INHALATION STUDIES OF COAL-QUARTZ DUST MIXTURE

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To investigate etiological and pathogenic problems, as well as to examine prophylactic and therapeutic possibilities in the field of experimental silicosis research, the following three methods are generally applied: inhalation, injection, and cytologic tests.[7, 10, 15, 21-23] There is no doubt that the inhalation test corresponds best to actual conditions.

First of all, some fundamental remarks concerning inhalation tests are in order. Inhalation tests run for several hours or a few days if short-term deposition or elimination studies are to be performed.[3] To examine the results, dust is recovered from the lungs and pulmonary lymph nodes, and the number of washable macrophages, their phagocytosis rate, and phagocytosis index are determined. In these short inhalation tests, the quality of the test arrangement is essential, whereas the problems connected with animal maintenance scarcely affect the experiment and its results.

If, however, it is of principal experimental interest to investigate the importance of dusts for reasons of industrial hygiene or to study prophylactically or therapeutically efficacious substances, the long-term inhalation test satisfies the required test conditions best. This test concerns, above all, deposition, elimination, and retention of dusts as well as development of functional and pathological changes.[20, 25] Long-term inhalation tests generally run for at least 12 months and may extend over several years. Test results are interpreted by means of functional and histopathological examinations, body weight and organ weight, spontaneous death rate, and performance of dust recovery. Certain results can be obtained only from long-term inhalation tests. Thus, problems of animal maintenance are paramount. At the same time, the close connection between animal maintenance and experimental arrangement becomes particularly clear. Animal material and animal maintenance have to be of such a kind that, particularly at the end of the experiment, qualitatively acceptable pulmonary material is available for further investigations.[24, 28] These lungs should, hopefully, not show any pathogenic changes that complicate the exact interpretation or make it impossible. In the case of "conventional" inhalation tests, these changes have often occurred.

Lymphoid peribronchial infiltrations, illustrated in FIGURE 1, have already formed in the lungs of experimental animals during early test stages. Because of these infiltrations, wet and dry weights of organs are distorted and lung functions affected. Elimination troubles may also occur.[5] In later experimental stages, the lungs of about 80% of the animals may show bronchiectasis. Connected with this condition, the spontaneous death rate presents a specific problem because it may rise up to 5% per month. It may thus happen that at the end of the experiment—the end of the lifetime in the case of rats—the number of animals available will be insufficient. Besides the use of a suitable dust exposure unit,[27] it is of fundamental importance, if optimum test results in a long-term experiment are to be obtained, to use SPF animals maintained in isolated and air conditioned units.[28] From the following figures, it can be seen that the quality of lung tissue has been considerably improved by observing these restrictions.

In FIGURE 2, the lung of a rat maintained under conventional conditions is shown. A cellular infiltration of the peribronchial tissue and of the alveolar walls can be seen. In FIGURE 3, in contrast, a "clean" lung is shown. It is the lung of a specific-pathogen-free rat maintained under clean conditions. Besides the complete lack of bronchiectasis and peribronchial cell linings, the lack of cellular infiltrations of the alveolar septa is particularly worth noting. Without any doubt, dust-exposed lung changes are easier to interpret in such pulmonary tissue, particularly in cases in which the dusts were only slightly silicogenic.

FIGURE 1. Lymphoid infiltration of the peribronchial tissue in the rat. ×6.5. Hematoxylin and eosin.

The inhalation tests to be discussed here have been carried out observing the aforementioned conditions. Male rats and female rhesus monkeys have been used as experimental animals. For five hours daily on five weekdays, the animals inhaled a coal-quartz mixture consisting of 60% of finely ground hard coal and 40% of Dörentrup quartz in the initial mixture. The fine dust concentration was about 45 mg/m^3. The quartz portion in the fine dust was 30–35%. The dust exposure of rats lasted up to 18 months. In the experiments with monkeys, results are reported after a dust exposure of 36 months. After sacrificing the animals, the following examinations were made: determination of body weight and organ weight; determination of the coal, quartz, and ash contents in the lungs and pulmonary lymph nodes; measurement of diverse

