FILE NAME: German Articles - Some with English Translation (GER)

DATE: 1951

DOC#: GER010

DOCUMENT DESCRIPTION: Medical Journal Article - On Experimental Asbestosis - No German Original

On Experimental Asbestosis (1951)

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I. Introduction

Asbestosis occupies a special position among pneumoconiosis diseases. This is because it represents the to-date only thoroughly researched pneumoconiosis caused by silicates.

We differentiate between pure silicosis, mixed dust silicosis (especially silico-anthracosis) and the silicatosen (Rüttner, 55), although this last group has been the subject of little experimental research.

A detailed study of the literature on the clinical instruction and pathological anatomy of asbestosis yields a clinical picture which must be sharply differentiated from that of silicosis. The history, clinic and pathology of asbestosis have been treated thoroughly elsewhere (Behrens, 8.)

The credit for recognizing asbestosis as an occupational disease goes to Murray (48) (1906) and Fahr (18, 19) (1914). The disease first attracted more general interest following the work of Cooke (10, 11, 12), McDonald (43, 44), Oliver (52), Seiler (60, 61) and Simson (62). To briefly summarize, we are dealing with a diffuse fibrosis of the pulmonary parenchyma, increasing in strength from top to bottom, without involvement of the lymphatic system. The histological profile of asbestosis is completely different from that of silicosis. The little lumps and masses typical of silicosis are not found (except in a few cases, in which quartz was probably inhaled too). Another important

finding are the so-called asbestosis bodies (1, 32, 65) found in the lung tissue, i.e., asbestos needles, which have a drumsticklike or dumbbell-shaped, often segmented, iron-containing organogenetic protein casing.

Despite numerous studies the pathogenesis of asbestosis is not yet fully explained. There are two opposing views today. One begins with the assumption that the fibrosis is caused by a dissolving of the asbestos and the released silicic acids (Beger, 1-7). The other considers a mechanical irritation of the tissue by the asbestos threads to be the essential pathogenetic moment (Sundius and Bygden, 65; Di Biasi, 16; Gardner, 21, 22, 23, 41; Langelez, 40; Mottura, 46, 47).

A number of questions have arisen from these contradictory, but in part well-supported theories, which we attempted to address with animal experiments.

II. Approach to the Problem

In its present meaning the expression asbestos is actually a technical collective term which covers chemically and physically very different threadlike, basic magnesium silicates (chrysotile asbestos, hornblende asbestos) (15).

The question thus arises whether the deleterious effect is linked to one certain kind of asbestos or whether all varieties of asbestos are involved. The human pathology is not in a position to determine this immediately. In industry one practically never finds dusts composed exclusively of one mineral. Especially in the asbestos industry one can

count on a mixture of chysotile and hornblende asbestos dust being inhaled. In people therefore one cannot observe and study the reaction of the lung tissue to chrysotile or hornblende asbestos,

The fact that chrysotile asbestos is chemically much less stabile than hornblende asbestos took on crucial significance under these circumstances in trying to ascertain the pathogenesis of asbestosis. Under the influence of the solubility theory with silicosis[1] ([1]This theory rests primarily on the experimental results by Kettle (35), who observed a neutralization of the quartz effect when quartz dust was coated with a fine layer of lead oxide), the hypothesis was also presented that the silicic acid released from the chrysotile asbestos was the damaging agent causing the fibrosis (Beger; Koppenhoefer, 38; Mc Donald, 44).

A number of research results from different authors support the notion that chrysotile asbestos dissolves in the organism:

Sundius and Bygdén (65) isolated the dust content of an asbestosis lung, which was examined pathologically-anatomically by Di Biasi (16). Despite the fact that it was known that predominantly chrysotile asbestos was processed, the two Swedish mineralogists only found hornblende asbestos in this case. (Their results are corroborated with x-ray spectrography by Ruska [54], but have recently been questioned by Beger [7]).

Kühn (39) examined the dust from three asbestosis lungs crystal-optically, two of which have been worked on by Wedler pathologically-anatomically. He too could only identify hornblende asbestos, yet he specifically emphasizes that the workers involved had inhaled large amounts of chrysotile asbestos in their lifetimes.

