, butter, and milk. Ergocalciferol is formed from ergosterol. *Cholecalciferol* is formed from 7-*Dehydrocholesterol* in the skin after exposure to ultraviolet light. In the human body, *Cholecalciferol* is hydroxylated to *Calcifediol* (25-hydroxyvitamin D_3) in the liver and then to *Calcitriol* (1,25-dihydroxyvitamin D_3) and *Secacalcifediol* (24,25-dihydroxyvitamin D_3) in the kidneys (Fig. 24). *Ergocalciferol* has the same conversion as *Cholecalciferol*.

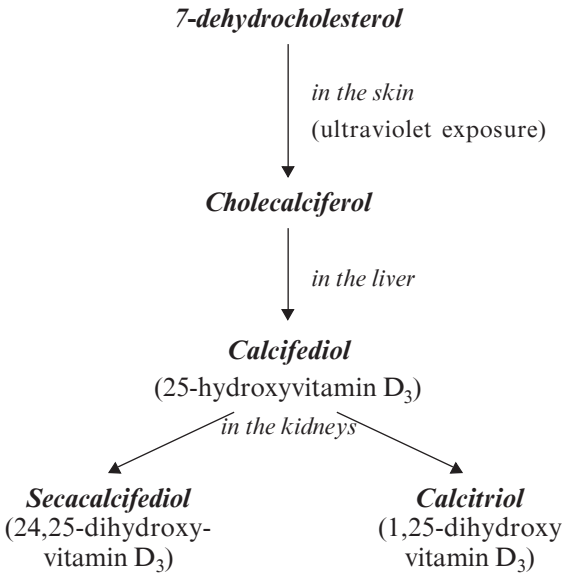


Fig. 24. Synthesis of *Vitamin* D_3

Calcitriol and *Calcifediol* enhance the efficiency of intestinal calcium and phosphorous absorption in the small intestine and stimulate renal reabsorption of calcium and phosphate. They exhibit potent antiproliferative and prodifferentiation effects. Recent evidence suggests that 24,25-dihydroxyvitamin D_3 stimulates bone formation. *Vitamin D* deficiency results in skeletal demineralization. In children, *Vitamin D* deficiency leads to rickets that is characterized by skeletal deformations (e.g. frontal bossing), and outward and inward deformities of the lower limbs resulting in bowed legs and knocked knees, respectively. In adults, *Vitamin D* deficiency leads to osteoporosis (reduced bone mass) and osteomalacia (softening of the bones). Any alteration in cutaneous production of *Cholecalciferol*, GI *Vitamin D* absorption, or metabolism of the vitamin to its active form (i.e. calcitriol) can result in it's deficiency.

Vitamin D is readily absorbed from the GI tract following oral administration. The presence of bile is required for its absorption. *Vitamin D* is incorporated into chylomicrons and absorbed via the lymphatic system and then associates mainly with a specific α-globulin as well as *Vitamin D* hydroxylated metabolites. 25-hydroxylated vitamin D_2, D_3 are stored in fat and muscles. The metabolites of *Vitamin D* analogs are excreted principally in bile and feces. Activity of *Ergocalciferol* and *Cholecalciferol* is expressed in IU.

For clinical use, *Vitamin D* is available as *Cholecalciferol, Ergocalciferol,*and *Calcitriol*. *Vitamin D* is used to prevent or treat rickets, osteoporosis, hypocalcemia tetany, and to manage psoriasis and hypoparathyroidism. Administration of excessive doses of *Vitamin D* may lead to hypervitaminosis D manifested by hypercalcemia. Early symptoms of hypercalcemia may include weakness, drowsiness, metallic taste, vomiting, vertigo, and bone pain. Later consequences of hypercalcemia may include impairment of renal function, osteoporosis, and metastatic calcification of organs and vessels. Treatment of *Vitamin D* intoxication consists of withdrawal of the drug, administration of fluids, corticosteroids, and calciuria diuretics (e.g. Furosemide and Ethacrynic acid).

Vitamin E (antisterility vitamin) is a fat-soluble vitamin, which is present in many foods including vegetable oils, cereal grains, animal fats, meat, eggs, fruits, and vegetables. The vitamin exists in a variety of forms: α-, β-, and γ-*tocopherols*. The most biologically active natural form of the vitamin is α-*tocopherol*.

The exact biologic function of vitamin E in humans is unknown, although the vitamin is believed to act as an antioxidant. It has been postulated that *Vitamin E* protects polyunsaturated fatty acids (which are components of cellular membranes) and other oxygen-sensitive substances *(Vitamins A, C)* from oxidation. *Vitamin E* delays the accumulation of free radicals resulting in excessive lipid peroxidation. Thus, it limits atherosclerosis and CNS neuronal generation (Alzheimer's disease). *Vitamin E* also may inhibit platelet aggregation and adhesion. *Vitamin E* deficiency does not cause specific disease in adults; however, in premature neonates thrombosis and hemolytic anemia may occur. In animals, avitaminosis E

is associated with infertility in male and spontaneous abortion in female, dystrophy of skeletal muscles and myocardium.

Absorption of *Vitamin E* from the GI tract depends on the presence of bile and only half of the vitamin obtained from dietary sources is absorbed. After absorption, *Vitamin E* reaches the lymph circulation and then is transported with plasma proteins. *Vitamin E* is distributed to all tissues and is stored in adipose tissue. *Vitamin E* is metabolized in the liver and excreted primarily in the bile.

Vitamin E has been used for the treatment of habitual abortion, infertility, myodystrophy, dementia, angina pectoris, and thrombophlebitis. For drug use, *Vitamin E* is available as *Tocopherol acetate*. *Vitamin E* is usually nontoxic; however, it may cause allergic reactions and pain in site of injection.

Lecture 29
ENZYME PREPARATIONS AND ENZYME INHIBITORS

Enzyme agents are the preparations of enzymes. They are widely used in medicine for the different purposes. The first enzyme agents group *(Trypsin)* is indicated for **purulent-necrotic processes**; the second group *(Pancreatin)* increases **digestive activity**; the third group *(Streptokinase)* has **fibrinolytic properties**; the fourth group includes **different enzyme drugs** *(Lydase, Penicillinase)*.

Trypsin is a proteolytic enzyme that formed in the small intestine. It hydrolyzes peptides, amides, etc. *Crystallized trypsin*, a purified preparation of the pancreatic enzyme. It is used in medicine for debridement (excision) of wounds and ulcers for dead tissues, fibrin, and viscous secretes. In addition it has anti-inflammatory activity and permits antibodies, leukocytes, and antibiotics better access to the infected area. *Trypsin* is non-active (safe) relatively for undamaged tissues. It is used in inhalation for the cleaning of bronchi for viscous mucus or exudate during bronchitis, pneumonia. *Trypsin* is injected intramuscularly or used topically for the treatment of thrombophlebitis, parodontitis, osteomyelitis, and purulent infections of soft tissues. The agent can irritate tissues at the site of its application and can cause allergic reactions or intoxication that predominantly are evoked by absorption of necrotic tissues. *Chymotrypsin* is a proteinase of the gastrointestinal tract. It hydrolyzes proteins. *Chymotrypsin* is similar in indications to *Trypsin.*

Deoxyribonuclease and *Ribonuclease* are the enzymes. They hydrolyze phosphodiester bonds in DNA and proteins. These agents have the same to *Trypsin* using. *Deoxyribonuclease* and *Ribonuclease* are obtained from the cattle pancreas as well as *Chymotrypsin* and *Trypsin.*

Collagenase is a proteolytic enzyme capable of specifically hydrolyzing peptide bonds of collagen. The enzyme debrides necrotic tissue without damaging granulation tissue. It is derived from cattle pancreas. *Collagenase* is used to promote debridement of necrotic tissue in the treatment of severe burns and dermal ulcers. Pain and burning may occur at the site of *Collagenase* application.

Pepsin is the principal digestive enzyme *(Protease)* of gastric juice, formed from pepsinogen; it hydrolyzes peptide bonds at low pH values, reducing proteins to smaller molecules. For medical purpose it is obtained from stomach mucous membrane of hog. Pepsin is indicated for replacement therapy of stomach upset such as achlorhydria (absence of hydrochloric acid in the gastric juice) or hypoacidity (lower than normal level of hydrochloric acid). *Natural gastric juice* is digestive fluid secreted by the stomach glands of the dogs or horses. It normalizes secretion and motility of the gastrointestinal tract. *Abomin* is received from the stomach mucous membrane of calf or lamb. It contains the summary of proteolytic enzymes. *Gastric Juice* and *Abomin* have the same indications as *Pepsin*.

Pancreatin is a substance containing enzymes, principally *Amylase*, *Lipase*, and *Protease*, obtained from the pancreas of the cattle and hog. *Pancreatin* is used as replacement therapy in the symptomatic treatment of chronic pancreatitis, pancreatectomy, or other conditions in which pancreatic insufficiency impairs fat digestion. Pancreatic exocrine replacement therapy should not delay or supplant treatment of the primary disorder. The medication is taken before meals. Because pancreatin has a high purine content, hyperuricemia, uric acid renal stones may be seen as a side effect. Hypersensitivity reactions have been reported. *Panzynorm forte N* (contain pancreatin, bile extract, and extract of stomach mucous membrane), *Festal* (pancreas enzymes and bile extract), *Mezym® forte* (pancreas enzymes) are the digestive enzyme replacement products also. They are used for the treatment of digestive insufficiency of the gastrointestinal tract.

Fibrinolytic drugs (Fibrinolysin, Streptokinase, and Urokinase) are discussed in the lecture "Drugs used in disorders of coagulation".

Hyaluronidase (Lydase) is a protein enzyme that found widely distributed in nature. *Hyaluronidase* for injection is a sterile, dry, soluble enzyme product prepared from cattle's testes. The potency of the drug is expressed in conventional units. *Hyaluronidase* modifies the permeability of connective tissue through the hydrolysis of hyaluronic acid. Occurring as one of the principal viscous polysaccharides of connective tissue and skin, hyaluronic acid is one of the chief ingredients of the tissue cement, which offers resistance to the diffusion of liquids through tissue. *Hyaluronidase* is indicated in the treatment of ankylosis (stiffening) of the joints and postburn scars. The enzyme also hastens the disappearance of swelling after hemorrhage. Adverse effects from *Hyaluronidase* are rare. Occasional sensitivity reactions (e.g. urticaria) have been reported.

Penicillinase is a β-lactamase enzyme, which destroys all biosynthetic and majority of semisynthetic penicillins. It is produced by certain strains of microbes (e.g. staphylococci). *Penicillinase* is used in case of acute or delays hypersensitivity for penicillins.

Asparaginase is an enzyme that is isolated for clinical use from various bacteria. The drug is used to treat leukemia. It acts indirectly by catabolic depletion of serum asparagine. These results in inhibition of protein synthesis in neoplastic cells, requiring an external source of asparagine (see lecture "Immunotropic agents").

Enzyme inhibitors are discussed in other topics: (1) **proteinase inhibitors** *(Aprotinin (Contrykal))* one can see in lecture "Drugs used in gastrointestinal diseases"; (2) **fibrinolytic inhibitors** *(Aminocaproic acid)* see in "Drugs used in bleeding disorders"; (3) **cholinesterase-inhibiting drugs** *(Neostigmine methylsulfate (Proserine))* see in "Cholinomimetics"; (4) **monoamine oxidase (MAO) inhibitors** *(Nialamide)* see in "Antidepressant agents"; (5) **carbonic anhydrase inhibitors** *(Acetazolamide (Diacarb))* see in "Diuretic agents"; (6) **xanthine oxidase inhibitors** *(Allopurinol)* see in "Drugs used in gout"; (7) **acetaldehyde dehydrogenase inhibitors** *(Teturamum)* see in "The alcohols".

Available forms:

Retinol acetate — in bottles 3.44% oil solution 10 ml each; in ampoules oil solution 1 ml (contain 25,000; 50,000 or 100,000 IU) each; in capsules 0.2 (3,300; 5,000 or 33,000 IU) each

Ergocalciferol — in dragee 500 IU each (for prophylaxis); in bottles 0.5% solution 5 ml (1 ml contain 200000 IU) each (for prophylaxis and treatment); in bottles 0.0625%; 0.125% or 0.5% oil solution 10 ml each (1 ml contains 25,000; 50,000 or 200,000 IU correspondently)

Tocopherol acetate — in bottles 5%; 10% or 30% oil solution 10; 20 or 50 ml each; in ampoules 5%; 10% or 30% oil solution 1 ml each

Trypsin crystallized — in bottles or in ampoules 0.005 or 0.01 each, to dilute in 2 or 20 ml of physiologic solution before injection or applying correspondently

Pancreatin — in tablets 0.25 each

Hyaluronidase (Lydase) — in bottles 64 conventional units (CU) each, to dilute in 1 ml of physiologic solution (for injection)

EXAMINATION QUESTIONS

1. A patient with severe diarrhea as a result of a carcinoid tumor is a candidate for which of the following treatments?
   (A). Pulsatile administration of GnRH.
   (B). Nasal administration of *Desmopressin.*
   (C). Depot injections of *Octreotide.*
   (D). Oral administration of *Bromocriptine.*

2. The actions of ADH include all of the following EXCEPT
   (A). Stimulation of ACTH release.
   (B). Stimulation of bile secretion.
   (C). Constriction of most blood vessels.
   (D). Stimulation of coagulation factor VIII production.
   (E). Production of concentrated urine.

3. A patient with endometriosis who is being treated with *Leuprolide* has hot flashes and dry skin and vagina. What additional treatment would relieve these unpleasant effects?
   (A). Estrogen and *Progesterone.*
   (B). *Ganirelix*.
   (C). *Testosterone*.
   (D). *Bromocriptine*.

4. A 30-year-old woman has secondary amenorrhea and serum prolactin levels of 75 ng/mL. She has visited a fertility clinic to attempt to become pregnant. What treatment should be given?
   (A). *Clomiphene.*
   (B). *Ganirelix.*
   (C). *Cabergoline.*
   (D). *Estradiol.*

5. Growth hormone deficiency in children must be determined by measuring hormone levels after giving an agent that stimulates release because
   (A). Normal growth hormone secretion in children is too low to be measured by current assays.
   (B). Growth hormone secretion occurs only during sleep.
   (C). Growth hormone secretion is episodic.
   (D). A different form of growth hormone is secreted after stimulation.

6. During the period of withdrawal from extended glucocorticoid therapy
   (A). Prompt recovery of the hypothalamic-pituitary-adrenal axis results in restoration of endogenous corticotrophin release.
   (B). The patient may be eager to further reduce the dose of glucocorticoid.
   (C). The physician should rapidly reduce glucocorticoid therapy to physiological doses.
   (D). Patients should not require an increment in steroid therapy during increased stress (e.g. severe infection).
   (E). The appearance of fever and malaise attributed to steroid withdrawal may be difficult to distinguish from reactivation of rheumatic disease.

7. Which one of the following enzymes is required for cortisol biosynthesis?
   (A). 21-hydroxylase.
   (B). 17,20 lyase.
   (C). Cyclooxygenase.
   (D). 11-β-hydroxysteroid dehydrogenase-2.
   (E). 18-hydroxylase.

8. The primary goal of glucocorticoid treatment in rheumatic arthritis is
   (A). Suppression of inflammation and improvement in functional capacity.
   (B). Eradication of all symptoms.
   (C). Reversal of the degenerative process.
   (D). Development of a sense of well-being in the patient.
   (E). Prevention of suppression of the hypothalamic-pituitary-adrenal axis.

9. The addition of a fluoride group on ring C of cortisol to give 9-α-fluorocortisol
(A). Will shorten its half-life.
(B). Will increase both glucocorticoid and mineralocorticoid activity.
(C). Shares an advantage over *Cortisol* in that sodium retention is not as marked at equipotent inflammatory doses.
(D). Will not cause suppression of the hypothalamic-pituitary-adrenal axis when applied topically.
(E). Provides a steroid widely used in the treatment of rheumatoid arthritis.

10. Dexamethasone
(A). Is adequate replacement therapy in an adrenalectomized patient.
(B). Has a half-life equivalent to that of *Cortisol*.
(C). Produces salt retention in therapeutic doses.
(D). Possesses most of the undesirable side effects of *Cortisol.*
(E). Has antiinflammatory potency equivalent to that of *Cortisol.*

11. Which answer is most appropriate for the action of *Ketoconazole*?
(A). It has a single major action that is confined to the adrenal cortex.
(B). It provides long term treatment for Cushing's disease.
(C). It has an action on the adrenal cortex that is irreversible.
(D). Its action may be associated with liver dysfunction.
(E). It preferentially blocks *Cortisol* synthesis as opposed to testosterone production.

12. All of the following are common adverse effects associated with drug overdose of thyroid hormone replacement therapy EXCEPT
(A). Cardiac palpitation.
(B). Arrhythmias.
(C). Tachycardia.
(D). Weight gain.
(E). Heat intolerance.

13. An adequate dietary intake of *Iodine* is essential to prevent hypothyroidism. In many areas of the world, dietary *Iodine* intake is insufficient and must be supplemented. There is another element in which a dietary intake may be insufficient that is also associated with thyroid hormone metabolism. This element is
(A). Calcium.
(B). Selenium.
(C). Fluorine.
(D). Sodium.
(E). Potassium.

14. What is the primary reason for administering β-adrenergic receptor blocking drugs as adjunct therapy in the treatment of thyrotoxicosis?
(A). They reduce the elevated thyroid hormone levels.
(B). Many of the effects of elevated thyroid hormones result from an increase in number of β-adrenoceptors.
(C). They elevate the levels of prostaglandins through indirect mechanism.
(D). The effects of elevated thyroid hormones are directly antagonized by β-adrenoceptor agonists.

15. The following statements regarding the mechanism of action of thionamide drugs in the treatment of hyperthyroidism are true EXCEPT
(A). The clinical effects are apparent soon after administration.
(B). The compounds inhibit the action of the enzyme TPO.
(C). The drugs inhibit thyroid hormone synthesis.
(D). These drugs do not inhibit secretion of preexisting stored thyroid hormone.

16. Why are elderly individuals more likely to be *Vitamin D* deficient than young adults? All of the choices are true EXCEPT
(A). They spend less time outdoors exposed to the sun, which is important in the synthesis of *Vitamin D*.
(B). Their appetite and intake of essential nutrients is diminished because of chronic medical conditions associated with aging.
(C). The formation of the active form of *Vitamin D* is diminished by chronic liver and renal conditions.
(D). The *Vitamin D* receptor has less affinity for D_3 with aging.

17. A 48-year-old white man is noted to have osteopenia on a routine LS spine film while being evaluated for back pain. His bone density reveals osteoporosis of both his hip and LS spine. All of the choices are possible EXCEPT
(A). He has been taking *Gabapentin (Neurontin)* for the past 2 years for a seizure disorder.
(B). He has Crohn's disease and has had to take *Prednisone* off and on since the age of 16.
(C). He has had multiple calcium kidney stones over the past few years and has been on a low-calcium diet.
(D). He had glomerulonephritis at the age of 24 and developed chronic renal failure but received a kidney transplant 10 years ago.
(E). He drinks 2 to 3 glasses of wine each day at dinner.

18. The main reason *Metformin* should not be used in patients with renal failure is that
(A). It increases the risk of lactic acidosis.
(B). It increases the risk of ketoacidosis.
(C). It causes development of congestive heart failure.
(D). It causes hepatic necrosis.
(E). It causes hypoglycemia.

19. Hypoglycemia is rarely seen with these drugs when used as monotherapy EXCEPT
(A). *Metformin.*
(B). *Rosiglitazone.*
(C). *Miglitol.*
(D). *Glyburide.*
(E). *A, B, and C.*

20. Breast cancer is the second most common cancer in women. All of the following statements concerning breast cancer at true EXCEPT
(A). Hormonal therapy is reserved for patients with advanced metastases.
(B). *Estrogen* treatment is an acceptable form of hormonal therapy.
(C). *Progestin* treatment is an accepted form of hormonal therapy.
(D). *Tamoxifen* is an accepted form of nonhormonal therapy.

21. The mechanism of action of the compound RU486 is to
(A). Block estrogen binding to Ers.
(B). Block progestin binding to progesterone receptors.
(C). Act as an estrogen agonist.
(D). Act as a progesterone agonist.

22. The formation of what as a principal precursor of testosterone is considered the biosynthetic ratelimiting step?
(A). *Pregnenolone.*
(B). *Cholesterol.*
(C). *Androstenediol.*
(D). *Estrogen.*
(E). *Progesterone.*

23. Normal skeletal muscle cells
(A). Typically lack androgen receptors and thus are not affected by high concentrations of testosterone.
(B). Respond more readily to dihydrotestosterone than to testosterone.
(C). Have higher levels of 5α-reductase than do prostatic tissue cells.
(D). Use the androgen receptor to enhance protein anabolic activity.
(E). Produce testosterone in response to FSH stimuli.

24. Upon examination, a 68-year-old married man was found to have a greatly enlarged prostate. Which one of the following drugs is most likely to suppress prostatic growth without affecting libido?
(A). *Spironolactone.*
(B). *Finasteride.*
(C). *Ketoconazole.*
(D). *Flutamide.*
(E). *Stanozolol.*

25. A patient with pancreatic disease complains of difficulty driving at night because of vision problems. Ulceration of the cornea is detected on ophthalmic examination. Which of the following should be recommended?
(A). Supplementation with *Vitamin B* complex.
(B). Supplementation with *Vitamin A.*
(C). Decreased intake of *Vitamin A.*
(D). Supplementation of diet with more red meat.
(E). Decreased *Vitamin C* intake.

26. A patient comes into the clinic for a pregnancy test. It is positive. Which of the following should be recommended?
(A). A multivitamin without iron.
(B). A multivitamin with iron.
(C). A diet rich in carrots.
(D). No vitamin supplement.
(E). A *Vitamin A* supplement.

27. Capillary fragility, malaise, and abnormal bone and tooth development describe a deficiency of which vitamin?
(A). *Vitamin A.*
(B). *Vitamin B_6.*
(C). *Vitamin C.*
(D). *Riboflavin.*
(E). *Vitamin E.*

28. Which vitamin can mask the symptoms of pernicious anemia by alleviating the anemia but not preventing the neurological damage?
(A). *Vitamin B_{12}.*
(B). *Niacin.*
(C). *Folic acid.*
(D). *Vitamin C.*
(E). *Vitamin D.*

29. An epileptic patient who is taking *Phenytoin* and *Lamotrigine* to control her seizures is in the first month of pregnancy and definitely wants to have the baby. What vitamin supplement would be essential?
(A). *Vitamin B_6.*
(B). *Vitamin D.*
(C). *Vitamin C.*
(D). *Niacin.*
(E). *Folic Acid.*

ANSWERS

1. **(C)**. Carcinoid tumors arise from neuroendocrine cells of the gut and secrete serotonin and gastrointestinal hormones, which activate the gastrointestinal tract and result in diarrhea. Most of these tumors have receptors for somatostatin, which inhibit secretion when activated, resulting in reduced activity of the gut. Octreotide is a stable analogue of somatostatin that is effective in treating carcinoid-induced diarrhea and that may slow tumor growth. The long-acting form requires only monthly injections to maintain effective levels. GnRH, *Desmopressin*, and *Bromocriptine* will not inhibit secretion from these neuroendocrine tumors.

2. **(B)**. ADH has many actions through three receptors but does not affect bile secretion. It stimulates ACTH release, although the predominant control occurs through corticotropin-releasing hormone. It has pressor activity by causing smooth muscles cells of most blood vessels to constrict. It stimulates production of coagulation factor VIII and von Willebrand's factor, and it increases the permeability of the collecting duct in the kidney to water, resulting in urine that has high osmolarity and low volume.

3. **(A)**. Endometriosis is growth of the endometrium beyond the uterine cavity. Leuprolide is a GnRH analogue that suppresses LH and FSH when present continuously, resulting in endometrial atrophy and low estrogen levels, causing hot flashes and skin dryness; long-

term use may also reduce bone density. Low-dose estrogen and progesterone replacement therapy relieves the side effects caused by reduced estrogen levels, usually without stimulating endometrial growth. However, the recent warning of relative cancer risk of estrogen-progesterone combinations as short-term versus long-term hormonal replacement therapy must be carefully considered. *Ganirelix*, *Testosterone*, and *Bromocriptine* would not relieve the side effects.

4. **(C)**. High prolactin levels may cause amenorrhea and infertility through mechanisms not understood. Prolactin levels in normal women are less than 20 ng/mL. The primary control of prolactin is through inhibition of secretion by dopamine from the hypothalamus. Cabergoline is a stable dopamine agonist that reduces prolactin secretion. *Clomiphene*, an estrogen antagonist, is used to stimulate LH and FSH release to enhance fertility but should not be used until it has been determined whether reducing prolactin levels alone is sufficient to cause fertility. *Ganirelix* and *Estradiol* are not useful in treating infertility.

5. **(C)**. Growth hormone secretion is episodic, and a single measurement without stimulation may give a false impression of growth hormone levels that are too low (<5 ng/mL). Growth hormone release occurs not only immediately after sleep but also after eating and after exercise. A 20-kilodalton form of growth hormone is secreted with the normal 22-kilodalton form, but the former is present in about one-fifth the amount. Both forms have biological activity and are secreted basally and after stimulation of growth hormone release.

6. **(E)**. Recovery from prolonged steroid therapy is slow, and the withdrawal may be unpleasant. The patient may be reluctant to reduce the dose of steroid because of its salutary effects on the psyche. Tapering the dose of steroid is important in steroid withdrawal; however, the patient may temporarily require a dose increase during periods of heightened stress.

7. **(A)**. 17, 20 lyase is required for androgen synthesis, cyclooxygenase for prostaglandin production, 11-β-hydroxysteroid dehydrogenase-2 acts as a reductase-converting cortisol to its inactive 11-keto derivative cortisone, whereas 18-hydroxylase is required for aldosterone production.

8. **(A)**. Glucocorticoid treatment of rheumatoid arthritis does not eradicate all symptoms, nor does it reverse the degenerative process. Suppression of the hypothalamic-pituitary-adrenal axis is an unwanted side effect of glucocorticoid therapy. While development of a sense of well-being may be attributed to the relief of symptoms, it is not the primary basis for employing the potent glucocorticoids.

9. **(B)**. The addition of a fluoride group to ring C of cortisol to give 9-α-*fluorocortisol* greatly increases and prolongs all biological activity. The result is an agent with potent glucocorticoid and mineralocorticoid activity, making it inappropriate to use in rheumatoid arthritis. Because of its potency and extended action, *Fluorocortisol* will have a greater tendency to depress the hypothalamic-pituitary axis than cortisol, even when applied topically.

10. **(D)**. *Dexamethasone* is a fluorinated glucocorticoid that is more potent and longer acting than *Cortisol*. While devoid of salt-retaining activity in therapeutic doses, this glucocorticoid does possess most of the adverse effects observed with *Cortisol*. Because it lacks mineralocorticoid activity, *Dexamethasone* is not used in replacement therapy.

11. **(D)**. In addition to its ability to block steroid biosynthesis, *Ketoconazole* is frequently used as an anti-fungal agent. Its action is readily reversible and is used principally for interim management of Cushing's disease prior to surgery or radiotherapy. *Ketoconazole* preferentially blocks the C17, 20 lyase reaction that is involved in the synthesis of sex steroids.

12. **(D)**. The cardiac effects (**A**), **(B)**, and **(C**) are symptoms of hyperthyroidism, as is **(E)**. Instead of weight gain, a loss in body weight would be expected.

13. **(B)**. Selenium in the form of selenocysteine is required for three enzymes that remove iodide from thyroid hormones. There are no significant areas in which dietary intake of sodium or potassium are problems. Fluorine deficiency is not associated with thyroid hormone metabolism.

14. **(B)**. The symptoms of thyrotoxicosis are largely mediated through the adrenergic nervous system, and (3-adrenoceptor blockers may ameliorate some of the manifestations of the disorder. They have no effect on thyroid hormone levels or on prostaglandins. The effects are directly antagonized by antagonists rather than agonists.

15. **(A)**. The clinical effects are not apparent until the preexisting intrathyroidal stores of thyroid hormone are depleted. This may take several weeks. This class of drugs do inhibit the action of the enzyme TPO and thus inhibit thyroid hormone synthesis. They do not inhibit secretion of preexisting stored thyroid hormone.

16. **(D)**. There is no evidence that affinity for D_3 with its receptor is altered during aging. Aging is associated with *Vitamin D* deficiency for several reasons. It is important for the elderly to receive *Vitamin D* supplementation to prevent osteoporosis and the other problems associated with hypocalcemia. If they have chronic liver or renal conditions, use of one of the specific metabolites should be used, such as *Calcitriol*.

17. **(E)**. There is no good evidence that moderate amounts of alcohol contribute to osteoporosis. All of the other listed conditions can contribute to osteoporosis. Antiseizure medications interfere with activation of *Vitamin D*; glucocorticoids stimulate bone resorption of calcium; renal loss of calcium can result in secondary hyperparathyroidism; and organ transplantation is associated with osteoporosis because of the glucocorticoids and other immunosuppressive medications used. Individuals chronically taking these medications should take a bisphosphonate for prophylaxis. In patients prone to form kidney stones, a low dose of a thiazide diuretic will often block the renal loss of calcium and prevent osteoporosis and further stone formation.

18. **(A)**. *Metformin* causes lactic acidosis in patients with renal failure and severe congestive heart failure. It does not increase the risk of ketoacidosis and has shown a reduction in cardiovascular comorbidities in a large study. It is contraindicated in patients with severe liver disease but does not cause hepatic necrosis. When used as monotherapy, *Metformin* rarely causes hypoglycemia.

19. **(D)**. One of the most important therapeutic objectives is to maintain normal glucose levels without producing frequent hypoglycemia. The main class of hypoglycemic drugs that have a propensity to cause hypoglycemia are the sulfonylureas, of which glyburide is one. This is not a problem with the other choices.

20. **(B)**. *Estrogen* therapy is contraindicated in the presence of breast cancer. Normal breast growth is stimulated by estrogens, and estrogen administration is therefore contraindicated. Hormonal therapy is normally reserved for patients with advanced metastases. Surgery and local irradiation are the preferred therapy for early breast cancer. *Progestin* treatment and *Tamoxifen* therapy are both accepted forms of therapy. Both are more effective in treatment of cancers with high-affinity receptors for estrogen, progesterone, or both.

21. **(B)**. RU 486 acts as a competitive progesterone antagonist and blocks progesterone binding at its receptors. It has no activity at estrogenic receptors.

22. **(A)**. In the Leydig cell the rate-limiting step in testosterone synthesis is the enzymatic cleavage of side chains from cholesterol to form pregnenolone.

23. **(D)**. Skeletal muscle cells use the androgen receptor to bind testosterone that promotes the anabolic effect of this hormone.

24. **(B)**. Finasteride is a 5a-reductase inhibitor, which essentially makes dihydrotestosterone unavailable to the prostate but does not reduce serum testosterone levels. The decreased prostatic levels of dihydrotestosterone frequently result in a size regression of the prostate, while the relatively normal testosterone levels minimize a depressed libido. *Flutamide* and *Spironolactone* exhibit antiandrogen effects by competing for the androgen receptor; *Ketoconazole* inhibits testosterone synthesis; and *Stanozolol* is an oral anabolic androgen preparation.

25. **(B)**. Supplement with *Vitamin A*. *Vitamin A* deficiency symptoms include night blindness that can lead to corneal ulceration. This deficiency can occur in patients with impaired liver storage or fat malabsorption. Dairy products, such as milk, are a good source of *Vitamin A*. (β-*Carotene*, a *vitamin A* precursor, is found in pigmented vegetables, such as carrots. When a deficiency is diagnosed, it is appropriate to treat the patient with a supplement rather than to rely on increased consumption of *Vitamin A*-rich foods. A patient with pancreatic disease and malabsorption syndrome will need parenteral supplementation.

26. **(B)**. Pregnancy increases the need for vitamins and iron in general. *Folic acid* has been shown to decrease the risk of neural tube defects, such as spina bifida. It is important to assess the nutritional status of the patient to determine whether higher levels of *Folic acid* are needed. *Vitamin A* is a teratogen and should not be given in high doses during pregnancy.

27. **(C)**. Early symptoms of *Vitamin C* deficiency, or scurvy, include malaise. Hemorrhages, especially of the gums, may result from capillary fragility.

28. **(C)**. The only effective treatment of pernicious anemia is supplementation of *Vitamin* B_{12}. It is important to determine whether megaloblastic anemia is from a deficiency of folic acid or *Vitamin* B_{12}. Treatment of *Vitamin* B_{12}-deficient anemia with *Folic acid* may result in neurological damage if *Vitamin* B_{12} is not adequately supplemented.

29. **(E)**. *Folic acid* supplements should be given to all pregnant women. In addition, *Phenytoin* use is associated with lowered folate levels.

Lecture 30
DRUGS INFLUENCING THE ERYTHROPOIESIS

Agents influencing the erythropoiesis are divided into **drugs that stimulate the formation of erythrocytes** (red blood cells) and **drugs that inhibit erythropoiesis**. Drugs stimulating erythropoiesis are used for the treatment of anemias. Anemia is a condition in which the number of red blood cells and the amount of hemoglobin in the blood are less than normal. Nowadays hypochromic and hyperchromic, hypo- and aplastic, hemolytic anemias are known.

Hypochromic anemia is characterized by a decrease in the ratio of the weight of hemoglobin to the volume of the erythrocyte. It means that erythrocytes contain less hemoglobin than they could have under optimal conditions. Mostly, hypochromic anemia is accompanied by iron deficiency state that's why it sometimes is named as hypoferric anemia.

Iron forms the nucleus of the heme, which when combined with appropriate globin chains forms hemoglobin. Hemoglobin is a protein whose structure allows for reversible binding of oxygen, providing the critical mechanism for oxygen transport from the lungs to other tissues. Ionic iron is a component of myoglobin and enzymes necessary for energy transfer (e.g. *cytochrome oxidase, xanthine oxidase, and succinic dehydrogenase*), however the vast majority of iron is normally present in hemoglobin. In addition, iron is stored in the form of ferritin and hemosiderin (in the liver, spleen).

Iron deficiency is commonly seen in children during rapid growth periods, in menstruating women, and in pregnant or lactating women. The most common cause of iron deficiency in adults, however, is blood loss. These situations are all associated with increased iron requirements.

Iron is normally available in the diet from a wide variety of foods but is especially abundant in meat protein (Fig. 25). Iron is absorbed only in ionic condition, especially in *ferrous* form (Fe^{2+}). That's why iron absorption is increased in the presence of hydrochloric acid (convert nonionic iron to ionic) and ascorbic acid (reduce ferric iron [Fe^{3+}] to ferrous). Absorption is decreased by the presence of chelators or complexing agents in the intestinal lumen. Gastric resection decreases iron absorption by decreasing hydrochloric acid production. Iron is transported across the intestinal mucosal cell by active transport. The absorbed iron can combine with the protein apoferritin to yield *ferritin* and stored in mucosal cells which are exfoliated and excreted in the feces or can be transported to the plasma where it is bound to *transferrin* (globulin). Thus, iron is transported to the developing erythroid cells in bone marrow.

Iron can be stored in two forms: *Ferritin* and *Hemosiderin*. Both *Ferritin* and *Hemosiderin* are stored in macrophages in the liver, spleen, and bone marrow. Most of the iron liberated by destruction of hemoglobin is conserved and reused by the body. Excretion of iron occurs primarily as desquamation of cells of GI mucosa.

The only clinical indication for the use of iron preparations is the treatment or prevention of iron deficiency anemia. The treatment of iron deficiency anemia consists of administration of oral or parenteral iron preparations. *Ferrous lactate*, and *Ferrous sulfate* are commercially available for oral administration.

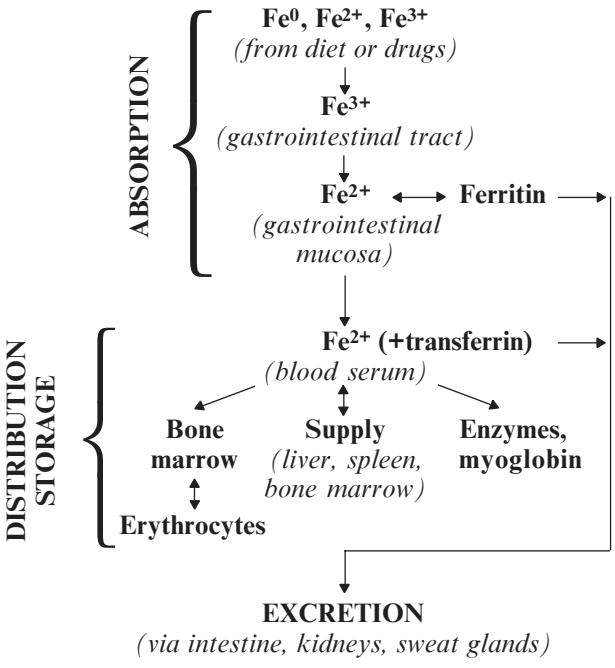


Fig. 25. Absorption, distribution, and excretion of iron

Also combine iron preparations such as *Ferroplex®* (*Ferrous sulfate* plus *Ascorbic acid*), *Ferramidum* (complex compound of *Iron* with *Nicotinamide*) can be used. Oral iron preparations should be taken between meals for maximum absorption but may be taken with or after meals, if necessary, to minimize adverse GI effects.

Adverse effects of oral iron therapy include teeth darkening, epigastric discomfort, dark stools, and constipation. These effects are usually dose-related and can often be overcome by lowering the daily dose of iron. It is postulated that iron interfere with hydrogen sulfide (H_2S) that leads to the iron sulfide (FeS) production. The last one can cause the teeth darkening. On the other hand, hydrogen sulfide is known as stimulate of bowel motility, that's why decreasing of free hydrogen sulfide volume associated with constipation.

Parenteral therapy should be reserved for patients that unable to tolerate or absorb oral iron and patients with extensive chronic blood loss. Parenteral iron agents include *Ferbitol*, *Fercoven*, and *Ferum-Lek*. *Ferbitol* is injected intramuscularly, *Fercoven* is for intravenous injection, and *Ferum-Lek* can be used by both routes. Chest tightness, shock, hypotension, tachycardia, flushing, and arrhythmias have occurred in patients receiving parenteral iron preparations.

Large amounts of oral iron cause necrotizing gastroenteritis, with vomiting, abdominal pain, and bloody diarrhea followed by shock and dyspnea. Urgent treatment of overdosing includes stomach lavage with sodium bicarbonate solutions to form insoluble iron salts. *Deferoxamine* (iron chelating compound) should be given by injection to bind iron. Appropriate supportive therapy for shock and dyspnea (heart glycosides, hypertensive agents, and analeptics) must also be provided.

Some agents of cobalt are indicated for the treatment of the hypochromic anemia. One of them is *Coamide*. It is a complex compound of cobalt with nicotinamide. *Coamide* stimulates erythropoiesis and promotes assimilating of iron. It is administered subcutaneously. In addition, copper-containing agent *"Hemostimulin"* (*Copper sulfate*, *Ferrous sulfate*, and dry dietary blood) is indicated for the treatment of hypochromic anemia as well as *Nicotinic acid*.

Erythropoietin is a glucoprotein that stimulates erythroid proliferation and differentiation. It is produced by the kidney in response to tissue hypoxia. When anemia occurs, more erythropoietin is produced by the kidney. *Recombinant human erythropoietin (Epoetin alpha)* is produced in a mammalian cell expression system using recombinant DNA technology. *Erythropoietin* is indicated in the treatment of anemia associated with renal failure, chronic inflammation, AIDS, and cancer.

Hyperchromic anemia is characterized by an increase in the ratio of the weight of hemoglobin to the volume of the erythrocyte. It means that the erythrocytes contain more hemoglobin than normal. Usually hyperchromic anemia is associated with *Vitamin* B_{12} and/or folic acid deficiency. It leads to impaired DNA synthesis, inhibition of normal mitosis, and abnormal maturation of the cells. These changes are most apparent in tissues where cells undergo rapid cell division, such as the bone marrow and the gastrointestinal epithelium. It is characterized by diminished cell division in the face of continued RNA and protein synthesis. This leads to production of large (macrocytic) erythrocytes that have a high RNA:DNA ratio and are defective in the sense that they are highly susceptible to destruction. Also, anemias caused by *Vitamin* B_{12} and *Folic acid* deficiency is called *megaloblastic anemia*.

Vitamin B_{12} is a group of cobalt-containing substances *(Cobalamins)*, having biologic activity in humans. *Vitamin* B_{12} is synthesized by microorganisms and it is present in many foods of animal origin, particularly liver, kidney, fish, and meat; plants contain minimal amounts of the vitamin. *Cyanocobalamin* is a *Cobalamin* that found in food. In humans, an exogenous source of *Vitamin* B_{12} is required for nucleoprotein and myelin synthesis, cell reproduction, normal growth, and the maintenance of normal erythropoiesis. Cells characterized by rapid division (e.g. epithelial cells, bone marrow, and myeloid cells) appear to have the greatest requirement for *Vitamin* B_{12}. *Coenzyme* B_{12} is essential for synthesis of *Methionine. Vitamin* B_{12} also can be involved in maintaining sulfhydryl (SH) groups in the reduced form required by many SH-activated enzyme systems. Through these reactions, *Vitamin* B_{12} is associated with fat and carbohydrate metabolism and protein synthesis. *Vitamin* B_{12} deficiency results in megaloblastic (pernicious) anemia of Addison-Biermer, GI lesions (glossitis) and neurological damage (paresthesia, disorder of gait) that begins with an inability to produce myelin.

Vitamin B_{12} is absorbed from the small intestine following oral administration. In the stomach, free *Vitamin* B_{12} (extrinsic Castle's factor) is attached to intrinsic factor (IF or intrinsic Castle's factor); IF, a glycoprotein secreted by the gastric mucosa, is necessary for active absorption of the vitamin from the GI tract. Absorption of *Cyanocobalamin* following oral administration is decreased by structural or functional damage to the stomach or ileum. In the intestinal mucosal cell, *Vitamin* B_{12} is released from the *Vitamin* B_{12}*-If* complex and becomes rapidly bound to plasma proteins. *Vitamin* B_{12} is distributed into the liver, bone marrow, and other tissues.

Cyanocobalamin is usually considered the *Vitamin* B_{12} preparation of choice. It is used in the treatment of pernicious anemia and in patients with malabsorption of *Vitamin* B_{12}, such as those with partial or total gastrectomy, regional enteritis, and ileal resection. The drug has been used for the management of hepatitis, neuralgia and neuropathies, and multiple sclerosis. *Vitamin* B_{12} is usually nontoxic even in large doses; however, mild diarrhea, peripheral thrombosis, and itching have been reported.

Folic acid (*Vitamin* B_c, *Pteroylglutamic* acid) is a compound composed of a pteridine heterocycle, *p-Aminobenzoic acid*, and *Glutamic acid*. It is present in a wide variety of foods, particularly liver, kidneys, yeast, and leafy, green vegetables. Also it has been synthesized in bowel by microflora. In man, an exogenous source of *Folate* is required for nucleoprotein synthesis and the maintenance of normal erythropoiesis. *Folic acid* is the precursor of active *Tetrahydrofolic acid*, which is involved in the biosynthesis of purines and thymidylates of nucleic acids. The *Folate* cofactors are inter-convertible by various enzymatic reactions and serve the important biochemical function of donating

one-carbon units at various levels of oxidation. Impairment of *Thymidylate* synthesis in patients with *Folic acid* deficiency is thought to account for the defective DNA synthesis that leads to megaloblast formation and megaloblastic and macrocytic anemias.

Folic acid is absorbed rapidly from the small intestine following oral administration. *Tetrahydrofolic acid* and its derivatives are distributed into all body tissues; the liver contains about one-half of total body folate stores. *Folic acid* is largely metabolized in the liver and is excreted by kidneys.

Folic acid is used for the treatment of megaloblastic and macrocytic anemias, resulting from *Folate* deficiency, megaloblastic anemias of pregnancy and infancy, tropical sprue, megaloblastic anemia associated with liver disease and alcoholism. It is used orally. *Folic acid* is relatively nontoxic. Allergic reactions to it have been reported rarely.

Drugs that **inhibit erythropoiesis** are used for the treatment of polycythemia (erythremia). Bone marrow hyperplasia and an increase of erythrocytes in blood characterize this disease. *Radioactive phosphorus-32 isotope* (^{32}P), which is a β-emitter, is used for polycythemia treatment. Also, it causes leukopenia and thrombocytopenia.

Lecture 31
BLOOD SUBSTITUTES

DRUGS FOR PARENTERAL NUTRITIONAL THERAPY

This group includes *Hydrolysine, Aminocrovinum,* and *Polyamine*. These drugs contain amino acids and are indicated for nutrition during therapy of cachexia, unconscious state, starvation, pre- and postoperative state. They should be used only when the gut cannot be used (operation at gullet or stomach). *Hydrolysin* is obtained by hydrolysis of serum proteins of cattle; *Aminocrovinum* is the hydrolysate of human blood proteins; and *Polyamine* is the complex of 13 amino acids. *Lipofundinum (Intralipid)* is fat emulsion that produced from safflower oil. It contains emulsified fat particles, similar to naturally occurring chylomicrons. Intravenous fat emulsion provides the patient requiring parenteral nutrition with a source of calories and the essential fatty acids (polyunsaturated).

PLASMA SUBSTITUTES AND DEINTOXICATION SOLUTION

Dextran 60 (Polyglucinum) and *Dextran 40 (Reopolyglucinum)* are a glucose polymers (dextrans) with average molecular weights of approximately 60,000 and 40,000 correspondently. The principal effect of dextrans following intravenous administration is plasma volume expansion, resulting from the drugs colloidal osmotic effect in drawing fluid from the interstitial to the intravascular spaces. Plasma volume expansion is accompanied by an increase of cardiac and urinary output, of blood pressure (hemodynamic action). *Polyglucinum* possesses more strong hemodynamic effect than *Reopolyglucin*. However, *Reopolyglucinum* improves microcirculation by diminished erythrocyte aggregation and blood viscosity. About 70% of a dose of *Reopolyglucin* are excreted unchanged in urine within 24 hours after administration. *Polyglucinum* is not excreted by the kidneys but is slowly degraded to glucose.

Dextrans, especially *Polyglucinum*, are used for fluid replacement and for plasma volume expansion in the treatment of shock resulting from burns, surgery, hemorrhage, or other trauma in which a circulating volume deficit is present. *Reopolyglucin* is also used for prophylaxis and treatment of thromboembolic complication, during extracorporeal circulation.

Adverse effects of dextrans include allergic reactions such as urticaria, hypotension, and sometimes anaphylactoid reactions. Care must be taken in administering dextrans to patients with impaired renal function, pulmonary edema, or congestive heart failure.

Human's albumin is a solution of serum albumin prepared from blood obtained from healthy human donors. Serum albumin is an important factor in the regulation of plasma volume through its contribution to the oncotic pressure of plasma. Intravenous administration of albumin human causes a shift of fluid from the interstitial spaces into the circulation, reducing hemoconcentration and blood viscosity, and raising of blood pressure. Albumin contains amino acids and provides modest nutritive effect. Albumin functions as a carrier of intermediate metabolites (bilirubin), trace metals, and some drugs, thus affecting their transport, and inactivation. *Human's albumin* solutions are used in the treatment of shock resulting from burns, surgery, and hemorrhage; of hypoproteinemia (hepatic cirrhosis, postoperative patients); of cerebral edema. Adverse reactions, which may be caused by allergy or protein overload, include chills, fever, vomiting.

Gelatinolum is an agent of split food gelatin. It is used as a hemostat, plasma substitute, and protein food adjunct in malnutrition.

Polyvinylpyrrolidone (Povidone) **derivative** solutions are *Neohaemodesum* and *Enterodesum*. *Polyvinylpyrrolidone* is a synthetic polymer. All above-mentioned derivatives has low molecular weight (8,000 and 12,000). Also, these agents contain ions of sodium, potassium, calcium, magnesium, and chlorine. *Polyvinylpyrrolidone* binds with toxins in blood and eliminate them quickly from organism. In addition, these preparations improve the blood circulation in kidneys, enhance the diuresis, and can act as a plasma extender. *Neohaemodesum* is injected intravenously for deintoxication that caused by gastrointestinal diseases (e.g. the dysentery and salmonellosis), acute liver and kidney insufficiency, burns, etc. Quick infusion of *Neohaemodesum* can diminish the blood pressure. *Enterodesum* has the same indications as *Neohaemodesum* but it used orally.

Glucose (Dextrose) is a monosaccharide. It increases blood glucose concentrations, provides calories, induces diuresis depending on the volume administered. 5% *Glucose* solution is isotonic solution and 40% *Glucose* solution is hypertonic. *Glucose* injections are used for the treatment of hypoglycemia, and as

source of calories and water for hydration/deintoxication during infection diseases, liver disorders, heart insufficient, shock, and collapse. Hypertonic glucose injections are used to provide adequate calories in a minimal volume of water. Hyperglycemia may occur as a result of the rate of administration or metabolic insufficiency.

SALT SOLUTIONS

Solution of *Sodium chloride* provides electrolyte supplementation. *Sodium* is the major cation of extracellular fluid and functions principally in the control of water distribution, fluid and electrolyte balance, and osmotic pressure of body fluids. Sodium is also associated with chloride and bicarbonate in the regulation of acid-base balance. *Chloride*, the major extracellular anion, closely follows the physiologic disposition of sodium. *0.9% solution of Sodium chloride* is an isotonic solution because it has approximately the same osmotic pressure as body fluids. *3%* and *5% Sodium chloride* are the hypertonic solutions. *Isotonic Sodium chloride* is used for extracellular fluid replacement during shock or collapse; irrigation of wounds, eyes, noise, and mucosa; deintoxication during poisoning; and dilution of drugs before their using. Hypertonic *Sodium chloride* is used in the management of purulent wounds (it promotes outflow of pus); uterine and gastrointestinal bleeding; as weak antimicrobial agent. Excessive administration of *Sodium chloride* may result in hypernatremia and lose of bicarbonate with an acidifying effect.

Ringer's solution includes *Sodium chloride, Sodium bicarbonate, Potassium chloride, Calcium chloride* and water for injection. It has even more "physiologic" content than 0,9% solution of *Sodium chloride*. *Ringer's solution* has the same indication as *Sodium chloride*. Such solutions as *Quartasol®, Trisol®, Acesol®,* etc. contain sodium chloride and potassium chloride; *Quartasol®* and *Trisol®* include sodium bicarbonate. These solutions decrease hypovolemia and blood viscosity, hinder the development of acidosis, promote microcirculation, increase diuresis, and cause deintoxication. Thus, they are used for the treatment of intoxication and hypohydremia during different diseases (e.g. cholera, dysentery).

PREPARATIONS OF CALCIUM AND POTASSIUM

Calcium is essential to transmission of nerve impulses, contraction of muscles, bone formation, and blood coagulation. Calcium also plays regulatory roles in the release of hormones, in the maintenance of the capillary permeability. Calcium deficiency is characterized by reduced bone mass (osteoporosis) and tetany (twitches, cramps). Calcium is absorbed from the GI tract. *Vitamin D* and parathyroid hormone increase the capability of the absorptive mechanisms. More than 99% of total body calcium is found in bone and teeth.

Calcium salts are used for the treatment or prevention of calcium depletion. Also, calcium therapy is used for the treatment of heart arrest, allergic reactions, bleeding, hyperpermeability of vessels (vasculitis), skin diseases (psoriasis, itching), hepatitis. For oral and intravenous administration, the *Gluconate, Lactate,* and *Chloride* salts of calcium are available.

Calcium salts, especially chloride, by any route of administration can produce irritation. They may cause local necrosis if they will be injected subcutaneous. Rapid injection may cause vasodilation, decreased blood pressure, and arrhythmias.

Potassium is the major cation of intracellular fluid and is essential for maintenance of isotonicity and electrodynamic characteristics of the cell. Potassium is essential to transmission of nerve impulses, contraction of muscles, gastric secretion, and renal function.

Potassium supplements are used for treatment of arrhythmias, potassium depletion. Conditions, which may result in potassium deficiency, include vomiting, diarrhea, and administration of certain drugs including diuretics, corticosteroids, and cardiac glycosides. In addition, potassium chloride is a component of several multiple electrolyte intravenous infusion fluids.

For oral and intravenous administration, *"Panangin" (Potassium asparaginate)* and *Potassium chloride* are available. Hyperkalemia is the most common hazard of potassium therapy. It is accompanied by paresthesia, arrhythmias, and vomiting.

ACIDIFYING AND ALKALINIZING AGENTS

Ammonium chloride is an acid-forming salt that result from dissociation of the salt to an ammonium cation and a chloride anion. The chloride anion combines with fixed bases in the extracellular fluid, thereby reducing the alkaline reserve of the body and acidosis results. It increases sodium and water excretion that leads to diuretic effect.

Ammonium chloride is used orally. Also it increases bronchial secretion and facilitates its expulsion. *Ammonium chloride* is used for the treatment of metabolic alkalosis, edematous conditions, and bronchitis. It may cause metabolic acidosis and irritation of gastric mucosa.

Hydrochloric acid (HCl) is the acid of gastric juice. It possesses strong irritant potency. It is used internally as *diluted Hydrochloric acid* for hypo- or achlorhydria.

Sodium bicarbonate is an alkalinizing agent, which dissociates to provide bicarbonate ion. *Sodium bicarbonate* is used in the treatment of metabolic acidosis, certain intoxications (e.g. *Phenobarbital*, and *Salicylates*), for increasing of the solubility of certain weak acids (e.g. *Sulfanilamides*, *Uric acid*), for bettering of expulsion of the bronchial secretion during bronchial asthma. For the use of *Sodium bicarbonate* as an antacid, see "Antacids".

Available forms:

Cyanocobalamin — in ampoules 0.003%; 0.01%; 0.02% or 0.05% solution 1 ml each

Folic acid — powder; in tablets 0.001 each

Ferri lactate — in capsules 1.0 each

Haemostimulinum — in patented tablets

Ferrum-Lek — in ampoules solution 2 ml (for intramuscular injection) or 5 ml (for intravenous injection) each

Coamidum — in ampoules 1% solution 1 ml each
Aminocrovinum — in bottles 250 or 500 ml each
Polyglucinum — in bottles 100; 200 or 400 ml
Reopolyglucinum — in bottles 100; 200 or 400 ml
Neohaemodesum — in bottles 100; 200 or 400 ml
Sodium chloride — powder; in tablets 0.9 each; in ampoules 0.9% solution 5; 10 or 20 ml each; in bottles 0.9% solution 400 ml each
Quartasol — in bottles solution 100; 200 or 400 ml each
Sodium hydrocarbonate — powder; in ampoules 4% solution 20 ml each; in suppository that contain 0.3; 0.5 or 0.7 of *Sodium hydrocarbonate* each
Glucose — powder; in tablets 0.5 or 1.0 each; in ampoules 5%; 10%; 25% or 40% solution 10; 20; 25 or 50 ml each; in bottles 5%; 10%; 20% or 40% solution 200 or 400 ml each
Calci gluconate — powder; in tablets 0.5 each; in ampoules 10% solution 10 ml each
Potassium chloride — powder; in ampoules 4% solution 20 ml each

Lecture 32
DRUGS USED IN DISORDERS OF COAGULATION

Hemostasis is the spontaneous arrest of bleeding from a damaged blood vessel. The immediate hemostatic response of a damaged vessel is vasospasm. Within seconds, platelets stick to the exposed collagen of the damaged endothelium (platelet adhesion) and to each other (platelet aggregation). This localized stasis triggers blood coagulation that is characterized by the transformation of soluble fibrinogen into insoluble fibrin. Blood coagulation and thrombus formation must be confined to the smallest possible area to achieve local hemostasis in response to bleeding from trauma or surgery without impaired blood flow. Fibrinolysis regulates and delimits hemostasis.