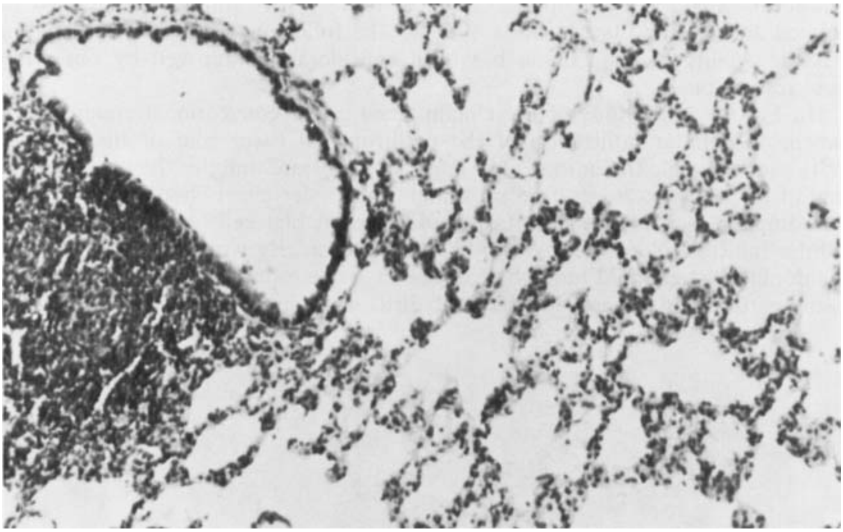

FIGURE 2. Lung of a normal animal maintained under normal conditions. 17-month-old rat. ×6.5. Hematoxylin and eosin.

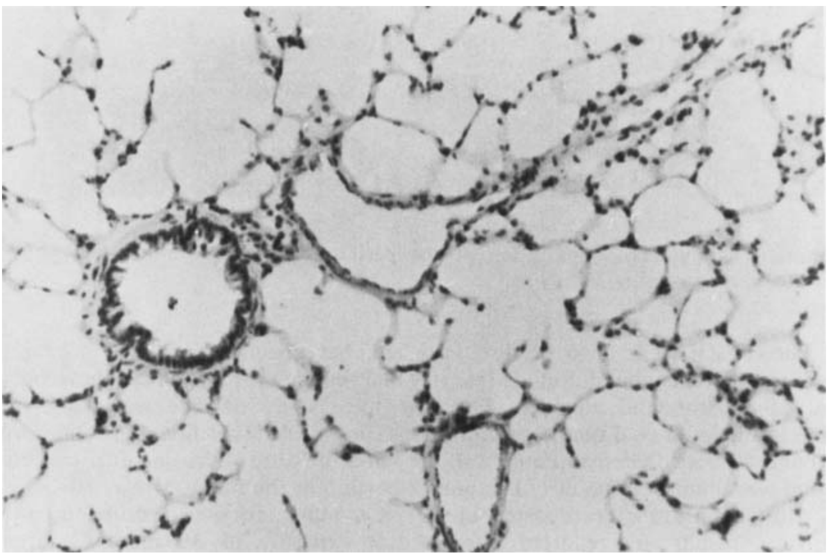

FIGURE 3. Lung section of a specific-pathogen-free animal maintained under clean conditions. 15-month-old rat. ×6.5. Hematoxylin and eosin.

parameters of respiration and circulation; as well as histological examination of lungs and pulmonary lymph nodes.

RESULTS

First, some general observations: (1) Animal weight increases uniformly during the experimental period; there are no appreciable differences in weight between dust-exposed and control groups. (2) Spontaneous death rate increases in both the groups with increasing length of the experiment. Up to the end of the dust exposure time, the average spontaneous death rate is 0.79% per month, that is, about 50% higher in the dust-exposed rats than in the controls. In rhesus monkeys, such differences of spontaneous death-rate have not been observed.

TABLE 1

DEVIATION OF THE DIFFERENT MEASURE VALUES OF RESPIRATORY AND CIRCULATORY FUNCTIONS OF DUST-EXPOSED GROUPS COMPARED WITH CONTROLS

Measured Value * After 18 Months of Dust Exposure	Deviation in % fromValues of the Control Group †
Lung volume	+12
Rate of breathing	+10
Tidal volume	+ 1
Minute volume	+18
Intrapleural pressure (Δp)	+ 6
Compliance	−15
Diffusing capacity (CO)	−14
O_2—Consumption	+ 1
Right ventricular pressure	+ 3

* Average values of 20 rats.
† Values of the control group = 100%.

