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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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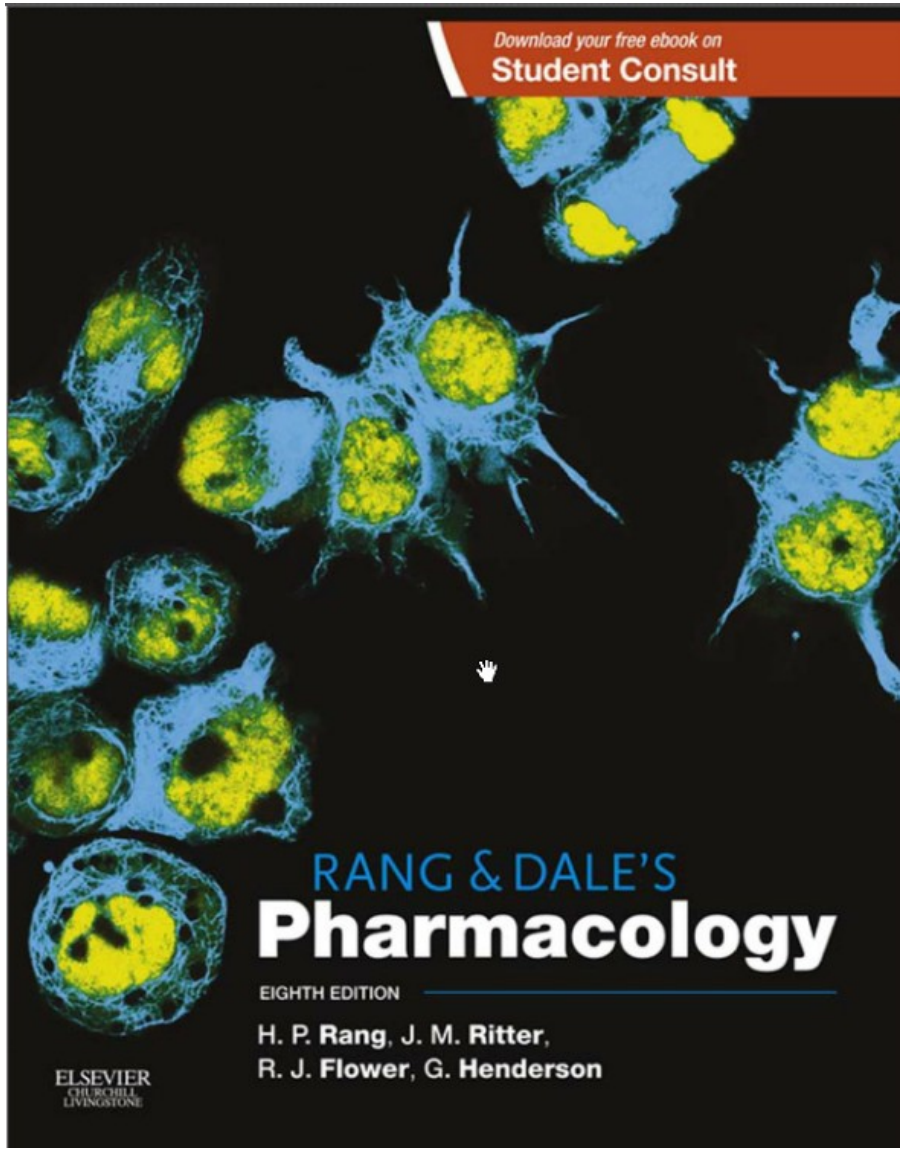
Download your free ebook on
Student Consult
RANG & DALE'S
Pharmacology
EIGHTH EDITION
H. P. Rang, J. M. Ritter,
R. J. Flower, G. Henderson
ELSEVIER
CHURCHILL
LIVINGSTONE