Bleeding and thrombosis are altered states of hemostasis. Impaired hemostasis results in spontaneous bleeding; stimulated hemostasis results in thrombus formation. The drugs used to arrest bleeding and to inhibit thrombosis are the subjects of this lecture.

Drugs that used for the prevention or treatment of thrombosis are the next:

1. Anticoagulant drugs:

a) anticoagulants of direct action *(Heparin, Enoxaparin, Sodium citrate, Hirudin);*

b) anticoagulants of indirect action or oral anticoagulants *(Neodicumarin, Syncumar, Phenylin).*

2. Antiaggregate drugs *(Acetylsalicylic acid, Ticlopidine, and Dipyridamole).*

3. Fibrinolytic drugs *(Streptokinase, Streptodecase, Urokinase, and Alteplase).*

Effects of agents that influence coagulation and fibrinolysis are illustrated in Fig. 26.

Heparin is an anionic, sulfated glycosaminoglycan present in mast cells. Its average molecular weight is about 12,000. *Heparin* is strongly acidic and reacts with certain basic compounds resulting in a loss of pharmacologic activity. Commercial *Heparin* is prepared from either porcine intestinal mucosa or bovine lung tissue. *Heparin* potency is expressed in IU.

Actions. *Heparin* acts as a catalyst to markedly accelerate the rate at which *Antithrombin* III (heparin cofactor) neutralizes *Thrombin* and activated coagulation factor IX, X, XI, XII. In low doses *Heparin* prevents the conversion of *Prothrombin* to thrombin and in higher doses it inhibits the conversion of fibrinogen to fibrin. Patients with familial antithrombin III deficiency may appear to be resistant to the effects of *Heparin*, since adequate levels of *Antithrombin* III are necessary for the drug's anticoagulant effect.

Heparin therapy produces prolongation of the activated coagulation time, whole blood clotting time, etc. *Heparin* clears lipemic plasma by stimulating of

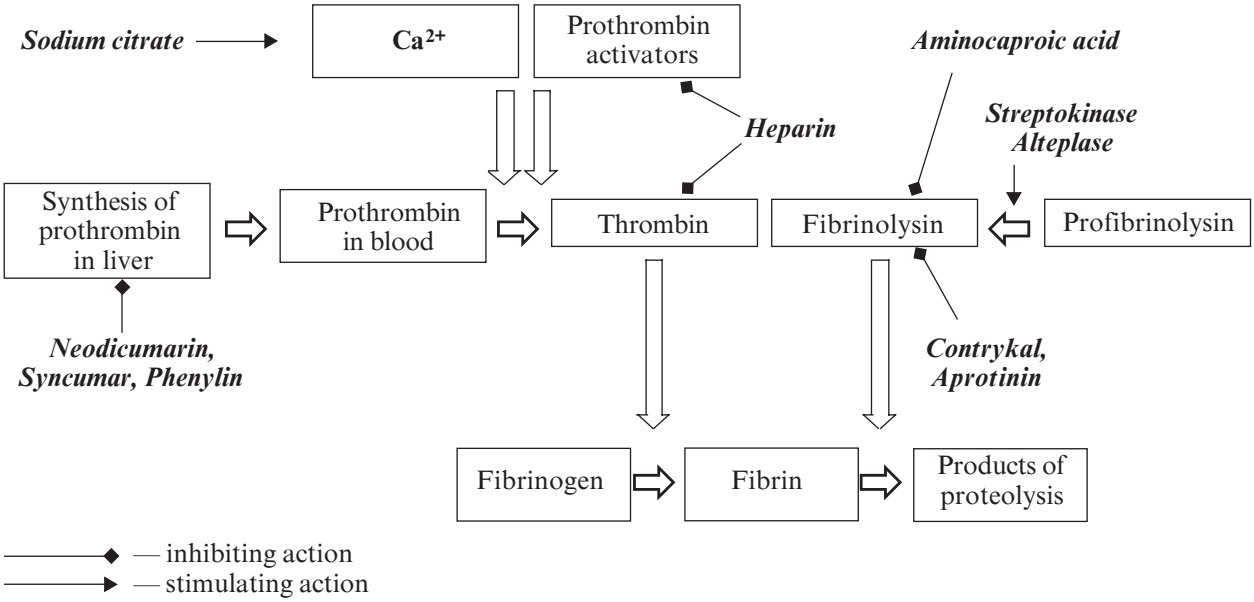


Fig. 26. Direction of effects of agents that influence coagulation and fibrinolysis

lipoprotein lipase, which hydrolyze triglycerides to free fatty acids and glycerol. *Heparin* in high doses has been reported to decrease on platelet aggregation.

Heparin is not absorbed from the GI tract and must be administered parenterally. The onset of anticoagulant activity is immediate following direct intravenous injection and occurs within 30–60 minutes following subcutaneous. The duration of action is about 2–6 hours. The drug is metabolized in vessels endothelium and in the liver.

Indications. *Heparin* is used for prophylaxis and treatment of venous thrombosis, pulmonary embolism, chronic consumptive coagulopathies (disseminated intravascular coagulation). Fixed low-dose subcutaneous *Heparin* therapy is used for prevention of postoperative deep-vein thrombosis and pulmonary embolism in patients undergoing major abdominal or thoracic surgery who are at a risk of thromboembolic disease. *Heparin* is the anticoagulant of choice when an immediate effect is required. An oral anticoagulant (usually a *Coumarin* derivative) is generally used for follow-up anticoagulant therapy after the *Heparin* therapy has been established and when long-term anticoagulant therapy is indicated. In first case therapy with the two drugs should be overlapped for a short period of time.

Adverse effects. Hemorrhage, the major adverse effect of heparin therapy, is an extension of the pharmacologic action of the drug and may range from minor local ecchymosis to major hemorrhagic complications. Nosebleed, hematuria, or tarry stools may be noted as the first sign of bleeding or overdosage; easy bruising or petechiae may precede frank bleeding. That's why the coagulation time and whole blood clotting time should be determined during *Heparin* therapy in all patients. Discontinuance of *Heparin* will usually correct minor bleeding or overdosage within a few hours. If severe hemorrhage or overdosage occurs, protamine sulfate should be administered immediately. In adequate dosage, protamine sulfate neutralizes the anticoagulant effect of *Heparin*. Deep subcutaneous injection of *Heparin* may rarely cause local irritation, hematoma, or cutaneous necrosis.

Enoxaparin is a depolymerized *Heparin.* The average molecular weight of *Enoxaparin* is approximately one-third that of regular *Heparin*; therefore, *Enoxaparin* is referred to as a *low molecular weight Heparin*. *Enoxaparin* has less effect on *Thrombin* than does unfractionated *Heparin*. However, *Enoxaparin* has more antiaggregating properties. Compared with unfractionated *Heparin*, *Enoxaparin* has greater bioavailability after subcutaneous administration and a longer half-life, allowing less frequent administration (1–2 times per day). *Enoxaparin* is used for the prevention of postoperative deep-vein thrombosis. The usual precautions and contraindications associated with heparin anticoagulation therapy should be followed in patients for whom *Enoxaparin* therapy is considered.

Sodium citrate binds calcium ions in blood that prevents blood clotting. It is used as stabilizer of blood during its conserving. *Hirudin* is a powerful and specific *Thrombin* inhibitor from the leech, which is now being prepared by recombinant DNA technology.

ORAL ANTICOAGULANTS

Coumarin anticoagulants

Coumarin anticoagulants (Neodicumarin, Syncumar) are the derivatives of 4-oxycoumarin. Indandione anticoagulant *(Phenylin)* is a derivative of indandione. Coumarin and indandione derivatives are indirect-acting anticoagulants.

Actions. *Coumarin* and *Indandione* derivatives alter the synthesis of blood coagulation factors II *(Prothrombin),* VII *(proconvertin),* IX (Christmas factor), and X (Stuart-Prower factor) in the liver by interfering with the action of *Vitamin K*, which is necessary for the gamma-carboxylation of several glutamic acid residues in the precursor proteins of these coagulation factors. In adequate dosage, *Phytonadione (Vitamin* K_1*)* reverses the effect of coumarin and indandione derivatives on the hepatic synthesis of *Vitamin K*-dependent coagulation factors. In contrast to *Heparin*, coumarin and indandione derivatives have no anticoagulant effect in vitro.

Because *Coumarin* and *Indandione* derivatives do not alter catabolism of blood coagulation factors, depletion of circulating functional *Vitamin K*-dependent coagulation factors must occur before effects of the drugs become apparent. An anticoagulant effect generally occurs within 24 hours following administration of *Neodicumarin*, but peak anticoagulant and antithrombogenic effects may be delayed for 72–96 hours. Similarly, there is a period of latency following discontinuance of the drugs until blood concentrations of functional *Vitamin K*-dependent coagulation factors return to pretreatment levels. *Coumarin*- or *indandione*-derivative therapy inhibits thrombus formation and may prevent extension of existing thrombi. The drugs have no direct effect on established thrombi.

Neodicumarin, *Syncumar*, and *Phenylin* are well absorbed from the GI tract. *Coumarin* and *Indandione* derivatives are usually detectable in plasma within 1 hour following oral administration, and peak plasma concentrations of the drugs are usually attained within 1–12 hours. They are 97% or more bound to plasma proteins, primarily albumin. *Coumarin* and *Indandione* derivatives are hydroxylated by hepatic microsomal enzymes to inactive metabolites. In general, *Coumarin* and *Indandione* derivatives are excreted in bile as inactive metabolites, then they are reabsorbed, and excreted in urine.

Indications. The most widely accepted indications for anticoagulant therapy include the treatment of venous thrombosis and pulmonary embolism and prevention of these conditions in high-risk patients. A coumarin derivative is generally used for follow-up anticoagulant therapy after the effects of full-dose heparin therapy have been established and when long-term anticoagulant therapy is indicated.

The efficiency of indirect-acting anticoagulants is measured by prothrombin ration: it must be not less than 40–50% (normal is 80–100%).

Adverse effects. Hemorrhage is the most common adverse effect of indirect-acting anticoagulants. If moderate or severe hemorrhage occurs or if the prothrombin time is excessively prolonged, the drug should be discontinued immediately and *Phytonadi-*

one administered. *Coumarin* and *Indandione* derivatives should be used with caution in any condition where added risk of hemorrhage is present. Concurrent administration of numerous drugs has been reported to affect patient response to indirect-acting anticoagulants. Nonsteroidal anti-inflammatory agents *(Aspirin, Butadion (Phenylbutazone))* can inhibit platelet aggregation and displace of albumin-bound indirect-acting anticoagulants, increasing their free fraction. These changes can cause GI bleeding and peptic ulceration. *Barbiturates* and *Rifampin* cause a marked decrease of the anticoagulant effect by induction of the hepatic enzymes that transform *Neodicumarin*. *Cumarin* derivatives potentiate the action of the hypoglycemic agents and *Diphenin (Phenytoin)*, because *Coumarins* inhibit hepatic metabolism of these drugs.

FIBRINOLYTIC AGENTS

Fibrinolytic drugs rapidly lyse thrombi by catalyzing the formation of the serine protease *Plasmin (Fibrinolysin)* from its precursor *Zymogen*, *Plasminogen (Profibrinolysin)*. These drugs create a generalized lytic state when administered intravenously. Thus, both protective hemostatic thrombi and target thromboemboli are broken down.

Actions. *Streptokinase* is a nonenzymatic protein produced by group C β-hemolytic streptococci. The activity of streptokinase is expressed in IU. *Streptokinase* promotes thrombolysis. *Streptokinase* converts plasminogen into the proteolytic enzyme plasmin. Plasmin degrades fibrin, fibrinogen, and other plasma procoagulant proteins. Plasmin is inactivated by circulating inhibitors, including α_2-antiplasmin. Plasmin generated in the circulation is bound to antiplasmin and is released at the thrombus site resulting in external lysis. The effects of *Streptokinase* on coagulation usually disappear within a few hours but may persist for up to 12 hours after discontinuance of intravenous infusion. Laboratory control during fibrinolytic therapy includes assure of thrombin time and fibrinogen amount. During the first few hours of streptokinase therapy, the drug may rapidly activate plasminogen and cause hyperplasminemia that may lead to coagulation defects.

Streptokinase has been shown to decrease the viscosity of blood and plasma, and to decrease the erythrocyte and platelet aggregation tendency, thus increasing blood flow and perfusion of collateral blood vessels.

Following intravenous infusion, *Streptokinase* is rapidly cleared from the circulation. The serum half-life is about 80 minutes.

Indications. *Streptokinase* is used as a thrombolytic agent in selected cases of myocardial infarction, pulmonary embolism, acute vein or arterial thrombosis. The drug is generally most effective in lysing recently formed thrombi. For example, *Streptokinase* therapy should be initiated as soon as possible after myocardial infarction, preferably within 3–6 hours, since potential clinical benefit diminishes as the time period to initiation of therapy increases. *Streptokinase* therapy should be initiated no later than 3 days, after the onset of the thromboembolic episode.

Adverse effects. The most frequent and severe adverse effects of *Streptokinase* therapy are hemorrhage, fever, and allergy. Severe spontaneous bleeding has occurred during *Streptokinase* therapy. If serious spontaneous bleeding occurs, *Streptokinase* therapy should be terminated immediately. Plasma volume expanders and aminocaproic acid may be used. Streptokinase is strongly antigenic; repeated administration elicits antibodies that diminish the effect of the drug and may cause allergic reactions, including anaphylaxis.

Streptodecase — is an agent of *Streptokinase* that binds with polysaccharide water-soluble molecule. It ensures prolong releasing of *Streptokinase.* One infusion of *Streptodecase* provides fibrinolytic effect during subsequent 3 days.

Urokinase is an enzyme produced by the kidneys and excreted in urine. Commercially available *Urokinase* is isolated from human kidney tissue cultures. The activity of *Urokinase* is expressed in IU. *Urokinase* has the same mechanism action as *Streptokinase*. The fibrinolytic effect of *Urokinase* usually disappears within a few hours but increased thrombin time, decreased plasma levels of fibrinogen and plasminogen may persist for up to 12–24 hours following discontinuance of the infusion.

Agent reportedly is not absorbed from the GI tract. Following intravenous infusion, the drug is rapidly cleared from the circulation. *Urokinase* is estimated to have a plasma half-life of 10–20 minutes. *Urokinase* has the similar indications with *Streptokinase*. The most frequent and severe adverse effect of *Urokinase* therapy is hemorrhage. In contrast to *Streptokinase*, *Urokinase* is reportedly nonantigenic.

Alteplase, a biosynthetic (recombinant DNA origin) form of the enzyme human *tissue-type plasminogen activator* (T-PA), is a thrombolytic agent. Endogenous human t-PA is a serine protease secreted principally by vascular endothelial cells. It may be activated by several endogenous proteases, including *Plasmin*, tissue *Kallikrein*, and *Trypsin*.

Alteplase is a thrombolytic agent. T-PA as well as *Streptokinase* and *Urokinase* promote conversion of *Plasminogen* into form of *Plasmin*. During physiologic fibrinolysis, the activity of circulating *Plasmin* is inhibited rapidly (half-life approximately 100 msec) by α_2-*antiplasmin.* The fibrinolytic activity of *Plasmin* is maintained within the thrombus because the active sites of *Plasminogen* (and thus plasmin) at which fibrin binds are the same sites at which α_2-antiplasmin binds. Fibrin-bound plasmin within the thrombus, therefore, is relatively protected from inactivation. Thrombolytic agents such as *Streptokinase* and *Urokinase* activate both fibrin-bound and circulating *Plasminogen* indiscriminately; systemic activation of *Plasminogen* results in the release of large amounts of *Plasmin* into the circulation that leads to degradation of plasma procoagulant proteins. Predominantly, *Alteplase* activates fibrin-bound plasminogen.

Alteplase is not absorbed after oral administration and must be administered parenterally. It has the resemble uses to *Streptokinase*. The most frequent and severe adverse effect of *Alteplase* therapy is hemorrhage.

ANTIAGGREGATE AGENTS

Platelet function is regulated by two categories of substances. The first group consists of agents that induce the platelet aggregation, e.g. *Thromboxane A_2*, *Collagen*, *Thrombin*, *ADP*, *Calcium ions*, *Prostaglandin E_2*, *Serotonin*, and *Catecholamines*. The second category contains agents that inhibit platelet aggregation, e.g. *Prostacyclin I_2*, *AMP*, *Adenosine*, *Methylxanthines*, and *Heparin*. The prostaglandin *Thromboxane A_2* is an arachidonate product that causes platelets to aggregate. It is synthesized in platelets. *Prostacyclin I_2* is an arachidonate product also, but it inhibits aggregation and adhesion of platelets. *Prostacyclin I_2* is formed in endothelium of vessels wall.

Acetylsalicylic acid (Aspirin) inhibits the synthesis both of *Thromboxane A_2* and *Prostacyclin I_2* by inactivation of the enzyme cyclooxygenase. However, inhibition of cyclooxygenase in platelets is irreversible, because the anuclear platelet cannot synthesize new proteins, it cannot manufacture new enzyme during its 10-day lifetime. That's why diminish of *Thromboxane A_2* is more evident. Other salicylates and other nonsteroidal anti-inflammatory drugs also inhibit *Cyclooxygenase* but have a shorter duration of inhibitory action because their action is reversible. Daily dose 325 mg of aspirin is approved for prophylaxis of myocardial infarction. The risk-versus-benefit measure of *Aspirin* as a prophylactic drug is questionable for patients with peptic ulcer disease.

Ticlopidine reduces platelet aggregation by inhibiting the ADP pathway of platelets. Unlike *Aspirin*, the drug has no effect on prostaglandin metabolism. It is used in the prevention of vascular events among patients with transient ischemic attacks, completed strokes, and unstable angina pectoris. Adverse effects include nausea, diarrhea, hemorrhage, and, most seriously, leukopenia. It is particularly useful in patients who cannot tolerate aspirin.

Dipyridamole (Curantyl) increases endogenous concentrations of adenosine and cyclic adenosine monophosphate (cAMP) by inhibiting their destruction. It is postulated that adenosine and cAMP are the platelet aggregation inhibitors. Also adenosine is a coronary vasodilator. *Dipyridamole* is indicated to prevent thromboembolic complications, in the treatment of occlusive vascular diseases as well as to reduce the recurrence of transient ischemic attacks and risk of reinfarction.

Dipyridamole may preferentially dilate, and increase blood flow through, nondiseased coronary blood vessels, leading to a redistribution of blood flow away from significantly stenotic coronary vessels. This "coronary steal" effect may lead to angina pectoris. *Dipyridamole* dilates the blood vessels and its using can be accompanied by hypotension, tachycardia, and flushing.

Drugs used in bleeding disorders are divided into:

— Coagulant drugs:

a) drugs for topical using *(Thrombin, Gelatin sponge)*;

b) drugs for general using *(Fibrinogen, Cryoprecipitate)*.

— Antagonists of anticoagulant drugs *(Protamine sulfate, Vitamin K)*

— Inhibitors of fibrinolysis (Aminocaproic acid, Contrykal, Aprotinin, etc)

— Coagulating substances of plant nature (*leaf of Nettle, Water pepper*, etc.)

Thrombin is a hemostatic agent. It is commercially available as a powder containing the protein substance prepared from prothrombin of human serum. *Thrombin* affects hemostasis principally by converting *Fibrinogen* to *Fibrin*. Agent is used topically as an aid in hemostasis when oozing blood and minor bleeding from capillaries and small venules is accessible. *Thrombin* solutions may be used in conjunction with absorbable gelatin sponge for hemostasis. *Gelatin* increases blood thickness.

Fibrinogen is prepared from normal human *Plasma.* It is a coagulant (clotting factor II) and used as an adjunct in the management of acute, congenital, or acquired chronic hypofibrinogenemia. It is injected intravenously. Cryoprecipitate is a plasma protein fraction and is obtainable from whole blood. It is used to treat deficiencies of factor VIII in patients with hemophilia A and occasionally to provide *Fibrinogen.*

Calcium ions stimulate forming of *Thromboplastin,* transforming of *Prothrombin* to *Thrombin* and polymerization of *Fibrin.* Calcium drugs are administered during hypocalcemia (transfusion of citrate blood), during increased permeability of capillaries (hemorrhagic vasculitis), before operations.

Protamine is a cationic protein that occurs in the sperm of certain species of fish. Commercially available *Protamine sulfate* is prepared from the sperm of salmon. *Protamine sulfate*, which is strongly basic, acts as a *Heparin* antagonist *in vitro* and *in vivo* by complexing with strongly acidic *Heparin* to form a stable nonactive salt. *Protamine sulfate* is used in the treatment of severe *Heparin calcium* or *Heparin sodium* overdosage. Hypersensitivity reactions including urticaria, angioedema, and anaphylactoid reactions have occurred occasionally after administration of *Protamine sulfate*.

Vitamin K (antihemorrhagic vitamin) is a fat-soluble substance. Two natural forms exist: *Vitamins K_1 and K_2. Vitamin K_1 (Phylloquinone)* is found primarily in leafy green vegetables. *Vitamin K_2 (Menaquinone)* is found in animal liver, and is synthesized by intestinal bacteria in human organism. *Vitamin K* is required for the synthesis of blood coagulation factors II *(Prothrombin),* VII *(Proconvertin),* IX *(Christmas factor),* and X *(Stuart-Prower factor)* in the liver. In adequate doses, *Vitamin K* reverses the inhibitory effect of *Coumarin* and *Indandione* derivatives on the synthesis of these factors. *Vitamin K* deficiency, which occurs in the presence of malabsorption syndromes (colitis, enteritis, and jaundice), is associated with low blood level of *Prothrombin* and other coagulation factors that is exhibited by bleeding.

Phytomenadione (Phytonadione) is identical to naturally occurring *Vitamin K_1*. Like other lipid-soluble vitamins, *Vitamin K_1* is absorbed from the GI tract only in the presence of bile salts. *Vicasol (Menadione)* is the water-soluble salt of *Vitamin K_3. Vi-*

casol is available both for oral using and for injection. *Vitamin K* is used in the treatment of bleeding that associated with hypoprothrombinemia, hemorrhagic disease of the newborn. The hemostatic effect of *Vitamin K* is delayed for 6 hours. *Vitamin K* is relatively nontoxic; however, allergic reactions and thrombosis may appear.

Aminocaproic acid is an inhibitor of fibrinolysis. It inhibits the activation of profibrinolysin *(Plasminogen)* and it also inhibits the action of *Fibrinolysin (Plasmin)*. *Aminocaproic acid* is rapidly and completely absorbed from the GI tract. It is excreted in urine as unchanged drug within 12 hours following the dose. *Aminocaproic acid* is used intravenously as well as orally in the treatment of excessive bleeding resulting from systemic hyperfibrinolysis. Use of the drug should be accompanied by laboratory tests to determine the degree of fibrinolysis present. Adverse effects of *Aminocaproic acid* are mild. They include vomiting, abdominal pain, diarrhea, dizziness, and fever.

Contrykal, Aprotinin, an animal origin drugs, are the serine protease *(Trypsin, Kinins, Plasmin,* etc.) inhibitors that inhibits fibrinolysis by free *Plasmin. Aprotinin* will reduce bleeding from many types of surgery, especially that involving extracorporeal circulation for open-heart procedures. It is currently approved for use in patients undergoing coronary artery bypass grafting who are at high risk of excessive blood loss. *Contrykal* inhibits *Trypsin, Kinins,* and *Fibrinolysin.* It is used for the treatment of acute pancreatitis because it is associated with excessive serum level of proteases. The most serious adverse effects of these agents are allergic reactions.

Coagulating substances of plant nature (leaf of nettle, water pepper, etc.) include tanning substances, *Vitamins K, C, P*, etc. They cause stabilizing action on vascular wall and increase firmness of capillaries. They are used in form of decocts, tinctures, extracts during chronic bleeding (uterine, intestinal, etc.).

Available forms:

Heparin — in bottles 5 ml (1 ml — 5,000; 10,000 or 20,000 IU) each

Ethyl biscoumacetate *(Neodicumarin)* — in tablets 0.05 or 0.1 each

Ticlodipine — in tablets 0.25 each

Dipyridamole — in tablets (or dragee) 0.025 or 0.075 each; in ampoules 0.5% solution 2 ml each

Streptokinase — in bottles 100,000 or 250,000 IU each (to dilute in 50 ml of physiologic solution before using)

Thrombin — in bottles or ampoules 0.125 IU each (to dilute in 10 ml of physiologic solution before using)

Fibrinogen — in bottles 1.0 each (to dilute in 250 ml of applied solution)

Protamine sulfate — in bottles 1% solution 5 ml each; in ampoules 1% solution 2 or 5 ml each

Vicasol — powder; in tablets 0.015 each; in ampoules 1% solution 1 ml

Aminocaproic acid — powder; in bottles 5% solution 100 ml each

Folia Urtica — infusion, MD — 0.6

Lecture 33
IMMUNOTROPIC AGENTS

The immune system is designed to protect the host from invading pathogens and to eliminate disease. It is provided by two major components: the innate and the adaptive (acquired) immune systems. The innate immune system is the first line of defense against an antigenic insult and includes physical (e.g. skin), biochemical (e.g. complement, lysozyme), and cellular (macrophages, neutrophils) components. The adaptive immune system includes production of antibodies, which are the effectors of **humoral immunity**; and the activation of lymphocytes, which are the effectors of **cell-mediated immunity**. The generation of specific immunity requires the participation of antigen-presenting cells (macrophages, Langerhans cells) and B-lymphocytes. Cell-mediated immunity is ensured mainly by T-lymphocytes that able to discriminate between foreign ("non-self") antigens and "self" antigens of the host and to respond to a previously encountered antigen in a learned way by initiating a vigorous memory response.

IMMUNOSTIMULATING AGENTS

Such drugs can be used to increase the immune responsiveness of patients who have immunodeficiency. The major potential uses are in immunodeficiency disorders, chronic infectious diseases, and cancer.

Classification of immunostimulating agents:

— Agents that stimulate nonspecific immunity (*Methyluracil, Pentoxil*)

— Agents that mostly stimulate macrophages and T-lymphocytes *(Sodium nucleate, BCG, Prodigiosan®, Pyrogenal®, Thymus agents, Levamisole, Interferon)*

— Agents that hasten macrophages and granulocytes formation *(Filgrastim, Molgramostim)*

— Agents that predominantly stimulate B-lymphocytes *(Myelopid)*

Methyluracil and *Pentoxil* are the derivatives of *Pyrimidine.* These drugs hasten cell regeneration, wounds healing; stimulate cellular and humoral immunity. They indicated in the cure of mild leukopenia, badly closed wounds, burns, bone crash, and ulcer disease of duodenum. *Meth uyluracil* and *Pentoxil* are well absorbed from the intestine. These drugs are good tolerated. However, *Pentoxyl* may cause gastrointestinal disorders.

Sodium nucleate, a sodium salt of nucleic acid, is formed by hydrolysis of yeast. It promotes the acceleration of restoring processes; stimulates leukopoiesis, cooperation of T- and B-lymphocytes, and phagocytic properties of macrophages. *Sodium nucleate* is indicated for different diseases that accompanied with leukopenia.

BCG is a viable strain of *Mycobacterium bovis* that has been used for immunization against tuberculosis. It has also been employed as a nonspecific adjuvant immunostimulator in cancer therapy (leukemia, can-

cer of intestine, bladder, and breast). *BCG* appears to act at least in part via activation of macrophages to make them more effective killer cells.

Prodigiosan is a microbial polysaccharide that is extracted from *Bac. prodigiosum*. It stimulates cellular immunity (T-lymphocytes) and adrenal cortex. It postulates that *Prodigiosan* augments the interferon synthesis. *Prodigiosan* is prescribed as adjuvant drug in the treatment of diseases that characterized by depressed immunity. For instance, chronic inflammation processes, postoperative period, during antibiotic therapy, badly closed wounds, etc. Agent is injected intramuscularly once per 3–7 days. Fever, headache, arthralgia, and fatigue sometimes are observed after *Prodigiosan* administration.

Pyrogenal (Grecian: *pyr*- fire, *gen*- producing) is a microbial polysaccharide that is synthesized by *Pseudomonas aeruginosa*. It is a fever-inducing agent. *Pyrogenal* is similar in action to *Prodigiosan*. In addition, *Pyrogenal* stimulates the restoring of central and peripheral nervous system; activates the disappearance of scars. *Pyrogenal* is indicated in the treatment of chronic prostatitis, chronic inflammation of women reproductive system, inflammation and damages of peripheral and central nervous system, and post-burn scars. Agent is prohibited during fever and pregnancy.

Levamisole was first synthesized for the treatment of parasitic infections. Later studies suggested that it appears to act as an immunorestorative agent in the presence of immunosuppression, but does not stimulate the immune response to above normal levels. Thus, it modulates the immune response or acts like immunomodulating agent. Mechanism of action is related to T-cell activation and proliferation, augmentation of monocyte and macrophage activity, and an increase in neutrophil mobility, adherence, and chemotaxis. *Levamisole* is used for the treatment of both primary and secondary immunodeficiency, autoimmune disease, chronic and relapse infections, cancer, etc. It has also been widely tested in rheumatoid arthritis and found to have efficacy. Agent is taken orally. However, it can induce severe agranulocytosis, which required discontinuation of its use. Thus, *Levamisole* therapy must be under regular leukocyte measurement.

Thymalinum consists of a group of protein hormones synthesized by the thymus. These proteins have been isolated and purified from bovine thymus glands. *Thymalinum* regulates the amount of T- and B-lymphocytes and activates cell immunity. *Thymalinum* is used for the treatment of different states that are associated with immunodeficiency and depression of hemopoiesis. For example, acute or chronic purulent processes, burns, chemotherapy of patients with cancer, etc. *Tactivin* is an agent of protein structure, which is obtained from bovine thymus gland. It appears to convey T-cell specificity to uncommitted lymphoid stem cells and to induce the maturation of pre-T cells. *Tactivin* increases the number of T-lymphocytes. It induces enhanced production of interleukins. This agent is indicated for the treatment of T-lymphocyte deficiency states including psoriasis, leukosis, etc. *Thymalinum* and *Tactivin* are prohibited during pregnancy and in case of hypersensitiveness to these drugs. *Vilosenum* as well as previous drugs are an extract of cattle thymus. It is used locally in drops or inhalation for the treatment of allergic disorders of the upper respiratory ways (allergic rhinitis and sinusitis).

Interferons belong to cytokines. They have antiproliferative, antimicrobial, and antitumor effects (see lecture "Antiviral agents"). The production of highly purified *Interferons* has been greatly facilitated by the pharmaceutical application of gene cloning techniques. Three major classes of *Interferons* are now recognized: α- (leukocyte), β- (fibroblast), and γ-(immune, T-lymphocyte). Each type can function as a potent cytokine with complex antiviral and immunomodulatory activity. γ-Interferon has the stronger action on the immunity than other *Interferons*. *Interferons* activate macrophages, T-lymphocytes, and natural killer cells. Natural α-interferon has been used for prophylaxis and treatment of the common cold virus's infections and herpes keratitis. *Recombinant α-interferon (Reaferon (Interferon alfa-2a), Intron A (Interferon alfa-2b))* is approved for the treatment of hepatitis B and C, leukemia, bladder and renal carcinoma, and malignant melanoma. *Poludan® (Polyadenylic acid + Uridylic acid), Tilorone (Amixin)* stimulates the synthesis of endogenous interferon and thus possess antiviral activity. *Poludan* is a topical agent for the treatment of viral eyes diseases. *Amixin* is active in case of viral hepatitis B and C.

Three cytokines with colony-stimulating properties have been studied extensively and are now being used in humans. They are *Erythropoietin* (see lecture "Drugs influencing the erythropoiesis"), *Granulocyte Colony-stimulating factor (G-CSF)*, and *Granulocyte-macrophage colony-stimulating factor (GM-CSF)*. G-CSF stimulates mainly the forming of granulocytes. GM-CSF promotes the forming of macrophages or activates combine granulocyte-macrophage colonies. *Filgrastim* (G-CSF) and *Molgramostim* (GM-CSF) are produced by recombinant techniques. These drugs hasten recovery from neutropenia in patients with malignancies who are receiving chemotherapy and accelerate marrow recovery after autologous bone marrow transplantation.

Myelopid is an immunomodulating agent of peptide structure, which is received from cattle or porcine bone marrow tissue cultures. At immunodeficient patients it restores the indicators of T- and B-lymphocytes, restores the formation of antibodies, and promotes the restoring of other indicators of humoral immunity. *Myelopid* is used in the cure of acquired immunodeficiency states with predominant confound of humoral immunity, including postoperative aggravations, osteomyelitis, etc. Agent is injected subcutaneously. Adverse effects include vertigo, fatigue, nausea, and fever.

IMMUNOSUPPRESSIVE AGENTS

Agents that suppress the immune system play an important role in the retention of organ or tissue grafts and in the treatment of certain diseases that arise from dysregulation of the immune response. There is definite overlap between the drugs used for immunosuppression and those used in cancer chemotherapy (cytotoxic drugs).

Classification of immunosuppressive agents:

— Alkylating agents *(Cyclophosphane, Embichin, Chlorbutin, and Busulfan)*

— Antimetabolites *(Mercaptopurine, Azathioprine, Methotrexate, and Ftoruracil)*

— Anticancer antibiotics *(Dactinomycin, Rubomycin, Doxorubicin and Bruneomycin)*

— Alkaloids *(Vinblastine, Vincristine)*

— Steroid hormones and their antagonists *(Tamoxifen, Leuprolide)*

— Enzymes *(Asparaginase)*

The major clinically useful alkylating agents are *Cyclophosphane, Embichin (Mechlorethamine)*, *Chlorbutin*, and *Myelosan (Busulfan)* are the most useful. As a class, the alkylating agents exert cytotoxic effects via transfer of their alkyl groups to various cellular constituents. Alkylation of DNA within the nucleus probably represents the major interactions that lead to cell death. *Cyclophosphane*, *Chlorbutin* are used in the treatment of lymphocytic leukemia, lympholeukosis, Hodgkin's disease, multiple myelosis, neuroblastoma, ovarian carcinoma, breast cancer, etc. *Myelosan* used for specialized purposes for chronic myeloid leukemia.

One of the major and dose-limiting adverse effects of alkylating drugs is hematological toxicity. Hematopoietic adverse effects include leukopenia, thrombocytopenia, and anemia. Repeated blood counts are essential during administration of these agents because the development of severe leukopenia or thrombocytopenia necessitates interruption of therapy. Anorexia, nausea, and vomiting occur commonly with alkylating drugs, especially at high doses. It is reported that these effects respond to treatment with antiemetics.

Mercaptopurine and *Azathioprine* are the chemical analogs of the physiologic purines. They are the purine antagonist antimetabolites. Ultimately, the synthesis of RNA and DNA is inhibited. Absorption of *Mercaptopurine* from the GI tract is variable and incomplete, but about 50% of a dose is usually absorbed. It is rapidly and extensively oxidized in the liver by the enzyme xanthine oxidase. *Mercaptopurine* is used mainly for the treatment of acute leukemia. Adverse hematopoietic effects include leukopenia, anemia, and thrombocytopenia. Adverse GI effects include nausea, vomiting, diarrhea, anorexia, abdominal pain, and ulceration of the intestinal epithelium. Also it is hepatotoxic.

Azathioprine is well absorbed from the gastrointestinal tract and is metabolized primarily to *Mercaptopurine*. Although *Azathioprine* action is presumably mediated by *Mercaptopurine* as the active form, it has been more widely used than *Mercaptopurine* for immunosuppression in humans. Immunosuppression with *Azathioprine* therapy seems to result from interference with nucleic acid metabolism at steps that are required for the lymphoid cell proliferation. *Azathioprine* to be of definite benefits in maintaining renal allografts and may be of value also in transplantation of other tissues. It has proved useful as well in cases of autoimmune diseases (rheumatoid arthritis, acute glomerulonephritis, and Crohn's disease).

Methotrexate is a folic acid antagonist. *Methotrexate* inhibits dihydrofolate reductase, the enzyme that reduces folic acid to tetrahydrofolic acid. Inhibition of tetrahydrofolate formation limits the synthesis of purines, DNA and cell reproduction. *Methotrexate* also has immunosuppressive activity, in part possibly as a result of inhibition of lymphocyte multiplication. It is completely absorbed from the GI tract. *Methotrexate* is retained for several weeks in the kidneys and liver. It is used orally, intravenously, and intramuscularly. *Methotrexate* has the similar uses and adverse effects with *Mercaptopurine*.

Ftoruracil (Fluorouracil) is a fluorinated pyrimidine antagonist. It acts as an antimetabolite that inhibits DNA and RNA synthesis. *Ftoruracil* is used for the palliative treatment of carcinoma of the colon, rectum, breast, stomach, and pancreas that is not amenable to surgery or irradiation. The major toxic effects of *Ftoruracil* are on the normal, rapidly proliferating tissues particularly of the bone marrow and lining of the GI tract. Anorexia, nausea, leukopenia, thrombocytopenia, and anemia occur commonly with *Ftoruracil* therapy.

Screening of microbial products has led to the discovery of a number of growth inhibitors that have proved to be clinically useful in cancer chemotherapy. Many of these antibiotics bind to DNA through intercalation between specific bases and block the synthesis of new RNA or DNA (or both), cause DNA strand scission, and interfere with cell replication. These agents possess also immunosuppressive properties. Anticancer antibiotics include *Dactinomycin*, *Rubomycin (Daunorubicin)*, *Doxorubicin*, *Bruneomycin* and others. In clinical use, all mentioned above drugs are administered by the intravenous route.

Doxorubicin is one of the most important anticancer drugs, with major clinical application in carcinomas of the breast, endometrium, ovary, testicle, thyroid, and lung. The major use of *Rubomycin* is in acute leukemia. *Dactinomycin* is used in the complex treatment of Wilms' tumor, chorioepithelioma, etc. *Bruneomycin* is indicated for lymphogranulomatosis, chronic lympholeukosis, Wilm's tumor, etc.

In common with many other cytotoxic drugs, anticancer antibiotics cause bone marrow depression. All blood elements are affected, but platelets and leukocytes are affected most profoundly, and severe leuko- and thrombocytopenia sometimes occurs. Nausea and vomiting, diarrhea, and oral ulcers may also be noted. Alopecia and various skin abnormalities occur occasionally.

Vinblastine and *Vincristine* are the alkaloids derived from *Vinca rosea,* the periwinkle plant. Their mechanism of action involves depolymerization of microtubules, which are an important part of the cytoskeleton and the mitotic spindle. This results in mitotic arrest at metaphase. *Vinblastine* has value in the treatment of systemic Hodgkin's disease and other lymphomas. *Vincristine* has been used with considerable success for acute leukemia. These drugs produce nausea and vomiting and marrow depression as well as alopecia. In addition, *Vincristine* causes a significant incidence of neurotoxicity, which limits its use to short courses.

Steroid hormones (glucocorticoids, androgens, estrogens and their antagonists) bind to receptor proteins in cancer cells, and high levels of receptor proteins are

predictive for responsiveness of endocrine therapy. As in normal cells, steroid hormones form a steroid-receptor complex that ultimately binds directly to nuclear nonhistone protein of DNA to activate transcription of associated clusters of genes.

Glucocorticoids have immunosuppressive and anti-inflammatory properties. Administration of a glucocorticoid (e.g. *Prednisolone*, *Dexamethasone*) reduces the size and lymphoid content of the lymph nodes and spleen, though it has essentially no toxic effect on proliferating myeloid or erythroid stem cells in the bone marrow. Their immunology effects are probably due to their ability to modify cellular functions rather than direct cytotoxicity (see lecture "Drugs affecting the endocrine system").

Indications for glucocorticoids include autoimmune disorders such as autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, inflammatory bowel disease, and lupus erythematosus. Corticosteroids are also used liberally in organ transplant recipients. The glucocorticoid analogs have been useful in the treatment of acute leukemia, lymphomas, myeloma, and other hematologic cancers.

The estrogen inhibitor *tamoxifen* has proved to be extremely useful for the treatment of breast cancer and endometrial cancer. An antiandrogen, *flutamide*, has been approved for use in the treatment of prostate cancer. *Finasteride*, a nonsteroidal inhibitor of 5α-testosterone reductase, the enzyme that converts testosterone to dihydrotestosterone, is approved only for the therapy of benign prostatic hyperplasia.

Leuprolide is a synthetic peptide analog of naturally occurring gonadotropin-releasing hormone. It inhibits the releasing of follicle-stimulating hormone and luteinizing hormone. This results in reduced testicular androgen synthesis. The latter effect underlies the efficacy of this agent in the treatment of carcinoma of the prostate.

Aminoglutethimide is an inhibitor of adrenal steroid synthesis. It also inhibits the extra-adrenal synthesis of estradiol. *Aminoglutethimide* is effective in the treatment of metastatic breast cancer in women whose tumors contain significant levels of estrogen or progesterone receptors. *Aminoglutethimide* is normally administered with adrenal replacement doses of hydrocortisone to avoid symptoms of adrenal insufficiency.

Androgens, estrogens, and adrenocortical hormones all can produce fluid retention through their sodium-retaining effect. Prolonged use of androgens and estrogens will cause masculinization and feminization, respectively. Extended use of the adrenocortical steroids may result in hypertension, diabetes, increased susceptibility to infection, and cushingoid appearance.

Asparaginase catalyzes the conversion of the amino acid asparagine to aspartic acid and ammonia. Some leukemic cells are unable to synthesize asparagine, which is required for the synthesis of DNA and essential proteins. Because normal cells are able to synthesize asparagine, they are less affected by asparaginase-induced depletion of the amino acid. Resistance to the cytotoxic effects of asparaginase develops rapidly. Agent is used for the treatment of acute lymphocytic leukemia.

AGENTS FOR THE TREATMENT OF HYPERSENSITIVITY

Whereas the normally functioning immune response can successfully neutralize toxins and eliminate pathogens, clinical instances occur in which an inappropriate response leads to extensive tissue damage (hypersensitivity). Hypersensitivity can be classified, as immediate or delayed depending on the time required for clinical symptoms to become manifest following exposure of the host to the sensitizing antigen.

Three categories of immediate hypersensitivity are recognized. Type I hypersensitivity *(anaphylaxis)* results from cross-linking of membrane-bound IgE on blood basophils or tissue mast cells by antigen. This interaction causes cells to degranulate, releasing substances (histamine, leukotrienes, etc.) that induce bronchospasm, collapse, or hay fever. Type II hypersensitivity *(cytotoxic reaction)* results from the formation of antigen-antibody complexes between foreign antigen and immunoglobulins. It results in lysis of cells that keep antigen. This type of hypersensitivity occurs during blood transfusion reactions and in hemolytic disease of the newborn. In both cases, antibodies are formed against foreign red blood cell membrane antigens to which they bind. It can also be drug-induced and occurs during the administration of *Levomycetin* to allergic patients. In these patients, *Levomycetin* binds to red blood cells or other host tissue to form a neoantigen that evokes production of antibodies capable of inducing complement-mediated cell lysis.

Type III hypersensitivity *(immune complex reactions)* is due to the presence of elevated levels of antigen-antibody complexes. The formation of these complexes activates complement to produce components that increase vascular permeability and recruit neutrophils to the site of complex deposition. It can cause skin rashes, glomerulonephritis, serum sickness, and arthritis. *Delayed-type hypersensitivity* is cell-mediated. Delayed-type hypersensitivity is characterized by the influx of the activated macrophages and neutrophils. The activated macrophages display increased phagocytic and antigen-presenting functions; and release copious amounts of enzymes that contribute to the extensive tissue damage and local inflammation (parasitic granuloma, nodular leprosy).

Histamine is a physiologically active, endogenous substance that binds to and activates histamine **H_1-** and **H_2-receptors** at various sites in the body causing characteristic allergic signs and symptoms. The principal pharmacologic effects of histamine involve the stimulation of gastric and bronchial secretions; microvascular dilation, hypotension (involving H_1-, H_2-receptors) and increased vascular permeability (H_1-receptors); stimulation of the bronchial and gastrointestinal tract muscles. The term antihistamine has historically been used to describe drugs that act as H_1-receptor antagonists. Drugs that antagonize H_2-receptors (e.g. cimetidine, famotidine) are used for the lowering of gastric acid secretion. Antihistamines competitively antagonize most of the smooth muscle stimulating actions of histamine on the H_1-receptors of the GI tract, uterus, large blood vessels, and bronchial muscle. Antihistamines appear to act by blocking H_1-receptor sites, thereby preventing the action of histamine on the cell.

Classification of agents used for the treatment of hypersensitivity:

1. Agents used for the treatment of immediate type hypersensitivity:

a. Agents that decrease the releasing of histamine and other active substances — *Cromolyn*, *Ketotifen*, *Glucocorticoids*.

b. Antihistamines — *Diphenhydramine (Dimedrolum), Promethazine (Diprazin), Diazolin (Mebhydroline + Zinc sulfate), Quifenadine (Phencarol), Loratadine*.

c. Agents that bind with histamine — *Histaglobulin*.

d. Agents that inhibit efferent limb of the allergic response — Adrenomimetics, *Aminophylline (Euphyllin)*.

e. Agents that decrease the tissue damage — steroid and non-steroid anti-inflammation drugs.

2. Agents used for the treatment of delayed type hypersensitivity:

a. Immunodepressive agents — *Cyclosporine*, *Azathioprine*.

b. Agents that decrease the tissue damage — steroid and non-steroid anti-inflammation drugs.

Antihistamines include following drugs: *Diphenhydramine, Diprazin (Promethazine), Diazolin, Phencarol, Loratadine,* etc. *Diprazin*, *Dimedrolum* are possess m-cholinolytic, ganglionblocking and sedative effects. The antiemetic, antimotion-sickness, and antiparkinson actions of these antihistamines appear to result, at least in part, from their central anticholinergic and CNS depressant properties. *Diprazin* probably is the most potent antihistamines. Also it has α-adrenolytic activity (hypotensive action). *Diazolin*, *Phencarol*, and *Loratadine* are poorly distributed into the CNS at usual dosages. That's why they do not cause sedative effect.

Antihistamines generally are well absorbed following oral or parenteral administration. The duration of action is variable but allergic symptoms usually are relieved for 3–6 hours after oral administration of most antihistamines. Some antihistamines (e.g. *Loratadine*) exhibit prolonged duration of effect that lasts in excess of 24 hours.

Indications. Antihistamines are used for the treatment of nasal allergies, allergic dermatosis, and allergic conjunctivitis. Antihistamines are useful in the ancillary treatment of pruritus, urticaria, angioedema, and bronchospasm associated with anaphylactic reactions. Some antihistamines (e.g. *Dimedrole*, *Diprazin*) are useful for the prevention and treatment of nausea, vomiting, and/or vertigo associated with motion sickness. They are used for their sedative effects as nighttime sleep aids.

Adverse effects include sedation, ranging from mild drowsiness to deep sleep, anticholinergic effects (e.g. dryness of mouth, urinary retention, and visual disturbances), and gastrointestinal disorders (e.g. anorexia, nausea, and vomiting). Also they potentiate the depression of the CNS that caused by alcohol, neuroleptics, narcosis agents.

Cromolyn is an antiallergic drug. *Cromolyn* inhibits mast cell release of histamine, leukotrienes, and other substances that cause hypersensitivity reactions. It does not possess any intrinsic antihistamine, anti-inflammatory, glucocorticoid, or vasoconstrictive activity. *Cromolyn* administered orally is indicated in the treatment of ulcerative colitis. Its inhalation is indicated as first-line medication for the prevention of acute bronchospasm. *Cromolyn* inhalation is not indicated for the relief of acute asthma attacks, especially in status asthmaticus, because it has no immediate bronchodilating activity.

Ketotifen has antihistamine and antiallergic activities. It is postulated, that *Ketotifen* inhibits mast cell release of histamine, leukotrienes, and other substances that cause hypersensitivity. On the other hand, *Ketotifen* blocks H_1-receptors. Agent is well absorbed from gastrointestinal tract. The serum half-life is about 20 hours. *Ketotifen* is used for the prevention of acute bronchospasm, for the treatment of allergic bronchitis, hay fever, and allergic dermatitis. Adverse effects include drowsiness and thrombocytopenia.

Histaglobulin is a preparation of the human gamma globulin, containing the antibodies of normal adults, and histamine. It is obtained from pooled liquid human plasma from a number of donors. *Histaglobulin* increases the production of antihistamine antibodies those results in higher ability of serum to inactivate the histamine. It is used subcutaneously for the treatment of different allergic diseases including bronchial asthma, dermatitis, etc.

Drugs that modify allergic responses act at several links in this chain of events. *Glucocorticoids (Prednisolone)* that are often used in severe allergic reactions including anaphylactic reaction, and probably blocks proliferation of the IgE-producing clones. In addition, glucocorticoids increase the sensitiveness of adrenoreceptors to noradrenaline, thus they potentiate the action of adrenomimetics. In the efferent limb of the allergic response adrenomimetics (e.g. *Adrenaline*, *Isoprenaline*, *Salbutamol*) and direct spasmolytic *Euphyllin* produce bronchodilation (see lecture "Adrenergic agonists").

For the treatment of delayed-type hypersensitivity immunosuppressive agent's glucocorticoids are used also. They have anti-inflammation activity (see lecture "Drugs affecting the endocrine system"). Glucocorticoids reduce the concentration of T-lymphocytes, monocytes, and eosinophils. They also decrease binding of immunoglobulin to cell surface receptors and inhibit the synthesis, and release of interleukins, thereby decreasing T-lymphocyte blastogenesis and reducing expansion of the primary immune response. Glucocorticoids may also decrease concentrations of complement components and immunoglobulins.

Cyclosporine is an antibiotic that appears to act at an early stage in the antigen receptor-induced differentiation of T-cells and blocks their activation. Recent *in vitro* studies have indicated that *Cyclosporine* inhibits the gene transcription of interleukins and other factors produced by antigen-stimulated T-cells. *Cyclosporine* is an immunosuppressive agent in human organ transplantation, after bone marrow transplantation, and in the treatment of selected autoimmune disorders. Agent is given orally and intravenously. Toxicities include nephrotoxicity and transient liver dysfunction.

Available forms:

Thymalinum — in ampoules 0.01% solution 1 ml each

Myelopid — in bottles 0.003 each (to dilute in 1 ml of physiologic solution before using)

Prodigiosan® — in ampoules 0.005% solution 1 ml each

Levamisole — in tablets 0.05 or 0.15 each

Azathioprine — in tablets 0.05 each

Fluorouracil (Ftoruracil) — in ampoules 5% solution 5 ml each

Dimedrolum — powder; in tablets 0.02; 0.03 or 0.05 each; in ampoules 1% solution 1 ml each

Loratadine — in tablets 0.01 each

Ketotifen — in tablets or capsules 0.001 each

Cyclosporine — in capsules 0.05 or 0.1 each

EXAMINATION QUESTIONS

1. Which of the following statements describe why *Warfarin* is not used to prevent blood coagulation in blood collection devices used at blood donating centers?
   (A). *Warfarin* does not bind to plastic tubing or glass.
   (B). The anticoagulant effect of *Warfarin* occurs only in vivo.
   (C). *Warfarin* is a prodrug, which must be activated in the liver into the active compound.
   (D). The gastric enzymes needed to convert R-warfarin into S-warfarin are unstable near plastic.
   (E). Warfarin is chemically unstable and is degraded unless made fresh and used immediately.

2. All of the following statements about *Warfarin* are true EXCEPT?
   (A). An adverse drug reaction may occur if *Warfarin* is displaced from plasma protein binding sites.
   (B). *Warfarin* crosses the placenta.
   (C). Drugs that are metabolized by the liver can alter the anticoagulant effect of *Warfarin*.
   (D). *Warfarin* is eliminated from the body unchanged in the urine.
   (E). *Warfarin* is a vitamin K antagonist.

3. Which of the following is an adverse effect associated with pharmacotherapy using *Heparin*?
   (A). An increase in the number of circulating platelets
   (B). Thrombocytopenia
   (C). Purple toe syndrome
   (D). Teratogenicity to the fetus
   (E). An increase in the circulating level of antithrombin III

4. Which of the following is a drug that blocks the ADP receptor on the antiplatelet membrane?
   (A). *Aspirin*
   (B). *Abciximab*
   (C). *Dipyridamole*
   (D). *Clopidogrel*
   (E). *Eptifibatide*

5. In what respect is the thrombolytic drug *Reteplase* improved over older drugs like streptokinase?
   (A). *Reteplase* may be taken orally.
   (B). *Reteplase* is antigenic.
   (C). *Reteplase* binds to fibrin.
   (D). Bleeding does not occur with reteplase.
   (E). *Reteplase* produces less thrombocytopenia.

6. Cytotoxic agents such as *Azathioprine* are effective immunosuppressants because they
   (A). Bind to and inactivate circulating immunocomplexes.
   (B). Specifically inhibit IL-2 gene transcription.
   (C). Prevent the clonal expansion of T and B cells by inhibiting purine synthesis.
   (D). Induce the synthesis of antiidiotype antibodies.
   (E). Alkylate and cross-link DNA, preventing blastogenesis.

7. *Interleukin-2* can be beneficial in the treatment of AIDS because it can
   (A). Attach to the HIV virus, making it more susceptible to phagocytosis.
   (B). Bind to IL-2 receptors on responsive immune cells and stimulate the production of T helper and T cytotoxic cells.
   (C). Cross-link antibodies on mast cell surfaces leading to degranulation.
   (D). Activate the complement cascade by binding to the C5a fragment.
   (E). Inhibit T suppressor cell activity and thereby stimulating the immune response

8. A 4-year-old boy has significantly reduced levels of IgA, IgM, IgD and IgE in his blood. Testing demonstrates that he did not develop the appropriate antibody titer following standard childhood vaccinations. The most probable cause of these deficiencies is
   (A). Deficiency in macrophage function that is preventing the proper presentation of antigens to T cells.
   (B). Lack of a specific component of the complement cascade.
   (C). Alcohol abuse by the mother during pregnancy.
   (D). A primary immunodeficiency disease that is blocking the maturation of B cells into plasma cells.
   (E). An autoimmune disease targeted at basophil surface receptors.

