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THE CONNECTION OF PHYSICAL AND CHEMICAL FEATURES OF ASBESTOS WITH THEIR PATHOGENIC EFFECT

by

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П п	*П п*	P, p	Я я	*Я я*	Ya, ya

* ye initially, after vowels, and after ъ, ь; e elsewhere. When written as ё in Russian, transliterate as yё or ё. The use of diacritical marks is preferred, but such marks may be omitted when expediency dictates.

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THE CONNECTION OF PHYSICAL AND CHEMICAL FEATURES OF ASBESTOS WITH THEIR PATHOGENIC EFFECT

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One of the important contemporary investigators on the problem of asbestosis, Gilson, the Chairman of the Committee on Asbestos and Cancer of the International Union on the fight against cancer, has calculated (1965) that for the last 60 years the comsumption of asbestos increased 1000 times, while the consumption of oil - this is a universally recognized condition of progress - increased only 50 times. Asbestos has extensive application in an ever increasing number of branches of production.

At the same time, along with quartz it is hardly possible to find a mineral dust capable of so serious a pathogenic effect on the organism of workers. In recent years there appeared a basis for considering asbestos dust considerably more harmful in view of its established connection with cancer of the lungs and other organs.

The nature of the aggressive biological effect of asbestos cannot be considered established with finality in spite of the large number of works carried out both here and abroad.

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This considerable gap in the theory impedes the solution of such major practical problems as the standardization of asbestos-bearing dust, the individual preventive medicine and therapy of asbestosis.

For many years the special fibrous structure of asbestos was examined as the basic reason for its pathogenic effect. Gardner, Cummings (1931), Mottura (1939), King et al (1946), Behrens (1949), Vorwald et al (1951) and many others consider that only rigid, relatively long asbestos fibers, introduced in the tissue of the lung, cause its traumatization and, as a consequence, sclerosis.

Seemingly testifing in favor of such hypotheses are such facts as the more considerable fibrous changes during the introduction of long filaments (15-20 μ) and the insignificant changes during the introduction of particles of respirable fractions (< 7 μ) (Vorwald, 1951, Szimczikiewicz, Wicek, 1962, Klosterkötter, 1968).

Another argument is the development of fibrosis predominantly around the place of the implantation of filaments, peribronchialarly, which is explained by the mechanical trauma of tissue during respiratory movements. Also given are such facts as the absence of fibrosis in lymph nodes and the development of fibrosis under the effect of brucite, a fibrous mineral of nonsilicate nature ($MgO \cdot H_2O$).

At the same time the particles of serpentine, the rock which carries asbestos, according to Vorwald et al, are not capable of causing fibrosis. The situation comes down to the fact that the industrial dust taken at Canadian factories "gave rise to," according to the head physician of Canadian enterprises Cartier (1949, 1955), a large number of patients sick with asbestosis

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and, not indifferent for the inhabitants of the surrounding area, the dust turned out to be in Vorwald's experiment barely fibrogenous. Uncritically going along with the indicated authors, some of our investigators asserted without proof that unlike quartz, asbestos acts mainly because of its own acicular structure and traumatization of tissue.

Another group of researchers, Beger (1935), M. M. Vilenskiy (1940), M. A. Kovnatskiy (1957), proceeded from the fact that asbestos, as any other silicate, is slowly dissolved upon contact with tissue juices, and resorbed silicic acid causes damage to pulmonary tissue with its subsequent substitution with the connective tissue. In favor of such a hypothesis such facts were advanced as the increased content of SiO_2 in the blood of the asbestosis patients (Emdina, V. A., 1940, Pleshchitser, A. Ya., 1948), the appearance of extrapulmonary pathological changes and finally the development of pneumoconiosis among those working with non-fibrous silicates: nepheline, olivine and others.

Our first doubts of the legitimacy of these hypothesis were conceived when upon routine examination those working on recovery of asbestos ores, cases of asbestosis were revealed, although, in the composition of the suspended dust, the major portion is made up of particles of serpentine (average percentage of asbestos equalling 4-5). However it was not possible to exclude the fact that even a small admixture of the long filaments of asbestos could play a decisive role in the genesis of asbestosis.