Gardner (23) reports on the basis of animal experiments that chrysotile asbestos disappears in a few weeks in every extrapulmonary tissue; in cats it could even dissolve completely in the lung in a week.

Berger, who has defended the soluble theory most strongly, assumes that the casing substance of the asbestosis bodies mediates the dissolving of the silicic acid, which leads to diffuse asbestos fibrosis. In his opinion the unsaturated valencies of the crystal lattice attract protein molecules, which for their part break out SiO_2 complexes from the fibers. Berger (1) offers, among many other results, the observation that chrysotile asbestos fibers treated beforehand with H_2SO_4 developed in egg albumin a casing formation analagous to the asbestosis bodies; Koppenhoefer (38) however considers this the result of an unspecific process.

In this regard, the details given by Gloyne (32) on unsuccessful attempts to form asbestosis bodies in vitro are interesting. Gardner and Girous (20, 27) produced formations similar to asbestosis bodies by introducing asbestos fibers impregnated with ferrichloride or concentrated hemoglobin solution into a natrium silicate solution. Gardner (23) emphasizes later, however, that it has not yet been possible to produce asbestosis bodies in vitro.

All of these observations and hypotheses are contrasted by the fact that the degree of solubility of silicates, quartz and other silicic acid modifications cannot be related to the eventual appearance of a fibrosis producing effect (Geßner, Rüttner and Bühler, 25; Gardner, 21; King, 37; Giese, 26). This follows alone from the fact that fibrosis due to easily soluble chrysotile asbestos is difficult to reconcile with the particularly strong fibrosis-producing effect of surely less soluble quartz.

The numerous animal studies directed at researching the pathogenesis do not yield a unified picture; individual results even contradict each other. The results of animal experiments may also never be considered completely analagous to changes in humans. It is certain, however, that not every species reacts to asbestos with a fibrosis; the fibrosis is moreover different in the same species depending on the place the asbestos is deposited. Despite this it must be recalled that quartz produced a fibrosis in all animals tested so far. Comparative studies with different asbestos types were carried out only on guinea pigs (Gardner, 21; Miller and Sayers, 45). Interestingly the tissue reaction was always the same - inert reaction.

Table I offers an overview of the animal studies with asbestos available to me in the literature.[1a] ([1a] During printing of the present study a comprehensive report appeared by A. J. Vorwald, Th. M. Durkan and Ph. C. Pratt under the title "Experimental Studies of Asbestos," a comprehensive report on the experiments at the Saranak Lake Institute. [Arch. of Ind. Hyg. and Occupational Medicine, Vol. 3, No. 1, Jan. 1951.] The results of this research substantiated by Gardner correspond in large part with the results which could be obtained at our institute.)

New viewpoints, which speak against the solubility theory and make a mechanical genesis of the asbestos fibrosis very probable, result if the role of the "particle sizes" is examined more closely.

Independent of the question of the harmfulness of the individual asbestos varieties, it can be deduced from human pathology that the fibrosis arises where *long* asbestos fibers lie. In the bronchial lymph nodes, which according to tests by Sundius and Bygden (64) contained a

great deal of very fine asbestos dust, Di Biasi (16) could not ascertain any heavier induration. Mottura (46), who carried out a comprehensive examination of lymph nodes in two asbestosis cases, did not find any increase in connective tissue along the lines of a asbestos fibrosis either.

The results of animal experiments with asbestos of differing fiber lengths also speak strongly in favor of a mechanical effect.

Experiments at the Histopathological Institute of the University of Zurich (Rüttner, 57) showed that hornblende asbestos in a fiber length of 2 µ is phagocytized intraperitoneally in mice without any increase in connective tissue being detectable, whereas the same asbestos type in fiber lengths of up to 50 µ, under the same experimental setup, caused a strong fibrosis (Rüttner and Behrens, 58). Analogous results were obtained by King (36) with hornblende asbestos (Rhodesian asbestos) 2, 5 and 15 µ in length in rabbit lungs.

Guinea pigs, which reacted to the inhalation of long-fibered chrysotile asbestos with a strong fibrosis, are reported to have shown only phagocytolytic processes after dusting with a fraction of fiber lengths under 3µ in a concentration four times stronger (Gardner, 21, 41).