9. Which of the following best describes the side effects of *Cyclosporine* therapy?
   (A). Leukopenia, hypotension, hemolytic anemia.
   (B). Nephrotoxicity, neurotoxicity, hirsutism.
   (C). Thrombocytopenia, hypokalemia.
   (D). Hemorrhagic cystitis, hypoglycemia.
   (E). Increase circulating immune complexes, cardiac arrhythmia.

10. The antigen-mediated release of histamine can
   (A). Be inhibited by the binding of histamine to H_3-receptors on mast cells.

(B). Be stimulated by (β_2-adrenoceptor agonists.
(C). Be initiated by organic bases such as morphine without prior sensitization.
(D). Occur only in the tissues, not in the blood.
(E). Produce pain and itching through an effect on sensory nerve endings.

11. Effects mediated by the H1 histamine receptor include
(A). Inhibition of gastric acid secretion.
(B). Induction of hepatic cytochrome P450 enzymes.
(C). Maintenance of a wakeful state.
(D). Bronchodilation.
(E). Vasoconstriction of arterioles.

12. All four types of histamine receptors
(A). Are found on the surface of mast cells and basophils.
(B). Are G protein-coupled.
(C). Modulate adenylyl cyclase activity.
(D). Are involved in the release of multiple neurotransmitters.

ANSWERS

1. **(B)**. *Warfarin* does not produce an anticoagulant effect *in vitro*. It inhibits coagulation of blood only *in vivo*, because the effect depends upon *Warfarin*'s effect in the liver on the production of clotting factors. *Warfarin* does not require conversion into an active drug. It inhibits the post-ribosomal carboxylation of glutamic acid residues in the vitamin K-dependent clotting factors. Therefore, *Heparin* rather than *Warfarin* is used when blood is collected from donors and stored.

2. **(D)**. *Warfarin* is metabolized in the liver by P450 enzyme system and is appreciably metabolized before it is eliminated. Adverse drug reactions are seen in patients taking *Warfarin* if a second drug displaces *Warfarin* from its protein binding sites in the blood or induces or inhibits the hepatic P450 system. *Warfarin* can cross the placenta and exert anticoagulant and other effects in the fetus at normal doses given to the mother.

3. **(B)**. Thrombocytopenia is a frequent side effect association with *Heparin*. This reduction in the level of circulating platelets increases bleeding. Purple toes are encountered during *Warfarin* therapy. Heparin may be administered to pregnant mothers without risk to the fetus. *Heparin* requires antithrombin III for its anticoagulant action, but does not increase the level of this protein in the blood.

4. **(C)**. *Aspirin* inhibits platelet cyclooxygenase. Abciximab, a monoclonal antibody, binds to and inhibits the platelet glycoprotein IIb/IIIa receptor. Dipyridamole inhibits platelet cyclic AMP phosphodiesterase and raises cyclic AMP levels. Eptifibatide binds to the glycoprotein IIb/IIIa complex.

5. **(C)**. Reteplase binds to fibrin to cause a selective activation of fibrin-bound plasminogen. All fibrinolytic drugs are administered IV. Streptokinase is antigenic, whereas reteplase is not. Thrombocytopenia is not normally caused by thrombolytic drugs.

6. **(C)**. *Azathioprine* is a phase-specific cytotoxic agent that functions by inhibiting purine synthesis. The other answers are wrong because *Azathioprine* is nonspecific, is not an alkylating agent, has no effect on immune complexes, and does not induce antibody synthesis.

7. **(B)**. IL-2 stimulates the immune system by binding to the IL-2 receptors on responsive immune cells, causing differentiation and proliferation of T helper and T cytotoxic cells. It has no direct effect on the HIV virus, complement or basophils.

8. **(D)**. The boy has significantly reduced serum antibody levels and a reduced ability to mount an antibody response to childhood vaccinations. The most probably cause is a primary immunodeficiency disease affecting humoral immunity.

9. **(B)**. The primary side effect of *Cyclosporine* therapy is nephrotoxicity, occurring in up to 75% of cases. Unwanted hair growth and neurotoxicity are also commonly noted. The other answers are wrong because *Cyclosporine* therapy is associated with hypertension, hyperkalemia, and hyperglycemia. There are no references to cyclosporine having cardiac or immune complex effects or causing hemorrhagic cystitis.

10. **(E)**. Histamine inhibits its own release through an effect on H_2-receptors on mast cells. Its release is inhibited, not stimulated, by β_2-adrenoceptor agonists. Organic bases can displace histamine from its storage granules and cause non-antigen-mediated release of histamine; antigen-mediated release requires prior sensitization. Antigen-mediated histamine release occurs in both tissues and blood. Histamine stimulates sensory nerve endings, resulting in pain and itching.

11. **(C)**. Histamine stimulates gastric acid secretion through an effect on H_2-receptors of gastric parietal cells. Although certain antihistamines are metabolized by cytochrome P450 enzymes, histamine does not induce their production. Histamine helps to maintain a wakeful state through an effect on H_1-receptors. Histamine-mediated bronchoconstriction is mediated by H_1-receptors, while histamine-mediated vasodilation occurs as a result of stimulation of H_1 and H_2-receptors.

12. **(B)**. H_2-receptors are found on the surface of mast cells and basophils. All four types of histamine receptors belong to the G protein-coupled receptor superfamily. Only H_2-receptors are coupled to adenylyl cyclase through the G protein G_s.

ANTIMICROBIAL, ANTIPROTOZOAL AND ANTIVIRAL DRUGS

Lecture 34
DISINFECTANTS AND ANTISEPTICS

Antimicrobial drugs are the greatest contribution of the present century to therapeutics. As the class they are one of the most frequently used in medicine.

J. Zemmelweiss, the Hungarian obstetrician used lime for medicine stuff hands washing. An English surgeon J. Lister suggested phenol as an antiseptic to surgery. Further development of antiseptics was based on Pasteur's discovery of pathogenic microorganisms and researches of R. Koch, I. I. Mechnikov and others.

Drug in this class differs from all others in that they designed to inhibit or to kill the infecting organism and to have minimal effect on the recipient. If agent primary inhibits the germ growing, it acts *bacteriostatic*. Direct lethal action is the feature of *bactericidal* activity. A practical distinction between these two mechanisms action is futile as these are often concentration dependent action.

Antimicrobial preparations are subdivided into the following groups: disinfectants, antiseptics and chemotherapeutic agents.

Disinfectants are chemical agents that inhibit or kill microorganisms on inanimate objects (walls, floor, air, and medical tools). The process of disinfection prevents infection by reducing the number of potentially infective organisms either by killing, removing, or diluting them.

Antiseptics are agents with sufficiently low toxicity for host cells that they can be used directly on the skin, mucous membranes, or wounds. Disinfectants and antiseptics can be used both for disinfecting of medical tools and human skin depending on their concentration. There is considerable overlap and many agents are used in either way.

Chemotherapeutic agents are used for germs killing inside the organism. Disinfectants and antiseptics differ from chemotherapeutic agents by their low parasite selectivity and high toxicity for systemic use.

A good disinfectant/antiseptic should be active against all pathogens (bacteria, fungi, viruses, protozoa etc.), active even in the presence of blood, pus and exudates. A disinfectant in addition should be not corrode instruments. An antiseptic also should be non-irritating to tissues, produce minimum toxicity.

Spectrum activity of agent is the list of microorganisms, that sensitive to him. Spectrum activity of majority of antiseptic/disinfectants is wide, reflecting nonselectivity of action.

Evaluation of effectiveness of antiseptics, disinfectants although seemingly simple in principle, is very complex. Factors in any evaluation include the intrinsic resistance of the microorganism, the number of present microorganisms, mixed populations of microorganisms, amount of present organic material (e.g. blood, feces, tissue), concentration and stability of disinfectant or sterilant, time and temperature of exposure, pH, and hydration and binding of the agent to surfaces.

Classification of disinfectants and antiseptics:

— Halogens *(Chlorinated lime, Chloramine B, Chlorhexidine, Iodinol (Iodine + Potassium iodine), Iodovidon (Povidone-Iodine))*

— Oxidizing agents *(Hydrogen Peroxide, Potassium permanganate)*

— Acids *(Salicylic Acid, Boric acid)*

— Phenol derivatives *(Phenol, Cresol, Resorcinol, Vagotil)*

— Aldehydes and alcohols *(Formaldehyde, Glutaraldehyde, Ethanol, Isopropanol)*

— Metallic salts *(Silver nitrate, Zinc sulfate, and Copper sulfate)*

Dyes or tints *(Brilliant green, Ethacridine (Rivanol), Methylene blue)*

— Detergents *(Benzalkonium chloride (Roccal), Aethonium, Cerigelum, Decamethoxin, Soaps)*

— Derivatives of different chemical groups *(Nitrofural (Furacilinum))*

— Agents from plant source (*Novoimaninum*, *Chlorophyllipt*, and *Lysocim*)

HALOGENS

Anti-germ activity of halogens depends on their ability to release chlorine and iodine. They form chloric and iodic acids in water solutions. The latter release atomic oxygen and haloids. These ions denature proteins of germs and act bactericidal.

Chlorine is a strong oxidizing agent and universal disinfectant that is most commonly provided as a

5.25% sodium hypochlorite solution, a typical formulation for household bleach. Chlorine is used to disinfect urban water supplies.

Because chlorine is inactivated by blood serum, feces, and protein-containing materials, surfaces should be cleaned before chlorine disinfectant is applied. Solutions of chlorine are corrosive to aluminum, silver, and stainless steel.

Chlorophores (*Chlorinated lime*, *Chloramine B*) are compounds that slowly release hypochlorous acid (HOCl). Because of ease of handling, they are used in preference to gaseous chlorine. These agents retain chlorine longer and have a prolonged bactericidal action. *Chlorinated lime* (bleaching powder) is obtained by the action of chlorine on lime. It is used as disinfectant for medical tools, drinking water, swimming pools and sanitizer for privies. *Chloramine B* may be used for disinfecting of clothes, skin and instruments, which are not made from metal.

Chlorhexidine is a cationic biguanide with very low water solubility. Water-soluble *chlorhexidine bigluconate* is used in water-based formulations as an antiseptic. It is most effective against gram-positive cocci and less active against gram-positive and gram-negative rods. Spore germination is inhibited by *Chlorhexidine*. It is resistant to inhibition by blood and organic materials. *Chlorhexidine* is used in the treatment of inflammation of the oral mucosa caused by bacterial or fungal actions, for surgeon hands washing before operation, for medical tools disinfection. *Chlorhexidine* has a very low skin-sensitizing or irritating capacity. Oral toxicity is low because chlorhexidine is poorly absorbed through the alimentary tract. *Chlorhexidine* must not be used during surgery on the middle ear because it causes sensor neural deafness. Similar neural toxicity may be encountered during neurosurgery.

Iodine is a rapidly acting, broad spectrum (bacterial, fungi, and viruses) microbicidal agent. Acts by iodinating and oxidizing germ protoplasm. Iodine in a 1:20,000 solution is bactericidal in 1 minute and kills spores in 15 minutes. It is the most active antiseptic for intact skin. It is not commonly used because of serious hypersensitivity reactions, skin, irritation that may occur and because of its staining of clothing and dressings.

Iodophors are complexes of iodine with a surface-active agent such as polyvinylpyrrolidone (*Iodinole, Iodovidone*). The amount of free iodine is low, but it is released as the diluted solution. Iodophors retain the activity of iodine. Iodophors are less irritating and less likely to produce skin hypersensitivity than tincture of iodine. They kill vegetative bacteria, mycobacterium, fungi, and lipid-containing viruses. They may be sporicidal upon prolonged exposure. Iodophors can be used as antiseptics or disinfectants, the latter containing more free iodine. Dilution may release more free iodine. An iodophor solution must be diluted according to the manufacturer's directions in order to obtain full activity.

OXIDIZING AGENTS

Oxidizing agent are free atomic oxygen releasers. Atomic oxygen leads to irreversible damage of oxidizing-restoring reaction of germ.

The *Hydrogen peroxide* has high killing activity and a broad spectrum against bacteria, spores, viruses, and fungi when used in appropriate concentration. It has the advantage that its decomposition products are not toxic and does not injure the environment. *Hydrogen peroxide* is powerful oxidizer that is used primarily as antiseptic. Organisms with the enzymes catalase and peroxidase rapidly degrade hydrogen peroxide. The innocuous degradation products are atomic and molecule oxygen, and water. Molecule oxygen forms the foam that helps in loosing and removing slough dead tissues. *Hydrogen peroxide* has been proposed for wound irrigation, disinfection of respirators, acrylic resin implants, plastic eating utensils, soft contact lenses. *Hydrogen peroxide* has poor penetrability and a transient action.

Potassium permanganate. It liberates oxygen, which oxidizes bacterial protoplasm, and MnO_2, which cause astringent and irritating effects. Solution of *Potassium permanganate* is used for gargling, douching, and irrigating cavities, urethra and wounds. It has also been used for stomach wash in alkaloid poisoning. It promotes rusting and is not good for surgical instruments.

ACIDS

Boric acid possesses fungistatic and weak bacteriostatic properties. Drug has greater bacteriostatic activity in bases containing large amounts of water than in fatty bases. *Boric acid* retards the growth of fungi but is not fungicidal. Aqueous solutions of boric acid are used topically for ophthalmic irrigation to cleanse and refresh irritated eyes. It is used topically as a skin protection for relief of discomfort of chafed skin, dry skin, abrasions, or other skin irritations and has been used topically for the treatment of superficial fungal infections; however, the drug is generally considered as lacking substantial evidence of efficacy for these uses.

The risk of systemic toxicity from topical application of boric acid depends on the concentration used (more than 5%), age of the patient (children appear to be more susceptible), skin condition (increased with abraded, or macerated skin). Boric acid can produce severe and fatal poisoning, consisting of GI disturbances, erythematosus skin eruptions, and signs of CNS stimulation followed by depression. Treatment of acute boric acid intoxication consists mainly of intensive symptomatic and supportive therapy.

Salicylic acid has a potent keratolytic action and a slight antifungal and antiseptic action when applied topically to the skin. In low concentrations, the drug has keratoplastic activity (activation of keratinization) and in higher concentrations (i.e. 1% or higher), the drug has keratolytic activity (causes peeling of skin). At high concentrations, *salicylic acid* has a caustic effect. *Salicylic acid* is used topically for its keratolytic effect in controlling scaling dermatoses (seborrheic, psoriasis). It has also been used in the treatment of localized hyperkeratosis, such as occurs on the palms and soles. *Salicylic acid* is not used systemically because of its severe irritating effect on GI mucosa and other tissues.

PHENOL DERIVATIVES

Phenol itself perhaps the oldest of the surgical disinfectant/antiseptic. It is used to disinfect urine, feces, and pus, for drug conservation. *Phenol* no longer used as an antiseptic because of its corrosive effect on tissues, its toxicity upon absorption, and its carcinogenic effect. When swallowed (with suicidal purpose) it causes buccal, esophageal and stomach burns, excitation, convulsions, respiratory paralysis and vascular collapse.

Phenol derivatives (*Cresol, Resorcin,* and *Vagotil*) are less toxic than phenol. Phenolic compounds disrupt cell wall and membranes, precipitate proteins, and inactivate enzymes. They are bactericidal (including mycobacteria), fungicidal, and capable of inactivating lipophilic viruses. *Cresol* more active than phenol. It is used for hard surface decontamination in hospitals and laboratories, e.g. floors, beds, and counters or bench tops. *Resorcin* is $^1/_3$ as potent as phenol. It also has keratolytic activity, that's why resorcin employed on seborrheic dermatitis, eczema, acne as solution or ointment. *Vagotil* in addition acts on trichomonas — used for topical vaginitis treatment.

Detergents are often added to formulations to clean and remove organic material that may decrease the activity of a phenolic compound. Skin absorption and skin irritation still occur with phenol derivatives, and appropriate care is necessary in their use. They are not recommended for use in nurseries and especially bassinets, where their use has been associated with hyperbilirubinemia.

ALDEHYDES AND ALCOHOLS

The two alcohols most frequently used for antisepsis and disinfection are *Ethanol* and *Isopropyl alcohol (Isopropanol)*. They are rapidly active, killing vegetative bacteria, *M. tuberculosis,* and many fungi and inactivating lipophilic viruses. They are not sporicidal, may not be active against hydrophilic viruses, and lack residual action because it evaporates completely. Alcohols probably act by denaturation of proteins. Alcohols have been used for skin disinfecting in case of abrasion and before hypodermic injection. The rapidity of antiseptic action increases with concentration up to 70% and decreases above 90%. At 90% concentration they form a coagulum under which bacteria could grow.

Alcohols are an irritant and should not be applied to mucous coats. They are poor disinfectant for instruments — does not kill spores and promote rusting.

Aldehydes (Formaldehyde and Glutaraldehyde) act by alkylation of chemical groups in proteins and nucleic acids. Activated solutions are bactericidal, sporicidal, fungicidal, and virucidal for both lipophilic and hydrophilic viruses. They are not corrosive for metal, plastic, or rubber.

Formaldehyde has a characteristic pungent odor and is highly irritating to respiratory mucous membranes and eyes. *Formaldehyde* solutions are used for high-level disinfection of hemodialyzers, preparation of vaccines, and preservation and embalming of tissues. *Formaldehyde* is available as a 37% solution in water (100% *Formalin*). The 3.7% *Formaldehyde* (10% *Formalin*) solutions used for fixation of tissues and embalming may not be mycobactericidal. Including formaldehyde preparation decrease foot sweating. The urinary antiseptic *Hexamethylenetetramine (Methenamine)* acts by releasing *Formaldehyde* in acidic medium. It is used for urinary tract infections.

Those who handle *Formalin* can develop eczematoid reaction. It has declared that formaldehyde is a potential carcinogen.

Glutaraldehyde is less pungent and better sterilizing agent than formalin. Solutions of 2% *Glutaraldehyde* are most commonly used. It is used for disinfection or sterilization of instruments such as fiberoptic endoscopes, respiratory therapy equipment, hemodialyzers, and dental handpieces.

METALLIC SALTS

Metals cause antiseptic action, because they easily combine with sulfhydryl (SH) group of thiolic enzymes, thus stopping the oxidizing process of microorganisms. When metal-ions interact with human proteins, physical properties of the protein are usually altered; the protein may be denatured and precipitation usually occurs. When the concentration of metal is low, precipitation prevents deep tissue penetration and *astringent* action occurs. When the concentration of metal is high, membrane and intracellular structures are damaged and *caustic* or *escharotic* action occurs.

Metal-ions in the high concentration interact with sulfhydryl groups, inhibiting enzymes and altering cell membranes of human tissues, which leads to poisoning. The most distinct example is the case of mercury poisoning. Acute inhalation of elemental mercury vapors may cause chemical pneumonitis and noncardiogenic pulmonary edema. Acute gingivostomatitis may occur, and neurologic sequelae (tremor, memory loss, fatigue, insomnia, and anorexia) may also ensue. Acute ingestion of inorganic mercury salts, such as mercuric chloride, can result in a corrosive, potentially life-threatening hemorrhagic gastroenteritis followed within days by acute tubular necrosis and oliguric renal failure. In addition to intensive supportive care, acute chelation with *Dimercaprol (Unithiol)* or *Edetate calcium disodium (Calcium EDTA)* may be of value in diminishing nephrotoxicity after acute exposure to inorganic mercury salts. The sulfhydryl groups of dimercaprol form heterocyclic ring complexes with heavy metals (particularly arsenic, mercury, and gold), and these complexes prevent or reverse the binding of metallic cations to body ligands such as essential sulfhydryl-dependent enzymes. The calcium in *Calcium EDTA* can be displaced by divalent and trivalent metals to form stable soluble complexes which can then be excreted in urine.

Silver nitrate exhibits antiseptic, germicidal, astringent, and caustic or escharotic activity. Inorganic silver salts are strongly bactericidal. *Silver nitrate*, 1:100, has been most commonly used, particularly as a preventive for gonococcal ophthalmitis in newborns. *Silver nitrate* touch is used for hypertrophied tonsillitis and aphthous ulcers.

Silver salts stain tissue black because of deposition of reduced silver. Contact of 1% silver nitrate solution with skin or other surfaces should be avoided since staining of the skin may occur. *Silver nitrate* is caustic and irritating to skin and mucous membranes. Cauterization of the cornea and blindness may result from repeated application of silver nitrate ophthalmic solution. Mistaken or accidental single-dose administration of 5–50% *Silver nitrate* solutions has reportedly caused severe ocular injury including permanent corneal opacification and cataracts.

Silver sulfadiazine slowly releases silver and is used to suppress bacterial growth in burn wounds. *Collargol* (colloidal silver) and *Protargol* (protein silver) also slowly release silver ions, are not irritating. They are used in cases of conjunctivitis, ulcers.

Zinc sulfate exhibits astringent and mild antiseptic activity. These effects may result from precipitation of protein by the zinc ion. *Zinc sulfate* is used in ophthalmic solutions as an astringent for the temporary relief of discomfort from minor eye irritation. It has also been used in the treatment of angular conjunctivitis. *Zinc oxide* being mildly antiseptic, it is popular dermal protective and adsorbentive agent. Zinc is necessary for the proper functioning of over 200 metalloenzymes. Physiological functions that are zinc dependent include cell growth and division, sexual maturation and reproduction, night vision, wound healing, host immunity, taste acuity.

Copper sulfate as astringent and antiseptic has been used for conjunctivitis, ureteritis and vaginitis treatment. Copper is necessary for the proper functioning of many metalloenzymes. Physiological functions that are copper dependent include oxidation of iron, erythro- and leukopoiesis, bone mineralization, elastin and collagen cross-linking, myelin formation, and antioxidant protection of the cell. Such polyvitamins as "*Quadevit*", "*Complivit*" include copper sulfate ("*Complivit*" also contain zinc).

Mercury is now rarely used as disinfectant/antiseptic. Mercurials are poor antiseptics with low therapeutic index. But some are still used. For example *Hydrargyrum amidochloride* (ammoniated mercury) used for skin disease treatment.

Aluminum and *lead* preparations are used for antiseptic rinsing and applying. Aluminum hydroxide being an antacid is indicated for relief of symptoms associated with hyperacidity (heartburn, acid indigestion, and sour stomach).

DYES (TINTS)

Brilliant green active against fungi, staphylococci, and other gram-positive bacteria. Aqueous or alcohol solution is used on furunculosis, skin abrasion, cutting, infected eczema. Staining is a disadvantage with all dyes. *Brilliant green* is inactivated by blood serum, feces, and protein-containing materials.

Ethacridine lactate (Rivanol) influence mostly gram-positive germs. It's water solution, ointment, paste are used for wounds and cavities washing and in dermatology.

Methylene blue has mild antiseptic activity that may inhibit bacterial proliferation. *Methylene blue* has been used as a urinary tract antibacterial agent (irrigation), however, more effective agents have replaced this medication. It is used as a bacteriological stain, as a dye in diagnostic procedures, such as fistula detection, and for the selective staining of certain body tissues during surgery. *Methylene blue* is indicated in the treatment of acquired and idiopathic methemoglobinemia. In low concentrations, it acts as a cofactor to accelerate the conversion of methemoglobin to hemoglobin in erythrocytes.

DETERGENTS

Detergents or surface-active compounds decrease surface tension of cell membrane act, thus alter its permeability. There are two kinds of detergents. They are cationic detergents (quaternary ammonium compounds) and anionic detergents (soaps).

The quaternary ammonium compounds ("quarts") are bacteriostatic, fungistatic, and sporostatic. They highly effective against gram-positive bacteria and moderately active against gram-negative bacteria. Strains of M. *Tuberculosis* and *Pseudomonas aeruginosa* are often resistant and they are not effective against spore-forming organisms.

Quaternary compounds possess detergent, keratolytic, and emulsifying action. They are used for sanitation of non-critical surfaces (floors, bench tops, etc).

Quaternary compounds bind to the surface of colloidal protein in blood, serum, to fibers present in cotton, mops, cloths, and paper towels used to apply them, which can cause inactivation of the agent by removing it from solution. Anionic detergents (soaps) inactivate them. That is why before applying quaternary ammonium compounds to the skin for preoperative disinfection, all traces of soap should be removed with water and with 70% alcohol.

The representatives of quaternary ammonium are *Roccal (Benzalkonium chloride), Aethonium, Cerigelum, Decamethoxin.*

Properly diluted, *Roccal* is used for the preoperative disinfection of unbroken skin and prophylactic disinfection of the intact skin, in the treatment of superficial injuries and infected wounds. It is also used to preserve the sterility of surgical instruments and rubber articles during storage, and to preserve the sterility of ophthalmic solutions. *Aethonium* and *Decamethoxin* are used for the treatment of trophic ulcers, stomatitis, keratitis. Finally *Cerigelum* is used for hands washing of medicine staff before surgical treatment.

Soaps are anionic detergents. They are weak antiseptic and affect only gram-positive bacteria. Their usefulness primarily resides in their cleansing action. Other antiseptics can medicate soaps.

Furacilinum (Nitrofurazone) is a synthetic antibacterial nitrofuran derivative. *Furacilinum* acts by transforming it nitro-group into the amino-group that leads to inhibiting bacterial enzymes involved in carbohydrate metabolism. Organic matter (e.g. blood, pus, serum) inhibits the antibacterial action of *Furacilinum*. *Furacilinum* has a wide spectrum of activity against a variety of gram-positive and gram-negative organisms, however, particularly it does not inhibit fungi or viruses. *Furacilinum* may be active against or-

ganisms that have developed resistance to antibiotics and sulfanilamides. It is used topically in patients with burns, for prophylaxis and treatment of infections of the skin and mucous membranes, middle and external ear caused by susceptible bacteria. *Furacilinum* solutions have been used as a bladder irrigant in catheterized patients.

Allergic contact dermatitis is the most frequently reported adverse effect of topical *Furacilinum* and has occurred in approximately 1% of patients treated.

Novoimaninum is anti-germ agent, obtaining from the plant *Hypericum perforatum*. It acts primary on gram-positive microorganisms, including penicillin-resistance staphylococci. *Novoimaninum* has used topically as solution for abscess and infective wound treatment.

Chlorophyllipt is a mixture *of* chlorophylls getting form *Eucalyptus leaves* and *Myrta's seeds.* It can be used for the treatment of burns, trophic ulcers.

Lysocim is the protein structure enzyme. It is produced from hen egg protein. *Lysocim* breaks polycarbohydrates of cell membrane, acts mostly on gram-positive germs. In addition it stimulates host non-specific resistance, causes anti-inflammation and mucolytic action. *Lysocim* is used for chronic septic state, burns, conjunctivitis. It applies topically and injects intramuscularly. It has not irritant action.

Available forms:

Chlorhexidine bigluconate — in bottles 20% solution 0.5; 3 or 5 liters each

Iodovidon (Povidone-Iodine) — in bottles 1% solution

Hydrogen peroxide — in glasses 3% solution

Potassium permanganate — in bottles 0.01%; 0.1%; 0.5%; 2% solution

Boric acid — in bottles 0.5%; 1%; 2%; 3% spirit solution 10 ml each

Hexamethylenetetramine — powder or tablets 0.25; 0.5 g each; in ampoules 40% solution 5; 10 ml each

Resorcin — powder; 2–5% solution (water or spirit); 5–20% ointment

Argent nitrate — powder; 0.25–2% or 2–10% solution; 1–2% ointment

Zinc sulfate — powder; eyes drops in bottles 0.25% or 0.5% solution 10 ml

Methylene blue — powder; 1% spirit or water solution; in ampoules 1% solution of *Methylene coeruleus* in 25% glucose solution 20; 50 ml

Ethacridine lactate — powder; in bottles 1% or 2% spirit solution 10 ml

Decamethoxin — tablets 0.1 gram for solution preparing; in bottles 0.05% spirit solution 10 ml each

Furacilinum — powder; tablets 0.1 g (for ingestion) and 0.02 g (for solution preparing); ointment 0.2%

ANTIMICROBIAL CHEMOTHERAPEUTIC AGENTS

Chemotherapeutics are antimicrobial agents that are used for germs killing inside the organism; the antimicrobial action usually occurs after they're appearing in the blood circulation system.

Spectrum of activity of agent is the list of microorganisms, that are sensitive to it. ***Chemotherapeutic spectrum*** is the list of infectious diseases, which can be cured by this agent.

The principles of effective chemotherapeutic actions are the following:

— Rational choice of preparation according to clinical and bacteriologic diagnosis

— Optimal dosage, way and interval between drug using

— Beginning of therapy as soon as possible before destructive changes of organs

— If the clinical improvements after 2–3 days course are absent, the agent must be changed

— The therapy have been continued 2–3 days after the clinical symptoms disappear

— Chemotherapy should be performed with other remedies that enforce the immunity

Lecture 35
ANTIBIOTICS

Antibiotics are the products of certain mycotic organisms, different bacteria. With the help of antibiotics these microorganisms can suppress the growing of another microbes or kill them. Antibiotic, which formed by alive organism, is **biosynthetic (natural)** antibiotic, however after chemical conversions it becomes **semisynthetic** antibiotic. Finally, antibiotic that we get as a result of chemical reaction only named as **synthetic** antibiotic.

In 1929 Alexander Fleming reported his discovery of first antibiotic — penicillin. In 1940 Chain, Florey succeeded in producing significant quantities of the first penicillin and discovered its efficiency for infectious disease. Ermolyeva during World War II elaborated the commercial production of penicillin in the USSR. Waxman made educing of streptomycin in 1944.

Classification of antibiotics according to a spectrum of their antimicrobial activity:

— With the main influence on the gram-positive microbes: *Penicillins*; *Cephalosporins*; *Macrolides*; reserve antibiotics *(Lincomycin, Vancomycin)*

— With main influence on the gram-negative microbes: *Aminoglycosides*

— Influencing both gram-positive and gram-negative microbes: *Tetracyclines*; *Levomycetin (Chloramphenicol)*

— Influencing both gram-positive and gram-negative microbes, and used locally: *Polymyxins*; *Neomycin*; *Monomycin*; *Gramicidin*

— Antifungal antibiotics: *Nystatin; Griseofulvin; Amphotericin B*

— Anticancer preparations: *Actinomycin, Olivomycin, Bruneomycin*

Classification according to the mechanism of action:

— Antibiotics that inhibit bacterial microbe's cell wall synthesis: penicillins, cephalosporins, and *Vancomycin*

— Antibiotics disordering permeability of microbe's cell capsule (decreasing the surface straining or detergent effect): antifungal antibiotics, polymyxins

— Antibiotics inhibiting synthesis of DNA, RNA: *Griseofulvin*, *Rifampicin*, and anticancer antibiotics

— Antibiotics inhibiting the protein synthesis of the microorganisms: macrolides, aminoglycosides, tetracyclines, and *Levomycetin*

Antibiotics can act *bactericidal* (penicillins, cephalosporins, aminoglycosides, polymyxins) and *bacteriostatic* (macrolides, tetracyclines, levomycetin, antimycotic antibiotics). Also antibiotics are divided into **basic** (main) agents and **supplemental** (reserve) agents. Usually, reserve antibiotics are less effective and more toxic, than basic agents are. Thus, the reserve antibiotics are indicated only in case of resistance or hypersensitivity to basic antibiotics.

When the inhibitory or killing effects of two or more antimicrobials used together are significantly greater than expected from their effects when used individually, synergism is said to result. For example, *Benzylpenicillin* in combination with *Gentamicin* is superior to monotherapy with *Penicillin* or *Gentamicin* for the treatment of enterococcal endocarditis. Enzymatic inactivation of β-lactam antibiotics is a major mechanism of antibiotic resistance. Several β-lactam + β-lactamase inhibitor combinations (e.g. *Amoxicillin-Clavulanic acid*) have been successful against a variety of bacterial infections.

On the other hand, bacteriostatic agents such as tetracyclines and levomycetin can antagonize the action of bactericidal cell wall-active agents (e.g. β-lactam antibiotics). The bactericidal effects of cell wall active agents require that the bacteria be actively growing and dividing. This antagonistic interaction is thought to be due to inhibition of bacterial growth by the bacteriostatic agent. Tetracyclines and levomycetin have also been shown to antagonize the bactericidal effects of aminoglycosides. Also it is not recommended the concurrent using of agents with the similar adverse effect, e.g. aminoglycosides with polymyxins.

In spite of the specific activity of antibiotics, they may cause some adverse effects. There are the following adverse effects, characteristic for antibiotics:

a. **Allergic reactions** of immediate and delayed types. Anaphylactic shock, angioneurotic laryngeal edema, exfoliative dermatitis, bullous erythema are the most hazardous. They are often caused by penicillins, cephalosporins.

b. **Disbacteriosis** is the modification of normal gastro-intestinal microflora, with suppression of susceptible coliform organisms. It leads to superinfection — overgrowing of *Pseudomonas*, *Proteus, Staphylococci, Clostridia,* and *Candida*. This can result in intestinal functional disturbances, anal pruritus, vaginal or oral candidiasis, staphylococcus enteritis, and hypovitaminosis. Antibiotics with a wide efficiency spectrum (*Tetracyclines, Levomycetin,* and *Ampicillin*) usually cause such effect.

c. **Toxic reactions** that are specific for antibiotics and depend on the dose and therapy terms. For example, *Levomycetin* causes bone marrow depression: reticulocytopenia, anemia, and granulocytopenia. Aminoglycosides are neurotoxic (neuritis of vestibulocochlear nerve); aminoglycosides and polymyxins can cause nephrotoxic impairments while tetracyclines are hepatotoxic.

d. **Endotoxic reaction** that is usually appears at the beginning of specific treatment of syphilis, typhoid fever, and meningitis. It may cause a state of shock, accompanied by severe diarrhea, fever, and leukopenia followed by leukocytosis. The reason of endotoxic reaction is releasing of endotoxin, which form an integral part of the cell wall of a variety of gram-negative bacteria.

The **β-lactam antibiotics** are the most frequently used group of antibiotics. The β-lactam compounds are penicillins, cephalosporins, monobactams, carbapenems, and beta-lactamase inhibitors.

PENICILLINS

Penicillin is produced by different species of Penicillium cultures. It inhibits bacterial microbes cell wall synthesis. Penicillins are bactericidal agents. All penicillins are the derivatives of 6-aminopenicillanic acid, which consists of thiazolidine ring and β-lactam ring. If the beta-lactam ring is enzymatically cleaved by bacterial beta-lactamases, the resulting product, penicilloic acid lacks antibacterial activity.

Classification of drugs:

— Biosynthetic penicillins: *Benzylpenicillin sodium, potassium or novocain salts (Penicillin G); Phenoxymethylpenicillin (Penicillin V); Bicillin-1 (Penicillin G Benzathine); Bicillin-5*

— Semisynthetic penicillins:

a) penicillinase resistant agents: *Oxacillin*; *Methicillin*; *Nafcillin;*

b) extended-spectrum penicillins: *Ampicillin*, *Amoxicillin* and antipseudomonal penicillins: *Carbenicillin*, *Carfecillin*, *Azlocillin*.

The spectrums of activity of biosynthetic penicillins include gram-positive cocci *(staphylo-; pneumo- and streptococci)*, gram-negative cocci *(meningo- and gonococcus)*, anaerobes *(Clostridium tetani, Cl. perfringens)*. Some other organisms for which biosynthetic *Penicillin* has good activity include *Bacillus anthracis, Corynebacterium diphtheriae*, and *Treponema Pallidum.* However, many strains of staphylococci produce beta-lactamases, which destroy these penicillins.

Benzylpenicillin sodium and *potassium* are not absorbed from the gastro-intestinal tract, because they are destroyed in acidic medium of the stomach. After i.m. injection peak of blood concentrations are usually obtained within 30 min and stay during 3–4 h. For maintenance of blood stable concentration it must be administrated every 4 h. Benzylpenicillins are widely distributed to most tissues and body fluids. They also cross the placenta and are distributed into breast milk. Distribution into the cerebrospinal fluid is low in subjects with non-inflamed meninges, as is penetration into purulent bronchial secretions.

The normal half-life of benzylpenicillin sodium and potassium is approximately 30 min. Hepatic metabolism accounts for less than 30% of the biotransformation of benzylpenicillins. They are rapidly excreted by the kidneys into the urine. About 10% of renal excre-

tion is by glomerular filtration and 90% by tubular secretion. Blood levels of all penicillins can be raised by simultaneous administration of *Probenecid*, which impairs their tubular secretion.

Benzylpenicillin sodium and *potassium* are the drug of choice for the treatment of actinomycosis, anthrax, diphtheria, gonorrhea, scarlet fever, syphilis, and gas gangrene. They also are used in the treatment of bacterial endocarditis, bacterial septicemia, sore throat, acute otitis media, bacterial pneumonia, rheumatic fever, bone and joint infections, skin diseases caused by susceptible organisms.

Benzylpenicillin novocain dissolves slowly at the site of injection, maintaining therapeutic concentration during 8–12 h. It has been used 3–4 times a day intramuscularly. It has the same spectrum antimicrobial activity, as *Benzylpenicillin sodium* or *potassium* salts. On the other hand, *Benzylpenicillin novocain* contains *Novocain*, which increases the danger of allergic reactions.

Bicillin-1 and *Bicillin-5* are slowly released from the i.m. injection site and hydrolyzed to benzylpenicillin, resulting in serum concentrations that are much lower but much more prolonged than other parenteral penicillins. A single injection of *Bicillin-1* or *Bicillin-5* intramuscularly once every 2–4 weeks is satisfactory for the treatment of syphilis, and for prophylaxis or treatment of rheumatic fever.

Phenoxymethylpenicillin is acid-resistant. It is indicated only in minor infections: prophylaxis of diphtheria and rheumatic fever, treatment of scarlet fever and sore throat. It is prescribed four times a day.

Oxacillin is resistant to staphylococcal *penicillinase* (*β-lactamase*). The sole indication for the use of this agent is infection by penicillinase-producing staphylococci; however, it is less potent than *Benzylpenicillin* against penicillin-sensitive bacteria. *Oxacillin* is acid-stable and reasonably well absorbed from the gut. It is widely distributed to most tissues and body fluids. It is ingested four times a day. For serious systemic staphylococcal infections, *Oxacillin* is given by intermittent intravenous infusion of 1–2 g every 4–6 h. *Methicillin* is no longer used because of its nephrotoxicity.

Ampicillin, *Amoxicillin* are extended-spectrum penicillins. These drugs retain the antibacterial spectrum of *Penicillin*, differ in having greater activity against gram-negative cocci and bacteria such as *Escherichia coli*, *Shigella*, and *Salmonella* species. Like *benzylpenicillin*, they are inactivated by penicillinase.

Ampicillin and *Amoxicillin* are acid-stable and relatively well absorbed, achieving serum concentrations within 1–2 h (for intramuscularly injection — 0.5 h). Amoxicillin is better absorbed from the gut, than ampicillin. The duration of action is about 4–6 h. *Ampicillin* is excreted in the bile in high concentrations. *Amoxicillin* is only oral penicillins, than can be taken during mealtimes, all the other oral penicillins should be given 1–2 h before or after eating to minimize binding to food proteins and acid inactivation. *Ampicillin* and *Amoxicillin* can be used for the treatment of bone and joint infections, sore throat, bronchitis, pneumonia, meningitis, bacillary dysentery, typhoid fever, septicemia, urinary tract infections caused by susceptible organisms.

Ampicillin, *Amoxicillin* are also available in combination with one of several beta-lactamase inhibitors: *Clavulanic acid, Sulbactam.* The addition of a beta-lactamase inhibitor extends the activity of these penicillins to include beta-lactamase-producing strains of staphylococci as well as some beta-lactamase-producing gram-negative bacteria. For example, *Unasyn (Ampicillin + Sulbactam)*, *Augmentin (Amoxicillin + Clavulanic acid)*.

Ampiox (Ampicillin + Oxacillin) is the combination of *Ampicillin* and *Oxacillin*. Thanks to that it's active against both penicillinase-producing staphylococci and broad spectrum of gram-positive and gram-negative microbes.

The antipseudomonal penicillins (*Carbenicillin, Carfecillin,* and *Azlocillin*) are also extended-spectrum penicillins, but they have less activity against gram-positive organisms than the natural penicillins or ampicillin; however, unlike the other penicillins, these penicillins are active against some gram-negative bacilli, including *Pseudomonas aeruginosa*, *Proteus vulgaris*. *Carbenicillin* is the first antipseudomonal carboxypenicillin. *Carfecillin* is the converted carbenicillin; it can be used orally. It's active in lower doses, than *Carbenicillin*. The *Ureidopenicillins*, *Azlocillin*, resemble *Carbenicillin* except that it is also active against selected gram-negative bacilli, such as *Klebsiella pneumoniae*, and more potent against *Pseudomonas aeruginosa*, than *Carbenicillin.*

Carbenicillin, *Carfecillin*, and *Azlocillin* are indicated in the treatment of bone, joint, skin, and soft tissue infections, endocarditis, septicemia, pneumonia, meningitis, intra-abdominal infections, prostatitis, female pelvic infections, and urinary tract infections caused by susceptible organisms.

Adverse effects. The penicillins are remarkably nontoxic. Most of the serious adverse effects are due to hypersensitivity. It is appearing quite frequent (1–10%). All penicillins are cross-sensitizing and cross-reacting. Allergic reactions include fever, joint swelling, angioneurotic edema, pruritus, and rashes. Very rare anaphylactic shock may occur. In patients with renal failure, penicillins in high doses can cause seizures. Large doses of penicillins given orally may lead to gastrointestinal upset, particularly nausea, vomiting, and diarrhea. *Ampicillin* has been associated with pseudomembranous colitis. Secondary infections such as vaginal candidiasis may occur. *Ampicillin* and *Amoxicillin* can cause skin rashes that are not allergic in nature.

CEPHALOSPORINS

First cephalosporin was obtained from culture of *Cephalosporium acremonium*. Cephalosporins are similar to penicillins chemically, in mechanism of action, and toxicity. Cephalosporins are more stable than penicillins to many bacterial β-lactamases and therefore usually have a broad spectrum of activity. The nucleus of the cephalosporins is 7-aminocephalosporanic acid. Cephalosporins can be classified into four major groups or "generations", depending mainly on the spectrum of antimicrobial activity. As a general rule, first-generation compounds have better activity against gram-positive organisms and the later compounds ex-

hibit improved activity against gram-negative aerobic organisms.

Classification of drugs:

— First-generation cephalosporins: Cefazolin, Cephalothin, Cephaloridine, Cephalexin

— Second-generation cephalosporins: *Cefaclor*, *Cefuroxime*, *Cefoxitin*

— Third-generation cephalosporins: *Cefotaxime*, *Ceftriaxone*, *Cefixime*

— Fourth-generation cephalosporins: *Cefepime*, *Cefpirome*

First-generation cephalosporins are active against gram-positive cocci (pneumo-, strepto-, and staphylococci), *Neisseria gonorrhoeae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*. They are used to treat septicemia, bone and joint infections, otitis media, pneumonia, skin and soft tissue infections, including burn wound infections, and urinary tract infections caused by susceptible bacterial organisms. These medications are possible alternatives to the penicillins for staphylococcal and streptococcal infections.

Cefazolin can be used intramuscularly or intravenously every 8 h (Table 12). Excretion is via the kidney. *Cefazolin* penetrates well into most tissues. It is the drug of choice for surgical prophylaxis because of its longer half-life. *Cefazolin* may be a choice in infections for which it is the least toxic drug (e.g. *Klebsiella pneumoniae*). *Cephalexin* is absorbed from the gut to a variable extent. Urine concentration is usually very high. It may be used for the treatment of urinary tract infections, for minor staphylococcal lesions, or for minor polymicrobial infections such as cellulitis or soft tissue abscess.

In general, ***second-generation cephalosporins*** are active against organisms affected by first-generation drugs, but they have an extended gram-negative coverage, e.g. *Proteus vulgaris*, *Enterobacter*, *Haemophilus influenzae*. All second-generation cephalosporins are less active against gram-positive bacteria than the first-generation drugs. Some *Enterobacter* species can express a chromosomal beta-lactamase that hydrolyzes second-generation cephalosporins (as well as third-generation cephalosporins).

Cefuroxime is the only second-generation drug that crosses the blood-brain barrier, but it is less effective in treatment of meningitis than *Ceftriaxone* or *Cefotaxime* and should not be used. However, *Cefuroxime* more stable against certain β-lactamases. *Cefuroxime* is commonly used to treat community-acquired pneumonia because of its extend spectrum activity. *Cefuroxime axetil*, an oral prodrug of *Cefuroxime*, is hydrolyzed to *Cefuroxime* after absorption. It has been used to treat mild to moderate bronchitis, otitis media, skin and soft tissue infections, uncomplicated gonococcal urethritis, and urinary tract infections.

Cefoxitin has the greatest stability in the presence of β-lactamases produced by the Bacteroides fragilis group. Because of its activity against anaerobes, *Cefoxitin* can be useful in such mixed anaerobic infections as aspiration pneumonia, intra-abdominal and female pelvic infections. It is also used prophylactically to help prevent perioperative infections that may result from colorectal surgery and appendectomies, and in the treatment of penicillin-resistant strains of gonorrhea.

Cefaclor is more susceptible to β-lactamase hydrolysis compared with the other agents, and its utility is correspondingly diminished. It has been primarily used to treat sinusitis, otitis, or lower respiratory tract infections, in which these organisms have an important role.

Third-generation agents are less active against gram-positive cocci as are the first- and second-generation. However, in addition to the gram-negative bacteria inhibited by other cephalosporins, third-generation drugs are active against *Serratia*, *Enterobacter* as well as β-lactamase-producing strains of *Haemophilus* and *Neisseria. Ceftazidime* and *Cefoperazone* are useful against *Pseudomonas aeruginosa.* Some cephalosporins *(Ceftriaxone, Cefotaxime)* are able to cross the blood-brain barrier.

Third-generation cephalosporins are used in the treatment of serious gram-negative bacterial infections, including septicemia, bone infections, female pelvic and intra-abdominal infections, and urinary tract infections caused by organisms that are resistant to most other drugs. *Ceftriaxone* and *Cefotaxime* are first-line drugs for treatment of gonorrhea, meningitis. They are

Table 12. **Pharmacokinetics of cephalosporins**

Agent	Bioavailability, %	Protein binding, %	Half-life, h	Dosing information
Cefazolin/ i.m.		85	1.4–1.8	0.5 g 3 times a day
Cephalothin/ i.m.		70	0.5–1.0	0.5 g 4 times a day
Cephalexin/ oral	90–95	15–20	0.9–1.2	0.5 g 4 times a day
Cefaclor/ oral	50–95	25	0.6–0.9	0.25 g 3 times a day
Cefuroxime/ i.m.		50	1.2–1.9	0.75 g 3 times a day
Cefoxitin/ i.m.		70–80	0.7–1.1	1–2 g 3 times a day
Cefotaxime/ i.m.		38	1.0	0.5 g 2 times a day
Ceftriaxone/ i.m.		85–95	5.8–8.7	1–2 g once a day
Cefixime/ oral	40–50	65–70	3.0–4.0	

the most active cephalosporins against penicillin-resistant strains of pneumococci and are recommended for empirical therapy of serious infections that may be caused by these strains.

The excretion of *Cefoperazone* and *Ceftriaxone* is mainly through the biliary tract, and no dosage adjustment is required in renal insufficiency. The others are excreted by the kidney and therefore require dosage adjustment in renal insufficiency.

Cefepime is an example of a so-called *fourth-generation Cephalosporin*. It is in many ways similar to third-generation agents, but it is more resistant to hydrolysis by chromosomal beta-lactamases (e.g. those produced by *Enterobacter*), that inactivate many of the third-generation cephalosporins. It has good activity against *Pseudomonas aeruginosa*. The clinical role of *Cefepime*, which remains to be defined, will probably be similar to that of the third-generation cephalosporins except that it may be useful in treatment of infections caused by *Enterobacter*.

Adverse effects. *Cephalosporins* are sensitizing and may elicit skin rashes, pruritus, fever, granulocytopenia, and hemolytic anemia. The frequency of cross-allergenicity between cephalosporins and penicillins is around 5–10%. Local irritation can produce severe pain after i.m. injection and thrombophlebitis after i.v. injection. Renal toxicity, including interstitial nephritis has been caused by *Cephaloridine*. *Moxalactam, Cefoperazone* could cause hypoprothrombinemia, bleeding disorders, and disulfiram-like reactions. Many second- and particularly third-generation cephalosporins are ineffective against gram-positive organisms, especially methicillin-resistant staphylococci and enterococci. During treatment superinfection, mycosis may appear.

MONOBACTAMS

The representative of this group is *Aztreonam*. This is drug with a monocyclic β-lactam ring. *Aztreonam* inhibit bacterial cell wall synthesis and acts bactericidal. It is relatively resistant to β-lactamases and active against gram-negative rods (including *Pseudomonas*, *Klebsiella*, *Serratia*, and *Proteus mirabilis*). However, it has no activity against gram-positive bacteria or anaerobes. It resembles aminoglycosides in its spectrum of activity. *Aztreonam* is given i.v. or i.m. every 8 hours in a dose of 1–2 g. It is rapidly and widely distributed to body fluids and tissues. The half-life is 1–2 h. It is excreted via kidneys (60–75% excreted unchanged). *Aztreonam* is indicated in the treatment of bacterial pneumonia, skin and soft tissue infections, urinary tract infections, gynecologic and intra-abdominal infections, septicemia. Penicillin-allergic patients tolerate *Aztreonam* without reaction. Occasional skin rashes and phlebitis at the injection site may occur.

CARBAPENEMS

The carbapenems are structurally related to β-lactam antibiotics. *Imipenem* and *Meropenem* are the two that are available. They have a wide spectrum with good activity against many gram-negative rods *(Pseudomonas, Enterobacter, Serratia)*, gram-positive organisms, and anaerobes. They are resistant to most β-lactamases.

Carbapenems penetrate body tissues and fluids well, including the cerebrospinal fluid; the half-life is about 1–1.5 hours. *Imipenem* is inactivated by dehydropeptidase in renal tubules, resulting in low urinary concentrations. Consequently, it is administered together with an inhibitor of renal dehydropeptidase, *Cilastatin*, for clinical use. *Tienam (Imipenem + Cilastatin)* is example of such combination. *Meropenem* is not significantly degraded by renal dehydropeptidase and does not require an inhibitor. It is primarily excreted unchanged by kidneys. The usual dose is given i.v. or i.m. every 6–8 hours. Carbapenems are indicated in the treatment of intra-abdominal infections, skin and soft tissue infections caused by susceptible organisms. They have the same mechanism action as *Aztreonam*.

The most common adverse effects of carbapenems are nausea, vomiting, diarrhea, skin rashes, and reactions at the infusion sites. Carbapenems may lead to seizures in patients with a prior history of seizures or CNS abnormality. Patients allergic to penicillins or cephalosporins may be allergic to carbapenems as well.

MACROLIDES

The macrolides characterized by a macrocyclic lactone ring (usually containing 14 or 16 atoms) to which deoxy sugars are attached. *Erythromycin* is obtained from *Streptomyces erythreus* (since 1952), *Oleandomycin* — from *Streptomyces antibioticus*. *Clarithromycin* and *Azithromycin* are semisynthetic derivatives of *Erythromycin*. Macrolides are effective against gram-positive organisms (pneumo-, strepto-, staphylococci, and *Corynebacteria*), *Mycoplasma*, *Legionella*, *Chlamydia trachomatis*, *Helicobacter*, *Treponema pallidum*, and *Rickettsia* species. The antibacterial action of macrolides is bacteriostatic. They inhibit protein synthesis via binding to the ribosomal RNA and blocking aminoacyl translocation reactions. Activity is enhanced at alkaline pH.

Erythromycin base is destroyed by stomach acid and must be administered with enteric coating. Food interferes with absorption. Bioavailability varies between 30 and 65%, depending on the salt. The serum half-life is approximately 1.5 h. Large amounts of an administered dose are excreted in the bile and lost in feces. More than 90% of *Erythromycin* is hepatically metabolized. The absorbed drug is distributed widely except to the brain and cerebrospinal fluid. *Erythromycin* is taken up by polymorphonuclear leukocytes and macrophages. It traverses the placenta and reaches the fetus. Duration of action is about 4–6 hours.

Erythromycin is the drug of choice in bronchitis, sinusitis, acute otitis media, and diphtheria, in chlamydial or mycoplasmal infections. It is also useful as a penicillin substitute in penicillin-allergic individuals with infections caused by staphylococci (assuming that the isolate is susceptible), streptococci, pneumococci, or *Treponema pallidum*.

Adverse reactions. Nausea, vomiting, diarrhea, and hypersensitivity reactions occasionally accompany erythromycin administration. *Erythromycins*, particularly the estolate, can produce acute cholestatic hepatitis. *Erythromycin* metabolites can inhibit cytochrome P-450 enzymes and thus increase the serum concentrations of *Theophylline*, oral anticoagulants, and *Cyclosporine*. In general, *Erythromycin* has a low toxicity and can be taken by pregnant women (except erythromycin estolate). *Erythromycin*-resistant strains emerge frequently; they may appear after the first course therapy. That's why the current utility of *Erythromycin* is limited.

Oleandomycin is similar in antimicrobial activity and pharmacokinetic properties to *Erythromycin*.

Clarithromycin is derived from *Erythromycin*. This conversion improves acid stability and, therefore, oral absorption compared with *Erythromycin*. Its mechanism of action is the same as that of erythromycin. *Clarithromycin* and *Erythromycin* are virtually identical with respect to antibacterial activity except that *Clarithromycin* is more active against *Mycobacteria avium* and *Leprae*, *Toxoplasma gondii*. Erythromycin-resistant streptococci and staphylococci are also resistant to *Clarithromycin*. *Clarithromycin* is well absorbed from the gastrointestinal tract; stable in gastric acid; food does not delay the extent of absorption; bioavailability is approximately 55%. It is widely distributed into tissues and fluids. *Clarithromycin* is metabolized in the liver. The major metabolite is *14-Hydroxyclarithromycin*, which also has antibacterial activity. The serum half-life depends on giving dose (about 4–7 hours). Excreted by kidneys. The advantages of *Clarithromycin* compared with *Erythromycin* are lower frequency of gastrointestinal intolerance and less frequent dosing. It can be taken twice daily.

Azithromycin 15-atom lactone macrolide rings compound is derived from *Erythromycin*. Its spectrum of activity and clinical uses are virtually identical to those of *Clarithromycin*. *Azithromycin* is slightly less active than *Erythromycin* and *Clarithromycin* against staphylococci and streptococci and slightly more active against *Haemophilis influenzae* and *Chlamydia*. *Azithromycin* differs from *Erythromycin* and *Clarithromycin* mainly in pharmacokinetic properties. It is rapidly absorbed and well tolerated orally. Food decreases bioavailability of *Azithromycin*, which should be administered 1 hour before or 2 hours after meals. However, *Azithromycin* penetrates into most tissues (except cerebrospinal fluid) and phagocytic cells extremely well, with tissue concentrations exceeding serum concentrations by 10- to 100-fold. Drug is slowly released from tissues (tissue half-life of 2–4 days) to produce an elimination half-life approaching 3 days. These unique properties permit once-daily dosing and shortening of the duration of treatment in many cases. For example, a single 1 g dose of *Azithromycin* is as effective as a 7-day course of *Doxycycline* for chlamydial cervicitis and urethritis. *Azithromycin* is indicated for treatment tonsillitis, bronchitis, pneumonia, acute otitis media, cervicitis or urethritis, pelvic inflammatory, skin and soft. It may cause nausea, vomiting, and diarrhea.