An appropriate experiment was set up. On intratracheal introduction of pure asbestos and serpentine it was established that, disregarding its granulated structure, serpentine indisputably exerts a fibrogenous effect. During the inhalation of air with mean concentration on the order of 115 mg/m^3, for animals that inhaled the dust of serpentine there developed an interstitial fibrosis, as in "asbestos" animals, although in the first months

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for the latter it was more expressed. Here it is necessary to emphasize that we are consciously working with highly dispersed asbestos (see Table 1).

Table 1. Average* dispersed composition of the dust of asbestos and serpentine.

Form of dust	0-2 microns	2-4 microns	4-6 microns	6-10 microns	10 microns
Asbestos	79.1	15.4	2.6	1.7	1.5
Serpentine	78.9	12.4	3.3	2.1	3.3

* Average from 10 determinations.

After 3 months the average content of hydroxyproline in the lungs of serpentine" animals turned out to be equal to 4400 µg, in "asbestos" - 7907.1; in control - 2750. However, in 9 months it was even higher than in "asbestos" (8408 and 6616 µg respectively).

One of the indisputably interesting features of chrysotile asbestos is its relatively low degree of retention in the lungs. According to Guyton (1947), the rat inhales on the average 75 cm^3 of air per minute. In three months, for a mean concentration of dust in chamber air equaling 115 mg/m^3, one rat inhales 234 mg, and in 9 months, 702 mg of dust. Meanwhile, the dust of chrysotile-asbestos after 3 months of inhalation was in killed rats 3.4 mg, and after 9 months, 3.9 mg. For comparison let us say that the dust of serpentine identical in composition, other conditions being equal, was retained in much larger quantities: respectively 20.5 and 5.2 mg. In experiments on guinea pigs after 9 months of exposure the chrysotile-asbestos content in the lungs turned out to be equal to 9.9, while serpentine was almost 4 times greater - 36.7 mg. Thus, the retention of dust of chrysotile-asbestos is insignificant, which apparently is connected with better elimination of it. Wagner and Skidmore (1965) after 225 hours of exposure

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at a concentration of 69 mg/m^3 revealed on the average in the lungs of rats 0.98 mg of chrysotile-asbestos (at the same time, fiberglass - 8 mg) and established a three times more rapid elimination of chrysotile after the stopping of the dust.

Consequently, chrysotile-asbestos is eliminated well, but the remaining comparatively small quantity, by virtue of the high fibrogeneous nature of the dust, is sufficient for the development for fibrosis. The major portion of the dust is driven out through the bronchi. The part which fell in the interstice at the level of the alveolar bronchioles is removed by the lymph flow. However, the lymphatic drainage of alveoli is not able to remove the dust deposited in emplysematous vesicles formed in connection with the obliteration and obstruction of the alveolar passages.

Thus the prolonged accumulation of this dust is apparently the reason for the developing process of fibrosis.

So we have established that both fine-fibered asbestos and granulated serpentine are capable of causing active fibrosis. Subsequently, this capability of short-fibered asbestos was confirmed by Wagner (1958), Yoshikava (1960), Holt, et al., (1964), Donna, Cappa (1967).

The fact that the decisive role is not played by the fibrous structure and hardness of asbestos is borne out by the fact that fiberglass (hardness according to Mohs scale 5-7) does not possess any expressed fibrogenous action, in spite of its more than 8 times more gradual elimination from the lungs (Shepers, 1955, Matytskaya, 1954, Szmay, 1959, Sadkovskaya, 1959, Pushkin, 1962). Davis (1963, 1967) showed that only the few filaments are introduced inside the cells of the alveolar epithelium, a fact which also does not confirm the mechanical hypothesis of the action of asbestos.

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Having developed our experimental research, we even could not confirm the hypothesis about the chemical-toxic action of asbestos. During the analysis of the materials given by its supporters it is almost never possible to reveal the correlation between the manifestation of asbestos fibrosis and the SiO_2 content in individual persons.

Extrapulmonary changes in other organs being ascribed to the action of resorbed SiO_2 are completely explained by the migration of the asbestos fibers detected, in particular, in parenchymatous organs.

