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in BIAŁYSTOK

Supplement 24

INFLUENCE OF POLYVINYL CHLORIDE (PVC)

DUST ON RAT RESPIRATORY SYSTEM

Extremely heavy dust exposure

by

J. Popow

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AUG 6 1979

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Date
20 July 1979

Dear Nick

PVC DUST

Thank you very much for your letter of July 6.

I have pleasure in enclosing our translation of the paper by Popow which you requested. I do not know whether this will be of any interest to you in the liability case which you have. As you will see when you read it, Popow's experimental conditions were utterly extreme. I think any biological system will be overwhelmed by 97 g/m^3 of PVC or any other fine dust. These conditions are a long way from our TLV of 10 mg/m^3 .

I have just got back from my annual vacation and your letter was on the top of my pile. I have not given copies of this Popow translation to Ted Torkelson, Maurie Johnson or any of my other American friends. It may be some little time before I get around to doing this. If you could run off some quick copies for them, I would be grateful.

With best wishes

Yours sincerely

J Stafford
Division Manager
Health and Environment Protection

Enc

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I. INTRODUCTION

The pathological changes occurring in the respiratory system under the influence of inspiration of air contaminated with particles of various dusts have been described for about 100 years as dust disease - pneumoconiosis. Initially pathogenic action was only ascribed to silicon dust. Therefore the investigations undertaken mainly concerned silicosis. On the basis of clinical studies (Levin [73], Sokołow et al. [109], Vigliani et al. [122]) and experimental studies (Cabański et al. [13], Gross et al. [37], Policard et al. [95]) it was found that in the lungs silicon dust causes formation of fibrous nodules, composed of thick strands of collagenous fibres, undergoing hyalinization. Sometimes there are necrotic masses at the centre of such a nodule. The discovery of the pathogenic properties of silicon dust had the result that many authors turned their attention to the problem of dust diseases. Clinical and experimental investigations made it possible to determine the action of individual types of dust. As a result of this research it was established that coal dust accumulates in the lungs, damages the pulmonary alveoli and causes formation of dust nodules with the character of giant-cell granulomas. These nodules are of a constant character with susceptibility to fibrous atrophy (Niepołomski et al. [80], Schepers [106], Worth et al. [121], Sośnierz et al. [110-112]). However, talc dust causes so-called intraparenchymatous focal pneumonia, in which collagenous fibres appear at a very late stage in the inflammatory foci and there is no formation of pneumoconiotic nodules (Rakowski [100]). In the course of asbestosis we can distinguish an early stage, called the vaso-histiocytic stage, and a late stage, called the fibroblastic-collagenic stage (Avril [3]). A characteristic feature of this coniosis is diffuse fibrosis and hyalinization without formation of nodular lesions. Sometimes so-called asbestos bodies

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can be detected among the striae of connective tissue (Hames [40]). Cotton dust causes chronic bronchitis (Fetisova [25]), whereas cement dust causes acute tracheitis and bronchitis, and then chronic atrophic inflammation of these regions. In the lungs there is development of what is known as catarrhal-intraparenchymatous inflammation, leading to atrophy of the inter-alveolar septa. Fibrosis is not very pronounced and is of a constant nature (Niepołomski et al. [81]). Berylliosis is included among the toxic dust diseases in view of the mechanism of its development, and in the early stages there is exudative pneumonia, which quite quickly changes to a productive phase. There is formation of nodules composed of histiocytes and lymphocytes. These nodules are often surrounded by striae of collagenous fibres, undergoing hyalinization. Sometimes giant cells, similar to Langhans cells, are to be found in the centre of such a nodule (Marchand [75], Rüttner et al. [104], Stofer [114]).

There is no doubt concerning the existence of ~~ma~~coniosis as a distinct nosologic unit (Kleczeński [61], Zahorski [123]). Research undertaken so far has endeavoured to establish the mechanism of its genesis (Amoudru [1], Ottowicz [93]). Many authors (Ebert et al. [24], Hames et al. [40], Heppleston [44], Policard [95]) consider that pneumoconiotic changes in the lungs only develop with participation of living cells. In the opinion of the above authors these cells absorb many particles of dust and then carry them to the connective tissue around the vessels, to the wall of the bronchi and alveoli and to the lymphatic vessels. However, there are those (Gross [36, 37]) who assert that the dust particles reach the connective tissue without the participation of living cells, as a result of the respiratory movements of the lungs. In recent years the literature has contained reports on the possibility of pathologic changes developing in the respiratory system reminiscent of coniosis, but caused by the action of plastics

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(Boitsov [10], Roussel [102]). These reports drew my attention to plastics which are now in general use and have entered many spheres of daily life (Markiewicz [76], Kastierina et al. [57], Porejko et al. [97], Schildknecht [107]). On account of their plasticity, resistance to the action of acids and alkalies, ease of shaping and relatively low production costs, plastics products have also found application in biology and medicine [Frankowski [29], Jasiński et al. [53], Kawecki [58], Kawecki et al. [59], Kuś et al. [69, 70], Nowak [83, 84, 85, 87], Oleński et al. [89], Rob et al. [101], Rzepecki [105], Staniszevska [113], Szymańska et al. [116], Grabowski et al. [35], Kędra [60], Komczyński et al. [64]).

One of the most important and first synthetic thermoplastic macromolecular compound produced on an industrial scale was polyvinyl chloride (PVC) (Franty et al. [30], Wanderberg [119]). Pure polyvinyl chloride has the form of a white, tasteless and odourless powder. In industrial production, material made from it can be given various forms, with varying elasticity and hardness. Therefore these polyvinyl chloride products have found application in the meat industry (Bohosiewicz [9]), pharmaceuticals (Chwiałkowska et al. [15]), in sport (Kopczyński [65]) and in medicine (Goetzen [34], Homrowski et al. [47, 48], Jankowska [52] and others).