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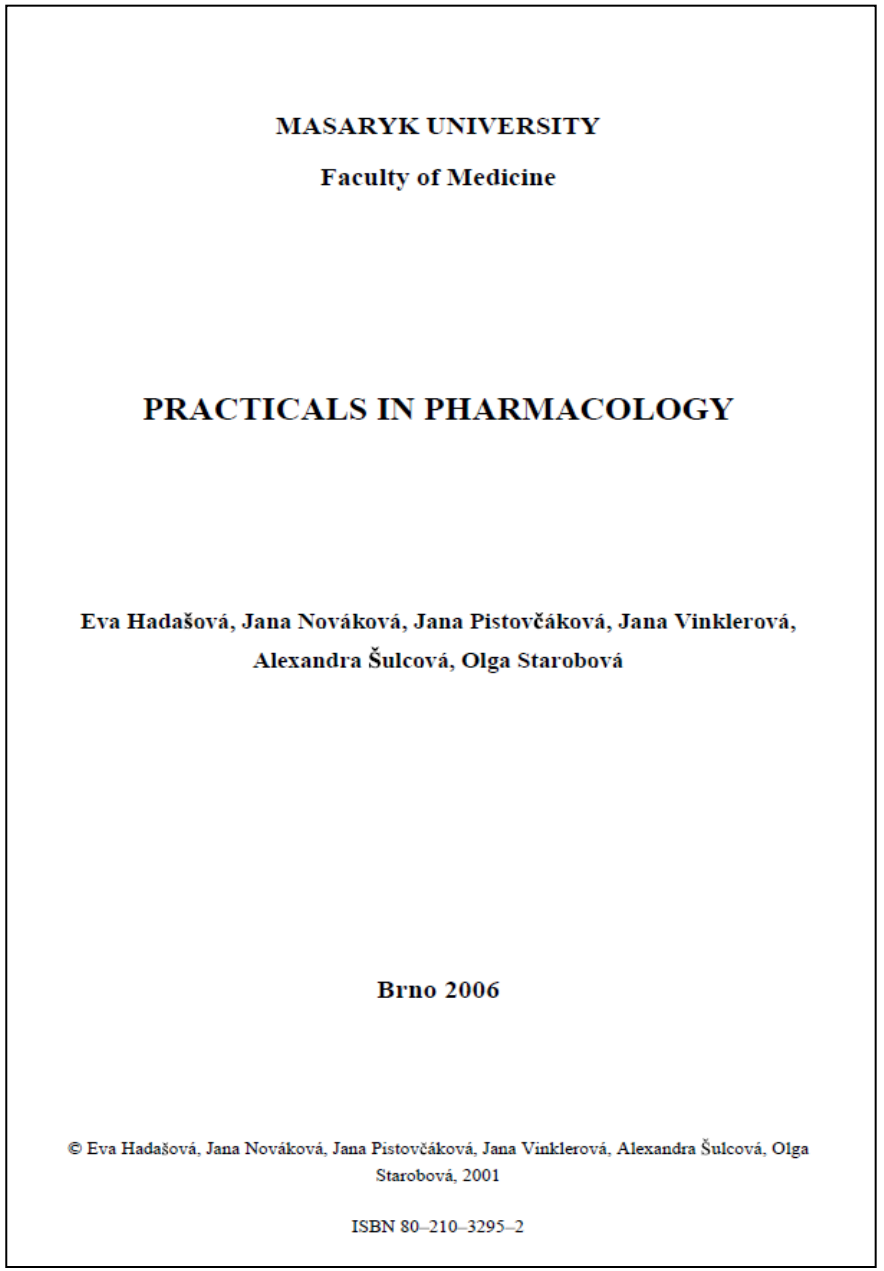
Literature

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 80–210–3295–2

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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

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Pharmaceutics

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

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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

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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)

