EXOGENEOUS CHEMICAL FACTORS AS CAUSES OF DISEASE

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1. INTRODUCTION

The human body interacts permanently with a number of chemical substances. Some are essential for life (water, oxygen, mineral salts, foodstuffs, vitamins and trace elements), others can damage biological macromolecules and cause health disturbances. This division into "good" and "bad" chemical substances is, however, a didactic simplification. In many cases the same substance in appropriate (mostly minute) amount is essential for health but its overdose can cause disease (e.g. selenium or chromium, see Chapter 5). The same is true for almost every drug used in medicine.

Substances which are alien to human body are called **xenobiotics.** Those which cause serious health problems in minute amounts are **poisons** or **toxins** (**toxicants**)**.** In addition to acute intoxications, manifesting themselves usually through dramatic clinical symptoms in the past few years the danger of accumulation of many non- or slow metabolizing chemical substances in the body has been graudally recognized. Chemical substances play an important role in the **carcinogenesis**, as well. Air, water and soil **pollution** has become one of the crucial problems of 20^{th} and 21^{st} century influencing the health of whole groups of population and the mankind as a whole. Sometimes the effect of these polluting chemical compunds is indirect. Chlorofluorocarbons (CFCs or freons, e.g. dichlordifluormethan, CCl_2F_2) used as stable and nontoxic gases in sprays, refrigerators and in the plastic material industry) deplete the ozone layer of the stratosphere. As a consequence more short-wave ultraviolet light reaches the surface of the earth with possible deleterious effects on humans, animals and plants. Carbon dioxide, CO_2 is a normal minor (less than 0,1 %) constituent of the air and has also important physiologic functions in respiration and acid-base balance. The slow rise (by 12 % from 1960) of its concentration in the athmosphere does not exert any short- or long-term health effect on humans and animals but it probably contributes considerably to the **greenhouse effect** - a change in heat radiation balance of the atmosphere and to its consequence, the global warming of the biosphere observed in the past few years. The climatic change due to accumulation of this nontoxic gas threatens the mankind with unpredictable ecological and economical dangers.

In this chapter it is impossible to deal with the whole range of **toxicology, occupational medicine and ecology** which are now independent medical resp. scientific

subjects. In addition to this short survey of the most common poisonings separate chapters are devoted to the health disorders caused by **smoking** and **alcohol**.

2. CLASSIFICATION OF TOXIC SUBSTANCES

The toxic substances can be classified according to various aspects. The quantitative classification is given in Tab. 1. The most plausible qualitative classification is according to the chemical nature of the toxins: **anorganic, organic and biological toxins** with various subgroups in each group. (Tab. 2). Some toxins (anorganic and biological) occur **naturally**, others (the vast majority of toxic organic compounds) are **synthetic.** The occurence of toxic substances is usually restricted to special locations such as laboratories, factories, workplaces, etc., where strict rules govern their handling, but there are also toxic substances occuring widely in the environment (air, water, food) and households. Medical drugs are unique in this respect, because they are widely used in treating diseases but their accidental or deliberate overdose is a frequent cause of poisoning**.**

Tab. 1 Toxicity rating

Probable Lethal Dose	Rating
> 15 g/kg	1 - Practically nontoxic
5 - 15 g/kg	2 - Slightly toxic
0.5 - 5 g/kg	3 - Moderately toxic
50 - 500 mg/kg	4 - Very toxic
5 - 50 mg/kg	5 - Extremely toxic
< 5 mg/kg	6 - Super toxic

The poisonings may be divided according to the timing and of exposure and dose to **acute** (one big dose) and **chronic** (repeated small doses) intoxications and to **accidental** or **voluntary** ones.

3. ENTRY OF TOXINS INTO THE BODY

Toxins can enter the body through airways **(inhalation)**, through the gastrointestinal system **(peroral route)**, through skin **(dermal route)** and sometimes directly through injuries or **parenteral** application (medicaments, drugs). A special but very important possibility is the **transplacental** transport of toxicants.

Tab. 2 The most important toxic substances

ANORGANIC TOXINS	
METALS AND METAL COMPOUNDS	
Lead (Pb)	Bismuth (Bi)
Mercury (Hg)	Silver (Ag)
Chromium (Cr)	Gold (Au)
Cadmium (Cd)	Cuprum (Cu)
Beryllium (Be)	Iron (Fe)
Arsen (As)	Mangan (Mn)
Cobalt (Co)	Baryum (Ba)
TOXIC GASES	
Carbon monoxide (CO)	
Hydrogen sulfide (H_2S)	
Carbon disulfide (CS_2)	
Phosgene ($COCl_2$) and chlorgas (Cl_2)	
CYANIDES	
Hydrogen cyanide (HCN) and the cyanides (e.g. KCN)	
NITRITES AND NITROCOPOUNDS	
STRONG ACIDS AND BASES (CAUSTIC AGENTS)	
HCl, H_2SO_4, NaOH	
ORGANIC TOXINS	
ORGANOPHOSPHATES	
CHLORINATED ORGANOCOMPOUNDS (DDT)	
HALOGENATED HYDROCARBONS (CCl_4, trichlorethylen)	
HERBICIDES, FUNGICIDES AND RODENTICIDES OF OTHER TYPES (Paraquat, warfarin, etc.)	
ORGANIC SOLVENTS	
Aromatic compounds (benzol, xylol, toluol)	
Methylalcohol	
Glycols (ethylenglycol)	
ORGANIC DYES (anilin)	
AROMATIC NITRODERIVATIVES (nitrobenzol, trinitrotoluol)	
ORGANIC METALLOCOMPOUNDS	
Tetraethyl lead, methyl mercury	
ALKALOIDS*	
BIOLOGICAL TOXINS	
ANIMAL TOXINS	
Venoms of snakes, spiders, scorpions	
PLANT TOXINS, **MYCOTOXINS**	
Hemlock, mushroom toxins, aflatoxin (moulds)	
BACTERIAL EXOTOXINS	
Botulotoxin, tetanotoxin, diphteric toxin, cholera toxin, toxins from staphyllococci and streptococci	

*Their listing into the group of biological (plant) toxins is also plausible

Each portal of entry permits a different rate of penetration and may also enable different metabolic pattern of the given compound. In general, the respiratory system offers the most rapid (apart from the rare direct entry) and the dermal the least rapid route of entry.

Toxicants pass a number of further barriers on their route into tissues and cells. Biologic membranes are in general much less permeable to compounds in the ionized state than to those in the nonionized form. A second parameter influencing penetration is the lipid solubility of the potential toxicant. The mechanism of the movement of toxicants across membranes includes all possibilities known from physiologic membrane transport: passive, facilitated and active transport, endocytosis (liquids) and phagocytosis (solid particles).

