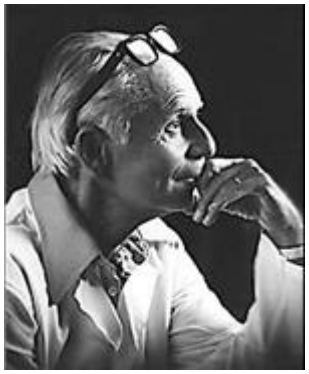
PLENARY LECTURE IN HYGIENE

Zavgorodnii I.V.

CLINICAL ENVIRONMENTAL MEDICINE

Kharkiv National Medical University, Ukraine

As the epigraph for our report we would like to take a statement of the scientist, who was born in Vienna, got his education at the University of Prague, later continued his studies in Rome and Paris. From 1931 he worked at John Hopkins University (USA), later at McGill University (Canada); this is a Rockefeller Fellow Hans Selye.



“In science, there are no small, limited areas - there are only small, limited scientists. In nature, each area merges with the neighboring ones, and it depends only upon you - and to a large extent upon your ability to read - where exactly the borders of your interests will be”.

Hans Selye

First of all, a question arises: why have we chosen medical and environmental problems as the subject of our report? And, moreover, in the context of clinical medicine of the environment? In addition, what are the features of the current state of the environment?

First of all, we would like to cite the data published by the World Wildlife Fund report, which provides an update on the Living Planet Index (LPI), calculated by scientists.

Data of 2010 report show that 30% of the planet's biological system has been lost over the past 40 years.

The annual 2014 LPI edition already describes the state of more than 10,000 representatives of populations of mammals, reptiles, amphibians and birds. It turns out that since 1970 their number has decreased by 52% (39% of the terrestrial, 39%

of maritime and 76% of limnetic animals), as the leading experts explain. That is, the planet lost 22 per cent of the biosystem during 4 years. The pace is impressive ... But the humans go on living.

That is why the time has come when the issues of the role of environmental factors in the genesis of diseases are regarded by the scientific world with special attention.

One of the first scientists who systematically studied these problems was a physician, allergist from University of Michigan (USA) Theron Randolph (1906-1995). He studied food allergies, chemical sensitivity and preventive measures. Randolph is the author of four books, including the first textbook “Human ecology and susceptibility to the chemical environment” (1962) and more than 300 medical articles; he is considered by rights as “the father of clinical ecology”.

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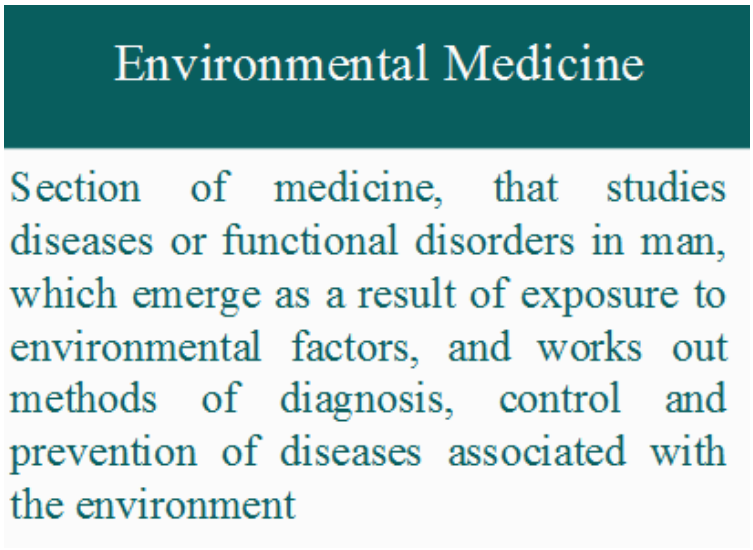
In the modern interpretation, we talk about environmental medicine that studies diseases or functional disorders in man, which emerge as a result of exposure to environmental factors, and works out methods of diagnosis, control and prevention of diseases associated with the environment.

Understanding the particular urgency of this research direction, a few years ago our university concluded a contract with the Institute of Occupational Medicine and Hygiene of Otto-von-Guericke Magdeburg University.

Therefore, today we make public the view of our integrated team on these problems.



