Unfinished report found in Dr. Gardner's desk after his death, October 24, 1946.

ASBESTOSIS

Etiology, Pathogenesis and Pathology

Asbestosis is a form of pneumoconiosis resulting from prolonged inhalation of asbestos dust. Asbestos, literally "unburnable," is not the name of a particular mineral, but is a term applied to a number of different minerals, all of them composed of long, parallel flexible fibers. Their structure is unusual because the films are capable of repeated longitudinal subdivision to units of molecular proportions. Their length varies from a few microns to six or more inches. Some varieties are stiffer than others, but many are sufficiently flexible to be spun into yarn and woven on modified textile machinery. Chemically, the asbestiform minerals vary in composition, but all but one of them are silicates, i.e., compounds of several different hypothetical silicic acids with varying proportions of magnesium, iron, aluminum and other bases. Some indication of their diverse structure is illustrated in the following table, but even this does not tell the whole story for particular specimens from different localities may not exactly conform to the appended formula.

Canadian Chrysotile	$H_4 Mg_3 SiO_9$
South African Crocidolite (Blue Asbestos)	Na. Fe^{III} $(SiO_3)_2$ - Fe SiO_3
Anthophyllite	(Mg. Fe) SiO_3
Amosite	(Mg. Fe Al) SiO_3 + Fe Si
Amphibole	(Na. K. Al) Si_4O_{11}
Brucite	Mg. $(OH)_2$

Pure chrysotile asbestos is a hydrated silicate of magnesium, $Mg.3\ (SiO_4)_2.\ (H_2O)_2$. However, these elements are not invariably crystallized in the form of long flexible fibers; under certain

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conditions they are combined in massive form to produce the mineral known as serpentine, which is composed of microscopic fibers without the parallel orientation characteristic of chrysotile. The massive blue black serpentine, which feels smooth and soapy, is traversed by veins of fibrous chrysotile varying in width from barely perceptible lines to six or more inches. The fibers run across and not lengthwise in the vein. Thus while identical in chemical composition, chrysotile and serpentine are very different in physical appearance.

Attention is directed to the mineral brucite, which is often found in the same formations with serpentine and chrysotile. Brucite is also fibrous and crystals three or more feet in length are not uncommon. It has no commercial value at the present time for its fibers are not sufficiently flexible to be used in textiles, but they are capable of repeated longitudinal subdivision. It is unique among asbestiform minerals in containing little or no silica, and for this reason it has been a valuable tool in an experimental evaluation of the action of such minerals upon lung tissue.

Industrial Asbestiform Dusts. Exposure of human subjects occurs in the mines, quarries and mills where the raw materials are procured and processed, in the textile plants where fibrous asbestos is spun and woven into yarn, cloth, brake linings, electrical insulation, etc., and in the use of finely ground asbestos as electrical or thermal insulation.

At the mines and mills in Quebec there is little exposure to dust of the longer fiber, as the wide vein material is hand cobbed with hammers and packed in bags for shipment. The thin veins and the serpentine rock is repeatedly crushed to a finer and finer state of

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subdivision under a system of exhausts designed to remove and save all fibrous elements regardless of their size. Such milling processes are attended by a very considerable degree of dust polution of the atmosphere but much of this dust is composed of either very short fibers or non-fibrous particulate matter.

The textile mills handle long fiber and, before the days of control programs, were dusty places. In crushing the asbestos to open the bundles of vein material, large flocks and some finer fibers were suspended in the air for varying periods. The process of mechanical mixing of the opened fibers with cotton was even more dusty. In the spinning and weaving, the dust concentrations were not as high, but the proportion of fiber of inhalable length was large. Even under the controlled conditions today it is difficult to apply exhaust systems that will exclude all fiber from the air and, at the same time, not interfere with the manufacturing processes.

Reports of dust counts would suggest that the total concentrations in many asbestos fabricating plants were never excessive. Whereas counts in excess of 100 million particles per cubic foot of air were common in unprotected plants handling non-fibrous minerals, in the asbestos industry counts above 25 million were exceptional. With exhaust systems, counts over 10 million are not common. In view of the fact that asbestosis is still being produced, it would appear that injury ensues from exposure to lower concentrations of fibrous asbestos than to particulate quartz. On the other hand, it is possible that standard methods of dust collection are not adequate for sampling air-borne material of fibrous nature. The latter possibility is the subject of current investigation.

