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MECHANISMS OF CARCINOGENIC ACTION OF VINYL CHLORIDE (Review of Literature)

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In 1835 the German chemist Regnault synthesized a low molecular, unsaturated, chlorinated hydrocarbon which acquired the name vinyl chloride (VC). The outstanding feature of this compound was its capacity to be polymerized which also determined its future fate as a starting material in the production of many plastics. At first in the USA (1928) and then in other countries construction was begun on large-tonnage factories for producing polyvinyl chloride (PVC). By 1980 the total capacity of these factories in the world reached 12-12.5 million tons per year. The factors which stimulated the increase in production of PVC were not only the significant economic demands for it but also the assurance of its complete harmlessness for the human being. The rather broad use of VC as an anesthetic in surgical practice (Fao and Bertazzi) will serve as an illustration of this fact. However, in the middle 50's - beginning of the 60's in the USSR the first publications appeared concerning the toxic effect of VC on the human organism (N.A. Smirnova). In subsequent years the said articles were confirmed by

research performed by professional pathologists abroad (Suciu et al.; Wilson et al.).

Prolonged intake of VC into the organism of workers leads to a systemic disorder of the connective tissue reminiscent of scleroderma (Juhe and Lange; Moulin et al.; Brichter). The clinical picture of vinyl chloride disease (VCD) is composed of a syndrome of a disorder of the central and peripheral nervous system (V.A. Antonuyzhenko; Foa and Bertazzi; Suciu et al.) the Reino syndrome and acro-osteolysis (V.A. Antonuyzhenko; N.A. Smirnova; A.V. Basalaev et al.; Wilson et al.; Cook et al.; Dodson et al.; Juhe and Lange; Biersack et al.; Rety et al.; Hahn et al.), the hepatolienal syndrome (Falk et al.; Thomas et al.; Creech and Makk; Berk et al.) disorders of the skin (Juhe and Lange; Duport et al.; Veltman) fibrosis of the lung (Lange et al.; Brichter; Gordasco et al.).

Experiments designed to study the mechanisms of vinyl chloride acro-osteolysis revealed an unexpected property of its pathological effect, that is, a carcinogenic effect. After Maltoni published his results of an experimental study in which he detected in many animals inocculated with the VC the manifestation of an extremely rare malignant tumor, that is to say a hemangiosarcoma of the liver, oncologically and pathologically concerted attention began to be given to this substance. In 1974 this tumor was discovered in one of some deceased workers who had been employed in a factory where PVC was produced (Creech and Johnson). After the article by Creech and Johnson a whole series of publications was printed concerning the occurrence of hemangiosarcoma of the liver in workers involved in producing PVC and in two residents of areas adjoining the factories where this product was produced (Makk et al.; Falk et al.; Fleig and Thiess; Conso). By the end of 1977 64 cases of death from hemangiosarcoma of the liver had been recorded, caused by

caused by contact with VC (Spirtas and Káminski). An analysis of the experimental and clinical material showed that VC induces the growth not only of hemangiosarcoma of the liver but also of adenocarcinoma of the stomach, and alveologenic tumor of the lungs, hepatocarcinomas, nephroblastomas, neuroblastomas, carcinomas of the mammary glands, of various forms of connective tissue tumors and also an increase in the quantity of systemic diseases of the blood (Maltoni; Suzuki; Brichter; Feron and Kroes; Winell et al.; Ott et al.). A correlation of this material made it possible for Maltoni to reach the conclusion that VC is an undisputable carcinogen with a broad spectrum of effect. According to the data of experimental studies conducted by B.A. Kurlyandsky et al., VC can be classified among the low level carcinogens (class IV of blastomogenic activity).

