The scope and historical development of modern pharmacology. Basic pharmacological terms, definitions. Drug regulation. Types of pharmacotherapy and drug effects.

General information

- 15 lectures
- topics are related to the general pharmacology, linked to practical exercises
- not all topics in the literature in comprehensive form, therefore, be advised to attend lectures
- practical exercises are registered. To get a credits a student has to pass 3 written tests

Contens of lectures

- March, 2: Drug-life cycle. Innovative and generic products. Biosimilars. Orphan drugs.
- March, 9: Drug delivery approaches, routes of administration, prolonged release preparations.
- March, 16: Pre-clinical and clinical drug development. Drug registration guidance. Regulation and guidelines for "Good Clinical Practice".
- March, 23: Concentration-response relationship. Pharmacokinetic principles. Drug absorption, distribution, metabolism and elimination. Changes of drug effects after the repeated administration.
- March, 30: Mechanisms of drug action, non-specific, specific. Receptors and ligand binding. Receptor subtypes, autoreceptors, heteroreceptors.

Contens of lectures

- April, 6: Physiological and pathological factors influencing drug effects. Drug interactions. Assessment of the seriousness of drug interactions. Adverse drug effects.
- April, 13: Purposeful pharmacotherapy. Importance of the pharmacological anamnesis, monitoring of drug pharmacotherapy, risk of pharmacotherapy.
- April, 20: The management of poisoning
- April, 27: Drug therapy in children, general principles, pharmacokinetic and pharmacodynamic peculiarities. Pharmacotherapy in neonates.
- May, 4: Specificities of pharmacotherapy in the elderly.
- May, 11: Pharmacogenetic, pharmacogenomic and their clinical implication.

Contens of lectures

- **May, 18: Principles of pharmacovigilance, duties of physicians and pharmaceutical companies, general rules in drug promotion.**
- **May, 25: Basic principles of pharmacoeconomics, types of pharmacoeconomic analyses and their relevant use in clinical practice.**
- **June, 1: . Immunomodulant and systemic enzyme pharmacotherapy.**

Required literature

- **Rang & Dale's pharmacology 7th Edition:with student consult online access. Edited by H. P. Rang. : Churchill Livingstone, 2012.**
- https://is.muni.cz/auth/el/1411/jaro2009/VLFA0621c/um/Practicals_in_Pharmacology_ENGL.pdf?fakulta=1411;obdobi=4504;kod=VLFA0621c

Recommended literature

- **Ritter, James M. - Lewis, Lionel D. - Mant, Timothy G.K. - Ferro, Albert. A Textbook of Clinical Pharmacology and Therapeutics, 5th Ed., Hodder Arnold, 2008. 465 s. ISBN 978-0-340-90046-8**
- **Waller, Derek - Renwick, Andrew G. - Hillier, Keith. Medical pharmacology and therapeutics. 3rd ed. New York : Elsevier Saunders, 2009. ix, 744 p. ISBN 0-7020-2991-2.**

Contens of lecture

- **The scope and historical development of modern pharmacology**

History of Pharmacology

- **The pharmacology as the exact science was founded in the fifties of the 19th century…**

Prof. Rudolf Buchheim (1820-1879) - founder of experimental pharmacology

- **1847 - Rudolf Buchheim became the first professor of a separate Department of Pharmacology, University of Dorpat, Estonia**

History of Pharmacology

Prof. Oswald Schmiedeberg (1838-1921) - founder of modern pharmacology)

- **graduating in r.1866, then worked at the same University as a Professor. Buchheim, respectively under his leadership.**
- **1872 - Professor of Pharmacology at the University of Strassburg "Muscarinic effects" are comparable with electric stimulation n.vagus ...**
- **1878 - publication of results in the Outline of Pharmacology**

Drug explosion

- the huge development of the drugs in the last century, mainly after 2nd war
- from „simple chemicals“ to the current treatment including „targeted or biological therapy“, advanced therapy (gene and cell therapy, tissue engineering)…
- progress in cellular, molecular medicine and methods, era of pharmacogenomics, pharmacogenetics, proteomics and metabolomics….

