Introduction to toxicology

Toxicology: studies the **deleterious effects of chemicals** on biological systems

“chemical" separates

-from physical effects (e.g. ionizing radiation)

-from living organisms, but not their products (toxins)

Poison: non-living material which, after entering the body, will result in damage by its

-chemical,

-physico-chemical or

-physical (except serious mechanical effects) properties

The concept of poison

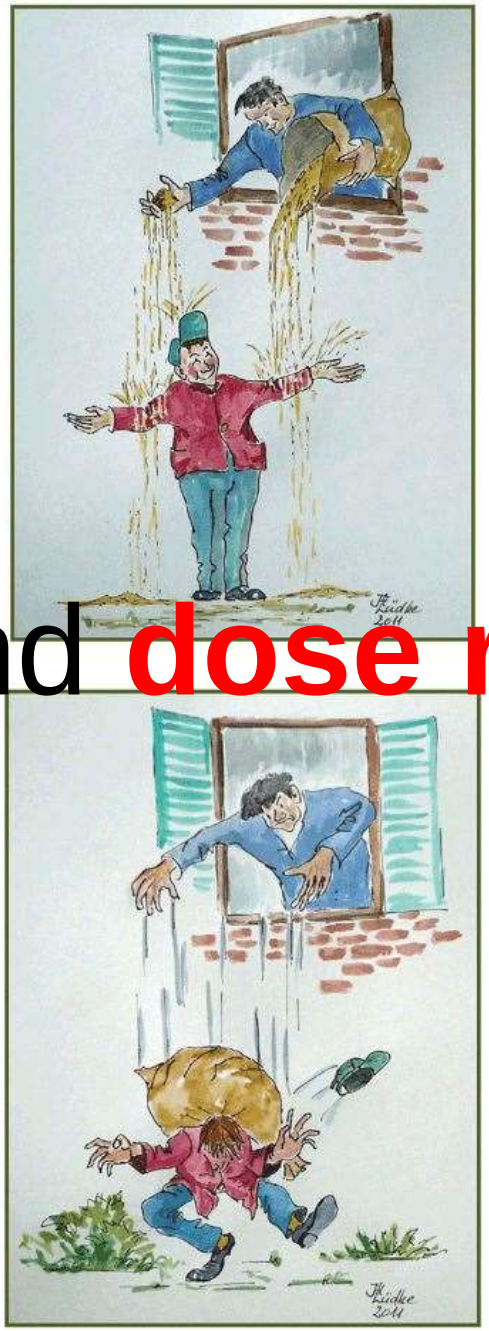
“Everything is poison, nothing is completely harmless. Only the **dose** can separate the poison from the drug."

"Dosis sola facit venenum"

(Paracelsus, 1493-1541)

In practice: poison can cause damage in small quantities.

Dose and Dose-Rate matter



Dose and **dose rate** matter.

Branches of toxicology

- **Descriptive toxicology**
  - direct testing in vitro or in vivo (animals)
- Occupational toxicology
  - chemicals found in the workplace
- Environmental toxicology
  - pollutants
- Ecotoxicology
  - impact on populations or ecosystems (not on individuals)
- Forensic toxicology
  - analysis with legal consequences
- **Clinical toxicology**
  - symptoms → diagnosis
  - therapy

Descriptive toxicology

direct toxicity testing in

cell cultures or

animal experiments:

-expensive, lengthy, cumbersome, but essential
-alternative methods *are searched*

lot of new chemical compounds – much less toxicological data

expectation**: unequivocal classification of chemicals**
toxic – non-toxic
Is that possible?

BUT better:

estimation of expected **risk**, if used according to
a given **way** and
quantity (dose and dose rate)

16.1. táblázat ○ Vegyületek minősítése az Európai Unió szerint patkányokon meghatározott akut orális toxicitásuk alapján (példákkal)

Vegyület	LD_{50} (mg / ttkg)	Felhasználás
I. Igen mérgező (LD_{50} < 25 mg / ttkg p. os)		
Nikotin	1–2	inszekticid
Paration	2–6	inszekticid
Indometacin	10–20	gyógyszer
II. Mérgező (LD_{50} = 25 – 200 mg / ttkg p. os)		
Kadmium-klorid	70–200	vegyszer
Nátrium-arzenit	25–50	vegyszer
Aldrin	40–80	inszekticid
Allilalkohol	50–150	
III. Ártalmas (LD_{50} = 200 – 2000 mg / ttkg p. os)		
Koffein	200–300	élvezeti szer
Phenobarbital	200–300	gyógyszer
Anilin	400–1000	vegyszer
Barium-karbonát	600–800	rodenticid / vegyszer
Nátrium-szalicilát	800–2000	gyógyszer
IV. Méregkategóriába nem sorolható (LD_{50} > 2000 mg / ttkg p. os)		
Butil-hidroxianizol	2000–5000	élelmiszeradalék
Acetonitril	2000–4000	oldószer
Etilénglikol	4000–8000	oldószer

other factors influencing the risk (apart from the dose)

other characteristics e.g.:

volatility

environmental persistence

elimination

bioaccumulation

biomagnification

e.g. DDT (dichloro-diphenyl-trichloroethane) *vs.* cholinesterase inhibitors

e.g. Minamata-disease: methylmercury in seafood

Factors influencing the effects of poisons

- species
- age
- dose
- concentration
- exposure time
- combinations (mixtures)