3.1 RESPIRATORY PENETRATION

Airborne toxicants are divided in two general types. Compounds that are subjects to gas laws include gases and vapors. These are easily carried to the alveolar areas. The rate of entry of vapor-phase toxicants is controlled by the alveolar ventillation rate.

The compounds of the second group are in particular form and include aerosols, clouds, fumes, etc. Particles of 5 μm and greater are usually deposited in the nasopharyngeal region. Particles down to 2 μm are deposited in the tracheobronchial region and are cleared upward by the mucus blanket that covers the backward-beating cilia. In addition to upper pathway clearance, phagocytosis in the lung is very active. If not phagocyted, particles 1 μm and smaller may penetrate to the alveolar portion of the lung. They are absorbed in the alveolar region, similarly to gases and vapors.

3.2 GASTROINTESTINAL PENETRATION

As gastrointestinal tract is specially designed to enable the ingestion of food and resorbtion of chemical compounds, this is the most common route of accidental or deliberate intoxications. For toxicants with structural similarities to compounds normally taken up by active transport, the entry is greatly enhanced. As an example, cobalt is absorbed by the same active transport mechanism that normally transports iron.

Every compound absorbed from the stomach or the intestines must cross the liver, where most of them are further transformed. An important aspect of gastrointestinal route is the enterohepatic circulation. In the first step the absorbed compounds are transported to the liver where they undergo different chemical reactions. Following secretion of conjugated metabolites from the liver through the bile duct into the intestine, a water-soluble metabolite may be altered to a less polar compound, reabsorbed through the intestine, and returned to the body in this, altered form.

3.3 SKIN PENETRATION

The skin is a complex barrier relatively impermeable to most ions as well as compounds in aqueous solutions. It is permeable to a large number of toxicants in the solid, liquid, or gaseous phase, however. Many examples of poisonong by the dermal route have been reported - organophosphate pesticides in agricultural works, chlorophenol in domestic and wild animals, etc. In general compounds mixed into unguents and ointments readily cross the skin.

4. DISTRIBUTION AND METABOLISM OF TOXICANTS IN THE BODY

After a chemical subtance enters the body, it is transported mostly in the blood. Toxicants interact with the blood proteins in various ways (simple nonspecific adsorption, use of specific transport proteins, formation of complexes or covalent bonds) according to their chemical nature. Some toxins enter the red cell and can interact with enzymes (e.g. Pb) or with hemoglobin (e.g. CO). In the tissues the toxicants may be sequestered either physically, such as solubilization of lipophilic chemicals in fat or chemically by binding to tissue components, such as proteins.

4.1 METABOLISM OF TOXICANTS

Some toxicants do not undergo metabolic changes, they only interact in some way with enzymes, membranes, nucleic acids or other physiologically important molecules and damage the cells and tissues (e.g. heavy metals, CO, cyanides). The others undergo metabolic changes (mainly in the liver) as follows:

Phase-one reactions (nonsynthetic reactions)

Phase-one reactions include microsomal monooxygenations, cytosolic and mitochondrial oxidations, reductions, hydrolysis, and epoxide hydration. All of these reactions introduce a polar group which, in most cases, can be conjugated during phase-two metabolism.

Phase-two reactions (synthetic reactions)

Metabolits of phase-one products and other xenobiotics containing functional groups such as hydroxyl, amino, carboxyl, epoxide, or halogen can undergo conjugation reactions with endogenous metabolites, these conjugation being collectively termed phase-two reactions. The endogenous metabolites in question include sugars, amino acids, glutathione, sulfate, etc. Conjugation products are more polar, less toxic, and more readily excreted than are their parent compouds.

5. THE MOST IMPORTANT INTOXICATIONS DUE TO TOXIC METALS

5.1 LEAD (PLUMBUM, $^{82}Pb_{207}$)

Lead is widely used in typography, storage batteries, and is a component of paints, solder, pottery glaze, rubber products, etc (current production is $\approx$ 3 800 000 tons/year). Tetraethyl lead was widely used as a gasoline additive and until introduction of lead-free gasoline led to substantial pollution in regions with high intensity of automobile traffic. In the last 10 – 20 years this burden is rapidly diminishing.

Historical remarks

According to some historians Nero´s madness the fall Roman Empire can be connected to lead intoxications from wine stored in pewter vases and water from lead water pipes.

Vincent van Gogh´s health problems and madness could be partly caused by lead in paints.

The fatal dose of absorbed lead has been estimated to be 0.5 g. Approximately 50 % of lead deposition in the lung is absorbed, whereas usually only 10 % of ingested lead passes into the circulation. Blood levels of Pb > 10 μg/l are harmful and can damage the tissues. Lead is accumulating mainly in bones replacing calcium and therefore children with developing bones are very sensitive to lead intoxication. The half life of lead in the body is very long, ≈ 15 – 20 years.

Lead interferes in the biosynthesis of porphyrins and heme (Fig. 1), and several screening tests for lead poisoning make use of this by monitoring either inhibition of the affected enzyme - aminolevulinic acid dehydratase (ALAD) or appearance in the urine of aminolevulinic acid and coproporphyrin.

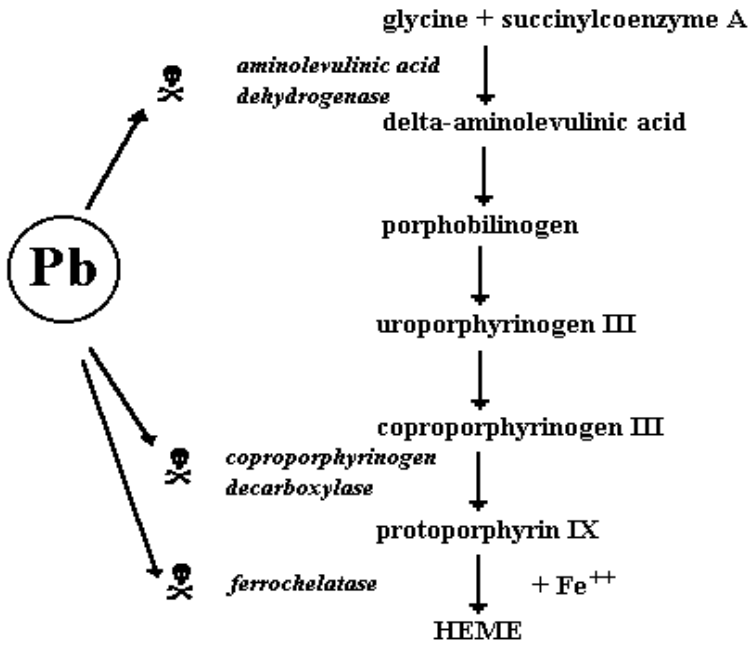

Fig. 1. The interaction of lead with heme biosynthesis.