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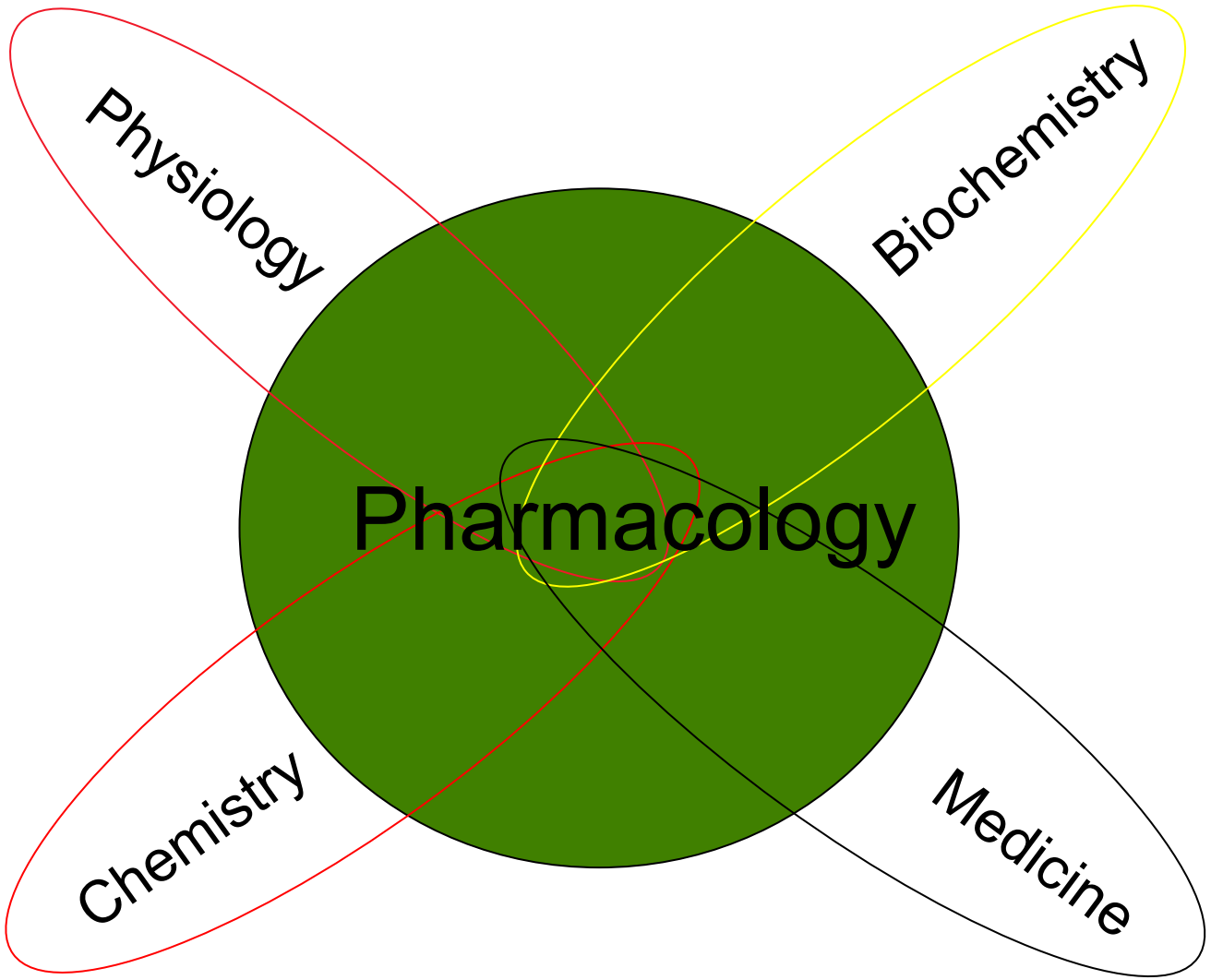
A synthesis of several biomedical sciences….



…but unique in its own right

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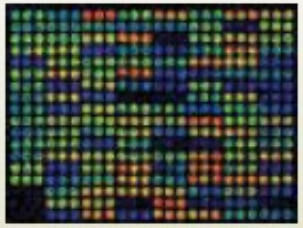
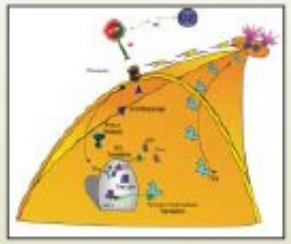
Pharmacologists study science at <u>every</u> level

Genetic



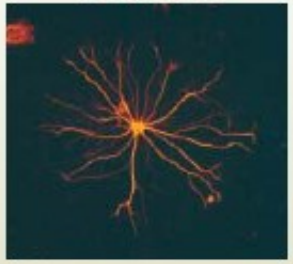
Gene Chip Microarray.
Courtesy of Annette Thelen, MSU Genomics Structure Facility.

