Toxicology

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Text book

Liptáková, D., Prachar, V., Valík Ľ.:

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TOXICOLOGY

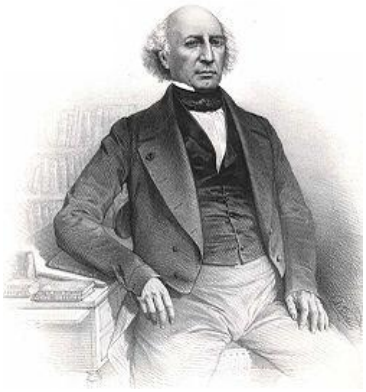
The oldest records on poisons: methods of their synthesis – Eber´s papyrus (1,500 BC). **Old Egyptians** recognized: conium, digitalin, opioids, Pb and Cu compounds etc.

At the beginning of ancient Greek culture (400 BC), physician **Hippokrates** has broaden knowledge on poisons – dosages and usage of poisons and medicaménts.

The king **Mithridates** used sentenced to search for antidota against poisons – **MITRIDATISM.**

The source of toxicology → exploition of poisons in assassinations, suicides. **Catherine di Medici** tested poisons on powerty and sick people and observed clinical symptoms. **Lucrezia Borgia** (1480 – 1519, daughter of the pope Alexander VI) belonged to the famous poisoners – used poisons to eliminate political counterpartners.

History of toxicology – continuation

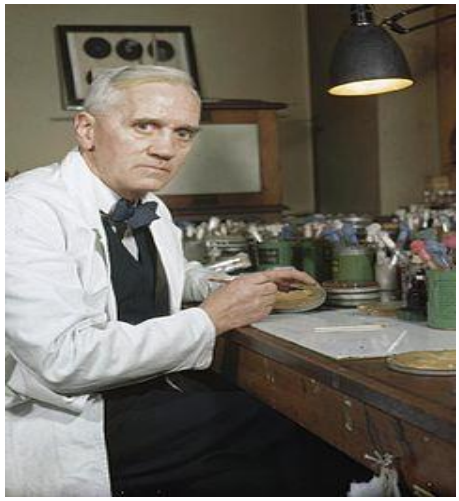


- Knowledge on poisons – together with development of medicine. Next to **Avicena, Paracelsus** (1492 – 1541): German chemist, physician and nature scientist, professor in Basel, Swithzerland – historically important person in toxicology.
- Alma mater: University of Ferrara
- Father of toxicology → Sola dosis facit venenum (The dose distinguishes poison and medicine)
- In 1521, 1526, 1527 and 1537, he visited the teritory of nowadays Slovakia – study of precious metals.

- Another important peson: Spanish physician **Orfila** (1787 – 1853): worked for the king Louis XVIII. He used the term „toxicology“ as study of poisons for the first time. He established toxicology and the separated science → study of toxic and therapeutic effects of chemical compounds.

- Padova, dr. **Ramazzini**: Diseases of workers (1700)

Newer history of toxicology



- Other development of toxicology: **Louis Lewin**, German pharmacologist, study of higher alkaloids, opioids, halucinogenes, etc. He built up the system of psychoactive drugs and plants according to their pharmacological effects.
- 20 ct. – laboratory preparation of one of the first antidota against organic compounds of As (**Voegtlin**, 1924). **Fleming´s** discovery of penicillin (Scotish biologist, pharmacologist and botanist) in 1928 – start of the isolation of antibiotics. In 1945, he got the Nobel prize for physiology and medicine, together with H. Florey and E. B. Chain.
- DDT (dichlordiphenyltrichlorethan) – later started evaluation of the total chemical risk of the compounds
- Recently, effects and relationships of compound mixtures in the organism and (bio)chemical reactions in the human (animal, plant) body. Some chemical catastrophies, e. g. in 1976 in Sevese – leakage of dioxins, became milestones in the development of toxicology in the end.

Toxicology

- Multidisciplinary science about:
- The effects of poisons and harmful compounds
- Diagnostics of poisonings and their therapy
- Analyses of the poisoning causalities

- Basic dividing:
- EXPERIMENTAL TOXICOLOGY – effects of poisons mostly on experimental models (cell cultures, animals etc.), clarifying mechanisms of these effects and metabolism of the poisons in the body and searching for antidota.