On intraperitoneal introduction of different types of asbestos (1968) we found its filaments not only in the liver and kidneys, but also in the lungs. Roe and Harington (1967) upon introduction subcutaneously of three forms of asbestos into mice found filaments and inflammatory changes, and also swelling in the pericardium, pleural cavity, myocardium and mesenter. The filaments can penetrate even through the wall of the bowels and reach the pleura (Westlake et al., 1965).

We compared further the solubility of the different forms of asbestos and asbestos-bearing dust, and also serpentine and brucite. Thus, after 15 days of contact of the dust of chrysotile-asbestos with 0.1% of Ringer's solution, the concentration of SiO_2 in solution comprised at most 3.8 mg%, and of anthophyllite - 4.8 mg/m^3 (see appendix). This agrees with the results of Clark and Holt (1961), who established the low solubility of chrysotile-asbestos. The corresponding index for asbestos-cement dust turned out to be equal to 7.8 mg%, for tremolite - 7.2 mg%.

As our experiments showed, and also the data of the [illegible] examination of workers over several years (1959, 1967) the most fibrogenous turned out to be the dust which is least soluble

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with respect to SiO_2: chrysotile- and anthophyllite-asbestos. True, chrysotile-asbestos shows relatively high solubility from magnesium, whose content in mineral is approximately 40%. The concentration of magnesium in Ringer's solution in 12 days contact with chrysotile-asbestos (12 mg%) was less than after contact with magnesium carbonate (22 mg%) and sovelite[1] (20 mg%). It seemed that detecting less than magnesium carbonate or sovelite, solubility with respect to magnesium, chrysotile-asbestos possesses the greatest tendency to fibrosis. For example the hydroxyproline content in lungs of animals in which sovelite was introduced, turned out to be equal to 2200 µg, and after the introduction of chrysotile-asbestos - 4200 µg. Magnesium carbonate turned out to be virtually not fibrogenous.

At the same time the dust of brucite ($MgO \cdot H_2O$) possesses both high solubility with respect to magnesium and a high tendency to fibrosis.

Thus, neither a mechanical nor chemical hypothesis can explain the emergence of fibrosis with asbestosis.

We focused attention on the mineralogical and crystal features of asbestos, and also the properties of their surface.

Chrysotile-asbestos is a fibrous variety of chrysotile, one of the forms of serpentine.

Serpentine ores consists almost completely of serpentine mineral. According to A. T. Betekhtin (1950) the crystals of asbestos consists of a layer of silicon-oxygen tetrahedrons (SiO_4) and a layer formed from paired sheets of hydroxyl ions of

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[1]Material which consists of 15% asbestos and 85% calcined dolomite.

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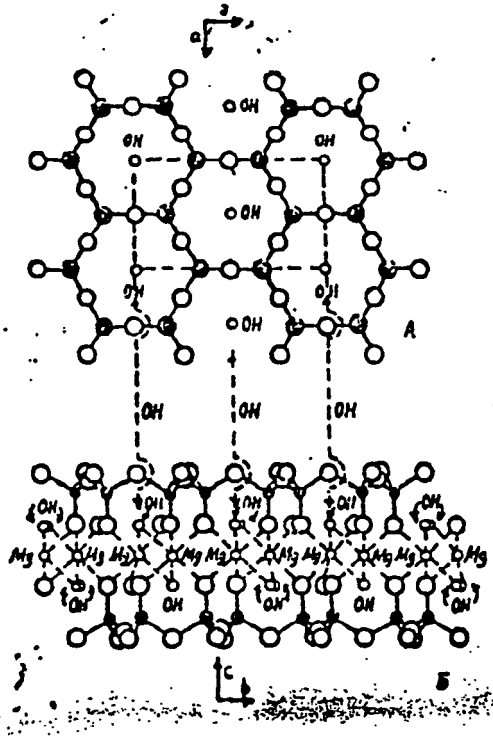
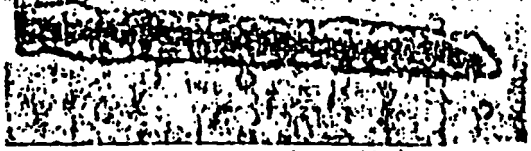


