Introduction to pharmacology

2019

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What is Pharmacology?

- **Studies the interaction between living organisms and compounds that affect their functions (i.e. *pharmacons*)**

- **A discipline dealing with compounds used for *prevention*, *diagnosis* and *treatment* of diseases**

Major chapters of Pharmacology

General pharmacology

- history
- physical / chemical characteristics
- pharma industry and drug development
- absorption
- distribution
- biotransformation
- elimination

Pharmacokinetics

- biochemical / physiological effects
- mechanism of action

Pharmaco-dynamics

Detailed

- therapeutic (and other) use
- clinical pharmacology
- toxicology, safety, pharmacovigilance

Pharmacology

Pharmacodynamics

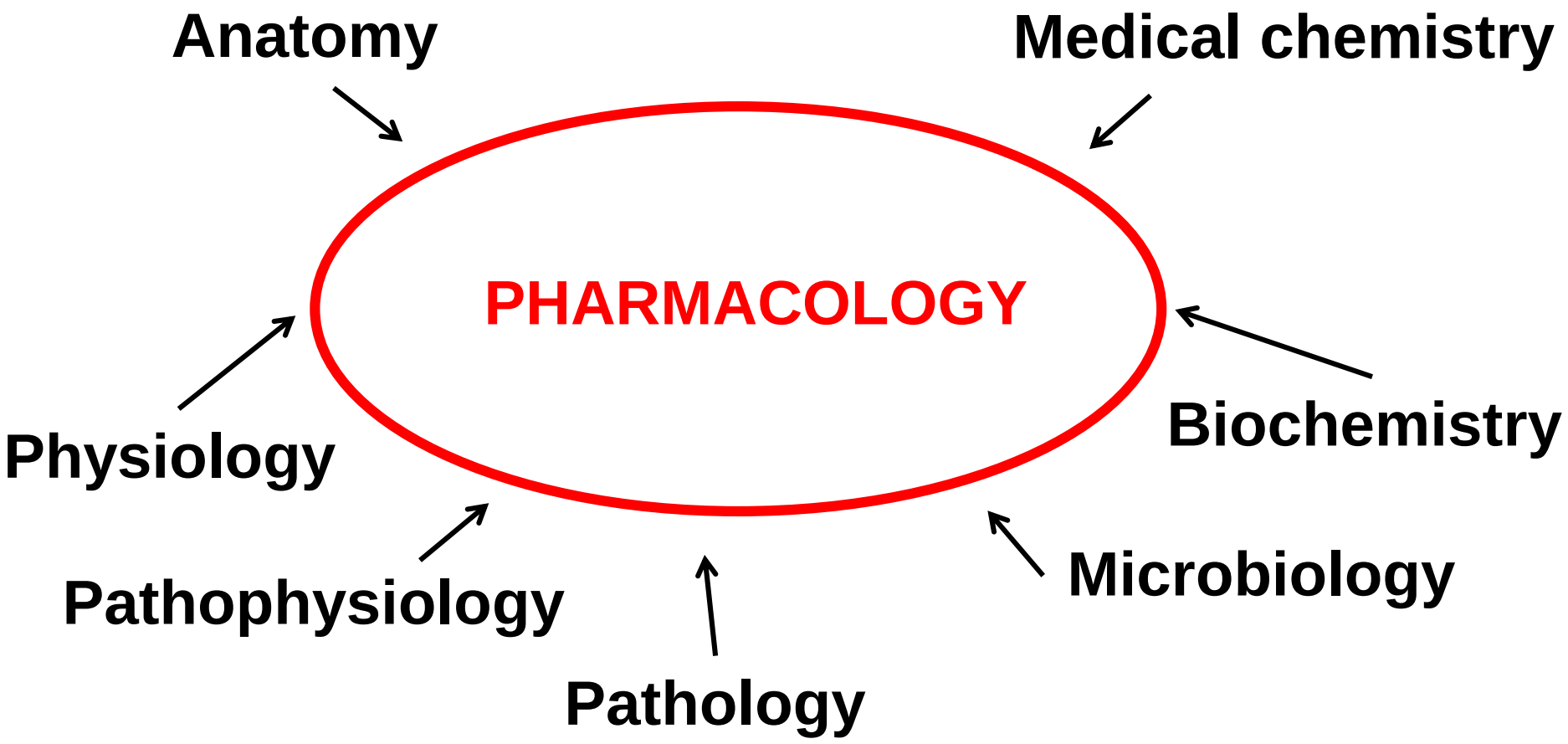
The actions of the drug on the body
(where, how, why does an effect occur?)

Pharmacokinetics

The actions of the body on the drug

(the fate of the drug in the body)

Pharmacology is multidisciplinary



History of medicinal treatment

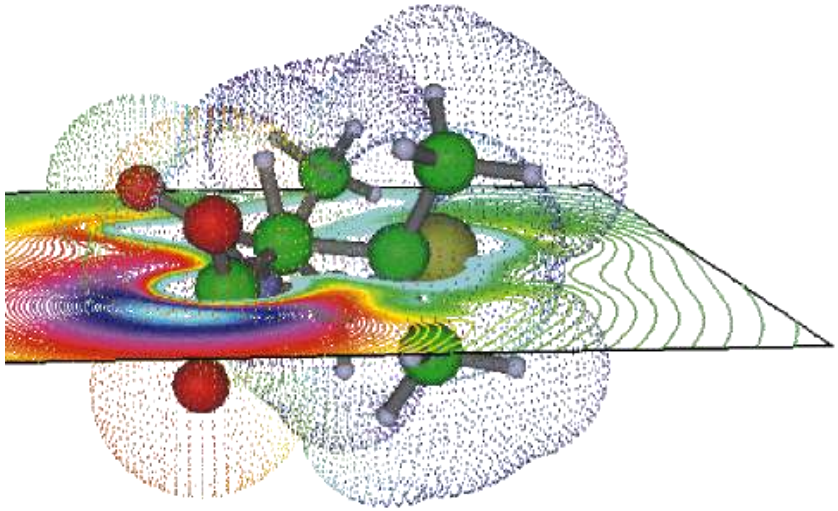
„The desire to take medicine is perhaps the greatest feature which distinguishes man from animals.”

