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# MINERAL CONTENT OF THE LUNGS AFTER EXPOSURE TO ASBESTOS DUST

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THE PATHOLOGICAL changes in the lungs of those who have been exposed to asbestos dust have been studied by many observers, but no information is available on the relation of these changes to the mineral content of the lungs. Four years ago we began to collect lungs from workers who had been employed in the asbestos textile industry to determine this relationship. The number of specimens collected was 27. As it seemed unlikely that this number would be increased materially within the next few years, it was decided to analyze the results obtained so far.

The studies which we have made have been modeled on the classical work of King and Nagelschmidt [1] (1945) which was carried out on the lungs from workers in the South Wales coal field. Our problem was in many ways simpler than theirs, for, while they had to consider several minerals as possible pathogenic agents, only one mineral (asbestos) was likely to be present in quantity in the lungs of asbestos workers. In their study different occupations had different mineral hazards, but in the asbestos textile industry the mineral constituent of the inhaled dust was the same in all occupations within the industry. The identification of the mineral constituents of the ash obtained from the incineration of the lungs forms the subject of another paper.

## MATERIAL

The workers from whom the lungs were obtained included both men (21) and women (6). The ages at death ranged from 31 to 74 years. The age distribution at death was as follows:

| Over 64 Years | 55-64 Years | 45-54 Years | Less than 45 Years |
|---|---|---|---|
| 4 | 10 | 9 | 4 |

The occupation of each worker was known, and details of the duration of exposure to asbestos dust and the interval between the last exposure and death were available to us. The lung material was placed at our disposal by the pathologists who had carried out the autopsies. They also provided us with reports on the microscopical appearances of the lungs from which it was possible to estimate the degree of pathological change which was present in those cases with asbestosis.

Some of the material was fragmentary, but complete lungs or whole lobes were available in most specimens. The mineral content was determined on "apparently healthy lung tissue" (Gloyne[2]). Where possible, samples of the lung parenchyma were taken from all lobes as thin slices to provide a complete section through each lobe. Hilar tissue and tissue from the pleural and subpleural regions were removed from these slices. The strips were dried to constant weight and then powdered. After incineration at 380 C. the ash was treated with dilute hydrochloric acid and then washed with distilled water by centrifuging. This technique has been described in detail by King and Nagelschmidt.[1] The weight of the incombustible and acid-insoluble residue was expressed as milligrams per gram of dried lung tissue. Samples were also

taken from the hilar region and also from the pleural and subpleural tissue when this was markedly thickened. These specimens were incinerated separately and their mineral content determined in the same way as that of the parenchyma.

The pathological reports indicated the degree of asbestosis present, and this degree was assessed on the character and extent of the fibrosis. Three degrees of asbestosis were recognized: minimal or slight (+); moderate (++), and severe (+++). Where no asbestosis was present, this has been indicated in the appropriate Table with a minus sign.

The cause of death was not necessarily related to asbestosis or other pulmonary lesions. For example, in the 27 cases there were five deaths due to coronary occlusion, one to cerebral hemorrhage, two to nonpulmonary carcinoma, and one to an ascending renal infection. There were three deaths due to cardiac failure in cases in which no asbestotic change was present and four deaths from the same cause in cases with only minimal asbestosis.