Fig. 1. The crystal structure of chrysotile-asbestos (according to A. V. Fedoseev, L. F. Grigor'yeva, T. A. Makarova, 1966).

crystal of chrysotile-asbestos (Fig. 1). The closeness between lamellar and fibrous serpentine is connected with their common geological origin. However, in chrysotile-asbestos, in connection with the difference in the dimensions of the silicon-oxygen and brucite layers there is bending of the plate which acquires therefore a tubular form and an internal capillary structure (I. M. Loshnes, 1968) (Fig. 2). They are close in crystalline structure, in particular, in the arrangement of the magnesium and hydroxyl groups and the degree of absorption of iodine (K. Frank, 1952).

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Fig. 2. Filament of chrysotile-asbestos. Distinctly visible tubular structure, magnification ×32000. According to I. M. Loshnev, 1968).



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Specially studying the surface and colloidal properties of chrysotile, Pundsack (1955) established that it behaves in this respect much like brucite.

If in fibrogenesis the crystal structure and surface conditions are important, then it was possible to assume that brucite and chrysotile-asbestos should have similar fibrogenic ability.

Our experiments showed that soft, fibrous, brucite, not containing SiO_2 mineral, is not inferior to chrysotile-asbestos in its fibrogenic nature. And this is not only for intratracheal but also for intraperitoneal introduction (see Figs. 3 and 4).

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Fig. 3

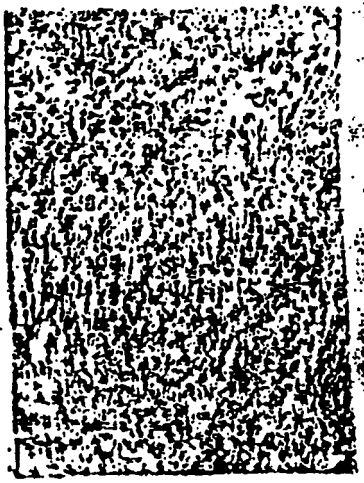


Fig. 4

Figure 3. Fibrotic changes in the lungs upon the introduction of brucite dust. Term 9 months; magnification about 5, objective 40.

Figure 4. Fibrotic changes in the mesenter node after the introduction of brucite. Term 6 months, magnification about 5, objective 40.

The value of crystalline bonds in the mechanism of the action of asbestos we have also shown in another experiment. During

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calcination (800°C) of chrysotile-asbestos it loses water of crystallization and in its crystallographic constants it approaches olivine. Our investigations showed that in this case the fibrogenic nature of chrysotile-asbestos decreases. Subsequently, this was confirmed in the experiments of Szymczykiewicz et al.(1962), erroneously examining calcined chrysotile-asbestos as amorphous, and noncalcined - as crystal. In 1966 they showed that "crystalline" chrysotile-asbestos, added to a tissue culture of the isolated lungs, absorbs considerably more oxygen than "amorphous" asbestos or fiberglass.

The significance of intracrystalline structures is indicated by the different fibrogenic nature of the individual forms of asbestos. Thus, it is widely acknowledged that the highest fibrogenicity is possessed by chrysotile-asbestos, and less by asbestos of the group of amphibole, in particular anthophyllite. Meanwhile, the basic distinction between them is in the fact that in the particles of amphibole the atoms of metal are connected with SiO_4 by double bonds, and in chrysotile-asbestos by one bond, which makes these bonds less stable. Furthermore, the weak lateral forces between the layers of the equally charged hydroxyl ions in the adjacent crystals of chrysotile-asbestos facilitate the best uncoupling of bundles into separate crystals and an increase in the total surface. Finally, the ratio of length to thickness of an elementary chrysolite filament is equal to 100:3, and for individual filaments of amphibole-asbestos is 100:20. According to Spell, Leineweber (1968) the elementary tubular crystals of chrysotile-asbestos have a thickness on the order of 150 Å, and amphibole - 1000 Å.