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Inhalability. Experience has demonstrated that most of the particulate matter inhaled into the lungs of man and animals is 10μ or less in maximum diameter. Larger particles are apparently excluded by the protective mechanisms of the upper respiratory tract. In the case of fibrous materials, however, this rule does not apply and fibers 100 and even 200μ in length have been found in the terminal air spaces of human lungs. In small laboratory animals exposed to asbestos dust the maximum length rarely exceeds 50 to 60μ. Not every kind of fibrous material is inhaled with equal readiness; for example, the synthetic fibers of glass wool are apparently too inflexible to pass through the nose, pharynx, trachea and bronchi. After daily eight hour exposures over a three year period no fibers were detected in the lungs of guinea pigs, rabbits, rats or mice.

Localization in the Lungs. Inhaled particulate matter comes to rest throughout the terminal air spaces in all parts of the lungs; inhaled fibers are first retained in the respiratory bronchioles. These very small tubes are immediately distal to bronchioles lined by ciliated epithelium. Their own essential lining is a low cuboidal type of epithelium but, as their name implies, they actually function in respiration through lateral alveoli given off as pouches along their walls. Either these pouches, or the abrupt change in the character of the lining epithelium, or the decrease in diameter of the tube, or perhaps the combination of all three factors is responsible for local retention of the inhaled fibre. Only after asbestosis is well established are many fibers carried into the more peripheral air spaces.

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Tissue Irritation. Inhalation experiments have demonstrated that the fibrosis of asbestosis begins in the walls of the respiratory bronchioles and spreads from there into the more distal parenchyma of the lungs. The nature of the irritation which produces this fibrosis has been the subject of much speculation and extensive study. This matter is of interest both from a theoretical standpoint and a practical one, as prevention or disease is dependent upon knowledge of its causes.

Two hypotheses have been proposed to explain the nature of tissue irritation and resultant reaction. One, based upon experience with quartz and other forms of free silica is chemical irritation. Its proponents assume that the asbestos minerals dissolve in the body fluids and that in this process their bases leach away to leave silica in a form capable of irritating tissues. This hypothesis would make asbestosis merely an indirect silicosis. The other view to which I now subscribe is mechanical irritation due to the peculiar physical structure of the inhaled foreign body.

Chemical Theory. If the irritation were chemical, the irritant should become increasingly potent as its particle size decreases. With quartz, for example, it has been demonstrated that the smaller the particles, the more rapid the tissue reaction. In sufficient quantities, particles of free silica under 0.1μ in diameter are highly toxic and will kill animals in a few minutes or hours. In the case of asbestos, however, the reverse is true; only long fibers have any specific effect. Some years ago we started an inhalation

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experiment with ball milled asbestos dust in which practically all of the fibers were less than 3μ in length. This was done to produce rapid reaction, as we had with quartz, so that advanced asbestosis might develop within the lifetime of small animals like the guinea pig. To our surprise, exposures to high concentrations of such dust for 48 hours a week over a three year period produced no changes visible on gross inspection of the lungs. The reaction was much less severe than we had previously observed in animals similarly exposed to lower concentrations of unground asbestos (1) containing longer fibers.

If asbestosis is in reality only a silicosis due to the silica component of the magnesium silicate, it would be reasonable to expect that, like quartz, asbestos would produce its effects in any organ of any species of animal. For example, injection of fine quartz into extrapulmonary tissues of guinea pigs, rabbits, rats, cats, dogs, chickens, and even tadpoles will produce silicotic nodules. But similar injections of long or short fiber asbestos have no such effect. It is possible that chemical factors may be involved here, for asbestosis bodies do not form in extrapulmonary tissues; in fact, they are not produced even in the lungs of all species of animals. However, as will be shown later, the formation of these bodies does not necessarily parallel the development of fibrous tissue reactions.

If the irritation were chemical due to liberation of silica in active form, it should be possible to neutralize such silica with alumina, as has been done with quartz, but experiment has demonstrated that this does not occur. Injection of particles of 1 to 3μ

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quartz suspended in 0.25 per cent amorphous aluminum hydroxide results in simple phagocytosis with nothing even suggestive of the progressive fibrosis of silicosis. Intratracheal injection of similar suspensions of 50 to 60μ chrysotile fibers in guinea pigs in no way retards the development of fibrous tissue. If anything, the rate of reaction is greater than that to fibers suspended in physiological saline solutions.