In acute poisoning (from ingestion or injection of soluble compounds of lead), pathologic findings include inflammation of the gastrointestinal mucosa (abdominal pain, vomiting, diarrhea) and renal tubular degeneration (oliguria).

In chronic lead poisoning (from ingestion, skin absorption, or inhalation of particulatae or organic lead), cerebral edema and degeneration of nerve and muscle cells occur. Clinical findings are: fatigue, sleep disturbances, anemia, colic, and a gray line (**lead line)** on the gums.

Organic lead has an affinity for brain tissue. Mild poisoning may cause insomnia, restlessness, and gastrointestinal symptoms, whereas severe poisoning results in delirium, hallucinations, convulsions, coma (encephalopathia saturnina), and even death.

5.2 MERCURY (HYDRARGYRUM, $^{80}Hg_{201}$)

Metalic mercury (Hg^0) and its salts (Hg^+ or Hg^{++}) are used in the manufacture of thermometers, felt, paints, explosives, electrical apparatures and batteries. In the past mercury compounds were used in the medicine and cosmetic industry, too (calomel – Hg_2Cl_2, Salvarsan – the first drug against syphilis, etc.) The diethyl and dimethyl mercury compounds are used in treating seeds against insects. From industrial and agricultural sources yarly 5 000 - 6 000 tons of mercury is released into the environment and most of it is finally accumulating in the marine sediment.

Mercury blocks cellular enzymatic mechanisms by interacting with sulfhydryl (-SH) groups and for this reason, soluble mercuric salts (e.g. $HgCl_2$, sublimate) are toxic to all cells. Inorganic and organic mercury differ in their routes of entry and absorption. Inhalation is the principal route of uptake of metallic mercury (Hg^0) in industry, with approximately 80 % of the mercury inhaled as vapor being absorbed. Metallic mercury is less readily absorbed by the gastrointestinal route. Recently the safety of **amalgames** (alloys of mercury with other metals) widely ased in dentistry was questioned, too. Organic mercury compounds are readily absorbed by all routes. Selenium can diminish the toxicity of mercury because it binds mercury as selenide compound in the form CH_3-Hg-Se-CH_3. The half life of mercury in body is about 2 – 4 months.

In fatalities from mercury poisoning, the pathologic findings are acute tubular and glomerular degeneration. Ingestion of mercuric salts causes inflammation, congestion and corrosion of the gastrointestinal tract. Symptoms of acute poisoning include abdominal pain, vomiting, bloody diarrhea. One day to 2 weeks after ingestion, urine output diminishes or stops. Inhalation of mercury vapor, dusts, or organic vapors, or skin absorption of mercury over a long period causes chronic intoxication - **mercurialism**. Findings are extremely variable and include tremor, anxiety, psychic irritation, inflammation of the mouth, blue line on the gums, and nephrotic syndrome characterized by proteinuria.

In Minamata Bay (Japan) mercury released from a factory into the sea water was transformed by bacteria to organic mercury compounds, then ingested by fish. Consuming of contaminated fish caused an epidemic of serious CNS injury including birth defects in newborns born to mothers in the region. In Iraq three epidemics were described in the years

1950 – 1970 caused by bread made from grain treated with organomercurial antifungal agents.

5.3 CADMIUM ($^{48}Cd_{112}$)

Cadmium is one of the most toxic metals. In industry is used for plating metals and in the manufacture of bearing alloys and silver solders. Cadmium plating is soluble in acid foods such as fruit juices and vinegar. Cadmium is a very cumulative toxicant, accumulation occurs mainly in the kidney and the liver, where it is bound to metallothionein (a 10 kD protein, rich in cysteine, binds 4 – 12 atoms of different metals). Cadmium interacts with SH groups of enzymes, binds covalently to DNA and interferes with the functions of zinc. The critical target organ after long-term exposure to cadmium is the kidney, with the first detectable symptom of kidney toxicity being an increased excretion of specific proteins. Others symptoms of chronic poisoning include anemia, severe bone and mineral loss. Symptoms of intoxication are more pronounced in Zn and Cs deficiency.

The deficiency of micronutrients was an important factor in the **Itai – itai disease** in Japan (1940 – 1960) where the waste water from a mine contaminated with cadmium the rice plants. The cadmium exposition is increased in heavy smokers, too, but it does not reach the permitted level (smokers $\approx$ 5 μg/d, nonsmokers $\approx$ 10 μg/d; permitted 50 μg/d).

5.4 BERYLLIUM ($^{4}Be_{9}$)

Soluble beryllium salts are directly irritating to skin and mucous membranes and induce acute pneumonitis with pulmonary edema. At least part of the changes present in acute pneumonitis and chronic pulmonary granulomatosis develop as a result of hypersensitivity to the beryllium in the tissues.

5.5 ARSEN ($^{33}As_{75}$)

White arsenic – As_2O_3 is historically the most common poison used for criminal purposes. (*An excellent description of arsene poisoning is found in Flaubert´s Madame Bovary*). It produces inflammation of the gastrointestinal tract, violent purging and vomiting, hemolysis with jaundice, hematuria, anuria. If death does not ensue in the early stage, sensory changes in the peripheral nerves cause pain, and paresthesias follow. Later there may be motor paralysis, loss of hair, deformities of the nails, skin lesions, and symptoms of upper respiratory tract irritation. Arsenic presumably interacts with sulfhydryl groups of enzymes interfering with cellular metabolism.

6. TOXIC GASES AND CYANIDE INTOXICATION

6.1 CARBON MONOXIDE (CO)

SEE CHAPTER ON HYPOXIA

6.2 HYDROGEN SULFIDE (H_2S) AND CARBON DISULFIDE (CS_2)

Hydrogen sulfide is released spontaneously by the decomposition of sulfur compounds and is found in petroleum refineries, tanneries, mines, and rayon factories. Carbon disulfide is a liquid which boils at 46 ^{O}C. Hydrogen sulfide causes both anoxic effects and damage to the cells of the CNS by direct action. Carbon disulfide damages chiefly the CNS, the peripheral nerves, and the hemopoietic system.