Sir William Osler 1849-1919
(Founder of the John Hopkins Hospital)

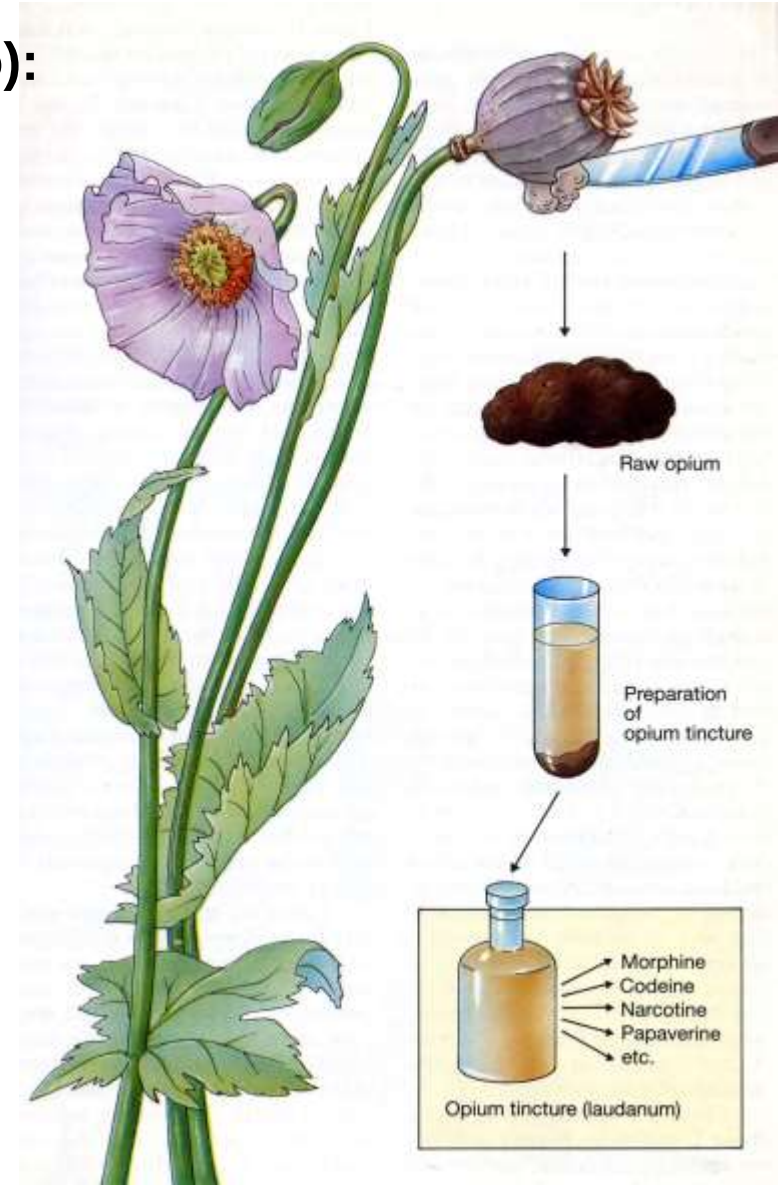
History of medicinal treatment

- **from plants (from thousands of years ago):**
  coffee, fungi, chinese medicines,
  arrow poisons

- **via computational chemistry**



to „biotechnological” processes



History of medicinal treatment

- Claudius Galenus (2nd century): classification of pharmacons
- Paracelsus (1493): use of metals (arsenic, mercury) – medicinal chemistry
- **allopathy** (18th century) – to treat or supress symptoms (emetics/laxatives, phlebotomy, etc)
- **homeopathy** (Hahnemann, 19th century)
  dilution increases efficiency (10^{60}× dilution)
- natural (plant-based) drugs (20th century)
- synthetic (chemical) + natural drugs
- biotechnology – gene therapy
  (antibodies, enzymes, hormones, cytokines, etc.)
- evidence-based medicine: clinical trials

History of medicinal treatment

Discovery of anesthetics

- Humphry Davy:
  1800: N_2O (nitrous oxide) inhalation: laughing, dizziness, erotic hallucinations

- Horace Wells:
  1844: discovery of the narcotic effect of N_2O, successful self test,
  1845: failure in Boston

- William Thomas Green Morton:
  1846: ether narcosis

- November 1947, succesfull narcosis with chloroform (became the anestehtic of choice)

The first public demonstration of operation under anesthesia: Boston, Oct 16, 1846 (William Thomas Green Morton)

History of medicinal treatment

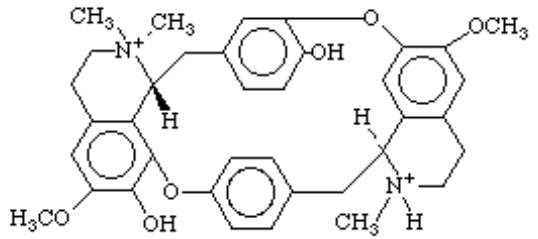
Curares - Non depolarizing muscle relaxants

