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An Experimental Study of the Effects of Talc Dust on Animal Tissue

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The occurrence of a series of deaths from pulmonary disease following exposure to talc mining in upper New York State caused The Saranac Laboratory to inquire experimentally into the precise causative agent of this form of pneumoconiosis. This series of experiments, in which one of us (T. M. D.) participated, was conducted at The Saranac Laboratory under the supervision of the late Leroy U. Gardner, M.D., during the period 1937-1941, and the results are now reported for the first time. They have lost neither their relevance nor importance, as instances of talc pneumoconiosis recur sporadically, and a recently resected lung apical lobe from a paper-mill worker, suspected to be suffering from tuberculosis, revealed on study by one of us (G. W. H. S.) that talc dust may cause lung disease in the most unexpected of occupations.

A study of the dust to which eight fatal cases were exposed and of the minerals recovered from their lungs[1] showed that the mineral talc is but one of the components of commercial talc, to which they were exposed. Along with the talc there occur in variable proportions tremolite, anthophyllite, quartz, serpentine, and dolomite. The animal experiments were, therefore, designed to probe the specific effects of each of these component substances. In these experiments the mineral, or mixture of minerals, in the form of a dust suspension was introduced into animals by the intravenous and by the intratracheal technique. Rabbits, guinea pigs, and rats were used, but not both techniques were employed for each species. Minerals selected for their purity were used, and in some instances contaminating substances were removed, or reduced in amount, by sedimentation in heavy liquids.

The progressive and essential steps followed in conducting these experiments are summarized in the accompanying Tables. A separate control study with quartz was not performed, as the effects of this substance had already been established by previous experiments at The Saranac Laboratory, and those experiments serve as a control standard.

The intravenous method of introducing dust into animals was used in an investigation in which the mineral dust, ground until the particles were 3μ and smaller in size, was injected into the vein of rabbits and of rats (Table 1). Both species were used in the studies with talc, soda tremolite, and serpentine, and rabbits only in experiments with soda-iron tremolite, anthophyllite, and dolomite.

The intratracheal technique was employed in three sets of experiments. In one set (Table 2), the four minerals studied were injected in the form of particles 3μ and less in size, and, in addition, two of the minerals (tremolite and anthophyllite) were used as a dust composed of particles 20μ and smaller in diameter. In the second set (Table 3), which was conducted with fibrous minerals, the material was crushed and then separated

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TABLE 1.—*Intravenous Injection Experiments with Talc and Associated Minerals*

Particle Size: 3 μ and less.

Dosage: For rabbits the total amount of dust injected was 1.0 gm. divided into 20 equal doses (each dose was 5 ml. of a 1% suspension) injected twice a week for 10 weeks into the ear vein.

For rats the total amount of dust injected was 100 mg. divided into 18 doses (beginning at 0.5 ml. of a 0.25% suspension and increasing to 0.5 ml. of a 1% suspension) injected twice a week for nine weeks into the tail vein.

Periods at Which Animals Were Killed: Usually at intervals of 3 to 6 months up to one year after injection and at intervals of 6 to 12 months thereafter.

Mineral	Time Ball-milled, Hr.	Animals	Maximal Survival After Last Injection, Mo.	Results
Talc (Georgia)	1,900	4 rabbits	24	Bronchitis, bronchiolectasia, endarteritis proliferans, macrophage catarrh, pleural thickening
Talc (Georgia)	72	8 rats	15	Inert
Tremolite (soda-iron)	140	4 rabbits	19	Inert
Tremolite (soda)	48	4 rabbits	24	Inert
Tremolite (soda)	310	4 rats	10½	Minute cellular infiltrates
Anthophyllite	1,400	4 rabbits	24	Minute cellular infiltrates
Serpentine	72	4 rabbits	12	Persistent paravascular granulomata
Serpentine	72	6 rats	12	Persistent paravascular granulomata
Dolomite	144	3 rabbits	24	Transient phagocytosis and toxemia

TABLE 2.—*Intratracheal Injection Experiments with Talc and Associated Minerals*
Dust Composed of Small Particles or Short Fibers

Dosage: The total amount of dust injected was 150 mg. divided into three equal doses (each dose was 0.5 ml. of a 10% suspension) injected a week apart.

Animals Used: Guinea pigs.

Periods at Which Animals Were Killed: Usually at intervals of 3 to 6 months up to one year after injection and at intervals of 6 to 12 months thereafter.

Mineral	Time Ball-milled, Hr.	Particle Size, μ	Animals	Maximal Survival After Last Injection, Mo.	Results
Talc (Georgia)	650	3 and less	13	28	Bronchiolectasia and bronchitis; perivascular and peribronchial cellular proliferation and fibrosis; fibrocellular pleural sclerosis
Tremolite (Alps)	48	3 and less	6	38	Transient macrophage reaction and persistent eosinophilia; perivascular and peribronchial lymphocytic infiltration
Tremolite (Alps)	...	20 and less	6	12	Incipient bronchiolectasia and peribronchial fibrosis; incipient periarteriolar cellular infiltrates
Anthophyllite	1,700	3 and less	6	12	Catarrhal bronchitis; peribronchial, periarteriolar and cellular masses; peribronchial fibrosis
Anthophyllite	...	20 and less	6	12	Bronchiolectasia and catarrhal bronchiolitis; peribronchial fibrosis
Serpentine	1,500	3 and less	8	12	Chronic bronchitis and bronchiolectasia

TABLE 3.—*Intratracheal Injection Experiments with Talc and Associated Minerals*
Dusts Composed of Long Fibers

Dosage: The total amount of dust injected was 75 mg. of tremolite and 50 mg. of anthophyllite, divided into equal doses (each dose was 0.5 ml. of a 5% suspension) injected a week apart. There were three injections of tremolite and two of anthophyllite.

