INTRODUCTION TO THE STUDY OF PHARMACOLOGY

Notes for Students

This study material is exclusively for students of general medicine and stomatology in Pharmacology I course. It contains only basic notes of discussed topics, which should be completed with more details and actual information during practical courses to make a complete material for test or exam studies. Which means that without your own notes from the lesson this presentation IS NOT SUFFICIENT for proper preparation for neither tests in practicals nor the final exam.

Literature

Rang, H.P. a kol. Rang and Dale‘s pharmacology 8th ed.(2016)

http://web.b.ebscohost.com/ehost/ebookviewer/ebook/bmxlYmtfXzExNjA0OTNfX0FO0?sid=82e7fdcf-dd4c-43d3-b3a3-7b4b24c21b8e@sessionmgr103&vid=0&format=EB&lpid=lp_1&rid=0

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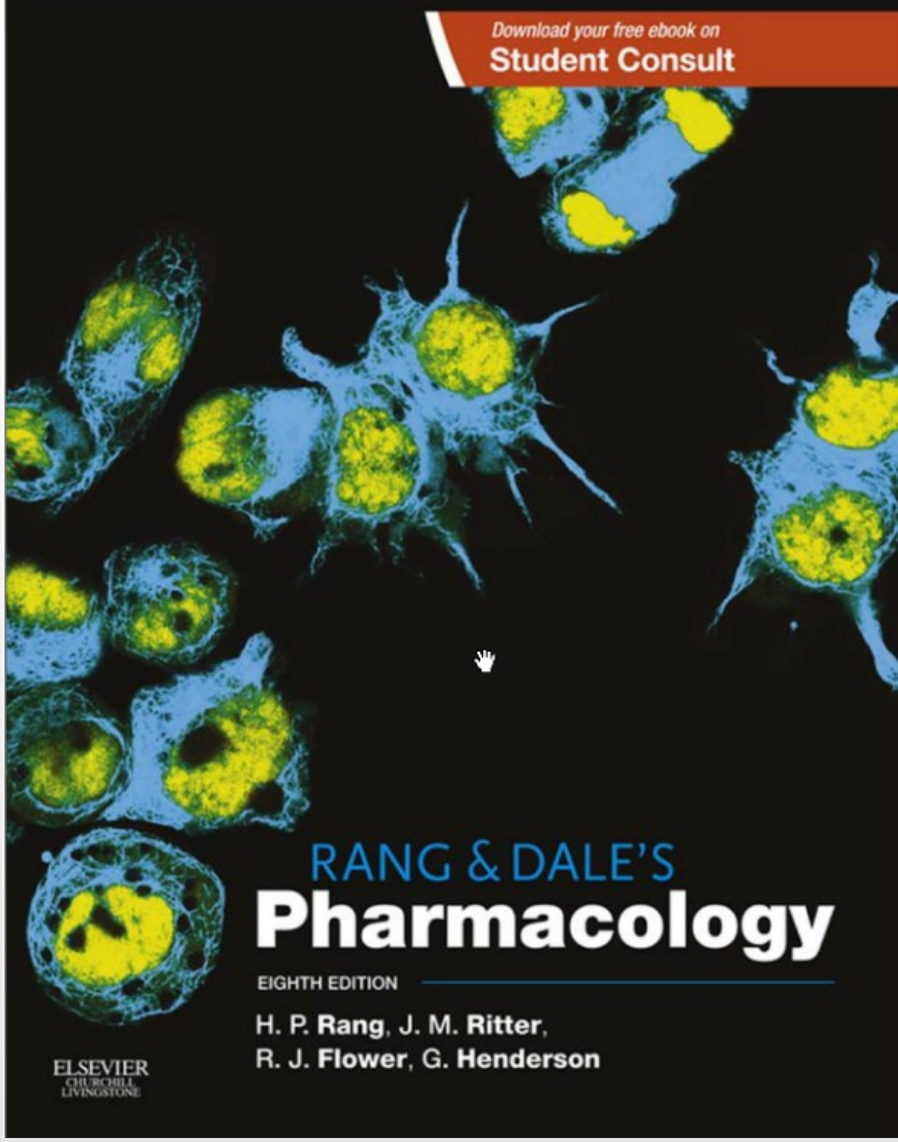
8th ed. Churchill Livingstone, 2016.

available online

http://www.elsevier-etextbooks.com/bookshelf

Hard copy available

BOOKSHOP IN CAMPUS



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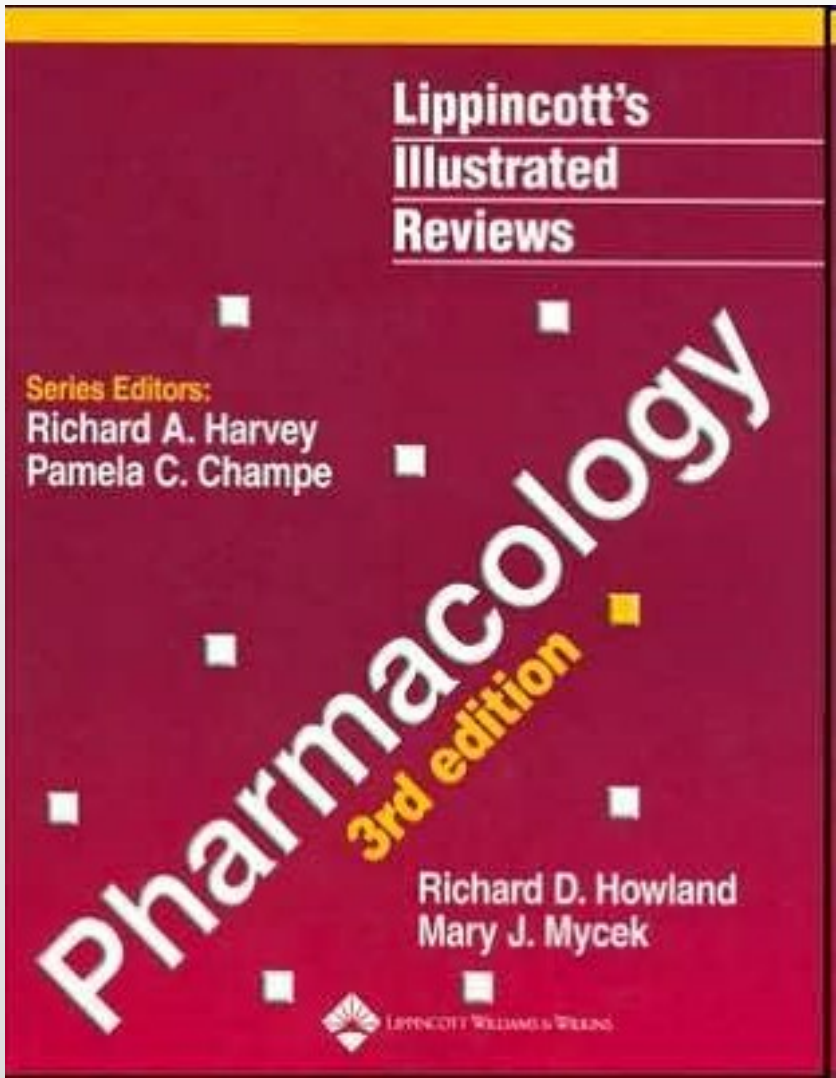
Pharmacology. Edited by R. D. Howland,M.J. Mycek. 3rd ed. Philadelphia : Lippincott Williams & Wilkins, 2006.