- **In South-America, (Amazonas-Orinoco) it was in use by natives a very effective arrow poison**
  - **stored in bambus tubes: „tubo” – tubocurare**

History of medicinal treatment

Curares - Non depolarizing muscle relaxants

- **the effect of curare was described by Claude Bernard in 1857**



- **it was the first pharmacological experimental procedure**


INTRODUCTION

MÉDECINE EXPÉRIMENTALE

M. CLAUDE BERNARD

PARIS

„In June 1844 I made my first experiment with curare: I inserted under the skin of the back of a frog a small piece of dry curare, and observed the animal. Initially, the frog moved and jumped around with great agility, then it became quiet, the body became flat and gradually subsided. After several minutes the frog was dead, that is to say, that it had become limp, and pinching the skin produced no reaction.

On opening the poisoned frog, I saw that its heart continued to beat. Its blood became red on exposure to the air and appeared physiologically normal. I then used electrical stimuli as the most convenient method of provoking a reaction in the nerves and muscles. Stimulating the muscle directly produced violent contractions in every part of the body, but on stimulating the nerves there was no reaction. The nerves, that is, the bundles of nervous tissue, were completely dead, while the other bodily components, the muscles, the blood, the mucous membranes, retained their physiological properties for a number of hours, as one sees in cold blooded animals....

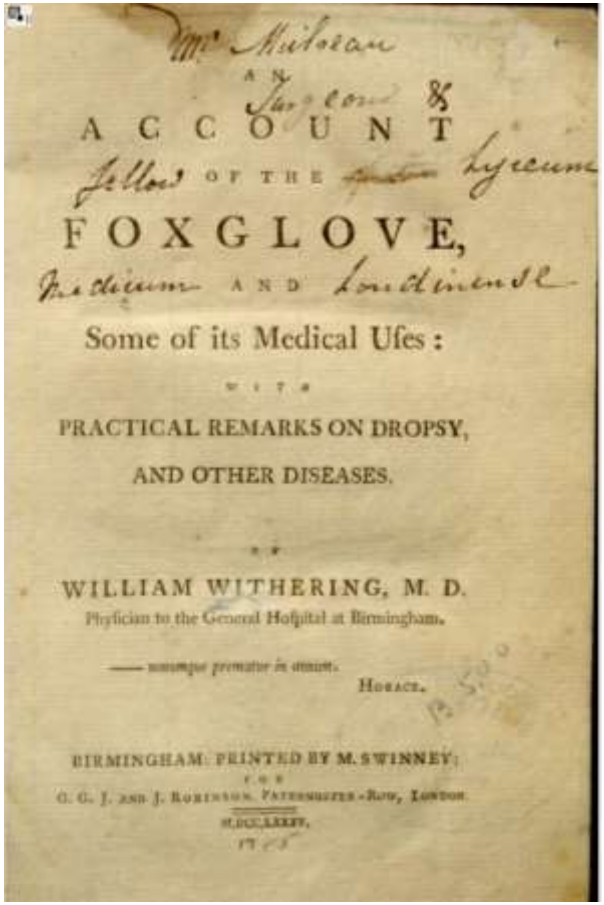
That first analytical experiment on the frog was later repeated on a number of animals more closely related to man and belonging to the classes of birds and mammals. I have found identical results, and the `physiological autopsy' showed me that, as in the frog, the motor nerves are the only tissues affected by curare, while the other components of the body retain their physiological properties."

History of medicinal treatment

Cardiac glycosides- effective in heart failure

Dr. William Withering – 1785

English physician and botanist published a monograph describing the clinical effects and side effects of the purple foxglove plant.



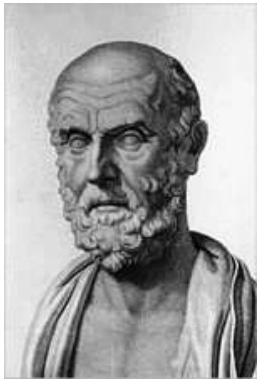
AN
ACCOUNT
OF THE
FOXGLOVE,
AND
Some of its Medical Ufes:
WITH
PRACTICAL REMARKS ON DROPSY,
AND OTHER DISEASES.

WILLIAM WITHERING, M. D.
Phyfician to the General Hofpital at Birmingham.

HORACE.

BIRMINGHAM: PRINTED BY M. SWINNEY;

History of medicinal treatment



willow bark (Salix alba)

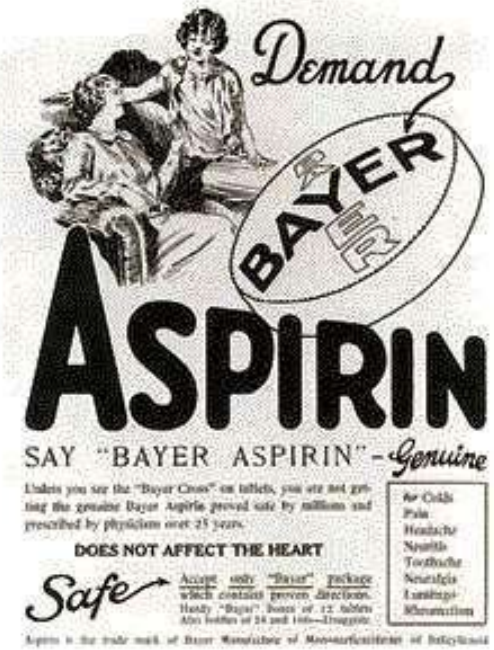
Filipendula (spiraea) ulmaria
- bridewort,meadowsweet