An analysis of the general death rate of workers involved in producing PVC did not turn up any changes in its structure (Ott et al.; Fox and Collier). The only thing detected was an increase in the frequency of some forms of malignant tumors, tumors of the stomach-intestinal tract (Chearu and Nichols), of the lungs and brain (Rawls). However, attention is drawn to the fact that, for example, in the Federal Republic of Germany, with the absence of any changes in the general structure of the death rate a pronounced shortening of life was noted in workers subject to VC exposure, that is to say the hydrocarbon under study, without changing the ratio between oncological and nononcological diseases it hastens their appearance and consequently it hastens the death of these workers. According to data by Thiess and Frentzel-Beyme, 68% of the deceased workers involved in producing PVC did not reach the age of 60.

Detecting the carcinogenic effect of VC was the impetus for carrying out numerous experimental studies focused on interpreting this effect. In and of

itself VC is not capable of stimulating the growth of malignant tumors (Antweiler); the carcinogenic danger comes in the form of its metabolism products in the organism. The carcinogenic process under the effect of VC takes place in two stages: the first is biochemical and the second is the immune stage.

It was established that the biotransformation of VC may take place in two ways. Initially under the effect of a microsomal monooxygenase (Tarkowski et al.) VC is oxidized into 2-chloroethanol, chloroacetaldehyde and monochloroacetic acid. The said method of oxidation is observed under the effect of VC on the organism at concentrations of up to 256 mg/m^3 (Binns). At higher concentrations of the carcinogen under study, the biodestruction process of VC takes place with the formation of unstable oxides and peroxides of chloroethylene (Antweiler; Binns). At the same time that the destruction process of the hydrocarbon is taking place in the organism, its "fragments" are bonding with the thiol radicals of the tissues. Chloroacetaldehyde and chloroethylene oxide have alkylating properties and they are capable of undergoing a divalent bond with the sulfhydryl groupings of the proteins, the adeno, cytosine and guanine portions of the nucleic acids (Binns; Tarkowski et al.; Bolt et al.). The basic enzyme which supplies the conjugation of the metabolites with the thiol groupings of the protons is glutathion-S-epoxytransferase (Green and Hathway).

As a result of the alkylation a whole complex of various compounds is formed which are gradually eliminated from the organism. By using gas and ion exchange chromatography in combination with mass spectrometry we were able to identify some of them, in particular, thiodiglycolic acid, N-acetal-S-vinyl cysteine (Green and Hathway), N-acetal-S-(2-oxyethyl)-cysteine, N-acetal-S-(2-chloroethyl)-cysteine, N-acetal-S-(2-hydroxyethyl)-cysteine

(Watanabe et al.), S-(2-chloroethyl)-cysteine (E.N. Dubankova and A.V. Bykhovsky), S-(2-carboxymethyl)-cysteine, thiodiacetic acid (Antweiler) and also modified nitrogen compounds of DNA - ethanodesoxyadenosine, ethanodesoxycytidine, ethanoadenine (Green and Hathway), oxyethylguanine (Laib et al.), diethylhexylphthalate (Gordasco et al.).

In experiments on a culture of S. typhimurium (strains TA 98, TA 100, TA 1535, TA 1538) the sulfhydryl metabolites of VC did not manifest a mutagenic effect (Green and Hathway).

However, the metabolic "fragments" of the hydrocarbon attached to the proteins and nucleic acids confer antigenic properties on the hydrocarbon (N.F. Borisenko et al.; Binns; Bolt et al.). One result of the said process is the producing of antibodies for these proteins and nucleic acids. This mechanism forms the basis for a second (immune) stage of the carcinogenic process under the effect of VC.

N.F. Borisenko et al., Hicks and Sahyoun write concerning the change in immunity with chronic exposure to VC. According to data by Mizerski et al. there is a reliable increase in the concentration of IgA in the blood serum, there is an absolute and a relative increase in the number of T-lymphocytes in workers employed in the production of PVC. Ward et al. detected a polyclonal increase in the concentration in the blood of one of the classes of immunoglobulins, most frequently IgG, the presence of mixed immunoglobulins and the conversion of the C_8 and C_4 complement in subjects subjected to VC exposure in production conditions. In most of these subjects who came into contact with high concentrations of VC, high concentrations of antinuclear antibodies were detected. In workers subjected to exposure to low concentrations of VC the levels of immunoglobulins is practically indistinguishable from those in the control groups, no antinuclear antibodies were

detected. All these antibodies are produced in response to proteins and nucleic acids which acquire antigen properties under the effect of VC metabolites. As a rule, the reaction of the antigens and antibodies takes place on the membranes of the small blood vessels (Ward et al.).