But what is an elementary crystal? According to the existing representation, chrysotile-asbestos is an inorganic polymer, the primary cell of which is ortho- and metasilicate of magnesium (A. B. Davydov, Z. T. Ivanov, 1961). In practice this is confirmed beyond question by the creation of synthetic inorganic fibrous

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polymers of asbestos (A. D. Fedoseev et al., 1966). Asbestos swells easily in water and alkaline solution, in consequence of which its total surface area is increased.

As has been shown earlier, chrysotile-asbestos possesses a tubular structure, which determines the high specific surface area and a number of colloidal properties, among which we attribute special importance to adsorptive properties.

Having compared the capability for adsorption of chrysotile-asbestos, serpentine, calcined chrysotile-asbestos, anthophyllite, tremolite, actinolite and magnesia-arfvedsonite, we established that the greatest capability for adsorption of ionic-molecular substances, and also albumin of the blood serum is possessed by chrysotile-asbestos, brucite and anthophyllite. Thus, after 3 days a charge of chrysotile-asbestos in 100 mg adsorbs 20-30 mg of albumin. The specific surface area of this dust turned out to be the greatest - 20 m^2/g. Asbestos easily adsorbs carbohydrates, amino acids etc. (Holzapfel, 1952).

According to contemporary ideas (K. Adamchik, 1952, Benson, Castle, 1958, McFee, Tye, 1964) upon fragmentation and swelling of silicates there occurs a rupture of internal ionic bonds and on the rupture surface nonsaturated ions will appear. The same nonsaturated ionic bonds can arise also as a result of hydration. The total quantity of charge is equal to the quantity of the destroyed bonds and is proportional to the total area of the particle, and also to the number silicon-oxygen tetrahedrons per unit of surface. It is possible to think that in the dust which possesses relatively larger specific surface area and a large number of fractures, a larger number of nonsaturated bonds is formed, and, as a consequence, physico-chemical and, in particular, its adsorptive activity will be higher. Obviously, there will be higher biological activity of such dust in relationship

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to the biosubstratum, in particular the adsorption and bonding of albumin on active centers (Benson, Castle, 1958).

The major value of the surface conditions and its activity can be judged from the results of several series of our experiments with asbestos-bearing dust. The asbestos content in them varied from 20 to 60%. They all, however, were distinguished by the fact that the surface area of the fiber was more or less covered by any bonding agent: polycondensed Bakelite, vulcanized rubber, hydrated cement, magnesia and calcium carbonate. Such powders are formed during the machining of asbestos-Bakelite, asbestos-rubber, asbestos-cement and sovelite articles.

All these powders revealed a very moderate fibrogenic nature in spite of the increased hardness and acicular form of some of them and the increased solubility of others.

The hydroxyproline content in animals into which the dust of sovelite was introduced (2200 µg.) is substantially less than in those receiving a mechanical mixture of 85% magnesium carbonate and calcium and 15% chrysotile-asbestos, i.e., in the same proportion as in sovelite. The introduction of asbozurite, a mechanical mixture of 15% asbestos and 85% diatomite, led to an even greater increase in the hydroxyproline content (3232 µg), this despite the fact that after 4 months the quantity of dust of the mixture of asbestos and magnesia alba in the lungs was equal to 3 mg, i.e, 1.5 times less than sovelite (4.5 mg). The indices of the fibrogenic action of these artificial mixtures confirm the hypothesis about the decisive importance of free nonsaturated ionic bonds.

Recently under our supervision there was conducted an investigation of the fibrogenic nature of faolite, a material which contains 60% anthophyllite, and as a bonding agent phenol-

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formaldehyde resin. The histological studies of lungs of experimental animals showed an extremely small fibrogenicity of faolite in comparison with anthophyllite. Nine months after the introduction of dust the average content of hydroxyproline turned out to be equal for "faolite" animals to 3284, for "anthophyllite" 5763, for the controls 2375 µg (differences with controls are statistically reliable). The average content of hydroxyproline for 1 mg of faolite dust was in this case 5 times less than for 1 mg of anthophyllite dust.

Thus, the covering of the active sections of the surface by the bonding agent sharply decreases the fibrogenic potential not only of chrysotile but also of anthophyllite-asbestos.