AMINOGLYCOSIDES

Aminoglycosides are a group that includes *Streptomycin*, *Neomycin*, *Kanamycin*, *Amikacin*, *Gentamicin*, *Tobramycin*, *Sisomicin*, and others. Aminoglycosides have a hexose ring, either streptidine (in streptomycin) or 2-deoxystreptamine (other aminoglycosides), to which various amino sugars are attached by glycosidic linkages. They are water-soluble, stable in solution, and more active at alkaline than at acid pH.

Aminoglycosides bind to specific subunit ribosomal proteins and irreversible inhibit the protein synthesis; they act bactericidal. The transport of aminoglycosides across the cell membrane into the cytoplasm may be enhanced by cell wall-active drugs, such as *Penicillin* or *Vancomycin*; this enhancement may be the basis of the synergism. **The spectrum of aminoglycosides** covers aerobic gram-negative bacilli, and some gram-positive organisms. They are generally active against *Pseudomonas*, *Escherichia coli*, *Proteus*, *Enterobacter*, *Klebsiella*, *Serratia species*, *Enterococcus faecalis* and staphylococci. They are not active against anaerobic organisms.

Aminoglycosides are absorbed very poorly from the gastrointestinal tract. After i.m. injection, aminoglycosides are well absorbed, giving peak concentrations in blood within 1–2 h. Aminoglycosides have been administered in two or three equally divided daily doses. Aminoglycosides are highly polar compounds that do not enter cells readily. They distributed primary to extracellular fluid (urine, serum, abscesses, and synovial fluids), however low concentrations found in bile, breast milk, and cerebral spinal fluid. Also distributed to all body tissues, where aminoglycosides accumulate intracellularly. High concentrations found in highly perfused organs (liver, lungs, and kidneys), but lower concentrations are seen in muscle, fat, and bone. They cross the placenta. All aminoglycosides has a low protein binding (0 to 10%). They are not metabolized. Aminoglycosides are cleared by the kidney. The normal half-life in serum is 2–3 hours.

Aminoglycosides are indicated in the treatment of serious systemic infections caused by gram-negative enteric bacteria for which less toxic antibacterials are ineffective or contraindicated. They are almost always used in combination with a β-lactam antibiotic in order to extend coverage to include potential gram-positive pathogens and to take advantage of the synergism between these two classes of drugs.

Adverse effects. All aminoglycosides are ototoxic and nephrotoxic. These effects are more likely to be encountered when therapy is continued for more than 5 days, at higher doses, in the elderly, and in the setting of renal insufficiency. Ototoxicity can manifest itself either as auditory damage (tinnitus and high-frequency hearing loss); or as vestibular damage (vertigo, ataxia, and loss of balance). Nephrotoxicity results in rising serum creatinine levels. Concurrent use with loop diuretics *(Furosemide)* or other nephrotoxic antimicrobial agents *(Amphotericin B)* can potentiate nephrotoxicity. In very high doses, aminoglycosides can produce a curare-like effect with neuromuscular blockade that results in respiratory paralysis. Hypersensitivity occurs infrequently.

Streptomycin is the oldest and best-studied of the aminoglycosides. It is obtained from a strain of *Streptomyces globisporus*. The antimicrobial activity of *Streptomycin* is typical of that of other aminoglycosides. Resistance has emerged in most species, severely limiting the current usefulness of *Streptomycin*, with the exceptions listed below. *Streptomycin* is used primarily as an antitubercular and is active against *Mycobacterium tuberculosis* and M. bovis. It is also considered the drug of choice for the treatment of infections caused by *Francisella tularensis* and *Yersinia pestis*, and is often used to treat Brucella infections in combination with *Tetracycline*. *Penicillin* plus *Streptomycin* is effective for enterococcal endocarditis. Fever, skin rashes, and other allergic manifestations may result from hypersensitivity to *Streptomycin*. Pain at the injection site is common. The most serious toxic effect is disturbance of vestibular function. Vestibular toxicity tends to be irreversible. *Streptomycin* given during pregnancy can cause deafness in the newborn.

Neomycin is a combination of antibiotics neomycins A, B, C, that synthesized by *Actinomyces fradiae*. It is active against gram-positive and gram-negative bacteria and some mycobacteria. Streptococci are generally resistant. A mechanism of antibacterial action is the same as with other aminoglycosides. *Neomycin* is not significantly absorbed from the gastrointestinal tract. After oral administration, the intestinal flora is suppressed or modified and the drug is excreted in the feces. Excretion of absorbed drug is mainly through glomerular filtration into the urine.

Neomycin is used widespread in bowel preparation for colon surgery. This reduces the aerobic bowel flora with little effect on anaerobes. Also it can be prescribed for topical administration as solution or ointment on infected surfaces or abscess cavities where infection is present. Topically *Neomycin* can be added by glucocorticoids. Such combination will cause antimicrobial and anti-inflammatory effects. Resistance to neomycin appear more rare comparatively with other aminoglycosides. *Neomycin* is too toxic for parenteral use. It has significant nephrotoxicity and ototoxicity. Auditory function is affected more than vestibular. Deafness occurrs.

Gentamicin is an aminoglycoside isolated from *Micromonospora purpurea*. It is effective against both gram-positive and gram-negative organisms, and many of its properties resemble those of other aminoglycosides. *Gentamicin* as much as *Tobramycin*, and *Amikacin* are the most widely employed aminoglycosides at present. *Gentamicin* is used mainly in severe infections, e.g. sepsis, intra-abdominal and urinary tract infections, meningitis, skin and soft tissues infections, bacterial pneumonia caused by gram-negative bacteria that are likely to be resistant to other drugs. It is also used concurrently with penicillins for bactericidal activity in endocarditis. *Gentamicin* should not be used as a single agent to treat staphylococcal infections because resistance develops rapidly.

Gentamicin can be used i.v., i.m. or topically. The daily dose of gentamicin is divided into three equal amounts and given every 8 h. Creams, ointments, or solutions have been used for the treatment of infected burns, wounds, or skin lesions and the prevention of intravenous catheter infections. It can exhibit reversible and usually mild nephrotoxicity. Ototoxicity, which tends to be irreversible, manifests itself mainly as vestibular dysfunction, perhaps due to destruction of hair cells by prolonged elevated drug levels. Loss of hearing can also occur.

Tobramycin has an antibacterial spectrum similar to that of *Gentamicin*. While there is some cross-resistance between *Gentamicin* and *Tobramycin*, although a few organisms resistant to *Gentamicin* remain susceptible to *Tobramycin*. *Tobramycin* has almost the same antibacterial spectrum as *Gentamicin* with a few exceptions. *Tobramycin* is slightly more active against *Pseudomonas* than others aminoglycosides. *Gentamicin* and *Tobramycin* are otherwise completely interchangeable clinically. The pharmacokinetic properties of *Tobramycin* are virtually identical to those of *Gentamicin*. Like other aminoglycosides, *Tobramycin* is ototoxic and nephrotoxic. Nephrotoxicity of *Tobramycin* may be slightly less than that of *Gentamicin*.

Sisomicin is similar in spectrum and indication to *Gentamicin*. But it has higher antimicrobial activity and less toxic, than *Gentamicin*.

Amikacin is a semisynthetic derivative of *Kanamycin*; it is less toxic than the parent molecule. *Amikacin* is similar to *Gentamicin* and *Tobramycin* in its spectrum of activity; however, *Amikacin* has the advantage of not being inactivated by the same enzymes. Thus, it therefore can be employed against some microorganisms resistant to the latter drugs. Many gram-negative enteric bacteria, including many strains of *Proteus*, *Pseudomonas*, *Enterobacter*, *Serratia*, and *Mycobacterium tuberculosis,* including streptomycin-resistant strains are inhibited by *Amikacin*. Like all aminoglycosides, *Amikacin* is nephrotoxic and ototoxic (particularly for the auditory portion of the eighth nerve).

LEVOMYCETIN (CHLORAMPHENICOL) GROUP

Chloramphenicol (Levomycetin) can be isolated from cultures of Streptomyces venezuelae and can be synthesized chemically. It is soluble in alcohol but poorly soluble in water. *Levomycetin succinate*, which is used for parenteral administration, is highly water-soluble. It is hydrolyzed *in vivo* with liberation of free *Levomycetin*. *Levomycetin* is a bacteriostatic broad-spectrum antibiotic that is active against aerobic both gram-positive and gram-negative organisms, including *Shigella species*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*. Bacteria that are generally considered to be resistant to *Levomycetin* include *Pseudomonas aeruginosa*, *Enterobacter species*, and *Enterococcus faecalis*. Forming of resistance to *Levomycetin* is quite slow. *Levomycetin* is a potent inhibitor of microbial protein synthesis. It binds reversibly to the 50S subunit of the bacterial ribosome. It inhibits the peptidyl transferase step of protein synthesis.

Levomycetin is rapidly and completely absorbed from gastrointestinal tract (bioavailability — 80%). After absorption, it is widely distributed to virtually all tissues and body fluids, including the breast milk, central nervous system and cerebrospinal fluid so that the concentration of *Levomycetin* in brain tissue may

be equal to that in serum. It crosses placenta. The drug penetrates cell membranes readily. The protein binding is moderate (50%). Most of *Levomycetin* (90%) is inactivated by conjugation with glucuronic acid in the liver. The therapeutic concentration of drug in serum remains during 4–6 h. Excretion of active *Levomycetin* (about 10% of the total dose administered) and of inactive degradation products occurs by way of the urine. The daily dose is divided in three-four times.

Because of this drug's serious toxicity, *Levomycetin* is indicated only for the treatment of serious infections in which less toxic antibacterials are ineffective or contraindicated. *Levomycetin* is indicated for the treatment of tularemia, plague, brucellosis, meningitis, caused by *Haemophilis influenzae*, *Neisseria meningitidis*; typhoid fever, caused by *Salmonella typhi*. It is also used in the treatment of rickettsial infections. Levomycetin-resistance strains are appearing slowly.

Adverse reactions. Occasionally nausea, vomiting, and diarrhea develop. Oral or vaginal candidiasis may occur as a result of alteration of normal microbial flora. *Levomycetin* commonly causes a dose-related reversible bone marrow depression: reticulocytopenia, anemia, and granulocytopenia. Aplastic anemia is an idiosyncratic reaction unrelated to dose. It tends to be irreversible and can be fatal. Hypersensitivity (rash, pruritus, fever), neurotoxic reactions (confusion, headache, and blurred vision) may elicit.

Newborn infants lack an effective glucuronic acid conjugation mechanism for the degradation and detoxication of *Levomycetin*. Consequently, when infants are given *Levomycetin*, the drug may accumulate, resulting in the *gray baby syndrome*, with vomiting, flaccidity, hypothermia, gray color, shock, and collapse. To avoid this toxic effect, *Levomycetin* should be used with caution in full-term and premature infants.

Levomycetin inhibits hepatic microsomal enzymes that metabolize several drugs. Half-life is prolonged, and the serum concentrations of *Phenytoin*, *Tolbutamide*, and *Chlorpropamide* are increased. Like other bacteriostatic inhibitors of microbial protein synthesis, *Levomycetin* can antagonize bactericidal drugs such as penicillins or aminoglycosides.

TETRACYCLINES

The tetracyclines are a large group of drugs with a common basic structure and activity. *Tetracycline* is isolated from streptomyces; *Oxytetracycline* is derived from *Streptomyces rimosus*. *Methacycline* and *Doxycycline*, semisynthetic antibiotics, are the derivatives of *Tetracycline* and *Oxytetracycline*, respectively. Free tetracyclines are substances of low solubility. They are available as hydrochlorides, which are more soluble. Tetracyclines are broad-spectrum antibiotics that inhibit protein synthesis. Tetracyclines bind reversibly to the 30S subunit of the bacterial ribosome, blocking the binding of aminoacyl-tRNA to the acceptor site on the mRNA-ribosome complex. This prevents addition of amino acids to the growing peptide.

The antibacterial activities of most tetracyclines are similar. Differences in clinical efficacy are minor and attributable largely to features of absorption, distribution, and excretion of individual drugs. They are bacteriostatic for many gram-positive and gram-negative bacteria, including anaerobes, *Escherichia coli*, *Shigella*, *Rickettsia*, *Chlamydia*, *Mycoplasma*, *meningo- gono-*, *streptococci*, and are active against some *Protozoa*, e.g. *Amebas*.

Absorption after oral administration is approximately 60–70% for *Tetracycline*, *Oxytetracycline*, and *Methacycline*; and 95–100% for *Doxycycline*. A portion of an orally administered dose of *Tetracycline* remains in the gut lumen, modifies intestinal flora, and is excreted in the feces. Absorption is impaired by food (except *Doxycycline*), by cations Ca^{2+}, Mg^{2+}, Fe^{2+}, or Al^{3+}, and by alkaline pH. Tetracyclines are 40-80% bound by serum proteins. Tetracyclines are distributed widely to tissues and body fluids except for cerebrospinal fluid. Tetracyclines tend to localize in bone, liver, spleen, tumors, and teeth. They cross the placenta and are also excreted in milk. Tetracyclines are excreted unchanged mainly in bile and urine, mainly by glomerular filtration. Some of the drug excreted in bile is reabsorbed from the intestine (enterohepatic circulation) and contributes to maintenance of serum levels. 20–40% of tetracyclines in the body is excreted in feces. *Doxycycline*, in contrast to other tetracyclines, primary is eliminated with feces (90%), does not accumulate significantly in renal failure.

Tetracyclines **are classified** as **short acting** *(Tetracycline, Oxytetracycline)*, **intermediate acting** *(Methacycline)*, or **long acting** *(Doxycycline)* based on serum half-lives of 6–8 hours, 12 hours, and 16–20 hours, respectively.

Systemic tetracyclines are indicated in the treatment of bronchitis, pharyngitis, pneumonia, sinusitis, septicemia, and intra-abdominal and genitourinary tract infections. They can be used in the treatment of chlamydial infections, gonorrhea, bacillary and amebic dysentery, syphilis, trachoma, rickettsial infections, cholera. A *Tetracycline* — usually in combination with an aminoglycoside — is indicated for plague, tularemia, and brucellosis.

Adverse reactions. Nausea, vomiting, stomatitis, glossitis, and diarrhea are the most common reasons for discontinuing tetracycline medication. These effects are attributable to direct local irritation of the intestinal tract. That's why, i.v. injection can lead to venous thrombosis, i.m. injection produces painful local irritation. Tetracyclines modify the normal flora, with suppression of susceptible coliform organisms and overgrowth of *Pseudomonas*, *Proteus*, staphylococci, *Clostridia*, and *Candida*. This can result in intestinal functional disturbances, anal pruritus, vaginal or oral candidiasis, or pseudomembranous enterocolitis.

Tetracyclines are readily bound to calcium deposited in newly formed bone or teeth in infants and children under 8 years of age. It can be deposited in the fetal teeth, leading to fluorescence, discoloration, and enamel dysplasia; it can also be deposited in the bone, where it may cause deformity or growth inhibition. It is also contraindicated during pregnancy. Sometimes hypersensitivity reactions (fever, skin rashes, and photosensitization) may occur.

POLYMYXINS

The polymyxins are a group of basic peptides active against gram-negative bacteria. They are formed by *Bacillus polymyxa*. To this group belongs *Polymyxin M sulfate* and *Polymyxin B sulfate*. The sulfates are water-soluble and very stable. *Polymyxins* are bactericidal for many gram-negative rods, including *E. coli*, *Shigella*, and *Pseudomonas*. Gram-positive organisms, *Proteus*, and *Neisseria* are resistant. In susceptible bacterial populations, resistant mutants are rare. Polymyxins act like cationic detergents. They attach to bacterial cell membranes, increase its permeability, and microbes cell essential substance are going outside. *Polymyxins* are active against extracellular microbes only. They also bind and inactivate endotoxin.

Polymyxin M is not used for systemic administration because of its poor tissue distribution, it substantial nephrotoxicity and neurotoxicity. *Polymyxin M* can be used locally. Commonly it is applied concurrently with neomycin to infected superficial skin lesions (burns, ulcers, abscesses) caused by susceptible microorganisms. Local reactions and hypersensitivity to topical administration are rare (Table 13).

Polymyxin B is used i.m., i.v. and orally. *Polymyxin B* sulfates is not absorbed from the normal alimentary tract, thus it is used for the treatment of enterocolitis, in bowel preparation for colon surgery. Active blood level is low. Repeated injections may give a cumulative effect. The drug is excreted slowly by the kidneys. Tissue diffusion is poor and the drug does not pass the blood brain barrier into the cerebrospinal fluid. That's why, in meningeal infections, *Polymyxin B sulfate* should be administered only by the intrathecal route. It may be indicated for serious infections caused by susceptible strains, when less potentially toxic drugs are ineffective or contraindicated. *Polymyxin B* is a drug of choice in the treatment of infections of the urinary tract, skin, meninges, and bloodstream caused by *Pseudomonas aeruginosa*. It may be indicated for the treatment of pneumonia, bacteremia caused by *Klebsiella pneumoniae*.

Table 13. **Indications for using of basic and supplemental antibiotics**

Infections	Antibiotic(s) of first choice	Alternative antibiotic
Staphylococci (susceptible to benzylpenicillin)	*Benzylpenicillin Phenoxymethylpenicillin*	*Cephalosporins, Macrolides Vancomycin, Tienam*
Staphylococci (resistant to benzylpenicillin)	*Oxacillin, Vancomycin*	*Cephalosporins, Macrolides*
Streptococci	*Benzylpenicillin, Ampicillin, Aminoglycosides*	*Cephalosporins, Macrolides, Tetracyclines*
Pneumococci	*Benzylpenicillin, Ampicillin, Macrolides,*	*Cephalosporins, Vancomycin*
Enterococci	*Benzylpenicillin + Gentamycin, Ampicillin*	*Aminoglycosides, Vancomycin*
Meningococci	*Benzylpenicillin, Ampicillin*	*Levomycetin, Cephalosporins,*
Gonorrhea	*Amoxicillin, Ampicillin Benzylpenicillin, Ceftriaxone*	*Cephalosporins*
Syphilis	*Benzylpenicillin*	*Macrolides, Tetracyclines Tetracyclines,*
Gas gangrene	*Benzylpenicillin*	*Levomycetin, Cephalosporins, Clindamycin*
Tetanus	*Benzylpenicillin*	*Tetracyclines, Cephalosporins, Clindamycin*
Diphtheria	*Macrolides, Benzylpenicillin*	*Amoxicillin, Clindamycin*
Infections caused by	*Ampicillin, Cephalosporins*	*Levomycetin, Gentamicin*
Proteus morganii *Pr. rettgeri, Pr. Vulgaris*	*Gentamicin, Amikacin, Carbenicillin*	*Levomycetin, Tienam, Cephalosporins*
Infections caused by *Pseudomonas aeruginosa*	*Aminoglycosides, Carbenicillin, Azlocillin*	*Aztreonam, Tienam, Cephalosporins III*
Infections caused by *E. coli*	*Ampicillin, Cephalosporins III Aminoglycosides*	*Azlocillin*
Abdominal typhoid	*Levomycetin*	*Ampicillin, Tetracycline*
Bacillary dysentery	*Ampicillin*	*Levomycetin, Tetracycline*
Brucellosis	*Tetracyclines (+Streptomycin)*	*Levomycetin, Streptomycin*
Tularemia	*Tetracyclines*	*Levomycetin, Streptomycin*
Plague	*Streptomycin + Tetracyclines*	*Levomycetin, Streptomycin*
Cholera	*Tetracyclines*	*Levomycetin*
Rickettsial infections	*Tetracyclines*	*Levomycetin*

Parenterally it should be given only to hospitalized patients, so as to provide constant supervision by a physician. Patients with nephrotoxicity due to *Polymyxin B sulfate* usually show albuminuria, cellular casts, and azotemia. Neurotoxic reactions may be manifested by drowsiness, ataxia, perioral paresthesia, numbness of the extremities, and blurring of vision. The concurrent use of other nephrotoxic and neurotoxic drugs, particularly aminoglycosides, cephaloridine should be avoided. The neurotoxicity of *Polymyxin B sulfate* can result in respiratory paralysis from neuromuscular blockade, especially when the drug is given soon after anesthesia and/or muscle relaxants. As with other antibiotics, use of this drug may result in superinfection, allergic reactions. It can cause severe pain at i.m. injection sites, and thrombophlebitis at i.v. injection sites.

DIFFERENT ANTIBIOTICS

Lincomycin is elaborated by *Streptomyces lincolnensis*. It resembles *Erythromycin* in activity. Streptococci, staphylococci, pneumococci, and anaerobes (*Bacteroides species*, *Clostridium tetani*, *Cl. perfringens*) are inhibited by *Lincomycin.* Enterococci and gram-negative aerobic organisms are resistant. *Clostridium difficile*, an important cause of pseudomembranous colitis, is resistant. *Lincomycin*, like *Erythromycin*, inhibits protein synthesis. It is usually considered bacteriostatic. Resistance to *Lincomycin* is generally confers cross-resistance to other macrolides.

Lincomycin rapidly absorbed from the gastrointestinal tract following oral administration; absorption decreased when taken with food. It can be injected i.m. or i.v. Widely and rapidly distributed to most fluids and tissues, except cerebrospinal fluid; high concentrations in bone, bile, and urine. *Lincomycin* readily crosses the placenta; also distributed into breast milk. Biotransformation takes place in the liver. Half-life is about 4–6 hours. *Lincomycin* is eliminated by urine and bile.

The most important **indication** for *Lincomycin* is the treatment of severe infections caused by susceptible strains of streptococci, pneumococci, and staphylococci, as much as anaerobic infection. *Lincomycin* forms a high antimicrobial concentration in bones, thus it can be used for the osteomyelitis treatment.

Common **adverse effects** are diarrhea, nausea, and skin rashes. Impaired liver function (with or without jaundice) and neutropenia sometimes occur. Pseudomembranous colitis (severe diarrhea, fever), that followed *Lincomycin* administration, is caused by *Clostridium difficile*. This potentially fatal complication must be treated with *Metronidazole* or *Vancomycin.*

Clindamycin is a chlorine-substituted derivative of *Lincomycin*. It is similar in spectrum activity and using to *Lincomycin*, however, it has higher antimicrobial activity.

Vancomycin is a glycopeptide antibiotic produced by *Streptococcus orientalis*.

It is active mainly against gram-positive bacteria, particularly staphylococci and anaerobes, including *Clostridium difficile*. It is resistance to β-lactamase. *Vancomycin* inhibits cell wall synthesis. It also may alter the permeability of bacterial cytoplasmic membranes and may selectively inhibit ribonucleic acid synthesis. It is poorly absorbed from the intestinal tract and is administered orally only for the treatment of antibiotic-associated enterocolitis caused by *Clostridium difficile.* Parenteral doses must be administered intravenously. The drug is widely distributed in the body. 80-90% of the drug is excreted unchanged by glomerular filtration.

The main indication for parenteral *Vancomycin* is sepsis or endocarditis caused by penicillin-resistant staphylococci. *Vancomycin* is irritating to tissue, resulting in phlebitis at the site of injection. Ototoxicity and nephrotoxicity are uncommon and mild with current preparations. However, administration with the other ototoxic or nephrotoxic drug, such as an aminoglycoside, increases the risk of this toxicity.

Fusidic acid is antibiotic broad-spectrum activity. Usually it is used as *Fusidin sodium*. It is active against staphylococci, meningococci, and gonococci. *Fusidin* inhibits the protein synthesis; acts bacteriostatic. Well absorbed in the gastro-intestinal tract. It is distributed widely to tissues and body fluids. Agent tends to localize in bones. *Fusidin* is metabolized in the liver and excreted by bile. Primary *Fusidin* is indicated for the treatment of disease caused by penicillin-resistant staphylococci. Adverse effects: nausea, vomiting, rash, jaundice.

Available forms:

Benzylpenicillin-sodium — in bottles 250,000; 500,000; 1,000,000 unites each

Bicillinum-1 — in bottles 300,000; 600,000; 1,200,000 unites each

Oxacillin-sodium — in bottles 0.25; 0.5 each; tablets or capsules 0.25; 0.5

Ampicillin trihydrate — tablets or capsules 0.25; 0.5 each

Ampicillin-sodium — in bottles 0.25; 0.5 each

Carfecillin — capsules 0.25 each

Cefazolin — in bottles 0.25; 0.5; 1.0; 2.0; 4.0 each

Cefoxitin — in bottles 1.0; 2.0 each

Cefotaxime — in bottles 0.5; 1.0; 2.0 each

Aztreonam — in bottles 0.5; 1.0 each

Gentamycin sulfate — in bottles 0.08 each; in ampoules 4% solution 1 ml or 2 ml each; 0.1% ointment 10.0 or 15.0

Amikacin sulfate — in bottles 0.1; 0.25; 0.5 each

Neomycin sulfate — tablets 0.1; 0.25 each; in bottles 0.5 each (to dilute at the rate of 1 ml *physiological solution* for 0.005 g); 0.5%; 2% ointment 15.0 or 30.0 each

Erythromycin — tablets 0.1; 0.25 each; 1% ointment

Azithromycin — capsules 0.125; 0.25 each; tablets 0.5 each

Tetracycline — tablets 0.05; 0.1; 0.25 each

Doxycycline hydrochloride — capsules 0.05; 0.1 each; in ampoules 0.1 each

Chloramphenicol (Levomycetin) — tablets 0.25; 0.5 g each; capsules 0.1; 0.25; 0.5 each

Polymyxin M sulfate — in bottles 500,000; 1,000,000 unites (to dilute at the rate of 1 ml physiological solution for 20,000 unites); tablets 500,000 unites each; liniment 30,0

Lincomycin hydrochloride — in ampoules 30% solution 1; 2 ml; capsules 0.25 each

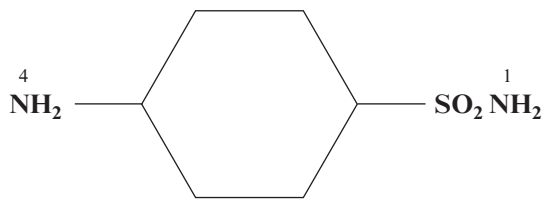
Lecture 36
SULFANILAMIDES

Sulfanilamides (sulfonamides) are synthetic derivatives of p-aminobenzenesulfonamide (sulfanilamide). If the N^4-amino group is replaced with radicals that can be converted to a free amino group in the body, the compound retains antibacterial activity (Fig. 27). Substitution in the N^1-amide group produces compounds varying in solubility, protein binding, tissue distribution, and rate and mode of metabolism and excretion. Sulfanilamides generally are insoluble in water. The drugs are weak acids and form salts with bases; their sodium salts are very soluble in water. Solutions of the sodium salts of most sulfonamides are strongly basic.

Prontosil (Red streptocide) was one of the dyes included by G. Domagk to treat experimental streptococcal infection in mice at 1935 and found it to be highly effective. Since that time the usage of sulfanilamides has begun. All sulfanilamide medicines are the products of streptocide amide group hydrogen atom replacement by various radicals. The differences between them are efficiency rate and terms only.

Mechanism of action. Sulfanilamides are structural analogs of PABA (paraaminobenzoic acid) and appear to interfere with PABA utilization by competitively inhibiting the enzyme dihydropteroate synthase, which catalyzes the formation of dihydropteroic acid (a precursor of tetrahydrofolic acid), from PABA and pteridine. Sulfanilamides are usually bacteriostatic in action. Only microorganisms that synthesize their own folic acid are inhibited by sulfanilamides; animal cells and bacteria which are capable of utilizing folic acid precursors or preformed folic acid (tetrahydrofolic acid) are not affected by these drugs. *Novocain* is a PABA derivative: it antagonizes sulfanilamides. The antibacterial activity of the sulfanilamides is reportedly decreased in the presence of pus, blood or purulent body exudate, because they contain purines and *Thymidine* that decrease bacterial requirement for folic acid.

Spectrum of activity. Sulfanilamides are active against gram-positive bacteria including some strains of staphylococci, streptococci, *Bacillus anthracis*, *Clostridium tetani*, and *C. perfringens*. The drugs are active *in vitro* against *Enterobacter*, *Escherichia coli*, *Klebsiella*, *Proteus mirabilis*, *P. vulgaris*, *Salmonella*, and *Shigella*. Sulfanilamides are active against some strains of *Neisseria gonorrhea*, *Chlamydia trachomatis* and also have some activity against *Toxoplasma gondii* and *Plasmodium*.



Sulfanilamide

Fig 27. Structure of sulfanilamides

Organisms initially sensitive to sulfanilamides may develop resistance. Sulfanilamide-resistant strains emerge frequently when therapy continues for 15 days or longer. Because of the availability of many safer and more effective antibiotics, sulfanilamides current utility is limited.

Classification of drugs:

— Sulfanilamides which are well absorbed from gastro-intestinal system, with resorptive action:

a) short acting (T1/2 about 8 h) — *Streptocide*, *Sulfathiazole (Norsulfazolum)*, *Sulfadimidine (Sulfadimezinum)*, *Sulfacarbamide (Urosulfanum)*, *Sulfaethidole (Aethazolum)*;

b) intermediate acting (T1/2 lesser 12–14 h) — *Sulfazinum* (*Sulfadiazine sodium*), *Sulfamethoxazole*;

c) long action time (T1/2 about 24–28 h) — *Sulfamethoxypyridazine (Sulfapyridazinum)*, *Sulfamonomethoxine*, *Sulfadimethoxine*;

d) ultra long action time (T1/2 about 65 h) — *Sulfalene*.

— Sulfanilamides which are badly absorbed from gastro-intestinal system, used for healing of intestinal infections — *Sulfaguanidine (Sulginum)*, *Phthalylsulfathiazole (Phthalazolum)*, *Phthalylsulfapyridazine (Phthazinum)*

— Combined preparations:

a) combination with salicylic acid for healing of non-specific ulceral colitis — *Salazodin (Salazopyridazinum)*, *Salazosulphapyridine (Sulphasalazine)*;

b) preparations containing *Trimethoprim* — *Cotrimoxazole* (*Biseptol*), *Sulfatonum (Sulfamonomethoxine + Trimethoprim)*.

— Preparations for local use — *Sulfacetamide* (*Sulfacyl-sodium*), *Maphenidum*, *Silver sulfadiazine*. Sodium salts of sulfanilamides

Approximately 70–90% of an oral dose of the absorbable sulfanilamides is reportedly absorbed from the small intestine. *Norsulfazolum*, *Sulfadimezinum*, *Aethazolum*, and *Urosulfanum* are absorbed rapidly; peak blood concentrations are usually obtained within 2–4 hours. *Sulfazinum*, *Sulfamethoxazole* and *Sulfapyridazinum* are absorbed at a slower rate with peak blood concentrations occurring within 3–7 hours. Absorbable sulfanilamides are widely distributed in the body. They may appear in breast milk, synovial and cerebrospinal fluids. Sulfanilamides readily cross the placenta.

Sulfanilamides are bound in varying degrees to plasma proteins. *Sulfazinum*, *Norsulfazolum* are reportedly 12–50% bound to plasma proteins and *Sulfadimethoxine* and *Sulfapyridazinum* are reportedly 85–90% bound to plasma proteins.

A portion of absorbed drug is mostly acetylated and also glucuronidated in the liver. The rate of sulfanilamides acetylation differ from each other — *Urosulfanum*, *Aethazolum* has the lowest extend, and *Streptocide*, *Sulfadimezinum* — the highest. The metabolites do not possess antibacterial activity. N^4-acetyl metabolites are usually less soluble than the parent sulfanilamide, particularly in acidic urine, however, glucuronide derivatives are water soluble. Sulfanilamides and their metabolites are excreted mainly by the kidneys via glomerular filtration. Alkalization of

the urine increases the solubility of sulfanilamides and decreases tubular reabsorption, resulting in increases of renal excretion of the drugs. Except for the poorly absorbed sulfanilamides only small amounts of sulfanilamides are excreted in feces.

The basic principles of sulfanilamide chemotherapy are following. The first dose (blowing dose) of absorbable sulfanilamides must be two times bigger than subsequent doses (keeping up dose), except *Cotrimoxazole*. The sulfanilamide therapy has to be continued during 2–3 days after clinical recover ("sulfanilamide train"). Patients also have to drink a lot (1.5–2 liters a day) of alkaline water.

Therapeutic uses

a. Urosulfanum, Aethazolum are highly soluble (free as well as acetylated form) even in acidic urine — crystalluria is less likely. More than 60% are excreted unchanged in urine. They are highly desirable for urinary tract infections, including pyelonephritis, pyelitis. They must be taken four times a day.

b. Norsulfazolum, Sulfadimezinum are also rapidly absorbed, very little acetylated and quickly excreted in urine. They can be used for the treatment of meningitis, pneumonia and other infection diseases. In addition *Sulfadimezinum* is indicated for toxoplasmosis and gonorrhea.

c. Sulfazinum has slower oral absorption and urinary excretion. It is used on twice daily schedule for pneumonia, bronchitis, and malaria treatment.

d. Sulfapyridazinum, Sulfadimethoxine are highly protein bound, lipid soluble, and slowly excreted sulfanilamides. They used once a day for the treatment of pneumonia, otitis, bile duct and urinary tract infections, malaria, lepra, *Sulfapyridazinum* — also for meningitis.

e. Sulfalene is ultra long acting compound, action lasting more than 7 days. It has been used in the treatment of malaria, infections of bile duct and urinary tract. *Sulfalene* can be taken orally 0.2 g (1 tab) every day or 2 g once a week.

f. Sulginum, Phthalazolum have N^4 as well as N^1 substitution. That's why, they are not active as such and are not absorbed in the small intestine. In the bowel, bacteria split off the N^4 substitution to release sulfanilamide, which is active locally. These agents have been used for colitis, gastroenteritis, and dysentery and for preparation of bowel before colonic surgery. Small amount of sulfanilamide that gets absorbed can cause toxicity including crystalluria.

g. Salazopyridazinum, Salazosulphapyridine are spitted by intestinal microflora to yield *Sulfapyridazinum* and *5-aminosalicylate* in first case; *Sulfapyridine* and *5-aminosalicylate* in second case. They are widely used in ulcerative colitis, enteritis, and other inflammatory bowel diseases. Salicylate is released in the colon in high concentration and is responsible for an anti-inflammatory effect, the major source of benefit from this drug. Comparably high concentrations of salicylate cannot be achieved in the colon by oral intake of ordinary formulations of salicylates because of severe gastrointestinal toxicity. In addition, it was found to suppress the disease in significant number of rheumatoid arthritis patients.

h. Cotrimoxazole is the combination of *Sulfamethoxazole* with *Trimethoprim*. *Trimethoprim* is a diaminopyrimidine derivative, it selectively inhibits bacterial dihydrofolate reductase. The two drugs cause sequential block of folate metabolism (Fig. 28). Individually both sulfanilamides and *Trimethoprim* are primarily bacteriostatic, but the combination becomes cidal against many organisms. *Trimethoprim* is about 50,000 times more active against bacterial dihydrofolate reductase than against mammalian enzyme. Thus, human folate metabolism is not interfered at antibacterial concentration of *Trimethoprim*.

Trimethoprim is usually given orally, alone or in combination with *Sulfamethoxazole*, the latter chosen because it has a similar half-life. *Trimethoprim* is absorbed well from the gut and distributed widely in body fluids and tissues, including cerebrospinal fluid. Because *Trimethoprim* is more lipid-soluble than *Sulfamethoxazole*, it has a larger volume of distribution than the latter drug. Therefore, when 1 part of *Trimethoprim* is given with 5 parts of *Sulfamethoxazole* (the ratio in the formulation), the peak plasma concentrations are in the ratio of 1:20, which is optimal for the combined effects of these drugs *in vitro*. About 65–70% of each participant drug is protein-bound, and 30–50% of the sulfanilamide and 50–60% of the *Trimethoprim* (or their respective metabolites) are excreted in the urine within 24 hours.

Sensitive to *Trimethoprim-Sulfamethoxazole* combination are *Escherichia* coli, *Salmonella typhus*, *Proteus mirabilis*, and *Klebsiella pneumonia*, *Enterobacter*, *Pneumocystis carinii*, many stains of *Staphylococcus.* A combination of *Trimethoprim-Sulfamethoxazole* is effective treatment for chronic bronchitis, pneumonia, urinary tract infections (cystitis, pyelonephritis, pyelitis), prostatitis, shigellosis, typhoid fever, and many others. It is the agent of choice *Pneumocystis carinii* pneumonia, especially in patients with AIDS. It may be used for gram-negative bacterial sepsis, including that caused by some multiple-drugresistant species such as *Enterobacter* and *Serratia*.

Trimethoprim produces the predictable adverse effects of an antifolate drug, especially megaloblastic anemia, and leukopenia. This can be prevented by the simultaneous administration of folinic acid, 6–8 mg/d. In addition, the combination *Trimethoprim-Sulfam-*

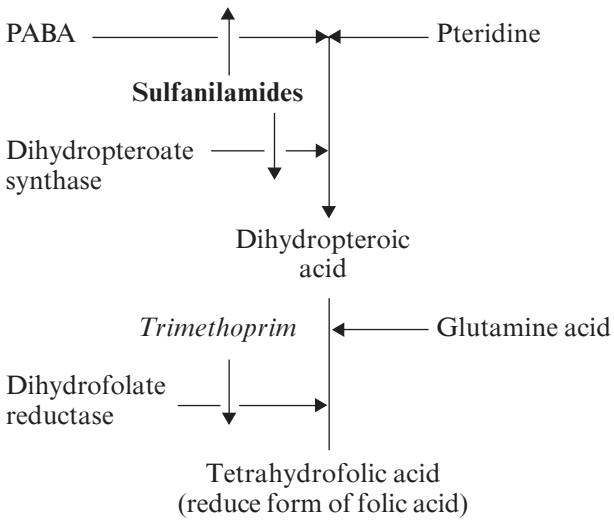


Fig 28. Mechanism of action of *Cotrimoxazole*

ethoxazole may cause all of the untoward reactions associated with sulfanilamides.

Sulfatonum is combination of *Sulfamonomethoxine* (0.25 g) with *Trimethoprim* (0.1 g). It's characteristic is similar to *Cotrimoxazole*.

i. *Sulfacyl-sodium* ophthalmic solution or ointment is effective treatment for bacterial conjunctivitis and as adjunctive therapy for trachoma. It has been most commonly used for treatment and prevention of gonococcal ophthalmitis, including newborns.

j. *Mafenide* is used topically to prevent bacterial colonization and infection of burn wounds. It is not inactivated by PABA.

k. S*ulfazinum silver* is a much less toxic topical sulfanilamide and is preferred to mafenide for prevention of infection of burn wounds. It slowly releases silver and are used to suppress bacterial growth in burn wounds.

Adverse effects of the sulfanilamides are numerous. Although serious, in some cases fatal, reactions have been reported, they occur infrequently. Various *dermatoid reactions*, including rash, eosinophilia, pruritus, photosensitivity, Stevens-Johnson and serum sickness syndrome have been reported. Acute hemolytic anemia may occur as a result of sensitization or glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. *Adverse hematoid effects*, including methemoglobinemia, sulfhemoglobinemia, leukopenia, aplastic anemia, thrombocytopenia, have been associated with sulfanilamide therapy. *Renal damage*, manifested by kidney stone formation, renal colic, toxic nephrosis is usually a result of crystalluria caused by precipitation of the sulfanilamide and/or its acetyl derivative in acid urine. Urinary alkalization may be achieved by administering 2.5–4 g of sodium bicarbonate orally every 4 hours. Nausea or vomiting, gastroenteritis, diarrhea also have been reported. *Adverse neurology effects*, including headache, dizziness, mental depression, fatigue, and acute psychosis may occur.

Drug interactions. Sulfanilamides may potentiate the effects of *coumarin anticoagulants* and *oral antidiabetic agents* by displacing them from their protein-binding sites. Some sulfanilamides may inhibit metabolism of phenytoin and should be used with caution in patients receiving the drug. Since *Hexamethylenetetramine (Methenamine)* requires acidic urine for its antibacterial effect, the drug should not be used concomitantly with less soluble sulfanilamides (e.g. *Sulfazinum*) which may crystallize in acidic urine.

Available forms:

Aethazolum — powder or tablets 0.5 g each.

Sulfamethoxypyridazine — powder or tablets 0.5 g each.

Phthalylsulfathiazole (Phthalazolum) — powder or tablets 0.5 g each.

Bactrim (480) — tablets, including 80 mg trimethoprim and 400 mg sulfamethoxazole; ***Bactrim (120)*** — tablets, including 20 mg trimethoprim and 100 mg sulfamethoxazole (for children).

Sulfacyl-sodium — powder, in ampoules 30% solution 5 ml each; in bottles 30% solution 5 or 10 ml each (eyes drops).

Lecture 37
ANTIMICROBIALS — DERIVATIVES OF DIFFERENT GROUPS

NITROFURANE DERIVATIVES

These are the medicines of a great efficiency spectrum. Their *mechanism of action* is the turning of nitro-group into the amino-group and germs cellular respiration suppression. Medium concentrations are bacteriostatic, large doses become bactericide.

Microorganism's resistance to nitrofuran derivatives develops slowly. No cross-resistance to antibiotics or sulfanilamides occurs. They may be combined with penicillins, streptomycin, other aminoglycosides and tetracyclines.

Furazolidone is broad-spectrum anti-infective that is effective against most gastrointestinal tract pathogens. *Furazolidone* is active *in vitro* against *Enterobacter* aerogenes, *Escherichia coli*, *Proteus species*, *Salmonella species*, *Shigella species*, and staphylococci. It is indicated in the treatment of bacterial diarrhea caused by susceptible organisms. *Furazolidone* is indicated in the treatment of lambliasis (giardiasis) caused by *Giardia lamblia*, and for the treatment of trichomoniasis.

It is well absorbed following oral administration. It is rapidly and extensively metabolized. *Furazolidone* and *Nitrofurantoin (Furadoninum)* may cause the dark yellow to brown discoloration of urine. *Furazolidone* also acts as a monoamine oxidize (MAO) inhibitor. That's why concurrent use of MAO inhibitors, tyramine- or other high pressor amine-containing foods and beverages, such as cheese; beer; liqueurs; smoked or pickled meat, or fish; and any overripe fruit with *Furazolidone* may precipitate hypertension.

Patients should be advised not to drink alcoholic beverages while taking *Furazolidone* and for 4 days after discontinuing it, because concurrent use of alcohol with *Furazolidone* may rarely result in a disulfiram-like reaction, characterized by facial flushing, difficult breathing, slight fever, and tightness of the chest.

Hypersensitivity reactions (fever; itching; joint pain; skin rash or redness) hemolytic anemia in glucose-6-phosphate dehydrogenase deficiency patients, and gastrointestinal disturbances (abdominal pain, diarrhea, nausea, or vomiting) also may appear during *Furazolidone* be used.

Nitrofurantoin (Furadoninum) is indicated in the treatment of urinary tract infections caused by susceptible strains of *Escherichia coli*, *enterococci*, *Staphylococcus aureus*, *Enterobacter species*, and *Proteus species*.

Nitrofurantoin is rapidly and completely absorbed in the small intestine. About 30–40% of *Nitrofurantoin* is rapidly excreted unchanged. Therapeutic concentrations are achieved only in the urine, serum concentrations are very low.

Gastrointestinal disturbances and hypersensitivity reactions are the principal side effects of *Furadoninum*.

Hemolytic anemia can occur in glucose-6-phosphate dehydrogenase deficiency patients. *Furadoninum* also antagonizes the action of nalidixic acid. Both *Furazolidone* and *Furadoninum* should preferably be taken with food or milk. This minimizes gastrointestinal irritation.

QUINOLONES

Quinolones are active against most of gram-negative organisms, including *Proteus species*, *Klebsiella species*, *Enterobacter species*, *Salmonella species*, *Shigella species*, and *Escherichia coli*. The majority of staphylococci strains are susceptible to quinolones. Quinolones appear to act by inhibiting bacterial DNA synthesis.

Nalidixic acid (Negram®) is the first antibacterial quinolone. It is the derivative of *Naftiridin*. It is bacteriostatic or bactericidal depending on the concentration. Resistance may develop rapidly during treatment.

Nalidixic acid rapidly and almost completely absorbed from the gastrointestinal tract. Since nalidixic acid achieves only low concentrations in the serum and is concentrated in the urine, it is indicated only in the treatment of urinary tract infections. Half-life of nalidixic acid in serum is about 1 to 2.5 hours; in urine – 6 hours. It crosses the placenta and is excreted in breast milk.

The main ***side effects*** are diarrhea, nausea, vomiting, hypersensitivity, dizziness, headache, seizures, photosensitivity (increased sensitivity of the skin to sunlight). Since nalidixic acid and other related compounds have been shown to cause arthropathy in immature animals, use is not recommended in first three months of pregnancy and in children up to 2 years of age.

Oxolinic acid (Gramurin) is similar in structure and function to *Nalidixic acid.* It has higher antimicrobial activity, than *Nalidixic acid*, but more neurotoxic.

Fluoroquinolones are synthetic fluorinated analogs of *Nalidixic acid*. Fluorinated derivatives (*Ciprofloxacin*, *Ofloxacin*, and others) have greatly improved antibacterial activity compared with nalidixic acid and achieve bactericidal levels in blood and tissues. Their **spectrum of antimicrobial activity** is similar to first quinolones. In addition fluoroquinolones act on *Pseudomonas*, *Neisseria*, and *Campylobacter*, intracellular pathogens such as *Legionella*, *Chlamydia*, and some *Mycobacteria*, including *M. tuberculosis*. Anaerobes generally are resistant. Fluoroquinolones block bacterial DNA synthesis by inhibiting bacterial topoisomerase II (DNA gyrase) that is required for normal transcription and replication. During fluoroquinolone therapy, resistant organisms emerge, especially among staphylococci, streptococci, pseudomonas.

After oral administration, the fluoroquinolones are well-absorbed (bioavailability of 80–95%) and distributed widely in body fluids and tissues. They badly bind with serum proteins. Serum half-life range from 4 hours *(Ciprofloxacin)* up to 8 hours (*Pefloxacin* and *Ofloxacin*). The fluoroquinolones are excreted mainly by the kidney mostly unchanged.

Ciprofloxacin, *Pefloxacin*, and *Ofloxacin* are indicated in the treatment of urinary tract infections (cystitis, and pyelitis); bacterial prostatitis caused by susceptible organisms. *Ciprofloxacin* and *Ofloxacin* are indicated in the treatment of bone and joint infections; skin and soft tissue infections; chronic bronchitis; pneumonia caused by susceptible organisms. Also they are indicated in the treatment of endocervical and urethral infections caused by *N. gonorrhea.* Finally parenteral *Ciprofloxacin* is indicated in the treatment of septicemia caused by *E. coli* or *S. typhi*.

Adverse effects. Fluoroquinolones at an alkaline pH may form crystals that have resulted in crystalluria. Because normal urinary pH is acidic (approximately 5 to 6) crystalluria is very unlikely to occur. They also may lead to diarrhea, nausea or vomiting, hypersensitivity reactions, photosensitivity, CNS toxicity (dizziness; headache; drowsiness; insomnia; tremor). Very rarely seizure and acute psychosis may appear. Fluoroquinolones are not recommended for use during pregnancy, breast-feeding, in children, and adolescents because they have been shown to cause arthropathy in immature animals.

Fluoroquinolones inhibit the cytochrome oxidizing (P-450) enzyme system of the liver that can intensify the effect of agents, which metabolized by these enzymes. For instance, concurrent use of *Theophylline (Aminophylline, Caffeine)* with fluoroquinolones may result in a prolonged theophylline elimination half-life, increased serum concentration, and increased risk of theophylline-related toxicity.

8-OXYQUINOLINES

8-Oxyquinolines (8-hydroxyquinoline) possess antimicrobial, antiprotozoal, and antifungal activity. Representatives of this group are *Chlorquinaldol*, complex agent *Attapulgite*, and *Nitroxoline* (5-NOK).

Chlorquinaldol is used for the treatment of intestine infection diseases such as dysentery, salmonellosis, intestine infections caused by staphylococci, *Proteus* species, and other *Enterobacter species*. In addition it may be prescribed for amebiasis and lambliasis. *Chlorquinaldol* is used orally. Most of an oral dose of the drug is not absorbed from the gastro-intestinal tract but is excreted in feces. It acts primarily in the intestinal lumen.

Adverse gastro-intestinal effects of *Chlorquinaldol* include nausea, vomiting, epigastric burning and pain, allergic reactions. The drug can cause optic neuritis, optic atrophy, and peripheral neuropathy, especially in children. Permanent loss of vision has occurred. Dysesthesia and weakness are reported to occur commonly in adults. Duration of *Chlorquinaldol* therapy less than 7 days.

Attapulgite is similar in activity and indications to *Chlorquinaldol*.

Nitroxoline is distinguished by rapid absorption from the gastrointestinal tract. It is excreted mainly by kidney mostly unchanged; thus it is concentrated in the urine. *Nitroxoline* can be used for urinary tract infections (pyelitis, cystitis). It causes the yellow discoloration of urine. In general it has low toxicity. Sometimes nausea and allergic reactions may occur.

IMIDAZOLE DERIVATIVES

Metronidazole acts microbicidal against most obligate anaerobic bacteria and protozoa (*Trichomonas vaginalis*, *Giardia lamblia*, and *Entamoeba histolytica*) by undergoing intracellular chemical reduction. Reduced *Metronidazole* interacts with DNA to cause inhibition of nucleic acid synthesis and cell death. *Metronidazole* is indicated in the treatment of protozoal diseases (amebiasis, lambliasis, trichomoniasis), bone, pelvic and intra-abdominal infections, endocarditis, septicemia caused by anaerobic bacteria (*Bacteroides* and *Clostridium species*). It is indicated for the prophylaxis of perioperative infections during colorectal surgery. *Metronidazole* can be prescribed for adjunct treatment of *Helicobacter pylori*-associated gastritis.

Metronidazole is well absorbed orally. It is widely distributed to tissues and fluids of the organism; it crosses the placenta and blood-brain barrier, also. The half-life is about 8–10 hours. *Metronidazole* and its metabolites mostly eliminated by kidneys that cause the red to brown discoloration of urine.

Adverse effects of *Metronidazole* are dry mouth, an unpleasant or sharp metallic taste, diarrhea, nausea or vomiting, loss of appetite, hypersensitivity, leukopenia, and vaginal candidiasis. It is contraindicated during active organic disease of the CNS, pregnancy, breast-feeding. *Metronidazole* should not be used concurrently with, or for at least 1 day following, ingestion of alcohol, because disulfiram-like effects may occur.

Tinidazole is similar in structure and function to *Metronidazole*. It is indicated in the treatment of amebiasis, lambliasis, and trichomoniasis. It acts longer than *Metronidazole*.

QUINOXOLINE DERIVATIVES

Chinoxydin and *Hydroxymethylhinoxilindioxide (Dioxydinum)* are active against *Proteus vulgaris*, *Cyanobacteria*, *Escherichia coli*, *Salmonella* and *Shigella species*, *staphylococci, Clostridium species*. These agents are indicated for severe purulent inflammation, such as pyelocystitis, cholecystitis, abscess of lungs, empyema, septicemia, that caused by susceptible organisms. The agents can be used only in adults. Usually, *Chinoxydin* is taken orally and *Dioxydinum* — locally, intracavitary and intravenous. During treatment of nausea, vomiting, dizziness, headache, allergic rash, seizure of the skeletal muscle can appear.

Available forms:

Furazolidone, Furadoninum — tablets 0.05 g each

Nalidixic acid — capsules or tablets 0.5 g each

Ofloxacine — tablets 0.2 g each

Ciprofloxacine — tablets 0.25; 0.5; 0.75 g each, in bottles 0.2% solution 50 or 100 ml each

Chlorquinaldol — tablets 0.03 (for children) or 0.1 gram each

Nitroxoline — tablets 0.05 g each

Metronidazole — tablets 0.25; 0.5 g each; vaginal suppositories 0.5 g

Chinoxydin — tablets 0.25 g each

Lecture 38
ANTITUBERCULOSIS DRUGS

Tuberculosis, mycobacterial infection are among the most difficult of all bacterial infections to cure. The lipid-rich mycobacterial cell wall is impermeable to many agents. A substantial proportion of mycobacterial organisms are intracellular, and inaccessible to drugs that penetrate poorly. Finally, mycobacteria are notorious for their ability to develop resistance to any single drug. Combinations of drugs are required to overcome these obstacles and to prevent emergence of resistance during the course of tuberculosis treatment. In practice, therapy is initiated with a 3–4-drug regimen. The response of *Mycobacterium tuberculosis* to chemotherapy is slow, and treatment must be administered for 6–12 months.

Classification of antituberculosis agents:

— Basic (first-line) agents:

a) antibiotics — *Streptomycin*, *Rifampicin*;

b) synthetic drugs — *Isoniazid*, *Ethambutol.*

— Supplemental (second-line):

c) antibiotics — *Cycloserine*, *Kanamycin*;

d) synthetic drugs — *Ethionamide*, *Pyrazinamide*, *Para-aminosalicylate sodium.*

Usually, **basic agents** are more effective and less toxic, than reserve agents are. Thus, basic agents are the drugs of first choice. The **alternative drugs** are usually considered only in the case of resistance to the drugs of first line and in case of the toxic effects. As a rule, synthetic drugs act on mycobacteria only. However, antituberculosis antibiotics are the broad-spectrum antimicrobial agents.

Rifampicin is a semisynthetic derivative of *Rifamycin,* an antibiotic produced by *Streptomyces mediterranei*. It is active *in vitro* against gram-positive and gram-negative cocci, some enteric bacteria (*E. coli, Salmonella*, some strains of *Pseudomonas* and *Proteus*), and *Mycobacteria*. Administration of *Rifampicin* as a single drug quickly selects the highly resistant organisms. *Rifampicin* binds strongly to the bacterial DNA-dependent RNA polymerase and thereby inhibits RNA synthesis. Human RNA polymerase does not bind rifampin and is not inhibited by it. *Rifampicin* is bactericidal for *Mycobacteria*. It can kill microorganisms that are poorly accessible to many other drugs, such as intracellular organisms and those sequestered in abscesses and lung cavities.