Lung Function

Results of the respiratory and circulatory functions correspond essentially to the values listed in TABLE 1 for all three examinations after an experimental time of 18 months. It can be concluded from them that differences exist for the various parameters measured between the dust-exposed group and the control, constituting impairment of respiratory and circulatory functions in the dust-exposed rats. The deviations are, in part, oriented, i.e., they are present in the same direction for all experimentation time. Except for the values for compliance, these differences are not significant however. The compliance values are about 15% lower in dust-exposed animals after an experimental time of 18 months and about 23% lower after an experimental time of 22 months than the values found for control groups. Examinations of rhesus monkeys gave similar results; all values, except those of static lung compliance, are in the normal range.

Dust Retention

The following Figures show the results of dust recovery. Sacrifice of the animals was made each time three days after the final dust exposure in order to avoid a distortion of results because of dust elimination by bronchial clearance. In FIGURE 4, results of examination of rats are represented.

It can be seen that the total dust content of the lungs increases linearly with increasing dust exposure time. The percentage of quartz does not, however, increase with increasing experimental time, i.e., no quartz enrichment takes place in the lungs. For the total dust, elimination four months after the end of exposure is only 9%. The quartz content is, however, particularly engaged in this elimination; it decreases about 15% in this time, 55% of this amount being transported into the lymph nodes. Total dust retention after an exposure time of 18 months is 5.5% of inhaled dust, based on an alveolar ventilation of 6 liters per hour for rats. Results of dust recovery from pulmonary lymph nodes show that the percentage fraction of coal and quartz during exposure time corresponds to the values obtained from the lungs. Only after the end of exposure does a strong quartz deposition take place within the lymph nodes. With increasing experimental time, the percentage fraction of dust deposited in the pulmonary lymph nodes increases from 8 to 15%.

Similar results are found with dusts recovered from monkeys' lungs. In FIGURE 5, the specific dust content per 1 g fresh weight and per 100 mg dry weight is graphed with reference to experimental time. The linear rise of dust retention is also visible here. The coal-quartz ratio of dusts recovered from the lungs corresponds closely to the coal-quartz ratio present in fine dust. Thus, in monkeys as well as in rats, no quartz enrichment is found in the lung tissue.

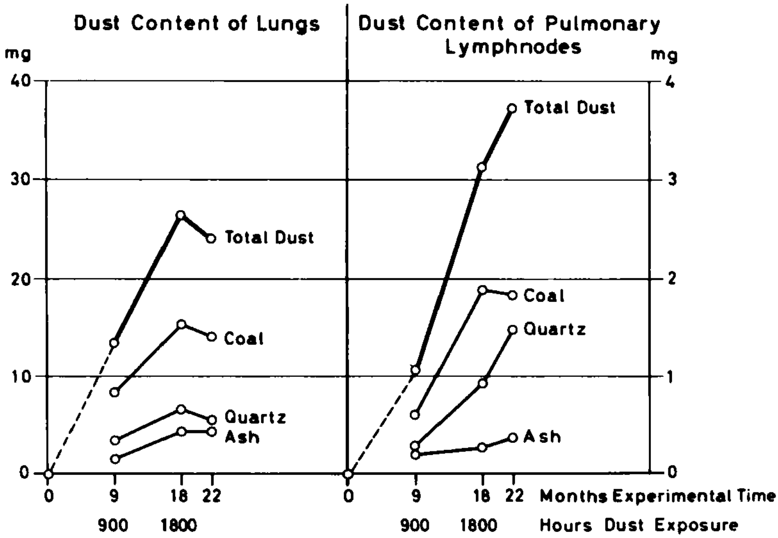

FIGURE 4. Results of dust recovery from lungs and pulmonary lymph nodes of rats related to experimental time. Average values of 20 lungs and pulmonary lymph nodes per examination date. The ash content consists of clay minerals, particularly Illite.