III. Our Own Experiments

Our own experiments were directed toward following the tissue reaction to chrysotile reaction in mice (introperitoneally) and in rats (intrapulmonally), if possible with consideration of different fiber lengths.

The injection of chrysotile asbestos together with blood aimed at an

investigation of the question of whether a direct role in the formation of asbestosis bodies can be attributed to hemoglobin (iron), as is maintained by Giroux on the basis of animal experiments.

Finally we attempted to produce asbestosis bodies in vitro (in blood and serum).

A. Material Used

Chrysotile asbestos of Czech origin was used, whose purity was tested by Dr. Glauser of the Mineralogical Petrographical Institute.[2] ([2] I would like to thank Prof. Geßner, Drs. Glause, Epprecht and Bühler for their help.)

[Two paragraphs follow describing the difficulties in producing asbestos fragments of varying lengths.]

The length of the asbestos fibers used for the experiment varies between 5 and 180 µ, the majority of the fibers was 20-60 µ long.

[The following sections are reported in smaller print than the rest of the article; as a result I did not translate them. If you want the fine print translated, let me know.]

B Experimental Set-Up and Results

1. Intraperitoneal Experiments with pure chrysotile asbestos on mice

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a) Macroscopic Changes . . .

b) Microscopic Changes . . .

2. Intraperitoneal Experiments with Chrysotile Asbestos and Blood in Mice

a) Macroscopic Results . . .

b) Microscopic Results . . .

3. Intrapulmonary Experiments on Rats

a) Macroscopic Results . . .

b) Microscopic Results . . .

4. In-vitro Experiments . . .

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IV Discussion of the Experimental Results

1. Intraperioneal Experiments on Mice

The first response of the peritoneal tissue to the injected chrysotile asbestos is expressed in an acute inflammatory cellular exudation, which subsides after 203 weeks. Almost simultaneously a mobilization of young histiocytes sets in. The attempt to fix the foreign bodies through phagocytosis and to make them harmless also becomes clear in the early formation of foreign body giant cells. The young masses of dust look different depending on their size: In addition to small ones, which have a uniform cell thickness, there are also bigger ones, which exhibit a deposit of asbestos in their center without cellular elements. Apparently too much asbestos was deposited in these places, so that that cellular excrescence forming around its exterior was not able to fully penetrate the dust.

Between this *non-specific early phase* and the following *phase of connective tissue encapsulation* one finds fluid transitions. The formation of delicate collagen fibers begins already after 10 days. The fibrosis develops in the same animal in the different dust masses at varying rates. After 2-3 months the connective tissue encapsulation of the dust is fully developed. Foreign body giant cells become more sparse, but never disappear completely. Large dust deposits are as a rule cell-free in the center and so can simulate necroses. A toxic effect of asbestos on the connective tissue cells or the connective tissue fibers of the fibrous edge portion, which surrounds the central cell-free dust deposit, cannot however be observed. The decline of individual phagocytes, which are pushed forward from the pallium zone of such masses, can be very easily explained by insufficient nourishment, since the center of the dust is not vascularized. After 10-12 months the *fibrous late phase* is reached. The edge portion of large dust masses is at this point rather low in cells, at spots it also shows hyaline transformation of its collagen fibers. However, one still finds even after a year's time smaller dust nodules consisting entirely of phagocytes and connective tissue cells. Between the cells lies a collagen net of fibers, in some spots delicate, in others thick, which also surrounds individual foreign body giant cells. Especially in older dust masses it is very clearly visible how borders of phagocytes divide large bunches of asbestos fibers, without degenerative changes in the cells being recognizable.

Evidence of a toxic effect of the injected chysotile asbestos dust cannot be found. The heavy fibrosis can be interpreted as a partial manifestation of an *encapsulation of a foreign body*, a reaction that the

organism also uses in response to chemically inert foreign body entities (e.g., thread granuloma). That the up to 180 µ long fibers effect a purely mechanical irritation on the surrounding tissue appears entirely possible.

It is noteworthy in the experiments under discussion that a *dissolution of the chrysotile asbestos could not be proven*. In every case, even after 360 days, it was possible to detect by sectional incineration and by polarizing-microscopic examination a lot of chrysotile asbestos in the dust masses.