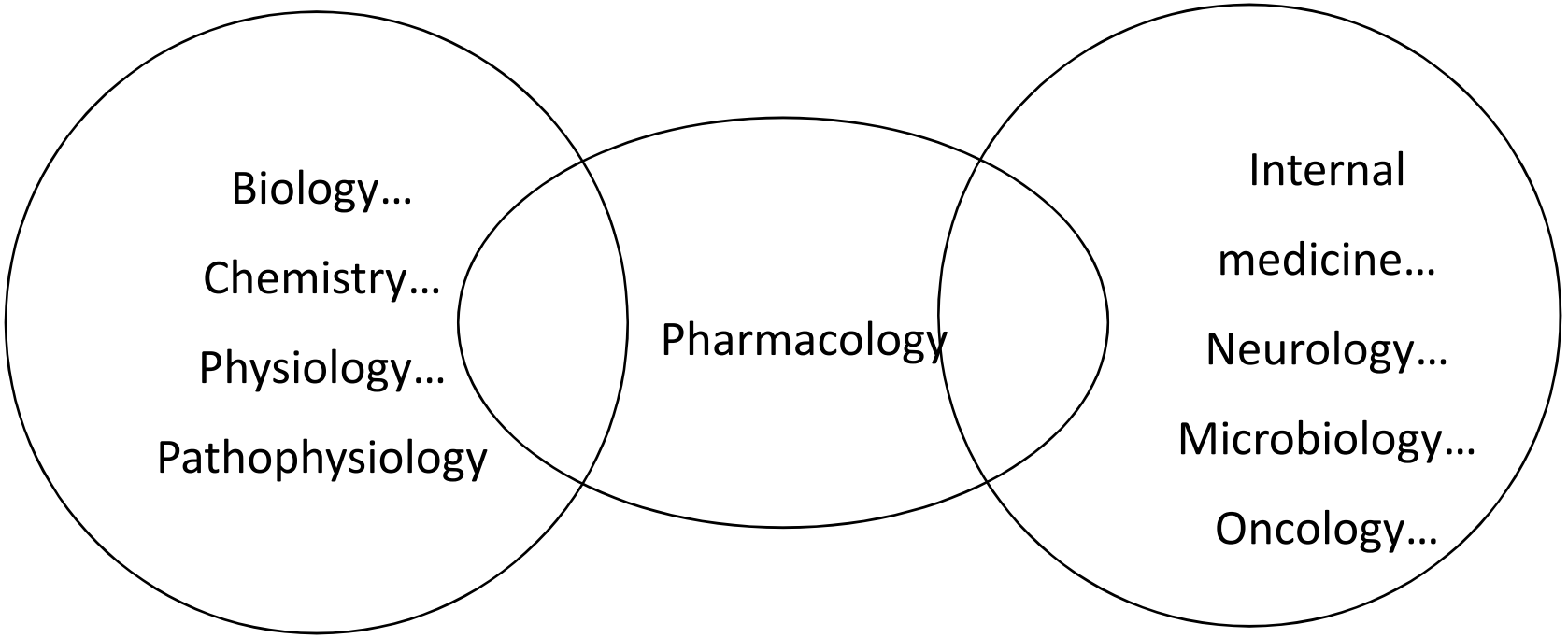
Drug explosion

- new challenge - how to harmonize the new sciences with the ‘old’ pharmacology

- be necessary to define a core of knowledge in pharmacology for every degree offered

Pharmacology is /and has to be/ interdisciplinary science…

- **interdisciplinary collaboration with the preclinical and clinical disciplines**



Definition of Pharmacology

- from the Greek pharmakon (φάρμακον) means "medicine" logos (λόγος) means "science")

- Definition: Pharmacology is the science that deals with interactions between substances (xenobiotics) and a living organism, at all levels (molecular, cellular, organ and whole organism)

Clinical Pharmacology

- The term "applied or clinical pharmacology" was first used by Austrian pharmacologist O. Love in 1910
- In the world its emergence occurs in the fifties of last century, especially in the U.S. and Great Britain.
- In the U.S. it was Harry Gold, a pharmacologist of Russian origin, who in 1952 became the first university professor of clinical pharmacology.
- In 1954 it established the first department of clinical pharmacology at Johns Hopkins University School of Medicine in Baltimore, led by prof. Lasagna L.