The introduction of various new chemicals and various products made from them in daily use has given rise to the problem of the action of these compounds on the human body, both of the producers and of the users. This problem has been dealt with in many works in the national and foreign literature (Cristea et al. [16], Bartenov et al. [4], Hervieux [45], Kalinin [54], Kalińska [56], Koelsch [62], Lachnit [71], Lefaux [72], Markiewicz [76], Moeschlin [78], Kowalska et al. [66], Kalinowska et al. [55], Smolik [108], Troszín [117], Cołow et al. [17], Deyanova et al. [20]). The problem of the toxicity of plastics, and especially polyvinyl chloride, is

still open, despite the fact that various investigations in this direction have been undertaken (Quooss [99], Russel [103], Pennerola et al. [94]). The opinion expressed in the vast majority of published works is that polymers are physiologically inert compounds, and the harmful effects are caused by auxiliary chemicals in the polymer manufacturing process (initiators, catalysts, emulsifiers) or taking part in forming the physical properties of the polymers (stabilizers, plasticizers) (Danishevskii et al. [19], Nowak [82]). Some authors (Filatova [26, 27], Gervais [32], Witnauer et al. [120]) ascribe harmful action to vinyl chloride, the toxic properties of which are already recognized and measures to prevent poisoning have already been taken in many factories (Beusnel [7], Broitman [11], Bugajska [12], Dmitreva [21], Gabor [31], Günther [39], Krivoglaз et al. [68]). However, many authors consider that certain plastics may have pathogenic properties and as confirmation of their viewpoint they cite the harmful effects of massive inhalation of polyamide dust. This dust causes acute catarrhal pneumonia with formation of granulomas of the type around foreign bodies (Giovacchini [33]), and sometimes even changes of the nature of storage disease (Medve et al. [77]). There are also those who ascribe carcinogenic action to plastics (Fitzhugh [28], Hueper [51], Nowak [88], Nesswetha et al. [79], Oppenheimer et al. [90], Russel et al. [103], Bates et al. [5], Druckrey et al. [22, 23], Oppenheimer et al. [89]). As a result of these investigations it was found that after implantation of plates there is nearly always appearance of neoplasms [Guess et al. [38]), after implantation of a thread they only develop occasionally (Kogan et al. [63]), and neoplasms are never found after implantation of powder (Oppenheimer et al. [92]).

Although most authors are of the opinion that polyvinyl chloride is a physiologically neutral compound, in recent years the literature has

contained occasional reports on the occurrence of various bodily disorders and changes in the organs of workers employed in factories manufacturing polyvinyl chloride or products made from this material, viz: in the liver (Pushin [98]), especially in older women (Troshina [117]), in the phalangeal bones of the hands and in the skin (Harris and Adams [42]), and in the vascular and nervous system (Suciu et al. [115]). Bugajska et al. [12] have drawn attention to the possibility of toxic action of PVC. Roussel et al. [102] found posthumous atypical changes in the lungs and were unable to assign these changes to a set of known nosologic units. These authors assume that these changes should perhaps be associated with work done for many years by this worker in a PVC factory. In addition to descriptions of clinical observations, the literature also contains experimental works conducted with polyvinyl chloride. Bernt (quoted by Danishevskii [6]), for example, fed animals an oily suspension of ground PVC and showed that it does not have any toxic properties, but he also ascertained that the material is soluble in the gastric and intestinal juice. Boitsov [10], however, mentions the possibility of development of coniosis in animals after intratracheal administration of PVC resin. He found that in their lungs there is thickening of the interalveolar septa and also peribronchial and perivascular inflammation. My preliminary investigations on rats (Popow [96]) submitted to the action of polyvinyl chloride also indicated that this dust is a noxious agent for the lungs. Lymphocyte-like cells multiply under the influence of inspiration of this dust. They accumulate in the form of cuffs around the blood vessels, and there is also intumescence of the muscles and proliferation of collagenous fibres in the wall of the bronchi, and pulmonary emphysema.

II. PURPOSE OF THE WORK AND ASSUMPTIONS

As follows from this review of the literature, the problem of the effect of plastics on the living organism has not yet been solved completely. Because polyvinyl chloride is one of the most frequently used plastics, we decided to conduct investigations of the respiratory system after long-term action of polyvinyl chloride and establish the nature of the resulting pathomorphological changes. Moreover, we tried to determine whether the changes in the lungs after cessation of exposure to PVC dust recede, whether they stop developing, or whether they still occur. Another interesting problem worthy of consideration is whether the changes occurring in the lungs promote the development of complications, as occurs for example in the course of silicosis. In the literature available to me I have not come across reports on this kind of experimental investigations on animals.

III. RESEARCH TECHNIQUE

The experiments were conducted on 60 white rats of both sexes of the Wistar strain. A control group comprised 10 rats. The age of the animals at the start of the experiment ranged from 3 to 4 months. The rats weighed from 190 to 220 g. The animals remained in separate cages, in a well-lit room which was aired every day, with its temperature maintained in the range from 16° to 20°C. The animals were given mixed, nonstandard food regularly. The test animals were divided into three groups.

Group I comprised 16 animals exposed to PVC dust from 1 to 4 months. In this group I observed the picture of all pneumoconiotic lesions. Group II comprised 22 rats, exposed to the dust from 5 to 12 months. In this group I observed the picture of late pneumoconiotic lesions. Group III comprised 22 rats which, after 12 months of exposure to the dust, were kept under observation for a period of 8 months. This group was employed for

investigating the behaviour of the pathologic changes that arose under the influence of polyvinyl chloride after its action had ceased. The control group comprised 10 animals. They were kept under observation for 20 months, 2 rats being killed by decapitation every 4 months.

Exposure to polyvinyl chloride dust was effected in the following way: the rats were placed in a special chamber with dimensions 1.46 m x 0.56 m x 0.38 m and were submitted to the action of polyvinyl chloride dust every day for 1 hour. A rubber hose was led into this chamber, and the other end of the hose was in a glass vessel with capacity of 2000 ml (mixer). Every day 30 g of PVC powder was poured into the mixer once. The mixer was connected by another rubber hose to an electric blower. When the blower was switched on, the PVC powder was mixed with air. Then using the outgoing rubber hose, the PVC-air mixture was led into the chamber where the animals were. The concentration and size of the PVC dust particles were monitored with a Zeiss coniometer during exposure to the action of the dust. At the start of the experiment, on average about 9000 dust particles were found in 1 mm³. As time passed, this figure gradually fell, as follows (figures given after rounding off): 7000 dust particles after 15 minutes, 5000 dust particles after 30 minutes and about 1000 dust particles in the final phase of dust exposure. The size of the dust particles was as follows: smaller than 1 μm - 1%, less than 5 μm - 92%, from 5 μm to 10 μm - 4%, larger than 10 μm - 3%. The concentration by weight was 97 g/m³. After exposure to the dust for 1 hour the rats were put back in the cages, where they remained for the rest of the time. The control group of animals was placed in the chamber for 1 hour every day and movement of air was created with the aid of the electric blower, but PVC was not introduced. All the animals were killed by decapitation.