6.3 PHOSGENE AND CHLORGAS ($COCl_2$, Cl_2)

Phosgene is used in chemical synthesis. It is hydrolyzed to hydrochloric acid in the body and thus irritates and damages cells. The principal manifestations in acute poisoning with phosgene are respiratory and circulatory failure. Chlorgas acts in similar way.

6.4 CYANIDE INTOXICATION

Hydrogen cyanide, (HCN, a blue-colored liquid) is used as a fumigant and in chemical synthesis, other cyanides (e.g. KCN, a solid substance) in chemical industry. Cyanides, the most potent inorganic toxicants act by inhibiting the cytochrome oxidase system responsible for oxygen utilization in cells. They interrupt the electron transport in the mitochondrial cytochrome chain at the cytochrome A step. Other enzyme systems are also inhibited, but to a lesser degree. Cyanide first causes a marked increase in respiration by affecting chemoreceptors in the carotid body and respiratory center and then quickly paralyzes all cells. The principal manifestations of poisoning with these compounds are rapid respiration, blood pressure fall, convulsions, and coma. *(Excellent representations in Agatha Christie´s novels and movies – remnants of poisoned coffee smell after bitter almonds).*

Stones of certain fruits (e.g. bitter almonds, apricots) contain glycosides (e.g. amygdalin) which upon acid hydrolysis release cyanide. Eating large amount of stones of bitter almonds can lead to serious intoxication. More dangerous are the cyanogenic glycosides of cassava and manioca roots, which are important foodstuffs in some parts of Africa and South America.

In January 2000 approximately 400 000 litres of toxic sudge containing as much as 8 g KCN/liter was released through a leak of tailing pond containing waste from a gold reprocessing plant in Baia Mare, Romania. The toxic waste got into Tisza river (Hungary) and killed most of the life in water (fish, crabs, frog, insects) and intoxicated also the birds, otters, beavers living on fish and some domestic animals, too. The only luck in this enormous ecological catastrophe was the big flood in spring which cleaned the water and the ecosystem was saved from the tributaries of Tisza.

Cyanates and isocyanates (e.g. HO-CN resp. HN=C=O) from chemical point of view are derivatives of carbonic acid (H_2CO_3). In 1984 large amount of a toxic compound, **methyl isocyanate** ($CH_3N=C=O$) seeped from an insecticide plant in Bhopal, India killing more than 2 000 and causing serious health damage to 150 000 persons.

7. THE MOST COMMON ORGANIC TOXIC COMPOUNDS

7.1 ORGANOPHOSPHATES

Organophosphates (cholinesterase inhibitors, e.g. parathion - Fig. 2a) are mostly used in agriculture as insecticides. Organophosphate derivatives act by inactivating the enzyme acetylcholinesterase (AChE). The inactivation of cholinesterase by organophosphates allows the accumulation of large amounts of acetylcholine, with resultant widespread effects which may be separated into 3 categories:

1. **Potentiation of postganglionic parasympathetic activity:** The following structures are affected: pupil (concstricted), intestinal muscles (stimulated) salivatory and sweat glands (stimulated), bronchial muscles (constricted), urinary bladder (contracted), sinus node (inhibited), and atrioventricular node (blocked).
2. **Persistent depolarization of skeletal muscles**, resulting in initial fasciculations followed by neuromuscular block and paralysis.
3. **Initial stimulation followed by depression of cells of the CNS**, resulting in inhibition of the inspiratory center (depression of phrenic discharge) and convulsions of central origin.

7.2 CHLORINATED ORGANOCOMPOUNDS (HALOGENATED INSECTICIDES AND HERBICIDES)

The mechanism of poisoning by these agents is not fully elucidated. They are mostly stable lipid soluble compounds. Their stability poses an environmental threat because they can circulate many years in the nature and cause chronic intoxications far away from the site of their original application. Their toxic action does not require metabolic alteration of their chemical structure. The most known agent from this group, **DDT** ((2,2-Bis(4-chlorphenyl)-1,1,1-trichlorethan; Fig. 2b) acts chiefly on the cerebellum and motor cortex of the CNS, causing characteristic hyperexcitability, tremors, muscular weakness and convulsions. The myocardium becomes sensitized so that injection of small doses of adrenaline may induce ventricular fibrillation. DDT was widely used from the 1940s to the 1960s as a succesful agent in malaria eradication, agriculture and households. After the dangers of its cumulation were discovered, it was replaced by other compounds belonging to this group (e.g. chlordane, aldrin, lindan) but even these can pose ecological and health danger.

7.3 Dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin, TCDD)

Dioxin (Fig. 2c) is a highly toxic contaminant arising during synthesis of different organic compounds. Among them was "Agent Orange" (2,4,5-trichlorophenoxyacetic acid or) used by the U.S. Army as a defoliant in Vietnam war. Dioxin is a very stable compound and circulates in the biosphere for a long time causing cancer, miscarriage, birth defects and other health damage years after the primary exposure. Acute intoxication is also possible, causes acne-like skin eruptions, liver and kidney damage.

7.4 HALOGENATED HYDROCARBONS

Carbon tetrachloride (CCl_4) is used as a solvent and intermediate in many industrial processes. CCl_4 injuries almost all cells of the body, including those of the central nervous system, liver, kidney, and blood vessels. The mechanism of toxicity appears to result from the intracellular breakdown of CCl_4 to more toxic intermediates. The oxidation of CCl_4 produce radicals such as CCl_3 with following lipid peroxidation and subsequent destruction of cellular components.

Trichlorethylene ($CHCl=CCl_2$) is used as an industrial solvent and cleaner. Trichlorethylene decomposes to dichlorethylene, phosgene, and carbon monoxide on contact with alkalies such as soda lime. The most striking effect of trichlorethylene is the depression of central nervous system function. Other areas affected include the myocardium, liver, and kidney.