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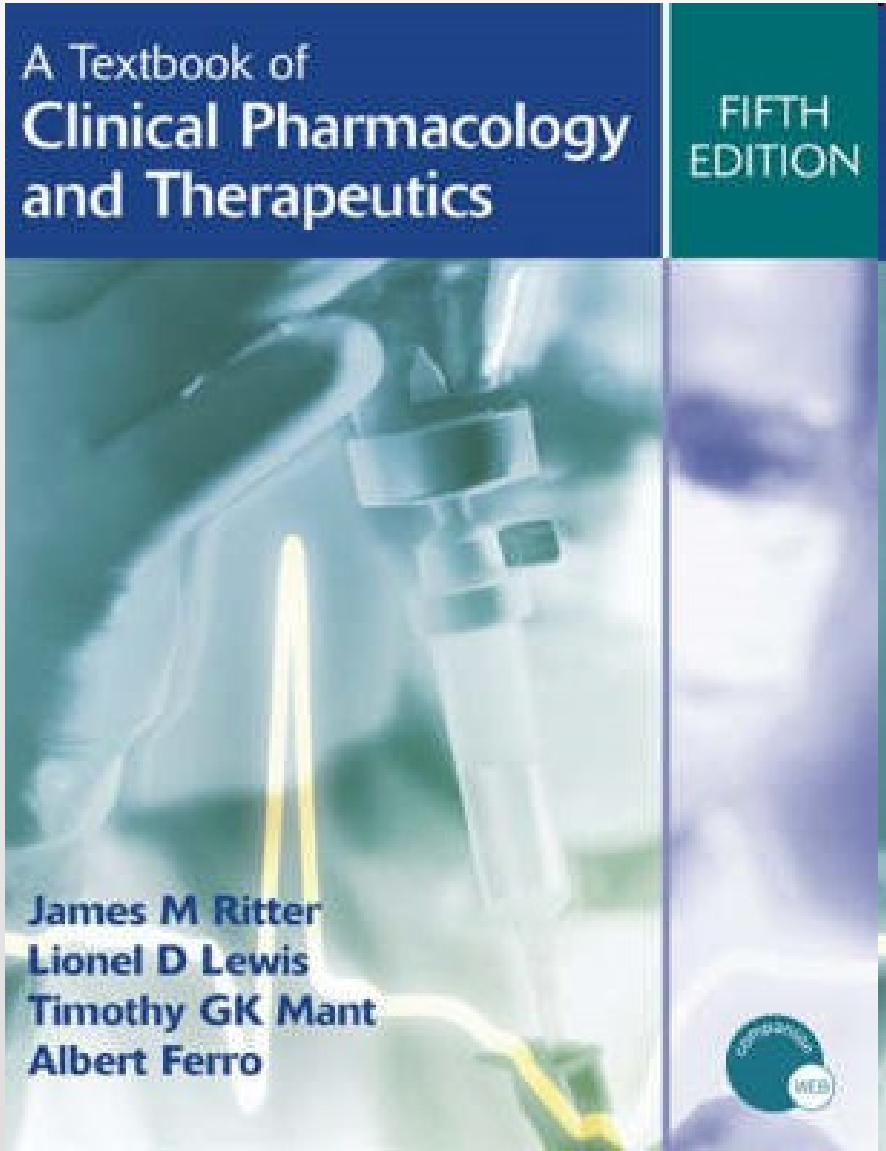

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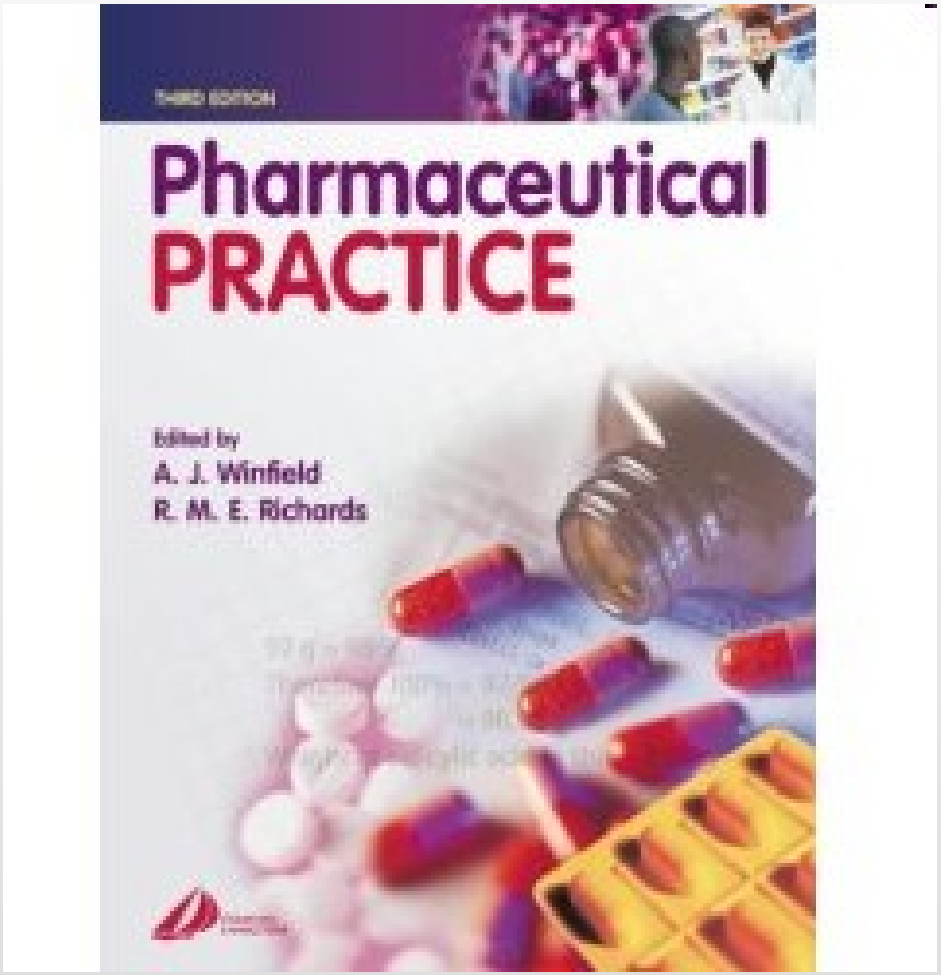