Finally, if chemical mechanisms were involved, serpentine, which has the same chemical composition as fibrous chrysotile, should produce the same kind of tissue reaction. But it does not; on injection into the lungs and other organs of susceptible animals serpentine is an inert material causing only phagocytosis and mild chronic inflammatory changes about foci of excessive local concentrations of the particles.

The general theory that any silicate can produce silicosis after its bases have leached away in body fluids finds no support in experimental observation. Animal assay of some fifty silicates of different mineralogical groups has failed to disclose any that acts like quartz. A few are toxic and produce acute inflammatory reactions; none causes progressive fibrosis. Only those that have unusual physical structure like the fibrous asbestiform minerals, fibrous tremolite, fibrous pyrophyllite and the plate-like micas provoke tissue fibrosis. Unlike quartz, these minerals exert their specific effects only in the lungs; in other organs, no fibrosis develops within two years after injection.

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Mechanical Theory. In addition to the negative evidence that prolonged exposure to high atmospheric concentrations of finely ground chrysotile asbestos will not cause appreciable reaction in animals' lungs, we have assayed the influence of pure asbestiform mineral fibers of various lengths. By intratracheal injection, it has been found that maximum tissue reaction is produced in guinea pigs by fibers 20 to 60μ in length; those less than 3μ long cause no fibrosis but merely chronic inflammatory changes comparable to the effects of serpentine and most other silicates. Fibers of intermediate size, between 10 and 20μ, are less irritating and scar tissue develops more slowly. The chemical composition of the fibrous mineral has little influence; non-siliceous brucite has just as much effect as the silicates like chrysotile, crocidolite and amosite. One month after a series of three intratracheal injections totaling 150 milligrams, all of these minerals in the larger sizes produce a fibrous reaction in the walls and within the lumen of the terminal bronchioles. Furthermore, such tissue changes antedate by about 6 weeks the development of the so-called "asbestosis" bodies.

In the extrapulmonary tissues of guinea pigs and other animals, the injection of long and short asbestiform fibers causes no fibrosis and practically no asbestosis bodies. However, we have verified the observation of ----- 8 ----- (2) that the addition of whole blood facilitates the development of asbestosis bodies, but even when they do form the tissue response is no greater than that to injected blood alone.

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Asbestosis Bodies. Cook (3) identified these peculiar structures as modified asbestos fibers and established their relationship to the disease, asbestosis. Later, Gloyne (4) and others described them more minutely and speculated on the mechanism of their development. Asbestosis bodies never occur in nature; they gradually develop after contact with the tissue fluids of the lungs. In guinea pigs this requires a period of 60 to 70 days. In some species like the dog, they do not form at all; in others like the rabbit, they develop slowly and in small numbers. In human beings with asbestosis, their number is variable but no correlation with the severity of the exposure has been possible.

The bodies consist of a bright yellow coating upon the surface of the fibers. Apparently it is first of uniform thickness except at the ends when smooth rounded bulbous swellings occur. Later the coating seems to crack into beadlike segments, which in turn enlarge laterally, become bulbous and produce very bizarre forms. The yellow coating has the same color as the blood pigment, hemosiderin, and gives the usual microchemical reactions for iron. It was proved by Sundina (5) to be a mixture of iron and protein.

The source of the iron was for a long time the subject of considerable speculation and many believed that it was derived from the mineral However, the development of typical yellow coatings about fibers of iron free chrysotile and brucite indicates quite clearly that the host fluid and not the mineral is the source. This belief found further support when it was shown that the injection of whole blood with fiber would produce asbestosis bodies in tissues other than the lungs. It is

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inferred that mechanical injury more readily damages the delicate capillaries in the immediate vicinity of individual fibers in the lungs than in other tissues. Furthermore, observation demonstrates the presence of variable numbers of red blood cells within the pulmonary air spaces in early experimental disease. Probably the fibers then adsorb the iron pigments and perhaps albuminous materials from the same source. However such an effect does not occur in the test tube and in tissues other than the lungs; injection of mixtures of blood and various asbestiform minerals produces asbestosis bodies only upon a few of the smallest fibers, usually at the periphery of the mass. The frayed ends of any unopened bundles of asbestos never show any iron coating.