Rifampicin is well absorbed after oral administration. Being lipid-soluble, *Rifampicin* diffuses well to most body tissues and fluids, including the cerebrospinal fluid. Therapeutic concentrations are achieved in the saliva, sputum, bones, and pleural cavity. It crosses the placenta and is distributed into breast milk. *Rifampicin* is relatively highly protein-bound drug (90%). Agent rapidly deacetylated by auto-induced microsomal oxidative enzymes to metabolites. *Rifampicin* excreted mainly through the liver into bile and then undergoes enterohepatic recirculation. The *Rifampicin* half-life initially 3–5 h; with repeated administration, half-life decreases to 2–3 h.

Rifampicin can be administered orally or i.v. The usual daily dose for adult is about 0,6 g given once a day. *Rifamycin* can be used i.v., i.m. or locally. *Rifampicin* is effective in tuberculosis and in leprosy. *Rifampicin* therapy is also indicated for treatment of bronchitis, pneumonia, osteomyelitis, and biliary tract infections caused by susceptible infections. *Rifampicin* imparts a harmless reddish-orange color to urine, sweat, and tears.

Occasional adverse effects include itching, rash, diarrhea, stomach cramps, and leukopenia. It may cause cholestatic jaundice and occasionally hepatitis (Table 14). *Rifampicin* induces microsomal enzymes (e.g. cytochrome P-450), which increases the elimination of numerous other drugs including oral anticoagulants, some anticonvulsants, and contraceptives. *Rifampicin* is not recommended during pregnancy, breast-feeding, and hepatitis.

The mechanism of action and the pharmacologic features of *Streptomycin* have been discussed in lecture "Antibiotics". *Streptomycin sulfate* remains an important drug in the treatment of tuberculosis, especially when an injectable drug is desirable, principally in individuals with severe forms of tuberculosis, e.g. meningitis, disseminated disease.

Isoniazid, introduced in 1952, is the most active drug for the treatment of tuberculosis. It is the hydrazide of isonicotinic acid. The *Isoniazid* structure is similar to *Pyridoxine*. *Isoniazid* may be bacteriostatic and bactericidal. It is active against both extracellular and intracellular organisms. *Isoniazid* inhibits its synthesis of mycolic acids, which are essential components of mycobacterial cell walls. *Isoniazid*-resistant mutants occur in susceptible mycobacterial populations less frequent than streptomycin or rifampicin ones.

Isoniazid is readily absorbed from the gastrointestinal tract. It diffuses readily into all body fluids and tissues, including CNS and cerebrospinal fluid. *Isoniazid* crosses the placenta and is distributed into breast milk. Metabolism of *Isoniazid*, especially acetylation by liver N-acetyltransferase, is genetically determined. The average concentration of isoniazid in the plasma of rapid acetylators is about 1/3 to 1/2 of that in slow acetylators and average half-lives are less than 1 hour and 3 hours, respectively. Patients who are slow acetylators may be more prone to development of adverse effects and may require lower doses. *Isoniazid* excreted by the kidneys within 24 hours; more than 90% of the *Isoniazid* excreted as the acetylated form in fast acetylators and less than 90% in slow acetylators. The typical adult daily dose of *Isoniazid* is 300–600 mg given 1–3 times a day. In case of serious infections or gastrointestinal disturbances it can be used i.m., i.v., or in inhalation.

Peripheral neuritis (unsteadiness, numbness, tingling, burning, or pain in hands and feet) can observed in patients, because *Isoniazid* acts as *Pyridoxine* (vitamin B_6) antagonist, hampering the conversion of pyridoxine into its active form. *Pyridoxine* is recommended for patients with conditions predisposing to neuropathy. CNS toxicity, which is less common, includes memory loss, psychosis, and seizures. Fever and skin rashes are occasionally seen. Diarrhea, vomiting, and hepatitis also may appear.

Ethambutol is a synthetic, bacteriostatic antituberculosis agent. It diffuses into mycobacteria and suppresses multiplication by interfering with RNA synthesis. *Ethambutol* is well absorbed from the gut. Agent is widely distributed to most tissues and body fluids except cerebrospinal fluid. The most common serious adverse event is retrobulbar neuritis causing loss of visual acuity and red-green color blindness. This dosage-related side effect which appears after 2 months of therapy. Thus, periodic visual acuity testing is desirable. *Ethambutol* is contraindicated during pregnancy.

Cycloserine, a broad-spectrum antibiotic, is bactericidal for *Mycobacteria*. *Cycloserine* is an analog of the amino acid D-alanine. It inhibits bacterial cell wall synthesis. *Cycloserine* is rapidly and almost completely absorbed from the gastro-intestinal tract following oral administration. It is distributed widely, to most body fluids and tissues. The most serious toxic effects are peripheral neuropathy and central nervous system dysfunction, including dizziness, muscle twitching or trembling, anxiety, nervousness, drowsiness, and nightmares. These may be minimized by glutamic acid, pyridoxine, and ATP.

Kanamycin is antibiotic of aminoglycoside group. It has the same mechanism of action, spectrum activity, and pharmacokinetic as streptomycin. *Kanamycin* has been used for treatment of tuberculosis caused by streptomycin-resistant strains.

Ethionamide is chemically related to *Isoniazid.* Its mechanism of action is not known exactly, but it appears also to block the synthesis of mycolic acids. It is rapidly and fully absorbed from the gastrointestinal tract following oral administration; widely distributed to most tissues and fluids. Agent may cause the intense gastric irritation, which accompanied by nausea, vomiting, loss of appetite, and abdominal pain. Orthostatic hypotension, peripheral neuritis, and skin rash

Table 14. **Typical adverse effects of antituberculosis agents**

Group	Agents	GI upset	CNS toxicity	Neuritis	Ototoxicity	Visual upset	Hepato-toxicity	Nephro-toxicity	Allergic reactions	Super-infections
I	*Rifampicin*	+					+		+	+
	Streptomycin			+	+				+	+
	Isoniazid		+	+					+	
	Ethambutol			+		+			+	
II	*Cycloserine*		+						+	
	Kanamycin				+				+	+
	Ethionamide	+							+	
	Pyrazinamide						+		+	
	P-aminosalicylate sodium	+							+	

can occur. *Ethionamide* is also hepatotoxic. Adverse effects may be alleviated by nicotinamide.

Pyrazinamide is a relative of *Nicotinamide*. *Tuberculosis bacilli* develop resistance to *Pyrazinamide* fairly readily. It is rapidly and completely absorbed from the gastrointestinal tract. *Pyrazinamide* has distributed widely, to most fluids and tissues. Major adverse effects of *Pyrazinamide* include hepatotoxicity (in 1–5% of patients), vomiting, drug fever, and hyperuricemia, which may provoke acute gouty arthritis.

Para-aminosalicylate sodium (PASA) is structurally similar to para-aminobenzoic acid (PABA) and to the sulfanilamides. It is a folate synthesis antagonist that is active almost exclusively against *Mycobacterium tuberculosis*, acts bacteriostatic. It is rapidly and well absorbed from the gastrointestinal tract. Agent diffuses readily into various body fluids except the cerebrospinal fluid. Gastrointestinal symptoms such as anorexia, nausea, diarrhea, and epigastric pain are often accompany full doses of p-aminosalicylate sodium. Hypersensitivity reactions, hepatitis, crystalluria, granulocytopenia, goiter or myxedema may occur.

Available forms:

Rifampicin — tablets or capsules 0.05; 0.15 g each; in ampoules 0.15 g

Isoniazid — powder; tablets 0.1; 0.2 or 0.3 g each; in ampoules 10% solution 5 ml each

Streptomycin sulfate — in bottles 0.25; 0.5; 1 g each

Cycloserine — tablets or capsules 0.25 g each

Sodium para-aminosalicylate — powder; tablets or capsules 0.5 g each; in bottles 3% solution 250 ml or 500 ml each

Lecture 39
ANTISYPHILITIC AGENTS

Syphilis is infectious disease caused by *Treponema pallidum* and transmitted by direct contact, usually through sexual intercourse. For syphilis treatment there are prescribed antibiotics and organic compounds containing arsenic and bismuth.

For syphilis drugs of first choice are agents of *Benzylpenicillin*. They possess rapid and considerable treponemicidal action. *Treponema pallidum* is unable to gain resistance to penicillins. In cases of allergic reactions, caused by penicillins, tetracyclines, macrolides and cephalosporins are used, though their efficiency is lower than of penicillins.

Organic arsenic-containing compound is *Myarsenolum*. Mechanism of action is the binding of arsenic with sulfhydrate groups of treponema enzymes and cessation of their activity. Because of *Myarsenolum* toxicity and the availability of a number of more effective agents, *Myarsenolum* current utility is limited. The adverse effects are encephalopathy, peripheral neuropathy, renal and hepatic dysfunction. Bismuth agents *(Biiochinolum, Bismoverol)* have the same mechanism of action as arsenic compounds, however, bismuth compounds are less toxic. After i.m. injections they are released slowly. Adverse effects are grey gingival colour (bismuth edge), gingivitis, stomatitis, gastrointestinal disturbances, dermatitis, and renal upset. *Sodium* and *Potassium iodide* are used in the late period of syphilis for enhance gumma dissimilation.

Available forms:

Biiochinolum — in bottles 100 ml each

Lecture 40
ANTIPROTOZOAL DRUGS

ANTIMALARIAL DRUGS

Four species of *Plasmodium* are responsible for human malaria: *P. vivax* and *P. ovale* that cause **three-day malaria**; P. malariae **(four-days malaria)** and *P. falciparum* **(tropical malaria)**. The transmitter of *Plasmodium* is mosquito. The *sporozoites* that develop in the mosquito are then inoculated into humans at its next feeding. In the first stage of development in humans, the **exoerythrocytic stage,** the sporozoites multiply in the liver to form *tissue schizonts*. Later, the parasites escape from the liver into the bloodstream as *merozoites* to initiate the **erythrocytic stage**. In this stage they invade red blood cells, multiply in them, and finally rupture the cells, releasing a new crop of merozoites. This cycle may be repeated many times. Meanwhile, partly merozoites are transformed in *gametocytes* (the **sexual stage**) and they may be taken in by another mosquito, which becomes infected, by taking human blood that contains gametes. In *P. vivax* and *P. ovale* infections, sporozoites also induce in hepatic cells the **dormant stage** *(the hypnozoite)* that causes subsequent recurrences (relapses) of the infection.

Drugs that eliminate developing tissue schizonts or latent hypnozoites in the liver are called tissue schizonticides (Fig. 29). Those that act on blood schizonts are blood schizonticides. Gametocides are drugs that prevent infection of mosquitoes by destroying gametocytes in the human blood. Sporonticidal agents are drugs that act on sporozoites noninfective in the mosquito. For causal malaria prophylactic are used sporonticides and tissue schizonticides (*Pyrimethamine* (*Chloridin*), *Proguanil (Bigumal)*, and *Primaquine*). However, blood schizonticides are prescribed for abortion and prevention of malaria attacks. Gametocides are useful for social chemoprophylaxis of malaria spreading.

Classification of antimalarial drugs:

Blood schizonticides: *Chloroquine*, *Mefloquine*, *Quinine*, *Chloridin*, *Bigumal*, and sulfanilamides.

Tissue schizonticides:

a. Agents that act on preerythrocytic forms (tissue schizonts) — *Chloridin*, *Bigumal*, *Primaquine*;

b. Agents that active against para-erythrocytic forms (hypnozoites) — *Primaquine*, *Quinocide*.

Gamete-tropic drugs:

c. Gametocidal drugs — *Chloroquine*, *Primaquine*, *Quinocide*.

d. Sporontocidal agents — *Chloridin*, *Bigumal*.

Chloroquine is a synthetic 4-aminoquinoline. Chloroquine is a highly effective blood schizonticide and is most widely used in chemoprophylaxis and in treatment of malaria attacks. It is also moderately effective against gametocytes. Chloroquine acts by blocking the synthesis of DNA and RNA in both mammalian and protozoal cells. Within the parasite, the drug interferes with the parasite's ability to metabolize and utilize erythrocyte hemoglobin. Selective toxicity for malarial parasites depends on a chloroquine-concentrating mechanism in parasitized cells. Also chloroquine has anti-inflammatory activity. It has been useful in the treatment of autoimmune disorders and for amebic liver abscess.

It is rapidly and almost completely absorbed from the gastrointestinal tract, reaches maximum plasma concentrations (50–65% protein-bound) in about 3 hours, and is rapidly distributed to the tissues. From tissues it is slowly released and metabolized. It is excreted in the urine with a half-life of 3–5 days. Renal excretion is increased by acidification of the urine. Gastrointestinal symptoms, pruritus, blurring of vision appear during prolonged treatment of autoimmune diseases. Chloroquine cumulation may contribute to the development of irreversible retinopathy, hepatoxicity, heart disorders.

Chloridin (Pyrimethamine) and *Bigumal (Proguanil)* are blood schizonticides. *Chloridin* is a derivative of *Diaminopyrimidine* related to *Trimethoprim* (lecture "Sulfanilamides"). *Bigumal* is a biguanide derivative. *Chloridin* and *Bigumal* are dihydrofolate reductase inhibitors (folic acid antagonists, antifols). They have a higher affinity for plasmodial dihydrofolate reductase than the human enzyme. Resistance to them is widespread in certain areas.

Both *Chloridin* and *Bigumal* are slowly but adequately absorbed from the gastrointestinal tract. *Chloridin* has an elimination half-life 3–4 days and *Bigumal* — 16 hours. Therefore, in prophylaxis, *Bigumal* must be administered daily, whereas *Chloridin* can be given once a week. *Chloridin* and *Bigumal* are used for personal malaria prophylaxis. Also they are indicated in combination with sulfanilamides or/ and *Chloroquine* in the treatment of malaria. *Metakelfin* contains *Chloridin* and *Sulfalene*; *Fansidar* includes *Chloridin* and *Sulfadoxine.* Such combination is the example of effect potentiation. Finally, *Chloridin* is used for toxoplasmosis treatment.

Chloridin and *Biguanide* can cause nausea, skin rashes, and alopecia. In the high doses *Chloridin* is used in toxoplasmosis, side effects of folic acid deficiency (megaloblastic anemia, agranulocytosis, and thrombocytopenia) are common. Also in high doses, neurologic symptoms (headache, insomnia, depression, ataxia, tremors, and seizures) may occur. Because *Chloridin* is teratogenic in animals, it should be avoided during the first trimester. *Bigumal* is considered safe in pregnancy.

Mefloquine is used in prophylaxis and treatment of chloroquine-resistant and multidrug-resistant malaria. *Mefloquine* hydrochloride is a synthetic 4-quinoline methanol derivative chemically related to quinine. It is well absorbed. The drug is highly bound to plasma proteins and concentrated in red blood cells. Its elimination half-life varies from 13 to 33 days. *Mefloquine* is used one time for malaria treatment and once a week for prophylaxis. Drug may lead to gastrointestinal disturbances, headache, and dizziness. In high doses visual disturbances can occur.

Primaquine is a synthetic 8-aminoquinoline derivative. It is active against the primary exoerythrocytic stages and late hepatic stages of Plasmodium. *Primaquine* is gametocidal against the four malaria species. The mechanism of action based on *Primaquine's* ability to bind to and alter the properties of DNA. At high doses, it may suppress myeloid activity. After oral administration, the drug is usually well absorbed, and then is almost completely metabolized and excreted in the urine. Its plasma half-life is 3–8 hours. *Primaquine* is widely distributed to the tissues, but only a small amount is bound there. It infrequently causes nausea, epigastric pain, abdominal cramps, and headache. The more serious adverse effects, leukopenia and methemoglobinemia (manifested by cyanosis) are rare. *Primaquine* may cause hemolysis in persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency. *Quinocide* is similar in structure and function to *Primaquine*.

Quinine, the principal alkaloid derived from the bark of the cinchona tree, has been used in malaria suppression and treatment for more than 300 years. Although superseded by other antimalarials, following the development of widespread resistance to chloroquine and other drugs, *Quinine* has again become an important antimalarial. *Quinine* is a rapidly acting, highly effective blood schizonticide. The mechanism of action based on quinine's ability to bind to and alter the properties of DNA. Agent is rapidly absorbed and is widely distributed in body tissues. When taken orally, *Quinine* commonly causes gastric irritation. The drug causes hypersensitivity reactions, myocardial depression and slight increasing of the uterus

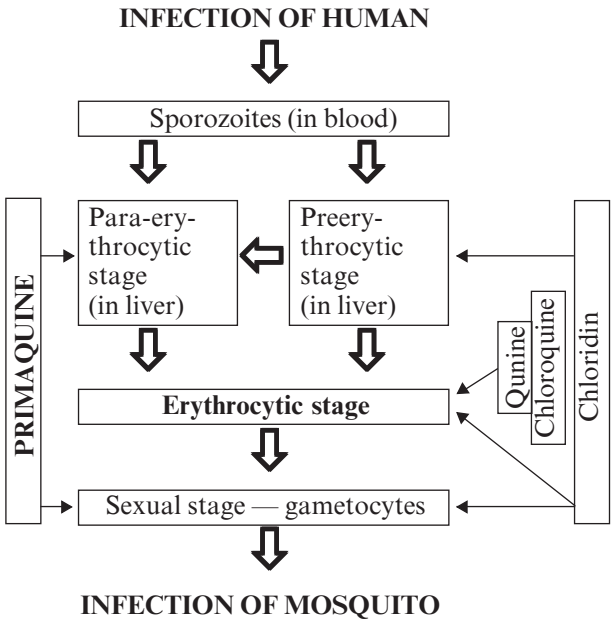


Fig. 29. Activity of antimalarial agents

tonus. A less common effect is cinchonism that includes headache, slight visual disturbances, dizziness, and mild tinnitus. Hemolysis may occur in G6PD-deficient persons.

Quinacrine a 9-aminoacridine, is a blood schizonticide that can effectively suppress all four types of human malaria. The mechanism of action based on acrichine's ability to bind to and alter the properties of DNA. Nowadays acrichine superseded by chloroquine. Its disadvantages include occasional drug deposits that turn the skin yellow and rare psychotic reactions. However, acrichine is indicated in the treatment of lambliasis (giardiasis), leishmaniasis, and cestodiasis.

TREATMENT OF AMEBIASIS

Amebiasis is infection by the protozoan parasite *Entamoeba histolytica.* Usually it leads to amebic dysentery that associated by ulcerative inflammation of the colon. It also may be associated with amebic infection of other organs (liver, lungs). The choice of drug depends on the desired site of drug action, i.e., in the intestinal lumen or in the tissues.

Classification of antiamebic agents

— Luminal amebicides. These agents act primarily in the bowel lumen: *Chiniofon*, *Chlorquinaldol*

— Agents that act against amebas in the bowel wall and lumen: tetracyclines

— Agents that act against amebas in the bowel wall and in the liver: *Emetine*

— Agents that act against amebas in the liver: *Chloroquine*

— Agents that act in any ameba's localization: *Metronidazole*

Metronidazole is the drug of choice in treatment of intestinal and extraintestinal amebiasis. The mechanism of action and the pharmacologic features of *Metronidazole* have been discussed in lecture "Antimicrobials — derivatives of different groups". However, it is only partially effective and not adequate as luminal amebicides. That's why, for amebic dysentery treatment *Metronidazole* is used concurrently with luminal amebicides.

Chiniofon is the derivative of 8-oxyquinolines. Agent is effective against organisms in the bowel lumen but not against trophozoites in the intestinal wall or extraintestinal tissues. Ninety percent of the drug is not absorbed. Thus, it produces a high amebicidal concentration in lumen. *Chiniofon* is a drug of low toxicity, but still it may cause diarrhea, optic neuritis, and peripheral neuropathy. *Intetrix*®, derivative of 8-oxyquinolines, is a patented drug. One tablet of *Intetrix* includes two active substances, which are similar to *Chlorquinaldol.* It is highly active against both gram-positive and gram-negative microbes in the bowel. Also, *Intetrix* is antiamebic and antifungal drug.

Emetine is the alkaloid of ipecacuanha root. It acts on organisms in the bowel wall and other tissues but not on amebas in the bowel lumen. *Emetine* blocks the synthesis of protein in ameba. The agent is administered parenterally, because oral preparation is absorbed erratically, and may induce vomiting. When given parenterally, it is stored primarily in the liver, lungs, and kidneys. The drug is cumulative; it is eliminated slowly via the kidneys more than month. Serious toxicity is common if they are given for more than 10 days. Therefore, use of this drug for more than 7–8 days is contraindicated. Hospitalization with careful supervision is essential. Pain in the area of the injection is frequent. Nausea and vomiting, which occur infrequently, are thought to be central in origin. The most serious symptoms are depression of cardiac conduction and contraction, which may cause a variety of atrial and ventricular arrhythmias, heart failure, and hypotension. Generalized muscular weakness (tenderness, stiffness, aching, or tremors), paresthesia are often reported. It should not be used during pregnancy.

The oral *tetracyclines* indirectly affect luminal amebas by inhibiting the bacterial associates of *E. histolytica* in the bowel lumen. Thus, the contents of oxygen in the bowel enhance that is harmful for ameba existing.

ANTILEISHMANIC DRUGS

Infection with a species of *Leishmania* resulting in a clinically ill-defined group of diseases may be divided into two types: visceral leishmaniasis (kala azar) and cutaneous leishmaniasis. Transmission is by various sandfly species. Treatment of leishmaniasis is not satisfactory because of drug toxicity, the long courses required, treatment failures, and the frequent need for hospitalization.

The drugs of choice for visceral leishmaniasis are pentavalent antimony compounds (*Solusurminum*, *Sodium stibogluconate*). *Solusurminum* is a frequently used drug. It binds with thiolic group of leishmania enzymes which leads to their inactivation. *Solusurminum* is injected i.v. The duration of treatment is about 3–4 weeks. The adverse effects are nausea, headache, skin rashes, and leukopenia. Hypotonia; liver, renal, and heart damages may appear. In case of *Solusurminum* overdosing *Unithiol* can be prescribed. *Sodium stibogluconate* can be administered i.m. or i.v. Most common adverse effects are gastrointestinal symptoms and rash. For cutaneous leishmaniasis the following drugs are useful: *Quinacrine* or *Chloroquine* (lecture "Antiprotozoal drugs"), *Aminoquinoline*, *Monomycin* (lecture "Antibiotics"), *Amphotericin* B (lecture "Antifungal agents"). *Aminoquinoline* is the quinoline derivative. It is effective in the treatment of cutaneous leishmaniasis as well as toxoplasmosis, lambliasis, and collagen diseases. *Aminoquinoline* is well-tolerated, sometimes gastrointestinal disturbances, headache and allergic reactions may appear.

ANTILAMBLIAL DRUGS

Lambliasis (giardiasis) is infection caused by protozoan parasite *Giardia lamblia* that may cause diarrhea, dyspepsia, and occasionally malabsorption in humans. For lambliasis treatment can be used metronidazole (see "Imidazole derivatives"), *Furazolidone* ("Nitrofuran derivatives"), and *Aminoquinoline.*

ANTITRICHOMONADAL DRUGS

Trichomoniasis caused by infection with a species of protozoan of the genus Trichomonas; often used to designate trichomoniasis vaginitis. For trichomoniasis treatment can be prescribed *Metronidazole*, *Trichomonacide*, and *Furazolidone*. *Trichomonacide* is a relative of *Aminoquinoline*. It can be taken locally or orally. It has irritate potency. *Acetarsol (Osarsol)*, arsenic compound, is seldom used for topical treatment of trichomoniasis.

ANTITOXOPLASMOSIS AGENTS

Toxoplasmosis caused by the protozoan parasite *Toxoplasma gondii* that can produce a variety of syndromes in humans, such as fever, encephalomyelitis, retinopathy, maculopapular rash, myalgia, myocarditis, and lymphadenopathy. For its treatment can be taken *Chloridin* ("Antimalarial agents"), *sulfanilamides*. During pregnancy sulfanilamides are preferable.

Available forms:

Chloroquine — powder; tablets 0.25 g each; in ampoules 5% solution 5 ml

Chloridin — powder; tablets 0.005 or 0.01 g each

Bigumal — powder; tablets or dragee 0.1 g (for adults) and 0.05 g (for children)

Primaquine — tablets 0.003 or 0.009 g each

Metronidazole — tablets 0.25 or 0.5 g each; vaginal suppository 0.5 g

Chiniofon — powder; tablets 0.25 g each

Intetrix — patented capsules

Solusurminum — in ampoules 20% solution 10 ml each

Aminoquinoline — powder; tablets 0.025 or 0.05 g each

Lecture 41
ANTIHELMINTIC DRUGS

Anthelmintic drugs are used to eradicate or reduce the numbers of helminthic parasites in the intestinal tract or tissues of the body. According to their localization helminths can be divided into intraintestinal and extraintestinal groups. Also helminths are distinguished as **nematodes (roundworms)** and **platyhelminthes (flatworms)**. The last one includes **cestodes (tapeworms)** and **trematodes (flukes, sucklings)**. Most anthelmintics in use today are active against specific parasites (Table 15). Therefore, parasites must be identified before treatment is started, usually by finding the parasite or eggs in the feces, urine, blood, sputum, or tissues of the host.

Mebendazole (Vermox) is a synthetic benzimidazole that has a wide spectrum of antihelmintic activity. It has been approved for use in ascaridiasis, trichocephaliasis, ancylostomiasis, and enterobiasis. In the treatment of trichinellosis and echinococcosis the drug should be taken with food containing fat, which enhances absorption. *Mebendazole* inhibits glucose uptake by parasites, decreasing formation of ATP. As a result, intestinal parasites are immobilized or die slowly. Less than 10% of orally administered *Mebendazole* is absorbed. The absorbed drug is rapidly metabolized in the liver. Within 24-48 hours, it is excreted mostly in the urine, either unchanged or as metabolites. A dosage of 100 mg twice daily for 3 days is used for adults. Treatment can be repeated in 2–3 weeks. Cure rates are 90-100% for ascaridiasis and trichocephaliasis. Mebendazole has a low incidence of adverse effects. Rash, nausea, vomiting, diarrhea, and abdominal pain have been reported infrequently. The drug is contraindicated during pregnancy.

Albendazole is similar in structure and activity with *Mebendazole*. It is also the drug of choice in echinococcosis and cysticercosis. Agent rapidly undergoes first-past metabolism in the liver to active metabolite. In large part, it binds to protein and is distributed to the tissues, including bile and cerebrospinal fluid, and enters hydatid cysts. When used for 1–3 days, *Albendazole* infrequently may cause nausea, diarrhea, headache, dizziness, and insomnia. In 3-month treatment courses for echinococcosis rash or pruritus, leukopenia were observed. Because the drug is teratogenic and embryotoxic in some animal species, it should not be used in pregnancy.

The *Piperazine adipinate* is alternative drug in the treatment of ascaridiasis. Cure rates are over 90% when patients are treated for 2 days. Also it can be used for enterobiasis treatment. *Piperazine* causes paralysis of nematodes by blocking *Acetylcholine* at the myoneural junction. Thus, the paralyzed roundworms are unable to maintain their position in the host and are expelled live by normal peristalsis. No pre- or posttreatment cathartics are used. Mild adverse effects occur occasionally, including nausea, diarrhea, abdominal pain, and headache. Patients with epilepsy may have an exacerbation of seizures.

Pyrantel is a broad-spectrum anthelmintic highly effective for the treatment of enterobiasis, ascaridiasis, and ancylostomiasis. Cure rates are greater than 95%. The drug causes stimulation of ganglionic receptors and worm paralysis, which is followed by expulsion from the host's intestinal tract. Because it is poorly absorbed from the gastrointestinal tract, it is active mainly against luminal organisms.

Adverse effects are infrequent and mild. They include vomiting, diarrhea, abdominal cramps, dizziness, headache, insomnia, and rash.

Levamisole is highly active for the ascaridiasis treatment. It causes contracture of ascaris that follows by it paralysis. In addition, levamisole inhibit a succinate dehydrogenase (essential enzyme) of helminth. Agent is rapidly absorbed from the gastrointestinal tract. The *Levamisole* half-life is about 3 to 4 hours. It is eliminated mostly via kidney (70% over 3 days). *Levamisole* is a single dose drug for ascaridiasis treatment. Also *Levamisole* has immunomodulating properties. Side effects of *Levamisole* are usually mild and transitory. It may lead to gastrointestinal disturbances and leukopenia.

Table 15. **The basic agents, which are used in the treatment of helminthiasis**

Localization	Class	Helminthiasis	*Mebendazole*	*Albendazole*	*Piperazine adipinate*	*Pyrantel*	*Levamisole*	*Naphthammonum*	*Praziquantel*	*Niclosamide*	*Aminoacrichinum*	*Diethylcarbamazine*	*Ivermectin*	*Chloxyle*	*Antimony sodium tartrate*	*Bithionol*
Intraintestinal	N	Ascaridiasis	+	+	+	+	+	+								
		Enterobiasis	+	+	+	+										
		Ancylostomiasis	+	+		+	+	+								
		Trichocephaliasis	+	+												
	C	Taeniarhynchiasis							+	+	+					
		Taeniasis							+	+						
		Diphyllobothriasis							+	+	+					
Extraintestinal	N	Trichinellosis	+													
		Filariasis										+	+			
	C	Echinococcosis	+	+												
		Cysticercosis	±	+					+							
	T	Schistosomiasis							+						+	
		Fasciolopsis							+					+		+
		Opisthorchiasis							+					+	+	

N — Nematodes; C — Cestodes; T — Trematodes.

Naphthammonum (Bephenium hydroxynaphthoate) primarily has been approved for Ancylostomiasis treatment. It is less useful in the treatment of ascaridiasis, trichocephaliasis, and enterobiasis infection. *Naphthammonum* causes contracture of nematodes that follows by their paralysis. The agent is badly absorbed in the gastrointestinal tract. There are special tablets of *Naphthammonum*, which are dissolved in the lower part of the small intestine — in the basic place of Ancylostoma localization. Nausea, vomiting, and diarrhea can appear in the period of *Naphthammonum* using.

Praziquantel is effective in the treatment of schistosome infections of all species and most other trematode and cestode infections, including cysticercosis. The drug's safety and effectiveness as a single oral dose have also made it useful in mass treatment of several infections. *Praziquantel* is a synthetic isoquinoline derivative. *Praziquantel* increases cell membrane permeability to calcium, resulting in marked contraction, followed by paralysis of worm musculature. It is rapidly and well absorbed after oral administration. Cerebrospinal fluid and bile concentrations of praziquantel reach 14–20% of the drug's plasma concentration. Most of the drug is rapidly metabolized to inactive products; the half-life of the drug is 0.8–1.5 hours. Excretion is mainly via the kidneys (60–80%). The adverse effects are headache, nausea, vomiting, abdominal pain, loose stools, and myalgia. The only specific contraindication is ocular cysticercosis; parasite destruction in the eye may cause irreparable damage. Because the drug induces dizziness and drowsiness, patients should not drive and should be warned if their work requires physical coordination or alertness.

Niclosamide (Phenasalum) is a drug of choice for the treatment of most tapeworm infections. It appears to be minimally absorbed from the gastrointestinal tract. Scoleces and segments of cestodes are rapidly killed on contact with *Phenasalum* due to the drug's inhibition of oxidative phosphorylation. With the death of the parasite, digestion of scoleces and segments begins. A single 2 g dose of *Phenasalum* results in cure rates of over 85% for *Diphyllobothrium latum* and about 95% for *Taenia saginata*. *Phenasalum* should be given in the morning on an empty stomach. The tablets must be chewed thoroughly and are then swallowed with water. Posttreatment purges to expel the worm are not necessary. Two hours after Taenia solium treatment an effective purge (such as 15–30 g of magnesium sulfate) should be given to eliminate all mature segments before ova can be released, that will prevent cysticercosis. Adverse effects are infrequent, mild, and transitory. Nausea, vomiting, diarrhea, and skin rash may occur.

Aminoacrichinum is relative of *Acrchinum* (see "Antimalarial drugs"). It has been used for the treatment of *diphyllobothriasis*, *hymenolepiasis*, and *Taeniasis*, however it's less effective agent than *Phenasalum* and *Praziquantel*. In addition, *Aminoacrichinum* is used for the treatment of *Trichomoniasis* vaginitis. It has high irritate potency, thus after ingestion *Aminoacrichinum* can cause stomach ache, nausea, and vomiting.

Diethylcarbamazine citrate (*Ditrazine citrate*) is a drug of choice in the treatment of Filariasis (Wuchereriasis, Loiasis). It alters microfilariae surface structure, making them more susceptible to destruction by host defense mechanisms. Adult parasites are killed more slowly. *Ditrazine* is rapidly absorbed from the gastrointestinal tract. Adverse reactions may be caused by to the agent itself and also occur as a result of the release of foreign proteins from dying worms in sensitized patients. For instance, headache, weakness, anorexia, nausea, vomiting, dizziness, and sleepiness are observed. Antihistamines may be given for the first 4–5 days of *Ditrazine* therapy to reduce the incidence of allergic reactions.

Ivermectin also indicated for *Filariasis (Onchocercosis)* treatment. In comparison studies, ivermectin is more effective than *Ditrazine*. Ivermectin appears to paralyze nematodes by intensifying GABA-mediated transmission of helminths. Ivermectin is given only orally. The drug is rapidly absorbed; it has a wide tissue distribution. It apparently enters the eye slowly and to a limited extent. The adverse effect of *Ivermectin* includes the reaction which caused by killing of microfilariae: fever, headache, dizziness, weakness, rash, diarrhea, joint and muscle pains, hypotension, lymphadenitis, and peripheral edema.

Chloxyle is the drug of choice for the treatment of *Fasciolopsis* and *Opisthorchiasis*. The agent is slowly absorbed from the gastrointestinal tract; mainly it is excreted with feces. Two days before and during treatment fat-food and alcohol are prohibited for patients. It has been taken 2 g of *Chloxyle* powder every 10 min (total dose — 10 g). Adverse effects are drowsiness, pain in the liver region, arrhythmia, and hypersensitivity reactions.

Bithionol is the drug of choice for the treatment of fasciolopsis. The agent is well absorbed in the gastrointestinal tract. Excretion appears to be mainly via the kidney. Adverse effects are generally mild. Diarrhea and abdominal cramps are most common. Anorexia, nausea, vomiting, dizziness, and headache may also occur.

Antimony sodium tartrate was for many years the principal drugs for the treatment of schistosomiasis, but because of it's toxicity and difficulty of administration, using of Antimony sodium tartrate is limited. Adverse effects are strong vomiting, skin rashes, arthralgia, and anaphylactic reactions. In case of overdosing, *Unithiol* is indicated. *Niridazole* is the drug of choice for the treatment of *schistosomiasis*. It is readily absorbed orally. The most frequent adverse effects are neurotoxicity (dizziness, headache, drowsiness), gastrointestinal disorders, and allergic reactions.

Available forms:

Mebendazole — tablets 0.1 each

Pyrantel — tablets 0.25 each; in bottles 5% suspension 15 ml

Praziquantel — tablets 0.6 each

Diethylcarbamazine citrate (Ditrazine citrate) — tablets 0.05 or 0.1 each

Chloxyle — powder

Lecture 42
ANTIFUNGAL AGENTS

Antifungal agents can be dividing into three main groups:

1. Agents for the treatment of system mycosis (Histoplasmosis, Blastomycosis, Coccidia mycosis) — *Amphotericin B*, *Amphoglucaminum (Amphotericin B + Methylglucamine)*, *Mycoheptinum*, azole derivatives.
2. Agents for the treatment of dermatomycosis (epidermophytosis, microsporiasis, and trichophytosis):
   a) antibiotic — *Griseofulvin*;
   b) azole derivatives — *Miconazole*, *Itraconazole* and *Fluconazole*;
   c) derivatives of undecylenic acid *(Zincundanum®, Undecinum®)*;
   d) different chemical groups representatives — *Terbinafine*, *Octicylum* (Octilcyclopronancarbonic acid), *Nitrofungin*, and iodine including agents.
3. Agents for the treatment of candidamycosis:
   a) antibiotics — Nystatin, Levorin;
   b) other agents — Clotrimazole, Decamine.

Amphotericin B is a polyene antifungal antibiotic produced by *Streptomyces nodosus*. It remains the drug of choice for nearly all life-threatening mycotic infections. *Amphotericin B* is selective in its fungicidal effect. The agent binds to ergosterol, a cell membrane sterol, and alters the permeability of the cell by forming pores in cell membrane. The pore allows the leakage of intracellular ions and macromolecules, eventually leading to cell death. *Amphotericin B* is poorly absorbed from the gastrointestinal tract; thus it is used intravenously. The serum half-life is approximately 15 days. The drug is widely distributed in tissues, but only 2–3% of the blood level is reached in cerebrospinal fluid, thus occasionally necessitating intrathecal therapy for certain types of fungal meningitis. Anemia, hypokalemia, renal function impairment are the most significant toxic reactions. Fever, muscle spasms, vomiting, and hypotension can appear during infusion of the drug. *Amphotericin B* should be given only to hospitalized patients, so as to provide constant supervision by a physician.

Amphoglucaminum is a synthetic derivative of *Amphotericin B*. It is well absorbed from the gastrointestinal tract and less toxic than parental agent. *Mycoheptinum* is similar in structure and function to *Amphotericin B*.

Azoles are synthetic compounds that can be classified as either imidazoles or triazoles. The imidazoles consist of *Ketoconazole, Miconazole*, and *Clotrimazole*. The triazoles include *Itraconazole* and *Fluconazole*. The antifungal activity of azole drugs results from the reduction of ergosterol synthesis. The effect is fungistatic or may be fungicidal, depending on agent concentration. The most common ***adverse reaction*** is relatively minor gastrointestinal upset. All azole drugs inhibit the mammalian cytochrome P_{450} system of enzymes to some extent. For instance, the metabolism of cumarin anticoagulants, oral antidiabetic drugs and *Diphenin* in the liver will slow down; thus the therapeutic effects of those agents will enhance and prolong.

Miconazole can be used in enteral way or i.v. in the treatment of systemic (endemic) mycoses. Also it is useful for local treatment of dermatomycosis (dermatophytosis, tinea) and candidamycosis. The adverse effects are burning and redness of skin, rash, or other sign of skin irritation, thrombophlebitis in site of injections. The systemic using of *Miconazole* is prohibited during pregnancy and hepatitis. *Ketoconazole* is prescribed for oral and topical usage. The agent is variable absorbed from the intestine; the serum half-life is 7–8 hours. *Ketoconazole* has the same indication as *Miconazole*, however *Ketoconazole* is more toxic. *Ketoconazole* inhibition of human cytochrome P_{450} enzymes interferes with biosynthesis of adrenal and gonadal steroid hormones, producing endocrine effects such as gynecomastia, infertility, and menstrual irregularities.

Itraconazole is available in an oral formulation. Like *Ketoconazole*, its absorption is increased by low gastric pH and it poorly penetrates into the cerebrospinal fluid. *Itraconazole* is the most potent of the available azoles. It is the azole of choice in the treatment of dermatomycosis, systemic mycoses. It interacts with hepatic microsomal enzymes to a lesser degree than *Ketoconazole. Fluconazole* is distinguished from the other azole medications by good cerebrospinal fluid penetration and excellent bioavailability by the oral route. That's why, it is the azole of choice in the treatment of mycotic meningitis. It is also effective for mucocutaneous candidamycosis. *Fluconazole* has the least effect on hepatic microsomal enzymes. As a result, this drug has a wide therapeutic window, which permits more aggressive dosing than with any other azole.

Griseofulvin is a fungistatic drug derived from a species of *Penicillium*. Its only use is in the systemic treatment of dermatomycosis. Griseofulvin inhibits the synthesis of mycotic nucleic acids. Absorption is variable and improved being given with fatty foods. Griseofulvin is deposited in newly forming skin where it binds to keratin, protecting the skin from new infection. It must be administered for 2–6 weeks for skin and hair infections to allow the replacement of infected keratin by the resistant structures. The serum half-life is approximately 24 hours. Adverse effects are diarrhea, nausea, headache, dizziness, insomnia, allergic reactions, and hepatitis. *Griseofulvin* is not recommended during pregnancy since it has been shown to be embryotoxic and teratogenic in rats.

Terbinafine, a fungicidal agent, is used in the treatment of dermatomycosis, especially onychomycosis. It is available in an oral formulation. Like griseofulvin, *Terbinafine* is a keratophilic medication. It inhibits the ergosterol biosynthesis. One tablet given daily for 12 weeks achieves an up to 90% cures rate for onychomycosis and is more effective than *Griseofulvin* or *Itraconazole.* Adverse effects are rare, consisting primarily of gastrointestinal upset and headache.

Undecylenic acid and undecylenate salts (e.g. ointments *Zincundanum®*, *Undecinum® (Undecylenic acid + Cuprum undecylenate))* are topical anti-dermatomycosis agents. The drugs usually are used in combination. Preparations containing the drugs are applied topically twice daily after cleansing the affected area. In addition, *iodine* including agents, *Nitrofungin*, and *Octicylum* are indicated for the topical treatment of dermatomycosis.

Nystatin is active against most *Candida species* and is most commonly used for suppression of local candidal infections. Some common indications include oropharyngeal thrush, gastrointestinal and vaginal candidiasis, and skin candidal infections. Candida, a species ordinarily a part of humans normal gastrointestinal flora, but which becomes pathogenic when there is a disturbance in the balance of flora or in debilitation of the host from other causes. *Nystatin* is a polyene antibiotic much likes *Amphotericin B* and has the same pore-forming mechanism of action. It is currently available in tablets, ointments, and suppositories for application to skin and mucous membranes. *Nystatin* is not absorbed from the gastrointestinal tract. As a result, it produces a high antifungal concentration at the intestine. *Nystatin* has a little significant toxicity. Sometimes, it can cause gastrointestinal disturbances (diarrhea, nausea or vomiting, stomach pain). *Levorin* is similar in mechanism of action and indications to *Nystatin*. It has higher anti-candidamycosis activity, than *Nystatin*. However, *Levorin* is more toxic.

For candidamycosis treatment are used *Clotrimazole*, *Decamine* as well. *Clotrimazole*, an imidazole derivative, is active against *Candida species* and dermatophytes. In connection with its high toxicity, clotrimazole is now used only in topical therapy. *Decamine (Dequalinium)*, a quaternary ammonium compound, possess antibacterial and antifungal (Candida, dermatophytes) activity. It can be prescribed in ointment or caramel. The last one has to be taken under the tongue or beyond of cheek. *Decamine* is well-tolerated agent.

Available forms:

Amphotericin B — in bottles 50,000 unites powder each

Amphoglucaminum — tablets 0.1 (10000 unites) each

Isoconazole — 1% cream 20,0

Fluconazole — capsules 0.05; 0.1; 0.15 or 0.2 each; in bottles 0.2% solution

Griseofulvin — tablets 0.125 each; 2.5% liniment 30.0

Terbinafine — tablets 0.125 or 0.25 each; 1% ointment

Nystatin — tablets 250,000 or 500,000 unites each; vaginal suppository 250,000 or 500,000 unites each; ointment 15 g (1 g contains 100,000 unites)

Lecture 43
ANTIVIRAL AGENTS

Viruses are obligate intracellular parasites; their replication depends primarily on synthetic processes of the host cell. Consequently, antiviral agents must be active inside the host cell. Nonselective inhibitors of virus replication may interfere with host cell function and produce toxicity.

According to the chemical structure, **antiviral agents are classified as:**

— synthetic agents — analogs of nucleosides *(Acyclovir, Idoxuridine, Ribavirin, Zidovudine)*, amantadine derivatives *(Rimantadine)*, and different chemical groups representatives *(Oxolin (Tetraoxotetrahydronaphthaline dihydrate), Florenalum (Fluorenonylgluoxal bisulfite)*;

— biological preparations — *Interferons*.

Acyclovir is an acyclic guanosine derivative with clinical activity against herpes simplex viruses and against varicella-zoster virus. Agent requires three phosphorylation steps for activation and is converted to the mono-, di- and triphosphate compounds. Because it requires the viral kinase for the first phosphorylation, *acyclovir* is selectively activated and the triphosphate accumulates only in infected cells. *Acyclovir* triphosphate inhibits the viral DNA polymerase and incorporates into the viral DNA. Oral and topical acyclovir is effective for treatment of primary infection and recurrences of genital and labial herpes. Intravenous *Acyclovir* is the treatment of choice for herpes simplex encephalitis. The bioavailability of the oral formulation is 20%. *Acyclovir* is cleared primarily by kidneys. The half-life is 3–4 hours. Agent well diffuses into most tissues and body fluids, including cerebrospinal fluid. *Acyclovir* is generally well tolerated. Nausea, diarrhea, and headache have occasionally been reported. Intravenous infusion may be associated with renal insufficiency or neurologic toxicity (the latter may include tremors or delirium).

Ganciclovir is similar in structure, mechanism of action, and activity to acyclovir. However, its activity against cytomegalovirus is up to 100 times greater than that of acyclovir. *Ganciclovir* is available in i.v. formulations. The oral bioavailability of ganciclovir is poor (6–9%). *Ganciclovir* is indicated for the treatment of cytomegalovirus retinitis and colitis inpatients with AIDS. The most common side effect of treatment with *Ganciclovir* is myelosuppression, particularly neutropenia. Central nervous system toxicity (headache, changes in mental status, seizures) has been reported also. Due to the high toxicity and mutagenic and teratogenic potential of *Ganciclovir*, use during pregnancy should be avoided.

Idoxuridine is a *Thymidine* analog. It has the similar mechanism of action with *Acyclovir*. *Idoxuridine* is used topically in the treatment of herpes keratitis, because it is too toxic for systemic administration (leukopenia).

Zidovudine (Azidothymidine) is a *Deoxythymidine* analog. After entering the cell by passive diffusion, *Zidovudine* is phosphorylated via three cellular kinases; the triphosphate is an inhibitor of the reverse transcriptase. *Zidovudine* has activity against human immunodeficiency virus. Resistance typically occurs after prolonged therapy. *Zidovudine* is available in i.v. and oral formulations. It is well absorbed from the gut and distributed to most body tissues and fluids, including the cerebrospinal fluid. Substantial first-pass metabolism to an inactive glucuronidated metabolite results in a systemic bioavailability of approximately 65%. The serum half-life is only 1 hour. Clinical efficacy is limited by the relatively rapid development of resistance, particularly when used as monotherapy. The combination of *Zidovudine* with one or two other agents, such as a protease inhibitor, is one strategy to enhance antiviral activity and retard the development of resistance. The most common adverse effect is myelosuppression, resulting in anemia or neutropenia.

Indinavir is a specific inhibitor of the human immunodeficiency virus protease, an enzyme essential for the production of mature, infectious virions. It is approved for the treatment of individuals with human immunodeficiency virus infection. Oral bioavailability is excellent. The most common adverse effects reported thus far are indirect hyperbilirubinemia and nephrolithiasis. Indinavir is inhibitor of as well as substrate for cytochrome P_{450}. Thus, numerous complex drug interactions can occur.

Rimantadine, an amantadine derivative, inhibit uncoating of the viral RNA of influenza A within infected host cells, thus preventing its replication. It is effective in the prevention of influenza A virus infection. The most common side effects are gastrointestinal intolerance and central nervous system effects (e.g. nervousness, drowsiness).

Ribavirin is a *Guanosine* analog that is phosphorylated intracellularly by host cell enzymes. Its mechanism of action appears with synthesis of *Guanosine* triphosphate and inhibition of RNA polymerase of certain viruses, including influenza A and B, parainfluenza, and respiratory syncytial virus. *Ribavirin* is administered in aerosolized form to patients with respiratory syncytial virus bronchiolitis or pneumonia, reducing the severity and duration of illness. I.v. *Ribavirin* decreases mortality in Lassa fever and other viral hemorrhagic fevers. Aerosolized *Ribavirin* is generally well tolerated but may cause conjunctival or bronchial irritation. Systemic administration of *Ribavirin* is associated with dose-dependent anemia and bone marrow suppression. The drug is contraindicated in pregnancy due to possible teratogenicity.

Oxolin and *Florenalum* are the topical agents that adopted for the treatment of skin and mucous membrane viral infections (mostly herpes). These agents have direct virucidal activity. They are too toxic for systemic administration. *Oxolin* and *Florenalum* can cause irritation in place of their application.

Interferons are a group of endogenous proteins that exert virus-nonspecific antiviral activities. Three major classes of *Interferons* are now recognized: α- (leukocyte), β- (fibroblast), and γ- (immune, T-lymphocyte). Each type can function as a potent cytokine with complex antiviral and immunomodulatory activity. They are not directly antiviral but appear to function by causing elaboration of effector proteins in infected cells, resulting in such effects as inhibition of viral penetration or uncoating, mRNA synthesis and translation, or virion assembly and release. Agents of natural a-interferon as well as recombinant α-interferon *(Reaferon)*, which produced by genetic engineering, are mostly used in clinics. Natural α-interferon have been used an intranasal route for prophylaxis and treatment of the common cold viruses infections *(Interferon)* and an intraconjunctival way for the treatment of herpes keratitis *(Interlock)*.

Recombinant α-interferon is approved for the treatment of hepatitis B and C, leukemia, bladder and renal carcinoma, and malignant melanoma. Recombinant β-interferon *(Betaferon)* is used for the treat-

ment of multiple sclerosis. Adverse effects of inetrferons include neutropenia, anemia, skin rashes, fever, myalgia, and fatigue. *Poludan, Amixin* stimulate the synthesis of endogenous interferon and thus possess antiviral activity. Poludan is a topical agent for the treatment of viral eye diseases. Amixin is active in case of virus's hepatitis B and C.

Available forms:

Interferon — in ampoules (2 ml) powder

Acyclovir — in ampoules 0,25 (to dilute in 10 ml physiological solution, for i.v. injection); tablets 0.2 each; 3% ointment 4.5 or 5.0

EXAMINATION QUESTIONS

1. Choose the best answer. Selective toxicity is
   (A). What the drug does to the patient.
   (B). What the patient does to the drug.
   (C). What the pathogen does to the patient.
   (D). What the drug does to the pathogen.
   (E). What the pathogen does to the drug.

2. A 60-year-old patient with AIDS presents to the emergency department with a temperature of 102°F, confused, and is going in and out of consciousness. He exhibits rapid respiration and a blood pressure of 80/40. You determine that both the sputum and urine are negative by Gram staining. Which of the following is the best choice?
   (A). Administer *Penicillin G* intravenously.
   (B). Administer *Vancomycin.*
   (C). Administer *Clindamycin* and *Amikacin*.
   (D). Send a clinical sample to laboratory to find out what the organism is before treating.

3. The term magic bullet was coined for
   (A). Ehrlich discovering the drug *Salvarsan* for the treatment of syphilis.
   (B). Fleming discovering the antibacterial effect of *Penicillium notatum.*
   (C). Florey showing the effectiveness of *Penicillin* in patients.
   (D). Wilson discovering the broad spectrum antibiotic *Streptomycin.*

4. Choose the best answer for the following. The emergence of microbial antibiotic drug resistance
   (A). Requires the concurrent administration of more than one antibiotic.
   (B). Is a direct result of the use of antibiotics in livestock.
   (C). Is a problem that was overcome by the devel opment of *Vancomycin*.
   (D). Is due in large part to the indiscriminate use of antibiotics in humans.

5. A patient refuses to continue to take *Erythromycin* because it makes him vomit. This is an example of which patient-drug-pathogen interaction?
   (A). Pharmacokinetics.
   (B). Pharmacodynamics.
   (C). Immunity.
   (D). Resistance.
   (E). Selective toxicity.

6. A 24-year-old AIDS patient is interested in starting chemoprophylaxis for *Pneumocystis* pneumonia (PCP) and cerebral toxoplasmosis. He has no drug allergies. Which of the following prophylactic agents is appropriate for the prevention of both PCP and cerebral toxoplasmosis?
   (A). *Nitrofurantoin.*
   (B). *Trimethoprim-sulfamethoxazole.*
   (C). *Norfloxacin.*
   (D). *Methenamine.*
   (E). *Nalidixic acid.*

7. Urinalysis of a 38-year-old woman with recurrent UTIs revealed pH 6.8, 30 to 50 WBC per high-power field, and gram-negative bacilli identified as *Proteus mirabilis.* Which of the following produces a bacteriostatic urinary environment for *P. mirabilis?*
   (A). Urease enzyme.
   (B). Hippuric acid.
   (C). Catalase enzyme.
   (D). Folic acid.
   (E). Coagulase enzyme.

8. A 3-day-old baby is given a presumptive diagnosis of kernicterus. Which of the following mechanisms is involved in *Sulfonamide*-induced kernicterus?
   (A). Competes for the bilirubin-binding sites on plasma proteins.
   (B). Defective bilirubin hepatic conjugation and metabolism.
   (C). Physiological jaundice due to destruction of fetal red blood mass.
   (D). Pregnancy-induced hepatic congestion and cholestasis.
   (E). Primary biliary cirrhosis of the liver.

9. A 6-year-old relatively healthy boy is diagnosed with external otitis and was prescribed a 7-day course of TMP-SMX. Which of the following is the basic mechanism of action of the *sulfonamides*?
   (A). Selective inhibition of incorporation of PABA into human cell folic acid synthesis.
   (B). Competitive inhibition of incorporation of PABA into microbial folic acid.
   (C). Inhibition of transpeptidation reaction in bacterial cell wall synthesis.
   (D). Changes in DNA gyrases and active efflux transport system resulting in decreased permeability of drug.
   (E). Structural changes in dihydropteroate synthase and overproduction of PABA.

10. Evaluation of a yearly chest radiograph of a 73-year-old patient taking *Nitrofurantoin* prophylactically for recurrent UTIs revealed new findings of bilateral interstitial fibrosis. What is the possible explanation for the patient's pulmonary presentation and what is the next step?
   (A). Acute urosepsis; add a broad-spectrum antibiotic to *Nitrofurantoin.*

(B). Possible allergic reaction to *Nitrofurantoin*; stop it immediately.
(C). *Nitrofurantoin*-resistant *E. coli* infection; stop it immediately.
(D). Acute community-acquired streptococcal pneumonia; treat accordingly.
(E). *Nitrofurantoin*-induced hemolysis; requires permanent urinary catheter.

11. A 16-year-old girl, a cystic fibrosis patient, is diagnosed with a *Ciprofloxacin*-resistant *Pseudomonas aeruginosa* lower respiratory tract infection. Bacteria acquire *Quinolone* resistance by which of the following mechanisms?
(A). Overproduction of PABA.
(B). Changes in the synthesis of DNA gyrases.
(C). Plasmid-mediated changes in efflux transport system.
(D). Inhibition of synthesis of *Peptidoglycan* subunits in bacterial cell walls.
(E). Inhibition of *Folic acid* synthesis by blocking different steps.