Clinical Pharmacology

- In 1960 it published a major book "Clinical Pharmacology", written by prof. Laurence D. R., UK pharmacologist
- At that time, controlled clinical trials have become a new entity…as a part of evidence based medicine

SCIENCE

Vol. 103, No. 2675 Friday, April 5, 1946

The Biological Actions and Therapeutic Applications of the B-Chloroethyl Amines and Sulfides

Alfred Gilman, Major, and Frederick S. Philips, 1st Lieutenant, SnC, AUS
Pharmacology Section, Medical Division, CWS, Edgewood Arsenal, Maryland

Science 103: 409-436, 1946

The fact that agents classified as "confidential" were involved in the above studies has heretofore precluded the possibility of presenting the results in the open literature. **(Page 409)**

The first clinical trial of the nitrogen mustards (65) was conducted on a group of six patients in the terminal stages of various neoplastic diseases. in two cases of lymphosarcoma in which X-ray therapy had been discontinued, a rapid dissolution of large tumor masses followed a course of injections. The results were sufficiently encouraging to warrant further clinical experimentation. To date approximately 150 patients have been treated by several groups of investigators (66-68). **(Page 414)**

References

65. GILMAN, A., GOODMAN, L., LINDSKOG, G.E. and DOUGHERTY, J., 1942-43.
66. JACOBSON, L.O., BARRON, E.S.G., DICK, G.F., SPURR, C.L. SMITH, T., and LUSHBAUGH, C.C., 1943-45.
67. GOODMAN, L., DAMESHEK, W., WINTROBE, M.M. and GOODMAN, M., 1943-45.
68. KARNOFSKI, D., CRAVER, L.F., and ABELS, J.C., 1945-46.

Nitrogen Mustard Therapy

Use of Methyl-Bis(Beta-Chloroethyl)amine Hydrochloride and Tris(Beta-Chloroethyl)amine Hydrochloride for Hodgkin's Disease, Lymphosarcoma, Leukemia and Certain Allied and Miscellaneous Disorders

Louis S. Goodman, M.D., Salt Lake City
Maxwell M. Wintrobe, M.D., Salt Lake City
William Dameshek, M.D., Boston
Morton J. Goodman, M.D., Portland, Ore.
Major Alfred Gilman
Medical Corps, Army of the United States
and
Margaret T. McLennan, M.D., Salt Lake City

JAMA 132:126-132, 1946

The New England
Journal of Medicine

Volume 238 JUNE 3, 1948 Number 23

TEMPORARY REMISSIONS IN ACUTE LEUKEMIA IN CHILDREN PRODUCED BY FOLIC ACID ANTAGONIST, 4-AMINOPTEROYL-GLUTAMIC ACID (AMINOPTERIN)*

SIDNEY FARBER, M.D.,† LOUIS K. DIAMOND, M.D.,‡ ROBERT D. MERCER, M.D.,§
ROBERT F. SYLVESTER, JR., M.D.,¶ AND JAMES A. WOLFF, M.D.‖

BOSTON

IT IS the purpose of this paper to record the results of clinical and hematologic studies on 5 children with acute leukemia who received a folic acid antagonist, 4-aminopteroyl-glutamic acid (aminopterin). Preliminary observations on the effect of this compound in the treatment of leukemia were obtained from studies on a four-year-old girl with a rapidly progressing acute

BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor W. S. Blacklock, Professor C. Cameron, Professor N. B. Capon, Dr. R. Cruickshank, Professor J. H. Gaddum, F. R. G. Heaf, Professor A. Bradford Hill, Dr. L. E. Houghton, Dr. J. Clifford Hoyle, Professor Raistrick, Dr. J. G. Scadding, Professor W. H. Tytler, Professor G. S. Wilson, and Dr. P. D'Arcy Hart (secretary). The centres at which the work was carried out and the specialists in charge of patients and bacteriological work were as follows:

Brompton Hospital, London.—Clinician: Dr. J. W. Crofton, Streptomycin Registrar (working under the direction of the honorary staff of Brompton Hospital); Pathologists: Dr. J. W. Clegg, Dr. D. A. Mitchison.

Colindale Hospital (L.C.C.), London.—Clinicians: Dr. F. V. Hurford, Dr. B. J. Douglas Smith, Dr. W. E. Snell; Pathologists (Central Public Health Laboratory): Dr. G. B. Forbes, Dr. H. D. Holt.