- CLINICAL TOXICOLOGY – clinical symptoms of poisonings in humans, particular organs and searching for the proper therapy.

Dividing of toxicology (according to sectors):

- Medical, toxicology of medicines
- Industrial (disasters) (incl. t**he food one**)
- Forensic
- Veterinarian (feed)
- Plant, toxicology of agrochemicals (pesticides, herbicides)
- Social (alcohol, tobacco, drugs)
- Environmental, incl. Ecotoxicology (dynamics of population)

The goal of food toxicology: To accumulate information on compounds present in the food (naturally / added intentionally / contaminants) that might damage the consument health.

Poisoning

- general disease – RT, GIT, skin and mucouses, CNS

- it is characterized by:

- The causative agent, incubation period, consequences, anatomic-patological finding

<u>Dividing of poisonings:</u>

- Accute
- Subaccute
- Subchronic
- Chronic

- Statistically highest percentual incidence: medicine poisonings (50 %), chemicals from the store (30 %), plant consumption (8 %), consumption of chemicals (5 %), of fungi (2 %), drugs (1 %), poisonings by animal venoms (1 %) and others (1 %).

Poison (noxa) vs. Injurant (noxious agent)

- The compound causing ill health changes, incl. the death, once being absorbed in the body after entering it in a small amount.
- Effects of poisons on the organism: local, irritative, choky, allergens, narcotics, organ toxicity, gene toxicity

Dividing of the poisons according to their origin:

- Natural (plant and animal: strychnin = LD_{50} p.o. 2 mg/kg, opioids, snake venoms, saxitoxín (mossels) = LD_{50} p.o. 5.7 µg/kg, etc.)
- Synthetic (organic, anorganic: dioxins, DDT = LD_{50} p.o. 100 mg/kg, heavy metals, PCB---Spolana Neratovice CR, Chemko Strážske SR etc.)

- One of the oldest definitions of the poison (by Paracelsus): all compounds are poisons and it depends just on its dose when the compound doesn´t act as the poison anymore. Even the chemicals and medicines not toxic or medicinal in low concentrations, might be poisons. Also, the compounds very common and important for lige, e. g. NaCl or glucose, might cause death in high concentrations and without medical help (LD_{50} NaCl = 3,000 mg/kg b.w.).

Entering of poisons into the organism

- **Mouth** (peroral; fast; used in the medicine: nitroglycerine in cardiacs)
- **Skin** (subcutanneous, the main barrier – the surface membrane = *stratum corneum*) – application of methanol, ethanol, acetone etc. increases the skin permeaeability to other toxins.
- **Mucoses**
- Into the venes (intravenous; rapid)
- Into the muscles (intramuscullar)
- Respiratory (gases, aerosols and dust particles); effects – irritative, choky, or systemic toxicity after absorption.

The dynamics of poison absorption in the organisms is affected by:

- Physical-chemical properties of the poison (lipo-, hydrophility)
- Concentration, exposition time, the way of entering, pH value (in stomach)
- Susceptibility of the organism (age, gender, health status, metabolism rate etc.)

Distribution of poisons and injurants in the body – blood (albumin)

Metabolism of toxins

- Elimination (biologic half-life)

vs. cumulation — cumulative poisoning

- Biotransformation – detoxication:

1st phase (cyt P-450): - hydrolysis

- oxidation

- reduction

2nd phase: - conjugation

Toxicity

- the ability of the compound to cause intoxication; characterized by the lethal dose

Toxicity categories:

- Extreme toxic <1 mg/kg b.w.
- High toxic 1-50 mg/kg
- Average toxic 50-500 mg/kg
- Weak toxic 05-5 g/kg
- Practically non-toxic 5-15 g/kg
- Relatively non-harmful > 15 g/kg

- Toxic symptoms on the particular organ (lungs, liver, kidenys ...) or on more sites → systemic toxicity

- **Riskiness** – the ability of the coumpound act as toxin

Toxicity studies: accute, subaccute, chronic and combined effect -

LABORATORY ANIMALS vs. ORGAN/CELL CULTURES

Accute toxic effect - 2 parametres:

- Upper parameter of toxicity (deadly concentrations)
- Lower parameter of toxicity (minimally effective concentrations)