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From each animal lung segments were taken from the perihilar and subpleural region for microscopic investigation. The segments taken were fixed in Carnoy fluid, embedded in paraffin blocks and stained: hematoxylin and eosin, orcein according to Weigert's method for elastic fibres, according to Gomori's method for argentaffine fibres, according to Heidenhain's modification of Mallory's method (with "azan") for collagenous fibres, according to Turnbull's method for divalent iron and Perls' method for trivalent iron and with mucicarmin for the presence of mucus. In addition the following histochemical tests were effected: paS for neutral mucopolysaccharides (supplementing it with control acetylation according to Gersh and employing blocking with dimedon), tripaS for acidic protein and Hale's test for acidic mucopolysaccharides. In addition, staining with toluidine blue at pH 3.4 and 5.6 was effected for the purpose of investigating metachromasia and detection of mast cells. Polyvinyl chloride, designated by the symbol ED, was obtained from the Zakłady Chemiczne (Chemical Works) in Oświęcim. The results of the microscopic investigations relate to lung segments taken exclusively from animals that were killed at the scheduled time.

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IV. RESULTS OF INVESTIGATIONS

1. CONTROL GROUP

Macroscopic picture. The animals in this group were killed at 4-monthly intervals. On dissection, in all the rats the lungs collapsed slightly after opening the thorax, and they were pale pink and airy on the external surface and on section. During cutting they crackle in the characteristic

way. No bronchiectasia and no nodular foci were found in the lungs of these animals.

Microscopic picture. The pulmonary alveoli are fairly regular, the interalveolar septa are of identical thickness with occasional slender elastic fibres (orcein staining). Around the thin-walled capillary vessels in the interalveolar septa we observed some lymphocyte-like cells (Fig. 1). The basement membrane of the capillary vessels contains slender thread-like collagenous fibres (staining with Azan) and slender argentaffine fibres (staining by Gomori's method), but do not contain paS-positive bodies, and stain yellow in the tripaS test.

The lobar bronchi are lined with simple cylindrical epithelium, which is multirowed with occasional beaker cells, and the ciliary apparatus is retained. In the cytoplasm of the beaker cells there are occasional, extremely minute mucus granules (staining pink with mucicarmin) and also paS-positive bodies (staining reddish-violet). Neither the cytoplasm of the cylindrical cells nor of the beaker cells contains acidic mucopolysaccharides (Hale's test proves negative). In the wall of these bronchi the muscle fibres run across circuitously in bundles and are separated by collagenous fibres (staining with Azan). The elastic fibres also run circuitously, slightly undulating (staining with orcein), and argentaffine in the form of tangles (staining by Gomori's method). Furthermore, in the wall of the bronchi there are a few lymphocyte-like cells and histiocytes. In the submucous membrane we can observe occasional glandular tubes with narrow lumen, containing neither mucus nor mucopolysaccharides (staining with mucicarmin; paS, tripaS and Hale's tests prove negative).

The lumen of the segmental bronchi and bronchioles is lined with cylindric cells, but beaker cells are not found among them (Fig. 1). The cytoplasm of the cylindric cells stains yellow in the tripaS test and does

not contain any granules: neither of mucus, nor of mucopolysaccharides (staining with mucicarmin and the paS and Hale's tests prove negative). The wall of the segmental bronchi has structure similar to the lobar bronchi.

No phagocytes with granules of haemosiderin were found in the cytoplasm in the rats of the control group. Occasional mast cells appear under the pleura (having fine-granular, reddish-violet cytoplasm when stained with toluidine blue).

2. GROUP I. EARLY CHANGES (RATS Nos. 1-16, PERIOD OF EXPOSURE TO DUST - 4 MONTHS)

Among the 16 animals in this group, 2 rats (Nos. 1 and 2) died at the start of the 4th month of experiment. Pulmonary emphysema and a considerable degree of passive congestion are found in all internal organs on dissection. A further 2 rats (Nos. 3 and 4) died in the last days of the 4th month of exposure to the dust. The macroscopic picture was similar to that of the 2 previous rats. The surviving 12 rats (Nos. 5-16) were killed at 1-month intervals (3 rats at a time).

Macroscopic picture. After opening the thorax, in all the rats of this group the lungs do not collapse but fill the whole thorax, and they are fluffy and pale. During cutting, they do not crackle as characteristically as normal lungs. On the cut surface they are pale pink and dry. A small quantity of mucous mass is discharged from the large bronchi on compression.

Microscopic picture. The pulmonary alveoli are inflated like balloons, the septa between them are of reduced thickness, are disrupted in places, as a result of which there is formation of large cysts, and the residues of the septa project in the form of spines into their lumen. In the first

few months of experiment the interalveolar septa are found to have aggregates of histiocyte-like cells, the cytoplasm of which possesses minute, diffuse golden-brown granules of haemosiderin containing trivalent iron (they stain greenish-blue according to Perls' method, Fig. 2). Sometimes in the vicinity of the blood vessels in the focally thickened interalveolar septa there are aggregates of cells of this kind, profusely charged with haemosiderin (Fig. 2). Towards the end of the 4th month of exposure to dust, cells with haemosiderin granules are seldom found. However, thickening of the septa persists.

In the first few months of this period the lobar bronchi, lined with cylindrical epithelium, have an irregular lumen. On the surface of the epithelium there are scant, amorphous, pink mucous masses (which stain pink with mucicarmin), containing minute granules of mucopolysaccharides (which stain reddish-violet in the paS test). Between the cylindrical cells there are occasional beaker cells, the cytoplasm of which contains mucus (which stains pink with mucicarmin) with a few, fine granules of neutral mucopolysaccharides (staining reddish-violet in the paS test). In the final phase of this period of the investigations the lumen of the lobar bronchi becomes roundish.

In some places the cylindrical epithelium undergoes flattening, and in some places there is even complete destruction (Fig. 3). This destruction is not restricted to the epithelium, but affects deeper layers of the bronchus. Between the lymphocyte-like cells filling such a defect in the bronchial wall there are no elastic fibres, or they have undergone fragmentation and have the form of fine, very thin brown filaments in orcein staining. On the other hand the argentaaffine fibres undergo thickening or fragmentation as well (staining according to Gomori's method). The rather small number of lymphocyte-like cells in the wall of the lobar bronchi in

the initial phase increases as time passes, and by the end of the fourth month such cells are quite numerous.