Molecular



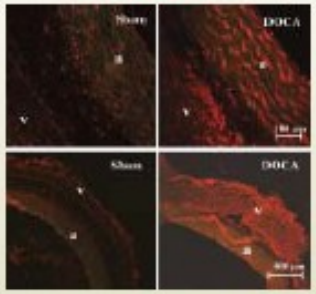
Interaction of the dopamine (D2) and dynorphin system in regulation of tuberoinfundibular neuronal function.
Courtesy of Y. Will-Murphy and K. Lookingland

Cellular



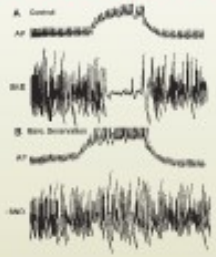
Astrocyte, labelled with Glial Fibrillary Acidic Protein
Courtesy of J. Edwards and B. Atchison.

Tissue



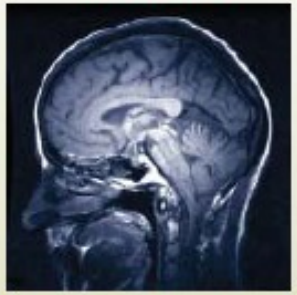
Superoxide measurement through dihydroethidium in artery (a) and vein (v) of normotensive (sham) and hypertensive (DOCA) rats.
Courtesy of H. Xu and J. Galligan

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

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What Pharmacology is NOT...

❖ Pharmacy

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

❖ Pharmaceutical Science

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Basic Pharmacology

General principles

Systems Pharmacology

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General principles

Principles which predestinate the interactions of the drug and body

Two important and interrelated areas:

- General Pharmacokinetics

- General Pharmacodynamics

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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“

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Systems Pharmacology

Is focused on individual organ systems and its pharmacotherapy

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

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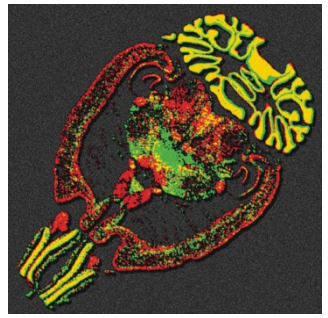
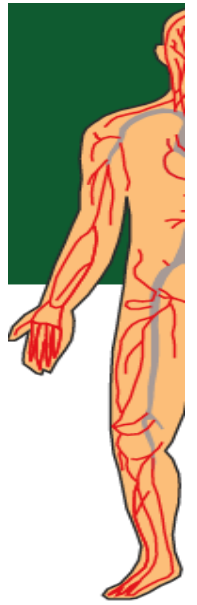
Systems Pharmacology

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



Example: treatment of Alzheimer‘s disease

❖ **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)

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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

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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…

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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

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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.

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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.)

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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

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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…)

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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

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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