Factors influencing the effects of poisons

1. Species

atropine LD

- human → 2 mg/kg
- rabbit → 1500 mg/kg

DDT: LD rat/LD fly ≈ 100000

dioxin: LD50 guinea pig/LD50 hamster ≈ 1000

extrapolation: animal → human ???

2. Age

infants are more sensitive

- morphine
- ethanol
- chloramphenicol

elderly

- slower elimination → $t_{1/2}\uparrow$

Factors influencing the effects of poisons

3. Dose

dose-response curves:

graded

quantal → sensitivity of a population

lognormal distribution

ED50, LD50

Factors influencing the effects of poisons

4. Concentration

corrosives (acids, bases)

5. Exposure time

gases: c x t ≈ can be constant

6. Combinations, mixtures

additive

potentiating

antagonist

Factors influencing the effects of poisons:

Toxikokinetics

absorption

distribution

elimination

- biotransformation
- excretion

ABSORPTION

depends on solubility

e.g. $Hg \leftrightarrow HgCl_2$

e.g. As_2O_3

Toxikokinetics: DISTRIBUTION/1

can depend on time

arsenic

acute: gastrointestinal, liver, kidney

chronic: hair, skin, bone

can influence the effect

$Hg^{++} \rightarrow$ kidney

$Pb \rightarrow$ bone

Toxikokinetics: DISTRIBUTION/2

Volume of distribution = V_d

V_d = (amount of poison in the body)/(C_{plasma} or C_{blood})

It is not possible to determine the amount of poison in the body based on C_{plasma} or C_{blood} without the knowledge of V_d

if V_d >> 1 liter/bwkg → hemodialysis is not effective (e.g. digoxin)

if V_d ≈ 80 ml/bwkg → poison is in the blood

→ blood exchange, plasmapheresis is effective

Toxikokinetics:

ELIMINATION

biotransformation can

decrease: $CN^- \rightarrow SCN^-$

or **increase**: methanol → formaldehyde → formic acid

toxicity

EXCRETION

for some poisons the only effective final elimination mechanism (e.g. Hg)

its location can determine the location of damage (Hg → kidney)

its promotion can be useful

change urine pH

increased diuresis

Toxikokinetics

Clearance = CL

$CL_{total} = CL_{kidney} + CL_{liver} + CL_{other}$

if target organ is the location of excretion → long duration of action

proportion of organ CL → detoxification strategy

Concentration in blood or plasma as a function of time

depends on the elimination mechanism

saturated: zero order kinetics, linear decrease (e.g. ethanol)