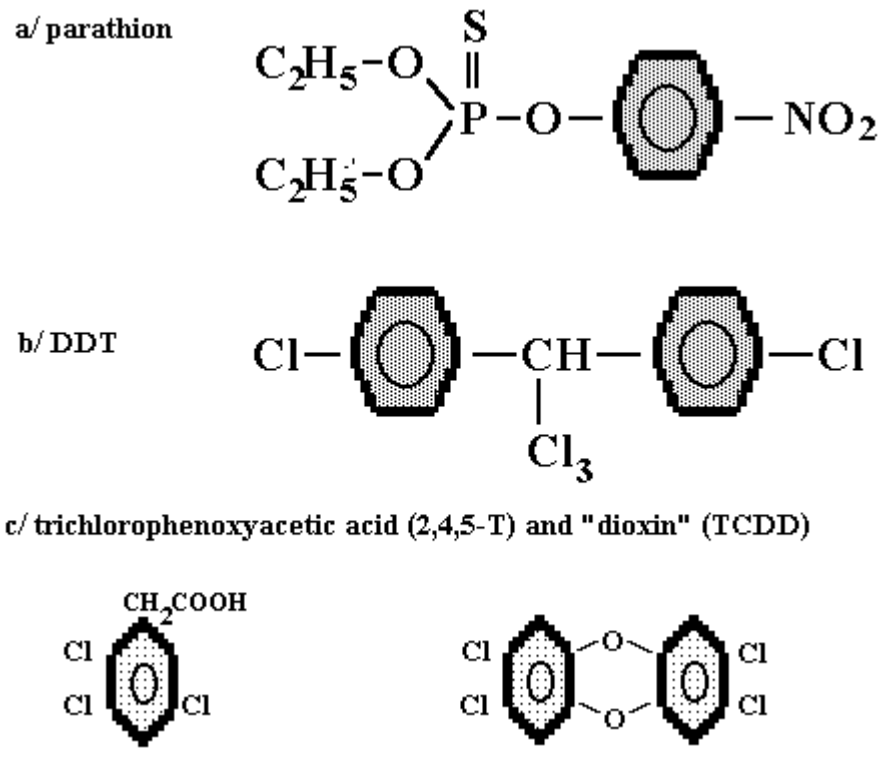

Fig. 2. Some important organic toxins
a/ Parathion - an organophosphate, b/ DDT - halogenated hydrocarbon (2,2-Bis(4-chlorphenyl)-1,1,1-trichlorethan), c/ Dioxin and the main component of Agent Orenge herbicide (2,3,7,8-tetrachlorodibenzo-p-dioxin, TCDD 2,4,5-trichlorophenoxyacetic acid; 2,4,5-T)

7.5 AROMATIC ORGANIC SOLVENTS

In this group compounds we include aromatic hydrocarbons: **benzol** (the most toxic among them), **xylol, toluol,** etc. These compounds are commonly used as solvents. Inhaled in large amounts or ingested, these compounds depress the function of the central nervous system: repeated exposure to small amounts of benzene or toluene depresses the bone marrow.

7.6 METHANOL

Methanol (CH_3OH, methyl or wood alcohol) is a widely used commercial solvent and is often mistaken for ethanol. In poisoning, about 30% of the dose is excreted as methanol by the respiratory tract; the remainder is converted, principally in the liver, by alcohol dehydrogenase to formaldehyde and then to formic acid by aldehyde dehydrogenase (Fig. 3). Symptoms of methanol poisoning may be delayed for 6-18 hours due to the delayed metabolism of methanol to the toxic products, formaldehyde and formic acid. The initial symptoms are similar to effects of ethanol followed by a mild drowsiness. This is followed by an asymptomatic period (6 - 30 hours) and then the characteristic symptoms and signs of methanol poisoning (dizziness, abdominal pain, vomiting, breathing difficulties, acidosis, blurred vision, dilated pupils, urinary formaldehyde smell) manifest. The local production of formaldehyde in the retina is thought to be responsible for the production of the **retinal edema and blindness**, the most characteristic signs of methanol poisoning.

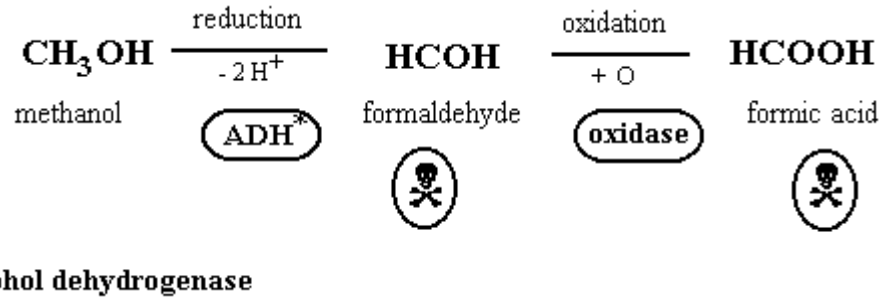

Fig. 3. The metabolism of methanol

The specific therapy for methanol poisoning is the administration of ethanol. The ethanol acts by competition for alcohol-metabolizing enzymes, thus permitting the excretion of methanol before it is transformed to formaldehyde and formic acid.

7.7 ALKALOIDS

Alkaloids are nitrogen-containig heterocyclic compounds of plant origin and complex structure. In plants they role is probably the defense from insects and animals. In animals and humans they exert a lot of pharmacologic and toxic effects and therefore from ancient

times they are widely used as remedies, narcotic drugs or poisons. The difference is often only a matter of dosage. **Nicotine, atropine, cocaine, morphine, codeine, papaverine, chinin, strychnine, coffeine, theobromine, digitalis, ergotamin** and **LSD** are some examples of this group.

8. TOXINS OF ANIMAL, PLANT, FUNGAL AND MICROBIAL ORIGIN

8.1 SNAKES

Poisonous snakes occur throughout most parts of the tropical and temperate zone of the world. The degree of toxicity resulting from snakebite depends on the potency of the venom, the amount of venom injected, and the size of the person bitten. Poisoning may occur from injection or absorption of venom through cuts or scratches. Snake venoms are complex and include proteins, some of which have enzymatic activity. The effects produced by venoms include neurotoxic effects eith senzory, motor, cardial, and respiratory difficulties, cytotoxic effects on red cells, blood vessels, heart muscle, kidneys, and lungs, defects in coagulation, and effects from local release of substances by enzymatic action (local swelling, local pain) and one or more puncture wounds or tooth marks.

8.2 BLACK WIDOW SPIDER (LATRODECTUS MACTANS)

The toxicity of the venom is probably greater than that of the snake venoms, but the spider injects only a minute amount of poison. The venom of the black widow spider causes various neurologic effects which have not been completely elucidated. The pathologic findings are not characteristic. The principal manifestation of black widow spider bite is immediate muscle spasm. Symptoms and signs consist of slight pain, blanching, and swelling at the site of the bite, progressing rapidly to pain in the chest, abdomen and joints and to nausea, salivation and sweating.

8.3 SCORPIONS

The mortality rate from scorpion stings may be over 1 % in children under 6 years but is negligible over this age. Local evidence of a sting is sometimes minimal or absent. The usual symptoms are a mild tingling or burning at the site of the sting, which may progress up the extremity. In severe cases, spasm in the throat, a feeling of thick tongue, restlessness, muscular fibrillation, abdominal cramps, convulsions, oliguria, cardiac arrhytmias, pulmonary edema, and failure of respiration occur.