- Smaller the difference between the parameteres → more dangerous the compound
- Symptoms, e. g. changes in blood pressure, arythmia, spasm, airway irritation, even the death
- E. g. ethanol or As poisoning
- Toxicity evaluation:
- Absolute lethal concentration
- LD50
- Minimal lethal concentration
- Maximal tolerable dose

- Subaccute effect – 10 % of life expectance (cumulative effect)

- Subchronic effect – the goal of the study is to get information on the biologic effect of the comounds – cumulative effects and pathologic changes (the concentrations causing that changes)

Chronic and combined effect:

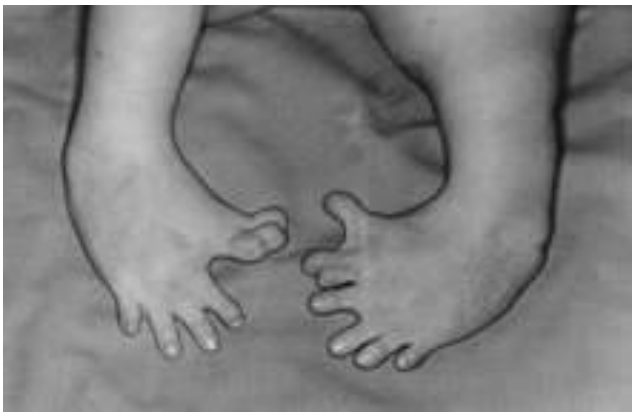
- Chronic effect: related to life-long exposition to the toxin (e. g. DDT, As, Pb, Hg). Evaluation of cumulative ability of the compounds and the synergism/addition of the effects. Carcingenicity study.
- The principle of the summation of the effects: the compound is eliminated or excreted from the organism after entering it → its effect lasts → changes on biolog. molecules (DNA)

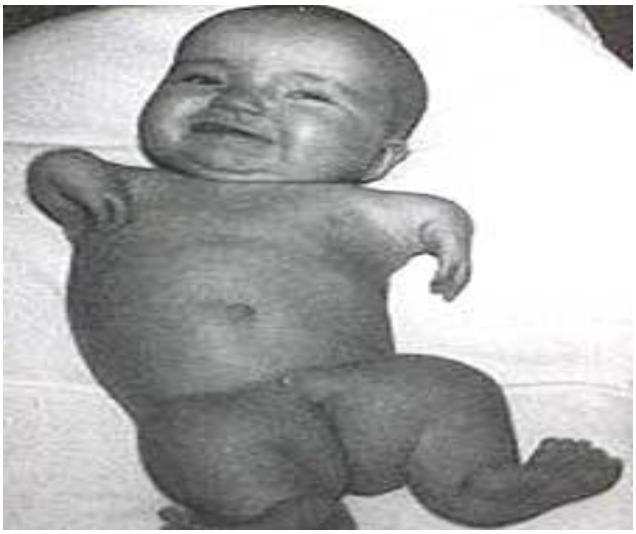
- Comb. effect: changes in organisms after interaction of more compounds are evaluated

a) Aditive effect (after combination of 2 or more compounds, the effect intensity is not changed, e. g. medicaments and alcohol)
b) Potentiation (the effect ot the combination is stronger than the additive one, e. g. warfarin and the drugs binding to albumin)
c) Antagonism (the effect is diminished/eliminated, e. g. poisons and antidota, e. g. EDTA and metals)
d) Synergism (e. g.. ethanol a carbon chloride)

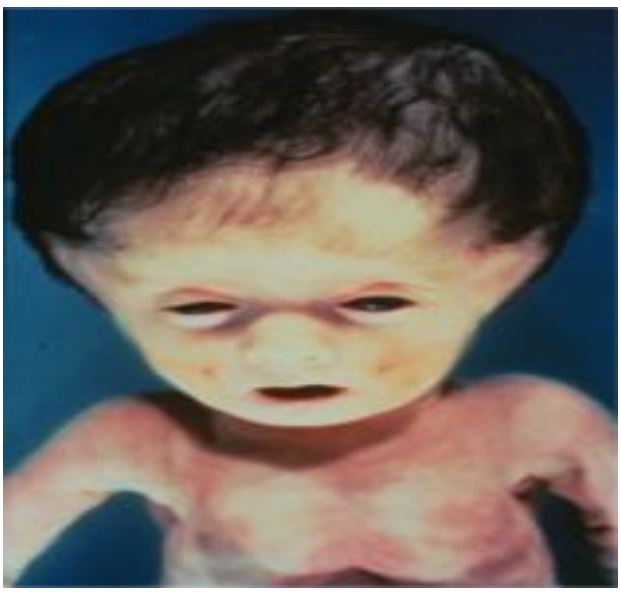
Teratogenic effect:

- Teratogen: structural, function and biochemic changes in the body
- Science dealing with failures of the organism in the course of development = teratology
- **Teratogen examples:**
- 1) chem. compounds, e. g. Hg, compounds, PCB, dioxins
- 2) viruses, e. g. rubeola virus ---cataracta; Zika virus---microcephalus; herpes virus, coxsackie B --- abortion, dead –born babies, microcephalus, menal retardation
- 3) infectious agents, e. g.. toxoplasmas --- brain damage
- 4) medicines, e. g. antibiotics, anaesthetics, warfarín, talidomid, antidepresivants
- 5) mother´s diseases, e. g. listeriosis---abortion; syphilis, asthma, diabetes ; fenylketonuria—mental retardation; mumps, smallpox, hepatitis B---abortion, dead-born babies, damage of liver, limbs and fingers, vision and brain

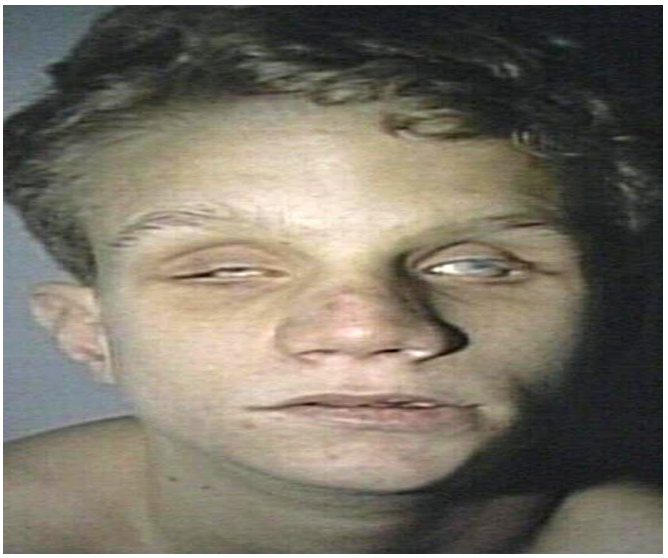




Developmental damage in children of mothers on talidomid treatment



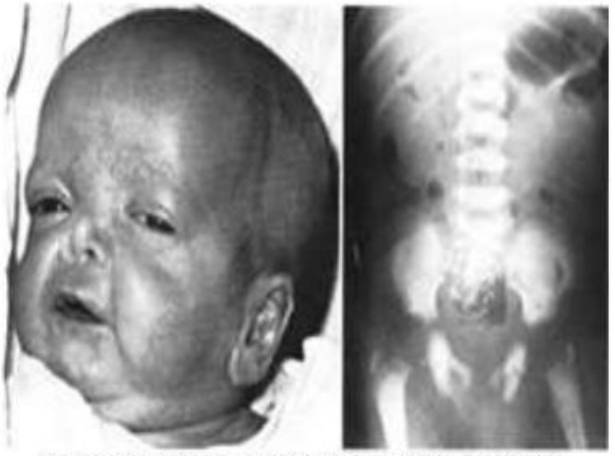
Teratogenic effects of retinoids used by mothers during pregnancy



Foetus damage during intrauterine development vy rubeola virus

FETAL WARFARIN SYNDROME

- Saddle nose
- Retarded growth
- Defects of limbs, eyes and central nervous system



Fetal Warfarin Syndrom e: infant with hypoplastic nose, flat face and low nasal bridge as well as altered calcific ation (Smith 1982).