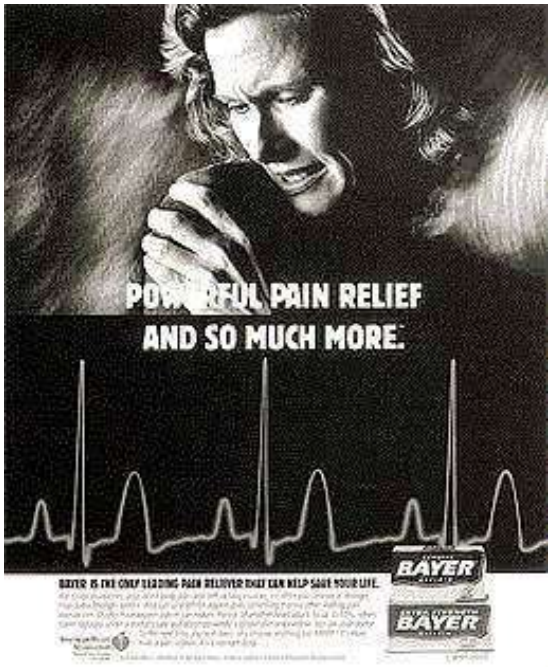
Charles Frederic Gerhardt 1853 - synthesized acetylsalicylic acid

Felix Hoffmann 1897 - rediscovered acetylsalicylic acid
(for his fathers' rheumatism)
and it was marketed as Aspirin

(the name comes from the '**A**" in acetyl chloride, the "**spir**" in spiraea ulmaria (the plant they derived the salicylic acid from) and the '**in**' was a familiar name ending for medicines)

History of medicinal treatment





1980's - The FDA approves aspirin for reducing the risk of recurrent myocardial infarction (MI) and preventing first MI in patients with unstable angina.

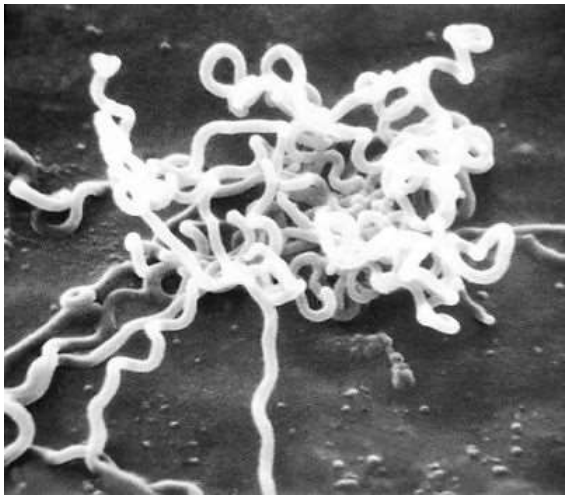
The FDA also approved the use of aspirin for the prevention of recurrent transient-ischemic attacks and made aspirin standard therapy for previous strokes.

History of medicinal treatment

Paul Ehrlich – 1910

- *Salvarsan*, a synthetic preparation containing arsenic, is lethal to the microorganism responsible for syphilis.

- This success inaugurated the chemotherapeutic era, which was to revolutionize the treatment and control of infectious diseases



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  (antibodies, enzymes, hormones, cytokines, etc.)
- evidence-based medicine: clinical trials

What can be a medicine?

any substance:

- synthesized in the body (e.g. hormones)
- not synthesized in the body (xenobiotics)
- poisons (e.g. arsenic)
- toxins (poisons with biological-, plant-, animal- origin)
- important features of drug molecules:

  - size 7-50000 Da
  - most drugs are **small molecules**, i.e. 100-1000 < Da)
  - macromolecules (peptides, proteins, nucleic acids)

    „biologics”
  - transportability (inactivation/elimination)
  - binding to drug receptors (enzymes, ion channels, nucleic acids, etc) „key and keyhole”

What can be a medicine?
Biologics / macromolecules

Medicines made **from biological sources** (extracted from plants, animals, humans, or synthesized by biotechnological techniques):

- **not possible to fully characterize (mostly proteins)**
- combination of **physical, chemical and biological methods are necessary for their production** and control of their quality
- safety problems: unexpected consequences
- pharmacokinetic problems: unusual pharmacokinetics, not fully understood
- **expensive** to develop and manufacture

- several hundred products on the market, e.g. recombinant insulin, growth hormone, antibodies, etc

What can be a medicine?
Biologics - „Advanced therapy medicinal products" ATMP

2009/120/EC Directive (Advanced Therapy Medicinal Products):

- **Gene therapy medicinal products:**

-recombinant nucleic acid for the regulation, repair, substitution, addition or delation of a specific gene sequence

- **Cell therapy medicinal products (manipulated cells):**

-E.g. autologus chondrocytes, corneal epithel cells

- **Tissue therapy medicinal products (manipulated tissues)**

- **Combination** of the above **with medical devices**

Drug development and pharma industry: research and preclinical phase

drug „target” discovery:

-Target discovery

- Target validation (genetically modified animals)

- Development of measurement of key parameters of the target

Discovery of the pharmacon:

- *in silico* molecular design (performed on computer)

- chemical synthesis

- HTS (High throughput screening) ***hit***

Development of „Lead molecule”:

- structure-effect analysis: ***„lead optimization”***

- testing the efficacy *in vitro, ex vivo*

- *in silico* toxicology

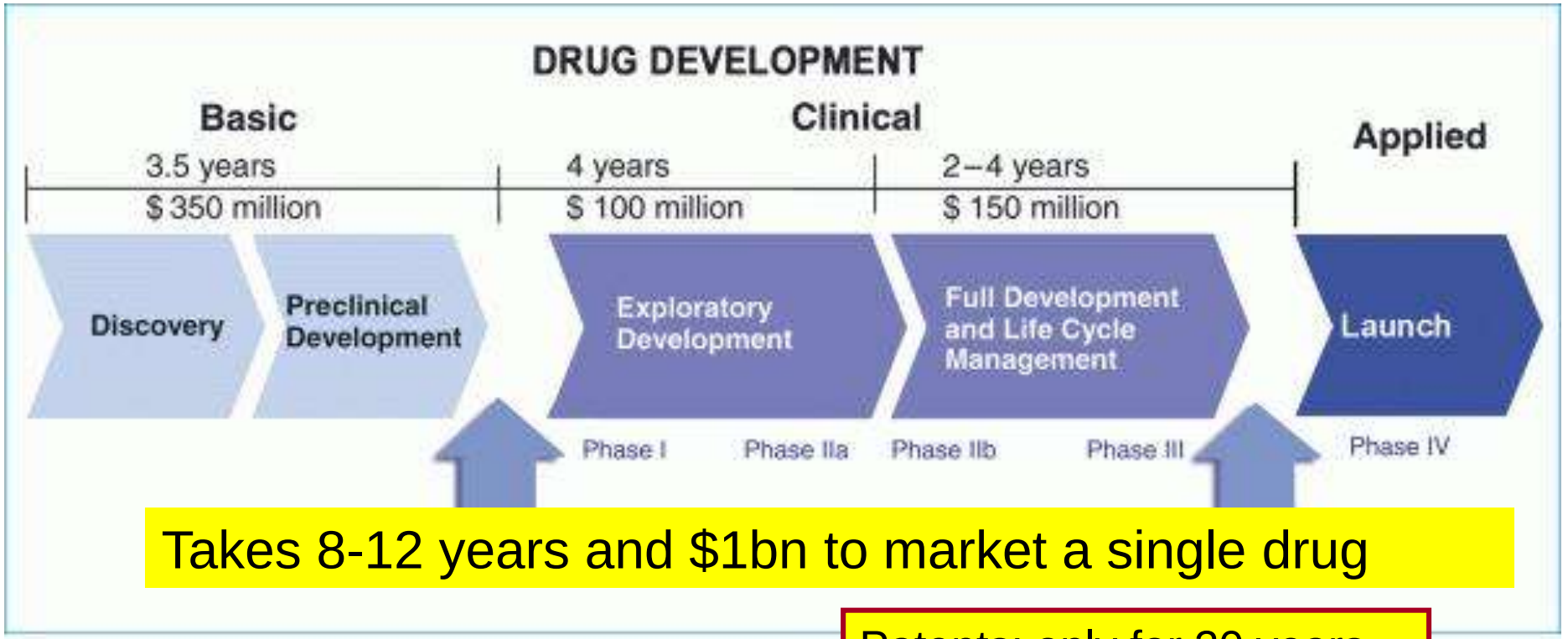
Preclinical pharmacology:

- pharmacokinetics & toxicology

- pharmacodynamics *in vivo*

- Safety pharmacology

Drug development and pharma industry:



Takes 8-12 years and $1bn to market a single drug

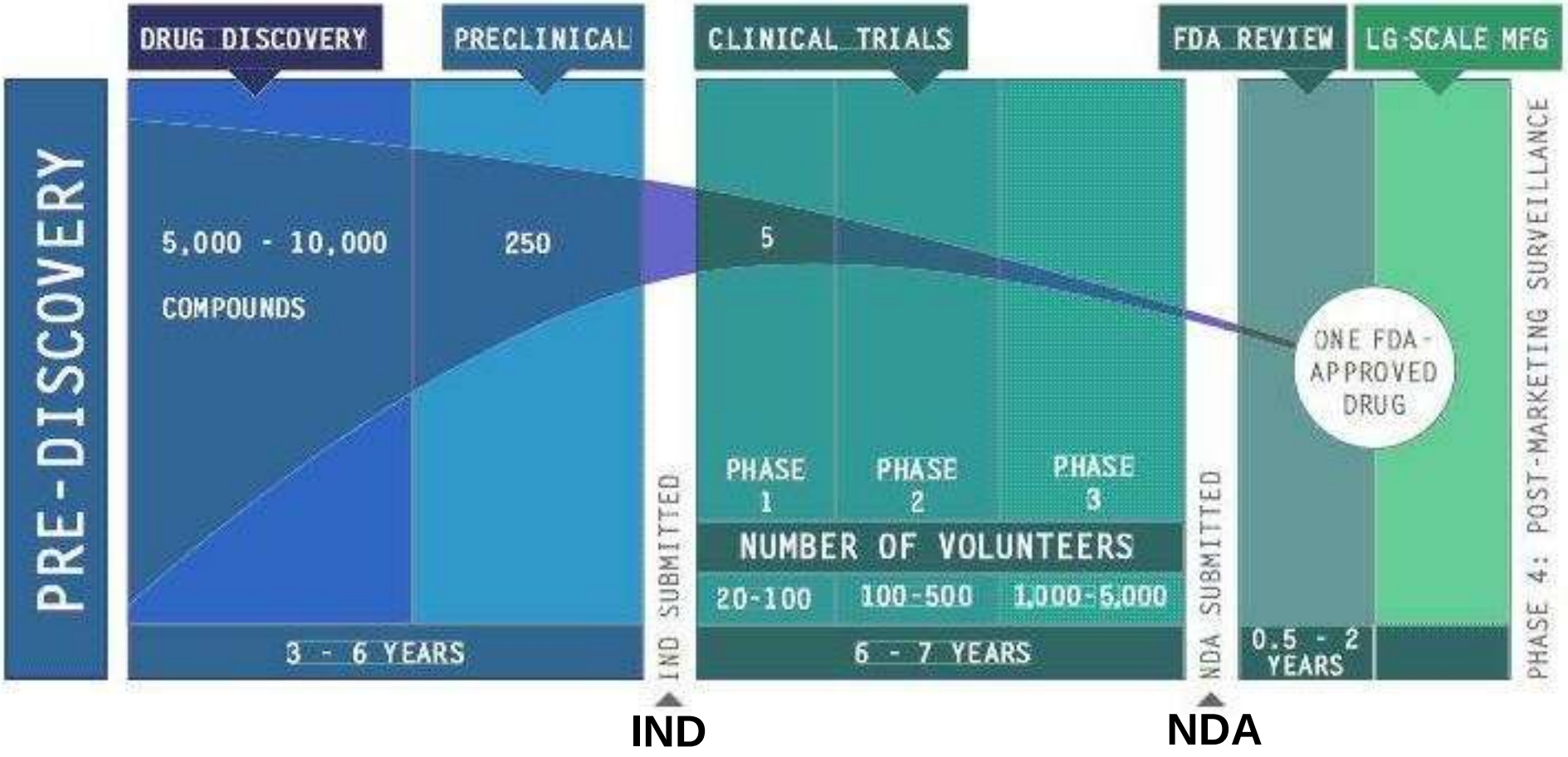
Mattisson DR, Mattison Faye AC Blickpunkt der Mann 2008;