12. A 32-year-old man with quadriplegia and neurogenic bladder was admitted to the hospital from a long-term care facility. The patient had vomiting, fever, and cloudy urine. A year ago, the patient developed urticaria, wheezing, and hypotension within an hour after his first dose of *Nafcillin*. Subsequently his penicillin skin test was positive. During the current admission, the physician examiner noted fever, quadriplegia, and chronic indwelling bladder catheter. Laboratory tests revealed leukocytosis in blood and urine. Urine stain showed gram-negative rods, and urine culture grew *P. aeruginosa*. Which of the following drugs would be most appropriate for this patient?
(A). *Ampicillin-sulbactam.*
(B). *Aztreonam.*
(C). *Cefazolin.*
(D). *Imipenem-cilastatin.*
(E). *Piperacillin-tazobactam.*

13. A 22-year-old woman had her first prenatal visit. Her physical examination was normal for a woman at 12 weeks' gestation. Both the nontreponemal (Venereal Disease Research Laboratory) and fluorescent treponemal antibody tests were positive. She denied previous treatment for syphilis. She could not recall signs or symptoms of primary or secondary syphilis in the past year. She had no previous syphilis serology tests for purposes of comparison. Which of the following would be the best treatment for the patient?
(A). *Benzathine penicillin G.*
(B). *Doxycycline.*
(C). *Spectinomycin.*
(D). *Streptomycin.*
(E). *Tetracycline.*

14. A 26-year-old woman, a kindergarten teacher, had pharyngitis last year treated with ampicillin for 3 days. She stopped the *Ampicillin* when she learned her throat culture was negative. Three days after she stopped the *Ampicillin*, she developed a rash. Her physician noted symmetrical erythematous confluent macular-papular eruptions on her extremities with no urticaria. The physician diagnosed non-IgE-mediated *Ampicillin* eruption. Now the patient returns with new fever and sore throat. She has no cough or rash. Her physical examination is normal except for fever, tender anterior cervical lymphadenopathy, and tonsillar exudate. Her rapid streptococcal test of a pharyngeal specimen is positive. Which of the following would be the most appropriate treatment for this patient?
(A). *Amikacin.*
(B). *Lomefloxacin.*
(C). *Metronidazole.*
(D). *Netilmicin.*
(E). *Penicillin V.*

15. A 24-year-old man came to the public health clinic because of a urethral discharge. He had had unprotected intercourse with multiple partners. Physical examination revealed a purulent urethral discharge with no penile ulcers or vesicles. There was no inguinal adenopathy. Gram stain of the discharge revealed gram-negative *diplococci* inside leukocytes. The antibiotic used to treat the patient's infection has which of the following mechanisms of action?
(A). Inhibits cell membrane integrity by binding to ergosterols to create pores.
(B). Inhibits *dihydrofolate reductase*, thereby blocking formation of *tetrahydrofolate* required for purine synthesis.
(C). Inhibits KasA, a β-ketoacyl carrier protein synthetase, thereby blocking mycolic acid synthesis.
(D). Inhibits RNA synthesis by binding to the b-subunit of DNA-dependent RNA polymerase.
(E). Inhibits transpeptidase, thereby blocking crosslinking of peptides in cell wall murein *(Peptidoglycan)*.

16. Parents brought their 3-year-old boy to the outpatient clinic because of a facial rash. Today the patient was one of several children sent home from day care because of similar rashes. Physical examination revealed a normal, healthy boy with discrete erythematous papular eruptions on his cheeks. There were no vesicles or bullae. The rash was covered with a honey crust, suggesting impetigo. Which of the following treatments would be most appropriate?
(A). *Dapsone.*
(B). *Dicloxacillin.*
(C). *Doxycycline.*
(D). *Ketoconazole.*
(E). *Penciclovir.*

17. Many antibiotics appear to have as their mechanism of action the capacity to inhibit bacterial cell wall synthesis. This does not appear to be a mechanism of
(A). *Aminoglycosides.*
(B). *Penicillins.*
(C). *Bacitracin.*
(D). *Cephalosporins.*

18. Many antibiotics are not useful in treating infections in the central nervous system because they do not readily penetrate the blood-brain barrier. Which one of the following agents gets into the brain in reasonable concentrations?
(A). *Penicillin G.*
(B). *Ampicillin.*
(C). *Cefotaxime.*
(D). *Kanamycin.*
(E). *Neomycin.*

19. Aminoglycoside antibiotics are frequently used in combination with the β-lactam antibiotics. Which of the following choices best explains the rationale for this use?
(A). The combination provides for a much greater spectrum of activity.
(B). A synergistic effect is often seen when the combination is employed.
(C). The β-lactam antibiotics prevent toxic effects of the *aminoglycoside* antibiotics.
(D). The combination decreases incidence of superinfections.

20. Patients with myasthenia gravis may exhibit greater toxicity to aminoglycosides than do patients without this condition. The most likely explanation is
(A). *Aminoglycosides* have muscarinic blocking properties.
(B). *Aminoglycosides* cause an increased metabolism of acetylcholine.
(C). *Aminoglycosides* cause a neuromuscular block by displacing Ca^{++} from the neuromuscular junction.
(D). *Aminoglycosides* inhibit second messenger activity at the neuromuscular junction.

21. As a class, the *aminoglycoside* antibiotics do not exhibit significant metabolism in the patient. The most likely reason is that
(A). Their chemical structure is unique and not prone to chemical reactions commonly seen in drug metabolism.
(B). The liver does not contain appropriate enzymes to break down the compounds.
(C). The body apparently lacks a necessary cofactor for the metabolism of aminoglycosides.
(D). *Aminoglycosides* do not readily get to the site of degradative enzymes.

22. A pediatric nurse is found to be colonized with MRSA in her nares during an outbreak investigation in the pediatric intensive care unit. The best strategies to eradicate her nasal carriage could be
(A). Parenteral therapy with IV *Vancomycin*.
(B). Oral *Vancomycin.*
(C). *Bacitracin* ointment application to her nasal passages.
(D). *Polymyxins.*
(E). A month-long furlough from patient care.

23. In the treatment of uncomplicated urinary tract infection caused by gram-negative bacteria, the therapy of choice would be
(A). *Teicoplanin.*
(B). *Bacitracin.*
(C). *IV vancomycin.*
(D). *IV polymyxin B.*
(E). *Trimethoprim-sulfamethoxazole.*

24. Effective interventions for treating a minor surgical suture site infection should definitely include one of the following choices:
(A). *Polymyxins.*
(B). *Bacitracin.*
(C). Triple antibiotics *(bacitracin, Polymyxin B, and neomycin)* ointment.
(D). *IV Vancomycin.*
(E). Observation.

25. A urine culture in an asymptomatic female patient with an indwelling Foley catheter comes back with more than 50,000 colonies of *enterococci*. The urinalysis is unremarkable. The best course of action would be to
(A). Start IV *Vancomycin* to cover *enterococci*.
(B). Seek the newly approved drug *Linezolid* for possibility of *Vancomycin*-resistant enterococci (VRE).
(C). Initiate a *Quinolone* like *Levofloxacin* with broad-spectrum coverage for UTIs.
(D). Discontinue use of the Foley catheter if possible and obtain follow-up cultures if she develops symptoms.
(E). Watchful waiting.

26. Which glycopeptide or polypeptide antibiotic is still investigational and not used in the United States for parenteral therapy?
(A). *Polymyxins.*
(B). *Vancomycin.*
(C). *Teicoplanin.*
(D). *Bacitracin.*
(E). *Linezolid.*

27. Which of the following best treats the initial stage of Lyme disease *in adults?*
(A). *Penicillin V.*
(B). *Erythromycin.*
(C). *Clarithromycin.*
(D). *Doxycycline.*
(E). *Clindamycin.*

28. *Chloramphenicol* is the drug of choice for which of the following?
(A). *S. pneumoniae* meningitis.
(B). *B. fragilis* in abdominal abscess infection.
(C). *H. influenzae* epiglottitis.
(D). Typhoid fever in the United States.
(E). Typhoid fever in some developing countries.

29. A 39-year-old man has AIDS and a CD_4 count less than 50. Recently he has had chills and fever. Several blood cultures drawn especially for acid-fast bacilli are positive. Which antibiotic should be included in a treatment regimen for this disease?
(A). *Tetracycline.*
(B). *Amoxicillin.*
(C). *Cephalexin.*
(D). *Clarithromycin.*
(E). *Doxycycline.*

30. A 37-year-old postal worker has a job at a mail sort facility. An envelope that passed through the facility and was delivered to a governmental office was noted upon opening to have anthrax spores. One of the postal worker's fellow employees subsequently developed inhalation anthrax. Because of this, medical authorities recommended that other employees working at the same facility be tested and receive prophylactic antimicrobial therapy. The drug of choice is a *Quinolone*. However, this employee has a history of allergy to *Ciprofloxacin*. Which of the following antibiotics is also recognized as being effective prophylactic therapy for potential anthrax exposure?

(A). *Amoxicillin.*
(B). *Erythromycin.*
(C). *Clarithromycin.*
(D). *Doxycycline.*
(E). *Clindamycin.*

31. An 18-year-old man sustains a minor laceration of his right forearm. Approximately 2 days later the laceration site becomes red and swollen. He also begins to develop fever and chills. The patient eventually goes to the local hospital's emergency department. By this point his forearm is swollen and the skin is light brown. Cultures of his wound and two blood cultures 15 minutes apart are obtained. Intravenous cephalosporin is begun. However, over 3 days the discoloration of his forearm begins to ascend to the upper arm and shoulder. Blood cultures are positive in approximately 12 hours for gram-positive cocci in chains. Wound cultures of the laceration also grow similar organisms, and high-dose *Penicillin G* is prescribed. What other antibiotic would be extremely useful in treating this condition?

(A). *Gentamicin.*
(B). *Clindamycin.*
(C). *Ciprofloxacin.*
(D). *Clarithromycin.*
(E). *Chloramphenicol.*

32. A 35-year-old man under treatment for pulmonary tuberculosis has acute-onset right big toe pain, swelling, and low-grade fever. His physical examination was consistent with gouty arthritis, and he was found to have high serum uric acid levels. Which of the following antituberculosis drugs is known to cause high uric acid levels?

(A). *Cycloserine.*
(B). *Thiacetazone.*
(C). *Pyrazinamide.*
(D). *Rifampin.*
(E). *Aminosalicylic acid.*

33. A 26-year-old truck driver, a recent immigrant from Mexico, could not obtain a Florida driving license because of his poor performance in red-green color vision discrimination. He denies any family history of color vision-related problems in the past. He is taking a four-drug regimen for pulmonary tuberculosis. He does not recall the names of the drugs. Which of the following antituberculosis drugs is responsible for his lack of color vision discrimination?

(A). *Ethambutol.*
(B). *Ethionamide.*
(C). *Aminosalicylic acid.*
(D). *Rifampin.*
(E). *Isoniazid.*

34. A 68-year-old white South African man receiving treatment for lepromatous leprosy has increasing red-brown pigmentation. Which of the following antileprosy drugs is responsible for the patient's skin pigmentation?

(A). *Dapsone.*
(B). *Rifampin.*
(C). *Clofazimine.*
(D). *Capreomycin.*
(E). *Thiacetazone.*

35. A 23-year-old college student is diagnosed with *Neisseria meningitidis* based on his clinical presentation, gram-negative *diplococci* on Gram stain, and isolation of bacteria from cerebrospinal fluid. Which of the following drugs can be used as a prophylactic agent for roommates and other close contacts?

(A). *Amoxicillin.*
(B). *Isoniazid.*
(C). *Dapsone.*
(D). *Clarithromycin.*
(E). *Rifampin.*

36. A 32-year-old Haitian man has acute-onset confusion and suicidal ideation. Two weeks ago he began combination therapy for multi-drug resistant pulmonary tuberculosis. He has a history of depression that required intermittent treatment in the past. Which of the following antitubercular agents is responsible for the patient's neurological symptoms?

(A). *Pyrazinamide.*
(B). *Aminosalicylic acid.*
(C). *Cycloserine.*
(D). *Rifampin.*
(E). *Ethambutol.*

37. Which drug, compared with the rest, would be expected to produce a significantly higher concentration of active metabolite in cells infected with its target virus?

(A). *Cidofovir.*
(B). *Foscarnet.*
(C). *Oseltamivir.*
(D). *Penciclovir.*
(E). *Lamivudine.*

38. Which of the following drugs should not be given in combination with *Zidovudine* because of an increased risk of myelosuppression?

(A). *Ganciclovir.*
(B). *Fomivirsen.*
(C). *Rimantadine.*
(D). *Famciclovir.*
(E). *Zanamivir.*

39. Caitlyn Doe is a 24-year-old woman in her third month of pregnancy. She has had severe pain, swelling, and redness in both eyes for several days and has been unable to see well enough to go to work. Ms. Doe's physician diagnosed herpes simplex keratoconjunctivitis; the infection has spread deep into the surrounding tissues. Which drug is indicated for HSV keratoconjunctivitis but is least likely to harm the fetus?

(A). *Cidofovir.*
(B). *Docosanol.*
(C). *Fomivirsen.*
(D). *Acyclovir.*
(E). *Ribavirin.*

40. Mitchell Jones, a 35-year-old man, began treatment for hepatitis C with *Interferon-a-2b* and *Ribavirin (Rebetron)* 4 weeks ago. On returning to his doctor for routine monitoring of his blood count and liver function, he complained of general fatigue and exertion when walking. His hemoglobin, CBC, differential, and platelet counts are shown in the accompanying table. Which is the most likely explanation of any abnormality?

(A). *Ribavirin* decreases erythrocyte counts.
(B). *Interferon-a-2b* decreases erythrocyte counts.
(C). *Interferon-a-2b* elevates lymphocyte counts.
(D). A and B are true.
(E). A, B, and C are true.

41. A 65-year-old man with acute leukemia recently underwent induction chemotherapy and subsequently developed neutropenia and fever (with no source of fever identified). Fever persisted despite the use of empirical antibacterial therapy, and *Amphotericin B* has been prescribed for possible fungal sepsis. Which laboratory test is LEAST helpful in monitoring for toxicities associated with *Amphotericin B?*

(A). Liver function tests.
(B). Serum potassium.
(C). Serum magnesium.
(D). Serum blood urea nitrogen and creatinine.
(E). Hemoglobin and hematocrit.

42. A 55-year-old obese woman with adult-onset diabetes mellitus has been receiving *Amoxicillin* for treatment of an acute exacerbation of chronic bronchitis. After a week of therapy, the patient develops dysuria and increased urinary frequency. Urinalysis shows 10 to 50 white blood cells per high-power field, and Gram stain of urine shows many budding yeasts. Which antifungal agent would be best in treating this patient for *Candida* cystitis?

(A). Oral *Ketoconazole*.
(B). Oral *Fluconazole*.
(C). Topical *Clotrimazole*.
(D). Oral *5-Flucytosine*.
(E). Oral *Itraconazole*.

43. A 43-year-old woman recently underwent allogeneic bone marrow transplantation after chemotherapy failed in the treatment of metastatic breast carcinoma. The patient has had a stormy hospital course after her transplant, with respiratory failure requiring mechanical ventilation. A month into her hospitalization, surveillance sputum cultures reveal *Aspergillus fumigatus,* and a new infiltrate appears on her chest radiograph. Which antifungal agent is recommended for the treatment of invasive pulmonary aspergillosis in this patient?

(A). *Fluconazole.*
(B). *Amphotericin B.*
(C). *Amphotericin B* with *5-Flucytosine.*
(D). *Capsofungin.*
(E). *Itraconazole.*

44. A 57-year-old man with extensive onychomycosis (fungal toenail infection) asks you for an evaluation. He requests a prescription for *Itraconazole* for treatment of this problem after seeing a television advertisement for this drug. He has chronic heartburn attributed to gastroesophageal reflux disease and is treated with the proton pump inhibitor *Omeprazole*. He is taking *Lovastatin* for treatment of hyperlipidemia. Three years ago he underwent cadaveric renal transplantation for end-stage kidney disease secondary to polycystic kidney disease and is taking *Cyclosporin* to prevent transplant rejection. In prescribing *Itraconazole* for this patient, what adjustments in his medication regimen do you recommend?

(A). Discontinue *Omeprazole* and substitute the H2 blocker *Ranitidine*.
(B). Discontinue *Omeprazole* and substitute liquid antacids.
(C). Discontinue *Omeprazole*.
(D). Continue *Lovastatin.*
(E). Increase *Cyclosporin* dosing.

45. A 35-year-old medical entomologist comes to the hospital with chief complaints of fever, headache, and photophobia. This illness began about 6 days prior to admission, when he returned from a 2-month visit to the jungles of Central and South America. On his return flight, about 6 days prior to admission, he described having fever and shaking chills. He saw his physician 2 days prior to admission; the physician made a diagnosis of influenza and prescribed *Tetracycline.* On the day of admission, the patient had shaking chills followed by temperature elevation to 104°F (40°C). Physical examination revealed a well-developed man who appeared ill. There is some left upper quadrant tenderness but no organomegaly; blood pressure — 126/90; pulse — 120; and respirations — 22. Laboratory findings were hemoglobin, 14.5 mg/dL (normal, 13.4-17.4 mg/dL); hematocrit, 45% (normal, 40-54%); Giemsa-stained blood smear (thick and thin) revealed *Plasmodium vivax.* What is the oral drug of choice to rid the blood of plasmodia?

(A). *Primaquine*.
(B). *Chloroquine*.
(C). *Sulfadiazine*.
(D). *Quinine*.
(E). *Mefloquine*.

46. A 27-year-old ecologist went to his physician with an ulcer on his left wrist 8 weeks after returning from Panama. The patient noted a small pink papule that was pruritic (itchy) and enlarged and developed a

crusted appearance. This in time fell off, leaving an oozing shallow ulcer about 2 cm in diameter with indurated margins. He applied over-the-counter topical agents without clinical improvement. No fever or lymphadenopathy was present. Scrapings were taken from the raised margins of the ulcer and stained with Giemsa, revealing intra-cellular and free small, round and oval bodies measuring 2 to 5 mm in diameter. While this is suggestive of the *Leishmania* amastigote stage in the vertebrate host, culture confirmed it to be *L. braziliensis panamensis.* The patient had New World cutaneous leishmaniasis. What is the drug of choice?

(A). *Praziquantel.*
(B). *Pyrimethamine-sulfadoxine.*
(C). *Pentavalent antimonials.*
(D). *Pyrantel pamoate.*
(E). *Primaquine phosphate.*

47. The patient is 43-year-old, Agency for International Development worker with chief complaints of fever and headache. He recently returned from a trip to western Kenya and Tanzania. While traveling cross-country through the woodland and savanna by Land Rover, he indicated that the cab appeared to be filled with tsetse flies of the genus Glossina. He was bitten on the forearm and developed a painful chancre with some exudate. Physical examination showed the patient to be febrile, with a temperature of 102°F (38.8°C); he had tachycardia, with a pulse of 120 beats per minute, and appeared acutely ill and lethargic. Low-grade posterior cervical lymphadenopathy was present. There was no edema of the extremities, no organomegaly, and no abnormalities in his neurological examination. Renal and hepatic functions were normal. Giemsa-stained thick and thin blood smears examined to rule out malaria revealed trypomastigotes. Parasites were also found in a drop of exudate from a needle aspiration of the chancre. A lumbar puncture revealed CSF having one white blood cell and two red blood cells with normal glucose and protein levels. No parasites were seen in a centrifuged sample of CSF. What treatment is indicated for this patient?

(A). *Sulfadoxine-pyrimethamine.*
(B). *Chloroquine.*
(C). *Suramin.*
(D). *Melarsoprol.*
(E). *Metronidazole.*

48. A 52-year-old real estate salesperson has a 2-week history of watery diarrhea without blood. The patient states that 4 to 5 weeks ago she and her husband visited Aspen, Colorado, on a backpacking vacation and on occasion drank water from mountain streams. They were sure the water was potable, as the unspoiled, pristine area abounded with fish, beaver, and plant life. She states she has enjoyed perfect health except that she takes antacids for what she describes as gastroesophageal reflux disease. Her physical examination produced unremarkable findings. Examination of liquid stool revealed trophozoites and cysts of *G. lamblia.* Which of the following is the correct treatment for this disease?

(A). *Melarsoprol.*
(B). *Mefloquine.*
(C). *Mebendazole.*
(D). *Metronidazole.*
(E). *Meglumine antimonate.*

49. The patient is a 12-year-old boy with fever and vomiting. The fever began a month prior to admission, spiking to approximately 104°F (40°C) each day. The family physician for a time entertained a presumptive diagnosis of chloroquine-resistant malaria and prescribed *Mefloquine* followed by a week of doxycycline, without effect. Then, 2 days prior to admission, the patient began vomiting after eating. About 4 months earlier the family visited their home of origin in Bihar state in nort-heast India. Physical examination revealed a thin, acutely ill child with a temperature of 103°F (39.4°C), pulse of 130, and respirations of 36. Positive finding on physical examination was a nontender distended abdomen with a liver edge palpable 5 finger breadths below the costal margin and a smooth, firm spleen extending to the umbilicus (hepatosplenomegaly). The skin was dry and darkly pigmented. Laboratory findings revealed hemoglobin of 8.5 mg/dL (normal, 13.4–17.4 mg/dL), white blood cell count 3,900 cells/mm^3 (normal, 4,000–12,000 cells/mm^3), platelet count 99,000 cells/mm^3 (normal, 150,000–400,000 cells/mm^3). A bone marrow aspirate revealed characteristic amastigotes of *L. donovani.* Which of the following is the drug of choice for visceral leishmaniasis?

(A). *Liposomal Amphotericin B.*
(B). *Albendazole.*
(C). *Atovaquone.*
(D). *Pyrimethamine-sulfadoxine.*
(E). *Proguanil.*

50. While serving with Doctors Without Borders in Malaysia, you are seeing a patient who has intermittent cough, shortness of breath, and wheezing. Investigation reveals eosinophilia, absence of micro-filaria in the blood, and a chest radiograph showing scattered reticulonodular infiltrates. Which of the following points is the most important if your diagnosis is tropical pulmonary eosinophilia (TPE) ?

(A). Symptoms get progressively worse and are not fluctuating.
(B). Absence of microfilariae in blood makes the diagnosis unlikely.
(C). Eosinophilia, although commonly seen, is not usually very high.
(D). *Ivermectin* is the drug of choice.
(E). *Diethylcarbamazine* is effective therapy.

51. A 10-year-old girl in North Carolina has had abdominal pain and cramps for the past few days. Her examination produced normal findings except for nonspecific abdominal discomfort with a complete blood count showing anemia and 22% eosinophils (elevated). A stool specimen revealed the characteristic eggs of *A. lumbricoides.* The drug of choice in treating this is

(A). *Piperazine.*
(B). *Pyrantel pamoate.*
(C). *Mebendazole.*
(D). *Albendazole.*
(E). *Thiabendazole.*

52. A 15-year-old Hispanic boy is brought in with seizures. No prior history of fever, chills, trauma, or headaches was reported on admission. Computed tomography reveals three ring-enhancing cystic lesions in the brain parenchyma, and a diagnosis of neurocysticercosis is made. Initial therapy in the management of this condition should include

(A). *Niclosamide.*
(B). *Praziquantel.*
(C). *Albendazole.*
(D). Surgery.
(E). *Thiabendazole.*

53. A patient with a history of frequenting sushi bars on the West Coast is admitted with abdominal pain, weakness, irritability, and dizziness. His neurological examination produced normal findings even though he had some complaints of paraesthesias. Diphyllobothriasis is diagnosed after stool studies are done. Management of this tapeworm infection is with

(A). *Praziquantel* or *niclosamide.*
(B). *Ivermectin.*
(C). *Albendazole.*
(D). *Vitamin* B_{12}.
(E). *Piperazine.*

ANSWERS

1. **(D)**. A drug may be selective to a particular enzyme system that is found only in the microbe and have no harmful effect on the patient. An example is *sulfonamides* blocking the enzyme dihydropteroate synthesis. This is a necessary step in the synthesis of dihydrofolic acid. Humans can use preformed *Dihydrofolic acid* and do not need this enzymatic step to produce purines. Pharmacodynamics describes what the drug does to the patient. Pharmacokinetics describes what the patient does to the drug. Sepsis describes what the pathogen does to the patient. Resistance is what the pathogen does to the drug.

2. **(C)**. The patient is very ill, and you cannot afford to wait for the diagnosis. You administer a combination of *Clindamycin* and *Amikacin* to ensure that you have coverage for gram-negative and gram-positive organisms and anaerobes. *Vancomycin* and *Penicillin G* are effective against Gram-positive organisms only.

3. **(A)**. Ehrlich called *Salvarsan* the magic bullet for its nontoxic effect to humans and to its toxicity against the organism responsible for syphilis.

4. **(D)**. The indiscriminate use of antibiotics in humans is the major reason for the emergence of microbial antibiotic resistance. Such resistance, which is most apparent in hospitals, has developed to all antibiotics, including *Vancomycin*. The use of antibiotics in livestock has compounded the problem.

5. **(B)**. Pharmacodynamics describes what the drug does to the patient. Erythromycin stimulates gut motilin receptors and may induce nausea; this leads to the patient refusing to continue therapy. Pharmacokinetics describes what the patient does to the drug. Immunity is what the patient does to the pathogen; resistance is what the pathogen does to the drug; and selective toxicity is what the drug does to the pathogen.

6. **(B)**. *Nitrofurantoin* **(A)** is a urinary antiseptic agent active against many of the Enterobacteriaceae. *Nitrofurantoin* has no effect on *Toxoplasma* or *P. carinii,* as both are protozoans. TMP-SMX **(B)** daily or three times a week has proved to prevent both PCP and toxoplasmosis in AIDS patients. *Norfloxacin* **(C)** and other second-generation fluoroquinolones are known for their antipseudomonal and *Enterobacteriaceae* activity. The antimicrobial activity is exerted through inhibition of DNA *gyrase* A and type IV *topoisomerase*. *Methenamine* **(D)** is active against various *Enterobacteriaceae*; it has no activity against protozoa. *Formaldehyde* denatures proteins and is bactericidal. *Nalidixic acid* **(E)** is used in urinary tract infections caused by *Enterobacteriaceae* (e.g. E. *coli, Klebsiella,* and *Proteus)*. It has no activity against protozoa.

7. **(B)**. Proteus species produce urease **(A)** that produces ammonia and urea, alkalizing urine. Urine requires acidification for effective therapy. Hippuric **(B)**, mandelic, or ascorbic acids or methionine are urinary acidifying agents. The normal acidic urinary environment is disturbed by recurrent *Proteus* infections. Catalase **(C)** is produced by staphylococcal spp. The catalase test differentiates Staphylococci from Streptococci. It has no urinary activity. *Folic acid* **(D)** is a water-soluble vitamin and has no effect on urinary pH or acidification. Humans cannot synthesize folic acid, which must be obtained from the diet. A coagulase enzyme **(E)** is produced by *Staphylococcus aureus.* Coagulase test differentiates *S. aureus* from other staphylococci. It has no urinary antimicrobial activity.

8. **(A)**. *Sulfonamides* **(A)** compete for bilirubin binding sites on plasma albumin and increase fetal blood levels of unconjugated bilirubin. Unbound bilirubin crosses the blood-brain barrier and can be deposited in the basal ganglia and subthalamic nuclei causing kernicterus, a toxic encephalopathy. Defective bilirubin hepatic conjugation **(B)** is due to glucuronyl transferase deficiency resulting in Gilbert's syndrome. When seen in adults it usually presents with jaundice that is precipitated by fasting. Physiological jaundice **(C)** usually occurs in the newborn within a week of birth. It is due to the immature fetal acetyl-transferase system resulting in peripheral destruction of a large fetal red cell mass. Pregnancy-induced hepatic congestion **(D)**, cholestasis, and acute cholecystitis are seen in pregnant women, not in the newborn. Primary biliary cirrhosis **(E)** is commonly seen in middle-aged women. It is a chronic progressive autoimmune disorder requiring steroids and sometimes liver transplant.

9. **(B)**. Humans cannot synthesize folic acid **(A)**; diet is their main source. *Sulfonamides* selectively inhibit microbially synthesized folic acid. Incorporation **(B)** of PABA into microbial folic acid is competitively inhibited by *sulfonamides*. The TMP-SMX combination is synergistic because it acts at different steps in microbial folic acid synthesis. All *sulfonamides* are bacteriostatic. Inhibition of the transpeptidation reaction **(C)** involved in the synthesis of the bacterial cell wall is the basic mechanism of action of β-lactam antibiotics. Changes in DNA gyrases **(D)** and active efflux transport system are mechanisms for resistance to quinolones. Structural changes **(E)** in dihydropteroate synthetase and overproduction of PABA are mechanisms of resistance to the *sulfonamides*.

10. **(B)**. Acute urosepsis **(A)** is possible, but the patient's physical examination produced benign findings. Adding a broad-spectrum antibiotic has no benefit without evidence of active disease. Possible allergic reaction **(B)** to *Nitrofurantoin*; it is appropriate to stop the drug immediately to guard against one of three potential pulmonary reactions:

1) acute presentation with basilar infiltrate and pleural effusion,
2) chronic progressive bilateral interstitial fibrosis;
3) a subacute presentation.

Nitrofurantoin-resistant *E. coli* infection **(C)** and urosepsis are possible in patients who are taking chronic prophylaxis, but his examination produced benign findings. Acute community-acquired streptococcal pneumonia **(D)** shows one or more lobar infiltrates on radiography. The patient described has bilateral interstitial fibrosis. *Nitrofurantoin*-induced hemolysis **(E)** is possible in G6PD patients, but physical examination produced benign findings; G6PD patients usually present with hematuria.

11. **(B)**. Overproduction **(A)** of PABA is one of the resistance mechanisms of sulfonamides. Changes in the synthesis of DNA gyrases **(B)** is a well-described mechanism for *Quinolone* resistance. Plasmid-mediated resistance **(C)** does not occur with *quinolones*. An active efflux system for transport of drug out of the cell has been described for *Quinolone* resistance, but it is not plasmid mediated. Inhibition of structural blocks **(D)** in bacterial cell wall synthesis is a basic mechanism of action of β-lactam antibiotics. Inhibition of folic acid synthesis **(E)** by blocking different steps is the basic mechanism of action of sulfonamides.

12. **(B)**. The patient has complicated urinary tract infection and nonsevere sepsis syndrome caused by *P. aeruginosa.* Effective antibiotics for *Pseudomonas* spp. include *Mezlocillin, Piperacillin, Piperacillin-tazobactam, Ticarcillin,* and *Ticarcillin-clavulanate*. The carbapenems (imipenem and meropenem) and the monobactam (aztreonam) are also active against *P. aeruginosa.* Ampicillin-sulbactam and cefazolin are ineffective against *P. aeruginosa.* The history defines a patient with type I allergic hypersensitivity to penicillin. The patient should avoid drugs in the penicillin class, including *Penicillin, Nafcillin, Oxacillin, Cloxacillin, Dicloxacillin, Ampicillin, Amoxicillin, Ticarcillin, Piperacillin,* and *Mezlocillin.* In addition, carbapenems (imipenem, meropenem) should not be administered to patients with a history of type I allergic response to penicillin or positive penicillin skin test. Cefazolin is a cephalosporin. Patients with type I allergy to *Penicillin* and positive penicillin skin test have a 5.6% rate of allergic reactions to cephalosporins. *Aztreonam* may be used safely in patients with history of type I allergic response to *penicillin.*

13. **(B)**. The patient is pregnant and has latent syphilis of indeterminate duration. The pathogenic organism is *T. pallidum. Benzathine penicillin G* is the drug of first choice for treating latent syphilis. *Doxycycline* and *Tetracycline* are alternatives treatments for non-pregnant patients with latent syphilis. *Spectinomycin* is not effective against syphilis; it is a treatment for disseminated gonorrhea in patients who are allergic to *cephalosporins. Streptomycin* is not effective against syphilis.

14. **(E)**. The patient has exudative pharyngitis, presumably secondary to group A streptococcus. Antibiotic treatment is indicated to reduce the duration and severity of symptoms and to prevent acute rheumatic fever. The antibiotic of first choice is *penicillin V*. Other reasonable alternatives are benzathine *Penicillin G, Erythromycin, Cephalosporin, Clindamycin, Azithromycin,* and *Clarithromycin. Amikacin, Lomefloxacin, Metronidazole,* and *Netilmicin* are not active against group A streptococcus.

15. **(E)**. The patient has uncomplicated urethritis caused by *N. gonorrhoeae.* Effective antibiotics for gonorrhea include cephalosporins *(Ceftriaxone, Cefixime, Ceftizoxime, Cefotaxime, Cefotetan, Cefoxitin), fluoro-quinolones (Ciprofloxacin, Ofloxacin, Enoxacin, Lomefloxacin, Gatifloxacin),* and *Spectinomycin*. Gonorrhea is resistant to *Trimethoprim* and *Rifampin.* Amphotericin B is an antifungal drug, and isoniazid is an antimycobacterial drug. Neither has antigonococcal activity. Cephalosporins and other β-lactam antibiotics act to inhibit bacterial transpeptidase and block cross-linking of peptides in cell wall murein (peptidoglycan). *Fluoroquinolone* antibiotics inhibit DNA gyrase (topoisomerase) and interfere with bacterial DNA transcription and replication. *Spectinomycin* and *Doxycycline* inhibit bacterial protein synthesis and act at the 30S ribosome subunit. *Azithromycin* inhibits bacterial protein synthesis and acts at the 50S ribosome subunit. *Trimethoprim* inhibits dihydrofolate reductase and blocks formation of tetrahydrofolate required for purine synthesis. *Rifampin* inhibits RNA synthesis by binding to the subunit of DNA-dependent RNA polymerase. *Amphotericin B* inhibits fungal cell membrane integrity by binding to ergosterols to create pores. *Isoniazid* inhibits KasA, a β-ketoacyl carrier protein synthetase, and blocks mycolic acid synthesis.

16. **(B)**. The patient has impetigo. The causative organism is either *Streptococcus pyogenes* (group A) or *S. aureus.* Recommended antibiotic treatment is *Dicloxacillin* or *Cloxacillin. Dapsone* is used to treat skin infections with *Mycobacterium leprae* (leprosy) and to treat brown recluse spider *(Loxosceles)* bites. *Doxycycline* is used to treat skin infections with *Bacillus anthracis* (anthrax), *Bartonella henselae* (bacillary angiomatosis), *Borrelia burgdorferi* (Lyme disease, erythema migrans), *Propionibacterium acnes* (acne vulgaris), *Vibrio vulnificus* and *Vibrio damsela* (hemorrhagic bullous cellulitis). The question does not provide historical or epidemiological information to support these diagnoses. *Ketoconazole* is used to treat fungal infections of the skin (tinea capitis, tinea cruris, tinea corporis, tinea pedis, tinea versicolor). Dermatophyte infections are usually erythematous, with vesicles, fissures, and scaling. *Penciclovir* is a treatment for herpes simplex virus infections including herpes labialis fever blisters.

17. **(A)**. The aminoglycosides appear to act by binding to various sites on bacterial 30S ribosomal subunits and disrupting the initiation of protein synthesis. The other agents appear to have the capacity to directly inhibit bacterial cell-wall synthesis.

18. **(C)**. The selection of agents to treat brain infections is quite limited because most agents do not penetrate into cerebrospinal fluid or the brain itself.

19. **(B)**. A synergistic effect when the combination of an aminoglycoside and β-lactam antibiotic are administered concurrently is well documented. The reasons for the synergistic response are not well documented but may be related to the actions of the β-lactam antibiotic to raise pH and oxygen tension in areas of abscess and thereby increase the penetrability of the aminoglycoside.

20. **(C)**. Aminoglycosides can cause neuromuscular junction blockade by the mechanism of displacing Ca^{++} from the neuromuscular junction and thus leading to the Ca^{++}-dependent prejunctional release of acetylcholine. This is of clinical significance only in patients with myasthenia gravis, hypocalcemia, and hypermagnesemia.

21. **(D)**. Aminoglycosides do not penetrate most cells, and most drug-metabolizing enzymes are found on the inside of the cells. Therefore, aminoglycosides are poorly metabolized, and nearly all of an intravenous dose can be recovered in the urine.

22. **(C)**. In an outbreak setting, involved hospital staff may undergo culture investigation of their skin flora and orifices to determine the source of infection. Oral *Vancomycin* is not usually absorbed from the GI tract to be effective, and IV *Vancomycin* is not indicated to eradicate colonization. *Bacitracin* ointment has been used with limited success and may be an option, along with strict handwashing and isolation precautions. Polymyxins are effective topical agents for gram-negative infections. A fur-

lough from patient care responsibilities is unlikely to eradicate her nasal colony.

23. **(E)**. *Trimethoprim*, which exhibits broad-spectrum activity, with *Sulfamethoxazole* is active against most aerobic and facultative gram-positive and gram-negative organisms. It is very effective in UTIs caused by gram-negative bacteria. *Teicoplanin, Bacitracin*, and *Vancomycin* are antibiotics with limited spectra of gram-positive coverage. Although polymyxins are active against gramnegative organisms, their only use is topical because of severe nephrotoxicity associated with IV therapy. Alternative therapy would be to use *Quinolone*.

24. **(C)**. Minor suture irritation and superficial infection can be treated topically. Effective agents in the absence of culture results would be an ointment such as triple antibiotic, which has gram-positive and gram-negative spectra. Generally, polymyxins are active only against gram-negative organisms, and *Bacitracin* works only against gram-positive organisms. Intravenous antibiotics are not indicated unless this evolves into a deeper soft tissue infection. Observation without any active management is unlikely to be successful.

25. **(D)**. It is not unusual to get colonized by hospital flora, especially with an indwelling Foley catheter. If the patient does not have any clinical evidence of infection, it is not necessary to start therapy with *Vancomycin* or for that matter, any antibiotic. Enterococcal UTI can still be treated with penicillins, but they are increasingly resistant to penicillins and even *Vancomycin*. Since susceptibility data are still pending, neither *Vancomycin* nor the new drug *Linezolid* is yet indicated. Levofloxacin, although a good drug for UTIs, does not have enterococcal coverage. Discontinuation of the Foley catheter if possible and follow-up appear to be the best option. Watchful waiting may not be effective because these patients may go on to develop complicated UTIs.

26. **(C)**. *Teicoplanin*, although used in Europe, is not approved for use in the United States. It can be used to treat a variety of gram-positive infections and should be considered in resistant gram-positive infections as well. Bacitracin and polymyxins are topical agents with potential for serious nephrotoxicity when used parenterally. *Linezolid* is recently approved for resistant gram-positive infections (VRE and MRSA) and is available in the United States.

27. **(D)**. *Doxycycline* is the preferred parenteral tetracycline for the primary state of Lyme disease in adults and children older than 8 years of age. *Penicillin V* **(A)** would be ineffective. *Erythromycin* **(B)** and *Clarithromycin* **(C)** also are not effective against *Borrelia burgdorferi,* the gram-negative anaerobe organism responsible for Lyme disease.

28. **(E)**. *Chloramphenicol* is no longer the treatment of choice for any bacterial infection because of the potentially fatal chloramphenicol-induced bone marrow suppression. In the past it has been used against the infections indicated in choices **(A)**, **(B)**, **(C)**, and **(D)**. It remains a major treatment for typhoid and paratyphoid fever in some developing countries, since alternative drugs are much more expensive.

29. **(D)**. *Clarithromycin* is one of the recommended antimicrobials for use in combination with other antimicrobials in treating disseminated *Mycobacterium avium* complex.

30. **(D)**. Although *Ciprofloxacin* is the primary agent recommended for prophylaxis against anthrax, *Doxycycline* is an equally effective agent. *Amoxicillin* **(A)** is not as effective. The macrolides **(B)** and **(C)** also are not as effective. *Clindamycin* **(E)** is not indicated for this use.

31. **(B)**. This individual most likely has a group A streptococcal infection due to a minor wound. Now it appears he is developing necrotizing fascitis, a serious complication. Sometimes when a large amount of group A streptococcal organisms are present, *Penicillin* is not effective. *Clindamycin* is usually very active against streptococcal infections because the size of the bacterial inoculum will not affect its efficacy. Actually, the treatment of choice for this condition is immediate and possibly repeated surgical debridement of the involved area. Antibiotics are supportive therapy.

32. **(C)**. *Pyrazinamide* is known to cause hyperuricemia and precipitate gouty arthritis. *Pyrazinamide*-induced gouty arthritis does not respond to urico-suric therapy with *Probenecid* but may respond to acetylsalicylic acid. *Cycloserine* **(A)** can cause headaches, confusion, tremors, and seizures, possibly secondary to low levels of magnesium in the cerebrospinal fluid; *Cycloserine* should be avoided in patients with epilepsy and mental depression. It is not associated with hyperuricemia. *Thiacetazone* **(B)** is an antibiotic that is rarely used in tuberculosis. The most common adverse reactions are general rashes and GI intolerance. Its use is not associated with hyperuricemia. *Rifampin* **(D)** is associated with hepatitis, GI intolerance, drug interactions and a red-orange discoloration of saliva, tears, and urine. It is not associated with hyperuricemia. *Aminosalicylic acid* **(E)** is sometimes associated with sodium overload and fluid retention when large doses of the sodium salt of PAS is administered; it is not associated with hyperuricemia.

33. **(A)**. *Ethambutol* is associated with retrobulbar neuritis, resulting in loss of central vision and impaired red-green discrimination. *Ethionamide* **(B)** is an analogue of isonicotinic acid and is associated with GI intolerance and peripheral neuropathy, but not the optic neuritis or color vision discrimination problems. *Aminosalicylic acid* **(C)** can cause GI irritation and bleeding problems, so caution is required in peptic ulcer patients. It has no neurological side effects. *Rifampin* **(D)** is associated with red-orange discoloration of saliva, tears, and urine but not the color vision problems. *Isoniazid* **(E)** is associated with peripheral neuritis in chronic alcoholics and malnourished individuals and requires pyridoxine supplements. It is not associated with optic neuritis.

34. **(C)**. *Clofazimine* has antilepromatous and antiinflammatory properties. Its most disturbing side effect is red-brown pigmentation of the skin, particularly in light-skinned persons. *Dapsone* **(A)** can produce rashes and erythema nodosum, including Stevens-Johnson syndrome (dapsone dermatitis), but it is not associated with altered skin pigmentation. *Rifampin* **(B)** imparts a harmless red-orange discoloration of saliva, sweat, urine, feces, tears, and contact lenses but is not associated with skin pigmentation changes. *Capreomycin* **(D)** is similar to *Streptomycin* and can cause ototoxicity and nephrotoxicity. Its use is not associated with skin discoloration or pigment problems. *Thiacetazone* **(E)** is rarely used in the treatment of leprosy. Rashes and GI intolerance are common side effects. It is not associated with any skin discoloration or pigment problem.

35. **(E)**. *Rifampin*, commonly used in the prophylaxis of Neisseriae meningitidis, is given to individuals who are in close contact with someone having the disease. Other drugs that can be used include *Ciprofloxacin* and sulfonamides. *Amoxicillin* **(A)** is used as prophylaxis of endocarditis in patients with a history of endocarditis or a preexisting valvular heart disease. *Isoniazid* **(B)** is a commonly used drug for latent tuberculosis infection in high-risk patients who are positive PPD and have a negative chest radiograph. *Dapsone* **(C)** is used as a chemoprophylactic agent for *Pneumocystis carinii* pneumonia in AIDS patients who are allergic or intolerant to *Trimethoprim-Sulfamethoxazole*. *Clarithro-*

mycin **(D)** is used as a chemoprophylactic agent for MAC in AIDS patients.

36. **(C)**. *Cycloserine* is associated with confusion, psychosis, and suicidal ideation; symptoms are usually seen within a week of therapy. *Cycloserine* should be avoided in patients with psychiatric disorders. *Pyrazinamide* **(A)** is associated with a hepatic dysfunction that must be closely monitored. Nearly all patients taking *Pyrazinamide* develop hyperuricemia. It has no neurological side effects. *Aminosalicylic acid* **(B)** is associated with GI intolerance, especially acute bleeding, due to severe gastritis. It has no neurological side effects. *Rifampin* **(D)** is associated with hepatitis, drug interactions, red-orange discoloration of body fluids, and rarely, the Flulike syndrome. It has no neurological side effects. *Ethambutol* **(E)** is associated with retrobulbar neuritis and color vision impairment. It may cause peripheral neuritis but is not associated with behavioral problems.

37. **(D)**. The conversion of *Penciclovir* to its active form requires initial monophosphorylation by viral thymidine kinases, then conversion to its active triphosphate form by cellular enzymes. Thus, the concentration of *Penciclovir triphosphate* is particularly high in cells infected with its target viruses (e.g. HSV, VZV, HBV). *Foscarnet* is a pyrophosphate analogue that does not require activation. *Oseltamivir* is a neuraminidase inhibitor that is converted by hepatic esterases to its active form, *Oseltamivir* carboxylate. *Lamivudine* is converted to its active triphosphate form by host cellular enzymes.

38. **(A)**. *Ganciclovir* commonly causes myelosuppression and may produce severe neutropenia when given in combination with *Zidovudine*. *Fomivirsen* is most commonly associated with iritis and other ocular information; *Rimantadine* with nausea, vomiting, anorexia, and dizziness; *Famciclovir* with headache, nausea, diarrhea, and CNS effects; and *Zanamivir* with bronchospasm.

39. **(D)**. *Acyclovir* is in pregnancy category B: animal studies have shown no evidence of harm to the fetus, but no large, controlled studies of human outcomes have been performed. *Cidofovir* may be used to treat HSV that is resistant to acyclovir; however, it is embryotoxic and teratogenic, and Ms. Doe should avoid it. *Docosanol* is used for cold sores and is not indicated for ophthalmic use. *Fomivirsen* is effective against CMV retinitis, not HSV keratitis. *Ribavirin* is indicated for RSV infection and is also mutagenic, teratogenic, and embryotoxic.

40. **(D)**. *Interferons* and *Ribavirin* are both likely to cause anemia; the combination of these two agents increases this possibility. Interferons do not stimulate lymphocyte proliferation.

41. **(A)**. Nephrotoxicity is the most common and most serious toxicity associated with *Amphotericin* B administration. This is manifested by azotemia (elevated serum blood urea nitrogen and creatinine), and by renal tubular acidosis, which results in the wasting of potassium and magnesium in the urine (leading to hypokalemia and hypomagnesemia, requiring oral or intravenous replacement therapy). Normochromic normocytic anemia is also seen with long-term *Amphotericin B* administration. Elevation of liver enzymes is not associated with the use of *Amphotericin B*.

42. **(B)**. Oral *Fluconazole* is well absorbed from the gastrointestinal tract, and 80% of drug is excreted into the urinary tract, allowing effective treatment of *Candida* cystitis. Subtherapeutic concentrations of *Itraconazole* and *Ketoconazole* are excreted into the urine; these agents are not effective in the treatment of *Candida* cystitis. Topical *Clotrimazole* would be effective in the treatment of *Candida* vaginitis, which can cause dysuria, but would not be an effective treatment for cystitis. While 90% of 5-*Flucytosine* is excreted unchanged in the urine, this more toxic agent is usually used only in combination therapy with a second antifungal agent (usually *Amphotericin B*) in the treatment of systemic candidiasis or cryptococcal meningitis.

43. **(B)**. *Amphotericin B* remains the drug of choice in the treatment of disseminated or invasive fungal infections in immunocompromised hosts; bone marrow transplant recipients are the most heavily immunocompromised patients encountered in the hospital setting. *5-Flucytosine* has no significant activity against *Aspergillus spp.*, and it has bone marrow toxicity as a common adverse effect; it should not be used in this setting. Fluconazole has not been shown to be effective in the treatment of aspergillosis. Itraconazole has been reported to be effective as salvage treatment in patients with aspergillosis if *Amphotericin B* therapy fails; it should not be used as initial treatment in this setting. *Capsofungin*, a new echinocandin antifungal agent recently approved by the U. S. Food and Drug Administration for the treatment of refractory aspergillosis when standard therapy with *Amphotericin B* fails, should also not be used to treat invasive aspergillosis until more data showing efficacy are available.

44. **(C)**. Patients receiving multiple medications may have adverse drug reactions when a new medication is added to the regimen. *Itraconazole* requires an acidic gastric environment for absorption; any drug reducing gastric acid production (H2 blockers, proton pump inhibitors) or neutralizing gastric acid (antacids) will significantly reduce *Itraconazole* absorption. *Itraconazole* inhibits the metabolism of *Lovastatin* and *Simvastatin* and should not be prescribed with these β-hydroxy- β-methyglutaryl-coenzyme A reductase inhibitors. *Itraconazole* will raise serum cyclosporin levels, resulting in cyclosporin toxicity, unless *Cyclosporin* levels are closely monitored with dose reductions as indicated.

45 **(B)**. The drug of choice for clinical cure of *P. vivax* malaria is oral chloroquine. The only isolated reports of *Chloroquine*-resistant *P. vivax* are from the western Pacific, not Central and South America. The patient should become afebrile in 24 to 48 hours, and parasitemia should decline in 72 hours. Since *P. vivax,* known as benign tertian malaria, responds well to *Chloroquine*, there is no need to resort to parenteral *Quinine* or *Quinidine* or oral Mefloquine; these agents have cardiotoxic and neu-rotoxic side effects. *P. vivax* also does not respond as well to the sulfonamides. In *P. vivax* and *P. ovale* infections, treatment with a blood schizonticide will result only in clinical cure, but radical cure requires additional treatment with a tissue schizonticide, primaquine, to destroy exoerythrocytic stages responsible for relapses. The patient should be checked for glucose 6-phosphate dehydrogenase deficiency before taking *Primaquine*. Also, *Primaquine* is not effective against erythrocytic schizonts at pharmacological levels, so it cannot be used in place of *Chloroquine*.

46. **(C)**. The first-line drug for cutaneous or mucocutaneous leishmaniasis is *Sodium stibogluconate (Pentostam)* or meglumine antimonate *(Glucan-time)*. Antimonials have not been approved by the U. S. Food and Drug Administration, but *Sodium stibogluconate* is obtained from the Centers for Disease Control and Prevention. Clinical response is determined by species and resistance patterns of *Leishmania* and by host immunity. These drugs are given by intravenous or intramuscular injection. Phlebitis and pain are reduced when these drugs are given intravenously. In advanced mucocutaneous leishmaniasis *Amphotericin B* may be an alternative, especially in areas of resistance to antimony drugs. Liposomal *Amphotericin B* is the drug of choice for visceral leishmaniasis and has been used successfully in the treatment of

cutaneous and mucocutaneous disease. *Pentamidine, Ketoconazole*, and *Itraconazole* have been used effectively to treat the cutaneous but not visceral form of leishmaniasis. *Pyrantel pamoate* is a roundworm treatment and not indicated here. Primaquine phosphate is used to prevent relapses in tertian malaria, and *Praziquantel* is the drug of choice in treating tapeworm and fluke infections. *Pyrimethamine-sulfadoxine* is used to treat malaria and is sometimes combined with *Quinine sulfate* in *Chloroquine* resistance. It is also used to treat toxoplasmosis when it is accompanied by *Leucovorin* (folinic acid).

47. **(C)**. *Suramin* is the drug of choice for the hemolymphatic stage of *T. rhodesiense* and *T. gambiense* with a normal CSF examination. This drug is almost 100% effective in eliminating trypanosomes from the blood of patients in the early stage of disease. Epidemiologically this patient appears to have East African trypanosomiasis caused by *T. rhodesiense. Pentamidine isethionate* results in lower cure rates in *T. rhodesiense* infections than those with *Suramin*. *Suramin* does not cross the blood-brain barrier, so it is not effective for patients with meningoencephalopathic involvement. Somnolence, or inability to concentrate, may be seen before the CNS is involved. Treatment for CNS late-stage trypanosomiasis is *Melarsoprol*; however, because of potential toxicity, this drug is reserved for late-stage disease only. *Metronidazole* is used to treat amebiasis, not trypanosomiasis. *Sulfadoxine-pyrimethamine* and *Chloroquine* are antimalarial and are not used for this indication. *Sulfadoxine-pyrimethamine* with *Leucovorin (folinic acid)* can also be used to treat *Toxoplasma gondii.*

48. **(D)**. *Metronidazole* is the drug most frequently recommended for treatment of this infection. *Quinacrine* has been used in the past, but because of toxicity and lack of availability it is not a first choice. *Albendazole,* not *Mebendazole*, has been used with a good outcome in giardiasis. *Mebendazole* is used to treat roundworm infections. *Melarsoprol* is used to treat advanced-stage CNS African trypanosomiasis. *Mefloquine* is an oral drug used to treat *Chloroquine*-resistant malaria. *Meglumine antimonate (Glucantime)* or *Sodium stibogluconate (Pentostam)* is used to treat cutaneous or mucocutaneous leishmaniasis by the IV route. Giardiasis, which may be chronic and the cause of malabsorption, sometimes requires multiple stool examinations or a duodenal aspirate. Infection may be through contaminated food or beverages or may be acquired through surface water contaminated by mammals such as beavers. The risk of human infection appears increased in those with reduced gastric acid production.

49. **(A)**. Liposomal *Amphotericin B* was approved by the U.S. Food and Drug Administration to treat visceral leishmaniasis. Pentavalent antimony compounds, *Pentamidine*, *Amphotericin B*, and *Aminosidine (Paromomycin)* have all been demonstrated efficacious here. The liposomal *Amphotericin* appears to be better taken up by the reticuloendothelial system, where the parasite resides, and partitions less in the kidney, where *Amphotericin B* traditionally manifests its toxicity. In addition to being better tolerated by patients, it has proved to be very effective in India, where resistance to antimony drugs is widespread. This patient appears to have acquired his infection there, where many infected patients develop darkening of the skin, hence the name kalaazar, or black sickness. *Albendazole*, an anthelmintic, has no role here. *Atovaquone*, *Naphthoquinone*, is used to treat malaria, babesiosis, and pneumocystosis. *Pyrimethamine-Sulfadoxine* is used to treat malaria and toxoplasmosis. Proguanil inhibits the dihydrofolate reductase of malaria parasites and is used in combination with *Atovaquone*.

50. **(E)**. TPE is caused by microfilariae in the lungs and hyperimmune responsiveness to bancroftian or malayan filariasis. Paroxysmal respiratory symptoms may fluctuate in severity. Eosinophilia, almost always present, is usually very high, and the absence of microfilariae in the blood does not rule out TPE. A presumptive clinical diagnosis can be made by response to therapy without a lung biopsy. *Diethylcarbamazine* for 14 days is an effective therapy that can be repeated if symptoms persist. The role of *Ivermectin* in TPE has not been established.

51. **(D)**. Intestinal helminths produce mild disease with nonspecific findings. *Piperazine* or *Pyrantel pamoate* may be used for the treatment of ascariasis. *Mebendazole* is an effective drug to be taken for 3 days. *Thiabendazole* is not used in this condition but is used commonly in strongyloidiasis. *Albendazole* at a single dose of 400 mg is the preferred mode of therapy. It is a convenient agent for mass treatment programs that target school children in endemic areas.