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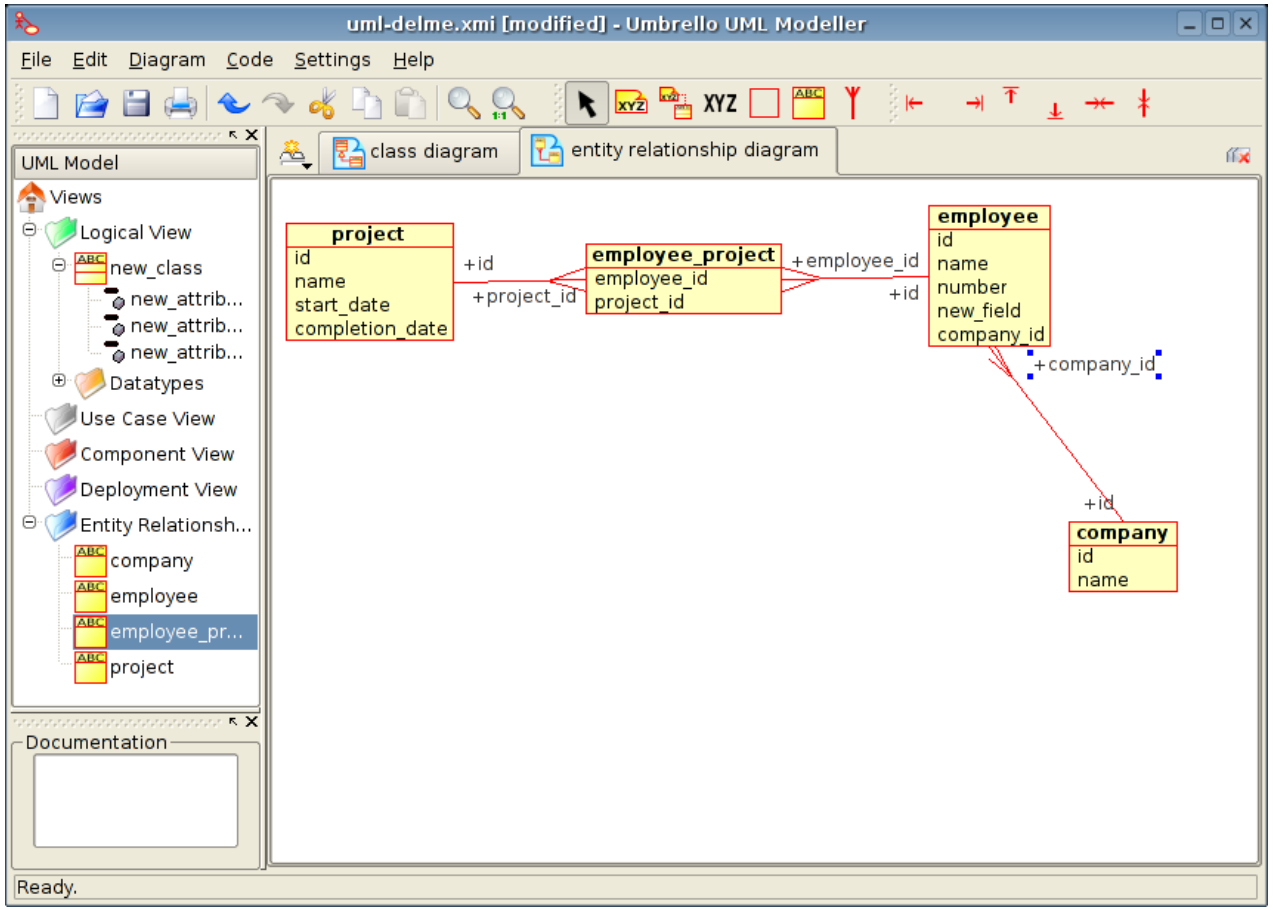
Biological experiment

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



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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

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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…

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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…)

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Experimental animal

Mammals

RODENTS: mouse, hamster, rat, guinea-pig

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

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Experimental animal

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

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Project – experiment - protocol

Certificates

for quarters, stabling and handling conditions,

qualified staff

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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

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Protocol of the experiment in pharmacology

Name of the experiment, aims

Methods

- Data about the animals
- Description of the method

Results

Discussion (evaluation), statistics

Conclusion

Date, number, support, statement of interests

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Laws

EU

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

Principle 3R: replacement

reduction

refinement

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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 protection, veterinary authorities, ethical comitties

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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

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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
…

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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

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„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

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„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)

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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“

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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)

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DOSE

DOSIS CURATIVA

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

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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 - produces 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