As is known, many silicates possess a fibrogenic ability. The especially increased fibrogenicity of chrysotile-asbestos is caused by its high specific surface area and weakness of the intracrystalline bonds which determine the formation of many topochemical centers which actively affect the biosubstratum. In turn, the indicated features of asbestos largely are caused by its tubular structure.

In accordance with this hypothesis the more expressed fibrogenicity of long filaments is determined anyway not by their larger traumatizing ability, but first of all by the relatively best retention in the lungs (Timbrell, Skidmore, 1968, Szymczyklewicz, 1968).

It was established that, although relatively long particles (> 8 mg) are 12% of the total number of particles in the lungs of those who died from asbestosis, their surface comprises more than 50% of the total surface of all particles (Landwehr, Bruckmann, 1962). Thus, better retention in the lungs and the relatively larger active specific surface area determine the higher fibrogenic ability of longer fibers.

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The next major question in the mechanism of the action of asbestos dust is its interaction with the cells of the organism. It has been established that even the long asbestos particles are absorbed by one or several macrophages (Vigliani, Pernis, 1964). In this case the authors did not reveal substantial changes in the macrophages.

According to our observations in conjunction with A. A. Gerasimenko (1966), during the introduction of chrysotile-asbestos into the peritoneum of white mice the number of morphologically changed and, probably, denatured macrophages is for certain 2 times higher than during the introduction of coal dust. There is reason to believe that the damage of macrophages can trigger a complex chain of immuniological reactions. Both our works (F. M. Kogan, A. A. Gerasimenko, G. I. Bunimovich, 1967) and observations of Z. S. Repnitskaya, 1967, N. T. Butkin and M. V. May, Medeka, 1960, Gambini, 1961, etc., testify to this. However, in this article we do not analyze the immunological aspects of the problem of the action of asbestos, but only focus our attention on the fate of macrophages.

In conjunction with A. P. Darinovskaya (1966) we succeeded in showing that under the effect of chrysotile-asbestos (and to a somewhat lesser degree serpentine) in twenty-four hours the growth of cells and their migration in the organ culture of the lungs of the human embryo is retarded.

Later, Vigliani and Pernis (1968) came to the conclusion that the dust of chrysotile-asbestos possesses hemolytic activity, damaging erythrocytes; around filaments there is observed an accumulation of young fibroblasts; Davis (1964) is inclined to examine these fibroblasts as a phase of evolution of the macrophage. In this connection we must give special attention to the fact that the same Vigliani and Pernis (1964), denying the cytotoxic action of asbestos, established that in the culture of fibroblasts which contacted with asbestos, the collagen content in albumin is 2 times higher than in controls.

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Once recently, the same authors (1968) again confirmed the nonconformity between the cytotoxic, hemolytic and fibrogenic properties of different types of asbestos. Klosterkotter (1968) also established that the decrease of lactic acid in the tissue culture which contacted with different samples of asbestos does not correspond to the fibrogenic ability of the latter. Unlike Vigliani and Pernis (1968) Schlipkotter established that the hemolytic activity of four forms of asbestos is identical. Polyvinylpyridine-N-oxide (PVN-O) retards the hemolytic activity of aphibolic asbestos; however, it does not affect the activity of fibrosis. Vigliani and Pernis (1968) showed that PVN-O and EDTA turned out to be incapable of protecting the macrophage from cytoxic action of asbestos.

On the other hand, in the experiments of Klosterkotter (1968) a certain decrease in fibrosis is achieved on subcutaneous introduction of PVN-O.

In the carefully presented work of Roe and Harington (1968) with the aid of histochemical and enzyme methods it was shown that chrysotile, as quartz, exerts a damaging action more actively than crocidolite and amosite. At the same time the macrophages do not lose their capability for transfer of asbestos particles; it is sufficient to say that even 18 months after subcutaneous introduction, they can be revealed in the pleura. Szymczykiewicz, Wozniak (1966) showed that the degree of oxygen intake (per 1 mg of dry tissue) in the culture of the isolated lungs corresponds to the degree of fibrogenicity of the dust of quartz, calcined and noncalcined chrysotile-asbestos.