52. **(C)**. *Albendazole* (approved by the U. S. Food and Drug Administration for this indication) has a 90% efficacy rate in neurocysticercosis. The initial therapy of parenchymal disease with seizures should focus on symptomatic treatment with anticonvulsants. However, while destroying the cyst, *Albendazole* may result in a profound parenchymal brain reaction and in severe neurological defects or retinal damage (i.e. loss of vision and optic neuritis) in eye lesions. Corticosteroids should be given concomitantly in these situations. In ventricular disease with obstructive hydrocephalus, surgery with shunting can be helpful. Treatment with *Niclosamide* or *Praziquantel* should be considered later to eliminate the adult tapeworm in the gut and prevent further reinfection. Neither *Piperazine* nor *Thiabendazole* is effective in this indication.

53. **(A)**. *D. latum,* the fish tapeworm acquired from consumption of raw fish in endemic areas, is best treated with *Praziquantel* or *Niclosamide*. *Ivermectin* is effective for filarial infections, especially *O. volvulus. Albendazole*, although highly effective in some tapeworm infections, is not used in fish tapeworm infections. *Vitamin* B_{12} deficiency is due to the parasite competing with the host for the vitamin, sometimes absorbing 80% of ingested amounts. Patients may develop megaloblastic anemia and mild to severe central nervous system manifestations (subacute combined degeneration of spinal cord). Mild B_{12} deficiency should be treated with vitamin injections in addition to specific drug therapy. *Piperazine*, a roundworm treatment, is not used for this indication.

DRUGS USED FOR PHARMACOTHERAPY OF DISEASES OF SPECIAL SYSTEMS

Lecture 44
DRUGS USED IN GASTROINTESTINAL DISEASES

Many drugs discussed elsewhere in this collection have applications in the treatment of gastrointestinal diseases. M-cholinolytic agents inhibit the food-stimulated secretion of gastric acid and also affect intestinal smooth muscle; these drugs are useful in some forms of functional bowel disease. M-cholinomimetics stimulate smooth muscle and are used to promote gastrointestinal motility. Several other groups of medications are used almost exclusively in gastrointestinal disease; these are grouped and discussed below according to their therapeutic uses.

DRUGS, REGULATING APPETITE

These drugs are divided into drugs that increase and decrease appetite. Action is related with influence on the appetite control center (centers of hunger and satiation), located in hypothalamus.

Drugs that increase an appetite include *bitters (amara)*. Bitters are the substances that possess strong bitter taste. Bitters irritate taste receptors of oral cavity and stomach mucosa that cause reflective increasing of gastric juice secretion and promote digestion. Bitters are used for the treatment of the atrophic gastritis, hypoacidity (lower than normal level of hydrochloric acid), and anorexia (aversion to food). Bitters should be used for 15–30 minutes before meals. Agents include *bitter (Amara) tincture, tincture of wormwood (Absinthium),* etc. Some taste substances (e.g. mint, pepper, and mustard) also exhibit features of bitters. They contain ether oil that stimulates an appetite. Bitters will be prohibited during hyperacidity, ulcer disease of stomach. *Cyproheptadine (Peritol)* is an antihistamine (H_1) drug that stimulates the center of hunger in the CNS. It is used for the treatment of anorexia.

Appetite suppressants are sympathomimetic agents. They are *Amfepramone (Phepranonum), Chlorphentermine* (*Desopimon*), and *Mazindol*. These agents have pharmacological effects similar to those of *Amphetamine* (*Phenaminum*), including CNS stimulation and elevation of blood pressure. It is believed that the main effect of these medications is decreasing of the appetite control center activity. *Phepranonum* and *Desopimon* (relatives of *Amphetamine*) are weaker than *Amphetamine* as appetite suppressants, but less stimulate the CNS and the cardiovascular system, seldom causing drug addiction. Appetite suppressants are indicated in the management of exogenous obesity for short-term use (a few weeks) in conjunction with a regimen of weight reduction based on caloric restriction, exercise, and behavior modification.

Adverse effects include insomnia, tachycardia, increasing of blood pressure, sleeplessness, accustoming and drug addiction. They are contraindicated during hypertonia, disorders of cerebral blood circulating, thyrotoxicosis, diabetes mellitus, and epilepsy.

SUBSTANCES, STIMULATING AND INHIBITING SECRETIVE FUNCTION OF THE STOMACH

Drugs that stimulate stomach juice secretion are the next: *Pepsin, Natural Gastric juice, Abominum,* and *Panzynorm* (see lecture "Enzyme preparations and enzyme inhibitors"). They normalize secretion and motility of the gastrointestinal tract and are indicated for replacement therapy of stomach upset such as achlorhydria (absence of hydrochloric acid in the gastric juice) or hypoacidity. *Pentagastrin* is a synthetic analog of the natural hormone, gastrin. Pentagastrin as well as gastrin stimulate the secretion of hydrochloric acid, pepsin, and increases GI motility. It is useful as a diagnostic test for achlorhydria and hypersecretion of stomach juice.

Drugs, decreasing the secretive function of stomach, include M-cholinolytics, ganglionblockers, and blockers of H_2-histamine receptors, antacids, adsorbents, astringents, and local anesthetics. Gastric acid secretion is under the control of histamine, acetylcholine, and gastrin. The final common pathway is through the proton pump, H^+/K^+ ATPase.

H_2(histamine)-receptors antagonists, e.g. *Cimetidine, Ranitidine, Famotidine,* and *Nizatidine* blockade H_2-receptors of stomach mucosa that leads to reduction in basal, food-stimulated, and nocturnal secretion of gastric acid. Many trials have demonstrat-

ed their effectiveness in promoting the healing of duodenal and gastric ulcers and preventing their recurrence. H_2-antagonists are rapidly and well absorbed following oral administration. Food delays and may slightly decrease absorption of the drugs. For active ulcer, any H_2-blocker can be given twice daily or once at bedtime. Reversible hematologic abnormalities have been a rare occurrence with all members of this class of drugs. *Cimetidine* may cause reversible gynecomastia. This has been reported only rarely with *Ranitidine* and *Famotidine*. *Cimetidine* also slows hepatic microsomal metabolism of some drugs, such as *Neodicumarin*, *Euphyllin*, *Diazepam*, and *Diphenin*. *Ranitidine* appears to have less effect and *Famotidine* and *Nizatidine* no effect on hepatic drug metabolism.

Cholinoreceptor antagonists (lecture "Cholinergic antagonists") such as *M-cholinolytics* (e.g. *Atropine, Pirenzepine*) and *Ganglionblockers* (e.g. *Pempidine (Pirilenum), Pentaminum (Azamethonium bromide))* decrease the influence of nervus vagus that results in lowering of gastric juice secretion. *Ganglionblockers* are now rarely used because they're adverse effects. *Pirenzepine*, an antimuscarinic agent with activity relatively selective for gastric M_1-receptors, is approved for ulcer therapy. It may cause the disorder of accommodation, dryness of mouth, but less frequent than other *M-cholinolytics*.

Omeprazole irreversibly inhibits the gastric parietal cell proton pump, (H^+/K^+ ATPase). Inactivation of this enzyme system blocks the final step in the secretion of hydrochloric acid by these cells. The drug requires activation in the acid environment of the secretory canaliculus of the parietal cell, i.e., it is a prodrug. *Omeprazole* inhibits basal and stimulated gastric acid secretion. *Omeprazole* is a more potent inhibitor of such secretion than are H_2-receptor antagonists. Although *Omeprazole* has a short terminal plasma half-life, the drug has a long duration of action (about 3 days). *Omeprazole* increases plasma gastrin concentrations via a negative feedback mechanism resulting from decreased gastric acid secretion. *Omeprazole* is approved for the treatment of gastric and duodenal ulcers as well as for prevention of recurrence of duodenal ulcers. The initial dose is 20 mg once daily. *Omeprazole* is well-tolerated drug. However, increase in gastric carcinoid tumors has been observed during long-term *Omeprazole* exposure in animals.

Gastric antacids are weak bases that react with gastric hydrochloric acid to form a salt and water. Their usefulness in peptic ulcer disease appears to lie in their ability to reduce gastric acidity. Antacid-induced increases in gastric pH inhibit the proteolytic action of pepsin. Some antacids, such as aluminum hydroxide, have astringent action. Most antacids in current use have as their principal constituent magnesium or aluminum hydroxide, alone or in combination, and occasionally in combination with sodium bicarbonate or a calcium salt.

Antacids include sodium bicarbonate, magnesium oxide, calcium carbonate, aluminum hydroxide, and a lot of complex drugs (e.g. *Almagel*, *Maalox*, *Phosphalugel*, *Vicair®*, *De-Nol*, etc.). *Sodium bicarbonate* possesses the most quick but short period of action. During interaction with acid, carbon dioxide is formed, which stretches stomach and causes secondary wave of secretion. Absorbing into blood, sodium bicarbonate may cause systemic alkalosis. *Magnesium oxide, Aluminum hydroxide* act slower, more durable, and more active than sodium bicarbonate. *Magnesium oxide* may cause purgative effect, however *Aluminum hydroxide* may cause constipation. *Calcium carbonate* is slowly solubilized in the stomach. In high doses it may cause hypercalcemia and alkalosis.

There are many complex antacids. They are *Almagel* (*Aluminum hydroxide* and *Magnesium oxide*), *Maalox* (*Aluminum* and *Magnesium hydroxide*). These agents possess antacid, adsorptive, astringent, and envelop activities. Also agents that contain bismuth such as *Vicair* (*Bismuth subnitrate*, *Magnesium carbonate*, *Sodium bicarbonate*, and powder of *Frangula bark*), *De-Nol* (*Bismuth subcitrate*) are well known. Bismuth salts have antacid and astringent effects. In addition, *De-Nol* has mild activity against *Helicobacter pylori* that is associated with gastritis and peptic ulcer.

Antacids are used as an adjunct to physical and emotional rest, other drugs for the relief of peptic ulcer pain and to promote the healing of peptic ulcers, hyperacid gastritis. Antacids also are used for the relief of dyspepsia, heartburn, and sour stomach.

Sucralfate is a gel (aluminum salt), which in acid surrounding forms glutinous and sticky substance, covering the ulcerous surface and protecting it from damages. *Sucralfate* is not absorbed. Supplementary information about adsorbents, astringents, and local anesthetics is discussed in lecture "Drugs that protect receptors".

A great meaning in treatment of gastritis and ulcer disease of stomach and duodenum is taken by **gastric protectors** – drugs that increase protection function of sputum and stableness of mucous layer (*Carbenoxolone, Misoprostol*). *Carbenoxolone* increases secretion of sputum, forming it more glutinous. It may cause retention of water in the organism, hypertension. *Misoprostol* is a synthetic prostaglandin E_1 that increase stability of gastric mucous, lower secretion of hydrochloric acid and fasten secretion of sputum. Now are widely used drugs, which promote stomach mucosa regeneration. *Solcoseril, Vitamin U, anabolic steroids (Nandrolone (Retabolil), Phenobolil,* etc.), *Riboxin* and *Methyluracil refer to them.*

EMETIC AND ANTIEMETIC DRUGS

Vomiting is a protective stomach reaction directed on its cleaning. Coordination of the complex motor activity of the stomach and abdominal musculature takes place in the vomiting center, which is located in the reticular formation in the medulla. The vomiting center receives input from the chemoreceptor trigger zone located on the floor of the fourth ventricle, the vestibular apparatus, and other areas.

Vomiting can be evoked for turning out irritate and toxic substances from the stomach (see lecture "Dugs that irritate receptors"). For that purpose *Apomorphine* is used. It stimulates dopamine receptors of trigger zone. *Apomorphine* is characterized by short period

of nausea. It is contraindicated during unconscious state, burns of esophagus and stomach by acid and alkaline. Sometimes it is used during treatment of alcoholism for forming of negative conditional reflex on alcohol.

Nausea and vomiting may be manifestations of a wide variety of conditions, including pregnancy, motion sickness, gastrointestinal obstruction, peptic ulcer, drug toxicity, myocardial infarction, cancer chemotherapy, etc. So choosing of antiemetic drugs is determined by reasons, caused vomiting.

The major categories of **antiemetic agents** include *H_1-antihistamines, neuroleptics, M-cholinolytics, Metoclopramide,* and *Ondansetron*.

The **antihistamines** with good antiemetic activity (e.g. *Dimedrolum*, *Diprazin*) possess significant antimuscarinic and sedative effects (see lecture "Immunotropic agents"). It appears probable that both of these actions and the H_1-blocking effect contribute to the antiemetic efficacy. They are particularly effective for the nausea and vomiting associated with motion sickness, perhaps because of specific depression of conduction in the vestibulocerebellum pathway. Anticholinergic agents, especially *Atropine, Scopolamine (Aeron)*, are also used to prevent motion sickness (see lecture "Cholinergic antagonists").

The **neuroleptics** block dopamine receptors in the trigger zone as well as other areas of the brain (see lecture "Neuroleptics"). *Chlorpromazine* (*Aminazinum*) and *Haloperidol* are often used as antiemetics. Extrapyramidal symptoms (Parkinsonism) can be severe when large doses of neuroleptics are used. *Thiethylperazine* is a *Phenothiazine* derivative (as *Aminazinum*). Agent is a strong antiemetic, however it causes mild extrapyramidal disorders.

Metoclopramide promotes gastrointestinal motility. In addition to its *M-cholinomimetic* properties, *Metoclopramide* is a potent dopamine antagonist. It does not increase gastric or pancreatic secretion. These drugs hasten esophageal clearance, raise lower esophageal sphincter pressure, accelerate gastric emptying, and shorten small intestine transit time. *Metoclopramide's* central dopamine antagonist effect is thought to be responsible for its significant antiemetic properties. *Metoclopramide* injection is indicated for the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy, in postoperative period. Oral *Metoclopramide* is indicated in adults for the symptomatic treatment of heartburn and reflux esophagitis, for correcting the slow gastric emptying. The most common side effects of *Metoclopramide* are somnolence and nervousness. Parkinsonism has also been reported.

Ondansetron is a selective inhibitor of serotonin (5-HT_3) receptors. The antiemetic activity of ondansetron appears to be mediated both centrally and peripherally via inhibition of 5-HT_3 receptors. *Ondansetron* is used orally or intravenously for the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy. *Ondansetron* appear to be more effective and better tolerated than the pharmacologically less selective *Metoclopramide* and therefore may be preferred for the management of acute emetic effects in many patients.

SUBSTANCES, INFLUENCING MOTILITY OF THE INTESTINE

They are divided into:

— drugs, depressing intestine motility (antidiarrheal agents);

— drugs, increasing intestine motility (laxatives).

Diarrhea is a symptom of many diseases (poisoning, infections, diseases of stomach and pancreas, etc.). For the diarrhea therapy its reason is necessary to confirm. If diarrhea is caused by infection process, antimicrobial agents must be taken. In the treatment of uncomplicated diarrhea that caused by modification of the intestinal flora by drugs (e.g. antibiotics) or during different diseases one can use *Chilac, Biphidumbacterin,* etc. These agents contain an acid-producing intestine bacterium (e.g. *Lactobacillus* acidophilus) or its extract prepared in a concentrated, dried, and viable culture for oral administration.

As drugs for symptomatic diarrhea therapy are used astringents, enveloping and adsorptive substances, which possess non-specific anti-inflammatory and protect intestine mucosa from irritating agents. *M-cholinolytics, ganglionblockers*, and *spasmolytics* of *Myotropic* action (*Papaverine*, *No-Spa*, *Dibasolum*, etc.) decrease the tonus of smooth muscles of the intestine wall that results in lowering of intestine motility. *Loperamide* is a synthetic piperidine-derivative antidiarrheal agent. Drug binds with opioid receptors of the intestine (like *Morphine*) and enhances contractions of intestinal circular musculature, thus increasing segmentation and retarding forward motion through the intestine. *Loperamide* is potent, specific, and long acting antidiarrheal agent. It has no analgesic activity. *Loperamide* is used in the control and symptomatic relief of acute nonspecific diarrhea and of chronic diarrhea associated with inflammatory bowel disease. Adverse effects of *Loperamide* are constipation, dizziness, and nausea. Also it has *M-cholinolytic* activity.

Drugs that increase the motility of the intestine include *M-* and *M-, N-cholinomimetics* (*Aceclidine*, *Proserinum*, *Galantamine*, etc.). These agents stimulate tonus of nervus vagus that leads to the activation of smooth muscles of intestine wall and intestine motility in general. Direct stimulating action on the intestine wall have purgatives.

Purgatives are the substances that fasten movement of intestinal content and promote defecation. In dependence of mechanism of action they are divided into next groups:

— drugs, acting basically on small intestine (*Castor oil*);

— drugs, acting basically on large intestine (*leaves of Senna*, *bark of Frangula*, *Phenolphthalein*, *Bisacodyl*);

— drugs, acting on all parts of the intestine (salt laxatives — *Magnesium sulfate*);

— bulk laxatives (Agar, Methylcellulose, Bran);

— stool softeners (*Mineral oil*, *Vaseline*).

Castor oil is hydrolyzed in the upper small intestine to ricinoleic acid, a local irritant that increases intestinal motility. The onset of action is prompt (2–6 hours) and continues until the compound is excreted

via the colon. It is administered during acute constipation. Castor oil is contraindicated during poisoning by fat-dissolved substances.

Bark of Frangula, leaves of Senna contain emodin alkaloids that are liberated after absorption from the intestine and are excreted into the colon, where peristalsis is stimulated. Thus, their onset of activity is delayed for 6–10 hours. So, they are usually administrated in the evening. These agents are used for the treatment of chronic constipation. Adverse effects include spasm of the intestine, meteorism. *Phenolphthalein* and *Bisacodyl*, which are synthetic drugs, are also potent colonic stimulants. They are absorbed in the small intestine and excreted in the large intestine, increasing its peristalsis.

Saline cathartics (Magnesium sulfate) distend the bowel and stimulate its contractions. These nonabsorbable salts hold water in the intestine by osmotic force and cause distention. In result magnesium sulfate increases the motility of all intestine. *Saline cathartics* serve for removal of ingested toxin and as colonic lavage solutions, chiefly in preparation for radiological or endoscopic procedures. It has to be administrated with enough volume of warm water (1–2 glasses). Potent laxative effect develops after 2–4 hours. *Magnesium sulfate* is taken seldom because it impairs the absorption of nutritious substances in the intestine.

Bulking laxatives. Agar and *Methylcellulose* are swelling in the large intestine lumen that is associated with their enlargement. They distend the intestine and thereby stimulating its peristaltic activity. *Bran* (by-product of the milling of wheat, containing the indigestible cellulose) and other forms of vegetable fiber have the same effect. Bulking laxatives are taken for chronic constipation.

Stool softeners become emulsified with stool. They serve to soften stool and make passage easier. Examples are *Mineral oil, Glycerin*. They have weak laxative effect. Adverse effects include impairment of food digestion, uncontrolled defecation, and soil of clothes.

Purgatives are contraindicated during acute appendicitis and cholecystitis, peritonitis, mechanical impassability of intestines, pinched hernia, bleeding in GI tract, menorrhagia. They are to be carefully used during pregnancy due risk of abortion.

HEPATOTROPIC DRUGS

Hepatotropic drugs consist of three groups. They are (1) ***bile-drive drugs***, (2) ***hepatoprotectors***, and (3) ***chololithics***.

Bile-drive drugs regulate the bile production and bile output. Lack of gall causes disorder of emulsion and absorption of lipids, fat-dissolved vitamins as well as development of putrid microflora in the intestine and depression of its motility.

Bile-drive drugs are divided as follows:

1. Drugs that stimulate bile production (Cholosecretics):

a) drugs that contain bile: *Allohol* (consist of bile, garlic and nettle extracts, and activated carbon), *Cholenzym* (bile, dry powder of cattle pancreas and intestine), etc.;

b) drugs of plant origin: *Cholosas* (syrupus of wild rose hips), *Corn oil*, etc.;

c) synthetic drugs: *Hydroxymethylnicotinamide* (*Nicodin*), *Cycvalonum*, etc.

2. Drugs promoting bile excretion into duodenum:

a) drugs that increase tonus and motility of gallbladder, and accelerate its emptying (***Cholokinetics***): *Cholecystokinin, Pituitrinum, Magnesium sulfate, Sorbitol,* etc.;

b) drugs that decrease tonus of bile ducts and Oddi's sphincter (***Spasmolytics***): *Atropine, Platyphyllinum, Papaverine, No-Spa,* etc.

3. Drugs that cause desaturation of the bile (Cholololithics).

Cholosecretics. Drugs of resorptive type action, which activate hepatocytes. Also they irritate the intestine chemoreceptors that in reflective way promotes bile secretion. In addition, drugs including bile can act as substitutive agents. Cholesecretics are indicated during insufficiency of bile production. They will be contraindicated during acute and considerable liver defeats, obturation of bile ducts by gallstone, etc., because they form additive loading on liver and may increase jaundice.

Cholokinetics are used for the hypotonia of gallbladder and bile ducts. ***Spasmolytics*** are used for removing of liver colic, Oddi's sphincter spasm.

That classification is quite comparative, because drugs, stimulating the gall formation, at the same time increase its excretion. And drugs, increasing the gall excretion, promote gall formation. The most important factor during treating of liver and gall-ducts diseases, is the bettering of gall outflow, what deletes it's stagnation and absorption to blood, lower risk of infection's development in gall-ducts, and forming of gall-stones.

Hepatoprotectors are the drugs that increase the resistance of hepatocytes membrane, induce the hepatocytes enzymes, and promote restoration of liver function (synthesis of proteins, detoxication). As a rule, these drugs possess antioxidant properties. These features are possessed by *Silibinin* (*Legalon*), *Essentiale*. The last one includes essential (important) phospholipids, *Vitamins* (B_6, B_{12}, *PP,* etc.). Hepatoprotectors are used for the treatment of hepatitis, cirrhosis.

Cholololithics are the drugs that cause desaturation of the bile by increasing the ratio of bile acids to cholesterol. The reduced cholesterol saturation allows for the gradual solubilization of cholesterol from gallstones, resulting in their eventual dissolution. Cholinolytics are *chenodeoxycholic acid (Chenofalk, Chenodiol)* and *Ursodeoxycholic acid (Ursofalk)*. Cholololithics are indicated for dissolution of cholesterol gallstones in selected patients with uncomplicated gallstone disease and functioning gallbladder.

DRUGS INFLUENCING OUTSECRETIVE (EXOCRINE) FUNCTION OF PANCREAS

They are divided into agents, which stimulate exocrine function of pancreas *(bitters, Hydrochloric acid)*, agents for replacement therapy *(Pancreatin,*

Panzynorm forte, Festal, Mezym forte), and agents, which inactivate pancreas enzymes. Uses of replacement therapy drugs are discussed in lecture "Enzyme preparations and enzyme inhibitors". Agents, inhibiting pancreas enzymes are discussed below.

Enzymes of pancreas take part in destruction of proteins, fats and hydrocarbons. Usually in pancreas enzymes are present in nonactive (pre-enzyme) form, which is transformed to active form in the intestine lumen only. During acute pancreatitis, activation of enzymes especially proteolytic begins in gland tissues that lead to "self-destruction" of pancreas. Treatment of acute pancreatitis is directed on lowering of pancreatic secretion, using *M-cholinolytics* (*Atropine*, etc.) and inactivation of proteolytic enzymes (*Trypsin* and *Kallikrein*) by using their inhibitors (*Contrykal, Trasylol*). *Contrykal* is obtained from cattle lung or pancreas tissues. Its activity is expressed in IU. *Contrykal* is injected intravenously dropwise. The most serious adverse effect of this agent is allergic reactions.

Available forms:

Tincture amara — in bottles 25 ml

Mazindol — in tablets 0.001 each

Panzynorm — in patented tablets

Famotidin — in tablets 0.02 or 0.04 each

Omeprazole — in capsules 0.02 each

Almagel — in bottles 170 ml

Apomorphine hydrochloride — powder; in ampoules 1% solution 1 ml

Metoclopramide — in tablets 0.01 each; in ampoules 0.5% solution 2 ml

Ondansetron — in tablets 0.004 or 0.008 each; in ampoules 0.2% solution 2 ml or 4 ml each

Loperamide — in capsules 0.002 each

Magnesia sulfate — powder 30.0 (to dilute in S of warm water, for one using, laxative)

Senadum — in patented tablets (contain extract of *leaves of Senna*)

Bisacodyl — in tablets 0.005 each

Cholenzym — in patented tablets

Cholosas — in bottles 300 ml

Nicodin — in tablets 0.5 each

No-spa — in tablets 0.04 each; in ampoules 2% solution 2 ml each

Legalon — in patented dragee (*Legalonum-70* and *Legalonum-140*)

Contrykal — in bottles 10,000 IU; 30,000 IU or 50,000 IU (to dilute before using content of the bottle in 300-500 ml of physiologic solution)

Lecture 45
DRUGS USED IN RESPIRATORY DISEASES

To this group are concerned drugs that are used for the treatment of (1) bronchial constriction, (2) cough, (3) depression of respiratory, (4) pulmonary edema, and (5) for the bettering of sputum expelling.

BRONCHODILATORS AND OTHER AGENTS USED IN BRONCHIAL ASTHMA

Bronchial asthma is physiologically characterized by widespread narrowing of the airways. It is a disease mediated by reaginic (IgE) antibodies bound to mast cells in the airway mucosa. Bronchial spasm appears in result of disorders in neural and humoral regulation of bronchial muscle's tonus. To neural factors are considered depression of β_2-adrenoreceptors and activation of M-cholinoreceptors. Humoral factors, that provoke bronchial spasm, are mediators of allergic reactions (histamine, serotonin, substance of anaphylaxis, etc.), that are excreted by basophilic cells and thrombocytes. Its pathologic features are contraction of airway smooth muscle, mucosal thickening from edema and cellular infiltration, and inspissation in the airway lumen of abnormally thick, viscid plugs of mucus. Of these causes of airway obstruction, contraction of smooth muscle is most easily reversed by current therapy; reversal of the edema and cellular infiltration requires sustained treatment with antiinflammatory agents. In case, when asthma has infective-allergic nature, antimicrobe drugs are also used.

Classification of bronchi widening (*Broncholytics*) drugs:

1. β-Adrenomimetics:

a) nonselective $\beta_1+\beta_2$-adrenomimetics (*Orciprenaline*, *Isoprenaline (Isadrinum)*) and α+β-adrenomimetics *(Adrenaline, Ephedrine)*;

b) selective β_2-adrenomimetics *(Salbutamol, Fenoterol, Terbutaline)*.

2. M-cholinolytics *(Ipratropium bromide, Atropine, Platyphyllinum)*.

3. Myotropic drugs *(Euphyllin, Theophylline, No-spa)*.

4. Antiinflammatory, antiallergic and desensitizing drugs (glucocorticoids, *Cromolyn-sodium*, *Ketotifen*, H_1-histaminoblockers).

5. Complex drugs *(Theophedrinum, Solutan, Antasman)*.

The **adrenoceptor agonists**, discussed in detail in lecture "Adrenergic agonists", have several pharmacologic actions that are important in the treatment of asthma — i.e. they relax airway smooth muscle and inhibit release of some broncho-constrictive substances from mast cells. As in other tissues, the β-agonists stimulate adenylate cyclase and catalyze the formation of cAMP in the airway tissues. Although there is no evidence for direct sympathetic innervation of human airway smooth muscle, there is ample evidence for the presence of adrenoreceptors on airway smooth muscle. The adrenomimetic agents that have been widely used in the treatment of bronchial asthma include adrenaline, ephedrine, isadrine, and a number of β_2-selective agents.

Adrenaline (Epinephrine) is an effective, rapidly acting bronchodilator when injected subcutaneously. Because adrenaline stimulates β- as well as α-receptors, tachycardia, arrhythmias, worsening of angina pectoris, and hypertension are troublesome adverse effects. Compared with *Adrenaline*, *Ephedrine* has a

longer duration (4–6 hours), oral activity, more pronounced central effects, and much lower potency. *Ephedrine* acts at indirect way — it stimulates the releasing of *Noradrenaline* from presynaptic membrane. It is prescribed in fixed-dose combination with spasmolytics (*Theophylline*), H_1-histaminoblockers (*Dimedrole*) in commercial formulations.

Isadrinum (Isoproterenol) is a potent bronchodilator; when inhaled as a microaerosol, it causes maximal bronchodilation within 5 minutes. *Isadrine* has a 60 to 90 minute duration of action. It stimulates both β_1- and β_2-receptors, that's why it causes tachycardia, arrhythmias, and evokes the attack of angina pectoris. Because nonselective adrenomimetics cause more cardiac stimulation (mediated by β_1 receptors), they are replaced by selective β_2-adrenomimetics.

The β_2-selective adrenoceptor agonist drugs are the most widely used adrenomimetics for the treatment of asthma at the present time. These agents are effective after inhaled or oral administration and have a long duration of action and significant β_2 selectivity. *Salbutamol (Albuterol), Terbutaline,* and *Fenoterol* are available as metered-dose inhalers. Bronchodilation is maximal by 30 minutes and persists for 3–4 hours. *Salbutamol* and *Terbutaline* are also prepared in tablet form. One tablet two or three times daily is the usual regimen. Of these agents, only *Terbutaline* is available for subcutaneous injection. The indications for this route are similar to those for subcutaneous adrenaline — severe asthma requiring emergency treatment. The principal adverse effects of selective β_2-adrenomimetics are skeletal muscle tremor, nervousness, and occasional weakness.

Interest in the potential value of *M-cholinolytics* has recently been increased by demonstration of the importance of the vagus in bronchospastic responses of laboratory animals and by the development of a potent agent that is poorly absorbed after aerosol administration to the airways and is therefore not associated with systemic *Atropine* effects.

M-cholinolytics competitively inhibit the effect of acetylcholine at muscarinic receptors. In the airways, acetylcholine is released from efferent endings of the vagus nerves, and *M-cholinolytics* can effectively block the contraction of airway smooth muscle and the increase in secretion of mucus that occurs in response to vagal activity. Very high concentrations are required to inhibit the response of airway smooth muscle to nonmuscarinic stimulation. This selectivity of muscarinic antagonists limits their usefulness in preventing bronchospasm.

M-cholinolytics are effective bronchodilators. When given intravenously, *atropine*, the prototypical *M-cholinolytic*, causes bronchodilation at a lower dose than that needed to cause an increase in heart rate. Deposition of the aerosol in the mouth frequently causes a local drying effect. Adverse effects due to systemic absorption include urinary retention, tachycardia, loss of visual accommodation, and agitation.

Systemic adverse effects limit the quantity of *Atropine sulfate* that can be given, but the development of a more selective quaternary ammonium derivative of *Atropine*, *Ipratropium Bromide (Atrovent)*, permits delivery of high doses to muscarinic receptors in the airways because the compound is poorly absorbed and does not readily enter the central nervous system. Its effect appears after 20–30 min, reaches maximum within 1.5–2 h and lasts for 4–8 h.

Theophylline as well as caffeine are the derivatives of methylxanthines. At high concentrations, it inhibits the enzyme phosphodiesterase, which hydrolyzes cyclic nucleotides. This inhibition results in higher concentrations of intracellular cAMP. This effect could explain the cardiac stimulation and smooth muscle relaxation produced by these drugs, but it is not certain that sufficiently high concentrations are achieved *in vivo* to inhibit phosphodiesterase. Another proposed mechanism is the inhibition of cell surface receptors for adenosine that has been shown to cause contraction of isolated airway smooth muscle and to enhance histamine release from cells present in the lung. These effects are antagonized by *Theophylline*, which blocks cell surface adenosine receptors. Besides broncholytic effect, theophylline dilates vessels of the lung, kidneys, heart, skeleton muscles, lowers hemodynamic loading on heart. It causes direct cardiotonic action and increases oxygen needs.

A lot of complex drugs include *Theophylline*. *Euphylline* (*Theophylline* + *Ethylenediamine*), *Xanthinol nicotinate* (*Theophylline* + *Nicotinic acid*), etc. are the most known. *Euphyllin* is well absorbed (90%) after enteral introducing. For removing of bronchial asthma attack it is introduced intravenously or intramuscularly, however it causes irritate action. Therapeutic effect lasts for 6 hours. Metabolism is done in the liver; it is slower during the depression of hepatic enzymes, evoked by drugs (e.g. H_2-histaminoblockers). In such cases smaller doses of *Euphylline* are needed. It is excreted by kidneys in form of metabolites (90%) and in non-transformed form (10%). Adverse effects include excitation of the CNS (anxiety, insomnia, tremor, cramps), tachycardia, arrhythmia, sometimes-cardiac insufficiency. *Xanthinol nicotinate* is used for the treatment of diseases that accompanied by vessel contraction (e.g. atherosclerosis).

Another spasmolytics are *Papaverine, No-spa*. They have a direct relaxant effect on vascular, bronchial and other smooth muscle due to inhibition of the enzyme phosphodiesterase and accumulation of cAMP in the smooth muscles. These agents are indicated for the treatment of spasm of the gastrointestinal tract, bronchi, etc. As a rule, *Papaverine* and *No-spa* are used in combination with other broncholytics.

Anti-allergic, desensitizing and **anti-inflammatory drugs** include *Cromolyn sodium*, *Ketotifen*, *Corticosteroids*.

Cromolyn sodium differs from most antiasthmatic medications in that it is only of value when taken prophylactically. *Cromolyn* inhibits mast cell release of histamine, leukotrienes, and other substances that cause hypersensitivity reactions. When used as aerosol (metered-dose inhalers), it effectively inhibits both antigen- and exercise-induced asthma, and chronic use (four times daily) may reduce the overall level of bronchial reactivity; however, this drug has no effect on airway smooth muscle tone and is ineffective in reversing asthmatic bronchospasm. *Cromolyn* is poorly absorbed from the gastrointestinal tract. For use in bronchial asthma, it must be applied topically by inhalation. When given by inhalation or orally,

less than 10% is absorbed, and most is excreted unchanged.

Ketotifen has antihistamine and antiallergic activities. It inhibits mast cell release of histamine, leukotrienes, and other substances that cause hypersensitivity. In addition, *Ketotifen* blocks H_1-receptors. Agent is well absorbed from the gastrointestinal tract. The serum half-life is about 20 hours. *Ketotifen* is used for the prevention of acute bronchospasm. Adverse effects include drowsiness and thrombocytopenia.

Like *Cromolyn*, **corticosteroids** do not relax airway smooth muscle directly but reduce bronchial reactivity, increase airway caliber, and reduce the frequency of asthma exacerbations if administered for some time. Their effect on airway obstruction may be due in part to their potentiation of the effects of β-receptor agonists, but their most important action is their inhibition of the eosinophilic airway mucosal inflammation in asthmatic airways. The principal anti-inflammatory action is the inhibition of the release of arachidonic acid from cell membranes and therefore reduction of the production of leukotrienes, prostaglandins, and cytokines. Aerosol treatment is the most effective way to decrease the systemic adverse effects of corticosteroid therapy. Inhalation of lipid-soluble corticosteroid such as *Beclomethasone* makes it possible to deliver corticosteroids to the airways with minimal systemic absorption. Effect develops gradually, so it is not used for turning out of attack. Because of severe adverse effects when given chronically, oral and parenteral corticosteroids (*Prednisolone, Beclomethasone, Triamcinolone*) are generally reserved for patients who require more urgent treatment, i.e., those who have not improved adequately with bronchodilators or who experience worsening symptoms despite maintenance therapy.

Adverse effects during short courses (less than 7 days) usually are absent, during prolonged using — hyperglycemia, hypertension, osteoporosis, adrenal cortex insufficiency, etc. may appear. A special problem caused by inhaled topical corticosteroids is the occurrence of oropharyngeal candidiasis.

Combined drugs *(Theophedrinum, Solutan, Antasman, etc.)* are used for turning out and prophylaxis of bronchial asthma attacks. Principe of combining is based on synergetic interaction of the drugs with different mechanism of action. For example, *Solutan* (*alkaloids of Belladonna* + *Ephedrine* + *Sodium iodide*, etc), aerosol of *Berodual* (*Fenoterol* + *Ipratropium bromide*), tablets of *Theophedrinum* (*Theophylline* + *Ephedrine* + *extract of Belladonna*), etc.

ANTITUSSIVE AND EXPECTORANT DRUGS

Self-cleaning of mucosa of the respiratory ways from strange bodies is done by fastening of bronchial glands secretion, increasing of epithelium's activity and bronchioles motility. Irritation of reflective zones, especially in region of trachea's bifurcation, is accompanied by cough. Couch is a protective reaction, which promotes deleting of irritate agent from breathing ways. But during inflammation of the mucosa, secret becomes glutinous due to cumulated proteins, leukocytes and is hardly excreted. Drugs that depress cough (anti-cough, ***Antitussive***) and drugs that better excretion of sputum (***Expectorants***) are used for weakening of cough.

Antitussive drugs **are divided into 2 groups:**

— Drugs of central action (*Codeine*, *Ethylmorphine*, *Glaucine*)

— Drugs of peripheral action *(Prenoxdiazine (Libexin))*

Codeine and *Ethylmorphine* are the phenanthrene-derivative opiate agonists that have antitussive properties. They cause suppression of the cough reflex by a direct effect on the cough centre in the medulla of the brain. Also these agents have mild analgesic and sedative effects. *Codeine* and *Ethylmorphine* are well absorbed from the GI tract. Following oral administration, peak antitussive effects usually occur within 1–2 hours and antitussive activity may persist for 4 hours. High doses of *Codeine* and *Ethylmorphine* can cause depression of breathing centre, lowering of lung ventilation, and constipation. Prolonged therapy may results in addiction (dependence). *Glaucine* is an alkaloid of *glaucium flavum*. It depresses cough centre. But it doesn't inhibit breathing, doesn't cause drug addiction and constipation. It possesses adrenolytic effect and may lower AP, so it is not recommended during hypotonia.

Libexin apparently inhibits cough production by anesthetizing stretch receptors of vagal afferent fibers in the bronchi, pharyngis, and trachea that mediate the cough reflex.

Antitussives are used in the symptomatic relief of nonproductive cough during bronchitis, bronchial asthma, pneumonia, etc. Since the cough reflex may be a useful physiologic mechanism, which clears the respiratory passages of foreign material and excess secretions and may aid, in preventing or reversing atelectasis, cough suppressants should not be used indiscriminately.

According to the mechanism of action ***expectorants*** **are divided into:**

— Drugs that stimulate the sputum expectoration *(**Secretomotor** drugs)*

— Mucolytic agents

Expectorants have been used in the symptomatic management of conditions such as chronic bronchitis, bronchiectasis, and bronchial asthma that are associated with high sputum viscosity and hard expulsion of sputum.

Secretomotor drugs are subdivided into agents of ***reflective action*** and agents of ***resorptive action***. It is postulated that expectorants of reflective action irritate the stomach mucosa. Because stomach mucosa as well as bronchi is innervated by nervus vagus, the irritation of stomach activates the centre of nervus vagus in medulla that results in hastening of bronchial gland secretion, stimulation of bronchial epithelium and bronchioles peristalsis. It is accompanied by diluting of sputum and mucus and their expelling by cough. Due to irritative properties, reflective expectorants in high doses may cause vomiting. Drugs of reflective action are administered primarily in form of infusions, decocts, tinctures, extracts, mixtures, some (e.g. *Thermopsis*) in form of tablets. For examples, infusion of

Thermopsis grass, *Althea roots*, tablets *Mucaltin* (contains the *extract of Althea root*), etc.

To drugs of *resorptive action* are concerned substances with *Iodine, Ammonium chloride, Sodium bicarbonate*, etc. After absorption those drugs are excreted by bronchial glands, stimulating secretion and motor function of epithelium and bronchioles. Finally, they decrease the viscosity of mucus and promote it expelling. Prolong iodine therapy may cause symptoms of iodism: rhinitis, salivation, lacrimation, rash. Hypersensitivity reactions to iodides may occur and may be manifested by angioedema, fever, arthralgia, and eosinophilia.

Mucolytics act directly on glutinous secret. They reduce the viscosity of purulent and nonpurulent pulmonary secretions and facilitate their removal by coughing or postural drainage. Mucolytics are *proteolytic enzymes (Trypsin, Chymotrypsin, Deoxyribonuclease), Acetylcysteine, Bromhexine,* etc. *Trypsin* hydrolyzes peptides, amides. *Deoxyribonuclease* hydrolyzes phosphodiester bonds in DNA and proteins. *Bromhexine* depolymerizes and hydrolyzes fibers of mucopolysaccharides. Also *Bromhexine* promotes the synthesis of surfactant (a surface-active agent that stabilize alveolar volume). *Acetylcysteine* reduces disulfide linkages of mucoproteins. Predominantly mucolytics are administrated in inhalation route, except *Bromhexine* that is used orally. Mucolytics are used in the adjunctive treatment of patients with abnormal, viscid, or thick mucous secretions in such conditions as pneumonia, bronchitis, emphysema, tracheobronchitis, bronchiectasis, etc. In general mucolytics are combined with antimicrobe drugs, broncholytics.

STIMULATORS OF THE BREATHING (ANALEPTICS)

Stimulators of respiratory and cardio-vascular centers of medulla are used during depression of these centers. Because they restore life-important functions (breathing and blood circulation), they are called analeptics (animate substances). Most analeptics in higher doses may cause cramps. Analeptics are the antagonists of narcosis and soporific substances, alcohol, narcotic analgesics and cause "awakening" effect, which is characterized by smaller deepness and durability of narcosis and sleep, restoring of reflexes, muscular tonus and consciousness. Mechanism of analeptic's action is related with increased excitability of neurons.

Analeptics are divided into 3 groups:

— Agents of direct action on breathing centre (*Bemegride*, *Strychnine*, *Caffeine*)

— **Agents of reflective action** (*Lobeline*, *Cytisine* (*Cytiton*))

— Agents with combined action (*Nikethamide* (*Cordiaminum*), *Camphor*, CO_2)

Bemegride is used basically during poisoning by barbiturates and narcosis substances, for quick turning out from narcosis. It is injected slowly intravenously by 5–10 ml of 0.5% solution every 3–5 min up to restoring of breathing, blood circulation and reflexes. Injecting has to be stopped on the first appearance of cramp contraction of muscles.

Caffeine is described in lecture "Psychostimulants". Analeptic effect appears during injection of high doses that simulate centers of medulla. It causes expressed cardiotonic action. Caffeine is administered for the treatment of alcohol poisoning and during combined respiratory and cardiac insufficiency.

Strychnine is an alkaloid from strychnos. It stimulates all parts of the central nervous system, and was used as an antidote for depressant poisons. It causes the bettering of vision, hearing, tactile sensitiveness, muscular tonus, and metabolism. So, *Strychnine* causes general tone action and sometimes used for the treatment of chronic fatigue, hypotension, functional impairment of vision and hearing, etc. *Strychnine* blocks the inhibitory neurotransmitter, *Glycine*, and thus can cause convulsions. It is a potent chemical capable of producing acute or chronic poisoning of humans or animals.

Cytiton and *Lobeline* are the N-cholinomimetics. They stimulate respiratory centre in reflective way due to excitation of N-cholinoreceptors in the carotid sinus (carotid bulb). After intravenous injection of *N-cholinomimetics* one can see quick but short respiratory stimulation. They are used for the treatment of reflective respiratory depression during different traumas, inspiration of irritating substances and carbon monoxide. *Cytiton* raises the blood pressure, thus it is recommended for the shock, collapse.

Analeptics of combined action both directly and indirectly (through the carotid sinus) stimulate respiratory centre. *Cordiaminum* is a derivative of nicotinic acid. It stimulates breathing and blood circulation due to the stimulation of medulla centres. Also it directly stimulates heart activity. It is administered during weakening of breathing and blood circulation, caused by intoxication, infection disease, shock, etc.

Camphor is a ketone distilled from the tree of *Cinnamonum camphora*, and also prepared synthetically from oil of turpentine. Part of *Camphor* is excreted through breathing ways that promotes expelling of the sputum. Locally agent causes irritate and antiseptic action. It directly stimulates centers of the medulla. Also camphor stimulates the contractility and metabolism of myocardium. *Camphor* increases blood pressure due to narrowing of the vessels in abdominal organs. In the same time it dilates vessels of the brain, lungs, and heart. It is used in the form of oil solutions subcutaneously for the treatment of acute and chronic cardiac insufficiency, collapse, depression of the breathing centre, etc. Locally it is administered in the form of ointments during inflammatory processes, itch, for prophylaxis of bedsores, etc.

Carbonic dioxide (CO_2) is a potent respiratory stimulant. Inspiration of 3% CO_2 increases the lung ventilation 2 times. *Carbonic dioxide* can be used for inhalation separately or in combination with oxygen (*Carbogen*). *Carbonic dioxide* activates the cardiovascular centre. At the same time it dilates the smooth muscles due to the direct action. *Carbonic dioxide* is used for the stimulation of respiratory during poisons by narcosis substances, *Carbonic monoxide* (CO), during asphyxia of newborns. In higher doses CO_2 can cause hypercapnia, acidosis, and paralysis of breathing centre.

DRUGS USED DURING PULMONARY EDEMA

Edema of lungs is accompanied by acute respiratory insufficiency, so it needs emergency therapy. Pulmonary edema can be an aggravation of left-ventricular cardiac insufficiency, poisoning by irritate gases, during uremia, anaphylactic shock, infections, craniofacial traumas, coma, etc. (Fig. 30).

The most characteristically features of pulmonary edema are fear, cyanosis, bubbling respiratory with pink foamy sputum. The main danger of pulmonary edema is foaming of edema's liquid in respiratory ways, which causes hypoxia. So, inhalation of antifoaming drugs, oxygen and also sucking of the foam are necessary. Antifoaming substances are *Ethyl spirit* and *Antifoamsilane*. They diminish the foam's surface tension and transform foam into liquid, which volume considerably smaller. They are administered in form of inhalations with oxygen. *Antifoamsilane* doesn't irritate breathing ways, doesn't depress CNS and acts quicker than spirit.

If pulmonary edema is associated with cardiac insufficiency, *cardiac glycosides* (*Strophanthin*, *Corglyconum*) are indicated. During edema that is associated with hypertension one can use *ganglionblockers* (*Hygronium*, *Benzohexonium*), *α-adrenolytics* (*Phentolamine*, *Aminazinum*), *Myotropic vessel narrowing drugs* (*Sodium* nitroprusside). Adrenomimetics (*Phenylephrine*, *Ephedrine*) are used in case of hypotension. In addition during pulmonary edema are indicated *diuretics* (*Furosemide*) that cause dehydration of lung parenchyma, *glucocorticoids* (*Prednisolone*) that possess antiedematous and anti-inflammatory action, *Narcotic analgesics* (*Morphine*) that lower venous input to heart and blood-filling of lungs, depress short breathing and coughing, cause sedative action.

Available forms:

Fenoterol — in aerosol 15 ml each

Terbutaline — in aerosol; in tablets 0.0025 each; in ampoules 0.05% solution 1 ml each

Ephedrine — powder; in tablets 0.000025 each; in ampoules 5% solution 1 ml each

Ipratropium bromide — in aerosol 15 ml each

Euphyllin — in tablets 0.015 each; in ampoules 24% solution 1 ml each (for intramuscular injection) and 2,4% solution 10 ml each (for intravenous injection)

Ketotifen — in capsules and tablets 0.001 each

Beclomethasone dipropionate — in aerosol

Glaucine hydrochloride — in tablets 0.05 each

Libexin — in tablets 0.1 each

Mucaltin — in patented tablets

Acetylcysteine — in ampoules 20% solution 5 ml or 10 ml each (for inhalation) and 10% solution 2 ml each (for i.m. injection)

Camphor — in ampoules 20% oil solution 2 ml each

Cordiaminum — in ampoules 2 ml each

Bemegride — in ampoules 0.5% solution 10 ml each

Cytiton — in ampoules 1 ml each

Lecture 46
DRUGS INFLUENCING THE CONTRACTILE ACTIVITY OF UTERUS

They are divided into:

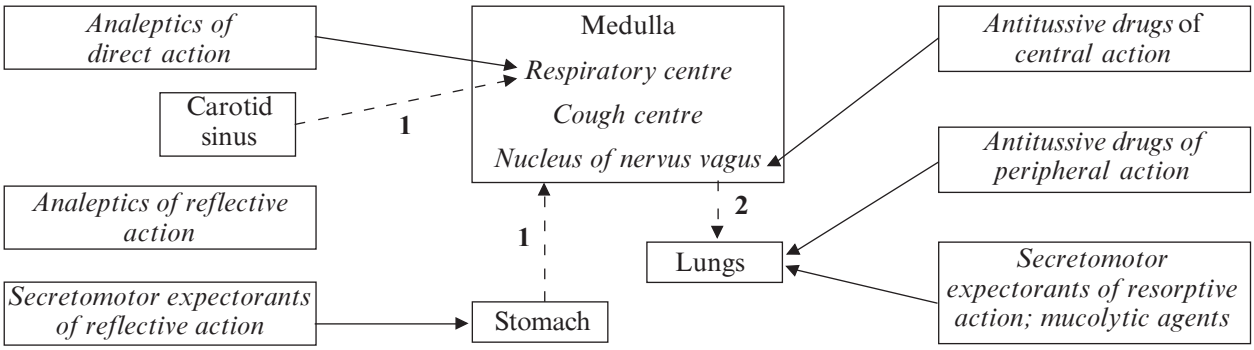
— substances, strengthening rhythmic contractions of uterus (Oxytocin, Desaminooxytocin, Pituitrinum, Dinoprost, Dinoprostone, Pachycarpinum, and Proserinum);

— substances, lowering tonus of uterine cervix (*Atropine sulfate, Dinoprost*, *Dinoprostone*, *Promedolum*);

— substances, increasing tonus of myometrium (*Ergot alkaloids*, *Cotarnine*, *Oxytocin*, and *Pituitrinum*);

— substances, weakening uterus contractions (*Fenoterol, Magnesium sulfate)*.

Drugs, strengthening rhythmic contractions of uterus are indicated during weakness of labor activity, for normalization of uterus involution in postpartum period, during hypotonic uterus bleeding.



1- afferent fibers; **2**- cholinergic fibers

Fig. 30. Main direction of agents that influence the respiratory organs

Oxytocin is a hormone secreted by the neurons of the hypothalamus and stored in the posterior pituitary in mammals. Commercially available *Oxytocin* preparations are prepared synthetically. *Oxytocin* stimulates contraction of uterine smooth muscle by increasing the sodium permeability of uterine myofibrils. High estrogen concentrations lower the threshold for uterine response to *Oxytocin*. Uterine response to *Oxytocin* increases with the duration of pregnancy. In the term uterus, *Oxytocin* increases the amplitude and frequency of uterine contractions, which in turn tend to decrease cervical activity producing dilation and effacement of the cervix and to transiently impede uterine blood flow. *Oxytocin* elicits milk ejection in lactating women. Also it produces vasodilation of vascular smooth muscle, increasing renal, coronary, and cerebral blood flow.

In pharmacologic doses, *Oxytocin* can be used for induction and augmentation of labor. It can also be used for control of postpartum uterine hemorrhage. *Oxytocin* is administered intravenously or intramuscularly. Its circulating half-life is 5 minutes. Contraindications include fetal distress, prematurity, abnormal fetal presentation, cephalopelvic disproportion, and other predispositions for uterine rupture. *Desaminooxytocin* is a synthetic analog of *Oxytocin*. It acts longer than parental agent and used subglossal.

Pituitrinum is an the extract of bovine pituitary gland. They contain two posterior pituitary hormones: vasopressin and oxytocin. *Pituitrine* posseses the activity of oxytocin, which is described beyond, and vasopressin that cause vasoconstriction and hypertension. These agents have the same indications as *Oxytocin*.

Prostaglandins are the class of physiologically active substances present in many tissues, with effects such as vasodilation, vasoconstriction, stimulation of intestinal or bronchial smooth muscle, uterine stimulation, and antagonism to hormones influencing lipid metabolism. Prostaglandins as well as leukotrienes and thromboxanes are synthesized from arachidonic acid via a cascade pathway. *Prostaglandin* $F_{2\alpha}$ (*Dinoprost*) and *Prostaglandin* E_2 (*Dinoprostone*) possess expressed influence on contractility of myometrium.

Dinoprostone stimulates uterine and GI smooth muscle. Although it is believed that the drug exerts its uterine effects via direct myometrial stimulation, the exact mode of this and other actions has not been fully elucidated. *Dinoprostone* increases the amplitude and frequency of uterine contractions throughout pregnancy, but uterine response to the drug increases with the duration of pregnancy. In early pregnancy, the uterus is more responsive to *Dinoprostone* than to *Oxytocin. Dinoprostone*-induced uterine contractions are usually sufficient to cause evacuation of both the fetus and the placenta. The drug also produces cervical dilation and softening. *Dinoprostone* causes stimulation of the circular smooth muscle of the GI tract, causes bronchodilation, and increases permeability of the vessels. Large doses of *Dinoprostone* may cause vasodilation and hypotension.

Dinoprostone is widely distributed in the mother and is rapidly metabolized in the maternal lungs, kidneys, and other tissues.

Dinoprostone is used intravenously to induce abortion during the second trimester of pregnancy (beyond the 12th week of gestation) and to improve cervical inducibility (cervical "ripening") near or at term in pregnant women for labor induction. Adverse GI effects (e.g. diarrhea), phlebitis, fever are the most frequent adverse reactions of *Dinoprostone*. Since *Dinoprostone*, like *Dinoprost*, is metabolized rapidly, discontinuing administration of the drug and supportive therapy are usually adequate treatments for serious adverse effects.

Dinoprost is similar in structure, action and uses to *Dinoprostone*. It is administered intravenously, vaginally, and as intra-amniotic injection. *Dinoprost*, unlike *Dinoprostone*, causes bronchospasm. That's why it is not recommended during bronchial asthma.

Pachycarpinum hydroiodide is a ganglionblocking agent. It increases the tonus and force of the uterus contractions. Agent lowers blood pressure, so it can be administered during labor in patients with hypertonia. It is used intramuscularly, subcutaneously and orally. *Pachycarpinum* is indicated for the weakness of labor. Anti-cholinesterase substances (*Proserinum*) and β-adrenoblockers (*Propranolol*) also stimulate activity of the uterus.

M-cholinolytic (*Atropine sulfate*), prostaglandins (*Dinoprost*, *Dinoprostone*), and narcotic analgesic (*Promedolum*) are used for the relaxation and softening the cervix of uterus, and bettering of labor current.

Drugs, increasing tonus of myometrium are used basically during atonic uterine hemorrhages and for fastening of uterine involution in postpartum period. Mechanism of bleeding stop is related with stable increasing of uterus tonus and pressing due to it of small vessels in myometrium.

Ergot alkaloids are produced by *Claviceps purpurea*, a fungus that infects grain rye under damp growing or storage conditions. *Ergot alkaloids* are the derivatives of lysergic acid. The main alkaloids are *Ergotamine* and *Ergometrine*. Their effects include agonist, partial agonist, and antagonist actions at α-adrenoreceptors and serotonin receptors. Ergotamine and related compounds constrict most human blood vessels in a predictable, prolonged, and potent manner. In the same time, they blockade the response of α-receptors to other agonists including noradrenaline. Dihydroderivatives of ergot alkaloids have much more selective α-receptor-blocking actions and they cause vasodilation.