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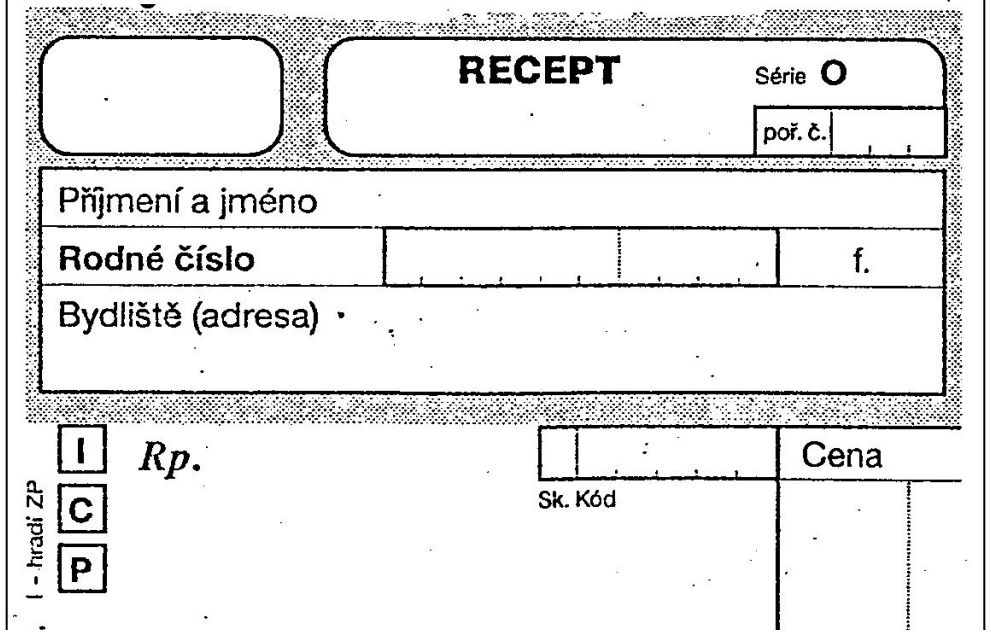
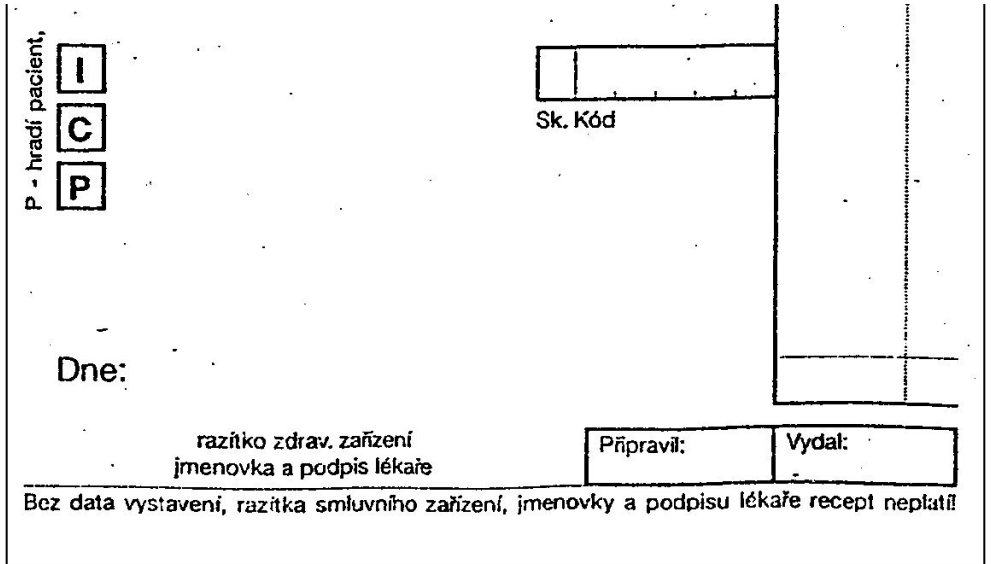


Latin terminology in drug prescription



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Pharmacopoeia

pharmacon = drug
poieo = prepare

Substances in pharmacopoeia- called **officinal** drugs

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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

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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*

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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

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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*

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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]*

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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!