Thus, in spite of the contradictions in the data of the various authors, it is possible to draw the conclusion that asbestos exerts a definite damaging action on macrophages by changing their exchange and changing the rate of increase in and nature of the development of these cells.

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Closely connected to the physicochemical features of asbestos and its action on a cell is, obviously, its malignant effect. An enormous number of publications in the last two decades leaves no doubt of the fact that among those who were subjected to the action of asbestos dust, one can observe considerably higher indices of mortality from the cancer of the lungs, mesothelioma of the pleura, or from cancer of other organs. The social significance of this question for all industrially developed countries is borne out by the fact that the International Union Against Cancer (U.I.C.C.) created the Committee "Asbestos and Cancer." The problem is found among those which interest the World Health Organization. In our work in conjunction with S. Yu. Troitskiy and M. R. Gulevskaya it was established that mortality from cancer of the lungs for 10 years among workers in asbestos-enriching factories was 3.6 times higher than among other populations (with standardization of sex and age). Among the patients with asbestosis, cancer of the lungs was the reason for death in 9%, and cancer other than that of the lungs in 31% of the cases. Even larger concern is caused by the reports from Canada (Cartier), USA (Selicoff et al, 1968; Cooper et al, 1968), YuAR (Wagner, 1960), Scotland (Maitr et al), Finland (Kiviluoto et al.), FRG (Bohlig), CSR (Navratil, 1968), etc.

In recent years many investigators were able to obtain malignant growth - cancer, mesothelic of the pleura and cancer of other organs - in experiment by means of the introduction of asbestos under the skin, intraperitoneal or intrapleural introduction (Schmall, 1968, Peacock, 1968, Roe and Harington, 1967). The dependence of carcinogenic effect on the introduced dose of asbestos and form of the latter is shown (Smith et al, 1968), J. and R. Graham showed the possibility for the development of cancer of the ovary upon intraperitoneal introduction of asbestos. The possibility for migration of filaments on through the lymphatic system and the formations of metastases in the lungs are shown.

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It is especially interesting that induction of cancer is increased with supplementary administration of stilbestrol. It is necessary to recognize that we still do not know the basic reason for the malignant action of asbestos. At the same time, based on the well-known physicochemical features of asbestos, we shall put forth a number of hypotheses which deserve, as it seems to us, a check.

Many authors ascribe the carcinogenic action to chronic stimulation of bronchial tissue by rigid fibers. However, it is known that only a small percentage of traumas is created by stimulus to malignant growth, relatively more solid powders of fiberglass or abradants do not possess such carcinogenic properties.

Scar itself can hardly be the basic reason for malignency; indeed with silicosis, where the fibrosis is more considerable, a considerable increase in the frequency of complications of cancer of the lungs is not observed. At the same time, as observed by us, the chronic pneumonia and the metaplasia of bronchial epithelium that appear under the effect of asbestos make the elimination of asbestos worse and thereby they indirectly lengthen its effect.

During the introduction of polymers, around them there occurs a formation of a connective-tissue capsule, within which young fibroblasts and a thickened layer of collagen develop (Shabad of L. N., 1967). The constant presence of metachromatic polysaccharides indicates the prolonged and constant process of forming of immature collagen. On the other hand, the proliferation of fibroblasts within the capsule leads to the appearance of increasingly less differentiated atypical cell.

In accordance with the hypothesis of Prof. L. M. Shabad, 1967, these multiplying and infiltrated (through the capsule) fibroblasts precede sarcoma. It is possible also that during the prolonged effect of asbestos, which is an inorganic polymer, there is a

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disorganization of the intermediate substance, development of atypical collagen and differentiation of fibroblasts, i.e., processes lying at the principle of the growth. Furthermore, in the cells surrounded by growing fibrous tissue, in connection with deterioration in the conditions for existence, these can be a selection and accumulation of more stable cell versions forming the initial tumoral rudiment (Warburg, 1956).

The results of electron-microscope investigations (Davis 1963, 1968) make it possible to think about the damage by filaments of mitochondrie and the endoplasmic reticulum; it is possible that intact cells change and acquire a capability for atypical multiplication.