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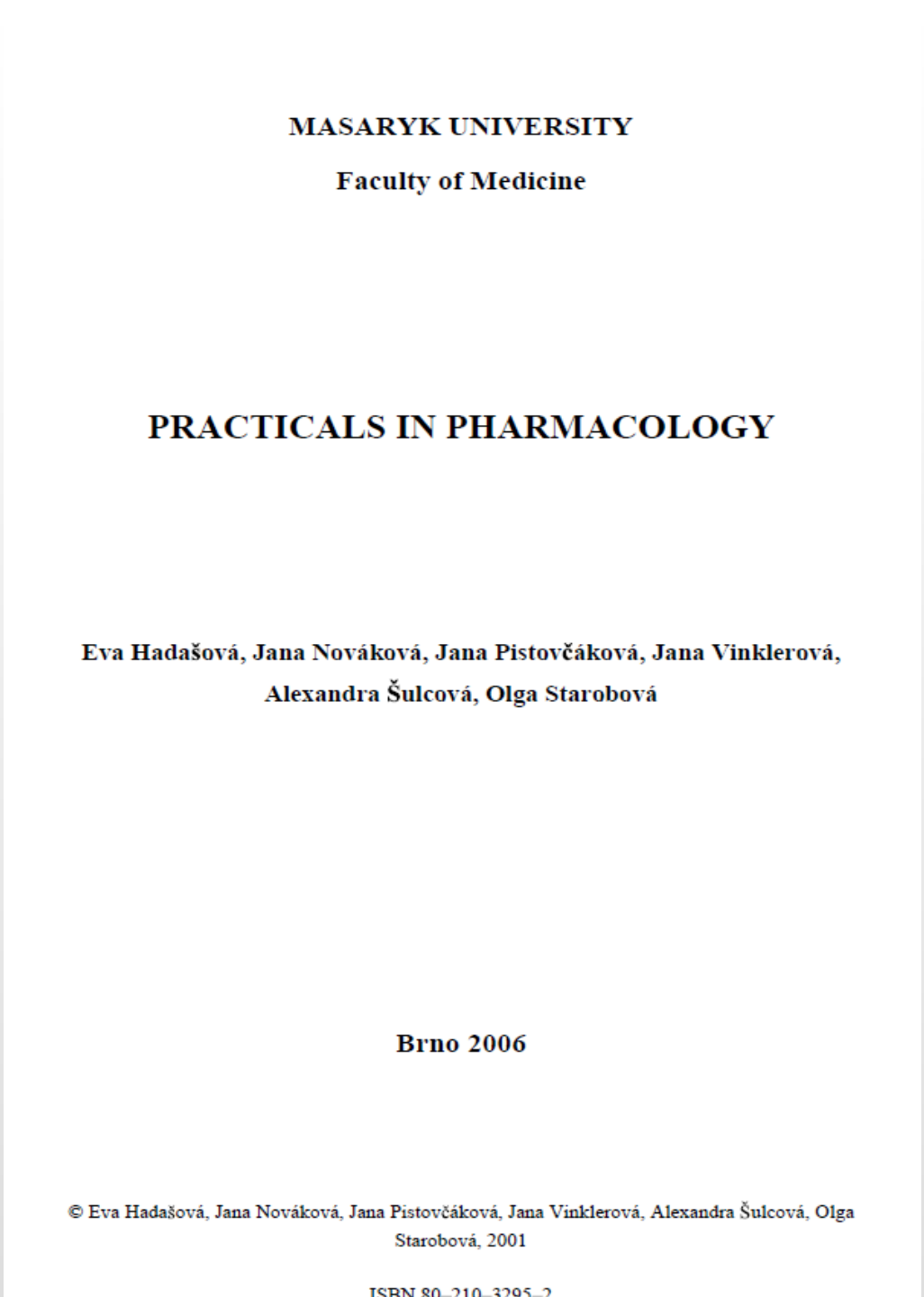
Practicals in Pharmacology, 2006

Hadasova, Novakova, Pistovcakova, Vinklerova, Sulcova, Starobova

Pdf available at: IS.muni.cz



MASARYK UNIVERSITY

Faculty of Medicine

PRACTICALS IN PHARMACOLOGY

Eva Hadašová, Jana Nováková, Jana Pistovčáková, Jana Vinklerová, Alexandra Šulcová, Olga Starobová

Brno 2006

ISBN 80-210-3285-2

Pharmacology, definition, aims

„pharmacon“ + „logos“ / „logia“

Scientific discipline dealing with
INTERACTIONS BETWEEN SUBSTANCES..
introduced into the organism from the environment

..AND THE LIVING ORGANISM
on all levels of complexity:
molecular
cellular
organ
organism as a whole

Pharmaceutics

- the general area of study concerned with the formulation, manufacture, stability, and effectiveness of pharmaceutical dosage forms

DRUG

„substance or mixture of substances, suppopsed to be administered to the humans or animals for prevention, treatment or diagnosis of diseases or its symptomes or for physiological function adjustment“