Patents: only for 20 years

High risks: private investments

Drug promotion: strictly regulated in the EU and USA

Drug development and pharma industry: risk of drug develpment is extremely high



High risk of development: role of private capital, health insurance

Drug development and pharma industry: clinical phases (efficacy & safety)

Phase I, human tolerance and pharmacokinetic study

- Titration of the clinically applicable dose range
- Description of the human pharmacokinetics and metabolism
- Number of subjects is small (20-100)
- Usually healthy volunteers
- In special cases, patients (e.g., oncology)

Drug development and pharma industry: clinical phases (efficacy & safety)

Phase II study

- Description of the clinical efficacy of the drug ***(proof of concept)***
- Titration of the clinically effective dose range
- Few, selected patients with typical symptoms and without interfering conditions not connected to the disease (e.g. no co-morbidities)
- Number of subjects is small (50 - 200)

Drug development and pharma industry: clinical phases (efficacy & safety)

Phase III study

- **Proof of the efficacy** of the drug
- Always prospective, randomized study
- Control: placebo or known, effective drug
- Large number of patients (500 -5000). The patients represent the general practice, other alterations e.g. co-morbidities which might interfere with the evaluation, may be present

Drug development and pharma industry: clinical phases (efficacy & safety)

Phase IV study

- Studies performed exclusively in the indication and dose range listed in the marketing authorization „on label”
- Further investigation of the efficacy and adverse effects of the drug in the broad clinical practice
- Investigation of the optimal application of a new drug
- Incorporation of the new drug in complex drug treatment strategies
- Very large number of patients (>10000)

Drug nomenclature

- Company code
- Chemical name
- ***INN (International Non-proprietary Name; WHO assigns)***
- Trademark name

ATC classification:

(**A**natomic, **T**herapeutic, **C**hemistry) (WHO regulates)

The ICD system: (Internationale Klassifikation der Krankheiten, WHO)

Drug registration categories

National Institute of Pharmacy (www.ogyi.hu)
European Medicines Agency (www.ema.europa.eu)

- **Prescription drug**
- **OTC (Over The Counter) drug**
- Paramedicinal product
- Traditional herbal medicine (used for more than 30 years)
- Homeopathic composition

Similar or identical to drugs, but other categories (other regulatory bodies: e.g. European Food Safety Authority, EFSA)**:**

- Food supplements (*not a drug!*, e.g. multivitamins)
- Special Medicinal Food (e.g. multivitamins for diabetics)
- Medical devices and their combination with drugs (drug-device combinations, e.g. drug eluting stents)

Clinical pharmacology

- **Right drug for the right patient –** at a good price (pharmaco-economy)
- **Human studies:**
  - basis of ***evidence-based medicine***
  - efficacy and safety
  - human trials of new drugs
  - bioequivalency studies: generics, biosimilars
- **Drug level measurements, monitoring**
- **Pharmacotherapy recommendations:**
  - risk-benefit assessment, guidelines