In this period there is also an increase in the number of beaker cells among the cylindrical cells of the epithelium of the lobar bronchi (Fig. 4). The cytoplasm of the beaker cells contains mucus in the form of spherical pink granules when stained with mucicarmin. The composition of this mucus includes neutral mucopolysaccharides (staining reddish-violet in the paS and tripaS test). These granules are located in the basal part of the beaker cells, near the nucleus. In addition, the cylindrical cells lining the lumen of the lobar bronchi undergo mucous degeneration and exfoliate into the lumen of these bronchi, which is filled with mucous mass (Fig. 5). The mucous masses mentioned above are stained pale pink by mucicarmin, but the paS and tripaS test proves negative. In the submucous membrane there are occasional glandular tubes, which have a narrow lumen and contain neither mucus nor mucopolysaccharides (staining with mucicarmin, and the paS, tripaS and Hale's tests prove negative).

In the initial phase of the period of investigation, with staining with Azan, a small number of slender, bluish collagenous fibres are noted in the wall of the lobar bronchi. The reddish-violet striae of muscle fibres are fairly wide in comparison with the control group. By the end of the fourth month, here and there the bluish collagenous fibres in the wall of the lobar bronchi have become "scattered", and nearby there are agglomerations of lymphocyte-like cells. On the other hand the muscle fibres are tumefied. The wall of the blood vessels located near the lobar bronchi has focal thickening as a result of considerable swelling of the muscle fibres, which is revealed by intense reddish-violet coloration in staining with "Azan". However, the adventitia appears as a very thin blue stripe. In places in the wall of these vessels we can see small amorphous, violet calcic lamellae.

In the peripheral part of the lung just under the pleura, around the capillary vessels with softened and thickened wall, we can detect "cuffs" with numerous small, rounded cells with a dark nucleus and a narrow fringe of cytoplasm (Fig. 6). The endothelium that was tumefied at the start exfoliates into the lumen of the vessels in the final phase, and sometimes closes it completely.

The cytoplasm of the cells lining the lumen of the segmental bronchi and bronchioles, which for the most part is not widened, is not found to contain granules of mucus, neither after 1 nor after 4 months of dust exposure. Also no beaker cells appear between the cylindrical cells of the epithelium of these bronchi, or of the bronchioles. In this period of the investigations, under the pleura we observe a few, isolated mast cells, which have reddish-violet, fine-granular cytoplasm in staining with toluidine blue.

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3. GROUP II. LATER CHANGES (RATS Nos. 17-38, PERIOD OF EXPOSURE TO DUST - 8 MONTHS)

Among the 22 rats in this group, 2 died (Nos. 17 and 18) in 6 months of exposure to PVC dust. On dissection they were found to have pulmonary emphysema and bronchiectasia in a suppurative state, and in a further 4 rats which died in 7, 8, 9 and 10 months of exposure to the dust (Nos. 19-22) there were small, scattered foci of suppurative pneumonia. Two rats died in each of the 11th and 12th months of exposure to the dust (Nos. 23-26) as a result of bronchiectasia and pulmonary suppuration. The surviving rats were killed in two's at monthly intervals, starting from the 5th month of observation.

Macroscopic picture. In the rats after 5 and 6 months of exposure to the dust (Nos. 27 to 30), after opening the thorax the lungs do not collapse but protrude from the thorax, they are moderately fluffy but do not crackle during cutting as markedly as normal lungs. Minute slate-like specks show through the pleura. On cutting the lungs are pale pink, and dry. Bronchi with widened lumen protrude from the cut surface, and on compression the ropy contents are discharged from them. In the lungs of rats after 7, 8, 9 and 10 months of observation we found nodular foci protruding above the surface, which had a honeycomb appearance on the cut surface. These foci contain a ropy, milky-opalescent fluid. In addition to these foci there were large formations, with the features of single-cell cysts filled with mucoatheromatous mass. These large cystoid formations were surrounded by a distinct undulant reddish fringe. Sometimes the cystoid formations were so large that they occupied the entire lobe of the lung. In rats after 11 and 12 months of exposure to PVC dust the nodular foci had enlarged to such an extent that sometimes they occupied the entire lobe. On the other hand there were fewer large cystoid formations, and they were also smaller.

Microscopic picture. Marked pulmonary emphysema is noted, more pronounced than in the animals of group I. However, in places the interalveolar septa are thick, and the blood vessels in them have irregularly thickened wall and tumefied endothelium. In the wall of these vessels, after 9 months of exposure to the dust, collagenous fibres appear instead of the muscle fibres, which is indicated by blue coloration of the vessel walls as a result of the action of Azan and orange coloration when the tripaS test is carried out. Cuff-like aggregations of lymphocyte-like cells and histiocytes are observed around these vessels. Sometimes these aggregations are connected to the aggregations of such cells around the segmental bronchi, forming a single complex. The lobar bronchi have a widened lumen and are filled with

mucous masses with numerous granulocytes submerged in them. The mucous masses give a strongly positive paS reaction (intense reddish-violet staining) and are closely adjacent to the surface of the epithelium. Between the cylindrical cells lining the lumen of these bronchi there are very many beaker cells. Their cytoplasm gives a weak reaction with mucicarmin: pale pink, but the reaction of paS and tripaS is very strong: intense reddish-violet. After blocking with dimedon, there was no change in the coloration of these masses in the paS test. Furthermore, in the cytoplasm of the cylindrical cells there are minute paS-positive granules. As time passes, the collagenous fibres in the wall of the lobar bronchi become thicker and thicker (staining blue with Azan), and the elastic fibres undergo fragmentation and are visible as short, thin brown filaments (staining with orcein). In addition, in some bronchi there is metaplasia of the cylindrical epithelium to stratified pavement epithelium (Figs. 7 and 8).

In the immediate vicinity of the bronchi we can see aggregations of lymphocyte-like cells and histiocytes. Sometimes we gain the impression that the cylindrical epithelium of the lobar bronchi forms in layers or grows in the shape of a tongue deep into the wall (Fig. 9).