Drugs are administered for

- Prevention,
- Diagnosis,
- Treatment of disseases

Pharmacon/um – drug

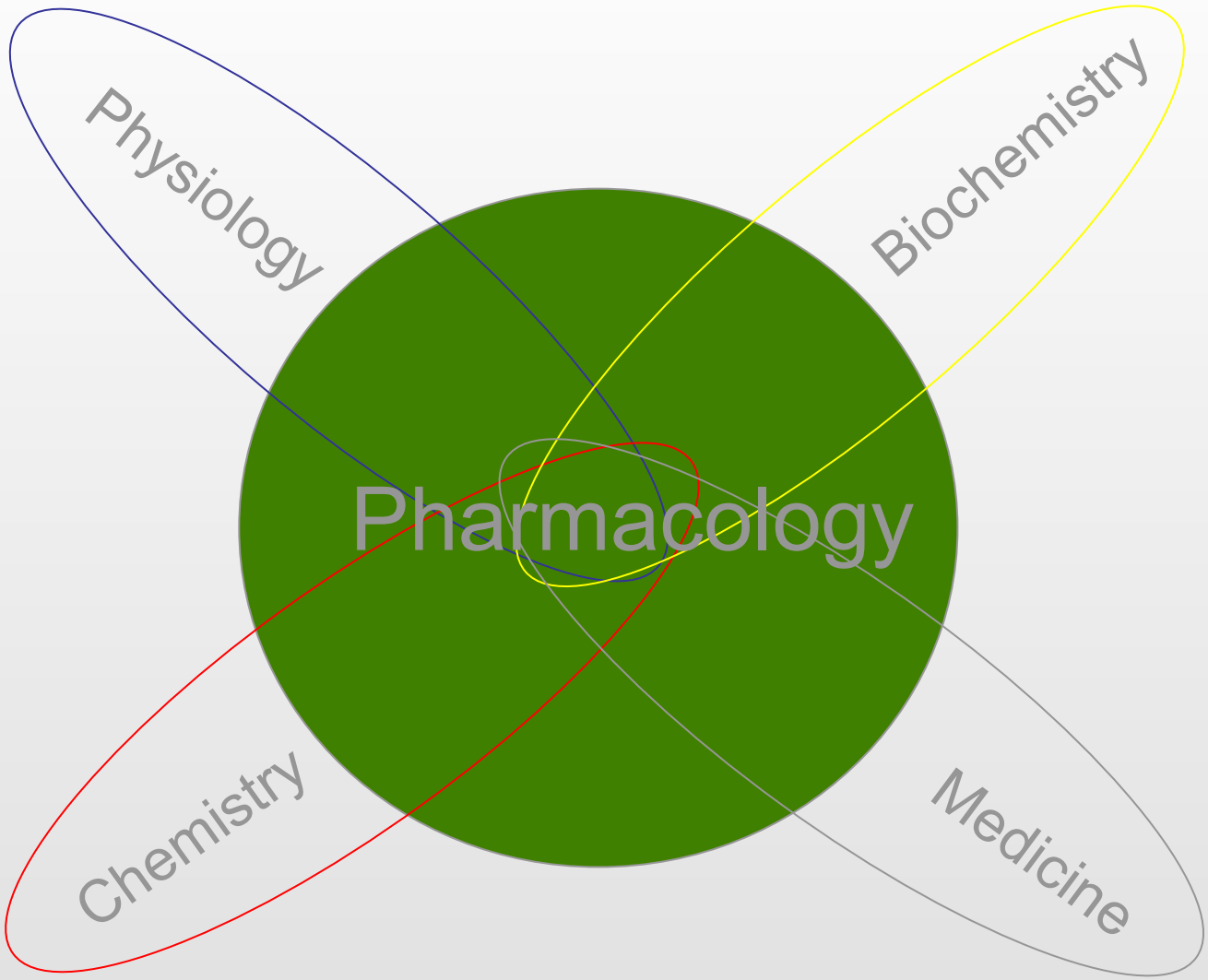
classical WHO definition:

- „Any substance (other than normal body components or substances necessary for normal body functions (food, water, oxygen), that, after administration into the organism evokes a change of a body function“

More precise definition according to Ph.Eur.:

- Substances or their mixtures designed to the administration in humans or animals with a purpose of treatment, mitigation, prevention or diagnose of a disease or its symptoms and also to modulation of physiological substances.
  - *European Pharmacopoea (Ph. Eur. 6th Ed.)*
  - *Pharmacopoea Bohemica 2009 (Ph. B. 2009)*

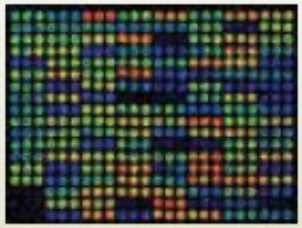
A synthesis of several biomedical sciences….



…but unique in its own right

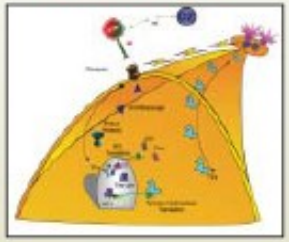
Pharmacologists Study Science at Every Level

Genetic



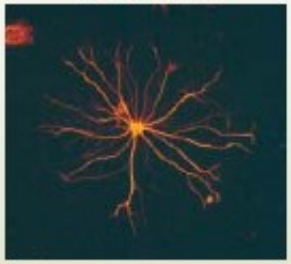
Gene Chip Microarray.
Courtesy of Annette Thelen, MSU Genomics Structure Facility.

Molecular



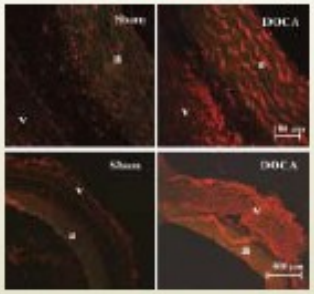
Interaction of the dopamine (D2) and dynorphin system in regulation of tuberoinfundibular neuronal function.
Courtesy of Y. Will-Murphy and K. Lookingland

Cellular



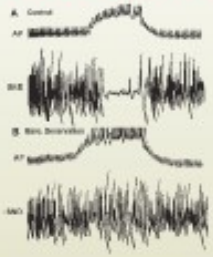
Astrocyte, labelled with Glial Fibrillary Acidic Protein
Courtesy of J. Eduards and B. Aschim.

Tissue



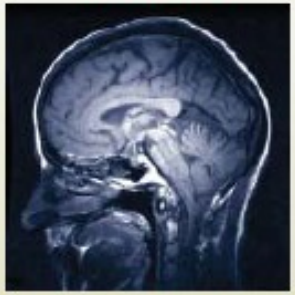
Superoxide measurement through dihydroethidium in artery (a) and vein (v) of normotensive (sham) and hypertensive (DOCA) rats.
Courtesy of H. Xu and J. Galligan

Whole Animal



Effect of sectioning baroreceptor nerves (denervation) on the inhibition of sympathetic nerve discharge during a rise in arterial pressure in an anesthetized cat.
AP = arterial pressure, SND = sympathetic nerve discharge.
Courtesy of S. Barman and G. Gebber.

Human



MRI of Human Head
Courtesy of Kevin Henley and James Potchen of the Radiology Department, MSU

What Pharmacology is NOT...

- **Pharmacy**

This is a separate profession responsible for the preparation and dispensation of medication.

- **Pharmaceutical Science**

Basic Pharmacology

- General principles

- Systems Pharmacology

General principles

Principles which predestinate the interactions of the drug and body

Two important and interrelated areas:

-General Pharmacokinetics

-General Pharmacodynamics

Pharmacokinetics (PK)

Deals with the fate of the drug in the body – processes of

Absorption,
Distribution
Metabolism
Excretion

„What the body makes with the drug“

…“ADME“

Pharmacodynamics (PD)

deals with the mechanism of action (e.g. receptor sites, molecular level of action..)