non-saturated: first order kinetics, exponential decrease

Toxikokinetics

Large doses

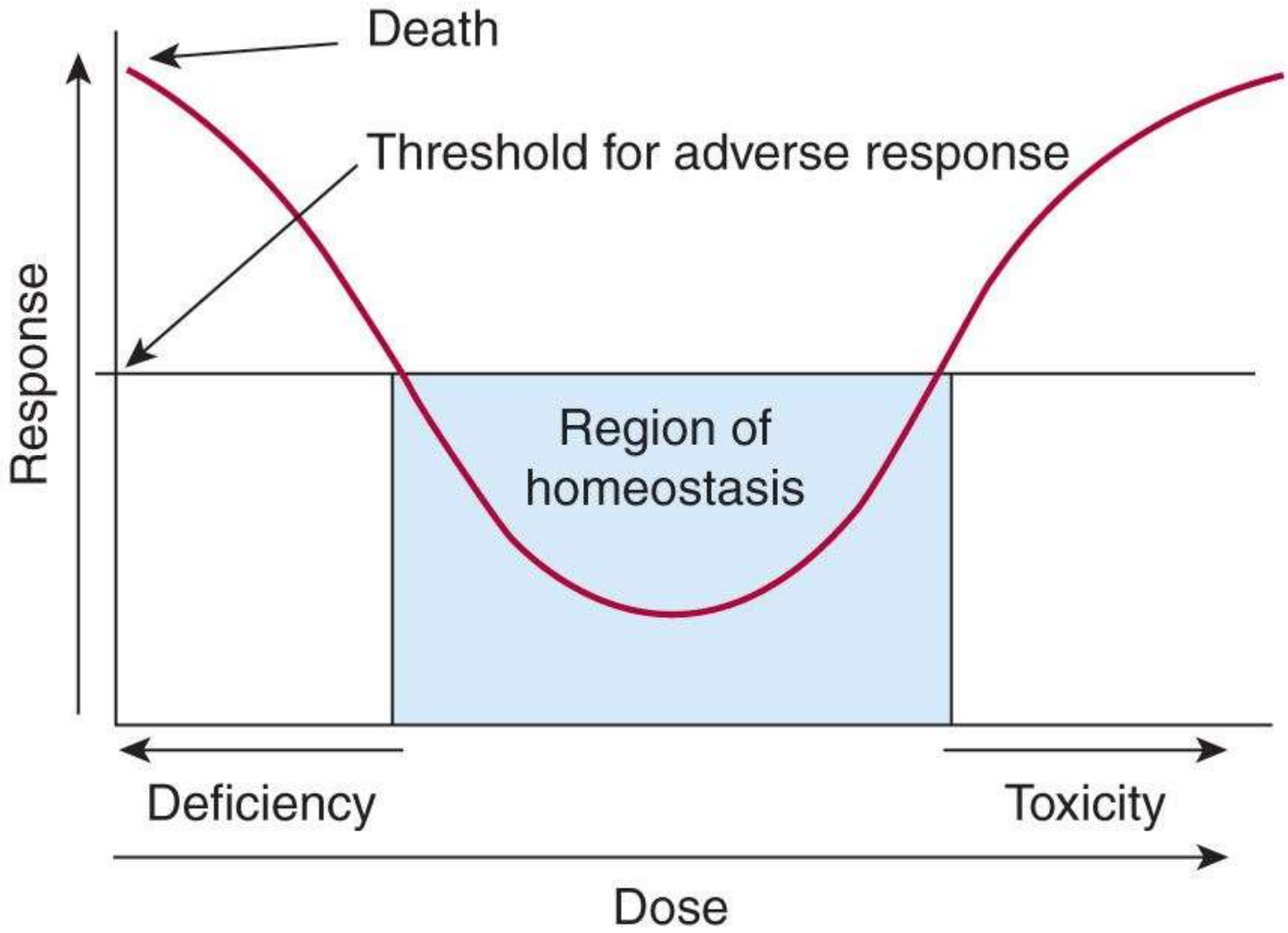
can saturate elimination mechanisms
can saturate plasma protein binding sites → free drug↑
can decrease first-pass effect
    thus increase bioavailability
can damage
    eliminating organs
    blood circulation

result:

decreased CL
increased half life
INCREASED TOXICITY

enterohepatic circulation

Dose-response relationship for an essential compound



Alcohol intake and risk of mortality

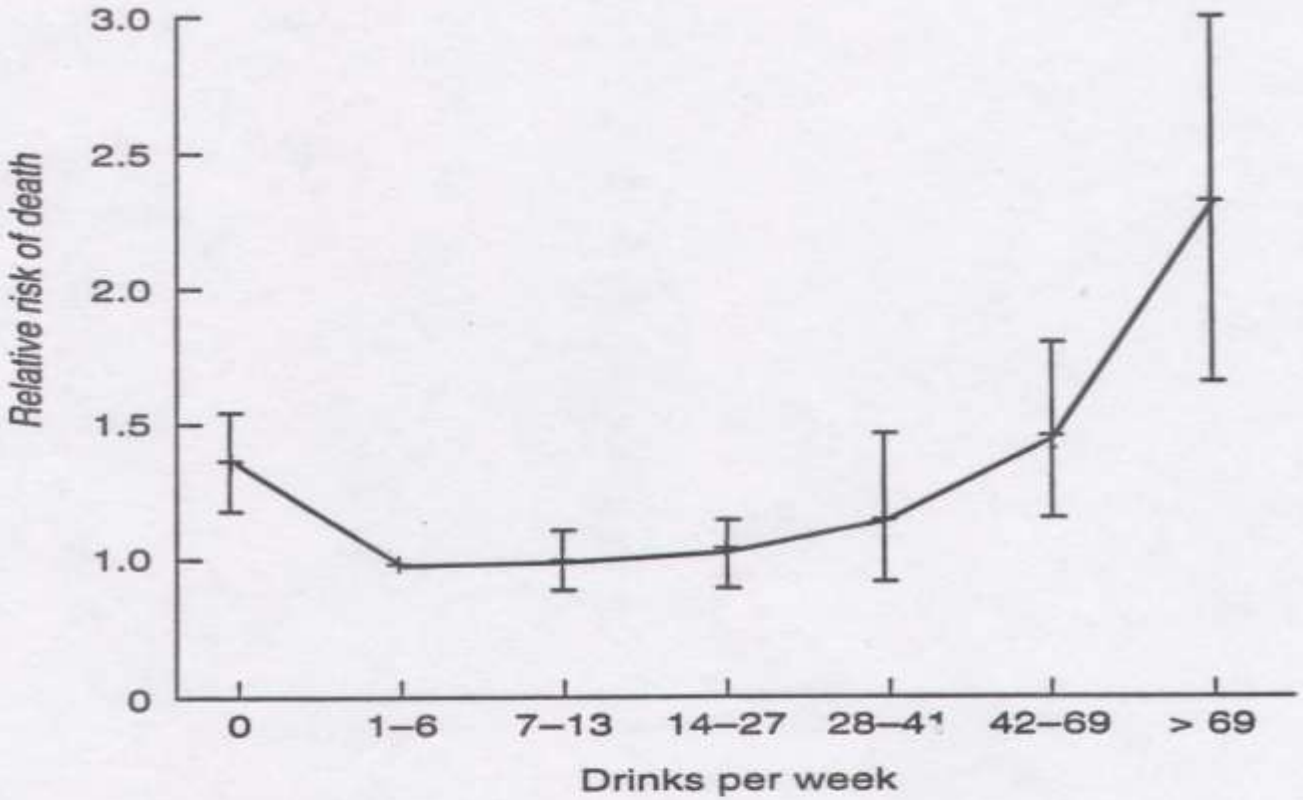


Figure 23–2. Risk of mortality relative to alcohol intake. The graph shows the results of a 10- to 12-year study of 13,000 Danish men and women. The risk of mortality was set at 1.0 for the group with the lowest mortality. (Modified and reproduced, with permission, from Grønbæk et al: Influence of sex, age, body mass index, and smoking on alcohol intake and mortality. Br Med J 1994;308:302.)

Management of the poisoned patients

MAINTAIN VITAL FUNCTIONS

see OXYOLOGY

TODO

1. Before absorption
2. After absorption

Before absorption

Skin

Remove contaminated clothes,

soak up

wash with large amount of water

acids, bases

neutralization $\rightarrow$ loss of time, exothermic reaction

lipid soluble compounds should be washed

- with alcohol,
- oil, or soap and water

Subcutaneous, intramuscular (injection, snake bite)

incision, wash out with sterile NaCl ?

adrenaline, tourniquets ?

Before absorption

Eye

wash with water: acid, bases 15-20 min
opened eyes!
do not neutralize

Oral

Emesis ? No !

obsolete emetics: NaCl, $CuSO_4$

apomorphine / fingertip stimulation of the pharynx: not effective

ipecac syrup

use is declining (10% in 1987, 0.1% in 2007), routine use is not recommended ?

keep the first vomit for poison identification

Before absorption

Gastric lavage

first with clean water: keep

Contraindications of emesis and gastric lavage

-unconsciousness – only when endotracheal intubation,
-**corrosives**
-**petroleum and derivatives**
-**drugs causing convulsions** (e.g. TCA, theophylline)
-pulmonary edema
-severe heart disease
-pregnancy (later stages)

Catharsis, enema

Balanced PEG – isosmotic electrolyte solution – no electrolyte disturbances

Before absorption
NEUTRALIZATION - BINDING

Physicochemical binding

Activated charcoal

not bind: $FeSO_4$, alcohol, corrosives

Bolus alba = white, kaolin, mixture of purified Al-silicates

binds only basic compunds

Proteins: milk, egg white

Paraffinum liquidum = mineral oil, not absorbed

bind lipid soluble compunds, used also as a laxative

Chemical neutralization

Poison must be known

acid, base ??? **DO NOT USE Na-bicarbonate (=Na-hydrogen carbonate=$NaHCO_3$)**

dilution, milk is better (but milk protein precipitation might disturb gastroscopic examination)

making the poison insoluble:

oxalic acid and fluorides: Ca-salts

After absorption

Interruption of enterohepatic circulation

binding of absorbed poison in the gastrointestinal tract

e.g. tallium – Prussian blue

After absorption: promote elimination

Promote biotransformation

Promote natural detoxifying biotransformation:

Na-thiosulfate ($Na_2S_2O_3$): $CN^- \rightarrow SCN^-$ (sulfur donor)

Chemical/immunological antagonists

acidosis: alkalinization

Antibodies against antigenic poisons:

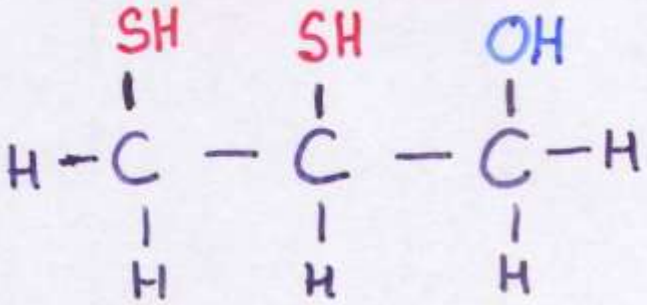
- snake and spider venoms
- botulinum-toxin
- digitalis-glycosides - sheep $IgGF_{ab}$