Teratogenity of warfarin: growth retardation, development failures of limbs, eyes and CNS, undeveloped nasal septum, heart defects, and upregulated growht of chest bone/cartilage

Mutagenic effect:

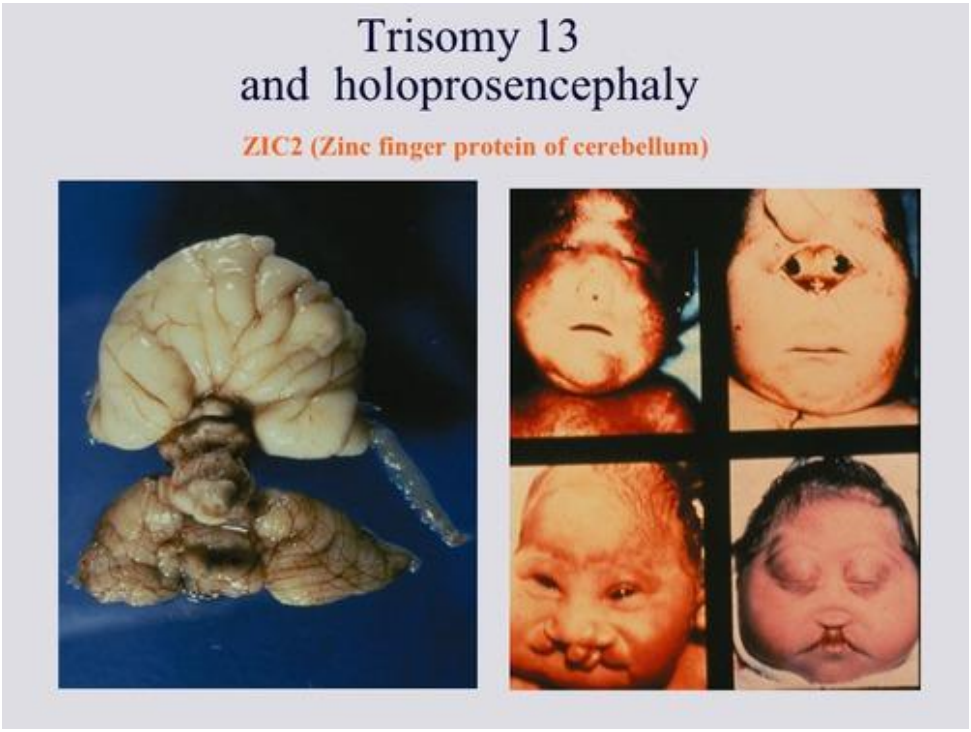
Mutagenic effect: Qualitative and quantitative change in genetic information of the organism

Known mutagens:

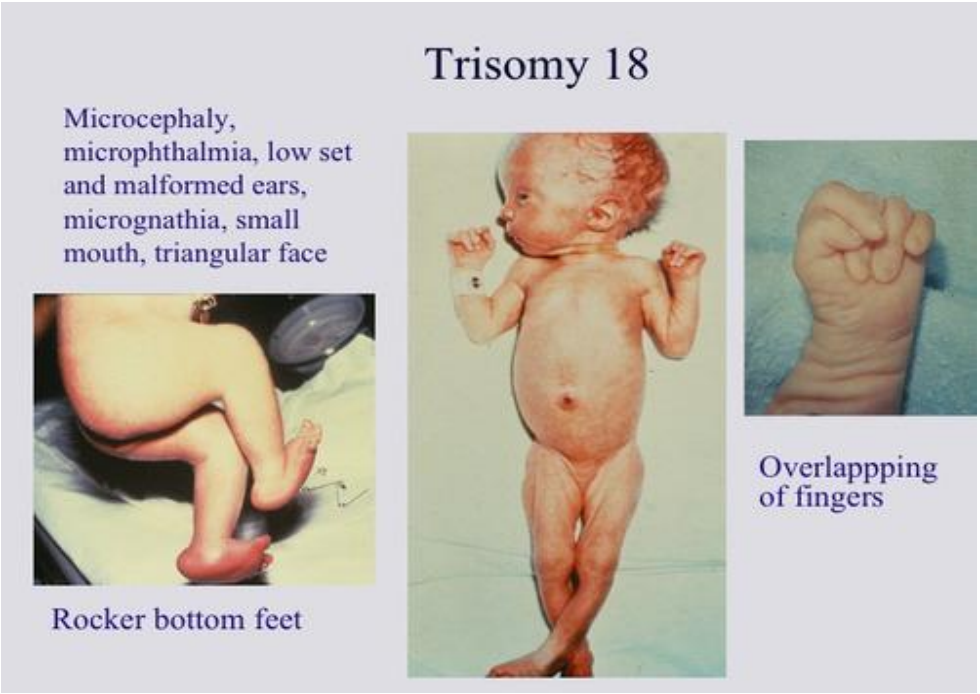
- Chemical compounds (polycyclic hydrocarbons, organic solvents DDT), ionization radiation (incl. x-ray), infection agents (oncogenic viruses, e. g. herpes viruses, Epstein-Barr virus, Rous virus, Rauscher virus), medicaments (contraception, cytostatics), psychotropic compounds (alcohol, drugs)