Animals Used: Guinea pigs.

Periods at Which Animals Were Killed: For tremolite 1, 4, 8, 12, 17, and 18 months and for anthophyllite 1, 8, and 12 months after last injection.

Mineral	Fiber Length, μ	Animals	Maximal Survival After Last Injection, Mo.	Results
Tremolite (Alps)	20-50	6	18	Bronchiolectasia and bronchiectasis with peribronchial proliferative fibrosis and cicatrization; interstitial fibrosis and macrophage proliferation; tremolite bodies; cellular metaplasia
Anthophyllite	20-50	6	12	Bronchiolectasia and bronchostenosis; focal peribronchial cellular reaction; irregular fibrosis

An experiment with long-fiber talc was not conducted because attempts to obtain mineral specimens containing long fibers of talc were unsuccessful.

TABLE 4.—*Intratracheal Injection Experiments*
Mixtures of Talc Minerals and Quartz

Dosage: The total amount of dust injected was 75 mg. divided into three equal doses (each dose was 0.5 ml. of a 5% suspension) injected a week apart.

Animals Used: Guinea pigs.

Periods at Which Animals Were Killed: Usually 1, 4, 8, and 12 months after last injection.

Mineral Mixture	Per Cent	Particle Size, μ	Animals	Maximal Survival After Last Injection, Mo.	Results
Talc Quartz	75 25	3 and less	6	12	Multiple fibrocellular granulomata; bronchiolitis and bronchiolectasia; perivascular fibrocellular reaction; periadenitis and lymphoid hyperplasia
Tremolite Quartz	65 35	3 and less	6	12	Massed macrophages and some central necrosis and peripheral minor fibrosis; transient bronchitis
Anthophyllite Quartz	55 45	20-50 3 and less	6	12	Massed confluent subpleural, alveolar mural and perivascular cellular proliferation; minimal fibrosis; bronchiolectasia and bronchitis
Tremolite Anthophyllite Talc	30 20 50	3 and less 20-50 3 and less	6	12	Subpleural, peribronchiolar, and perivascular macrophage and fibrocytic proliferation
Tremolite Anthophyllite Talc Quartz	26 17 43 14	3 and less 20-50 3 and less 3 and less	6	12	Massive exuberant macrophage and fibrocyte cellular proliferation; bronchiolectasia and bronchitis; minimal fibrosis

by sedimentation in alcohol to isolate fibers approximately 20μ to 50μ long. It is reported that the mineral talc may exist in fibrous form,[2] but attempts to obtain talc samples suitable for preparing fibers 20μ to 50μ in length were unsuccessful. The occurrence of talc as a long-fiber mineral would appear to be uncommon.

The third set of intratracheal experiments (Table 4) was specifically designed to mimic the dust exposures of the upper New York State industries and particularly to probe the influence of quartz on the combined or separate pathogenicity of the other components of commercial talc. The effects of these substances may now be scrutinized.

EFFECTS OF TALC AND OF ASSOCIATED MINERALS ON TISSUE

Dolomite.—The intravenous introduction of dolomite proved toxic to the rabbits, some dying while the injections were being made and others within a few days. Such animals showed a macrophage reaction in the alveoli by the third day, with perivascular and peribronchiolar cellular accumulations. Occasional eosinophile infiltrates were to be seen. The lungs of animals surviving to 24 months showed no abnormality, a condition suggesting either a complete recovery or a lack of chronic response in the first instance.

Serpentine.—When introduced into rabbits by the intravenous route, serpentine dust produced within three months a moderate degree of alveolar macrophage catarrh, with septal cellular proliferation. Dust particles could be seen particularly within perivascular macrocytic accumulations. In the case of the rat there is no comparable alveolar catarrh at 12 days, but there are some macrophage and multinucleated giant-cell accumulations at the angles between alveolar septa. In both the rabbit and the rat small isolated granulomata, composed of multinucleated giant cells, well-charged koniophores, unpigmented macrophages, plasma cells, lymphocytes, and fibrocytes with intermingled capillaries, may be found at 12 months. These foci have a perivascular and peribronchiolar distribution.

The intratracheal introduction of serpentine in guinea pigs provokes within the first month bronchial epithelial hyperplasia, with submucosal and adventitial cellular infiltration and scattered intra-alveolar koniophores. By the end of a year this condition has stabilized as a chronic bronchitis, with bronchiolectasia and distortion. There is considerable epithelial desquamation, with some papilloma formation.

Talc.—When introduced into the rabbit by the intravenous route, talc produces within one month numerous focal areas of alveolar macrophage catarrh and pleural thickening through superficial fibrocytic and macrocytic hyperplasia. The talc spicules are universally distributed throughout the pulmonary parenchyma but avoid the lymphoid tissue, and the alveolar macrophages do not yet show much talc. At the end of two years this talc is still present in the alveolar bronchial and vascular walls, and the intra-alveolar macrophages now also contain some talc. Isolated foci of marked vascular muscular proliferation may be seen. More usually there is a perivascular alveolar reaction. Endangiitis proliferans is commonly seen in the smaller blood vessels. Alveolar walls are thickened through cellular proliferation. A moderate degree of chronic bronchitis and bronchiolar dilatation is seen, together with bronchopneumonic foci displaying a high proportion of macrophages. The pleural cellular proliferation shows no advance on that seen at the end of the first month.

The rat lung is apparently immune to the effects of talc introduced by the intravenous route. No reaction is demonstrable at the end of the 1st month, and at end of the 15th month a few talc-laden macrophages may occasionally be seen in the alveoli. Practically all the talc introduced is still readily demonstrable in the lumina of blood vessels by means of polarized light.