In 11 and 12 months of exposure to PVC dust, the epithelium of the dilated lobar bronchi is low and flattened. The collagenous fibres in the wall of these bronchi have the appearance of thick, broad, uniform blue stripes (stained with Azan). The submucous membrane is greatly widened. The glandular tubes located in it are either dilated like cysts (Fig. 10) and filled with pale-pink contents, giving a weak reaction with mucicarmin, and stronger paS reaction, or have the appearance of solid tubular foci without a lumen, composed of malleolar epithelium (Fig. 8). Sometimes the dilated, cyst-like tubes are filled with paS-positive masses located just under the metaplastic, stratified squamous epithelium, into which their outgoing duct is probably set (Fig. 7).

Between these tubes we find quite numerous scattered lymphocyte-like cells and histiocytes (Figs. 8 and 10) and quite wide bands of collagenous fibres, which stain blue with Azan. The changes described above are observed starting from 7 months of exposure to the dust. The segmental bronchi undergo dilatation after 8 months of experiment. In this period the cells of their epithelium undergo flattening, and beaker cells appear between them. The cytoplasm of these beaker cells gives very weak reaction with mucicarmin, but the paS test is strongly positive - there is intense reddish-violet coloration of the cytoplasm. paS-positive granules also appear in the cytoplasm of the cylindrical cells. In addition the epithelium of these bronchi becomes stratified (Fig. 11), and sometimes even undergoes metaplasia into stratified squamous epithelium (Fig. 12). Then in the immediate vicinity we can see aggregations of histiocyte-like cells and occasional bands of hyalinizing connective tissue.

As time passes, the collagenous fibres in the wall of the segmental bronchi become thicker and thicker and have the appearance of broad blue stripes in staining with Azan. By the end of 12 months of experiment, the collagenous fibres undergo hyalinization (Fig. 13), and the epithelium undergoes atrophy. There is also atrophy of the glands located in the sub-mucous membrane. Starting from 8 months of exposure to the dust, round some segmental bronchi we observe profuse cuff-like aggregations of lymphocyte-like cells.

Pathologic changes do not appear in the bronchioles until 9 months of experiment. They result from enlargement of histiocytic and lymphocyte-like cells towards their lumen and intussusception in the wall of the bronchiole in the form of warts. Some wart-like formations are deprived of bronchial epithelium. As time passes, around the bronchioles there is accumulation of more and more lymphocyte-like cells and histiocytes (Fig. 14), which

fill defects in the epithelium of the bronchioles (Fig. 15). The elastic fibres in the wall of the bronchioles in defective regions undergo disintegration, and when stained with orcein they are visible as slender, short, isolated brown filaments.

The microstructure of the nodular foci with honeycomb appearance, which was found in rats after 7-12 months of exposure to PVC dust, can be described as follows: they contain cystoid formations lined with cylindrical epithelium. In places we can see wart-like protuberances, composed of connective-tissue stroma (thick blue stripes when stained with Azan) covered with cylindrical epithelium, which creates the impression of focal stratification or undergoes metaplasia into stratified squamous epithelium (Figs. 16 and 17). Squamous-epithelial metaplasia of this kind also occurs in lobar and segmental bronchi. Between the cylindrical cells without cilia there are quite numerous beaker cells, the cytoplasm of which gives a strongly positive paS reaction - it has intense reddish-violet staining. paS-positive masses also fill the lumen of these cystoid formations and are stained pale pink by mucicarmin.

However, the large cystoid formations filled with "mashy" masses, in rats with the same period of exposure to dust, have a different microstructure. These are large thin-walled cavities, and the wall is composed of hyalinized connective tissue, without epithelial ependyma. In the lumen of these cavities there are amorphous, fine-granular masses, and granulocytes are only seen among them in a few places. Hale's test proved negative in all the animals. The number of mast cells, the cytoplasm of which is stained reddish-violet by toluidine blue, does not increase; only a few of them are encountered under the pleura or near the dilated bronchi. The granules in the cytoplasm of the phagocytes, located in the interalveolar septa near the blood vessels, contain neither divalent nor trivalent iron (staining according to the method of Turnbull and Perl's proves negative).

4. GROUP III. CHANGES AFTER CESSATION OF EXPOSURE TO PVC DUST

(RATS Nos. 39-60, OBSERVATION FROM 1 TO 8 MONTHS)

Of the 22 rats in this group, by the end of the first month of observation after cessation of exposure to PVC dust, 6 rats died (Nos. 39 to 44). Upon dissection, in the lungs of all the rats in addition to emphysema and bronchiectasia we detected the presence of numerous nodular or cystoid formations filled with thick, creamy, ropy contents mixed with "mashy" masses. Sometimes the entire lung was composed of thin-walled, cystoid formations. The surviving 16 rats (Nos. 45-60) were killed at monthly intervals (2 rats at a time).

Macroscopic picture. Among the surviving 16 rats, during dissection of 8 animals killed at the scheduled time we determined the presence of apneumatic, fine-lobular, hard nodular foci (Fig. 18), as in the lungs of the animals in Group II. In addition, we observed large, quite soft cystoid formations (Fig. 18), and when cut they were found to have a thin wall and were filled with "mashy" masses mixed with mucilaginous, partially creamy contents.

The changes described above were observed in rats both 1 month and 8 months after cessation of exposure to the dust. In the other 8 rats, after opening the thorax the lungs do not collapse, they are excessively fluffy, pale pink, and during cutting they do not crackle as characteristically as normal lungs. The surface of the cut is pale pink, and dry. Bronchi with widened lumen and roller-shaped wall project from the cut surface. Mucilaginous contents are discharged from them on compression. Scattered slate-like and dot-like foci show through the pleura.

Microscopic picture. Pulmonary emphysema is found in all the animals in this group, though with less intensity than in the rats of Group II. As time passes, blood vessels surrounded by a cuff of lymphocyte-like cells

are observed less and less frequently in the interalveolar septa. In the eighth month of observation after the end of the experiment, only isolated lymphocyte-like cells are to be seen around the blood vessels. The lumen of these vessels is broad, the endothelia are flattened. In the wall we can see thinner (in comparison with Group II) thread-like blue collagenous fibres (staining with Azan). The lobar bronchi have a much widened lumen and for the most part filled with coagulated albuminous, acidophilic fluid, mixed with numerous neutrophilic granulocytes. The albuminous fluid contains mucus (distinctly pink in staining with mucicarmin) and a much smaller amount of paS-positive substances in comparison with group II (in the paS test it is pale reddish-violet). These bronchi are lined by a low cylindrical epithelium with numerous beaker cells, 1 month after cessation of exposure to the dust. Minute paS-positive granules appear in the cytoplasm of the cylindrical cells. As time passes there is a gradual decrease of the number of beaker cells, and there are only isolated ones by the end of 8 months of observation. At first the cytoplasm of the beaker cells contains very little mucus (it is stained pale pink with mucicarmin), but a large amount of paS-positive substances (it is stained intense reddish-violet). However, by the end of observation there is a pronounced mucus reaction, whereas the paS reaction is weakly positive (staining pale reddish-violet). At this time the minute paS-positive granules also disappear from the cytoplasm of the cylindrical cells, and their squamous-epithelial metaplasia is rarely encountered. In two rats (Nos. 59 and 60) killed 8 months after cessation of exposure to the dust, it was found that there were numerous greenish-blue granules of acidic mucopolysaccharides (Hale's test) in the cytoplasm of the cells of the epithelium of the lobar and segmental bronchi and also in the glandular tubes of the submucous membrane of these bronchi. Similar granules were present in the epithelium of the microlobular nodular foci. Hale's test proved negative in the other animals.