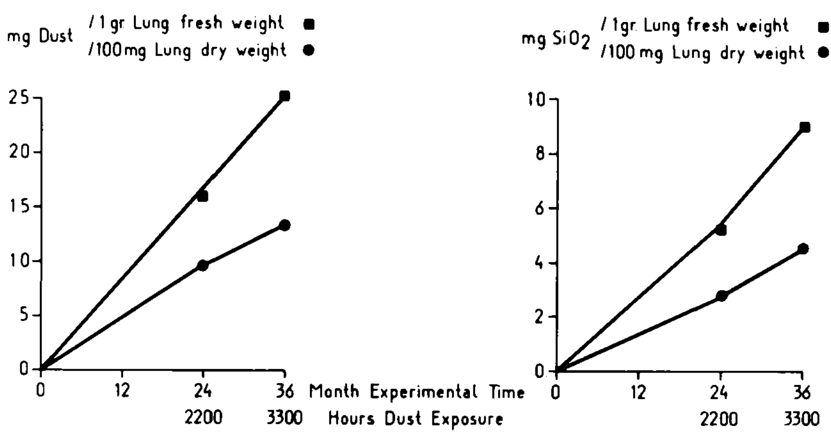

FIGURE 5. Results of dust recovery from lungs of rhesus monkeys related to experimental time. Dust content per 1 g lung fresh weight and 100 mg lung dry weight.

Pathology

Determination of organ weight is a relatively good measure for quantitative interpretation of dust-caused changes found in the lungs and the pulmonary lymph nodes. In the following Figure, (FIGURE 6) the increasing dry weight of the lungs and the pulmonary lymph nodes is shown to depend on the length of the experiment. Values of the dust-exposed groups clearly differ from those of the controls with increasing experimental time.

Histological examinations of the lungs of rats show that round granulomas have formed in them after an experimental time of 22 months. These granulomas are relatively uniformly distributed over the entire lung. The granulomas are often situated perivascularly. Around a portion of them, a defined perifocal emphysema has formed. The granulomas are well organized, i.e., cells and dust particles are uniformly distributed within the granuloma (FIGURE 7). Pursuing the development of the granulomas, it can be seen that most of them have formed from intra-alveolar depots. In the next Figure (FIGURE 8), the moderately dense network of reticular fibers and collagenous fibers can be seen after silver impregnation. According to King's classification, the fibrosis grade is to be interpreted as II. Changes in the pulmonary lymph nodes are similar to those in the lungs. The content of collagenous fibers is, however, slightly larger (FIGURE 9). As observations in polarized light have shown, no disintegration of coal and quartz particles takes place, either in lung tissue or in the tissue of pulmonary lymph nodes.

The histological pattern of monkey lungs looks slightly different. Examinations show that interstitial deposition is dominant and intra-alveolar deposition less. The following Figure (FIGURE 10) gives an insight into the pathologic changes after an exposure of 36 months. The perivascular and peribronchial forms of deposition are particularly striking. For the greater part, the depositions are well organized, i.e., there is a solid base of cells and fibers. The fiber network is composed of reticular and collagenous fibers. The fibrosis grade is to be classified as II–III, according to King's classification. No disintegration processes between coal and quartz are to be observed. Within the pulmonary