Ergot alkaloids possess stimulant action on the uterus. The uterus at term is more sensitive to *Ergot* than earlier in pregnancy and far more sensitive than the nonpregnant organ. These drugs induce powerful and prolonged tonic contraction of the uterus. *Ergometrine* is more selective than other ergot alkaloids in affecting the uterus and is the agent of choice in obstetric applications of these drugs. *Ergometrine* can be administrated enterally and parenterally. The onset of action is 10–15 minutes after ingestion and lasts for a few hours. Certain of the naturally occurring alkaloids are powerful hallucinogens. *Lysergic acid diethylamide (LSD, "acid")* is the *Ergot* compound that most clearly demonstrates this action.

Even moderate *Ergot* doses produce a prolonged and powerful spasm of the muscle quite unlike natural labor. Their use at that time to accelerate delivery caused an asphyxia and fetus death. Therefore, ergot

derivatives are useful only for control of late uterine bleeding and should never be given before delivery.

In medical practice there are used: Galen's *(extract of thick ergot)*, neo-Galen's drugs *(Ergotal)* and pure alkaloids *(Ergometrine maleate, Methylergometrine, Ergotamine hydrotartrate)*. *Ergotamine* is used for the treatment of migraine. Favorable effect of *Ergotamine* is related with weakening of cerebral vessel's pulsation and lowering of irritation of the cerebral cover's receptors.

Ergot alkaloids are **contraindicated** during angina pectoris, atherosclerosis, and spasm of peripheral vessels. They are excreted in breast milk, so they are not to be used during feeding.

The accidental ingestion of ergot alkaloids in contaminated grain as well as overdosing ergot agents causes *Ergot* poisoning *(ergotism)*. The most dramatic effects of poisoning are hallucinations and convulsions, prolonged vasospasm and damage of endothelium that may result in gangrene, and stimulation of uterine smooth muscle, which in pregnancy may result in abortion.

Cotarnine chloride also increases tonus of uterus and administered orally and parenterally during uterus bleeding.

Expressed action during atonic uterus bleeding is exhibited by *Oxytocin, Pituitrinum* and *prostaglandins* that are discussed beyond.

During atonic uterus bleeding some *plant drugs* are used in form of extracts, decoctions and tinctures: tincture of *Barberries*, *Water paper*, etc.

Drugs, weakening contractile activity of myometrium are used, basically, for stopping of premature labor and weakening of labor activity during fastened labor, for preventing of labor ways traumas. For those purposes β_2-adrenomimetics (*Fenoterol*), *Magnesium sulfate*, substances for narcosis are used.

Fenoterol (Partusisten) is a β_2-adrenomimetic. It causes tocolytic (uterine relax) action. Also it leads to bronchodilation. Agent is effective drug for prevention of premature labor and doesn't cause negative action on fetus. It is administered intravenously by drops and orally in tablets. It may cause tachycardia, muscular weakness, tremor, and hypotension. It is contraindicated during cardiac defects, arrhythmia, thyrotoxicosis, and glaucoma.

Magnesium sulfate during parenteral administration decreases uterus contractions. It acts as calcium antagonist. Also agent possesses sedative, hypotensive effects. In higher doses — soporific, anticonvulsive, and narcosis effects occur.

Substances for narcosis (*Nitrogen oxide*, *Ftorotan*, *Sodium oxybutyrate*, etc.) and *tranquilizers* (*Diazepam*) as well as *Progesterone*, *Tocopherol (Vitamin E)* inhibit contractile activity of uterus.

Available forms:

Oxytocin — in ampoules 1 ml and 2 ml that contain 5 IU and 10 IU

Dinoprostone — in tablets 0.0005 each; in ampoules 5 ml each

Ergometrine maleate — in tablets 0.0002 each; in ampoules 0.02% solution 1 ml each

Fenoterol (Partusisten) — in tablets 0.005 each; in ampoules 0.005% solution 10 ml

Lecture 47
BASIC ACTIONS AND MEDICATIONS USED IN INTOXICATIONS AND EMERGENCY STATES

Poisonings may be caused by any kind of chemical compounds or liquids for technical used adopted in technique, agriculture and household. Medicines may cause poisonings too. All poisonings are divided into professional, household and medical ones. We are going to overview the first aid in cases of medical poisonings. But they are effective in other cases too.

Most frequent medical poisons are sleeping pills, analgesics, neuroleptics, antiseptics, cardiac glycosides, anti-cholinesterase agents, etc. The pattern and severity of poisoning depends on its agent action. Thus, anti-cholinesterase agents poisoning (caused by phosphoorganic compounds) is characterized by cholinergic system enhanced symptoms. Alcohol, sleeping pills and drug intoxications are characterized by deep CNS depression.

Organism conditions and the way of poison entrance (oral, inhalation, skin, and mucous coat absorption) determine the severity of symptoms as well as the way of first aid. Children and elderly people are extremely sensitive to poisons and demonstrate the cases of the most severe poisonings. Environmental factors like temperature, humidity and atmospheric pressure influence the poison activity too.

There are general and specific first aid means. They are designed to achieve the following results:

a) prevention of further poisons absorption;

b) chemical neutralizing of the absorbed poison or its elimination with a specific antidote;

c) enhanced poisons extraction;

d) normalizing of organisms function by symptomatic therapy.

The sooner you begin the first aid, the more chances of success you have. Each case may need the adjustment of therapeutic pattern depending on the type and severity of poisoning. Thus, abrupt respiratory depression claims urgent restoring of the gas exchange system functions.

In the treatment of poisonings an important place is engaged by antidote. *Antidote* is an agent that neutralizes a poison or counteracts its effects. There are a few types of antidotes. ***Chemical antidote*** is a substance that unites with a poison to form an innocuous chemical compound (*Unithiol*, chelating compounds). ***Mechanical antidote*** is a substance that prevents the absorption of a poison (activated carbon). ***Physiologic antidote*** is an agent that produces systemic effects contrary to those of a given poison.

Prevention of poisons absorption. The pattern of these actions depends on the way poison entrance into the organism. Inhalation poisonings (caused by carbon monoxide, nitric oxide, insecticides aerosols, petroleum evaporations) claim immediate removal of patient from the danger zone. Poisons should be removed or washed away from skin and mucous coats. Oral intake of poisons is managed by stomach rinsing

(lavage). The early it is done, the more effective it is. Repeated rinsing help in cases of poisoning with hard-soluble powders and tablets that stay in stomach for a couple of hours.

Inactivation and binding of the poison in the stomach should be performed simultaneously to rinsing. Potassium permanganate, tannin, activated carbon, egg whites and milk are used for these purposes.

Potassium permanganate causes the oxidation of organic poisons. However it is unable to react with inorganic compounds. Its water solution ratio is from 1:5000 to 1:10000. It should be removed from stomach right after the rinsing due to its irritating properties.

Activated carbon (*Charcoal*) is a universal adsorbent. Water suspension, containing 20–30 g of activated carbon, is to be poured into the stomach. After the interaction with poison the suspension should be quickly evacuated with the help of laxatives due to possible release of poison.

Tannin sediments various poisons especially alkaloids. 0.5% solution of tannin is usually used. Removal of the suspension due to possible poison release is necessary also.

Eggs white form insoluble complex with poisons. Milk acts in the same way but it is contradicted in case of poisonings by fat-soluble agents.

Vomiting agents may be used in cases of impossibility of the gastric rinsing. *Apomorphine hydrochloride* (0.5–1 ml of 0.5–1% injected subcutaneously) is used most frequently. It is contradicted in case of patients unconsciousness.

Salt laxatives (*Sodium* and *Magnesium sulfate*) are used for poison removal from intestines. *Sodium sulfate* is better then *Magnesium sulfate*, because the latter causes CNS depression.

Chemical neutralization of the absorbed poison and usage of specific antidotes. There are certain compounds capable for neutralization of poison toxicity by chemical binding or functional antagonism. They act by chemical or functional interaction with poisons. *Unithiol*, *Sodium thiosulfate*, *Complexons*, *Methemoglobin-formers* and *Demethemoglobin-formers* are the examples of chemical concurrence interaction.

Unithiol (Dimercaprol) can bind metal ions, metalloids and cardiac glycosides molecules due to its two SH groups, which can donate electrons for coordination with the poison. Such bonding effectively prevents interaction of the metal with similar functional groups of enzymes, coenzymes, cellular nucleophils, and membranes. Usually this medicine is used in cases of poisonings by arsenic, mercury and gold. It is less effective against bismuth, cobalt, cooper, zinc, nickel, polonium and cardiac glycosides. Complex of *Unithiol* and poison is excreted by kidneys. Given intramuscularly, *Unithiol* is readily absorbed, metabolized, and excreted by the kidney in complex with poison within 4–8 hours. Adverse effects include hypertension, tachycardia, vomiting, salivation, fever (particularly in children), and pain at the injection site.

Sodium thiosulfate is an antidote in arsenic, mercury, lead, and cyanide poisoning. Sodium thiosulfate forms with metals nontoxic sulfites and with cyanides less toxic substances. Its 30% solution is injected intravenously.

Complexons make chelate compounds with most of metal ions and radioactive isotopes. These substances have low toxicity and are being extracted by kidneys. *Tetacine-calcium (EDTA, Edetate calcium disodium)*, the *Calcium chelate* of edetate (Ethylenediaminetetraacetate) *disodium*, is a chelating agent (*complexon*). The calcium in *calcium EDTA* can be displaced by divalent and trivalent metals, particularly lead, to form stable soluble complexes which can then be excreted in urine. Administration of calcium *EDTA* chelates greatly increases the urinary excretion of zinc, cadmium, manganese, iron, and copper. The manufacturer recommends that calcium *EDTA* injection be diluted with 0.9% sodium chloride or 5% glucose injection for intravenous administration. *Calcium EDTA* is used for the reduction of blood and mobile depot lead in the treatment of acute and chronic lead poisoning and lead encephalopathy. Agent may also be beneficial in the treatment of poisoning from other heavy metals such as chromium, manganese, nickel, zinc, and possibly vanadium. The principal and most serious toxic effect of *calcium EDTA* is renal tubular necrosis, which tends to occur when the daily dose is excessive and may result in fatal nephrosis.

Penicillamine is a monothiol-chelating agent, which is a degradation product of penicillins. Penicillamine chelates copper, iron, mercury, and lead to form stable soluble complexes, which are readily excreted by the kidneys. Copper is chelated by the combination of 2 molecules of *Penicillamine* with 1 atom of the metal. *Penicillamine* is readily absorbed from the GI tract. *Penicillamine* is used to promote excretion of copper in the treatment of Wilson's disease (hepatolenticular degeneration). Also it is used in the treatment of the active stage of rheumatoid arthritis. The mechanism of action of *Penicillamine* in the treatment of rheumatoid arthritis is not known but may be related to inhibition of collagen formation. Adverse reactions include allergic reactions, nausea, leukopenia, and proteinuria.

Deferoxamine chelates iron by binding ferric ions to its molecule. *Deferoxamine-iron* complex is formed in many tissues, but mainly in plasma; this complex is stable, water soluble, and readily excreted by the kidneys. *Deferoxamine* appears to have a specific affinity for iron; this affinity is greater than that of other chelating agents for iron. *Deferoxamine* is used in the treatment of acute iron intoxication as well as chronic iron overload.

Demethemoglobin-formers are the substances capable of converting methemoglobin to hemoglobin. They are *Methylene blue* (as a *Chromosmone* medicine) and *Cystamine. Methylene blue* reduces methemoglobin to hemoglobin. It is administered to patients who have been exposed to methemoglobin-forming compounds (e.g. aniline, nitrites, local anesthetics, sulfanilamides) and whose methemoglobin levels exceed 20 to 30%. However, in higher doses *Methylene blue* promotes methemoglobin forming that can be used for the treatment of cyanide poisoning.

Physiologic antidote as it is mentioned above is an agent that produces systemic effects contrary to those of a given poison. Antidotes can concurrent with poison for the same substrate, e.g. receptor, enzyme *(**functional antagonism**)*. For example phosphoorganic substances inactivate an enzyme acetylcholinesterase that

leads to exceed accumulation of acetylcholine. Cholinesterase reactivators (*Dipyroxime* (*Trimedoxime bromide*), *Isonitrosin*) bind with phosphoorganic substances and release *acetylcholinesterase*. *Choline-blockers* (*Atropine*) remove *cholinomimetics* (*Muscarine*, *Pilocarpine*) on *M-cholinoreceptors*; thus *Atropine* is useful during muscarine poisoning. The same concerns *histamine* and *anti-histamine* substances, *adrenoblockers* and *adrenomimetics*, *Morphine* and *Nalorphine*.

Enhanced poison extraction. That is achieved by organisms purifying. Large amounts of liquid and diuretics are to be taken *(forced diuresis)*. It causes the dilution of poison in tissues and decreases its concentration while osmotic diuretics and furosemide enhances its renal excretion. Drinks are given to conscious patients; unconscious ones receive 5% *glucose solution* or *isotonic sodium chloride* solution intravenously. This method is effective only when kidneys are still capable of excretion. Alkaline diuresis may aid in increasing renal clearance and reducing the elimination half-life of *Salicylates* and *Phenobarbital* (acids), because the reabsorption of acids at alkaline pH is lower. And on the contrary, alcohol and amphetamine (alkaline compounds) are better excreted with acidic urine that can be achieved by using of *Ammonium chloride*.

Extracorporeal techniques include hemodialysis, hemoperfusion, etc. that are used for different kinds of poisonings.

During the procedure ***hemodialysis*** of soluble substances and water from the blood by diffusion through a semipermeable membrane is appearing. The separation of cellular elements and colloids from soluble substances is achieved by pore size in the membrane and rates of diffusion. Hemodialysis is especially effective in case of kidney insufficiency (*Sublimate* poisonings). It promotes the evacuation of poisons with small molecular weight.

Hemoperfusion is a method of detoxication. It consists of blood passage through columns of adsorptive material, such as *Activated charcoal* (*Carbon*), to remove toxic substances from the blood. It is active against poisons, diluted in blood. Hemoperfusion is useful for intoxication with a drug known to be metabolized to a more toxic one and a drug known to produce delayed toxicity.

Peritoneal dialysis is a removal from the body of soluble substances and water by transfer across the peritoneum, utilizing a dialysis solution which is intermittently introduced into and removed from the peritoneal cavity. Transfer of diffusible solutes and water between the blood and the peritoneal cavity depends on the concentration gradient between the two fluid compartments. Acute peritoneal dialysis is used principally to treat patients with acute renal failure.

Supportive care (symptomatic therapy). Morbidity and mortality following an overdose are reduced by intensive appropriate symptomatic supportive therapy, which includes restoring of vital functions (cardiac status, airway, and mental status).

Respiratory depression claims endotracheal intubation, bronchial cleaning and artificial lung ventilation. Respiratory centre depression is managed by analeptics (camphor, bemegride). Respiratory depression caused by *Morphine* can be treated by *Naloxone* or *Nalorphine*. **Pulmonary edema** is treated with complex therapy according to blood pressure rate. *Spirit* and *Antifoamsilane* inhalations are performed to manage the foam; *glucocorticoids*, *diuretics* and *ganglion-blockers* are given depending on the indications. **Bronchospasm** can be managed by broncholytics (*adrenomimetics*, *choline-blockers*, *Euphylline*, etc). Hypoxia is managed by oxygen inhalation and special apparatus for respiration and blood circulation support.

Cardiac insufficiency claims glycosides with a quick onset of action (*Strophanthin*, *Corglyconum*); *antiarrhythmics* are used in cases of arrhythmia.

Vascular tonus and blood pressure are decreased during most of poisonings. Hypotonia causes tissue nutrition disorders, hypoxia, and poison retention. **Hypotonia** is managed with adrenomimetics (e.g. *Dopamine*, *Ephedrine*, *Adrenaline*, *Mesatonum (Phenylephrine)* and *Noradrenaline*). **Hypertension** (poisoning by vasoconstrictors) is the indication for the using of *Clophelinum*, *Magnesium sulfate*, *Phentolamine*, *Benzohexonium*, *Furosemide*, etc.

Cholinomimetics and *CNS agitators* often cause **cramps**. They are managed with narcosis agents, tranquilizers *(Diazepam)*, barbiturates *(Thiopental)*, muscle relaxants, and *Magnesium sulfate*.

Allergic reactions and especially **anaphylactic shock** first aid is urgent injections of adrenomimetics *(Adrenaline)*, glucocorticoids *(Prednisolone)*, antihistamines *(Dimedrolum)*, broncholytics *(Euphyllin)*, and cardiac glycosides *(Strophanthin)*.

Coma is the symptom of severe poisonings. It is prefer for the poisoning by CNS depressants. Treatment is designed to support vital functions. Analeptic use should be extremely cautious in these cases. Pain syndrome claims narcotic analgesics, which can inhibit the respiratory centre on the other hand.

The support of acid-base balance and liquid-salt balance are extremely important in cases of poisonings therapy. Acidifying and alkalinizing agents, salt solutions are discussed in lecture "Blood substitutes".

Thus, first aid means depend on the kind of poisoning and patients state.

Available forms:

Potassium permanganate — in bottles 0.01%; 0.1% solution

Carbo activated — in tablets 0.25 or 0.5 each

Unithiol — in ampoules 5% solution 5 ml each

Tetacine-calcium — in ampoules 10% solution 20 ml each

Penicillamine — in capsules 0.15 each

Chromosmon (Methylthioninium chloride) — in ampoules 10 ml and 20 ml each

Ephedrine — in ampoules 5% solution 1 ml each

Euphyllin — in ampoules 24% solution 1 ml each (for intramuscular injection) and 2.4% solution 10 ml each (for intravenous injection)

Cortisone — in bottles 2.5% suspension 10 ml each

Benzohexonium — in ampoules 2.5% solution 1 ml each

Camphor — in ampoules 20% oil solution 2 ml each

Bemegride — in ampoules 0.5% solution 10 ml each

Furosemide — in ampoules 1% solution 2 ml each

Diazepam — in ampoules 0.5% solution 2 ml each

EXAMINATION QUESTIONS

1. A 36-year-old woman with severe erosive esophagitis is prescribed *Pantoprazole*. One of the most common adverse side effects of such therapy is which of the following?
(A). Vomiting.
(B). Constipation.
(C). Headache.
(D). Heartburn.
(E). Paresthesias.

2. While taking a NSAID for arthritis, a 65-year-old man developed a gastric ulcer. He was prescribed *Ranitidine* for 8 weeks. This drug binds a receptor located where?
(A). Nucleus.
(B). Nucleolus.
(C). Cytoplasm.
(D). Cell membrane.
(E). Cell wall.

3. A 20-year-old woman goes to the emergency department, stating that within the past hour she ingested "a handful of sleeping pills." She is still awake. Which of the following drugs can be given to induce vomiting?
(A). *Metoclopramide.*
(B). *Ipecac.*
(C). *Morphine.*
(D). *Promethazine.*
(E). *Ondansetron.*

4. A 17-year-old boy with a history of sulfa allergy is diagnosed with left-side ulcerative colitis after a β-week history of bloody diarrhea and tenesmus. On examination he is afebrile and has no abdominal tenderness. The appropriate drug therapy to institute initially is which of the following?
(A). *Metronidazole.*
(B). *Sulfasalazine.*
(C). *Mesalamine.*
(D). *Cyclosporine.*
(E). *Prednisone.*

5. Gastric acid secretion is stimulated by the presence of
(A). *Gastrin* and *acetylcholine*.
(B). *Histamine* and *motilin*.
(C). *Norepinephrine* and *gastrin*.
(D). *Norepinephrine* and *histamine*.
(E). *Acetylcholine* and *pepsin*.

6. Which one of the following β-adrenoceptor agonists has such a slow onset of action that it is not indicated for the relief of acute asthma symptoms?
(A). *Salmeterol.*
(B). *Albuterol.*
(C). *Epinephrine.*
(D). *Terbutaline.*
(E). *Isoproterenol.*

7. The standard treatment regimen for asthma is best described by which of the following?
(A). *Theophylline* and exercise.
(B). Inhaled β_2-adrenoceptor agonists only.
(C). Inhaled corticosteroids only.
(D). A combination of inhaled bronchodilators and inhaled corticosteroids.
(E). Oral corticosteroids.

8. Symptoms typically produced by inhaled β-adrenoceptor agonists include which of the following?
(A). Tachycardia, dizziness, and nervousness.
(B). Dysphonia, candidiasis, and sore throat.
(C). Dyspepsia and Churg-Strauss syndrome.
(D). Nausea, agitation, and convulsions.
(E). Muscle tremor, tachycardia, and palpitations.

9. Which of the following is the drug of choice for inducing labor?
(A). *Oxytocin.*
(B). *Misoprostol.*
(C). *Methyl ergonovine.*
(D). *Dinoprostone.*
(E). *Carboprost tromethamine.*

10. Adverse reactions to the prostaglandin analogue carboprost tromethamine include all of the following EXCEPT
(A). Diarrhea.
(B). Fever.
(C). Water intoxication.
(D). Nausea.
(E). Dyspnea.

11. All of the following are properties of magnesium sulfate that may be related to its ability to relax uterine smooth muscle EXCEPT
(A). Uncoupling excitation-contraction in myometrial cells through inhibition of cellular action potentials.
(B). Decreasing calcium uptake by competing for binding sites.
(C). Activating adenylate cyclase.
(D). Stimulating calcium-dependent ATPase.
(E). Antagonizing prostaglandin action.

12. Which of the following is a special concern for the use of *Indomethacin* for inducing labor (tocolysis)?
(A). Fetal cardiac arrest.
(B). Fetal gastrointestinal bleeding.
(C). Fetal hematuria.
(D). Closure of the fetal ductus arteriosis.
(E). Fetal muscular paralysis.

ANSWERS

1. **(C)**. The most commonly reported side effects for all of the proton pump inhibitors are headache, diarrhea, and abdominal pain. Heartburn is improved by these agents. Vomiting, constipation, and paresthesias are not typical side effects of proton pump inhibitors.

2. **(D)**. *Ranitidine* is an H_2-receptor antagonist. H_2- receptors are found in the cell membrane of parietal cells, not in the nucleus, nucleolus, or cytoplasm. Mammalian cells do not have cell walls.

3. **(B)**. Two medicines, *Ipecac* and *Apomorphine*, induce vomiting. *Metoclopramide* is a prokinetic with antiemetic properties and therefore would have the opposite of the desired effect. *Morphine* is an opioid with analgesic and sedating properties. *Promethazine* and *Ondansetron* are also antiemetics, not emetics.

4. **(C)**. The information provided suggests the patient has mild to moderate disease. Initial therapy should be a 5-ASA containing product, which includes *Sulfasalazine* and *Mesalamine*. However, the patient has a sulfa allergy, precluding the use of *Sulfasalazine*. *Metronidazole* is useful in the treatment of some patients with Crohn's disease. *Cyclosporine* has been used in patients with fulminant ulcerative colitis. *Prednisone* may have to be added to this patient's therapy, but only if he fails to respond to the *Mesalamine*. It should not be used initially.

5. **(A)**. Gastrin, histamine, and acetylcholine stimulate gastric acid secretion. Pepsin is a digestive protein secreted by the stomach in response to a meal. Norepinephrine is a neurotransmitter that does not affect gastric acid secretion.

6. **(A)**. The other agents have rapid onset and are appropriate for acute symptomatic relief of asthma.

7. **(D)**. In all asthma treatment regimens, inhaled β_2-adrenoceptor agonists are used as bronchodilators as needed to relieve acute symptoms. As asthma is an inflammatory disease of the airway, inhaled corticosteroids are also used as standard therapy to control symptoms in all but the mildest cases. The potential for dangerous side effects and drug interactions has relegated *Theophylline*, once a mainstay of asthma treatment, to add-on therapy for hard to control symptoms. Inhaled β_2-adrenoceptor agonists or inhaled corticosteroids are not typically used as monotherapy, although the former class of agent can be used alone for patients with very mild symptoms. Because of extensive systemic side effects, oral corticosteroids are not typically used to treat asthma except when symptoms cannot be controlled by standard therapy.

8. **(A)**. Tachycardia, dizziness, and nervousness are often produced by larger doses of inhaled β-agonists. Dysphonia, candidiasis, and sore throat are associated with the use of inhaled corticosteroids. The emergence of Churg-Strauss syndrome, though uncommon, is associated with the use of oral leukotriene modulators. *Theophylline* produces a range of side effects, including nausea, agitation, and life-threatening convulsions. Muscle tremor and palpitations are frequently observed with oral (3-adrenoceptor agonists but rarely occur when these agents are administered via inhalation.

9. **(A)**. *Oxytocin* is considered the drug of choice for inducing labor. All other methods of labor induction are compared to oxytocin to establish their efficacy. Data demonstrate that *Oxytocin* is highly effective in inducing, establishing, and augmenting labor. *Oxytocin* is not as effective for labor induction when a woman has a cervix that is not favorable for labor. Another agent, such as *Misoprostol* or *Dinoprostone*, may be better for women with unfavorable cervices. Both *Misoprostol* and *Dinoprostone* are prostaglandin analogues. They cause changes in the substance of the cervix and uterine contraction. Although all agents used for labor induction carry the risk of uterine hyperstimulation, prostaglandins are more likely to cause hyperstimulation in women with favorable cervices. Furthermore, the current formulations of prostaglandins do not allow for tight control of blood levels and rapid clearance of medication if hyperstimulation occurs. *Methyl ergonovine* is an α-agonist that causes direct smooth muscle contraction. *Carboprost tromethamine* is a methylated analogue of prostaglandin F_{2a} It is highly potent in causing prolonged uterine contraction. Both medications are used for the control of uterine bleeding after delivery by causing tetanic uterine contractions. These medications are contraindicated for labor induction in women with live fetuses. Both medications can be used in facilitating medical abortions.

10. **(C)**. *Carboprost tromethamine* is methylated at the 15 position. This methylation causes the analogue to be 10 to 15 times more potent then the natural prostaglandin. Smooth muscles that are especially sensitive to prostaglandin F_{2a} are uterine, gastrointestinal, and bronchial. The uterine sensitivity allows for the therapeutic efficacy. The gastrointestinal sensitivity causes the diarrhea and nausea. Prostaglandins are involved in the pyretic response, and thus a side effect of their use may be fever. *Oxytocin* has antidiuretic hormone qualities, and with prolonged use may cause water intoxication.

11. **(E)**. *Magnesium* has no known effect on prostaglandins. The mechanism of action by which *Magnesium sulfate* causes smooth muscle contraction is complex and poorly understood. *Magnesium sulfate* uncouples excitation-contraction in myometrial cells through inhibition of cellular action potentials. Furthermore, *Magnesium sulfate* decreases calcium uptake by competing for binding sites, activating adenylate cyclase (reducing intracellular calcium), and stimulating calcium-dependent ATPase, which promotes calcium uptake by sarcoplasmic reticulum.

12. **(D)**. *Indomethacin* is a potent prostaglandin synthesis inhibitor. Patency of the ductus arteriosis depends on the formation of prostaglandins. Closure of the ductus arteriosis can lead to fetal heart failure and death. Also, fetal closure can lead to neonatal pulmonary hypertension. Neonatologists use *Indomethacin* for the treatment of neonatal patent ductus arteriosis, thus often obviating neonatal heart surgery. Prostaglandin synthesis inhibitors are associated with bleeding. Although bleeding is well documented in children and adults, the use of *Indomethacin* has not been shown to cause hematuria or gastrointestinal bleeding in the fetus. There is some evidence, however, that maternal use of *Indomethacin* may increase the risk of neonatal intraventricular hemorrhage. Neither muscular paralysis nor cardiac arrest has been demonstrated in the fetus with maternal use of *Indomethacin*.

Appendix A
MAIN INTERNATIONAL ABBREVIATIONS IN PHARMACOLOGY

A

aa	of each
ABG	arterial blood gas
ac	before meals
ADH	antidiuretic hormone
ADL	activities of daily living
ad lib	as much as desired
ADT	alternate-day therapy
ALT	alanine aminotransferase
AMA	against medical advice
AMI	acute myocardial infarction
AODM	adult-onset diabetes mellitus
ARC	AIDS-related complex
ASAP	as soon as possible
ASHD	arteriosclerotic heart disease
AST	aspartate aminotransferase

B

BE	barium enema; base excess
bid	twice a day
BMR	basal metabolic rate
B&O	belladonna and opium
BP	blood pressure
BRP	bathroom privileges
BUN	blood urea nitrogen

C

Ca	cancer; calcium
C&A	clinitest and acetest
CAD	coronary artery disease
caps	capsules
CBC	complete blood count
CC	chief complaint
CCU	Coronary Care Unit
CHF	congestive heart failure
CHO	carbohydrate
chol	cholesterol
CLL	chronic lymphocytic leukemia
CNS	central nervous system
C/O	complains of
COPD	chronic obstructive pulmonary disease
CPK	creatine phosphokinase
CRF	chronic renal failure
C&S	culture and sensitivity
CTZ	chemoreceptor trigger zone
CVA	cerebrovascular accident
CVP	central venous pressure

D

/d	per day
d	daily
DC (D/C)	discontinue
DJD	degenerative joint disease
DM	diabetes mellitus
DOE	dyspnea on exertion
DT	delirium tremens
Dx	diagnosis

E

ER	emergency room
ESR	erythrocyte sedimentation rate (sed rate)
et	and

F

F	Fahrenheit
FBS	fasting blood sugar
fl	fluid
fx	fracture; fraction

G

g	gram
GI	gastrointestinal
gtt	drop
GU	genitourinary

H

H	hour
HA	headache
Hct	hematocrit
Hgb	hemoglobin
hs	hour of sleep
HNT	hypertension

I

ICU	intensive care unit
IM	intramuscular
I&O	intake and output

IOP	intraocular pressure
IPPB	intermittent positive pressure breathing
IU	international units
IV	intravenous

J

JRA	juvenile rheumatoid arthritis

K

K	potassium
KVO	keep vein open

L

LDH	lactic dehydrogenase
LDL	low-density lipoproteins
LOC	level of consciousness
LP	lumbar puncture
lytes	electrolytes

M

mcg	microgram
MI	myocardial infarction (heart attack)
mL	milliliter
MOM	milk of magnesia
MS	morphine sulfate; multiple sclerosis; mitral stenosis

N

N	normal
NG	nasogastric
NPO	nothing by mouth
NS	normal saline
NGT	nitroglycerin
NVD	nausea, vomiting, diarrhea; neck vein distension

O

O_2	oxygen
OD	right eye
OOB	out of bed
OU	both eyes
OTC	over the counter (nonprescription)
OS	left eye

P

PAT	paroxysmal atrial tachycardia
PBI	protein-bound iodine
PC	after meals
PERRLA	pupils equal, round, react to light and accommodation
PERL	pupils equal and react to light
PID	pelvic inflammatory disease
PKU	phenylketonuria
PND	paroxysmal nocturnal dyspnea
PO	by mouth
postop	after surgery
preop	before surgery
prn	as needed
PT	prothrombin time
PZI	protamine zinc insulin

Q

qd	every day
qh	every hour (q2h, q3h, etc. – every 2 hours, every 3 hours, etc.)
qid	four times a day
qod	every other day

R

RA	rheumatoid arthritis; right atrium
RBC	red blood cell
REM	rapid eye movement
RF	rheumatoid factor
RHD	rheumatic heart disease; renal hypertensive disease
ROM	range of motion

S

SC	subcutaneous
sed	rate erythrocyte sedimentation rate (ESR)
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SL	sublingual
SOB	shortness of breath
SR	sedimentation rate (ESR)
STAT	as soon as possible

T

t	temperature
T3	triiodothyronine
T4	thyroxine
TB	tuberculosis
TEDS	elastic stockings
TIA	transient ischemic attack
tid	three times a day
TKO	to keep open
TLC	tender living care
TM	tympanic membrane
TPN	total parenteral nutrition
TPR	temperature, pulse, respiration
TSH	thyroidstimulating hormone

U

UGI	upper gastrointestinal
ung	ointment
URI	upper respiratory infection
UTI	urinary tract infection

V

VS	vital signs

W

WNL	within normal limits
Wt	weight

Appendix B
EXAMPLES OF COMBINATION DRUGS

ANTACID COMBINATIONS

Acid-X — calcium carbonate, acetaminophen

Advanced Formula Di-Gel — magnesium hydroxide, calcium carbonate, simethicone, sucrose

Alamag Plus — aluminum hydroxide, magnesium hydroxide, simethicone, parabens, sorbitol, saccharin

Alamag Suspension — aluminum hydroxide, magnesium hydroxide, sorbitol, sucrose, parabens

Alenic Alka — aluminum hydroxide, magnesium trisilicate, sodium bicarbonate, calcium stearate, sugar

Almacone — aluminum hydroxide, magnesium hydroxide, simethicone

Bromo-Seltzer Effervescent Granules — sodium bicarbonate, acetaminophen, citric acid, sugar

Calcium Rich Rolaids — magnesium hydroxide, calcium carbonate

Citrocarbonate Effervescent Granules — sodium bicarbonate, sodium citrate anhydrous

Di-Gel Liquid — aluminum hydroxide, simethicone, saccharin sorbitol, parabens

Extra Strength Maalox Suspension — aluminum hydroxide magnesium hydroxide, simethicone, parabens sorbitol, saccharin

Gas-Ban — simethicone, calcium carbonate

Gas-Ban DS Liquid — aluminum hydroxide, magnesium hydroxide, simethicone

Gaviscon Extra Strength Reliever Formula Liquid — aluminum hydroxide, magnesium carbonate, parabens EDTA, saccharin, sorbitol, simethicone, sodium alginate

Gaviscon Liquid — magnesium carbonate, parabens EDTA, saccharin, sorbitol, sodium alginate

Gelusil — aluminum hydroxide, magnesium hydroxide simethicone, dextrose, saccharin, sorbitol, sugar

Lowslum Plus Liquid — magaldrate, simethicone

Maalox — aluminum, magnesium hydroxide

Maalox Plus — aluminum hydroxide, magnesium hydroxide, simethicone, sugar

Maalox Suspension — aluminum hydroxide, magnesium hydroxide, saccharin, sorbitol, parabens

Marblen — magnesium carbonate, calcium carbonate

Marblen Liquid — calcium carbonate, magnesium carbonate

Mintox — aluminum, magnesium hydroxide

Mintox Plus — aluminum hydroxide, magnesium hydroxide, simethicone, saccharin, sorbitol, sugar

Mintox Suspension — aluminum hydroxide, magnesium hydroxide, parabens, sorbitol, saccharin

Mylagen Liquid — simethicone, parabens, sorbitol sucrose

Mylanta — aluminum hydroxide, magnesium hydroxide simethicone, sorbitol

Mylanta Gelcaps — calcium carbonate, magnesium carbonate parabens

Mylanta Liquid — simethicone, sorbitol

Nephrox Liquid — aluminum hydroxide, mineral oil

Original Alka-Seltzer Effervescent Tablets — sodium bicarbonate, aspirin, citric acid, phenylalanine

Riopan Plus — magaldrate, simethicone, sorbitol, sucrose

Riopan Plus Suspension — magaldrate, simethicone, saccharin sorbitol

Rulox # 2 — aluminum, magnesium hydroxide, simethicone

Rulox Plus — aluminum hydroxide, magnesium hydroxide simethicone, sugar, saccharin, dextrose

Rulox Suspension — aluminum hydroxide, magnesium hydroxide, parabens, sorbitol, saccharin

Simaal Gel 2 Liquid — aluminum hydroxide, magnesium hydroxide, simethicone

Tempo — aluminum hydroxide, magnesium hydroxide calcium carbonate, simethicone, sorbitol, corn syrup

ANTIASTHMATIC COMBINATIONS

Bronchial Capsules — theophylline, guaifenesin

Brondelate Elixir — theophylline, oxtriphylline, guaifenesin

Dilor-G Tablets — dyphylline, guaifenesin

Dyflex-G Tablets — dyphylline, guaifenesin

Glyceryl-T Liquid — theophylline, guaifenesin

Hydrophed Tablets — theophylline, hydroxyzine ephedrine sulfate

Lufyllin-EPG Tablets — dyphylline, ephedrine HCl guaifenesin, phenobarbitol

Marax Tablets — theophylline, hydroxyzine, ephedrine sulfate

Mundrane GG Tablets — theophylline, guaifenesin aminophylline anhydrous, ephedrine HCl phenobarbital

Primatene Dual Action Tablets — theophylline ephedrine, guaifenesin

Primatene Tablets — theophylline, phenobarbital ephedrine HCl

Quadrinal Tablets — theophylline, theophylline calcium salicylate, ephedrine HCl, potassium iodide, phenobarbital

Quibron Capsules — theophylline, guaifenesin

Slo-Phyllin GG Capsules — theophylline, guaifenesin

Slo-Phyllin GG Syrup — theophylline, guaifenesin

Tedrigen Tablets — theophylline, Phenobarbital, Ephedrine, HCl

Theodrine Tablets — theophylline, ephedrine HCl

Theolate Liquid — theophylline, guaifenesin

ANTIDIARRHEAL COMBINATIONS

Diasorb — activated attapulgite, sorbitol

Donnagel — attapulgite, saccharin

Kaodene Non-Narcotic — kaolin, pectin, bismuth subsalicylate sucrose

Kaolin w/ Pectin — kaolin, pectin

Kaopectate Maximum Strength — attapulgite, sucrose

Kapectolin — kaolin, pectin

K-C — kaolin, pectin, bismuth subcarbonate, peppermint flavor

ANTIHISTAMINE AND ANALGESIC COMBINATIONS

Aceta-Gesic Tablets — phenyltoloxamine citrate, acetaminophen

Coricidin HBP Cold and Flu Tablets — chlorpheniramine maleate, acetaminophen

Ed-Flex Capsules — phenyltoloxamine citrate, acetaminophen salicylamide

Major-Gesic Tablets — phenyltoloxamine citrate, acetaminophen

Percogesic — phenyltoloxamine citrate, acetaminophen

Percogesic Extra Strength Tablets — diphenhydramine HCl, acetaminophen

Phenylgesic Tablets — phenyltoloxamine citrate, acetaminophen

Tylenol PM Extra Strength Tablets — diphenhydramine HCl, acetaminophen

Tylenol Severe Allergy Tablets — diphenhydramine HCl acetaminophen

ANTIHYPERTENSIVE COMBINATIONS

Aldoclor — chlorothiazide, methyldopa

Aldoril — hydrochlorothiazide, methyldopa

Apresazide — hydrochlorothiazide, hydralazine

Avalide — hydrochlorothiazide, irbesartan

Capozide — hydrochlorothiazide, captopril

Chloroserpine — chlorothiazide, reserpine

Combipres — clonidine, chlorthalidone

Corzide — bendroflumethiazide, nadolol

Demi-Regroton Tablets — chlorthalidone, reserpine

Diovan HCT — hydrochlorothiazide, valsartan

Diutensen-R Tablets — methyclothiazide, reserpine

Enduronyl — methyclothiazide, desperidine

Esimil — hydrochlorothiazide, guanethidine monosulfate

Hydrap-ES — hydrochlorothiazide, reserpine, hydralazine HCl

Hydropres-50 — hydrochlorothiazide, reserpine

Hydro-Serp — hydrochlorothiazide, reserpine

Hydroserpine Tablets — hydrochlorothiazide, reserpine

Hyzaar — hydrochlorothiazide, losartan potassium

Inderide — hydrochlorothiazide, propranolol HCl

Inderide LA — hydrochlorothiazide, propranolol HCl

Lexxel Extended-Release — enalapril maleate, felodipine

Lopressor — hydrochlorothiazide, metoprolol

Lotensin HCT — hydrochlorothiazide, benazepril

Lotrel — amlodopine, benazepril

Marpres — hydrochlorothiazide, reserpine, hydralazine HCl

Metatensin Tablets — trichlormethiazide, reserpine

Minizide — polythiazide, prazosin

Prinzide — hydrochlorothiazide, lisinopril

Rauzide Tablets — rauwolfia, bendroflumethiazide

Regroton — chlorthalidone, reserpine

Salutensin Tablets — hydroflumethiazide, reserpine

Salutensin-Demi — hydrochlorothiazide, reserpine

Ser-Ap-Es — hydrochlorothiazide, reserpine, hydralazine HCl

Tarka — trandolapril, verapamil

Teczem Extended-Release — diltiazem maleate, enalapril maleate

Tenoretic — chlorthalidone, atenolol

Timolide — hydrochlorothiazide, timolol maleate

Tri-Hydroserpine — hydrochlorothiazide, reserpine hydralazine HCl

Uniretic — hydrochlorothiazide, moexipril HCl

Vaseretic — hydrochlorothiazide, enalapril maleate

Zestoretic — hydrochlorothiazide, lisinopril

Ziac — hydrochlorothiazide, bisoprolol fumarate

ANTITUSSIVE COMBINATIONS

Alka-Seltzer Plus Cold and Flu Liqui-Gels — dextromethorphan HBr, pseudoephedrine HCl, acetaminophen

Bromatane DX — dextromethorphan HBr, brompheniramine maleate, pseudoephedrine HCl

Cardec DM — dextromethorphan HBr, carbinoxamine maleate, pseudoephedrine HCl

Coricidin HBP Cough & Cold Tablets — dextromethorphan HBr, chlorpheniramine, acetaminophen

Dimetane-DX Cough — dextromethorphan HBr brompheniramine maleate, pseudoephedrine HCl

Hycodan Tablets or Syrup — hydrocodone bitartrate homatropine MBr

Hydromide Syrup — hydrocodone bitartrate, homatropine MBr

Nucofed Capsules — codeine phosphate, pseudoephedrine HCl

Promethazaine HCl/w Codeine Cough Syrup — codeine phosphate, promethazine HCl

Quad Tann Tablets — carbetapentane tannate, chlorpheniramine tannate, phenylephrine tannate ephedrine tannate

Robitussin Maximun Strength — dextromethorphan HBr, pseudoephedrine HCl

Rynatuss Tablets — carbetapentane tannate, chlorpheniramine tannate, phenylephrine tannate, ephedrine tannate

Sudafed Non-Drowsy Severe Cold Formula Maximum Strength Tablets – dextromethorphan HBr, pseudoephedrine HCl, acetaminophen

Tannic-12 Tablets — carbetapentane tannate, chlorpheniramine tannate

Tricodeine Cough & Cold Liquid — codeine phosphate pyrilamine maleate

Trionate Tablets — carbetapentane tannate, chlorpheniramine tannate

Tussafed Syrup — dextromethorphan HBr, carbinoxamine maleate, pseudoephedrine HCl

Tussend Tablets — hydrocodone bitartrate, chlorpheniramine pseudoephedrine HCl

Vanex HD Liquid — hydrocodone bitartrate, chlorpheniramine phenylephrine HCl

DECONGESTANT AND EXPECTORANT COMBINATIONS

Allegra-D Tablets — pseudoephedrine HCl, fexofenadine HCl

Allerfrim Syrup — pseudoephedrine HCl, triprolidine HCl

Aprodine Tablets — pseudoephedrine HCl, triprolidine HCl

Benadryl Allergy & Sinus Tablets — pseudoephedrine HCl, diphenhydramine citrate, diphenhydramine HCl

Bromfed Capsules — pseudoephedrine HCl, brompheniramine maleate

Bromfed Syrup — pseudoephedrine HCl, brompheniramine maleate

Claritin D — pseudoephedrine HCl, loratadine

Deconamine Syrup — pseudoephedrine HCl, chlorpheniramine maleate

Dynex Tablets — pseudoephedrine, guaifenesin

Ed A Hist Tablets — phenylephrine HCl, chlorpheniramine maleate

Genac Tablets — pseudoephedrine HCl, triprolidine HCl

Guaifed Capsules — pseudoephedrine, guaifenesin

Guiatuss PE Liquid — pseudoephedrine, guaifenesin

Histade Capsules — pseudoephedrine HCl chlorpheniramine maleate

Histatab Plus Tablets — phenylephrine HCl, chlorpheniramine maleate

Histex Liquid — pseudoephedrine HCl, chlorpheniramine maleate

Lodrane Liquid — pseudoephedrine HCl, brompheniramine maleate

Phenergan VC Syrup — phenylephrine HCl, promethazine

Profen II Tablets — pseudoephedrine, guaifenesin

Pseudovent Capsules — pseudoephedrine, guaifenesin

Respahist Capsules — pseudoephedrine HCl, brompheniramine maleate

Respaire-60 SR Capsules — pseudoephedrine, guaifenesin

Rinade B.I.D. Capsules — pseudoephedrine HCl, chlorpheniramine maleate

Robafen PE Liquid — pseudoephedrine, guaifenesin

Robitussin Cold Sinus and Congestion — pseudoephedrine guaifenesin, acetaminophen

Robitussin PE Liquid — pseudoephedrine, guaifenesin

Rondec Tablets — pseudoephedrine HCl, carbinoxamine maleate

Ryna Liquid — pseudoephedrine HCl, chlorpheniramine maleate

Rynatan Tablets — phenylephrine tannate, chlorpheniramine tannate

Severe Congestion Tussin Softgels — pseudoephedrine guaifenesin

Sinutab Nondrying Liquid Caps — pseudoephedrine guaifenesin

Sudafed Cold and Allergy Maximum Strength — pseudoephedrine HCl, chlorpheniramine maleate

Tanafed Suspension — pseudoephedrine, chlorpheniramine tannate

Versacaps Capsules — pseudoephedrine, guaifenesin

DECONGESTANT, ANTIHISTAMINE, AND ANALGESIC COMBINATIONS

Alka-Seltzer Plus Cold Medicine — phenylephrine HCl chlorpheniramine maleate, acetaminophen

Decodult Tablets — pseudoephedrine HCl, chlorpheniramine maleate, acetaminophen

Kolephrin Tablets — pseudoephedrine HCl, chlorpheniramine maleate, acetaminophen

Simplet Tablets — pseudoephedrine HCl, chlorpheniramine acetaminophen

Sinutab Sinus Allergy, Maximum Strength — pseudoephedrine HCl, chlorpheniramine maleate, acetaminophen

Tavist Allergy/Sinus/Headache Tablets — pseudoephedrine HCl, clemastine fumarate, acetaminophen

TheraFlu Flu and Cold Medicine Original Formula Powder — pseudoephedrine HCl, chlorpheniramine maleate, acetaminophen

Triaminic Cold, Allergy, Sinus Medicine — pseudoephedrine HCl, chlorpheniramine maleate, acetaminophen

Tylenol Sinus NightTime Maximum Strength Tablets — pseudoephedrine HCl, diphenhydramine HCl, acetaminophen

DECONGESTANT, ANTIHISTAMINE, AND ANTICHOLINERGIC COMBINATIONS

AH-Chew Tablets — phenylephrine HCl, chlorpheniramine maleate, methscopolamine nitrate

D.A. Chewable Tablets — phenylephrine HCl, chlorpheniramine maleate, methscopolamine nitrate

Dallergy Syrup or Tablets — phenylephrine HCl, chlorpheniramine maleate, methscopolamine nitrate

Dehistine Syrup — phenylephrine HCl, chlorpheniramine maleate, methscopolamine nitrate

Extendryl Syrup — phenylephrine HCl, chlorpheniramine maleate, methscopolamine nitrate

Pannaz Tablets or Syrup — phenylephrine HCl, chlorpheniramine maleate, methscopolamine nitrate

Rescon-MX Tablets — phenylephrine HCl, chlorpheniramine maleate, methscopolamine nitrate

DIURETIC COMBINATIONS

Aldactazide — spironolactone, hydrochlorothiazide

Amiloride/hydrochlorothiazide — generic

Dyazide — triamterene, hydrochlorothiazide

Maxzide — triamterene, hydrochlorothiazide

Maxzide-25MG — triamterene, hydrochlorothiazide

Modiuretic — amiloride, hydrochlorothiazide

Spironolactone/hydrochlorothiazide — generic

Triamterene/hydrochlorothiazide — generic

ESTROGEN AND PROGESTIN COMBINATIONS

Activella — estradiol, norethindrone acetate

CombiPatch — estradiol, norethindrone

Femhrt — ethinyl estradiol, norethindrone acetate

Ortho-Prefest — estradiol, norgestimate

Premephase — conjugated estrogens, medroxyprogesterone acetate

Prempro — conjugated estrogens, medroxyprogesterone acetate

ESTROGEN AND ANDROGEN COMBINATIONS, ORAL AND PARENTERAL

Depo-Testadiol — estradiol cypionate, testosterone cypionate

Depotestogen — estradiol cypionate, testosterone cypionate

Duo-Cyp — estradiol cypionate, testosterone cypionate

Estratest — esterified estrogens, methyltestosterone

Estratest H.S. — esterified estrogens, methyltestosterone

Valertest No. 1 — estradiol valerate, testosterone enanthate

GLAUCOMA COMBINATIONS

E-Pilo — pilocarpine, epinephrine

E-Pilo-2 — pilocarpine, epinephrine

E-Pilo-4 — pilocarpine, epinephrine

P6E1 — pilocarpine, epinephrine

GASTROINTESTINAL ANTICHOLINERGIC COMBINATIONS

Antrocol Elixir — atropine sulfate, phenobarbital, alcohol

Barbidonna — atropine, scopolamine HBr, hyoscyamine sulfate, phenobarbital

Bellacane Elixir — atropine, scopolamine HBr, hyoscyamine

Bellacane SR Tablets — l-alkaloids of belladonna, phenobarbital ergotamine tartrate

Bellergal-S Tablets — l-alkaloids of belladonna, phenobarbital ergotamine tartrate

Butibel Elixir — belladonna extract, butabarbital sodium, alcohol, sucrose, saccharin

Butibel Tablets — belladonna extract, butabarbitol

Chardonna-2 Tablets — belladonna extract, phenobarbital

Donnatal Elixir — atropine, scopolamine HBr, hyoscyamine HBr or sulfate, phenobarbital, alcohol, sucrose, saccharin

Donnatal Capsules and Tablets — atropine, scopolamine HBr, hyoscyamine sulfate, phenobarbital

Folergot-DF Tablets — l-alkaloids of belladonna, phenobarbital, ergotamine tartrate

Hyosophen Tablets — atropine, scopolamine HBr hyoscyamine sulfate, phenobarbital

Librax Capsules — clindinium, chlordiazepoxide HCl

Phenerbel-S Tablets — l-alkaloids of belladonna, phenobarbital ergotamine tartrate

Spasmolin Tablets — atropine, scopolamine HBr hyoscyamine sulfate, phenobarbital

ISONIAZID COMBINATIONS

Rifamate — rifampin, isoniazid

Rifater — rifampin, isoniazid, pyrazinamide

LAXATIVE COMBINATIONS

DDS 100 Plus Capsules — docusate, casanthranol

Doxidan Capsules — docusate, casanthranol, sorbitol

Nature's Remedy — cascara sagrada, aloe, lactose

Peri-Colace — docusate, casanthranol, sorbitol, parabens

Senokot-S tablets — docusate, senna concentrate, lactose Ophthalmic Decongestant and Antihistamine Combinations

Naphcon-A Solution — naphazoline HCl, pheniramine maleate

Vasocon-A Solution — naphazoline HCl, antazoline phosphate Ophthalmic Antibiotic Combinations

AK-Poly-Bac Ophthalmic Ointment — polymyxin B sulfate bacitracin zinc

AK-Spore — polymyxin B Sulfate, neomycin, bacitracin zinc

Neosporin Ophthalmic Ointment — polymyxin B sulfate neomycin, bacitracin zinc

Polysporin Ophthalmic Ointment — polymyxin B sulfate bacitracin zinc

Polytrim Ophthalmic Solution — polymyxin B sulfate trimethoprim sulfate

PERIPHERAL VASODILATOR COMBINATIONS

Lipo-Nicin — niacin, niacinamide, vitamins C, B_1, B_2, B_6

SEDATIVE AND HYPNOTIC COMBINATIONS

Tuinal — amobarbital, secobarbital

SKELETAL MUSCLE RELAXANT COMBINATIONS

Carisoprodol Compound — carisoprodol, aspirin

Flexaphen — chlorzoxazone, acetaminophen

Lobac — salicylamide, phenyltoloxamine, acetaminophen

Norgesic Forte — orphenadrine citrate, aspirin, caffeine

Norgesic — orphenadrine citrate, aspirin, caffeine

Robaxisal — methocarbamol, aspirin

Sodol Compound — carisoprodol, aspirin

Soma Compound — carisoprodol, aspirin

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LIST OF ABBREVIATIONS

AC	— acetylcholine
ACE	— angiotensin-converting enzyme
ACTH	— adrenocorticotropin
ADH	— antidiuretic hormone
ADP	— adenosine-diphosphate
ATP	— adenosine-triphosphate
ATPase	— adenosine triphosphatase
AV	— atrioventricular
BBB	— blood-brain barrier
BUN	— blood urea nitrogen
cAMP	— cyclic adenosine monophosphate
CAT	— choline acetyltransferase
cGMP	— cyclic guanosine-monophosphate
CHF	— congestive heart failure
CNS	— central nervous system
COMT	— catechol O-methyltransferase
CSF	— cerebrospinal fluid
CVS	— cardiovascular system
DOC	— desoxycorticosterone
DOCSA	— desoxycorticosterone acetate
DOPA	— dihydroxyphenylalanine
ECG	— electrocardiogram
EDRF	— endothelium-derived relaxing factor
EPSP	— excitatory postsynaptic potential
FAD	— flavin adenine dinucleotide
FMN	— flavin mononucleotide
FSH	— follicle-stimulating hormone
G (g)	— gram
GABA	— gamma-aminobutyric acid
GI	— gastrointestinal
GI	— gastrointestinal
GnRH	— gonadotropin-releasing hormone
H (h)	— hour
HDL	— high-density lipoproteins
HETEs	— hydroxyeicosatetraenoic

HMG — human menopausal gonadotropins
HPETEs — hydroperoxyeicosateraenoic
IF — intrinsic factor
IM (i.m.) — intramuscular
ISA — intrinsic sympathomimetic activity
IPSP — inhibitory postsynaptic potential
IU — international unites
IV (i.v.) — intravenous
Las — local anesthetics
LH — luteinizing hormone
LSD — lysergic acid diethylamide
MAC — minimum alveolar concentration
MAO — monoamine oxidase
MD — moment dose
NAD — nicotinamide adenine dinucleotide
NADP — nicotinamide adenine dinucleotide phosphate
NAPA — n-acetylprocainamide
NO — nitric oxide
NREM — non-rapid eye movement
NSAIDs — nonsteroidal anti-inflammatory drugs
PABA — paraaminobenzoic acid
PAG — periaqueductal gray
PASA — para-aminosalicylate sodium
PIH — pregnancy-induced hypertension
PRL — prolactin
PTH — parathyroid hormone
REM — rapid eye movement
SA — sinuatrial
SC (s.c.) — subcutaneous
SH — sulfhydryl
SSRI — serotonin-reuptake inhibitors
T1/2 — half-life period
TCAs — tricyclic antidepressants
TSH — thyrotropin
VMA — vanillylmandelic acid

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