By this moment we have performed 4 environmental projects: "With teacher's profession to be healthy and motivated until retirement: ways of prophylaxis and development of personality", "Study of loads and intensity in the banking area employees",

"Study of psychological stress among emergency workers". The total amount of the researches is more than 800 respondents by 10 European questionnaires. The processing was carried out in Germany with use of the Vienna Test systems. Since we used European questionnaires, the data are consistent with international ones and can be published in their journals of scientometric databases. Thus, the results of a survey of Kharkiv teachers show that 3.1% of respondents have symptoms of burnout, thereby confirming the results of Dr. Seibt's research group (Germany). Their works describe similar results, namely, approximately 3% of teachers in Germany are at risk of "burnout".

All in all 9.2% of the surveyed workers of Kharkiv ambulance service had a risk of burnout. The employees of the banking sector did not show any signs of burnout.

Now a few words about the technological effectiveness of international scientific communications.

We have received a new project proposal:

- Industry 4.0 (the fourth industrial revolution and industrial internet);
- digitalization of the working world;
- CPS - integration of cyber-physical systems into production processes.

New information projects, study of labour intensity when these new means of labour (from a small workshop to a giant - Volkswagen) are used. Our colleagues from

Magdeburg work now with that enterprise. Over 20 years 47% of jobs will be automated, and a million workers will lose their work. We talk about the formation of rational systems and anthropo-infrastructure of production.

The urgency of studying the influence of environmental factors on the human body is confirmed by the fact that in 2006 European universities introduced the interdisciplinary subject "Clinical Environmental Medicine". The teaching is carried out by experts of specialized departments and divisions. Thus, this problem is known to our colleagues and we were supported by the outcomes of our report in Berlin on the forum dedicated to cooperation between the two countries on issues of medical education (November, 2014).

Next, the talk about the problem of clinical aspects of environmental medicine can be either from the position of characteristics of the operating factors or from the discipline positions. The latter seemed to us more correct.

MENTAL DISEASES

The prevalence of mental illnesses in 15 most economically developed countries within the period from 1900 to 1993 increased by 10 times and now is

303.7 per 1,000 populations (including: neuroses by 62 times, alcoholism by 58 times, oligophrenia by 30 times).

CLASSIFICATION OF THE FACTORS LEADING TO THE DEVELOPMENT OF MENTAL DISEASES

(by O.K. Napreenko, K.N. Loganovsky):

physical factors: radiation, noise and vibration, infra- and ultrasound, climatic conditions, temperature, atmospheric pressure, accelerations and gravity, electrical currents and discharges;

chemical factors: intoxication with drug substances, substances of non-pharmacological nature (metals, inorganic and organic compounds, pesticides, chemical weapons);

biological factors: poisoning with seafood, mushrooms, berries, contacts with venomous animals, bio-substances for medical use, biological weapons;

poisons that affect the nervous system: psychotropic proper, indirectly psychotropic.

DISEASES OF THE BLOOD SYSTEM AND HAEMATOPOIETIC ORGANS

As far as the blood system and haematopoietic organs are concerned, small doses of radiation, benzene and cytostatics provoke the development of leukaemia. High nitrate amounts increase the level of methaemoglobin (MetHb) that in 60-70% of cases in infants is fatal. Lead exposure is accompanied by the development of lead-induced anaemia. The immunosuppressive effect of dioxins is known. The blood is also affected by the substances that cause oxidative stress: aniline, arsines (organic arsenic compounds: warfare agents - lewisite, Adam site).

Hemotoxic agents are classified as physical agents (ionizing radiation, electromagnetic fields) and chemical ones (aromatic nitro and amino compounds, benzene, halogenated hydrocarbons, pesticides, herbicides, dioxins, carbon

monoxide, nitrates/nitrites, lead, arsenic, vinyl chloride, isocyanates, leukotropic RNA-viruses, smoking).