It is possible also to think that chrysotile-asbestos, interacting with the protein of a microphage, adsorbs and joins those proteins which play a significant role in the regulation of growth. It is possible that as an answer antibodies which destroy the corresponding cells are formed. As a result cells lacking growth-regulating proteins are accumulated (G. Green). In the experiments carried out in conjunction with A. P. Dorinovskoy (1965) we focused attention on the fact that in the cultures of tissues of the pulmonary embryo which was subjected to the action of asbestos dust, the number of shared cells (78%) was reliably higher than in controls (46%). The impression was created that asbestos increases the activity of mitosis. When the phase coefficient was calculated, we established that the relationship of cells which are in the previous phases of mitosis (prophase and mitophase) to the number of cells in its later phases (anaphase and telophase) in the culture with asbestos turned out to be equal to 7.1, while in the control - 2.8. Impression is created that under the effect of asbestos the division of part of the cells is detained at the previous phase of mitosis. Should

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not one search here for the solution of the first stages of the process which was completed by the carcinogenase? If during the action of quartz dust the death of macrophages is almost universally recognized, then during the action of asbestos their damage takes place, giving rise to an initially atypical and then a malignant increase.

L. S. Salyamon assumes that the carcinogenic agents lower the ability to react to the subsequent damaging action. In connection with this atypical slow interstitial inflammation develops; against the background of such an inflammation, growths can develop.

It is not possible to exclude the fact that in connection with its adsorptive properties, on the dust the concentration of some metabolites - endogenic carcinogens - is increased. Such metabolites can be substances of the type of steroids either of derivatives of tryptophane (Boyland, 1960) or the blastomogenic metabolites contained in urine (A. Kh. Kogan, 1965).

Finally, the adsorptive properties of asbestos can condition the sorption of exogenous carcinogens.

The works of Harington et al, (1964) showed that ores and rocks of South-African deposits of asbestos contain 3.4 - benzopyrine and pitch. Chrysotile-asbestos actively sorbs carcinogens on its surface.

Moreover, the works of L. M. Shabad, L. N. Pylev, T. S. Kolesnichenko (1964) show that without a substance capable of sorbing and holding in the organism for a prolonged period the carcinogenic substance (e.g., benzopyrine), the latter are quickly removed and render no carcinogenic action.

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Appendix 1. Physicochemical and fibrogenic properties of asbestos and asbestos-bearing dust.

№	Name of dust	Specific gravity, in g/cm³	Specific surface area in m²/g	Content of free SiO_2 in %	Solubility on SiO_2 in Ringer (in 12-15 mg (after 12-15 days)	Solubility on SiO_2 in Ringer (after 12-15 days)	Absorption ability, methylene blue in % to control	Absorption of protein in % to control	Fibrogenic ability: With med. exam.	Fibrogenic ability: In experiment
1.	Chrysotile-asbestos	2,5	20	Practically none	3,8	12,0	75	7,5	++++	++++
2.	Anthophyllite	2,28	11,7	—	4,8	2,8	98	5,6	+++	+++
3.	Tremolite	3,12	6,45	—	7,2	1,92	62	2,8	Not studied	++
4.	Magnezia-arfvedsonsite	2,7	8,25	—	1,9	1,0	100	1,1	++	++
5.	Actinolite	2,76	5,4	—	3,5	1,52	59,7	3,2	Not studied *	++
6.	Paolite	1,68	—	6	3,23	—	—	3,7	+	+
7.	Asbozurite	2,24	2,5	40	1,0	8,0	43	2,2	++	++
8.	Vulcanite	2,45	1,6	20	9,0	6,5	74	1,6	+	+
9.	Sovelite	2,6	1,2	2,5	0,8	20,0	62	2,06	+	+
10.	Brucite	2,1	18,0	—	3,0	11,0	26,8	6,9	Not studied	++++
11.	Calcined chrysotile-asbestos	2,7	10,2	—	8,8	1,6	45,6	6,7	—	++

* — there are no working contingents in the USSR.

Naturally, our judgements are hypothetical. Moreover, we have not given up hope that in the near future in the USSR, the greatest asbestos-producing nation in the world, studies will be carried out enabling us to substantiate these hypotheses.

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