„How does it work“

Systems Pharmacology

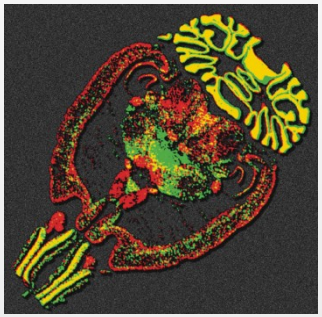
Is focused on individual organ systems and its pharmacotherapy

e.g.
Autonomic drugs
Psychoactive drugs
Drugs used in cardiovascular diseases….

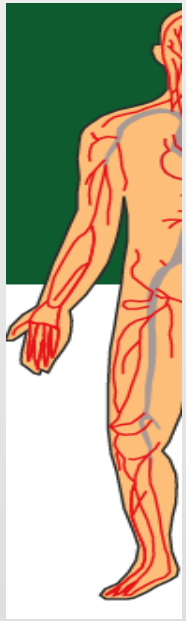
Systems Pharmacology

❖ **Neuropharmacology**: study of the effect of drugs on components of the nervous system (brain, spinal cord, nerves)

Example: treatment of Alzheimer's dissease



❖ **Cardiovascular Pharmacology**: study of the effects of drugs on heart, vasculature, kidney, nervous and endocrine systems that participate in cardiovascular function.



Example: treatment of high blood pressure (hypertension)

Branches of Pharmacology

Clinical pharmacology

- deals with different drugs and their varied clinical usage

- interdisciplinary branch, which integrates basic and experimental Pharmacology with the clinical and complementary branches

AIM: to study and evaluate the effect of the drug using objective methods (EBM)

Sub-branches of clinical pharmacology:
Clinical Pharmacokinetics, clin. Pharmacodynamics, Rational prescribing, Clinical toxicology

Toxicology

the study of the toxic effects of chemicals on living organisms

study of symptoms, mechanisms, treatments and detection of poisoning

Experimental (in vitro, in vivo)
Clinical - poisoning prophylaxis, diagnosis, treatment
Forensic toxicology…

Pharmacogenetics

deals with the influence of genetic variation on Pharmacokinetics and Pharmacodynamics

study of the drug response in patients by correlating gene expression or single-nucleotide polymorphisms with a drug's efficacy or toxicity

consequences can be either quantitative or qualitative

Pharmacogenetics

1959 Friedrich Vogel used first time term „pharmacogenetics“

1997 First time used term “**Pharmacogenomics“**

Pharmacogenetics considers one or at most a few genes of interest, while pharmacogenomics considers the entire genome.

Biochemical and molecular Pharmacology

detail study of the mechanism of action at molecular level

Chronopharmacology

Study of the action of the drugs with respect to the biorhythm

(antiasthmatics, glukocorticoids, statins, etc.)

Pharmacovigilance

Pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects

collecting, monitoring, researching and evaluating information from healthcare providers and patients on the adverse effects of medication

Drug safety monitoring

AIM: to minimize the risk of adverse effects

Pharmacoepidemiology

- study of the effect of drugs on populations; questions dealing with the influence of genetics are particularly important

risks and benefits of the therapy using epidemiological methods

Approach of the health specialists (GP, pharmacist)

patient (compliance)

society (drug abuse, marketing, financial resources…)

Pharmacoeconomy

- rationalize the use of sources in health care

- Compares the costs of therapeutic approaches by the pharmacoeconomical analyses

The goal is not „to decrease total money spent in health care“ , but to use the sources effectively

Experimental pharmacology

Biological experiment

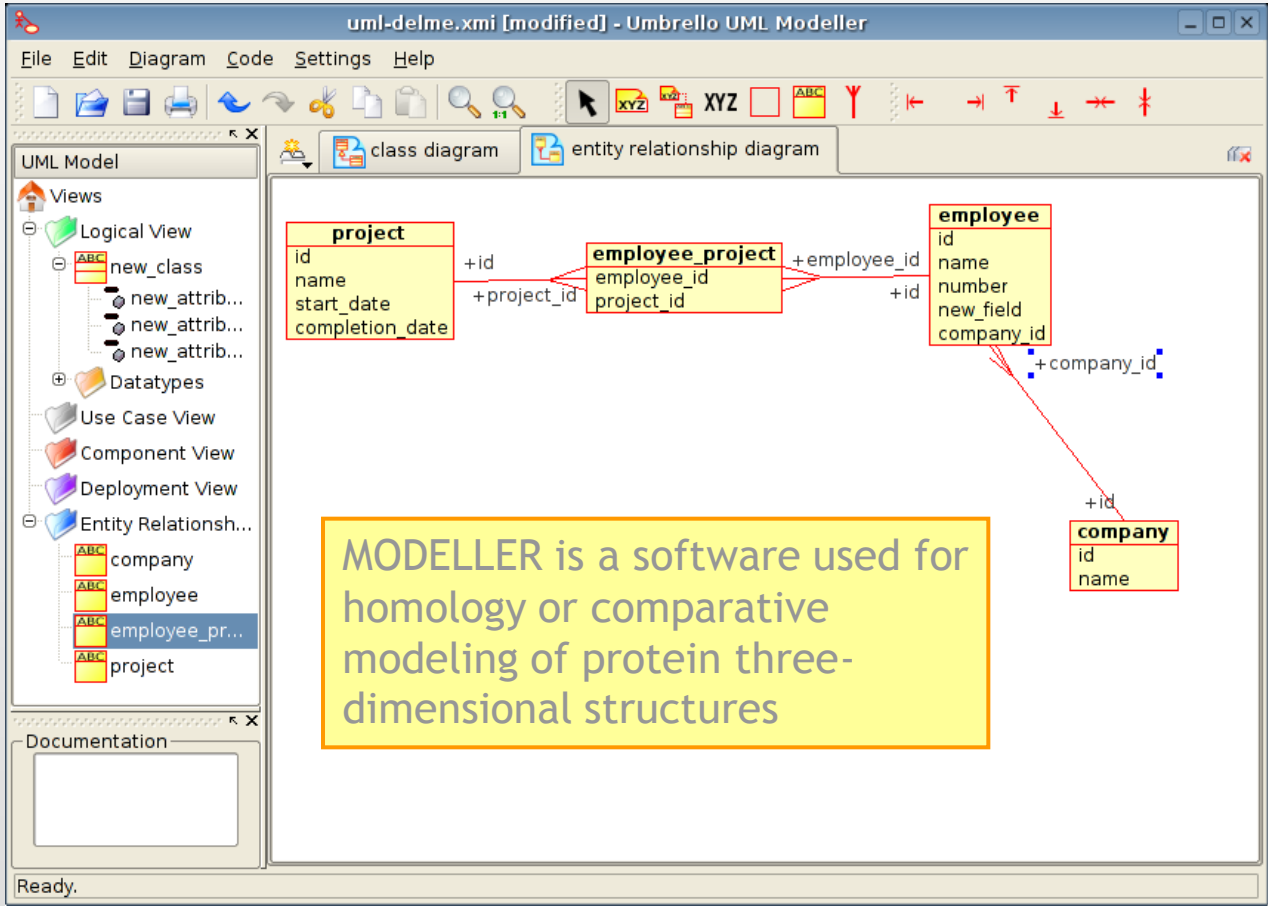
in vitro – isolated structures or organs,
cell cultures, microorganisms