Harefield Hospital (M.C.C.), Harefield, Middlesex.—Clinicians: Dr. R. H. Brent, Dr. L. E. Houghton; Pathologist: Dr. E. Nassau.

Bangour Hospital, Bangour, West Lothian.—Clinician: Dr. I. D. Ross; Pathologist: Dr. Isabella Purdie.

Killingbeck Hospital and Sanatorium, Leeds.—Clinicians: Dr. W. Santon Gilmour, Dr. A. M. Reevie; Pathologist: Professor J. W. McLeod.

Northern Hospital (L.C.C.), Winchmore Hill, London.—Clinicians: Dr. F. A. Nash, Dr. R. Shoulman; Pathologists: Dr. J. M. Alston, Dr. A. Mohun.

Sully Hospital, Sully, Glam.—Clinicians: Dr. D. M. E. Thomas, Dr. L. R. West; Pathologist: Professor W. H. Tytler.

The clinicians of the centres met periodically as a [illegible] chairmanship of Dr. Geoffrey Marshall; so also did the pathologists under the chairmanship of Dr. R. Cruickshank. Dr. Marc Daniels, of the Council's scientific staff, was responsible for the clinical co-ordination of the trials, and he also prepared the report for the Committee, with assistance from Dr. D. A. Mitchison on the analysis of laboratory results. For the purpose of final analysis the radiological findings were assessed by a panel composed of Dr. L. G. Blair, Dr. Peter Kerley, and Dr. Geoffrey S. Todd.

Introduction

In 1946 a special committee of the Medical Research

if based on adequately controlled clinical trials (Hinshaw and Feldman, 1944). The one controlled trial of gold treatment

British Medical Journal 2:769-782, October 30, 1948

Contens of lecture

- The scope and historical development of modern pharmacology
- **Definition of substance and medicinal product**

Substance ?

A substance shall mean any matter irrespective of origin which may be:

- a) human, e.g. human blood, its constituents, and human blood products;
- b) animal, e.g. micro-organisms, toxins, whole animals, parts of organs, animal secretions, extracts or blood products;
- c) vegetable; or
- d) chemical.

Medicinal product ?

A medicinal product shall mean

- a) a substance or combination of substances presented as having therapeutic or preventive properties in the case of human or animal diseases; **or**
- b) a medicinal product shall also mean any substance or combination of substances which may be used or administered to human beings or used or administered to animals with a view to **restoring, correcting or modifying the physiological functions by means of a pharmacological, immunological or metabolic effect or with a view to making a medical diagnosis.**

Medicinal products shall be…

- human immunological medicinal products consisting of vaccines, toxins, serums or allergen products
- human autogenic vaccines prepared for a specific patient from pathogens or antigens obtained exclusively from this patient;
- homeopathic products prepared from homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia
- radiopharmaceuticals, which shall mean medicinal products which, when ready for use, contain one or more radionuclides (radioactive isotopes) included for a medicinal purpose;

Medicinal products shall be…

- blood derivatives which shall mean industrially prepared medicinal products derived from human blood or human plasma; blood derivatives; include, in particular, albumin, coagulating factors, and immunoglobulins of human origin;
- vegetable medicinal products containing as active ingredients at least one vegetable
- substance or at least one vegetable preparation or at least one vegetable substance in combination with at least one vegetable preparation;
- transfusion products

Contens of lecture

- The scope and historical development of modern pharmacology
- Definition of substance and medicinal product
- **Regulation**

Why we need the regulation?

- International regulations
- Safety of the patients
- Efficacy approved in controlled trials
- …..???

The area of the regulation..

- research, production, preparation, distribution and elimination of drugs
- registration, post-marketing surveillance, prescribing and dispensing of medicinal products

- keeping records of the above activities

European legislation (1)

- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to **medicinal products for human use**
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of **good clinical practice in the conduct of clinical trials on medicinal products** for human use
- Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003, setting standards of **quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components**

European legislation (2)

- Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of **good laboratory practice**
- Council Directive 2001/18/EC of 12 March 2001 on the deliberate release into the environment of **genetically modified organisms** and repealing Council Directive 90/220/EEC.
- Council Directive 96/23/EC of 29 April 1996 on **measures to monitor certain substances and residues** thereof in live animals and animal products.
- Council Directive 2003/85/EC of 29 September 2003 on Community measures for the **control of foot-and-mouth disease** repealing Directive 85/511/EEC

European legislation (3)

- Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for **paediatric use** and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004.