The formation of asbestosis bodies appears to minimize further irritation of the tissue. Attempts to prove this point are not entirely satisfactory, but most of the evidence points in this direction. Intratracheal injection has demonstrated that fibrosis of the lungs develops before the bodies have formed. Similar injections of preformed asbestosis bodies recovered from a human lung have produced no fibrosis in the lungs of guinea pigs. The latter experiment was not entirely satisfactory as the quantity of bodies that could be recovered was small and the method of recovering them from the human tissue, antiformin digestion followed by repeated washing and centrifugation, fractured many of them and may have altered their composition. However, when the lung of the injected guinea pig was examined three months after the bodies were introduced, large numbers of variable length were found in the air spaces and no trace of fibrosis had developed. There was some question whether all of the coating material was that derived from the original human host or whether more had been added to broken bodies by

the guinea pig's lung. The bodies were widely scattered instead of being caught in the terminal bronchioles as occurs after injecting the fibers themselves, and reaction was limited to phagocytosis. The altered distribution suggested that the smooth bulbous ends of the bodies permitted them to glide over the irregular surfaces of the bronchioles and be carried on into the alveoli. The same change would minimize mechanical trauma to the delicate memoranes of the lungs. Whether enough coated fibers of sufficient length to provoke fibrosis were actually introduced is perhaps debatable, but at least the negative results of this test are in conformity with other evidence.

If, as indicated above, the coating of the fiber resulting in the formation of the asbestosis body neutralizes its irritating properties, progressive fibrosis would not be anticipated. Experimental observation confirms this supposition. Groups of guinea pigs exposed daily to high concentrations of long fiber chrysotile asbestos dust for periods of six months and eighteen months (check this) respectively and then allowed to live in normal atmospheres as long as two years have shown no progression of their reaction. The areas of fibrosis did not increase in size as is the case with silicosis produced by quartz. They tended to become smaller with contraction of the scar tissue and some of the fibrosis resolved and disappeared. The same was true of the reaction following three intratracheal injections of various kinds of asbestiform minerals.

The permanence of the coating in the asbestos body is a matter of interest and pertinent to this discussion. The evidence is somewhat difficult to evaluate. In old experimental lesions of animals exposed to dust and then removed to normal atmospheres for many months the number of bodies seem to be fewer than in those sacrificed at the end

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of the exposure period. The bodies are apparently too large to be transported out of the lungs by the lymph stream for they are almost never found in the tracheobronchial lymph nodes. They might conceivably lose their coating in extrapulmonary tissues, but naked fibers of any length are not detected in the nodes. One has to infer that they gradually dissolve in the lungs and the same must be true of the included fiber, for they likewise are no longer detectable. Some doubt is thrown on this deduction by the evidence in one human case reported by Mills (8) who has kindly furnished the writer with representative tissue. This patient died of heart disease some thirty years after engaging in prospecting for asbestos for an unspecified period. The details of his exposure are unknown. Sections of his lung present small foci of fibrosis, many fragments of asbestosis bodies and large numbers of very thin uncoated fibers. Petrographic analysis of this material indicates that

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The histological picture is complicated by the effects of prolonged cardiac decompensation. Since most asbestiform minerals tend to become coated with iron and albumen, one has to assume that these thin fibers have lost their original deposits but did not themselves dissolve over a period of 30 years. Study of more such cases is obviously essential. At least it may be affirmed that the amount of fibrosis in this lung was not proportional to the quantity of fiber seen in the tissue. Obviously, reaction had not progressed very far and something had stopped continued irritation.

Thus, while the evidence is in places imperfect, it would appear that the formation of asbestosis bodies is not essential to the development of scar tissue in the lungs and that such reaction probably prevents mechanical trauma. Fibrosis precedes asbestosis body formation; it does not progress after the bodies have developed. Injection into susceptible animals of bodies preformed in a human lung has not produced fibrosis although the conditions of this experiment were not beyond criticism.

Industrial Exposures. Cannot be discussed in detail in this paper. However, there are a few points that will be considered for their bearing on the pathogenesis of disease. It would appear that asbestosis is due solely to the fibrous components of the dust in industrial plants and that any particulate matter or finely broken fiber plays little part causing pulmonary reaction. The total dust counts reported from asbestos plants in various parts of the country are usually quite low, even where the amount of visible dust in the air seems to be excessive. When one attempts to determine how much of the dust from the air is fibrous in nature, the proportions are extremely small. These results would lead

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one to suspect that either the quantity of inhaled fiber necessary to cause disease is very small or that our methods of dust collection are faulty. Studies now in progress suggest that the electrostic precipitator may be a more suitable instrument for collecting samples of air-borne fibrous dusts than the standard impinger that is used so widely for particulate matter.