When introduced into guinea pigs by the intratracheal route, particulate talc calls forth within one month perivascular and peribronchiolar focal intramural cellular accumulations comprising histiocytes, fibrocytes, plasma cells, and rare eosinophiles. Dust-containing macrophages form irregularly distributed confluent pneumonic patches (Fig. 1). Within eight months multiple foci of dust-filled koniophores in alveoli surrounding bronchioles and arterioles may be seen, but dust cells may also effectively occupy pulmonary alveoli over extensive areas, producing a solid effect. Some eosinophile and fibrocyte infiltration into peribronchial tissue is seen, and there is some fibrosis, with bronchiolar distortion and epithelial proliferation. Where dust-laden macrophages reach

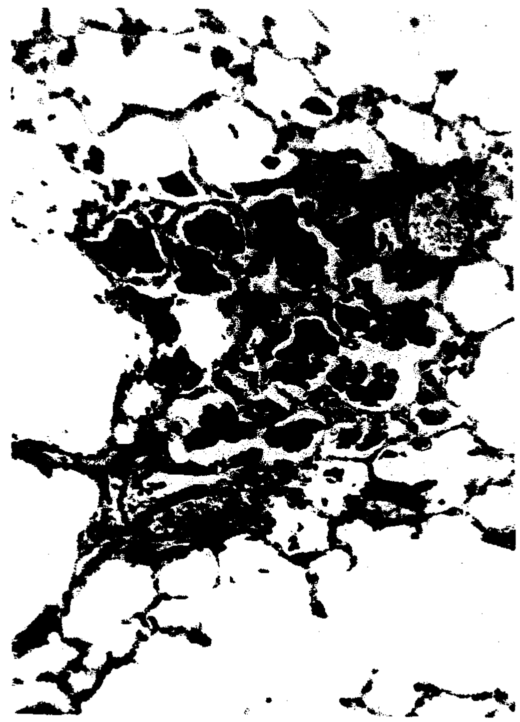


Fig. 1.—Pulmonary effects of talc injected intratracheally (Experiment 902—guinea pig lung: reaction one month after injection). Focal accumulation of talc-filled koniophores within pulmonary alveoli.

the pleural surface, a fibrocellular sclerosis with subpleural deposits may supervene.

At the end of the first year the pleural reaction is well established, consisting of an outer fibrocellular layer, a cellular inner zone, and interposed foci of pigment-filled macrophages. The dense perivascular sheaths of cells are now seen to be spilling over into the proximal alveolar walls. Immediately adjacent to the blood vessels is a zone of lymphocytes, and somewhat further afield are some fibrocytes. The hypertrophy of the bronchiolar mucosa has advanced further, and there is now some epithelial desquamation and muscular hypertrophy.

At the end of the second year the dominant residual change caused by the talc is the bronchiolectasia and bronchiolitis with epithelial catarrh. Marked focal cellular deposits and peribronchial fibrosis occur. Fibrocytes may now be seen to be intersecting the massed koniophores, and a delicate web of collagen is being laid down. Capillaries invade these areas.

When particulate talc and quartz of the same particle-size range are combined in the ratio of 3:1, the essential additional effects in the guinea pig on intratracheal injection of the mixture are perceptible within the first month. The effects consist essentially of a greater prevalence of masses of dust-filled koniophores, with numerous eosinophiles at the edges of the alveoli (Fig. 2*A*). There is a distinct tendency to alveolar septal cell proliferation, and in the cellular masses alveoli may survive as cuboidal-cell-lined spaces.

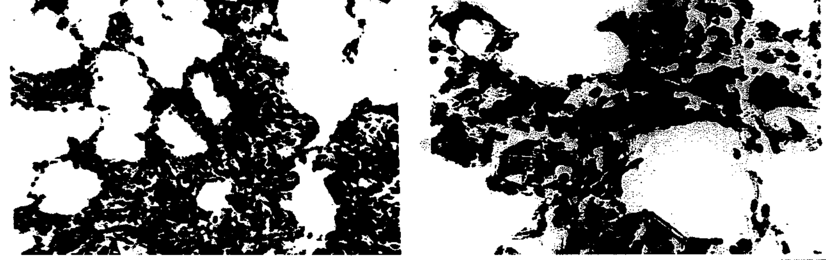
At the end of the first year the combined talc-and-quartz lesion may be defined as a fibrocellular granuloma (Fig. 2*B*), and now numerous multinucleated giant cells occupy alveoli at the periphery of the koniophore masses. There is a distinct increase in lymphoid tissue not only in the parenchymal nodes and hilar nodes but also around the small blood vessels. At the fringes of the lymph nodes there is considerable macrocytic infiltration.

The bronchiolar distention and distortion produced by exposure to pure talc, though present, are less marked when the quartz is added. There is, however, more marked epithelial desquamation, and there is more peribronchial and perivascular fibrosis.

Tremolite.—The reaction of the rabbit and the rat to the intravenous introduction of particulate tremolite (3μ and less in size), either of the soda-iron or soda varieties, is essentially negative. Most of the tremolite remains in circulation even at the end of the 19th month, though some particles may be demonstrable in alveolar walls and lymph nodes. However, even in the latter locations the dust may be within the capillaries. Very few macrophages are to be seen, and they are limited to minute perivascular infiltrates of macrophages and fibrocytes.

When tremolite of similar particle-size range is introduced into the lungs of guinea

Fig. 2.—Pulmonary effects of the intratracheal injection of talc combined with quartz (Experiment 902—guinea pig lung). *A*, reaction one month after injection; massed accumulation of talc-filled koniophores obscuring the alveolar pattern. *B*, reaction 12 months after injection; persisting macrophages; granuloma with slight fibrotic changes and some capillary infiltrations.