- Division of mutagens: broad-, narrowspectral

- Mutations: chromosomal, gene and genomic
- Carcinogen vs. mutagens - ca 80-85 % → every mutagenic compound is count as carcingenic untill the opposite is proven



Trisomy 13 = Pattau syndrome

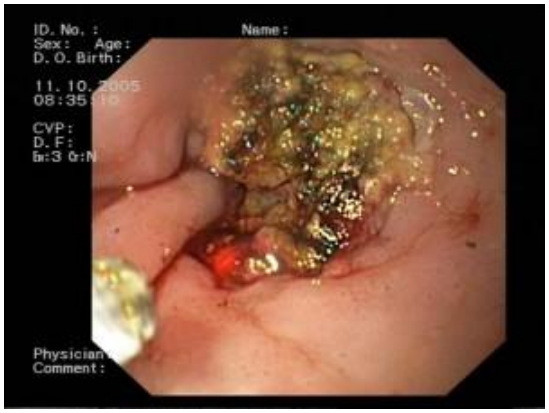


Trisomy 18 = Edwards syndrome

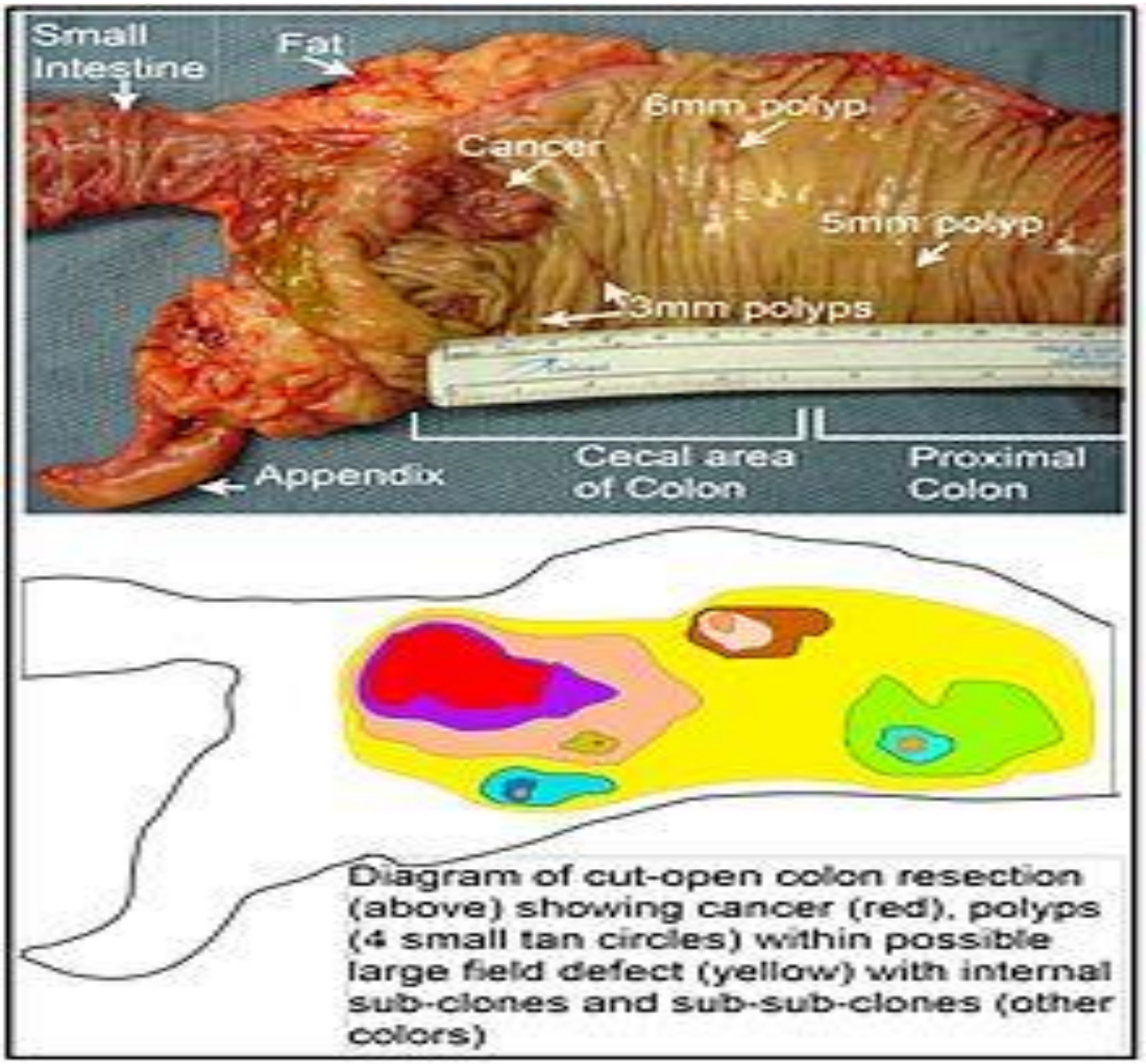
Carcinogenic effect

- Carcinogenity = multilevel proces of abnormal growth and differentiation of cells that may lead to carcinoma. There are 3 stages: initiation, promotion and progression