The collagenous fibres in the wall of the lobar bronchi are thick, homogeneous, and stain dark blue with Azan throughout the period of observation. Staining according to Gomori's method indicates inspissation of argentaffine fibres - thick black bands. On the other hand there are few elastic fibres, in the form of thin, discontinuous brown threads (staining with orcein), or they are completely lacking in the regions of defects in the bronchial wall.

The submucous membrane is wide, in it there are numerous glandular tubes with a wide lumen, filled with contents giving a weak reaction with mucicarmin, and strongly paS-positive (staining intense reddish-violet). Between the glandular tubes there are extremely numerous lymphocyte-like cells. After 5-8 months from the time of cessation to exposure to the dust, the lumen of the glandular tubes seems to collapse. Cells of new connective tissue and numerous collagenous fibres appear between the tubes (with Azan, staining in the form of broad blue bands, which surround these tubes) (Fig. 19). In places the connective tissue grows as broad bands, and between them there are numerous lymphocyte-like cells and histiocytes, either scattered or in aggregates. Among the bands of connective tissue there are argentaffine fibres (staining black according to Gomori's method), and there are no elastic fibres (staining with orcein). Some glandular tubes are enlarged in cystoid manner and filled with pale pink, homogeneous masses, giving a weak positive reaction with mucicarmin (they stain pale pink), and negative paS reaction (they do not stain). One month after cessation of dust exposure, the rounded or oval lumen of the segmental bronchi is lined with cylindrical epithelium with quite numerous beaker cells, indicating excessive secretion of mucus. This mucus contains a large amount of neutral mucopolysaccharides (intense reddish-violet staining in the paS reaction). There are also minute paS-positive granules in the cytoplasm of the cylindrical

cells. A broad band of fibrosing connective tissue is evident in the wall of the segmental bronchi (stains blue with Azan, and black according to Gomori's method) (Fig. 20).

As time passes, in the epithelium of the segmental bronchi there is a fairly rapid decrease of the number of beaker cells containing paS-positive bodies; these cells are no longer visible 4 months after cessation of exposure to the dust. At this time the minute paS-positive granules also disappear from the cytoplasm of the cylindrical cells. Eight months after cessation of dust exposure, the broad band of connective tissue is still present in the wall of the segmental bronchi and does not display signs of hyalinization. Between the cylindrical cells of the epithelium, the cytoplasm of which is stained yellow in the tripaS test, only isolated beaker cells are visible, with their cytoplasm containing mucus (stains pink with mucicarmin), but not containing paS-positive bodies. In 1 rat (No. 53) we observed several segmental bronchi alongside one another with cystoid enlargement, which were lined with considerably flattened epithelium. Around these bronchi there was growth of fibrous connective tissue, still containing quite a number of lymphocyte-like cells and histiocytes. The lumen of these bronchi is empty. The pulmonary alveoli in the vicinity of these enlarged bronchi are apneumatic, often copiously infiltrated with granulocytes, sometimes occupying some 10-20 alveoli each. Decay is found in the centre of these infiltrates.

In all the animals we observed slight, gradual decrease of the number of lymphocyte-like cells surrounding these bronchi like a cuff. By the end of the experiment (in 12 months of exposure to the dust), numerous histiocytes and lymphocyte-like cells had accumulated round the bronchioles, to such an extent that in places they intussuscepted the wall of the bronchiole in the form of a wart. Two months after cessation of dust exposure, the above-mentioned cells are still multiplying and now intussuscept the wall

of the bronchioles in numerous places (Fig. 21). Among the lymphocyte-like cells and histiocytes there are occasional thin collagenous fibres (they stain blue with Azan and brown according to Gomori's method). After 7 months from the end of the experiment, the lumen of the bronchioles is markedly constricted and distorted as a result of intussusception of the wart-like formations described above. In their subepithelial layer the connective tissue undergoes hyalinization (stains a uniform blue with Azan), and the surface is partially covered with flattened epithelium.

In addition to the changes described above, 1 month after cessation of exposure to the dust we may find bands of partially fibrosing connective tissue around some bronchioles, with lymphocyte-like cells and histiocytes between these bands (Fig. 22), or profuse aggregations of lymphocyte-like cells filling the defect in their wall. Four months after cessation of the experiment, sometimes the bronchioles have an irregular, stellate lumen and are lined with low epithelium (Fig. 23). Into these bronchioles there is intussusception of bands of connective tissue containing collagenous fibres (staining blue with Azan) and argentaffine (staining black according to Gomori's method). Moreover, we often observe proliferation of connective-tissue fibres (staining blue with Azan) in the vicinity of the bronchioles.

By the end of 8 months from cessation of the experiment, the picture is similar, but the new connective tissue gradually transforms into fibrous tissue (uniform dark blue staining with Azan). The microstructure of the microlobular nodular foci, observed both 1 month and 8 months after cessation of exposure to PVC dust, is similar to that described in Group II, and the lumen of these cystoid formations is filled with granulocytes immersed in mucus, which is stained pink with mucicarmin. However, the microstructure of the large, soft cystoid formations and their contents are the same as described in Group II.

In the first month of observation after cessation of exposure to the dust, under the pleura there is accumulation of, in each case, a few or about a dozen large phagocytes with scattered golden-brown, minute granules in the cytoplasm. These granules do not give positive paS and tripaS reaction, do not stain with mucicarmin, and also do not contain divalent or trivalent iron (staining according to the method of Turnbull and Perls). Only toluidine blue stained them golden-yellow. The appearance of fibroblasts and occasional very thin collagenous fibres (filaments staining blue with Azan) between these phagocytes was only determined after 8 months of observation. Throughout the period of observation the mast cells behave as in Group II.