After absorption: promote elimination

- chelators for metal poisons
  - two or more electronegative moieties (electron donor) - OH, SH, NH_2
  - coordination bound with metals (≥ 2)
  - the bound metal is
    - not available for toxic interactions
      - e.g. with functional groups of enzymes or other proteins
    - excreted in urine
      - may also result in **redistribution** (e.g. dimercaprol: Hg, As → brain / cadmium → kidney → nephrotoxicity)
  - dimercaprol
  - succimer
  - ethylenediaminetetraacetic acid (EDTA)
  - deferoxamine
  - D-penicillamine

DIMERCAPTOPROPANOL = DIMERCAPROLUM

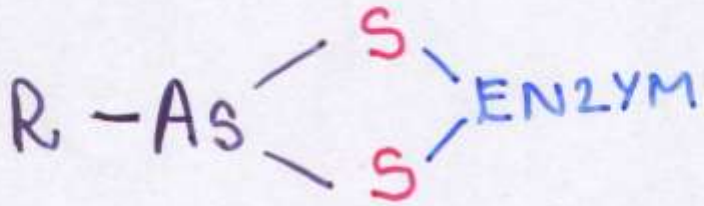
Ph. Hg VII



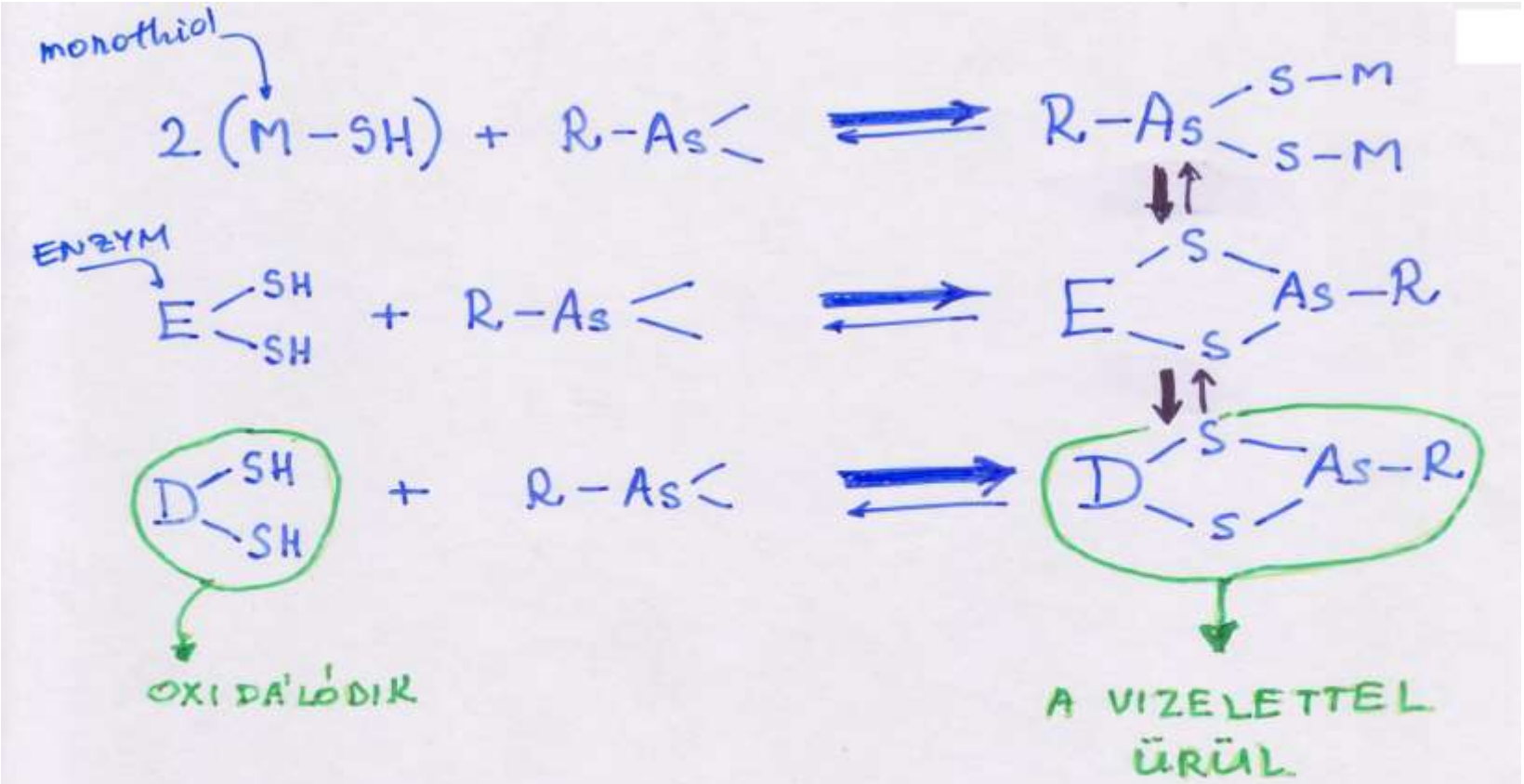
= DICAPTOL

= BAL

(BRITISH ANTI-LEWISITE)