8.4 HEMLOCK

The poisonous plants of the parsley family include poison hemlock (Conium maculatum), water hemlock (Cicuta maculata) and dog parsley (Aethusa cynapium).

Conium maculatum and Aethusa cynapium contain a number of piperidine derivatives, including coniine, which cause peripheral muscular paralysis similar to that from

curare. Nicotine-like ganglionic blockade also occurs. The pathologic findings in Cicuta poisoning are similar to those from picrotoxin.

8.5 MYCOTOXINS (POISONOUS MUSHROOMS)

The most dangerous species are **Amanita phalloides**, and other species of Amanita family. In this country about 100 accidents occur each year from eating poisonous mushrooms, some of them with fatal outcome.

Amanita muscaria is a nice red mushroom (fly-agaric), which in variable amounts contains, an atropine-like alkaloid that causes narcosis, convulsions, and hallucinations. Some mushrooms contain the alkaloid **muscarine**, which produces the same effect as parasympathetic stimulation on smooth muscles and glands.

The most fatal accidents are caused by **Amanita phalloides** (death cup) mistaken for champion mushrooms. It contains polypeptides amanitin and phalloidin, which damage cells throughout the body. These peptides are thermostable and cannot destroyed by cooking. Liver, kidneys, brain, and heart are especially affected. The intoxication often manifests only 24 - 48 hours after eating the mushrooms. The symptoms begin with intense colic pain and diarrhea, later jaundice with acute liver insufficiency develop together with signs of kidney and heart muscle damage. Due to early diagnosis and intensive treatment methods (e.g. hemoperfusion) the lethality of Amanita mushroom poisoning decreased in the past few years from 90 to 30 - 40 %.

8.6 OTHER MYCOTOXINS

A great number of moulds produce biologically active compounds from which the different **antiobiotics** are the most important. The ergot alkaloids **Ergotoxin** and **ergotamin** produced by Claviceps purpurea, a parazite of grain also belong here.

Aflatoxin B_1 produced by Aspergillus flavus striving on peanuts and other not properly stored and mildewy foods has recently been identified as an important carcinogen.

8.7 BACTERIAL EXOTOXINS

Botulism is caused by the exotoxin (protein, 150 kDa) produced by the anaerobic growth of Clostridium botulinum. Seven antigenic types of toxin occur, marked A - G; types A,B, and E are the most important. Botulotoxin is probable the most effective toxin at all - its lethal dose for humans is about 10^{-9} mg/kg. Among the foodstuffs most often responsible for it are meat, fish, and vegetables; olives and fruits are responsible only occasionally. The anaerobic environment of improperly canned foods favours the growth of bacteria and the production of toxin. The affected cans are filled with gas ("bombed"). Intoxication can occur also in infants fed honey, fresh fruit or vegetables or other foods containing the spores. Exotoxin production then occurs in the gut.

Botulotoxin causes paralysis of muscles by blocking the transfer of nerve impulses at the motor end plate. In acute poisoning, the symptoms begin 8 hours to 8 days after

ingestion, with nausea, vomiting, and sometimes diarrhea and abdominal distress, progressing to muscle involvement with marked fatigability, ptosis, dysarthria, blurred or double vision, dilated pupils, paralysis of the respiratory muscles, and quadriplegia.

Some other important bacterial exotoxins are listed in Tab. 2.

9. SMOKING

1. INTRODUCTION AND HISTORY

Cigarette smoking is the largest **preventable public health problem** in the western world. Approximately one sixth of the total mortality in these countries is associated with the consequences of the cigarette smoking. The cigarette consumption in the USA culminated in the sixties at 4300 pieces per capita and year and was declining slowly since. In EU a small decrease was registered in the last years. On the other side there is an alarming increase of cigarette smoking in eastern countries of Europe and in Asia.

According to recent research results cigarette smoking fulfills the criteria for an addiction, including a defined withdrawal syndrome (Tab. 1). The effect of **nicotine** on the central nervous system is probably the key factor in the addictive process. On the other side the health damaging effects of smoking are connected to **tobacco smoke**.

Tobacco is a member of Nicotinia genus and Solanaceae family. Chewing or smoking the dried leaves of tobacco was an ancient custom in natives of America long before the sailors of Columbus brought it to Europe at the end of XVth centrury. In those times smoking was persecuted by Holy Inquisition and prohibited by rulers. Later they recognized that selling and taxing tobacco is an important source of money and the ban was lifted.

King James, 1604 (and many others thereafter)

A custom loathsome to the eye, hateful to the nose, harmful to the brain, dangerous to the lung, and the black stinking fume thereof, nearest resembling the horribly Stygian smoke of the pit that is bottomless.

2. THE EFFECTS OF NICOTINE

Airway delivery is very effective system. The nicotine from a cigarette reaches the brain in less than 10 seconds, binds to the acetylcholine receptors, stimulates the secretion of the dopamine and affects the function of the mesolimbic system. Smoking activates both the sympathetic and parasympathetic nervous system and therefore it leads to relaxation in

stressful situations and stimulation in tranquil state. These physiological effects are apparent at very low doses – already 0,2 mg nicotine is effective (1 cigarette contains 8 – 9 mg; 0,3 – 3 mg gets in the body) and the half life of the compound is about 40 minutes. In high doses (e.g. an aqueous extract from 10 – 12 cigarettes) nicotine is strong toxin.

The proofs of addictive effects of nicotine are as follows:

- 70 – 90 % of smokers are unable to quit (not a moral weakness).
- Development of tolerance (more and more cigarettes during years of smoking)
- Presence of withdrawal symptoms.

Tab. 1 Comparison of smoking with other addicitons:

Alcohol	Moderate consumption is not harmful and does not lead to addiction. Alcoholism is extremely harmful to both the mental and physical health.
Drugs	Consumption is dangerous to mental health, high probablility od addiction.
Nicotine	Addictive but not harmful to personality, the health damage is NOT from nicotine

3. THE EFFECTS OF TOBACCO SMOKE

Tobacco smoke is a complex mixture containing nicotine and a great number of pyrolysis products. The burning of cigarette is a complex physico-chemical process and the average temperature of the tip is 900 ^{o}C. The product is smoke containing nicotine and a high number of organic and inorganic substances. The gas phase of the smoke contains agents with deleterious effect on cilia of the respiratory epithel and high concentration of carbon monoxide. The main particulate matter of the condensed smoke is tar which is responsible to its carcinogenic effect. One cigarette produces about 2 litres of smoke which contains about 30 mg of tar.