*Mineral Content of Lung Tissue—Incombustible and Acid-Insoluble Ash*

| Case No. | Sex | Exposure Time, Yr. | | Survival Time, Yr. | Mean Mineral Content, Mg./Gm. Dried Lung | | | Asbestosis |
|---|---|---|---|---|---|---|---|---|
| | | Total | Before 1932 | | Lung | Hilus | Pleura | |
| 3 | M | 26 | 6 | 0 | 6.9 | 7.5 | — | ++ |
| 23 | M | 28 | 5 | 0 | 5.8 | 6.3 | — | + |
| 26 | M | 20 | 0 | 0 | 3.5 | 5.9 | — | + |
| 17 | M | 12 | 0 | 0 | 3.7 | 6.5 | 2.6 | — |
| 9 | M | 11 | 0 | 0 | 3.0 | 5.4 | 1.8 | ..... |
| 25 | M | 8 | 0 | 0 | 3.2 | 4.1 | 3.9 | — |
| 12 | F | 32 | 12 | 1 | 6.7 | 4.9 | — | — |
| 2 | M | 27 | 10 | 2 | 5.9 | 7.7 | 7.9 | +++ |
| 5 | M | 28 | 10 | 2 | 5.8 | — | — | + |
| 21 | F | 33 | 13 | 2 | 7.9 | 8.2 | — | — |
| 4 | F | 14 | 0 | 2 | 2.9 | 7.1 | 2.1 | + |
| 19 | F | 8 | 0 | 2 | 2.4 | 7.5 | 3.7 | + |
| 6 | M | 22 | 5 | 3 | 5.8 | 9.1 | 8.6 | — |
| 10 | M | 9 | 0 | 3 | 2.7 | 8.7 | — | + |
| 14 | M | 27 | 11 | 4 | 6.7 | 8.8 | 7.4 | + |
| 22 | M | 7 | 0 | 6 | 2.2 | 6.6 | 4.1 | — |
| 1 | M | 23 | 11 | 7 | 5.2 | 8.2 | 6.9 | +++ |
| 27 | M | 21 | 8 | 8 | 4.5 | 6.1 | — | +++ |
| 20 | M | 25 | 11 | 8 | 6.2 | 7.1 | 7.2 | +++ |
| 8 | F | 27 | 15 | 8 | 5.5 | 8.4 | 6.8 | +++ |
| 13 | M | 27 | 14 | 8 | 5.3 | 6.3 | — | + |
| 7 | F | 6 | 0 | 9 | 1.5 | 8.2 | 3.9 | + |
| 28 | M | 5 | 0 | 11 | 1.1 | — | — | — |
| 11 | M | 22 | 15 | 14 | 3.1 | 5.5 | 4.7 | +++ |
| 24 | M | 19 | 12 | 14 | 3.4 | — | — | +++ |
| 15 | M | 14 | 1 | 17 | 3.4 | 6.2 | — | — |
| 16 | M | 10 | 9 | 21 | 2.1 | 7.6 | 5.6 | + |

## DUST HAZARD

In the early days of the asbestos-textile industry the atmosphere in the working areas was exceedingly dusty. By 1932 measures to reduce dust concentration in these areas became effective, and since then there has been a continuous improvement. Of the 27 cases in this series, 17 had been exposed to pre-1932 conditions. This exposure amounted to 168 man-years out of a total exposure time of 411 man-years. The pre-1932 exposure is given in each of the cases shown in the Table.

## RESULTS

The relevant data for each case have been summarized in the Table. As a matter of convenience, the cases have been arranged in order of increasing survival time, which is defined as the time interval between the last exposure to dust and death.

Exposure time and survival time have been given to the nearest year. When the survival time is shown as zero years, the interval between last exposure and death was less than six months.

*Rate of Accumulation of Mineral Material in the Lungs.*—The rate at which mineral matter accumulates in the lungs is the resultant of the rate at which the material is inhaled and held in the lungs and the rate at which such material is removed. Some indication of the mean rate of accumulation may be obtained from the six cases that died within six months of the last exposure to dust. This mean rate was 0.25 mg. per gram of dried lung per year (S. D. ± 0.08, S. E. ± 0.03). It is permissible to regard these cases as a homogeneous group, for, although two cases had been exposed to pre-1932 conditions, this exposure amounted to only 11 man-years out of a total exposure time of 54 man-years. The high standard deviation of the group indicates a very variable rate of accumulation. Assuming that the rate of removal of mineral material from the lung (after exposure to dust had ceased) is slow relatively to the rate of accumulation during dust exposure, then the mean rate of accumulation, calculated from 14 cases that died within three years after the last exposure to asbestos dust, might be expected to approximate that calculated from the six cases with six months or less exposure time. The mean rate was found to be 0.24 mg. per gram of dried lung per year (S. D. ± 0.06, S. E. ± 0.02). Again it is clear that the rate of accumulation of mineral matter is very variable. It should be pointed out that this group of 14 cases had a total survival time of 17 man-years, in contrast to a total exposure time of 278 man-years.

*Rate of Removal of Mineral Matter from the Lungs.*—Although it would appear from an inspection of the data in the Table that mineral matter disappeared from the lungs as the survival time increased, it is not possible to obtain a reliable estimate of the rate at which mineral matter is removed from the lung. An approximation, however, may be obtained by calculating the expected content of the lung in cases that survived from more than 10 years after the last exposure to asbestos dust, using the mean value calculated above for the rate of accumulation and then subtracting from this the mineral matter found. The difference expressed as milligrams per gram of dried lung per year would thus be an approximation to the mean rate of removal. This value was found to be 0.04 mg. per gram of dried lung per year. Beyond indicating that the rate of removal of mineral matter is slow relative to the rate of accumulation, this figure has little value.