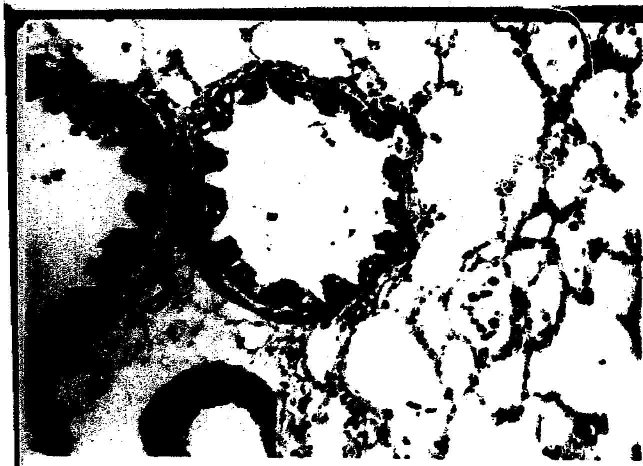


Fig. 3.—Pulmonary effects of tremolite injected intratracheally (Experiment 900—guinea pig lung: reaction one month after injection). Commencing crypt formation in a bronchiolar wall at the end of the first month under the influence of tremolite fibers 3μ in length.

pigs, many of the bronchioles are observed to have undergone erosion at the end of the first month, with peribronchiolar fibrocytic and macrocytic accumulation. The epithelium tends to be proliferated and to be desquamated. Giant macrophages filled with tremolite particles occupy the alveoli immediately adjacent to the alveolar ducts, and some scattered eosinophiles are to be seen among these cells. The reaction may, however, be limited to slight bronchiolar evagination (Fig. 3).

At the end of the first year there may be residual periarteriolar and peribronchiolar lymphocytic infiltration and isolated islets of particle-filled macrophages. Eosinophiles lie scattered among them. The bronchiolar mucosa also shows considerable eosinophilia.

When the tremolite is introduced in the form of particles up to 20μ in length, the spicules may be seen to be well dispersed and closely applied to the alveolar walls of the guinea pigs at the end of the first month. Numerous macrophages may also be seen containing such particles, but these dust cells are by no means comparable in size to the giants seen in the preceding instances. There is a great abundance of eosinophiles and commencing fibrocytic infiltration of alveolar walls. The bronchioles are a little distended and distorted and show incipient crypt formation.

The latter change is seen to have advanced appreciably at the end of the first year, and goblet cells are now present in greater profusion. There is also now more cellular infiltration and fibrosis of the bronchial walls, with macrophage discharge into the bronchial lumina.

The intratracheal introduction of tremolite fibers 20μ to 50μ long produces marked disease rapidly and extensively. Within one month the guinea pigs show complex masses of tremolite fibers trapped within the bronchi and bronchioles. There is considerable bronchiectasia and distortion, with peribronchial fibrosis and cicatrization. Many of the long fibers may be observed to have penetrated into the walls of the respiratory passages (Fig. 4). At the end of 18 months the resultant lesion is a marked fibrocellular diffuse pneumonitis, with marked bronchiectasia and epithelial destruction (Fig. 5) and vascular and perivascular damage (Fig. 6). This extensive lesion is directly comparable to the mature human lesion and is even replete with tremolite bodies, i. e., tremolite fibers surrounded by a brown iron-containing protein sheath, showing typical terminal clubbing and some measure of segmentation where it covers the shaft of the tremolite fiber. Many metaplastic cells are also found among the macrophages (Fig. 7). There is also a characteristic pleural and subpleural fibrocellular reaction (Fig. 8).

When particulate tremolite (3μ and less in size) is mixed with quartz dust of the same size range in a ratio of 13:7 and introduced into guinea pigs by the intratracheal route, the immediate effect is much greater than that observed with either the tremolite or the quartz alone. A permanent lesion comparable to that which may be expected with quartz alone is, however, not established. Apparently the healing process, seen when tremolite alone is introduced, also mitigates the quartz effect. Within the first month there is an exuberant koniophore and multinucleated giant-cell reaction which obliterates all semblance of preexisting pulmonary cytoarchitectonics around the bronchioles. Many of the trapped bronchioles are distended and distorted, with epithelial desquamation and pro-