ECOLOGICAL AND TOXIC EFFECT ON THE HEART AND VESSELS

The following chemical substances cause ecological and toxic effects on the heart and blood vessels: carbon disulfide as a raw material in the production of viscose fiber (up to 80% of produced carbon disulphide are used in the production of viscose - a raw material for the production of viscose fiber {rayon}), this is made of wood cellulose, and carbon disulphide makes up 30-50% of its weight (an increased risk of death); aliphatic nitrates - pharmaceutical production and explosives (coronary systemic reactions); solvents (effects on myocardial conduction and contractility); arsenic (damage of peripheral arteries); carbon monoxide - cardiomyopathy and violation of impulse formation; thallium - an insecticide and agent for pest control (poisoning). Thallium poisoning - when eating grain treated with thallium (thallium as an insecticide and agent for pest control).

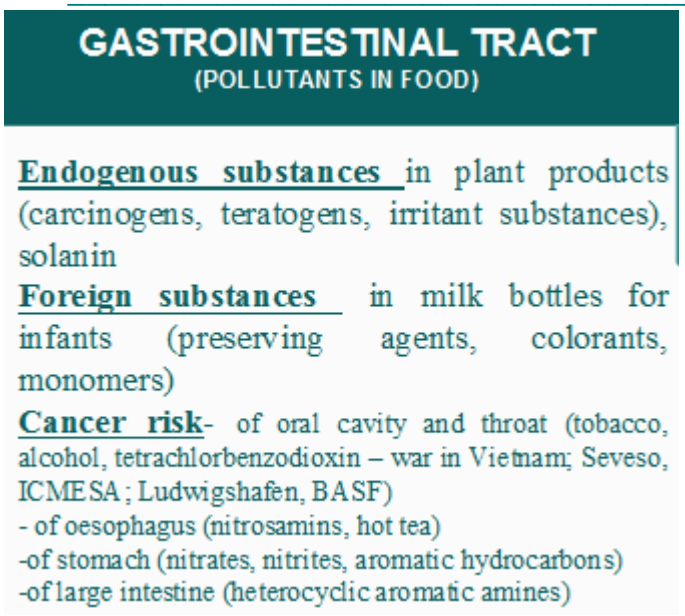
A direct relationship between population mortality from cardiovascular diseases and cadmium content in the atmosphere of large cities is established (cadmium-nickel accumulators, anti-corrosive coating, inorganic mineral paints, cadmium sulphide when laser printers are used). Bone lesions (osteomalacia), hypotension, anaemia, renal failure. These symptoms are known in itai-itai disease.

Cobalt chloride as a foaming additive, which is now forbidden (at least, it is illegitimate), provokes the development of cardiomyopathy.

Heavy metals cause kidney damage and renal hypertension – “illegally distilled homebrew-whiskey”. Such factors as traffic noise and passive smoking are important.

GASTROINTESTINAL TRACT

Ecological influence is often targeted at the gastrointestinal tract (GIT). Common are allergic gastrointestinal diseases: childhood allergies (cow's milk, chicken eggs, wheat, soy, peanuts), grass pollen allergy (birch, often combined with apple – cross-allergy), hazelnuts and other large fruits; tarragon and celery (cross-allergy), carrots, spices. Oncological gastrointestinal diseases are possible.



Here is a short list of major accidents with environmental release of dioxin-like compounds (these include 75 dioxins, 135 different furans and 209 polychlorinated biphenyls): defoliants (were used by the American army in Vietnam, Agent Orange); a disaster in Seveso (Northern Italy), when 3 tons of toxic substances settled on the area of 15 hectares (75 thousand poisoned animals were slaughtered, 79 people became ill with chloracne); Ludwigshafen (Germany) – at a BASF factory 75 people were involved when the factory area was contaminated with dioxins. The effect of dioxins is polysystemic and therefore they will be mentioned in this report again and again.

HEPATOTOXIC EFFECTS

In 1968, a massive outbreak of poisoning occurred in the southwest of Japan (Yusho village) after eating commercial rice oil, which was accidentally contaminated with PCBs and PCDF. 1,786 people were involved. The episode was called “Yusho disease”, or “oil disease”.

Toxic oil syndrome - Spain (1981), an outbreak of the disease, named toxic oil syndrome (TOS). As a result, this outbreak killed several hundred people, and the total number of victims exceeded 20,000 people. From the standpoint of toxin getting into the oil, the problem lied in the process of refinement of the suspected oil.