The detection of maximum immune shifts in subjects subjected to systematic exposure to high concentrations of VC is apparently related to the fact that the level of VC in the organism is a dosage-dependent factor, whereas the process of separating the thiol metabolites from the urine is a constant factor (Watanabe et al.) consequently the greater the concentration of VC in the organism the longer its metabolites will be found in the tissues thus stimulating the production of antibodies. Precisely because of this the most pronounced clinical picture of VCD and the grossest changes in the immunal homeostasis are observed in subjects having significant contact with VC. Watanabe et al., using chronic inhalation to innocculate white rats with VC labeled with ^{14}C, established that 72 hours after cessation of the innoccu-lation 14 to 15% of the VC introduced in the form of metabolites attached to proteins was still contained in the organism of the animals. This attests to the fact that the covalent bonds of the VC metabolites with the proteins and nucleic acids are stable and long lasting. Profound changes take place in the immune system when there is a large dosage of VC introduced into the organism. In the human being the quantity of VC metabolites attached to the tissues may turn out to be incomparably higher than the indicators obtained by Watanabe et al. in experiments on rats since the rate of its metabolism in the human being is four times lower than in the rat (Brichter).

Apparently the antibodies produced in response to proteins are responsible for the development of the clinical picture of a systemic schlerosis which occurs with VCD, whereas the antinuclear antiobodies cause a

carcinogenic effect. Antibodies attached to the nucleic acids of the nucleus block the functional centers of the cell formation and conversely they create new, pathological, functional centers. The morphological equivalent of this restructuring is the chromosomal aberrations whose quantity in subjects who have come into contact with VC definitely exceeds the given indicator in the control groups (V. Georgieva and M. Tsoneva; Heath and Dumont; Fleig and Thiess; Basler and Rohrborn). The greatest number of chromosomal aberrations is observed in subjects subjected to the effect of high concentrations of VC and, as indicated above, they are the ones who have the most pronounced immune disorders. The fact that there is an increase in the oncological morbidity only in subjects exposed to high concentrations of VC agrees well with this (V.S. Filatova et al.; Ott et al.).

Thus, both the clinical picture of a sclerodermo-like syndrome (systemic fibrosis, skin disease, Reino syndrome, acro-osteolysis) and the carcinogenic effect of VC are manifestations of one and the same thing, the immunopathological effect of a given substance. Proof of this assumption is provided in the fact of the occurrence of the experimental hemangiosarcoma only after the development of the clinical picture of a systemic toxic-immunal disorder of the vessels (Winell et al.; Maricq et al.). Subsequent proof of the pathoimmunogenesis of the tumors in VCD is supplied by analyzing the clinical picture for other immune diseases, large amounts of collagenoses (N.G. Guseva) for which it is characteristic to detect antinuclear antibodies frequently (S.I. Dovzhansky) and more frequently the development of tumors in comparison to the control groups (N.G. Guseva; Tuffanelli and Winkelmann; Kreysel et al.). The process of the reaction of the antibodies with the antigens of the tissues takes place basically in the cells of the connective tissue, in particular, membranes of the vessels. This explains why, when there is VCD, it is

primarily the connective tissue which suffers and sarcomas occur rather frequently.

The immunobiochemical schematic diagram of carcinogenesis under the effect of VC, proposed in the said survey is characteristic not only of chlorinated, saturated hydrocarbons but of many other mutagenic substances. Just like VC, all of them exert an alkylating effect (Koeman). The result of this effect is the formation of substances with antigen properties.

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