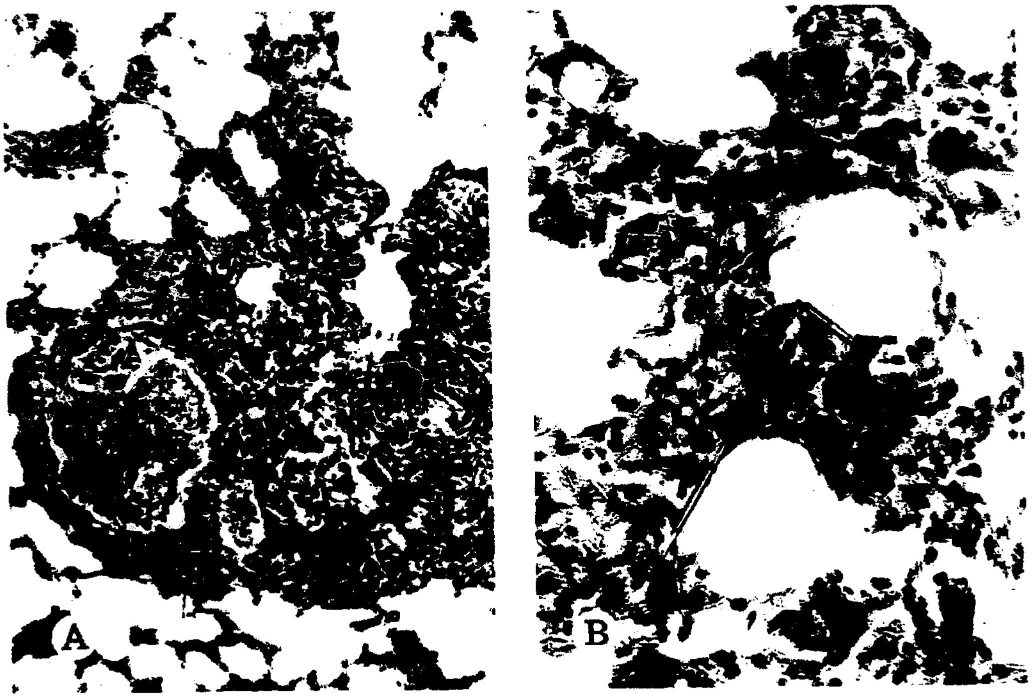
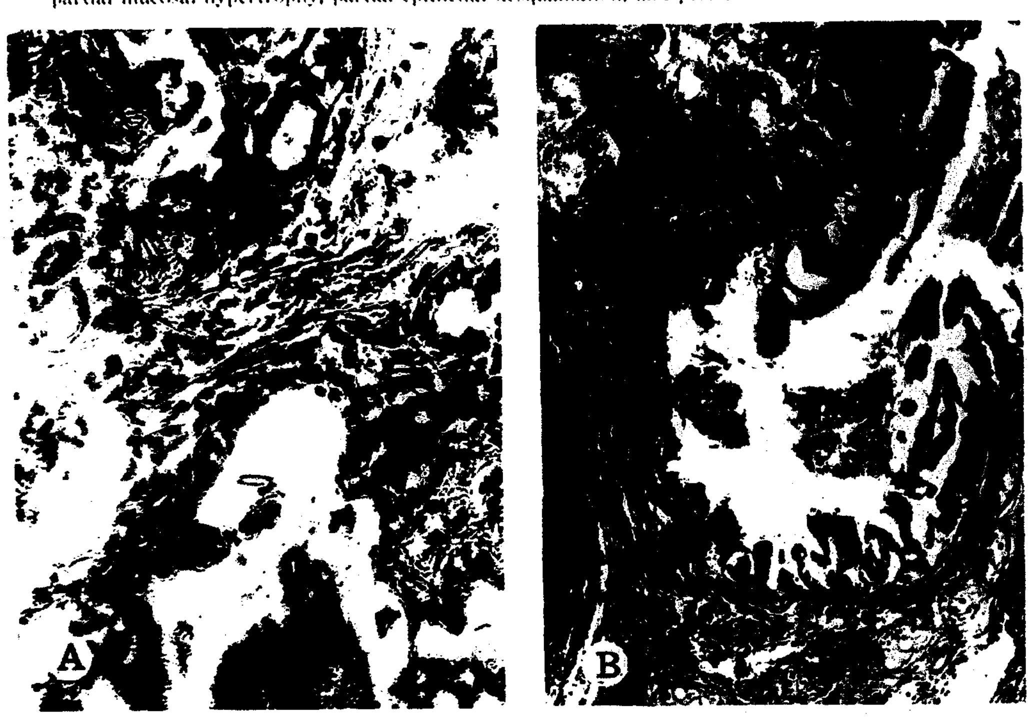


Fig. 4.—Pulmonary effects of tremolite fibers 20μ to 50μ long injected intratracheally (Experiment 995—guinea pig lung: reaction one month after injection). *A*, bronchiole choked with fibers and debris, showing breakdown of its wall and peribronchiolar cellular reaction in relation to trapped tremolite fibers. *B*, high-power view of parenchymal pulmonary reaction, showing tremolite fibers, macrophages, fibrocytes, plasma cells, and occasional lymphocytes.

Fig. 5.—Pulmonary effects of tremolite fibers 20μ to 50μ long injected intratracheally (Experiment 995—guinea pig lung: reaction 18 months after injection). *A*, interstitial pulmonary fibrosis, with prevalent cellular elements and trapped tremolite fibers. *B*, distortion, distention, partial mucosal hypertrophy, partial epithelial desquamation, and peribronchiolar fibrosis.



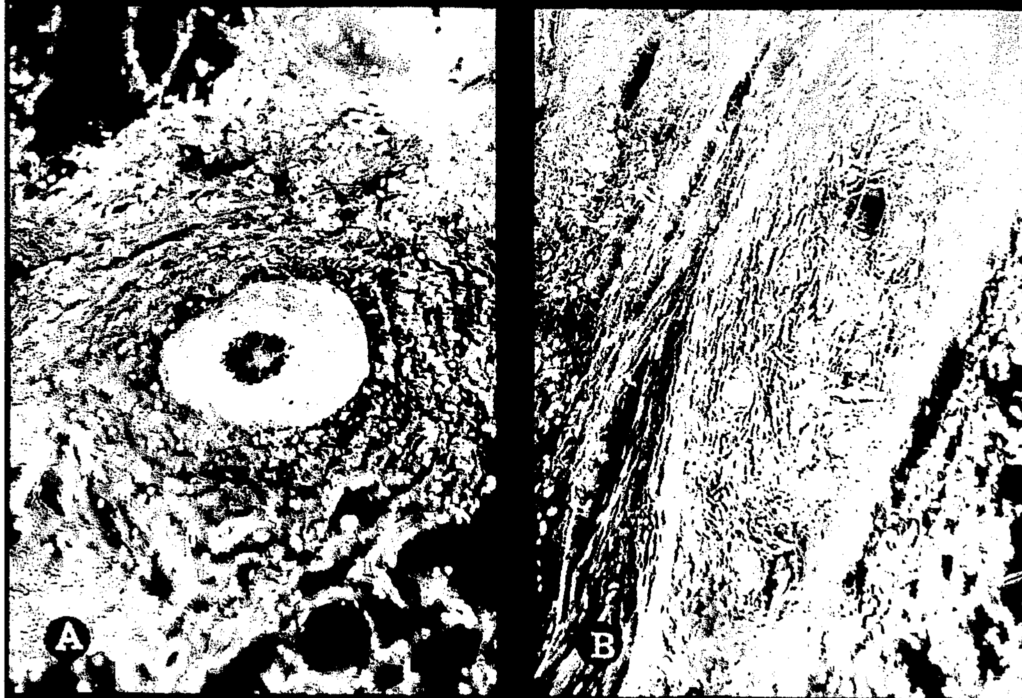


Fig. 6.—Vascular damage caused by tremolite fibers 20μ to 50μ long (Experiment 995—guinea pig lung; reaction 18 months after injection). *A*, periarteriolar fibrosis; fibers sparsely present. *B*, venule almost completely obliterated by fibrotic reaction around trapped fibers.