Tab. 2 Examples of harmful substances in smoke and tar

Condensed aromatic compounds (powerful carcinogens - benzpyrene, benzanthracene, aniline).
Nitrocomponds (mutagens, carcinogens).
Small organic molecules (formaldehyde, ammonia, cyanides).
Toxic metals (Cd, Ni, Co).
Reactive oxygen compounds ($\approx 10^{14}$ molecules in one puff).
Carbon monoxide in concentration 1 – 5% (inactivates Hb).

The reactive oxygen compounds (ROS) are not only in high concentration is smoke but their effect is amplified by metal catalysts which are well conserved in the tar. Two additional sources of oxidative stress are present in smokers (in the periods between smoking, too):

- ROS formation by activated phagocytes of respiratory organs (inflammation).
- Inactivation of antioxidants.

4. DISEASES ASSOCIATED WITH SMOKING

The major health risks of smoking are outlined in (Tab. 3). The individual effects depend on the daily and cumulative dose, depth of inhalation, type of cigarettes or other tobacco products and many other factors. The use of filters and “low nicotine” cigarettes do not help, they only increase the addictive demand for the next one.

Cardiovascular disease. Smoking is an independent risk factor of ischemic heart disease. The risk of developing myocardial infarction in smokers is almost twofold as compared to nonsmokers and the difference is even greater in young people. Smoking increases the adhesiveness of the platelets and leads to endothelial damage, increases the heart rate and the blood pressure which represent higher oxygen demand for the heart and decreases the oxygen delivering capacity of the blood through increased concentration of carboxyhemoglobin.

The damaging effect of smoking on **peripheral vessels** is even more pronounced. Over 90 % of patients with atherosclerotic peripheral vascular disease are smokers. Cessation of smoking in time is critical in these patients and can prevent amputation of limbs.

Respiratory problems and lung cancer. Every heavy smoker coughs and has mucus hypersecretion. Many of them develop chronic bronchitis with airflow obstruction and emphysema. Lungs of smokers contain increased number of macrophages and polymorphonuclear leukocytes as a part of the inflammatory response to the irritative effect of cigarette smoke. These cells produce elastase which degrades the elastic structural elements of the lung, resulting in a loss of elastic recoil. The sensitivity to the loss of elastic elements has also a genetic backgound, namely the hereditary deficiency of the α-1-antitrypsin. People with low acitivity of the enzyme are at high risk of early emphysema development.

The damaged airways represent a favourable basis for the action of the carcinogens, tumor initiators and promoters of the cigarette tar. The rates of the lung cancer begin to

increase in smokers after age of 35. The average risk factor of smoking for the development of lung cancer is about ten but heavy smokers (more than one pack per day) have about 20 - 25 times higher likelihood developing lung cancer (and other malignancies) as nonsmokers.

Involuntary or passive smoking. Inhalation of smoke constituents from the environment has the same deleterious effect as active smoking. Although the concentration of the smoke (and its constituents) in rooms and workplaces does not reach the level of the concentration in the airways of a smoker, the exposed persons are often infants, pregnant women or people with various health problems with exaggerated vulnerability towards the effect of tobacco smoke.

Tab. 3 Increased health risks due to smoking

CARDIOVASCULAR DISEASE
Ischemic heart disease, myocardial infarction
Peripheral vascular disease
Stroke
LUNG DISEASE
Lung cancer
Chronic obstructive bronchitis
Emphysema
GASTROINTESTINAL DISEASE
Cancer of oral cavity, larynx, oesophagus
Peptic ulcer
Oesophageal reflux disease
Cancer of pancreas
UROGENITAL DISEASE
Cancer of bladder
SENSES
Age related macular degeneration
COMPLICATIONS OF PREGNANCY
Infants small for gestational age
Stillbirth
High perinatal mortality
Abnormalities of placenta

ADDENDUM

THE HISTORY OF SMOKING AND THE BATTLE AGAINST SMOKING

XVth – XVIIth century	Tobacco and different forms of smoking appear in Europe. The rulers first ban this nasty habit, later they realize that tobacco tax in a good source of income for the state. (This is true also now)
1689	Peter the Great in Russia lifts the ban of smoking introduces by his predecessors. Reason: The Czar was himself a passionate smoker and needed a lot of money for his ambitious projects (e.g. building of St. Petersburg).
1809	Isolation of nicotine by N. Vaquelin.
1848	The citizens of Milano quit smoking as a protest against the control of tobacco business by Austria.
1939	Hermann Göring in Germany bans cigarette smoking for soldiers in the streets. Reason: Smoking is posing a risk for "race"
1950 – 1964	First scientific data about the harmful effects of smoking. Attempts of tobacco companies to influence researchers working in this topic through “support of research”. Concealment of data about the addictive effects of nicotine and smoking. Report of Surgeon General in USA on harmful effects of smoking.
1965	United Kingdom: Ban of tobacco product ads in TV.
1969	First nonsmoking sections in the aeroplanes of Pan American Airlines
End of XXth century	Legislative steps against smoking in public places and buildings, including schools, restarurants, theaters etc. Ban of tobacco product ads in the whole EU. Decrease of smokers in USA between 1965 and 2000 from 42 to 25 % The tobacco companies exert strong marketing pressure in countries outside Europe and USA.
Beginning of 3rd millenium	Even stricter ban on tobacco ads. Warning notices on cigarette packs. First successful lawsuits of individuals with lung cancer against tobacco companies.

10. ALCOHOL ABUSE

1. ALCOHOL METABOLISM

Alcohol is usually ingested in the form of different alcoholic beverages which contain 5 – 40% of ethanol. Ethanol is rapidly absorbed from the stomach and small intestine, enters the bloodstream and diffuses to all compartments of the body (it is miscible both with water and lipids); therefore its action is manifest already in some minutes.

About 10% of the ingested ethanol is eliminated directly through the kidneys and lungs, the remaining is metabolized in the liver. In the rate-limiting step catalyzed by alcohol dehydrogenase (an average, non-trained adult with undamaged liver can oxidize about 9 g ethanol per hour) toxic acetaldehyde is formed which is quickly transformed to active acetate. If the two reactions are not coordinated, acetaldehyde can cumulate (e.g. in most chinese and japanese individuals) and instead of alcoholic euforia first flush, later headache and nausea occurs. Acetaldehyde and its congeners (aldehydes, higher alcohols) are responsible for the hangover effects.