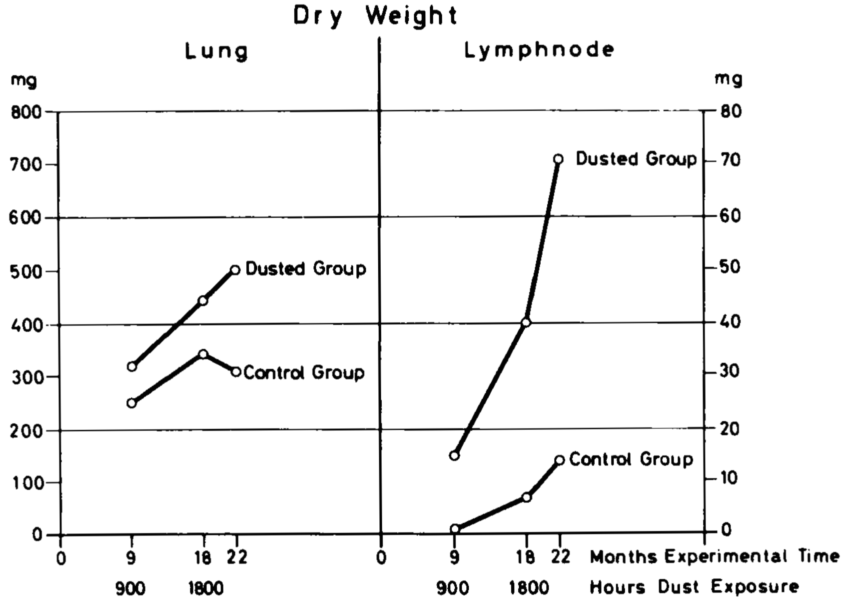

FIGURE 6. Dry weights of lungs and pulmonary lymph nodes of rats of the dust-exposed group and of control in relation to experimental time. Average value of 20 animals per examination date and test group.

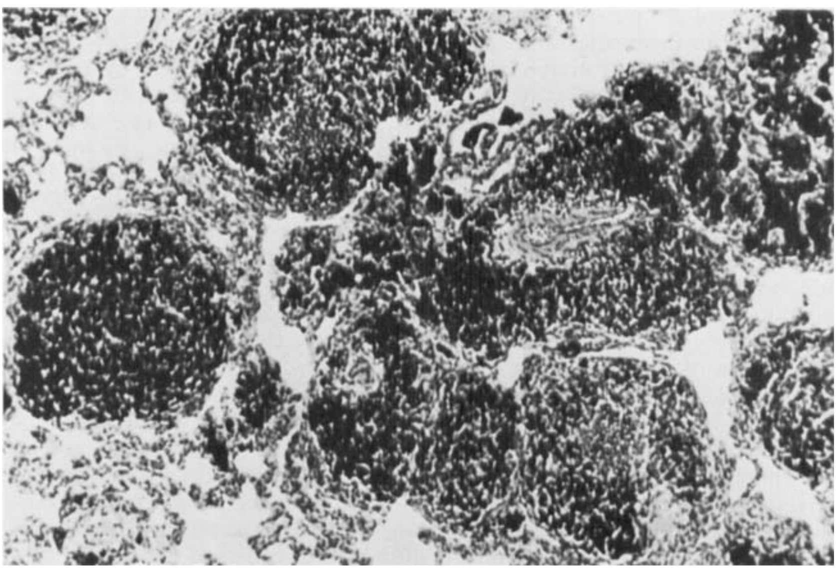

FIGURE 7. Group of mixed-dust granulomas, some of them perivascularly arranged. In the periphery of the granulomas, a perifocal emphysema can be partly seen. Rat lung, 22 months of experimental time (1800 hours of exposure time to dust). Hematoxylin and eosin. ×6.5.

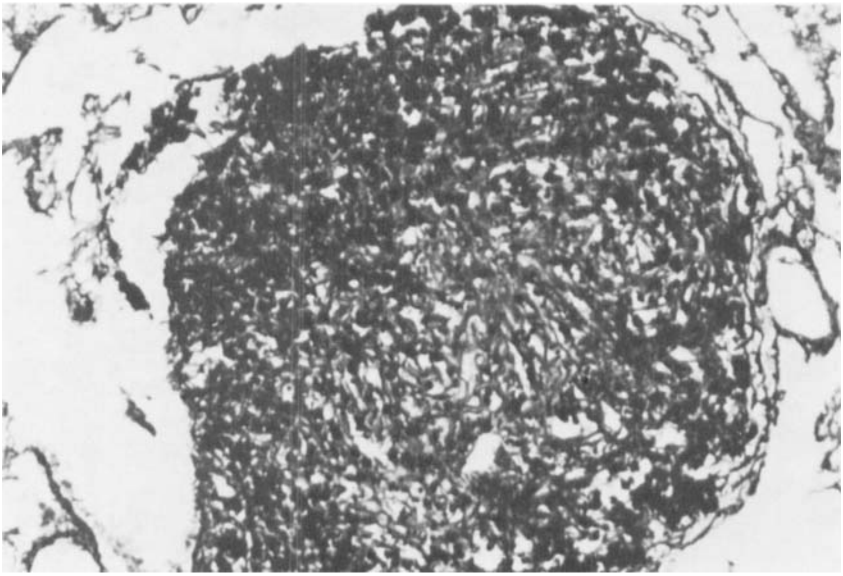

FIGURE 8. Typical mixed dust granuloma after 22 months of experimental time (1800 hours of dusting). Representation of the reticular and collagenous fibers. Relatively uniform distribution of dust particles within the granuloma. Rat lung. ×41.6. Gomörri-silver impregnation.