*Mineral Matter in the Hilar and Pleural Regions.*—As the hilar region of the lung contains large masses of lymphoid tissue into which drain lymphatics from the lung parenchyma, it may be presumed that if mineral matter migrates out of the lung parenchyma it would tend to accumulate in this tissue. Calculating the mean rate of accumulation of mineral matter in the hilar region from the six cases that survived for less than six months after the last exposure to asbestos dust, this value was found to be 0.34 mg. per gram of dried lung per year (S. D. ± 0.15, S. E. ± 0.06). Even when this rate is calculated from the 13 cases that survived for three years or less and whose hilar regions were studied, the mean value is the same but the standard deviation is ± 0.2, with a standard error of 0.06. It is clear that the rate of accumulation of mineral matter within the hilar tissue, while not significantly different from the rate at which the mineral matter accumulates within the lung parenchyma, is very variable and the mean value is only about 40% higher

than the mean rate of accumulation within the lung parenchyma. It would thus appear that the mineral material removed from the lung can pass through the hilar lymphatic tissue or that an alternative route of removal exists or that the mineral matter is dissolved in the lung parenchyma as Gloyne [2] suggested. The discovery by Stewart and associates [3] that asbestosis bodies may be present in the spleen is presumptive evidence that such bodies or asbestos particles reach the blood stream either from the lung or from the intestinal canal. It would appear more probable that asbestosis bodies in the spleen are of pulmonary origin, presumably reaching there as asbestos particles.

The alternative route of lymphatic drainage from the lung through channels which reach the pleural surface and eventually enter extrapulmonary lymph nodes would appear to be of some importance, as it has been shown in the Table that the pleural and subpleural tissues contain high concentrations of mineral material. It is unlikely that this route becomes important until drainage through the hilar lymphatic tissue is obstructed, presumably by fibrotic changes consequent on the presence there of fibrogenic matter.

While solution of the asbestos fiber in situ within the lung parenchyma is a possibility, our data supply no evidence either in support of or against this method of removal of mineral material. Transportation of asbestos fibers and asbestosis bodies by macrophages has been observed frequently (Gloyne [4]), and it would appear that this method of removing mineral material from the lung parenchyma is probably the usual one. Gloyne,[2] as the result of his long experience with the pathological appearances of the lungs in asbestosis, was of the opinion that asbestos was removed from the lungs. He stated that in "long-standing" cases there was less asbestos and fewer asbestosis bodies present than in the lungs of workers more recently exposed to asbestos. Moreover, because the size of the asbestos fibers and of the asbestosis bodies was less in the "long-standing" cases, he thought that in time the asbestos fibers were dissolved. It is not clear whether the "long-standing" cases were cases of long exposure with short survival times or cases of long survival times or both. The presumption is that his "long-standing cases" were those that had survived for a long time after the last exposure, as lungs from cases with a short survival time would have shown much raw asbestos material of all lengths (Beger [5]). The demonstration that mineral matter existed in large concentrations in the hilar and pleural regions in our series supports Gloyne's view that mineral matter leaves the lungs, but it leaves unsettled the question whether solution of the mineral may take place.

*Relation of Mineral Content to the Severity of Asbestosis.*—It has been suggested above that the amount of mineral matter in the lung parenchyma probably varies directly with the exposure time and inversely with the survival time. Although the rate of removal is probably low, it is a factor which must be taken into account. When the concentration of mineral matter in the lung parenchyma is compared with the degree of asbestosis found, there is no correlation between content and the severity of the pathological changes.

| Mineral Content, Mg./Gm. Dried Lung | | | |
|---|---|---|---|
| 3.8 (S. E. ± 0.82) | 4.1 (S. E. ± 0.54) | 6.9 | 4.8 (S. E. ± 0.45) |
| No Asbestosis | Minimal Asbestosis | Moderate Asbestosis | Severe Asbestosis |
| 8 cases | 11 cases | 1 case | 7 cases |

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4.8 (S. E. ± 0.45)
Severe
Asbestosis
7 cases



As there is no reason to assume that the effect of asbestos on the lung tissue ceases when the worker is withdrawn from exposure to dust, it would appear that a better correlation might exist between the combined exposure and survival times, on the one hand, and the pathological changes, on the other.

Mean Values for Combined Exposures and Survival Times, Yr.

| No Asbestosis | Minimal Asbestosis | Moderate Asbestosis | Severe Asbestosis |
|---|---|---|---|
| 20 (S. E. ± 3.9) | 23 (S. E. ± 2.6) | 26 | 32 (S. E. ± 1.1) |
| 8 cases | 11 cases | 1 case | 7 cases |

These figures indicate that there is no significant difference between the mean combined exposure and survival times in the groups which showed no asbestosis at death and those which showed minimal asbestosis changes. It may be significant that there was a small standard error in the seven cases with severe asbestosis, which had a mean combined exposure and survival time of 32 years.