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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**

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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

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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

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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*

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PHARMACOPOEIA BOHEMICA

- 3 volumes + CD, 2017
- Translation of 7th ed. of Eur. Pharmacopoeia
- Issued by The Czech Ph. Comm. Of Ministry of Health

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- **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

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PHARMACOPOEIA

WHAT we can not find there !

pharmacological properties of drugs, their pharmacodynamics, pharmacokinetics

indications, contra-indications
toxic effects

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Drug dosology in paediatrics

Doses divided into 3 age groups

0-1 1-6 6-15

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

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

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

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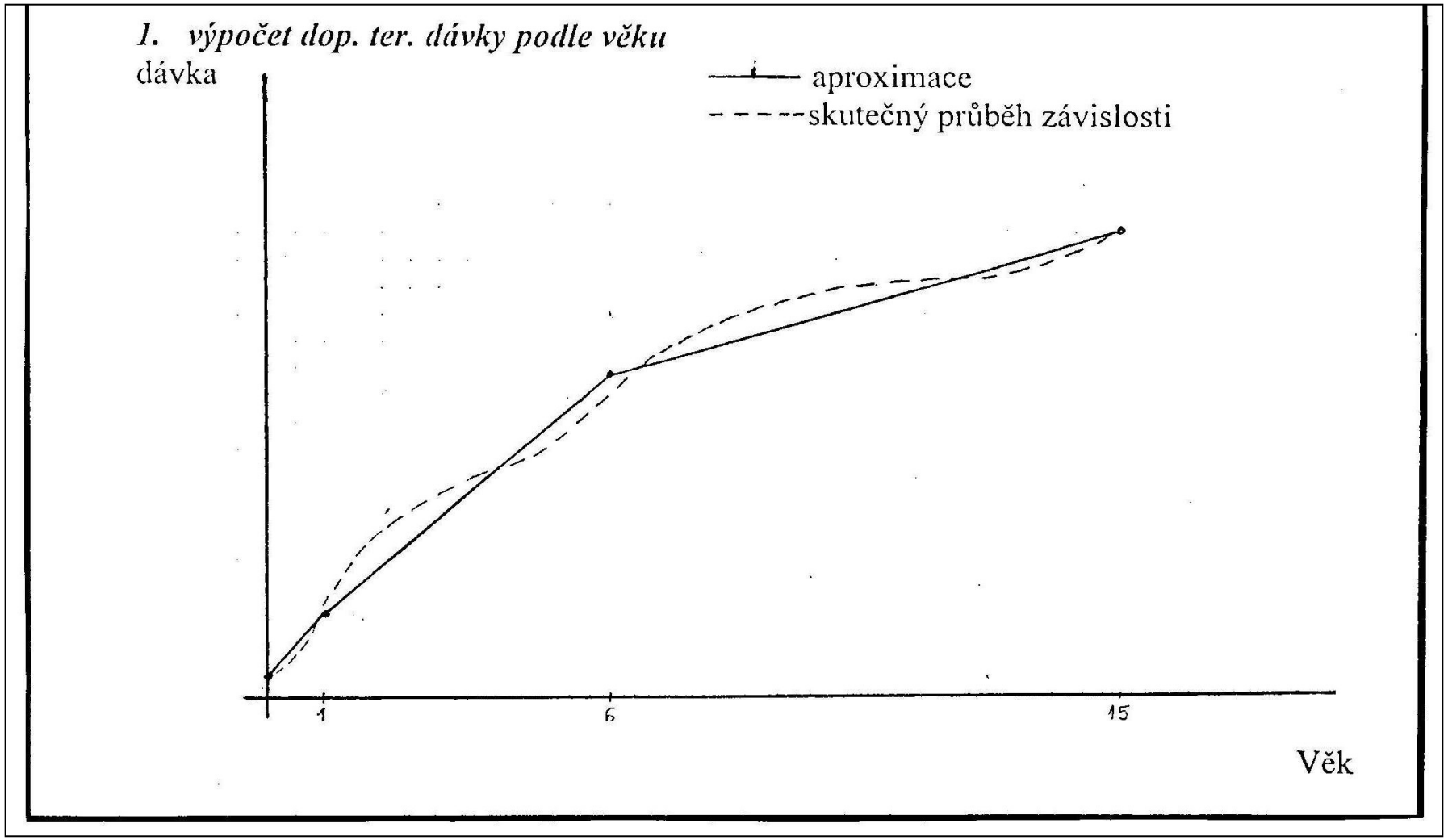
1. výpočet dop. ter. dávky podle věku
dávka
aproximace
skutečný průběh závislosti
1
6
15
Věk

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

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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

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

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