- regulatory factors we have to satisfy:
  - ☺ ethical (replacement, refinement, reduction)
  - ☺ small amounts of drugs
  - ☺ use of human cells

  - ☹ elimination of systhemic reaction of the whole body

Biological experiment

in silico – use of IT, especially computer modelling (f-kinetics), databases



Biological experiment

in vivo –

- whole animal
  - systhemic effects
  - we record toxicity, possible adverse and alergic effects
  - impact on memory and other cognitive faculties, learning abilities, depression

Experimental animal

Experimental animal (is born, breed and maintained for experimental purposes)

Defined genetic features:

- **randombred** – natural breeding - heterozygots
- **inbred** – breeding of brosthers and sisters, approx. 20 generations - homozygots
  - diabetic mice, hypercholesterolemic mice, hypertonic mice…

Experimental animal

Defined microbial settlement

- **SPF** – have 4-5 saprofyte patogens

- **Gnotobiotic animals** – are born by hysterectomy, pathogens free

- **Conventional breeding** – not defined settlement (there may be: brucela, leptospira, mycobakteria, salmonela, toxoplasma…)

Experimental animals

- Mammals

RODENTS: mouse, hamster, rat, guinea-pig

NON-RODENTS (e.g. Lagomorpha): rabbit

Experimental animals

- Mammals

  carnivores: dog, cat, ferret

- Mammals

  monkeys: macaque (Macacus sp.), green monkey (*Erythrocebus* sp.)

- Birds

  common quail, hen, duck

- Amphibians

  Xenopus sp.

- Fish

  guppy (Poecilia reticulata), carp, trout

- Crustaceans

  Cladocera, Cyclops strenuus

Project – experiment - protocol

- Certificates

  for quarters, stabling and handling conditions, qualified staff

Experimental design

- Suitable animal
- Homogeneity of the group

  - gender, weight, age, feeding
- Control experiment

  - the same treatment and number of animals
- Repetition of the experiment

  - Limitation of influence of the individual variability

Protocol of the experiment in pharmacology

1. Name of the experiment, aims
2. methods
   - Data about the animals
   - Description of the method
3. results
4. Discussion (evaluation), statistics
5. conclusion
6. date, number, support, statement of interests

Laws

EU

- **1986 Council of Europe** – rules of protection for vertebrates used for experimental purposes in Europe

Principle 3R: replacement

reduction

refinement

Laws

Czech Republic

Law no. 149/2004 „*na ochranu zvířat proti týrání*“ – about animal protection against cruelty

Notice no. 207/2004 „*o ochraně, chovu a využití pokusných zvířat*“ - about protection, breeding and use of laboratory animals

- Authorities encharged of animal protection:

- Ministry of agriculture, Comission for animal protercion, veterinary authorities, ethical comitties

Drug names

Chemical name

- according to the IUPAC nomenclature rules
- e.g.: N-acetyl-para aminophenol

Generic name (non-proprietary)

INN (International Non-proprietary Name)

- not registered, supposed to be used internationally
- has to be printed on the packing of the drug (under the registered trade name)
- for the universal terminological identification of the medicines
- formed from the chemical name (shortness) accordingly with the rules (WHO)
- each drug has its own CAS No (Chemical Abstracts Sevice Number)

e.g. paracetamol

Drug names

Trade name (proprietary)

registered, patent-protected ®

has to be acompanied with the INN

e.g. Panadol, Coldrex, Paralen

Officinal name

latin name in Pharmacopoeia (e.g. Paracetamolum)

usually very similar to INN

has to be prescribed on Rx formulary in case of individually prescribed medicines

established name for a drug substance is usually found in the originating country's Pharmacopeia

Paracetamolum

…

Some drug-family names

-olol	betareceptor antagonists
-caine	local anaestethics
-tidine	histamine receptor antagonists
-dipine	calcium channel blockers of dihydropyridine type
-statin	inhibitors of HMG CoA transferase

„GENERICS“

Drug which is produced and distributed after ending of patent protection - mostly manufactured by other company which has not developed the original drug (the same active substance!)

Mostly cheaper than original preparation

Assumed to be identical in dose, strength, route of administration, safety, efficacy, and intended use

Bioequivalent trials are needed before registration

Registration procedures are much easier than in orig. preparation

Drug patents give 10 years of protection, but they are applied for before clinical trials begin, so the *effective* life of a drug patent tends to be between 7 and 12 years

- **„GENERIC PRESCRIPTION“**

  prescription of the generic name (INN) on Rx formulary

  \+ dose, number of doses

Pharmacist will chose apropriate ready-mady preparation after consultation with the patient

- **„ GENERIC SUBSTITUTION“**

  substitution of the prescribed preparation with another one (generic)

DOSE

- A specified quantity of a therapeutic agent, prescribed to be taken at one time or at stated intervals.

- If administered in the body, desintegrates, solutes, and distribute across the barriers in the body compartments. Than it is measured like „concentration“

DOSE

- DOSIS SINGULA - single dose

on Rx !

- DOSIS PRO DIE - daily dose
  - for 24 h !!
- DOSIS CHRONICA
  - (adjusted) dose in the chronic treatment (long-term)