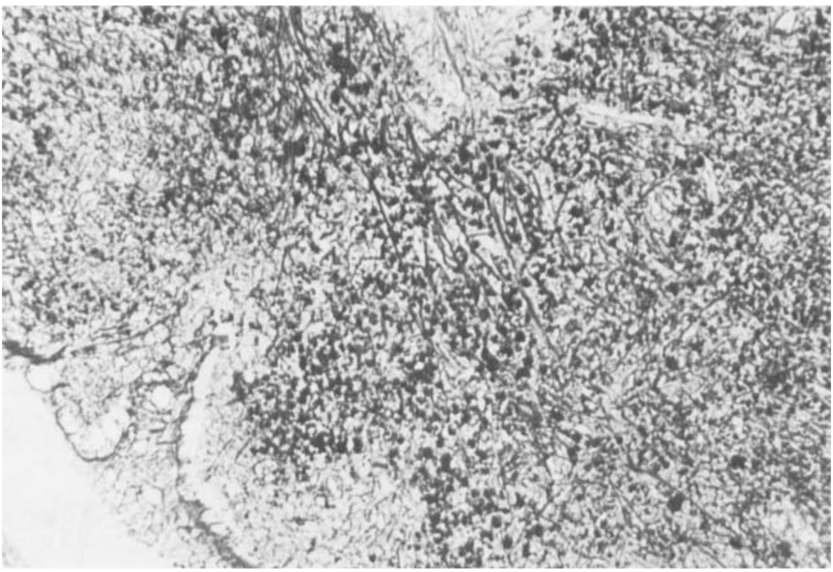

FIGURE 9. Dust incorporation and fiber formation in a pulmonary lymph node after an experimental time of 22 months (1800 hours of exposure to dust). Representation of reticular and collagenous fibers. Rat, paratracheal lymph nodes. ×41.6. Gomörri-silver impregnation.

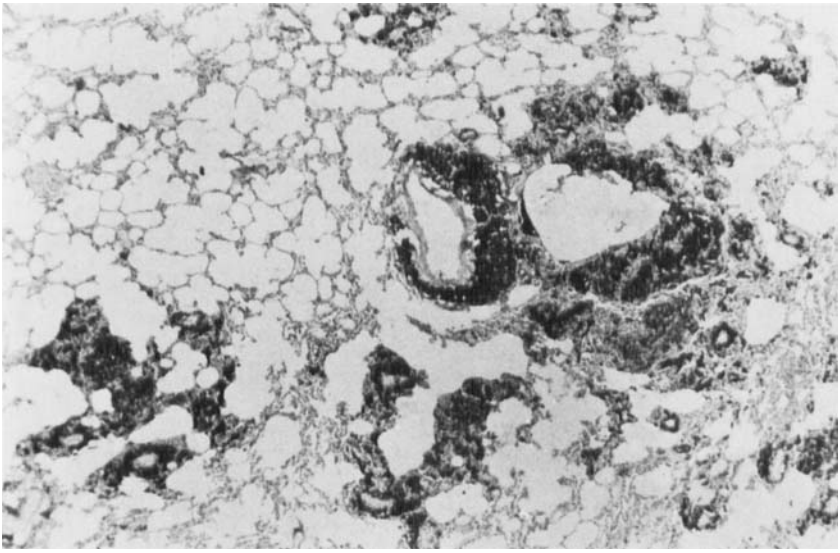

FIGURE 10. Lung of rhesus monkey. Three years' (3300 hours') inhalation of a coal-quartz dust mixture. Typical perivascular, peribronchial, and interstitial deposition of dust. ×6.5. Hematoxylin and eosin.