Fig. 7.—Fate of tremolite fibers 20μ to 5 μ long in lung tissue (Experiment 995—guinea pig lung; result 18 months after injection). *A*, tremolite fiber engulfed by macrophages with commencing clubbing of the fiber ends. *B*, birefringence of trapped fibers, some intracellular and some extracellular.

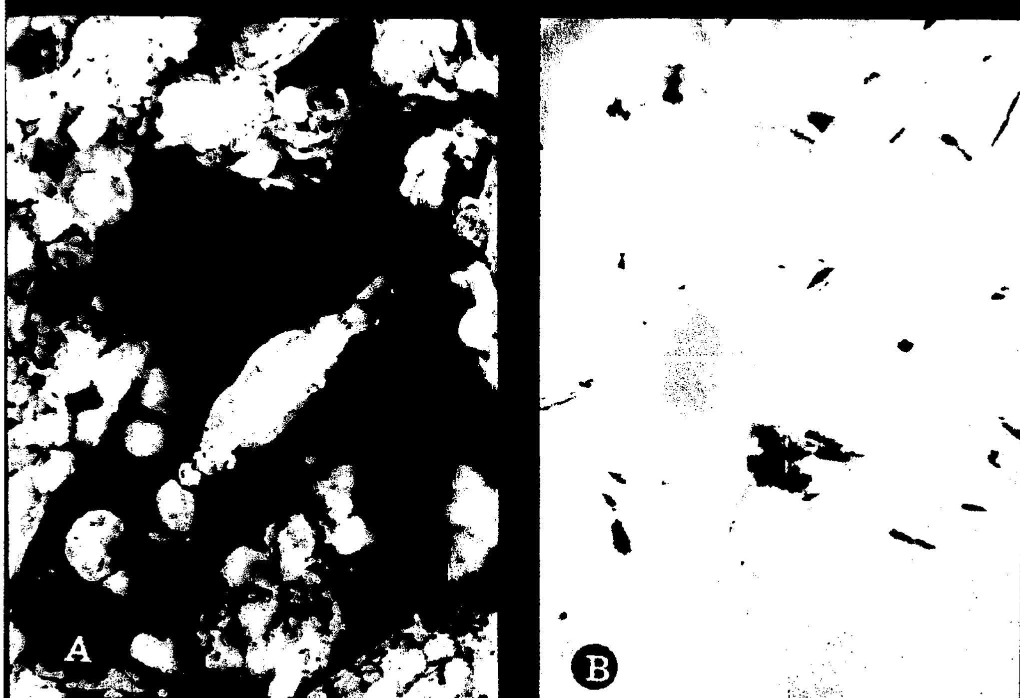


Fig. 8.—Pulmonary effects of tremolite fibers 20μ to 50μ long (Experiment 995—guinea pig lung: result 18 months after injection). Pleural sclerosis and subpleural dominantly cellular reaction around tremolite fibers.

liferation. Foci of necrosis are present, and fibrosis is commencing at the periphery. The majority of alveolar walls are infiltrated with macrophages, and there is some perilymphatic koniophore accumulation as well.

At the end of the first year there has been a measure of recovery from the initial exaggerated reaction. Foci of massed koniophores may still be found, but there is very little reaction around these cells. Necrosis is still seen at some areas. Small lymphocytic sheaths accompany some of the bronchioles and arterioles, and the bronchiolar epithelium has recovered in large measure.

Anthophyllite.—The intravenous introduction of particulate anthophyllite (less than 3μ in size) produces minimal pulmonary lesions only in rabbits. The lesions are limited to macrophage proliferation and plasma cell accumulation at pericapillary and intra-alveolar sites, and the reaction should be classified as inert.

An intratracheal introduction of anthophyllite in this particle-size range was performed in spite of the essentially negative intravenous result. At the end of the first month areas of intramural and intra-alveolar cellular accumulation occur. Most of these are dust-filled macrophages, but there are several eosinophiles among them. After one year areas of irregular fibrosis may be seen to surround distorted and distended bronchioles. Numerous areas of bronchiolar epithelial desquamation with necrotic cellular plugs in the lumina may be found. There are also massed peribronchiolar accumulations of koniophores with commencing interstitial fibrosis.

The effects of the introduction of anthophyllite fibers in the less than 20μ length range are comparable to the effects produced by the 3μ particles, with the exception that fewer macrophage masses are formed at points distant from the bronchioles. There is a greater tendency also for diffuse alveolar wall thickening through cellular infiltration and a higher proportion of fibrocytes to macrophages where cellular reactions are provoked, especially in the peribronchial tissues. The birefringent particles all seem to lie in relation to the fibrocytes. Bronchiolectasia and catarrhal bronchiolitis reach a somewhat more advanced degree (Fig. 9).