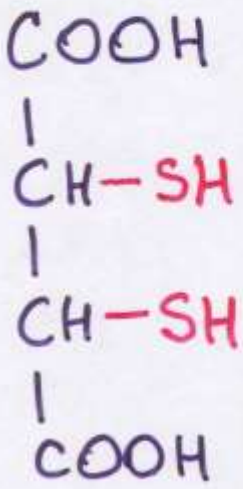
Dimercaptopropanol - BAL



painful **intramuscular** injection (aqueous unstable → peanut oil)
administer a lot, quickly and repeatedly

acute As, Hg and Pb (in combination with $CaNa_2EDTA$)
frequent **adverse effects** → rarely used nowadays

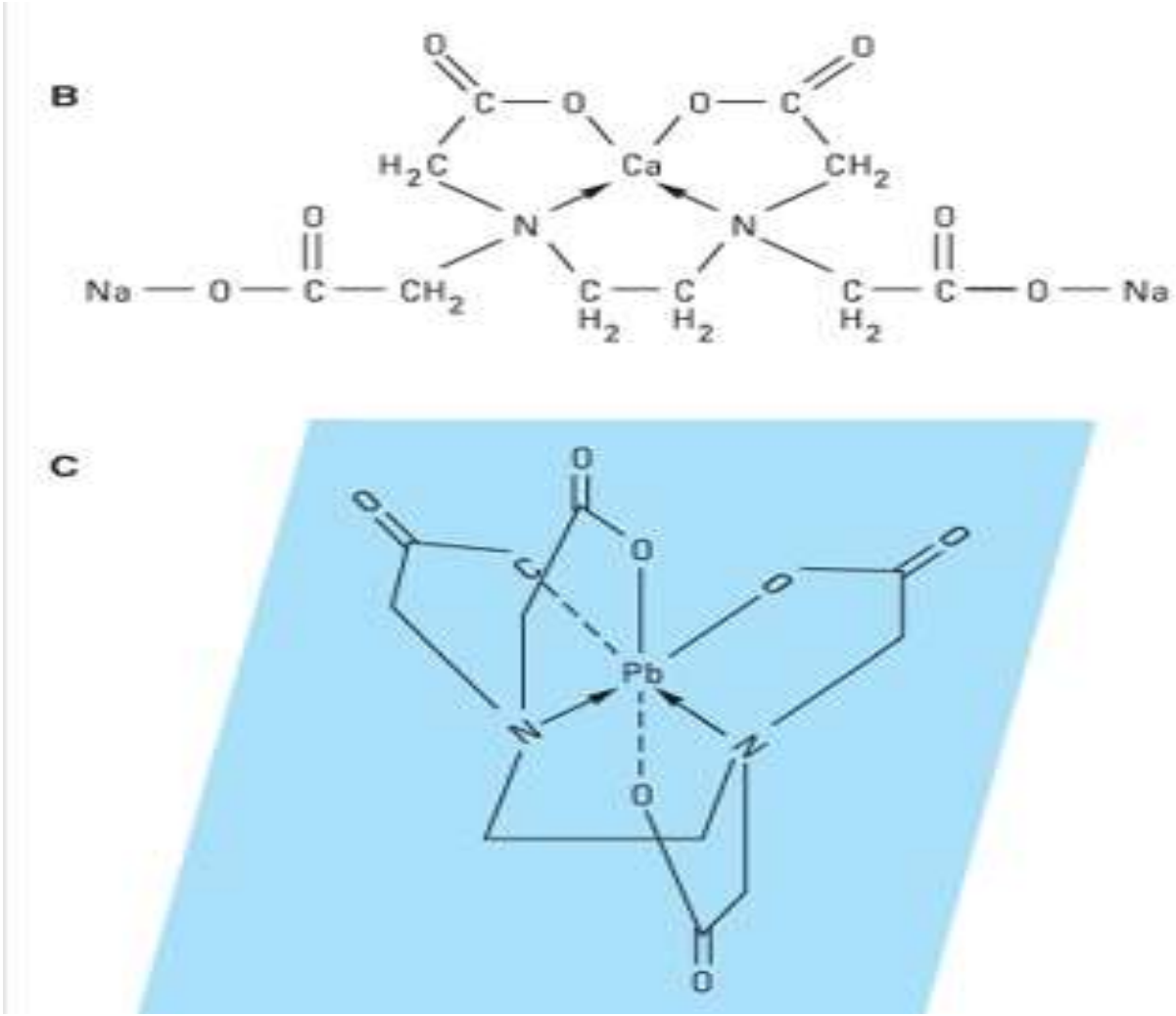
DIMERCAPTOSUCCINIC ACID
(= DMSA = SUCCIMER)