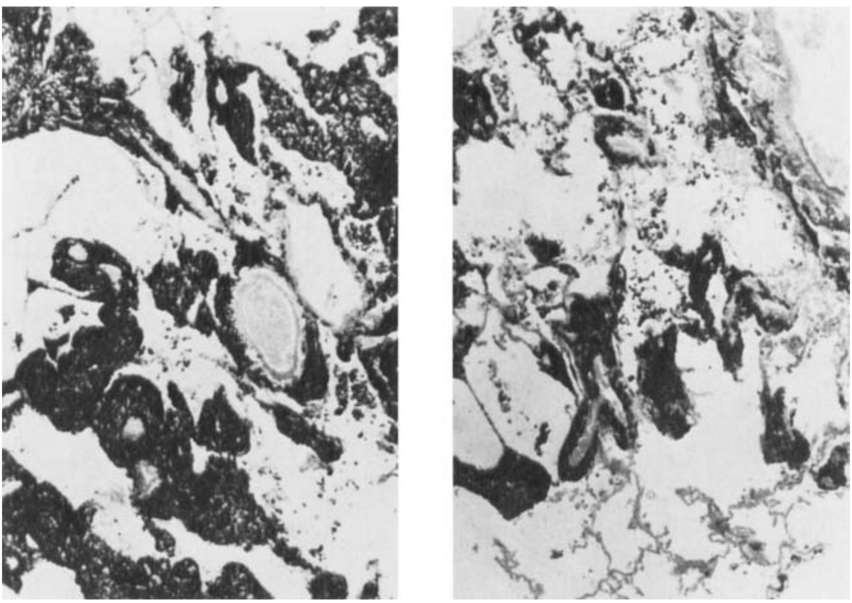

FIGURE 11. Section of a human lung. Miner with coal workers' pneumoconiosis. 20 years of dust exposure. ×7.

lymph nodes the dust depots are present as uniform coal-quartz mixtures, i.e., there is no tendency to disintegrate. In the sites with dust depots, a moderately dense reticulum of reticular and collagenous fibers has formed.

In the following Figure (FIGURE 11), the histologic lung section of a miner affected with coal workers' pneumoconiosis after a dust exposure of 20 years is shown for comparison. The resemblance to the previously shown histologic findings of the animal experiments is evident, particularly to the pathologic changes obtained after dust exposure of rhesus monkeys.

DISCUSSION

Examinations of the respiratory and circulatory functions did not indicate any differences worth mentioning between dust-exposed animals and nonexposed controls. Although numerous granulomas are present in the lungs of the exposed animals, also associated partly with perifocal emphysema, the functional integrity of the lungs is not significantly disturbed. This observation is in agreement with the results of the examinations of miners suffering from coal workers' pneumoconiosis as long as no PMF (progressive massive fibrosis) changes, grade B and C, are present.[11, 19]

The most important point of the results of dust recovery is that a linear dust retention has to be assumed. Up to now, general opinion, based on findings from animal experiments in short-term inhalation tests, as well as on the results in dust recovery from human lungs, was that dust retention decreases with increasing temporal dust exposure.[2, 6, 18] The retention curve for man that was assumed to be flattened,[2] proves to be linear, however, if men who have been away from the mines longer are not considered.

A further important observation based on dust recovery is that, evidently, no quartz enrichment occurs within the lungs and that, furthermore, the recovered dust nearly corresponds in its composition (percentage-wise) to the distribution of these dust components in fine dust. With regard to the dust content of pulmonary lymph nodes in rats, it is interesting that quartz enrichment during exposure time is not very marked. This enrichment only begins to a larger extent after the end of exposure.

Findings of the histopathological examinations indicate, first of all, that silicotic changes are very small, considering the high quartz portion of the dust. In regard to the relatively long experimental dust exposure time of 18 months for rats and 36 months for monkeys, silicotic changes are also slight. The quartz portion in the fine dust corresponds to a concentration of about 15 mg/m^3. On the other hand, marked silicosis has been provoked in animals after inhalation of pure quartz in a similarly high concentration, even in a relatively short time.[1, 9, 17] In the case of artificially mixed dusts, as used in our experiments, it has been emphasized again and again that even quartz portions of 3% are able to change tissue reactions considerably in line with a silicotic reaction.[8, 14, 16] Experiments carried out recently with actual mine dusts nevertheless furnished different results.[4, 12, 16]

In the case of the artificially mixed dusts, it is therefore assumed that a distintegration of the dust components occurs that adds to the specific activity of the quartz portion.[4, 14, 16] These disintegration processes could yet not be verified in our experiments, either in the lungs or in the pulmonary lymph nodes. In this respect, differences also clearly exist between the findings of long-term inhalation tests and the results of intraperitoneal or intratracheal experiments. Some examples will be mentioned, in whose light the problems of the different investigation methods will be discussed.