The long-fiber anthophyllite (20μ to 50μ) has an enhanced and even more rapidly injurious effect on the guinea pig lung. Within one month it produces a marked and extensive focal peribronchial fibrotic and cellular reaction, consisting mainly of macrophages, fibrocytes, and eosinophiles with areas of lymphocytosis (Fig. 10). Anthophyllite fibers and spicules are embedded within these cells, and some may be partly engulfed by giant cells. Areas of necrosis occur. Bronchitis and bronchiolitis with distortion and distention are present, and the lumina of such passages contain necrotic cellular debris. At the end of 12 months a more advanced stage of essentially the same lesion may be seen, with, however, more central and irregular fibrosis within the nodules of reaction. There is now some bronchiolar stenosis as well as ectasia.

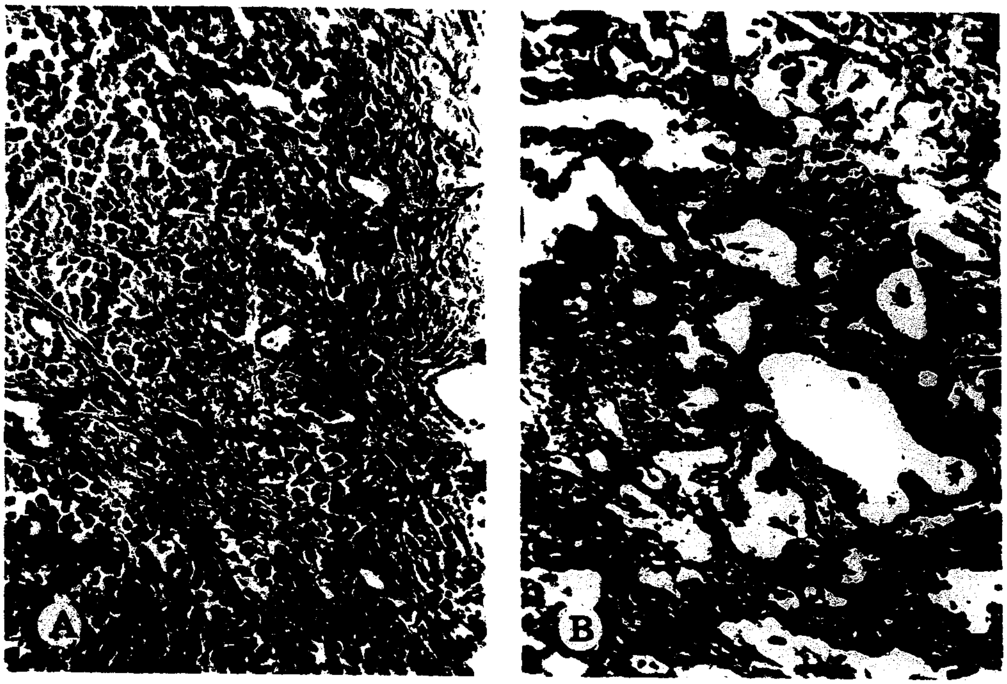
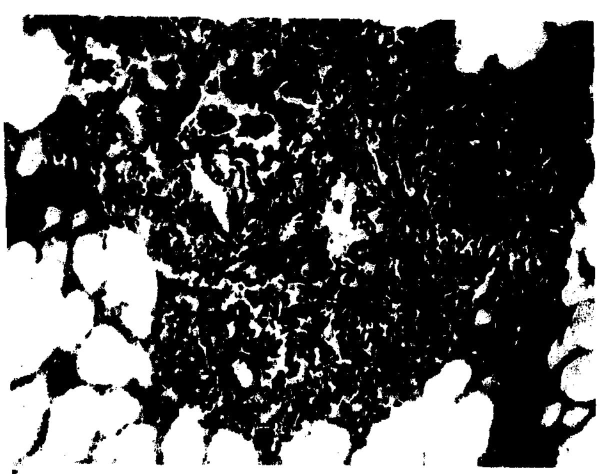


Fig. 9.—Pulmonary lesions caused by anthophyllite fibers less than 20μ long (Experiment 885—guinea pig lung: result 12 months after injection). *A*, mixture of dust-filled macrophages, fibrocytes, occasional plasma cells, and collagen strands. *B*, bronchiolectasia within an area of fibrocellular reaction; multiple evaginations create a cystic effect.

When anthophyllite fibers and quartz are mixed with each other in a ratio of 11 : 9 and introduced into guinea pigs, a marked subpleural cellular reaction, confluent mural proliferations, and perivascular cellular accumulations may be found within one month. Solid foci of macrophages occur, and there is commencing distention and distortion of bronchioles. By the end of a year the lungs are occupied by multiple masses of cellular reaction consisting mainly of fibrocytes, though some macrophages are still present. Advanced multilocular bronchiectasia may be found within these cellular zones. An interesting feature of the reaction, which shows forcibly the modifying influence of the anthophyllite on the quartz, is the fact that, though such cell masses may encroach on and surround the lymphoid nodules, they do not involve them. Small foci of acellular necrosis occur in some of the larger cell masses, but there is no distinctive tendency to fibrosis, such as may be seen in a pure quartz lesion at a comparable stage.

Fig. 10.—Pulmonary effect of anthophyllite fibers 20μ to 50μ long injected intratracheally (Experiment 993—guinea pig lung: reaction one month after injection). Section shows rapid degeneration of bronchiole, peribronchiolar dominantly cellular deposit in relation to trapped fibers, but failure to involve the lymph node.



COMBINED EFFECT OF TREMOLITE, ANTHOPHYLLITE, AND TALC

The purpose of this experiment was to attempt to define the relative influence of quartz on a mixture of components which simulates the natural talc product mined in upper New York State. The study was therefore conducted in two stages, viz., with and without the quartz.

When no quartz is included, the initial reaction to talc, tremolite, and anthophyllite is very mild. At the end of one month there is slight bronchiolar epithelial catarrh and some plasma cell infiltration into the bronchiolar mucosa. Isolated small foci of dust-filled macrophages may be found. At the end of a year the area of reaction around the pigmented macrophages is somewhat more extensive and includes some capillary hyperemia. Such areas may occur in relation to the bronchioles and subpleurally. A little bronchiolar distention and distortion may be seen.