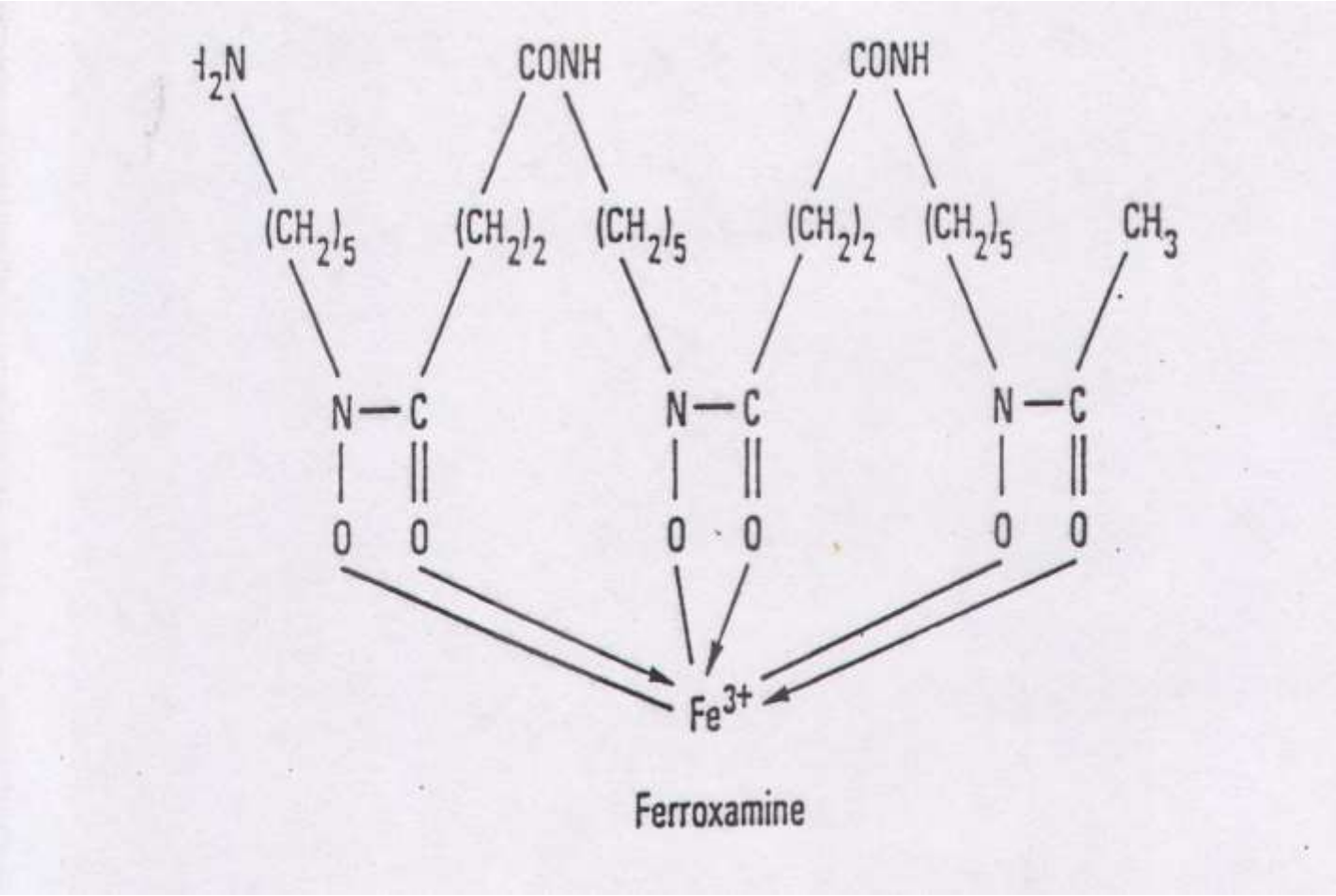
oral and less toxic than dimercaprol

Hg, Pb, As

EDTA + Pb



DEFEROXAMINE

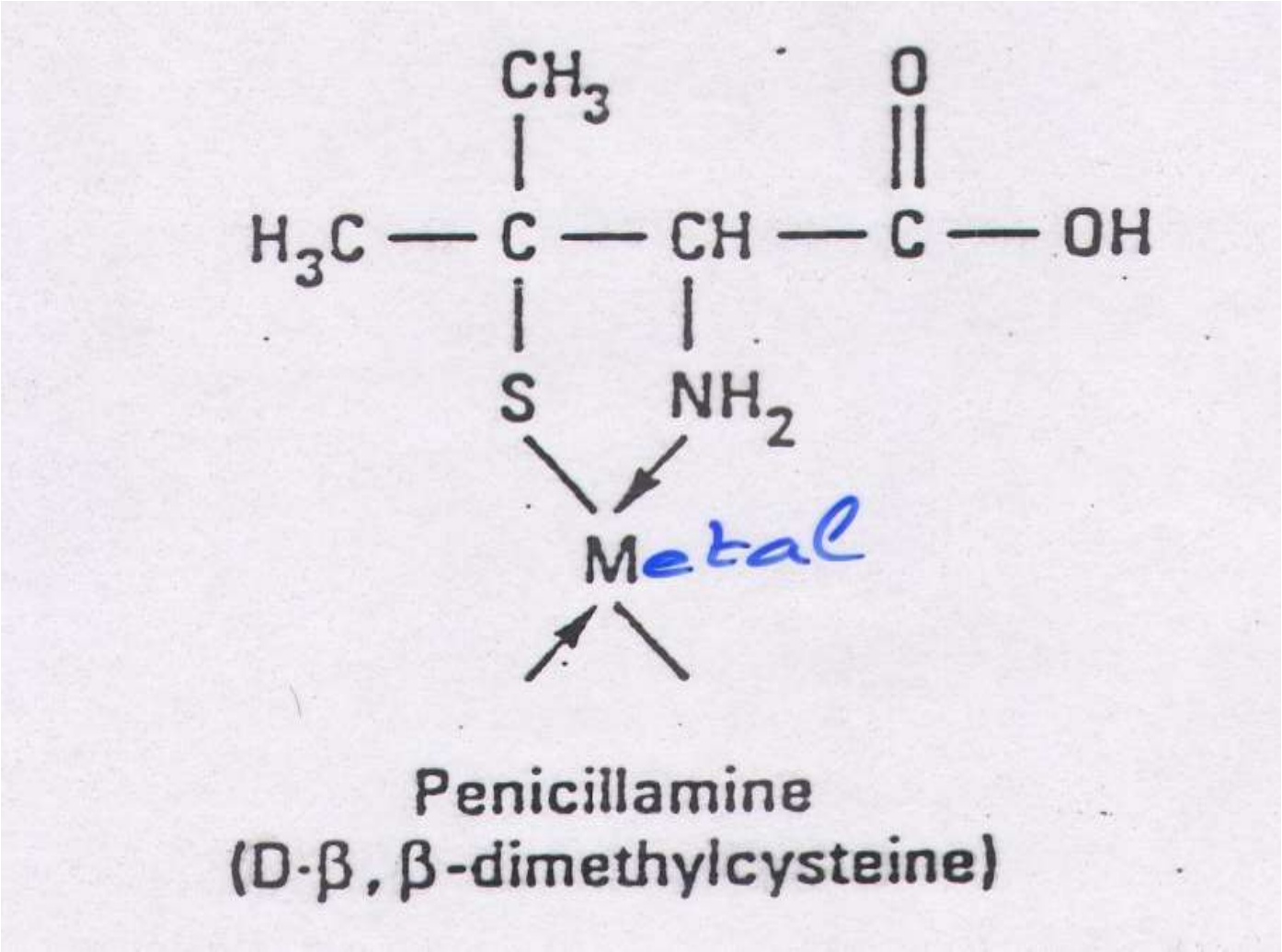


Ferroxamine

Acute iron intoxication

- as few as 10 tablets can be lethal in toddlers / children
- necrotising gastroenteritis
  - shock → death
- improvement, maybe only transient
  - liver damage
  - metabolic acidosis
  - coma → death
- treatment
  - whole bowel irrigation with balanced PEG solution
    - activated charcoal is **NOT** useful
  - deferoxamine (Desferal – from *Streptomyces pilosus*)
    - oral: binding of not absorbed Fe (?)
    - slow **i.v. infusion** (risk of hypotension)

penicillamine



Penicillamine
(D-β, β-dimethylcysteine)

Extracorporeal drug removal

- peritoneal dialysis
- hemodialysis
  - e.g. methanol, ethylene glycol, salicylate
- hemoperfusion
- plasmapheresis

Mérgező ágens	Antidótum
Gyógyszerek	
Antikolinerg szerek	Physostigmin
Benzodiazepinek	Flumazenil
Digitálisz-glikozidok	Digitalis-antitoxin
Opioidok	Naloxon
Paracetamol	N-acetilcisztein
Fémek	
Arzén	Ditiol-kelátorok (dimercaprol, succimer)
Higany	Ditiol-kelátorok + penicillinamin
Ólom	$CaNa_2$-EDTA + ditiol-kelátorok + penicillamin
Réz	Penicillamin, trientin
Vas	Deferoxamin
Egyéb mérgek	
Cianid, kénhidrogén	Amilnitrit + $NaNO_2$ + $Na_2S_2O_3$
Kolinészteráz-gátlók	Atropin + pralidoxim
Metanol, etilénglikol	Etanol, 4-metil-pirazol
Szénmonoxid	O_2