- Carcinogenesis = generation of tumors
- Tumors: benign and malign
- Generation of metastases:
- 1) release from the primary tumor
- 2) entering the blood and lymphatic system
- 3) proliferation at the secondary site

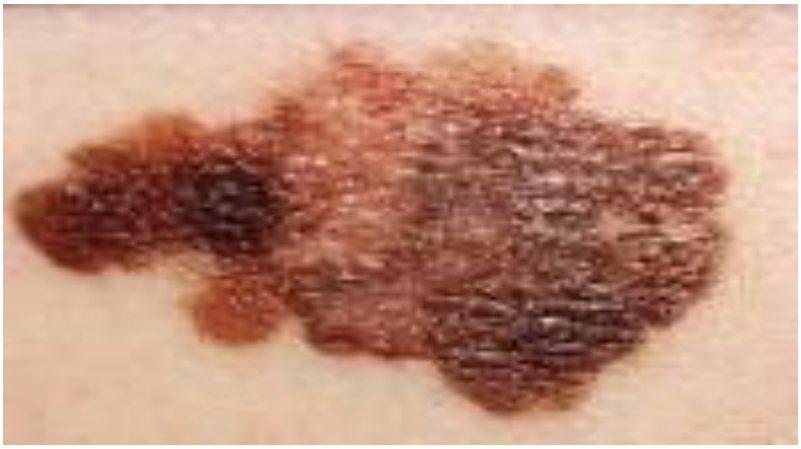
- Carcinogens according to IARC= International agency for research on cancer – divided into 4 categories:
- 1) proven carcinogens (As, aflatoxins, ionization radiation/rays)
- 2) potential carcinogens (Pb, PCB)
- 3) compounds suspected from carcinogenicity (DDT, chloramphenicol)
- 4) probably non-carcinogenic for humans