The addition of 14% quartz to the talc, tremolite, and anthophyllite mixture rapidly provokes massive focal lesions consisting of macrophages and fibrocytes with scattered giant cells. Multiple foci of diffuse alveolar wall thickening due to macrophage invasion and septal cell proliferation also occur. In the air passages there are incipient epithelial hyperplasia and submucosal plasma cell or lymphocytic infiltration. At the end of a year this exuberant cellular response still persists, but fibrocyte accumulation is limited almost to being a fringe phenomenon. The distortion and distention of the bronchioles and epithelial catarrh have also progressed somewhat, but the degree to which this has occurred is by no means comparable to the lesions which may be provoked by either long-fiber tremolite or anthophyllite alone.

COMMENT

Though one must acknowledge at the outset the limitations of the techniques employed in this series of experiments, the diversified results obtained, not only by exploiting different minerals but also through modifying their particle sizes or varying the route of introduction or the species of experimental animal, justify the inference that at least some progress has been made in elucidating the role played by components of commercial talc in producing disease and the mechanisms by which the terminal results are achieved.

Thus it seems that the basic reaction to the presence of any of these dusts is a macrophage catarrh into the alveoli, the cells becoming engorged with large particles so rapidly that they remain immobilized and fail, except in rare instances, either to return to the tissues or to be extruded from the lung via the respiratory passages. It is possible that this is merely a mechanical result due to their large size. On the other hand, it is possible that the koniophores are actually paralyzed. They certainly do not tend to undergo necrosis; nor are collagen or other types of fibrous elements stimulated to invade the cell masses in the majority of instances, except when the component fibers are long.

The degree to which fibrosis supervenes depends on the length of fibers rather than on their chemical composition. Thus when the minerals have been reduced to 3μ and less in maximal dimension, they have practically no fibrogenic effect. On the other hand, the 20μ to 50μ length tremolite and anthophyllite fibers produce extensive regional fibrosis. Unfortunately talc could not be obtained in this fibrous form, so that it is not certain whether this rule applies to talc also. It was observed, however, that talc evokes fibrocytes, but the presence of these cells does not tend readily to lead to collagen deposition.

Attention must be drawn to the triple localization of the lesions produced by talc, tremolite, or anthophyllite, namely, at perivascular, peribronchiolar, and subpleural or pleural sites. In addition, cellular accumulations having no such apparent topographical relation to the blood vessels, air passages, or pleura may occur. It is possible, however, that these macules are merely examples of the standard lesion cut at a tangent. The lymphatic tissue escapes almost entirely, and alveolar walls are not affected except near the focal deposits or when quartz is present too.

The marked tendency to bronchiolar distention and distortion is readily explained when large masses of sharp elongated fibers are trapped within the bronchioles or when there are extensive peribronchiolar cellular masses of fibrotic cicatrization. The mechanism is less readily apparent when such obvious causes are in abeyance. The mineral particles could not be readily demonstrated in the bronchial wall except when advanced disease was present. On the other hand, it must be granted that we do not yet know the lower size range of particles of those minerals which may be active.

The lack of secondary infection in spite of the marked pulmonary changes observed is remarkable. Unfortunately the study was not elaborated to include observations on the influence of the talc minerals on the course of tuberculosis. Such a project would be worth pursuing in view of the conflicting reports concerning the prevalence of tuberculosis among human talc victims. It would, however, involve a costly inhalation study.

Contrary to expectation, the addition of quartz did not materially enhance the pathogenicity of the talc minerals. Indeed, there seems to be some indication that the fibrogenic effect of the quartz is reduced by the presence of talc in particular. This may be explicable on the supposition that if all the koniophores are effectively occupied and immobilized by the talc the quartz cannot influence them to the contrary and thus does not truly enter the body, remaining trapped in the koniophores lying in alveoli and thus truly still outside the body. The lack of a lymphoid tissue response favors such a simple and mechanistic explanation. On the other hand, the difference in reaction may be more subtle and dependent on chemical or physical interaction between the quartz and the other minerals.

While there are these evidences of opposing or inhibiting actions, and, as has been shown, they are not limited to quartz, there is also some suggestion that in certain combinations separate components may augment one another. This applies particularly to the combination of quartz with tremolite or anthophyllite.

The successful experimental production of a tremolite body provides strong evidence that the bodies found in human "talcosis" [1] are truly provoked by the tremolite component of the talc dust. Comparable bodies were not demonstrable in the anthophyllite series. There is, therefore, more than length of fiber required to cause them to develop.

This feature firmly links the animal pathology to the human disease. Indeed, this series of experiments elucidates most satisfactorily the nature of the human talcotic reaction and the factors responsible for its production. At the same time it sheds further light on the asbestos problem while confirming certain observations previously recorded concerning silicosis. Furthermore, the relative immunity shown by certain animal types serves to confirm the general concept of variable susceptibility of man and animals to disease.

SUMMARY

The pulmonary response of rabbit, rat, and guinea pig lungs to dolomite, serpentine, talc, tremolite, anthophyllite, and quartz, either separately or in combination, was explored by the intravenous and intratracheal techniques.

Dolomite and serpentine are relatively inert.

While talc is dominantly cytogenic, tremolite and anthophyllite have both cytogenic and fibrogenic propensities.

Quartz modifies the effects of these substances.

The effects of these substances are different from the effects of the substances in combination acting singly.

Talc, tremolite, and anthophyllite all tend to damage the smaller respiratory passages and blood vessels to a variable degree.

The long tremolite and anthophyllite fibers produce rapid and grave peribronchiolar lesions.

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