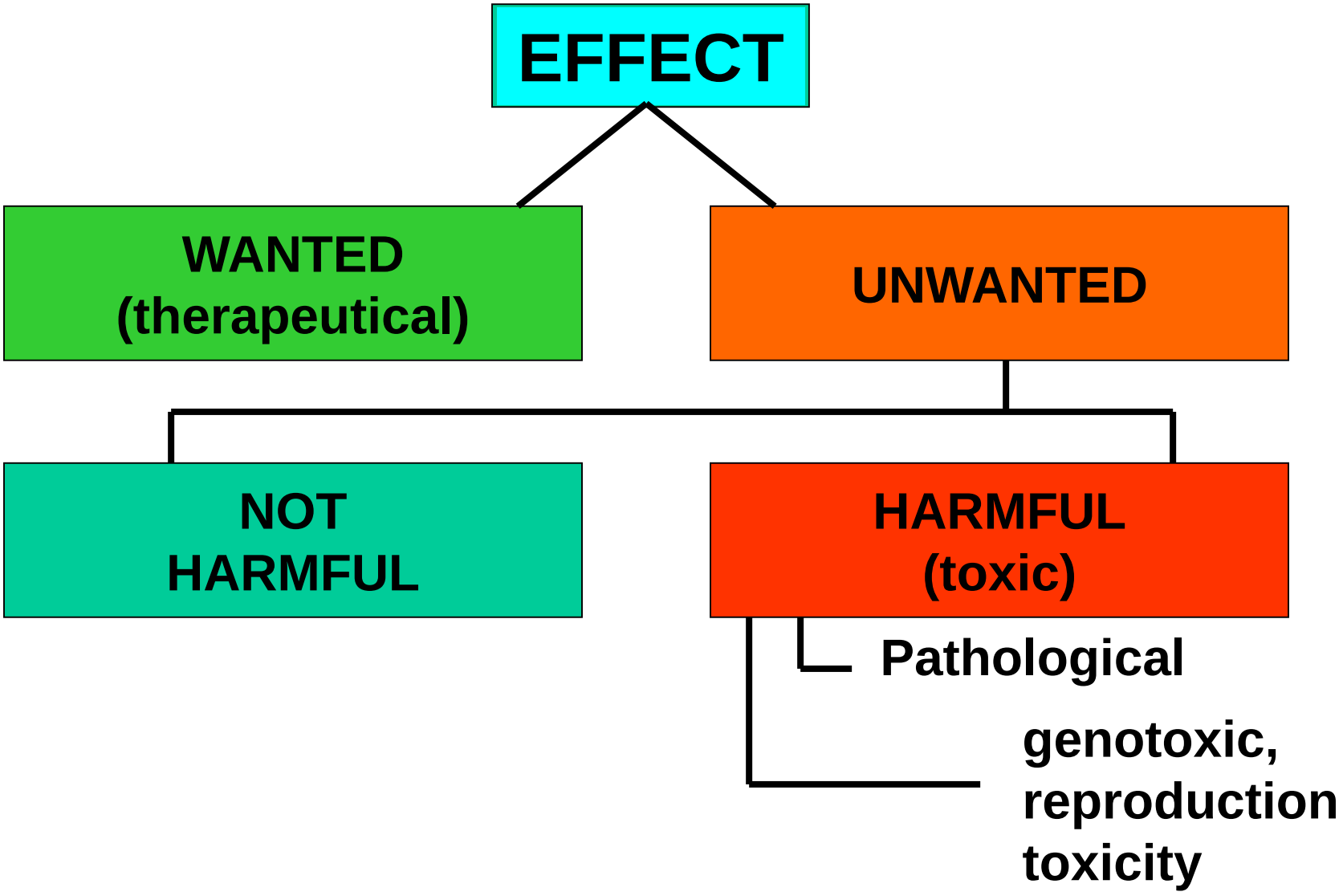
Toxicology

- A branch of pharmacology, that studies the **harmful effects** of medicinal products to the body
- Not only pharmacons, other chemicals as well
- **Prevention, diagnosis and treatment of these harmful effects**
- Studying the effects from cellular to ecosystem level

„THE DIFFERENCE BETWEEN A MEDICINE AND A POISON IS THE DOSAGE THEREOF”

(Paracelsus)

Toxicology


EFFECT
WANTED
(therapeutical)
UNWANTED
NOT
HARMFUL
HARMFUL
(toxic)
Pathological
genotoxic,
reproduction
toxicity

Toxicology: the „contergan scandal”

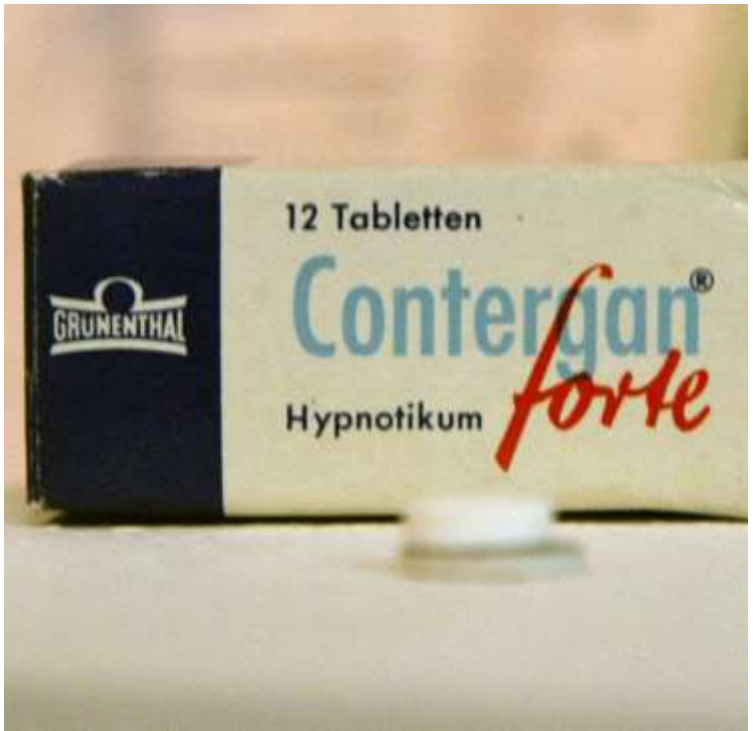
Thalidomide:

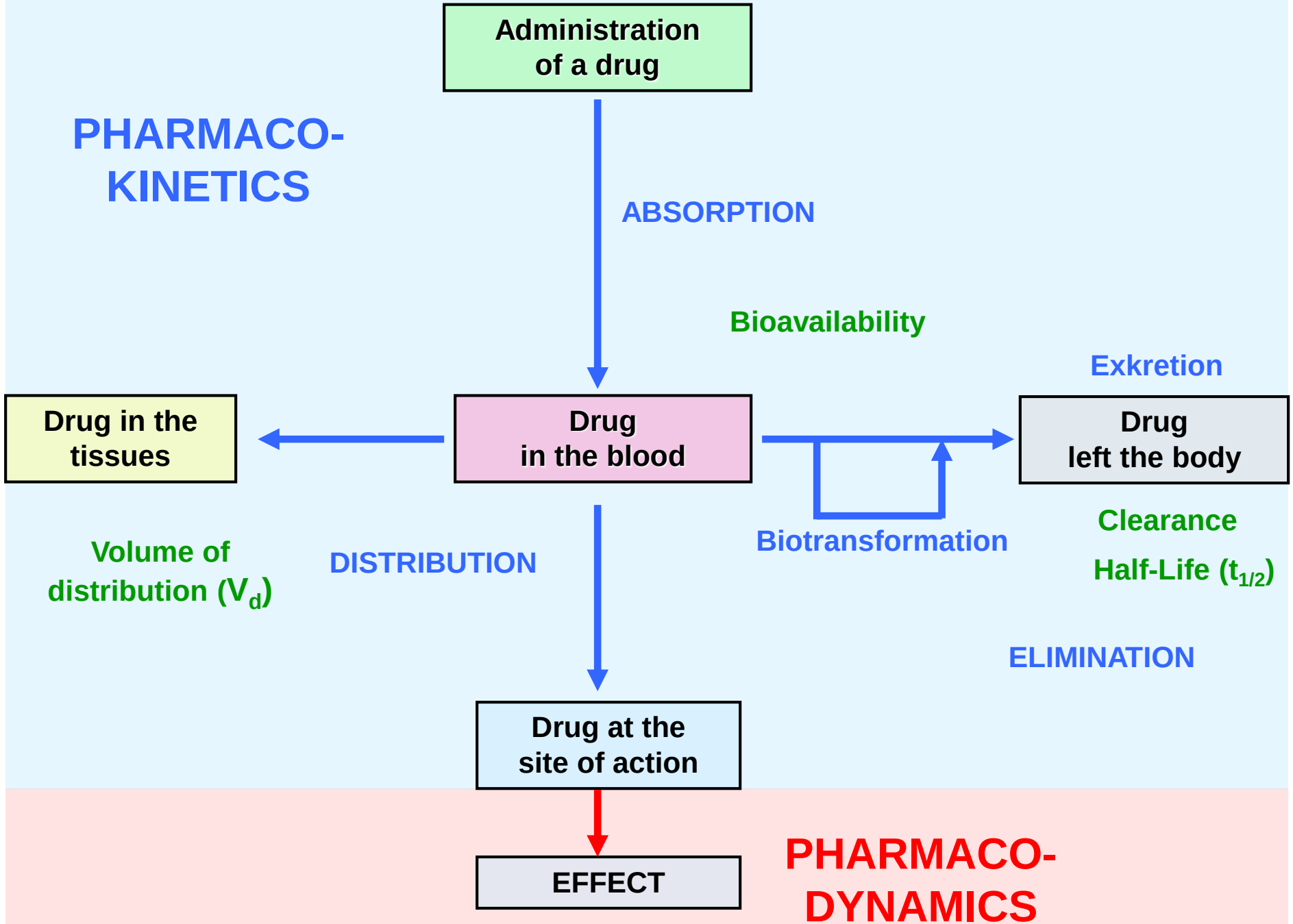
-sedato-hipnotic, 1957

- became OTC drug, also used against nausea and vomiting for pregnant women

- thousands of infants was born with deformities, 50% died – due to thalidomide (revealed in 1961)

- the scandal led to the development of modern drug regulations




Administration of a drug
PHARMACO-KINETICS
ABSORPTION
Bioavailability
Exkretion
Drug in the tissues
Drug in the blood
Drug left the body
Volume of distribution (V_d)
DISTRIBUTION
Biotransformation
Clearance
Half-Life ($t_{1/2}$)
ELIMINATION
Drug at the site of action
EFFECT
PHARMACO-DYNAMICS

Mechanism of action

- **non-specific**

  no specific interaction with biological structures

- **specific (receptor theory)**

  specific interaction with macromolecules - receptors

  L+R⇆[LR]→→E

Pharmacological receptor

dual fuctions

- **recognize the signal (bind the ligands)**
- **forward the signal and convert it to an effect**

Classification of the ligands

agonists

- bind to the receptor and activate it (cause an effect)

pure antagonists

- bind to the receptor but do not activate it (don't cause an effect)

Intrinsic activity

The ability of a ligand, after binding to the receptor, to cause an effect

$$\frac{E}{E_m} = \alpha \, f \frac{[LR]}{[R]}$$

$\alpha = 1$	full agonists
$\alpha = 0$	(pure, neutral) antagonists
$1 > \alpha > 0$	partial agonists
α is negative	inverse agonists

Antagonists

- pure (neutral) antagonists
- partial agonists as antagonists

- competitive antagonists
  - reversible antagonists
  - irreversible antagonists
- non-competitive antagonists

- chemical, functional and physiologic antagonists