Hexachlorobenzene is a fungicide used especially for treatment of seeds.

Intoxication with pyrrolizidine alkaloids: data on medicinal herbs indicate the need for their very cautious use, especially in the conditions of promotion of non-traditional methods of treatment and putting into practice a tremendous number of their various combinations.

Pyrrolizidine alkaloids are present in many herbs belonging to the families of Asteraceae, Leguminosae and Boraginaceae. The alkaloid of pyrrolizidine is contained, but in smaller quantities, in such widely known and used herbs as medicinal comfrey and coltsfoot. Hydrazine is a component of rocket fuel. Its sulphate is used in pharmacotherapy for certain types of tumours.

HEPATOTOXINS

- Iron, copper, phosphorus, arsenic, selenium, beryllium, mercury, cadmium
- Hydrazine
- Halogenated hydrocarbons (vinyl chloride, trichloroethylene, solvents, detergents)
- Dioxins, dibenzofurans
- Resin hardeners
- Fungus hepatotoxins (aflatoxicosis)
- Bacterial hepatotoxins

Polyvinyl chloride: its decomposition or exposure to temperature results in release of a monomer, i.e. vinyl chloride (linoleum, plastic packages, toys). The monomer migrates into water, air, foodstuffs. Interestingly, since January 1, 2016 the French Ministry of Ecology has prohibited using of any plastic bags in department stores and supermarkets of their country.

Aflatoxins cause acute toxicosis in children when peanut flour is used for their feeding (patients with kwashiorkor in Senegal, India). The products of high attention are as follows: peanuts, oilseeds, cereals, legumes, coffee.

NEPHROTOXIC EFFECTS

TOXIC NEPHROPATHY

Manifestations	Trigger agent
Acute renal failure	Heavy metals (Hg-salts, lead, bismuth) Aminoglycosides
	Antibiotics Penicillins Cephalosporins Rifampicin
Chronic renal failure	Analgesics Cadmium, lead Cyclosporins
Nephrotic syndrome / renal failure	Mercury, gold, bismuth, Penicillamine, Penicillin G, Captopril, Sulphanilamides

Nephrotoxic effects manifest themselves under the influence of pharmaceutical products (analgesics – acetaminophen, NSAIDs; antibiotics – aminoglycosides, cephalosporins, vancomycin, amphotericin B; cytostatics – cisplatin, methotrexate; immunosuppressors – cyclosporine; iodinated radiographic contrast agents).

Ethylene glycol is a component of solvents for paints, plastics, antifreezes, windshield washer fluids, brake fluids, defrosters (antidote for poisoning - ethanol, as ADH affinity for it is higher and the time of ethylene glycol metabolism increases with a slower formation of products of its metabolism – glycolic, glyoxylic and oxalic acids).

Trigger agents of toxic nephropathy are as follows: heavy metals (Hg salts, lead, bismuth), aminoglycosides and antibiotics (penicillins, cephalosporins, rifampicin), which are manifested by acute renal failure; analgesics, cadmium, lead, and cyclosporins result in chronic renal failure; mercury, gold, bismuth, penicillamine, penicillin G, captopril and sulphanilamides cause nephrotic syndrome or renal failure.

REPRODUCTIVE TOXICOLOGY

Reproductive toxicology explores toxic effects that occur before and after birth. Thalidomide (opiate) provokes severe malformations of limbs; about 7,000 people were affected from 1959 to 1962. Extremely vulnerable is the human reproductive system; so much that we can talk about isolation of a separate field of research, namely, reproductive toxicology and toxicity.

This anticonvulsant and sedative drug was developed in Germany in 1954. It was recommended for pregnant and lactating women (in order to get rid of insomnia, anxiety and morning nausea). One of the employees of this pharmaceutical company took thalidomide, which had not yet been delivered officially, brought it home and gave to his wife. Their baby was born without ears. The teratogenic effect. Also awful is the fact that these physical deformities can be inheritable.