There was no evidence of the transport of asbestos fibers in the lymphatic system. In the fibrous late stage we could identify small islands of lymphatic tissue deposited in the collagen-hyaline nodule capsule, this must however be a secondary manifestation. The development of fibrous dust nodules could not be detected in any of the numerous large mesentery lymph nodes that were examined, nor any toxic distant effect of the asbestos.

In closing our discussion of the intraperitoneal experiments we would like to emphasize that *no asbestosis bodies were observed*. Neither in the animals that had received serous chrysotile asbestos suspension (experiment 1) nor in the animals that were injected with chrysotile and blood (experiment 2) could we find asbestosis bodies or asbestosis-like formations. Small granular and diffuse iron precipitates in phagocytes were seen especially peripherally around the dust masses in animals with serous asbestos suspension after 5-6 months. In the mice that had been additionally injected with blood, these iron precipitates appeared after only one month. They could however in no way be compared with asbestosis bodies.

Beger's hypothesis, which asserts that the asbestosis bodies forms the essential prerequisite for asbestos fibrosis as a solvent for silicic acid, cannot be reconciled with our own experimental results. In the intraperitoneal mouse experiment a fibrosis without asbestosis bodies developed within several months up to one year. Gardner (23), on the other hand, found asbestosis bodies in mice lungs after 24 months of constant dusting, without observing any fibrosis.

In evaluating the role of asbestosis bodies for the pathogenesis one must also take into account that there are more and more reports of similar bodies which are based on fibriform minerals other than asbestos (so-called pseduo-asbestos bodies). The core of such formations consists of hornblende, rutile (Sundius and Bygdén, 65); biotite, fusain (Cooke, 13, 14); graphite (Gloyne, 34); kieselgur (or diatomite) (Nordmann, 50; Luton et al., 42); carborundum (Glauser and Rüttner, 28).

2. Intrapulmonary Experiments on Rats

We were able to confirm the finding of Gardner (23), Gloyne (32) and Stewart (cited in 17) that a fibrosis without asbestosis bodies develops in rat lungs. In the peripheral sections of the dust mass intracellular iron precipitates appeared as in the mouse, but asbestosis bodies could not be found. The asbestos-fiber bunches, which were deposited primarily in connective tissue around small bronchia and bronchioli, were surrounded by phagocytes. Foreign body giant cells were sparse. Degenerative changes in the cells were not found. Over the course of months a heavy fibrosis developed around and in the dust massed, in part with hyaline transmutation of the connective tissue fibers. Rather sharply delimited

dust massed developed; a diffuse lung fibrosis could not be observed after more than 330 days. In the bronchial lymph nodes there were no asbestos fibers and no fibrosis detectable.

3. In-vitro Experiments

The fact that we were not able to produce asbestosis bodies in human blood or serum supports the thesis of Simson and Sutherland-Strachen (63), which posits that asbestosis bodies arise through the depositing of an iron-containing substance produced by phagocytes onto the asbestos fibers.

If asbestosis bodies arose simply through occlusion of a material (protein [Beger, 1]; hemoglobin, [Giroux, 27]) on the surface of the asbestos needle, then there would be no reason why this process could not take place in human blood or serum.

It follows from the tabular compilation of the animal experiments [these tables appear on pp. 280-83 of the article; if you want them translated, let me know] that asbestosis bodies can arise in the lung, in isolated cases in the musculature and connective tissue. Further experiments will perhaps show that their development may be interpreted as the product of the reaction of certain tissue to long-fibered foreign bodies.

Summary

Chrysotile asbestos (fiber length 5-180 μ) causes a focal fibrosis intraperitoneally (mice) and intrapulmonally (rats), which represents the end result of a non-specific foreign body reaction.

A dissolution or toxic effect of the chrysotile asbestos was not observed, nor was the formation of asbestosis bodies. Asbestosis bodies could not be produced in vitro. The asbestosis bodies are considered to be the product of a non-specific reaction of certain tissue to long-fibered foreign bodies. They appear to be of no significance for the genesis of asbestos fibrosis.