DOSE

- **DOSIS CURATIVA**

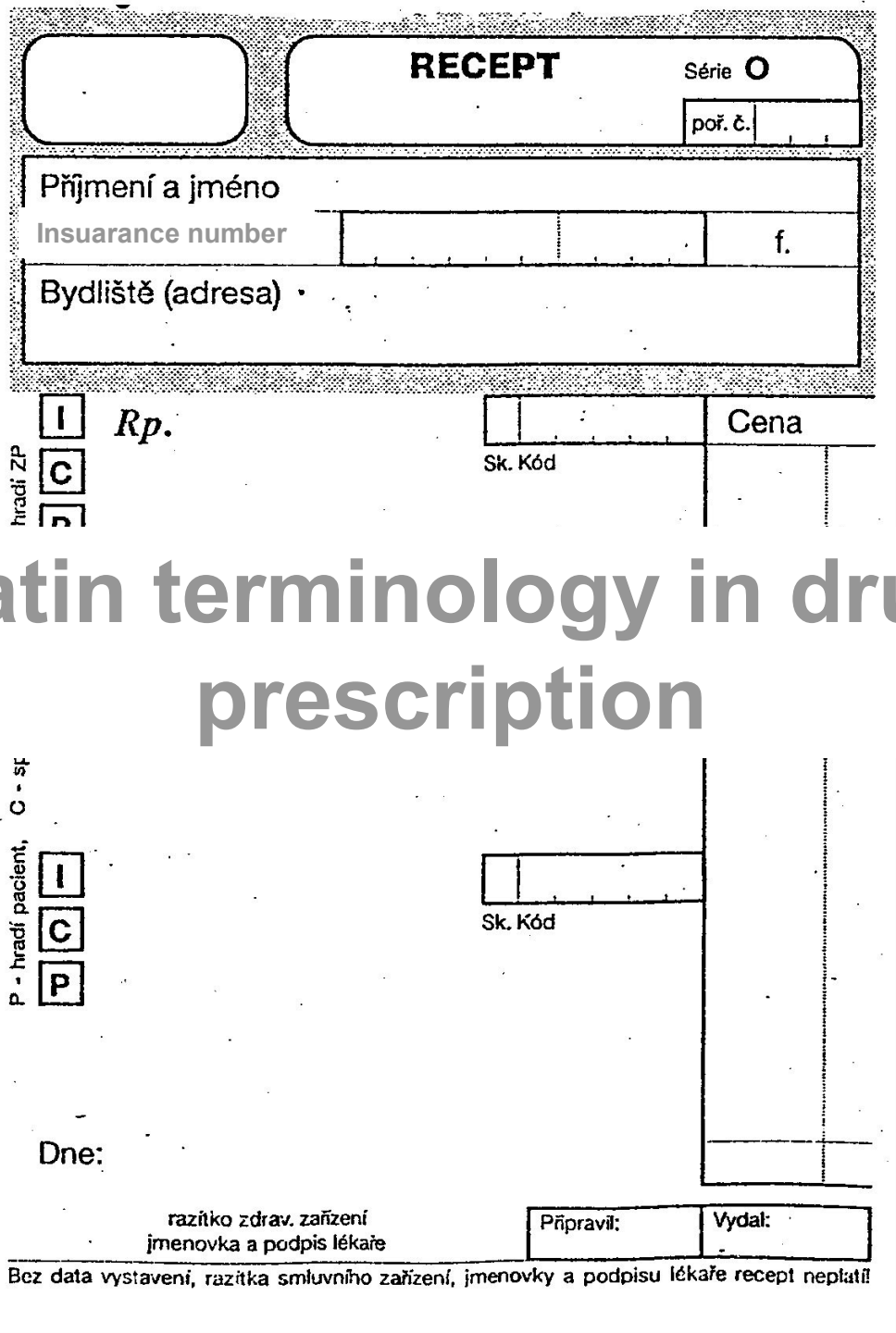
  - total dose of the drug needed for whole period of treatment

DOSE (from effect point of view)

- Sub-threshold - cause no observed biological effect
- Threshold - minimally effective dose; dose, after which can be observed any effect

- Therapeutic dose
  - produce mostly beneficial effects;
  - ►MAXIMAL
  - does not produce harmfull effects
  - ►►DOSIS MAXIMA SINGULA
  - ►►DOSIS MAXIMA PRO DIE

- TOXIC – mostly harmfull effects (RISK>BENEFIT)
- LETHAL – cause death

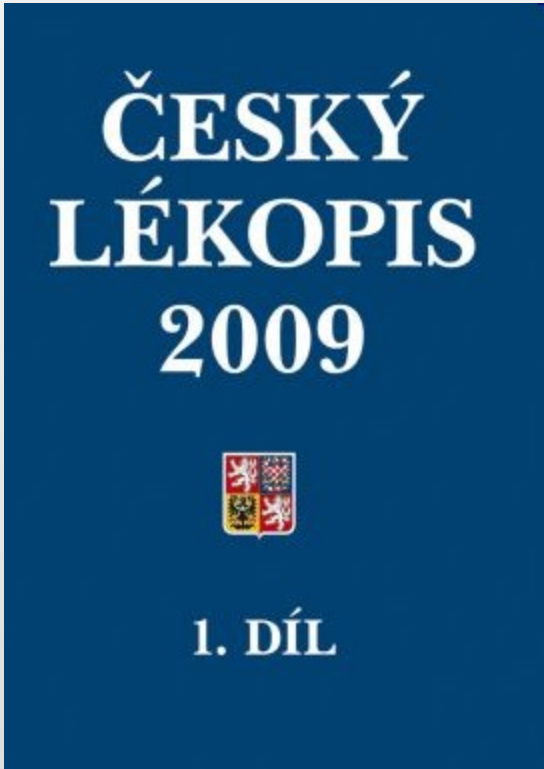


Latin terminology in drug prescription

➢ Pharmacopoeia

- *pharmacon* = drug
- *poieo* = prepare

Substances in pharmacopoeia- called **officinal** drugs



Definition

- basic reference work for pharmaceutical drug specifications
- published by the authority of a government or a medical or pharmaceutical society

- book containing directions for the identification of samples and the preparation of compound medicines
- assures quality, efficacy, safety, standards

Pharmacopoeias may be:

- National e.g. Brazilian, British, Chinese, Indian, Japanese, Mexican, Spanish, United States

- Regional e.g. European (Ph.Eur.)
  The 7th Edition of the European Pharmacopoeia

- International *The International Pharmacopoeia*

National and regional pharmacopoeias

- Cover medicines used in the relevant country or region
- Are legally binding "official" in the relevant country or region
- Are prepared by a national or regional authority

International Pharmacopoeia

A few dates…

- The history of the *International Pharmacopoeia* dates back 1874…

- → **1948** First ***World Health Assembly*** established Expert Committee on Unification of Pharmacopoeia

- → **1950** WHA approved publication of *Pharmacopoeia Internationalis*

International Pharmacopoeia

→*implementation:* **“ready for use” by Member States**

"The Ph.Int […] is intended to serve as source material for reference or adaptation by any WHO Member State wishing to establish pharmaceutical requirements. The pharmacopoeia, or any part of it, shall have legal status, whenever a national or regional authority expressly introduces it into appropriate legislation."

*[**World Health Assembly resolution WHA3.10**, WHO Handbook of Resolutions and Decisions, Vol. 1, 1977, p. 127]*

Scope since 1975

→ Model Lists of Essential Medicines

→ Medicines recommended and specifications needed by WHO Programmes, e.g. to treat Malaria, TB, HIV/AIDS and

→ Medicines for children!