During alcohol metabolism the balance between the oxidized and reduced forms of NAD is shifted towards NADH. The rate of lactate to pyruvate is increased and **hyperlactacidemia** leads to **metabolic acidosis**. The excretion of uric acid in kidneys is dimnished – **hyperuricemia** can lead to gout especially in obese and genetically predisposed people (Fig. 1). As a consequence of the increased availability of NADH the **lipogenesis** is augmented, the Krebs cycle is blocked and from acetate **ketone bodies** are formed. The excess fat deposites in the liver and causes **steatosis** of the liver occuring of almost every alcoholic.

Acute alcohol (mostly after drinking short drinks) abuse can cause **hypoglycemia** – by inhibiting the gluconeogenesis in the liver. Chronic alcoholics, on the other side may develop secondary diabetes due to damage of the pancreas.

2. THE EFFECT OF ALCOHOL ON THE BRAIN

Ethanol in small doses has euphoric and anxiolytic effect. It causes first **excitation** by blocking the inhibitory functions of the nervous system. In the excitatory stage some persons instead of euphoria and relaxation may become hostile and aggressive. At higher doses a **depressive** phase follows which can end in coma and death (Tab. 1). Heavy drinkers with yet undamaged liver can tolerate higher doses.

The different parts of the brain are affected by ethanol from above downward - first the cortex, then the limbic system and the cerebellum, the reticular system and finally the brain stem. Its effect on neurons is probably exercised through entry of the calcium ion in the cell, upon the disturbed action of the Na/K-ATPase and through increasing the fluidity of the cell membrane.

After occasional heavy drinking postintoxication symptoms (**hangover)** occur with headache, giddiness, tremor, nausea and digestive complaints (alcohol directly damages the mucosa of stomach).

3. CHRONIC ALCOHOLISM AND WITHDRAVAL SYNDROMES

Dependence on alcohol develops in "high risk" individuals in favourable social conditions. The predisposing factors include a genetic component but its nature is not yet fully elucidated. Chronic alcoholism is characterized by an **addictive cycle** that perpetuate heavy drinking. The ingestion of alcohol provides some relief from psychologic and physical tension. Drinking, on the other side, induces psychologic and somatic processes which increase the desire for more alcohol.

In chronic alcoholics first a **primary psychologic dependence** develops followed by **increased tolerance** to alcohol. This allows the increases of the dose which in turn leads to **physical dependence.** In this stage abstinence causes alcohol withdrawal syndromes and these force the alcoholic to drink steadily. At the end of this course **complete inability to abstain** ensues. The attitude of adult population toward alcohol is in (Tab. 2). From this statistics the high percentage of people in the fourth group (occasionaly heavy drinkers) is alarming. They are not yet „alcoholics“ from medical and legal point of view but are already affected by most of the sequels of alcohol abuse.

Cessation of alcohol intake from whatever reason in chronic alcoholics leads to withdrawal syndromes, from which **delirium tremens** is the most severe. Delirium tremens represents an acute medical emergency. The patients are disoriented, agitated, hallucinating, tremulous. The heart and respiration rate is rapid, the body temperature elevated and the blood pressure low. Muscle cramps and general seizures can occur. The symptoms in untreated patients may last weeks and complications (pneumonia, hepatitis) can develop.

4 ALCOHOL-RELATED DISEASES

The pathogenesis of alcohol-related diseases can be explained by

- **direct toxic effects of ethanol and**
- **dietary insufficiency.**

In som cases also the presence of toxic substances present in some beverages should be considered.

Alcohol and alcoholic beverages are rich in energy and therefore the caloric intake of heavy drinkers can be covered by alcohol alone. This "diet" is, however, deficient in every essential component of healthy diet (proteins, trace elements and vitamins). The dietary insufficiency is superimposed to the toxic effects of ethanol and therefore in actual organ or system damage usually both type of damage is involved.

Alcohol related diseases involve every organ and system of the human body and even small doses of alcohol pose a tremendous threat to the fetus during intrauterine development (Tab. 3).

5 POSITIVE HEALTH EFFECTS OF MODERATE ALCOHOL CONSUMPTION

Both the cultural traditions of Europe and several well conducted epidemiological studies claim that moderate alcohol consumption has beneficial effects on health. This is mainly connected to the drinking of red wine (the French paradox – low occurence of coronary heart disease as compared with Scotland despite the same level of cholesterol) and the delay of atherosclerosis and atherosclerosis related diseases. These studies revealed that 1–14 drinks in a week but not more (1 drink is approximately 1 glass of wine) decreases the risk of coronary heart disease. It is not clear, that the elevated HDL cholesterol, increased fibrinolytic activity, decreased coagulation and increased insulin sensitivity is related to the effect of alcohol (not probable), to the antioxidants in red wine (plausible) or merely to the relaxed life style (possible).

Tab. 1 Acute alcohol intoxication

BLOOD LEVEL OF ALCOHOL mg/l	**PHASE**	**MAIN SYMPTOMS***
0.50	**excitatory**	euphoria
0.75		garrulity
		sometimes aggresivity
1.0		loss of motor coordination
1.5		unrestrained behaviour
2.0	**depressive**	alertness loss
3.0		stupor
5.0		coma and death

TAB. 2 ALCOHOL DRINKING IN WESTERN COUNTRIES

ABSOLUTE ABSTAINERS	10 %
CONSISTENT CONSUMERS (never drunk)	20 %
NONCONSISTENT CONSUMERS (sometimes slightly drunk)	20 %
OCCASIONAL HEAVY DRINKERS	27 %
ADDICTIVE ALCOHOLICS	3 %

TAB. 3 ALCOHOL RELATED DISEASES AND PATHOLOGICAL PROCESSES

ORGAN OR SYSTEM	DAMAGE OR DISEASE
Brain	Alcoholic dementia
	Wernicke-Korsakoff sy.
Nerves	Polyneuropathy
Heart	Cardiomyopathy
Blood	Anemia
Gastrointestinal	Acute and chronic gastritis
tract	Acute and chronic pancreatitis
	Carcinoma of the oesohpagus
Liver	Steatosis
	Acute hepatitis
	Cirrhosis
Endocrine system	Male sexual impairment
and reproduction	Fetal alcohol syndrome
Metabolism	Hyperlipidemia (triacylglycerols)
	Hyperuricemia, gout
	Hypoglycemia
	Secondary diabetes
	Hypovitaminoses
	Acidosis, ketosis
Immune system	Increased susceptibility to infections

Fig. 1 Alkohol metabolism