Esophageal carcinoma

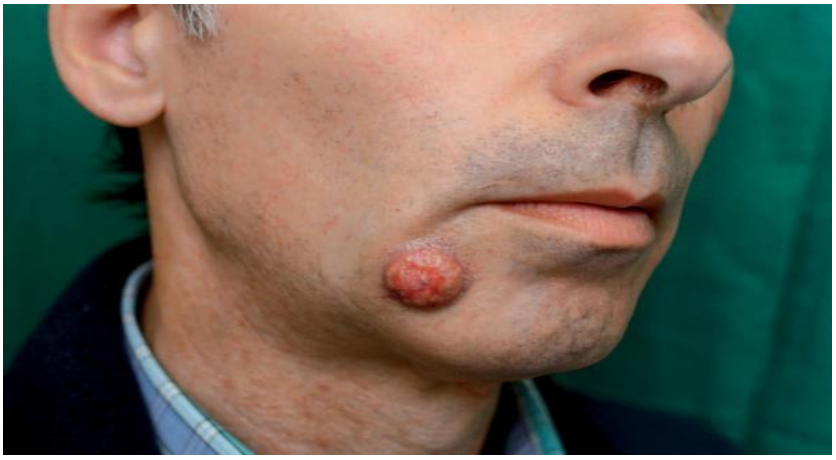


Colorectal carcinoma and polyps in large intestine

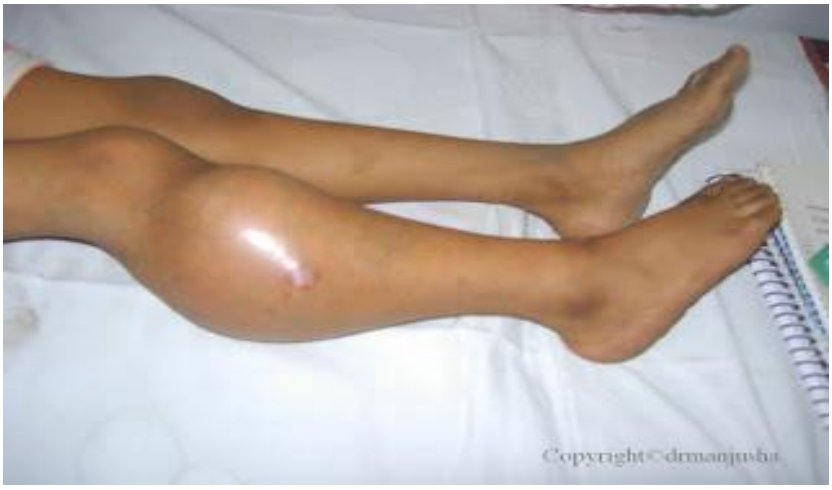


Melanoma

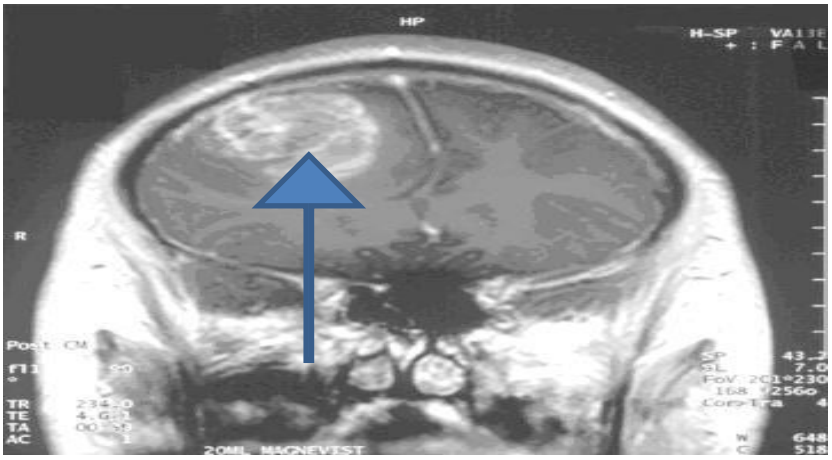
Basalioma



Metastasis of a stomach carcinoma



Ewing sarcoma in children



Brain tumor - glioblastoma

Thyroid tumor

Developmental toxicity

- Toxicity acting from embryo till sexual maturity. Exposition: before conception, during pregnancy, after birth till maturity.

Symptoms of negative effects onto the organism:

1. Death before/after the birth
2. Abnormalities
3. Growth changes, functional deficits

Stages of development:

- Gametogenesis and fertilization
- Preimplantation
- Embryonal period
- Foetal period
- Postnatal period

Stages of development:

- Embryonal stage: intense growth and differentiation of cells, building up of organs and their systems, the most critical period 17th – 90th day after fertilization. Exposition to unfavorable conditions leads to abortus, heavy developmental damages (e. g. cleft palate and neural tube)

- Foetal stage: proliferation and defferentiation of organ systems. Exposition of the foeatus to improper environmental factors can cause growth retardation, start of carcinogenesis, developmental damages etc.

- Postnatal stage: exposition to improper environmental factors via inhalation, ingestion, intradermal or in breast milk. Negative exposition, e. g. yellow teeth (dioxins, tetracyclin), growth retardation, carcinogenesis (heavy metals) etc.

Evaluation of the end-toxic effects in the mother:

mortality, inferetility, changes in body mass (incl. changes in organ masses in the case of weight gains), clinical changes, food and water intake, sectional and histologic findings

Evaluation of developmental end-toxic effects:

Abortus, structural abnormaliies, foetus mass, gender ratio, dead-born babies, malfunctions, sectionalpitevné a histologic findings.