International Pharmacopoeia

A collection of monographs and requirements for:

→ **Drug substances**

→ **Excipients**

→ **Finished dosage forms**

→ **General methods and requirements:**

dosage forms, *e.g. tablets, liquid preparation for oral use*

dissolution testing

→ **Supplementary information,** *e.g. General guidelines for Chemical Reference Substances*

→ **Infrared reference spectra**

Specifications of substances

- **Description, Chemistry, Solubility, Storage, Labelling**
- **Definition,** with information on **polymorphism** if relevant
- **Identification**
- **Assay**
- **Specific tests** (sulphated ash, optical rotation, loss on drying…)
- **Related substances**

Specifications of substances

- **Precise description of analytical methods**
- **Impurities** (chemical names, structures, origin)
- Any relevant information on

  Performance testing (e.g. dissolution)

  Stability

  Validation of analytical methods

International Pharmacopoeia

current: **4th Edition + 1st Supplement**

→ Consolidated in : **2 Volumes**

Vol. 1: *pharmaceutical substances* (A-O)

Vol. 2: *pharmaceutical substances (P-X)*

+ dosage forms + radiopharmaceuticals

+ methods of analysis + reagents

1st Supplement - *new requirements and revisions*

PHARMACOPOEIA BOHEMICA

- 3 volumes + CD, 2009
- Translation of 7th ed. of Eur. Pharmacopoieia
- Issued by The Czech Ph. Comm. Of Ministry of Health

- **Vol. 1 General methods and requirements**

- **Vol. 2 Monographs A-N**
  - Medicines, excipients
- **Vol. 3**
  - **Monographs N-Z**
    - Medicines, excipients

National part

- **General methods and requirements**
- **Tables** (I-XII)

  - Medicines, excipients

PHARMACOPOEIA

- **WHAT we can not find there !**
  - pharmacological properties of drugs, their pharmacodynamics, pharmacokinetics
  - indications, contra-indications
  - toxic effects

Drug dosology in paediatrics.

Doses divided into 3 age groups

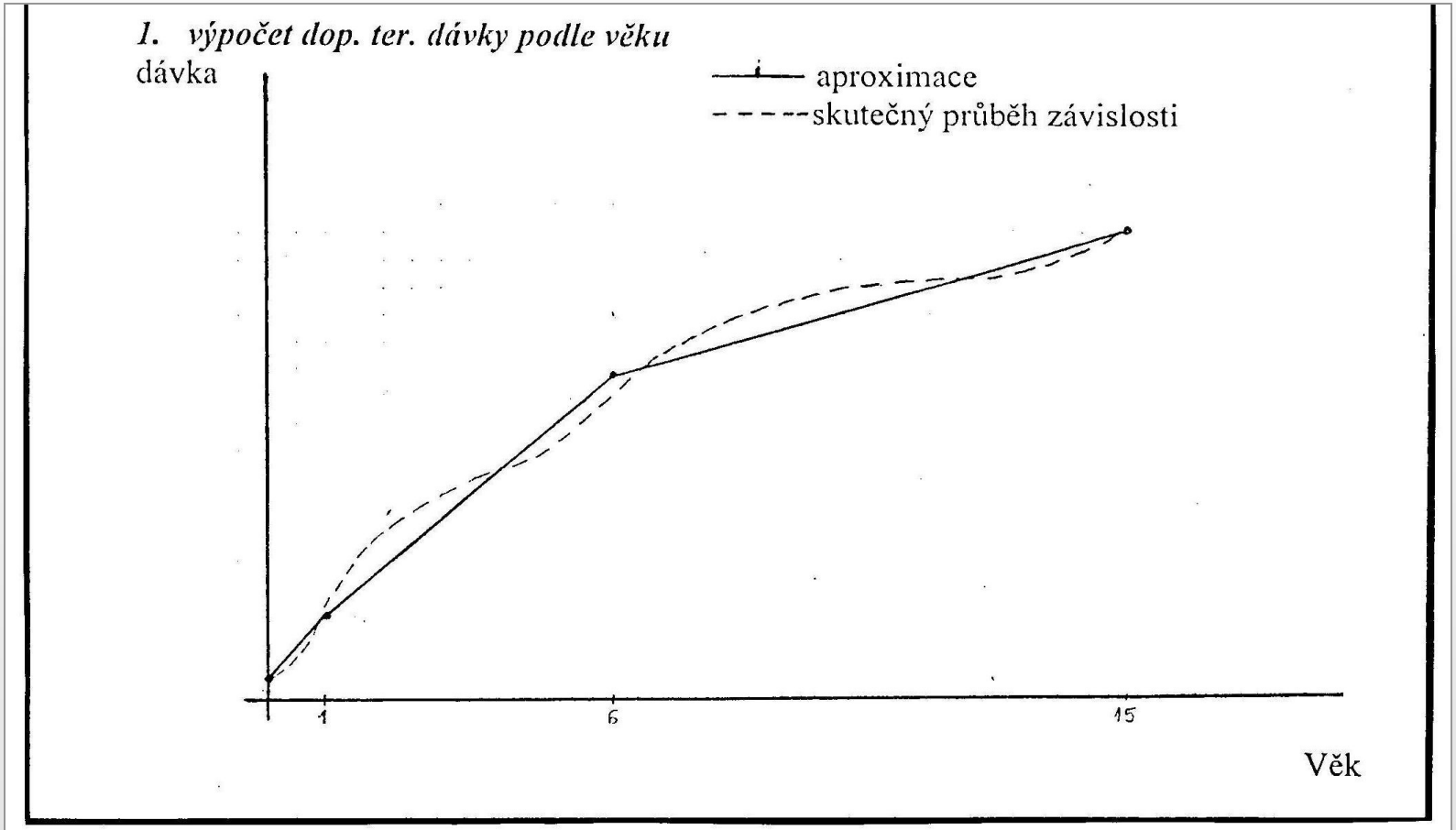
0-1 1-6 6-15

<u>Calculation according to the body surface</u>

$$\text{Dose for children} = \frac{\text{body surface}[m^2]}{1{,}73} \times \text{adult dose}$$

- $$\text{Body surface } [m^2] = \frac{7 * \text{age (yrs)} + 45}{100}$$

1. výpočet dop. ter. dávky podle věku



Doses for children

Interpolation

$$d = d_1 + \frac{d_2 - d_1}{n}. n_d$$

d…..recommended dose for the given age

d_1….recommended dose for lower limit of the age interval

d_2 … recommended dose for upper limit of the age interval

n…..number of year intervals within the range of age

n_d….number of year intervals from the beginning of range of age to the age of the given child

Calculate the DTS of a substance X for 10 years old child, if the dose interval from 6 to 15 years of age is 0,7-1,5 g.

$$d = d1 + \frac{d2 - d1}{n} . nd$$

d1 = 0,7

d2 = 1,5

n = 9

nd = 4

$$d = 0,7 + \frac{1,5 - 0,7}{9} . 4 = 0,7 + 0,088*4 = \underline{1,05\ g}$$