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V. INTERPRETATION OF THE RESULTS AND DISCUSSION

The results obtained in my investigations indicate that PVC dust is not a physiologically neutral compound. Long-term inhalation of it leads to the development of a variety of pathologic changes in the respiratory apparatus. At the earliest, after just one month of exposure to this dust, there is development of catarrhal inflammation of the lobar bronchi with mucoid degeneration of the cells of the epithelium and focal pulmonary emphysema. The development of focal emphysema even in the first month of exposure to PVC dust depends most probably on mechanical obstruction of the small bronchi in the form of a valve. The muscle fibres and collagenous fibres of the bronchial wall undergo tumefaction, and the lymphatic follicles undergo focal hyperplasia. In this period the segmental bronchi as well as the bronchioles do not exhibit catarrhal lesions, but the basement membrane of the capillary blood vessels in the interalveolar septa undergoes

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Among the changes observed in animals exposed to PVC dust for a further 8 months on top of the first schedule, hyperplastic and metaplastic lesions appear, in addition to intensification of the degenerative changes. They affect the epithelium of the lobar bronchi and of the segmental bronchi, and even appear in the epithelium of the bronchioles. Against a background of hyperplastic lesions of components of the bronchus, there is development of cystoid foci, with wart-like protuberances covered with cylindrical or squamous epithelium. The epithelium lining these foci exhibits mucoid degeneration. The excessive quantity of mucus accumulates in the lumen of these wart-like foci, often there is secondary infection, which leads to suppuration. The microscopic picture of these foci is similar to the picture of a cystadenoma.

In the wall of the lobar and segmental bronchi, with widened lumen, we find broad bands of connective tissue with lymphocyte-like cells between its fibres. The muscle fibres in the wall of these bronchi undergo atrophy. The resulting dilatation of the bronchi often leads to secondary infection. Then their lumen is filled with mucopurulent fluid, and the epithelium undergoes atrophy.

In the final stage of exposure to the dust, i.e. after 12 months, granulocytes and histiocytes accumulate around the bronchioles. Sometimes the granulocytes and histiocytes intussuscept the wall of the bronchioles like warts into the lumen, distorting and constricting it. There is often mucus with granulocytes in the lumen. Pulmonary emphysema, developing in the initial period of exposure to the dust, most probably depends on mechanical obstruction of the bronchi. The emphysema increases as time passes. Its development in the later stage is associated with degenerative-inflammatory lesions in the bronchi and bronchioles; large bullae form, in which an exudate accumulates, mainly composed of neutrophils. The walls

of these large bullae undergo fibrosis, and then hyalinization, and the exudate accumulated in their lumen undergoes decomposition ("mashy" masses). In addition to the hyperplastic and metaplastic lesions of the epithelium, in this period we also observe growth of the glands in the wall of the lobar bronchi. New solid glandular foci develop, containing high epithelium or typical glandular tubes. Then some of these tubes underwent cystoid dilatation. In their lumen we detected mucus containing neutral mucopolysaccharides. Between the glandular tubes there were disseminated inflammatory cells, such as lymphocytes and histiocytes.

On the basis of analysis of the microscopic images of the lungs of animals exposed to polyvinyl chloride dust from 5 to 12 months it can be stated that the pathologic changes produced in this time are more intense than after 4 months of exposure to the dust. During exposure to the dust from 5 to 12 months, bronchiectasia develops, with proliferation and metaplasia of the bronchial epithelium. These lesions are often supplemented by an inflammatory reaction, which affects not only the dilated bronchi, but also the bronchioles, and sometimes even the pulmonary alveoli. To generalize, this period can be called the hyperplastic-inflammatory stage.

The animals in Group III were kept under observation for 8 months from cessation of exposure to the PVC dust. (The animals in this group had previously been exposed to the dust for 12 months). It was found that despite cessation of exposure to the dust, the pathologic changes in the respiratory system display varied development. Some of them continue developing, but others recede. In the dilated bronchi the epithelium undergoes atrophy, but the inflammatory process already in progress around them does not recede. The thick bands of connective tissue in the bronchial wall only undergo partial hyalinization, and the catarrhal lesions in the epithelium lining their lumen remain even after 5 months of observation.

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In the lumen of some dilated bronchi there are copious granulocytes, sometimes exhibiting signs of decay. The inflammatory process often also affects the nearest pulmonary alveoli. In the wall of the dilated lobar bronchi, the lymphocyte-like cells remain in the form of a fairly wide ridge up to the end of observation. Only a few glands in the wall of the lobar bronchi undergo atrophy and then connective tissue grows focally between them. Inflammatory infiltrates mainly of histiocytes also remain in the bronchial wall and between the glandular tubes. The connective tissue around the bronchioles behaves differently. In the first months of observation this tissue grows repeatedly, leading to considerable constriction of their lumen. It is transformed to fibrous connective tissue only by the end of the 7th month of observation. However, the inflammatory infiltrates mainly of histiocytes remain between the bands of connective tissue. Moreover, bronchioles in a state of exfoliating catarrh are observed.

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After cessation of exposure to PVC dust, accumulation of a number of phagocytes with golden-brown granules in the cytoplasm was observed under the pleura. These granules contained neither divalent nor trivalent iron. Toluidine blue stained them golden-yellow. It follows that these granules are not haemosiderin in the strict meaning of this word. They can be regarded as so-called old haemosiderin, which is not synonymous with true haemosiderin. My opinion in this matter is confirmed by the result of staining with toluidine blue. By the end of 8 months of observation after cessation of exposure to the dust, fibroblasts appear between the phagocytes. The following lesions undergo regression: disappearance of the cuff-like aggregations of lymphocyte-like cells around the blood vessels in the intervalveolar septa, regression of mucoid degeneration of the bronchi, disappearance of paS-positive granules from the cytoplasm of the beaker cells and cylindrical cells of the lobar and segmental bronchi, decrease

of the number of beaker cells in the mucous membrane of these bronchi and decline of metaplasia of the pavement epithelium.