As was already mentioned, experimental silicosis research is carried out by means of inhalation experiments, injection, and cytologic tests. Considering the expense necessary for constructing and operating an efficient unit, the question arises as to the necessity of such methodology. Considerably less expensive investigations are at our disposal in the form of injection tests and, particularly, cell tests. But the decisive criterion in choosing the method to be applied is the enlightenment provided by the test findings to be expected in connection with the problems to be solved. Only by means of the inhalation test can the conditions of natural dust exposure be pursued. In contrast to the intratracheal injection, dust supply runs continuously. This factor greatly affects the formation and assessment of functional changes. As was demonstrated before, the functional exploration did not reveal considerable dust-caused changes in spite of extended pathological changes. In contrast, we could measure, in an intratracheal injection test, for example, an elevated pressure of 100% in the right ventricle as compared to the normal value after an experimental time of three months. By means of the long-term inhalation test, it is also possible to investigate chronic effects and changes developing over a long period of time, some of which may only be revealed in this way. Consider the results of an inhalation test running for two years with a coal-quartz mixture with simultaneous application of P 204 as aerosol.[23, 26]

The nature of pathological changes also seems to be different in inhalation and injection tests. As was shown previously, no dominant silicotic reaction has been observed in spite of a quartz portion of 30% in the dust mixture. But in the intraperitoneal test, in which the same dusts were initially used as in the inhalation test, a markedly silicotic reaction could already be provoked by a quartz addition of 10%.

By means of inhalation and injection tests, the fibrogenic action of dusts and dust mixtures can be proved. Through the cell test, however, the acute cytotoxic reaction can be observed. We must state here that a causality between cytotoxicity and fibrogenity and dust could not be verified up to now.[23] Considering the actual state of scientific knowledge it is therefore not permissible to draw conclusions about the possible risk for dust-exposed persons or even to establish correlations between cytotoxicity and the incidence of pneumoconiotic changes in the lungs of miners based on cell test results.[13] In basic research it was also found that so-called non-toxic pure crystalline quartzes, according to cell tests, have proved to be fibrogenic in injection tests.

From all these results, it is clearly evident that in order to judge reliably the importance of diverse dusts and dust mixtures from the view of industrial health or to examine prophylactically or therapeutically efficient substances as means against pneumoconiosis, the inhalation test and, above all, the long-term inhalation experiment cannot be replaced as regards its results and diagnostic importance. The question of what species of animal should be used thus seems to be of secondary importance. It is true that our investigations have shown that the pathological changes found in rhesus monkeys particularly resemble those found in coal workers' pneumoconiosis. But considering the pathological changes only, without taking into account the deposition form, the changes are not so considerably different that one has to speak of principal differences between monkeys and rats.

Finally, we would like to mention the following pertinent points:

1. For long-term experiments specific-pathogen-free animals should be used. This stricture applies, above all, for rats. In any case, it is necessary to use a closed and air conditioned experimental unit.

2. In spite of dust-caused pathological changes, respiratory and circulatory functions are only slightly affected. These findings are in agreement with more recent examination results on man.

3. Examination of the dust content of lungs and pulmonary lymph nodes shows that dust deposition within the lungs increases linearly corresponding to exposure time.

4. Furthermore, the dust content recovered from the lungs corresponds in its composition to the composition of fine dust. Histopathological investigations show that, through long-term dust exposure to an artificial dust mixture of coal and quartz, changes can be provoked which correspond to the changes found in miners affected by coal workers' pneumoconiosis. This is particularly true of the pathologic changes produced in monkeys.

5. The long-term inhalation experiment, in regard to its results and diagnostic importance, cannot be replaced, at this point, by any other test to assess the industrial hygienic importance of diverse dusts and dust mixtures, as well as to examine prophylactically or therapeutically efficient substances against pneumoconiosis.

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