Dibromochloropropane (a nematocidal drug) causes disruption of spermatogenesis. Workers of banana plantations developed testicular damage, infertility. This is a classic example of occupational hazards for the male reproductive

system. Also a negative effect on spermatogenesis is produced by: alcohol, tobacco, narcotic drugs; pesticides, herbicides; heavy metals, solvents, cooling fluids; flame retardants, plasticizers; disinfectants; synthetic estrogens; heat, ionizing radiation, electromagnetic fields; cytostatic agents, antiepileptic drugs, sulphanylamides; diuretics, imidazoles, glucocorticoids; steroid hormones, etc.

COMBINED ACTION

So far, we have characterized effects of an isolated action of the above factors, but in real life it occurs very seldom. Most commonly we come across a combination of the factors. In particular, chemical factors are combined with physical ones. And in this scientific field we got some interesting data on the part of the reproductive system (figure 1).

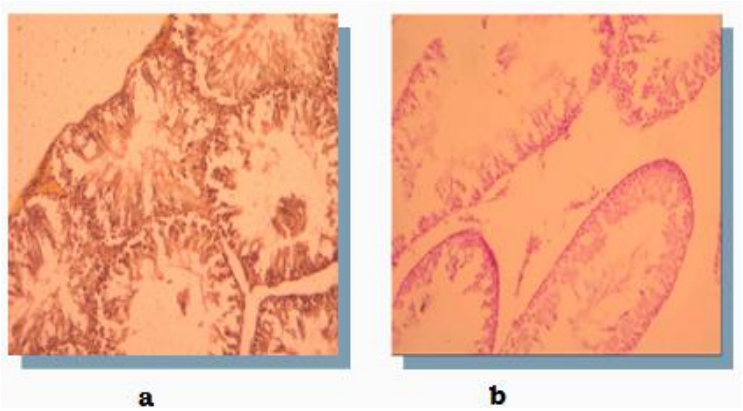


Fig.1 Micrograph of rat testes *(a – thinning of the seminiferous epithelium, a reduced amount of dividing spermatids; b – tubules with total emptying and uncovering of PAS-positive basal membrane)*

Left - an isolated effect of a chemical factor: thinning of the seminiferous epithelium, a reduced amount of dividing spermatids. This is the result of nitrobenzene action. Right - its combination with positive low temperatures (from +2°C to 4°C). That is, the animal is under conditions of cold stress. The total emptying of the tubules is clear. Cold has been the hardest stress factor throughout the whole evolution. The above facts made it possible for us to substantiate the term "cryotoxicology" with a report at a congress of toxicologists of Ukraine.

Imagine that instead of nitrobenzene there is a pharmaceutical drug and the effect of its action is intensified in conditions of cold stress. The above suggests the rationale for the scientific term “cryopharmacology”.

TERATOGENIC EFFECT

The teratogenic effect, caused by the action of dioxins, is manifested by the split spine, spina bifida, an open spinal cord; this is observed in Vietnamese and descendants of the American veterans of the Vietnam War.

Large doses of vitamin A must not be administered at the early stages of pregnancy and even six months before pregnancy.

Ethyl alcohol belongs to the group of the strongest chemical teratogens. Violation of the molecular structure of the cells (including germinal ones) is caused by alcohol and its metabolites, particularly acetaldehyde. The so-called fetal alcohol syndrome can cause abnormalities of fetal development: face deformities, visual and hearing impairments, retarded physical development, mental deficiency and mental retardation, behavioral problems (low self-control, attention deficit and hyperactivity), small head circumference and brain size (microcephaly), defects of the cardiovascular system, poor coordination of movements, poor learning ability. Other damaging mechanisms include: lack of vitamins and microelements in the mother's diet, violation of the transplacental transport of essential amino acids, fetal hypoglycemia, reduced placental blood flow and fetal hypoxia.

In the prenatal period, appearance of PCB in food develops Yusho disease and functional changes in the central nervous system; ACE inhibitors are dangerous during pregnancy; methylmercury causes Minamata disease, spastic cerebral palsy and behavioral changes.

During the postnatal period: effects of nuclear weapons result in mental deficiency and a higher risk of tumours; fluoroquinolones - gyrase inhibitors - cause cartilage lesions; diethylstilbestrols lead to vaginal cancer; dichlorodiphenyltrichloroethane insecticides affect the CNS; polychlorinated dibenso-p-dioxins and dibenzofurans develop polyneuropathy.