Metaplasia of the pavement epithelium deserves further consideration. In the rats of Group II this metaplasia was very pronounced. In Group III, however, either it was not very marked, or it was completely absent. It would be difficult to accept that the 16 rats in Group III would react so very differently to exposure to PVC dust, i.e. that their reaction characteristics would differ markedly from the reactivities of the rats in Group II. I assume that in these animals, which after all are derived from inbreeding, there cannot be marked differences in reactions. Then we should assume that metaplasia of the pavement epithelium also occurred in the bronchi in these 16 rats, but after cessation of exposure to PVC dust the metaplastic epithelium gradually exfoliated and normal epithelium was completely restored. The validity of this idea is supported by the fact that there is metaplasia of the pavement epithelium in 8 rats out of 16, though this metaplasia was of a low level of intensity.

As follows from 8 months of observation after cessation of exposure to PVC dust, some of the pathologic changes in the lungs recede, but some show no significant signs of receding. It can therefore be concluded that the pathomorphologic changes in the lungs, produced as a result of the action of PVC dust, persist even after its action has ceased. We must then ask what happens to the PVC dust. Is it deposited in the lungs, or is it dissolved in the body fluids? It is not easy to answer this question, for it turns out that PVC dust probably has the same refractive index as Canada balsam and therefore it cannot be detected. Moreover, PVC dust particles do not retain any pigments which are employed in the research. It could be assumed that these dust particles dissolve in the tissue fluid in the lungs. That this possibility cannot be rejected is demonstrated by the observations of Bernt [6], Cylwik [18], Lachnit [71] and others.

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The results of investigations of rat lungs after exposure to PVC dust indicate that this dust produces lesions of the nature of coniosis. Hames [40] and Harris [41] consider that the type and nature of the pathomorphologic changes developing in the lungs during coniosis depend not only on the biological activity of the dust introduced, but also on the size of the dust particles. Khukhrina [14] proposed a classification of dusts into 7 types, placing highly toxic dusts in first place. Danishevskii [19] considers that primarily macromolecular compounds (polymers) are toxic to the organism. They are precisely characterized by biological activity. The toxic action of polymers is also reported by Hopkins et al. [50]. These authors described poisoning with acrylamide, which took place with symptoms of toxic lesion of the nervous system. My investigations seem to show that particles of PVC dust, 92% of which are smaller than 5 μ m, reach the respiratory system and also have a toxic effect, though an influence also results from their mechanical action, by obstruction of the small bronchi. The toxic action of PVC is mainly indicated by dilatation of the bronchi and their suppurative inflammation. According to Ashbel [2], development of dilatation of the bronchi and their suppurative inflammation are characteristic features of toxic conioses, defined by French authors as toxic bronchopathies (Marchand [75]). The mechanism of the toxic action of macromolecular compounds was explained by Hueper [51] in the following way: after coming in contact with body fluids a macromolecule may undergo degradation (depolymerization - my comment) and then be incorporated in protein or nucleoproteins as pathologic granules. A new polymer-protein combination is formed, which may have toxic properties. On the other hand, Fitzhugh [28] associates the toxic action of polymers with free radicals, being the residues from initiators. These groups are able to combine with protein. The resultant combination is toxic and can even cause tissue to undergo neoplastic proliferation. Such toxic properties of macromolecular

compounds have been explained by Oppenheimer et al. [90]. They consider that free radicals are released and react with the cell constituents. These free radicals repeatedly lead to depolymerization of nucleic acids and so have an influence on the enzymatic processes of the cell. Hedri et al. (cited by Homrowski [43]) and Kowalski et al. [67] demonstrated that if dibutyl phthalate is used as a plasticizer in the production of PVC, the finished PVC has marked toxic properties, probably as a result of insufficient polymerization. The investigations of Nowak [86] and Bober [8] showed that dibutyl phthalate can cause inflammatory reactions. However, Smolik [108] considers that the toxic properties of macromolecular compounds are associated with monomer residues. In his opinion they cause acute and chronic disorders of the respiratory passages. On the basis of my research I cannot say with complete certainty whether the PVC molecule undergoes depolymerization and becomes associated with protein, or whether free radicals react with the constituents of the serous fluid of the bronchi, or whether the residues of monomers perhaps exert an action. It is a fact, however, that paS-positive bodies appear in the cells of the epithelium of the bronchi, in their lumen and in the bronchial glands under the influence of PVC dust, and the number of such bodies increases as time passes. After exposure to the dust has ceased, the paS-positive bodies gradually disappear. This might indicate that PVC dust irritates the bronchial epithelium, causes an increase of the number of beaker cells and promotes their secretion. This secretion does not have the typical nature of mucus (slightly positive result of staining with mucicarmin), but it contains paS-positive bodies. This is emphasized by the fact that with the passage of experiment time, this secretion becomes more and more deprived of the constituents that are characteristic of mucus (staining with mucicarmin is almost negative), but it contains more and more paS-positive bodies. After cessation

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of exposure to PVC dust, the paS-positive bodies disappear quite quickly from this secretion, and the constituents that are characteristic of mucus appear instead (staining with mucicarmin is strongly positive). It is significant that PVC administered perorally does not cause any symptoms of toxic lesion of internal organs (Homrowski et al. [46, 49]). Research by Hervieux, Tessier [45] and Truffert [118] showed that macromolecular compounds that are derivatives of vinyl possess toxic properties. Toxic action of polyvinyl chloride is indicated by investigations of the liver of rats exposed to inhalation of PVC dust, undertaken by Cylwik [18]. In addition to far-advanced degenerative lesions of the liver cells and reactive hyperplasia of the cells of the reticuloendothelial system, he noted that paS-positive bodies appear in the liver cells during the experiment, but disappear when exposure to the dust ceases. Appearance of paS-positive bodies in the bronchial epithelium and in the lymph nodes of test animals exposed to polyvinylpyrrolidone dust (a vinyl derivative) is also described by Lowsma et al. [74], who also note that these paS-positive bodies are also found in the lymph nodes of people employed in the production of this polymer. The reports of Lachnit [71] and Lefaux [72] show that nontoxic macromolecular compounds administered perorally may prove highly toxic on inhalation to the respiratory system. It seems that polyvinyl chloride can be included among the macromolecular compounds with such properties.

Comparing the morphologic pictures in coniosis caused by PVC dust with the pictures of conioses that have already been described, it must be stated that the changes produced by polyvinyl chloride dust are somewhat similar to the changes in berylliosis, though to a slight degree. This comparison is based on identical cells in the inflammatory infiltrates. However, in berylliosis there is formation of granulomatous nodules, but pronounced granulomas were not observed in PVC coniosis. In PVC coniosis