A most surprising variation in incidence of asbestosis occurs between the fabricating plants of this country and the mines and mills where chrysotile asbestos is produced in Quebec. In the latter, the atmospheres are generally very dusty and yet not enough asbestosis develops to be diagnosed upon x-ray examination. Men who have worked over thirty years in the plants present films characterized by non-specific linear exaggeration with none of the diffuse changes accepted as pathognomonic of asbestosis in other parts of the world. In four autopsy specimens that I have obtained from Quebec mill employees with a lifetime of exposure, there were microscopic lesions of asbestosis but the disease had not progressed sufficiently to be recognizable on gross examination. It is temporarily assumed that much of the dust in the air of these plants is made up of particulate matter for all the machinery is designed to collect and save the fiber, but reject the particles. Studies are now in progress to compare the relative numbers of fibers and particles in air-borne dust from these Canadian plants with those of fabricating mills in this country. This study should be of great assistance in determining whether the observations upon animals will be verified in man.

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Pathology. The reaction to asbestos minerals like all others varies with the condition of the lung into which it is inhaled. If the organ is free from infection, either recent or healed, the effects of the dust will be different from that where other influences complicate the picture.

In an otherwise normal lung the inhaled fibers come to rest in terminal bronchioles widely and quite uniformly scattered throughout all parts of the organ. Caught in the walls, these stiff sharp fibers scratch the surfaces of the small tubes as they change shape and length with inhalation and exhalation. Fibrosis results from this irritation, the walls of the bronchioles become less elastic and smooth in contour as the lateral alveoli are obliterated. As more fibers are inhaled, they are carried out further along the bronchioles with the same effect. Finally, they come to be deposited in terminal alveoli and these in turn are obliterated.

The gross picutre of the asbestotic lung almost invariably presents adhesive fibrous pleurisy. The septa between the lobules are usually thick and fibrous and on section there may be gross areas of dense fibrous replacement especially common beneath the pleura. In such scar tissue emphysematous blebs are common and they vary in size from small smooth walled cavities a few millimeters in diameter to large bullae. Elsewhere the parenchma of the lung may appear normal except for grey foci of pigmentation usually located in the centers of the lobules. Most of the lung still seems to contain air and crepitation is felt on compression, although an impression of doughy-ness is obtained. The bronchial and tracheobronchial nodes are pigmented, but normal in size and consistence.

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The microscope in the advanced case reveals a diffuse fibrosis with no particular pattern of distribution that obliterates most, but not all, of the air spaces in a given area of parenchyma. Included in it are islets of apparently normal alveoli and others that are widely dilated and lined by low cuboidal epithelium. Asbestosis bodies, both free and wholly or partially ingested by giant cells, are scattered everywhere, but are most numerous in the lumina of still patent air spaces. They are very rare or absent in the thickened pleura and interlobular septa. Only in the early case or as a result of a fortunate choice of sections can one find evidences of the initial fibrous sleeves about respiratory bronchial nodes. The lymph nodes are filled with phagocytes containing particulate matter, but asbestosis bodies are almost never found and then they are very short fragments. The other organs show no changes. Apparently, as in guinea pigs, the asbestosis body only develops readily within the lungs and they are so large that phagocytes do not transport them to the regional lymph nodes. Whether the coating never develops about fibers that penetrate the pleura and septa, or whether the coating subsequently dissolves in these locations, is not clear. One suspects, however, that conditions are not right for their formation outside the lungs.

The X-ray Pattern of uncomplicated early asbestosis is surprisingly insignificant. The lower third of each lung field has a diffuse haziness which tends to obliterate the normal linear pattern. As the disease progresses, the haze increases in intensity and assumes the so-called "ground glass" appearance. It also creeps upward toward the apices, but usually does not involve the supraclavicular regions. In very advanced cases the outline of the heart is obscured by the development of heavy

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radiating bandlike shadows that are apparently the result of pleuro-pericardial adhesions. This is the so-called "porcupine heart." The mediastinal shadows are not unusual.

Asbestosis and Pulmonary Infection.

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