OCULOTOXIC SUBSTANCES

In 1900 there was a mass poisoning with beer in Manchester; the poison was contained in artificial yeast and malt. The global scale of contamination with arsenic (underground waters, arsenic ores) resulted in retinopathies and optic neuropathies. The effect of mercury in Japan in 1956 (Minamata disease) developed an atrophy in the optic cortex area, narrowing of the visual field, blindness.

The visual organs are damaged under the effects of: thallium (retrobulbar neuritis or optic neuropathy with paresis of the eye muscle); ethanol (nystagmus, diplopia, transient blindness, visual disturbances, moderate reduction of contrast sensitivity, visual field defects, optic neuropathy); methanol (amblyopia, spots in front of the eyes, blindness).

NEUROTOXIC EFFECTS

- Pesticides (foodstuffs and agricultural lands);
- insecticides (developed on the base of chemical poisonous substances in order to affect the nervous system);
- industrial products (solvents and cleansing agents, paints);
- fuel on the base of carbon-containing materials and combustion products (incomplete combustion products, e.g. carbon oxide);
- petrol (mixed with lead);
- dentistry (mercury restorations);
- formaldehyde (glues for chipboards, fibreboards and plywood; in textile industry);

“Chinese restaurant syndrome” – sodium glutamate (E621, a flavour intensifier in foodstuffs) (paresthesiae on the face, neck and trunk).

CHRONIC EFFECT OF METALS AND METALLOIDS

Clinical manifestations of the chronic effect of metals, metalloids and their compounds are as follows:

- chromium – dermatitis (chromium holes – ulceration of the finger skin), ulceration and perforation of the nasal septum;

- phosphorus – periostitis, necrosis of the jaw ("phossy jaw"), hepatitis, dermatitis;
- cadmium – lesions of bones (osteomalacia, osteoporosis, spontaneous fractures), pulmonary lesions (emphysema, obstructive syndrome, diffuse interstitial fibrosis), renal lesions;
- tin – stannosis (deposition of tin oxide in the lungs, lymph nodes, liver and spleen);
- manganese – encephalopathy (akinetic-rigid syndrome of parkinsomism), asthenia, adynamia, muscle pains, paresthesiae, speech disturbances, chronic bronchitis, pneumonias;
- arsenic – obliterating endarteritis ("black foot disease" - Taiwan), Raynaud's syndrome, myocardial infarction.

ECOLOGICAL PATHOLOGY

ECOLOGIC PATHOLOGY

Disease	Etiology, routes of entry	Region	Lesions of systems	Fell sick/ died
Minamata (1953)	Methylmercury Food (fish)	Kyushu island, Minamata town	Cardiovascular, nervous system, kidneys	10000/2325
Yokkaichi asthma(1960)	Sulfur dioxide Air	Yokaichi town	Lungs, stomach, thyroid gland	1200/300
Itai-itai (1967)	Cadmium Air	Iitsu river	Osteoarticular	117/85
Yusho (1968)	Polychlorinated phenyls Food, rice oil	Kiushu district	Lungs, skin	1788/112

There are many syndromes and conditions, which have already received their nominative names; thus, for example, the world already knows a group of "Japanese" ecological diseases, caused by methylmercury (Minamata disease) and sulphur dioxide (Yokkaichi asthma).

By the way, sulphur dioxide is also a preserving agent, E220, whose negative effect consists in the fact that this chemical compound simultaneously destroys vitamin B1 and disulphide bridges in proteins. After their treatment with sulphur dioxide the foodstuffs inevitably get a strong smell. Therefore, sulphur dioxide is mainly used in the foodstuffs, which will be reprocessed. The orange colour of dried pitted apricots and raisins results from addition of sulphur dioxide (E220). Besides fruits, E220 is also used for treatment of alcoholic drinks, beer, potato products and soft drinks. Cadmium compounds cause itai-itai disease, polychlorinated phenyls cause Yusho disease.

Unfortunately, the number of such patients often exceeds several hundreds, sometimes even thousands.

We would like to end this report with the following words: “Only *alma mater* is worthy of scientific discoveries… thanks to its teachers and with a hope for its students”.

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