- Council Regulation (EC) No 141/2000 of 16 December 1999 on **orphan medicinal products.**

Czech legislation

- **ACT of 6 December 2007 on Pharmaceuticals and on Amendments to Some Related Acts (the Act on Pharmaceuticals)**


SÚKL
Státní ústav pro kontrolu léčiv

The main responsibilities…

- Approval of clinical trials
- Monitoring of the use of unregistered medicines and on specific treatment programs
- Supervision over the implementation of production, distribution, preclinical testing, clinical evaluation, and operation of pharmacies selling restricted drugs, including the authorization of certain activities and issuance of certificates
- Supervision over advertising

The main responsibilities…

- Supervision of the use of medical devices
- Pharmacovigilance and vigilance of medical devices and associated safety interventions
- Registration of Medicinal Products and its amendments and extensions, including decisions about dispensing without a prescription and the inclusion of selected pharmaceuticals

Contens of lecture

- The scope and historical development of modern pharmacology
- Definition of substance and medicinal product
- Regulations
- Types of pharmacotherapy and drug effects.

Three Phases of Drug Action

I. PHARMACEUTICAL PHASE

II. PHARMACOKINETIC PHASE

III. PHARMACODYNAMIC PHASE

I. PHARMACEUTICAL PHASE

- A solid drug (tablet) has to disintegrate before it can be absorbed
- The process where a solid (tablet) goes into solution is known as dissolution
- ALL drugs must be in solution to cross biologic membranes

II. PHARMACOKINETIC PHASE

- What the body does to the drug- refers to the study of how the body processes drugs
- It includes the 4 basic components of : Absorption , Distribution, Metabolism (Biotransformation) , Excretion
- Acronym ADME

Drug Absorption varies by form

Liquids, elixirs, syrups	Fastest
Suspension solutions	↓
Powders	↓
Capsules	↓
Tablets	↓
Coated tablets	↓
Enteric-coated tablets	Slowest

Distribution

- Distribution: the transport of drugs from the blood to the site of action. A drug must be distributed to its site of action to have an effect
- Drugs are also distributed to tissues where it has no effect. Competition for drug binding sites affects the amount of drug available for action in the body.

METABOLISM

- **Biotransformation: process by which the body changes the chemical structure of a drug to another form called a metabolite.**
- **Metabolite: a more water soluble compound that can be easily excreted. The major organ for this process is the liver**

Excretion

- Excretion: process where drugs are removed from the body. Kidneys are the major organs of excretion.
- Lungs excrete gaseous drugs.
- Biliary excretion (bile & feces) is important for a few drugs. These drugs may be reabsorbed when passing through the intestines from the liver
(enterohepatic re-circulation).
- Intestines, sweat, saliva and breast milk constitute minor routes of drug excretion.

III. PHARMACODYNAMIC PHASE

- **What a drug does to the body- refers to the study of the mechanism of drug action on living tissue.**
- **Drugs *may increase, decrease or replace* enzymes, hormones or body metabolic functions.**
- **Chemotherapeutic drugs alter an abnormal parasite or growth on the body such as bacteria, viruses or neoplastic tissue. *examples: antibiotics and antineoplastic drugs*.**

THEORY OF DRUG-RECEPTOR INTERACTIONS

- The majority of drugs are believed to exert their effects by combining with a specialized area on the cell or within the cell called receptors. *Drug + Receptor → Drug receptor (binding) = Response*
- A drug receptor may be on the cell surface or within the cell
- Receptors come in many shapes that are specific for particular drugs.
- The greater the degree of specificity and selectivity for receptors, the fewer undesirable side effects and the greater drug efficacy.

Types of Drug-Receptor Interactions

- **Agonists: Drug that has the ability to produce a desired therapeutic effect when bound to the receptor.**
- **Antagonists: Drugs that bind well to the receptor but produce no receptor response. This can prevent other drugs from having an effect, thus they are called blockers.**

- **Therapeutic range: plasma drug concentration between minimum and toxic concentrations.**
- **Loading doses: higher amount of drug given once or twice to achieve maximum effective dose quickly**
- **Maintenance dose: intermittent doses given to maintain plasma levels.**