It must be understood that the degree of asbestosis found in these cases may have existed for some time before death occurred. It cannot be concluded from these figures that when asbestosis occurs with a combined exposure and survival time of around 30 years such asbestosis must necessarily be of the severe type. On the other hand, it is remarkable that all the cases of severe asbestosis were found within 29 to 35 years after the first exposure to asbestos dust.

It may be noted here that, while there is a clear indication that in the cases of asbestosis in this series mineral content tended to decline with increasing survival time and an equally clear indication that the severity of the lesion was associated with a lengthening of the combined exposure and survival times and not with increasing mineral content, the experience of King and Nagelschmidt [1] in their study of the pneumoconiosis of coal miners was that the severity of the pathological lesions was in general related to the mineral content of the lungs (siliceous minerals).

## COMMENT

The small number of cases in this series makes it difficult to draw statistically valid conclusions. While it is true to say that severe asbestosis was not observed in persons surviving less than 29 years from the first exposure to asbestos dust, it is not true to say that those who survive for around 30 years from the first exposure to dust must necessarily develop severe asbestosis. The series contains cases that survived for this length of time and yet did not develop asbestosis or showed only slight pathological changes. Obviously there are differences in susceptibility to asbestos dust inhalation, such as King and Nagelschmidt found in coal mines. These observers were of the opinion that a long working life was compatible with a long survival time and suggested a positive correlation between these times. Our figures for asbestos workers do not indicate such a correlation. While we can agree in general that the amount of mineral material in the lungs declines with lengthening survival time, we have not found that with increasing length of exposure to asbestos there is a decline in mineral content. The reverse was found. The difference between the experience of King and Nagelschmidt and ours would seem to be explained by the relatively rapid clearance of siliceous material from the lungs which occurred in some cases of pneumoconiosis and the relatively slow rate of clearance which would appear to obtain in our cases. Moreover, susceptibility to asbestos is not a matter of being able to clear material from the lungs more rapidly in the least

susceptible cases and more slowly in the more susceptible cases. Our finding that asbestosis was noted at death only in the third decade after the first exposure and the severe form at the end of this decade or later suggests that the cause of the pathological findings may not lie in the mere presence of the raw asbestos fiber but rather in the breakdown of the asbestosis bodies formed around such fibers.

Experimental asbestosis as produced by the workers at Saranac Laboratory (Vorwald and associates [6]) appears within a very short time after the beginning of exposure to the dust concentrations used and is well established within two years after the first exposure. On withdrawal from the dusty conditions, the fibrotic changes do not progress but rather tend to regress. Gardner [7] suggested that the changes in experimental asbestosis were due to the local irritative properties of the flexible asbestos fiber. It is possible that such fibrotic changes may occur in man after relatively short exposures to asbestos dust and yet not produce any clinical symptoms. If this effect of the physical presence of the asbestos particle or fiber were the only cause of human asbestosis, it would be difficult to explain why the mean time for the development of pathologically recognizable minimal asbestosis was 23 years and that for the development of the severe type was 32 years. It appeared to us that a more probable explanation of the appearance of the fully developed human lesions was to be found in the consideration that products of disintegration of the asbestosis bodies were a relevant pathogenic factor. Disintegration of these bodies is a slow process and may take several decades. On this point, however, we have no precise information. Beger [5] has figured what appear to be successive stages in the disintegration of the asbestosis body.

The idea of Vorwald and associates [6] that only asbestos fibers within a certain size range are pathogenic cannot be dismissed as unimportant in the etiology of human asbestosis. The fibers in this size range are those which obtain lodgment in the distal air spaces of the lungs. It is conceivable that particles below the lower limit of the critical size range are removed soon after inhalation by macrophages and deposited elsewhere. Fibers above the critical size range may not reach the distal air spaces in sufficient numbers and so be removed mechanically along the airway. Those which remain in the lung parenchyma are almost certainly converted into asbestosis bodies, which appear to be inert as fibrogenic agents (Vorwald and associates [6]).

Our findings, therefore, lead us to the conclusion that in man the onset of asbestosis is not determined by the absolute amount of mineral material present in the lung parenchyma but is related to changes occurring in the inhaled material after a time interval from first exposure, which may be as long as 20 to 30 years. As a result of these changes, a fibrogenic agent is released which is capable of exerting its effect under favorable circumstances. The nature of this agent is unknown, and the environmental factors are not yet clarified.

## SUMMARY

The mineral content of the lung parenchyma, the lung hilar region, and the tissues of the pleural and subpleural regions of the lung has been determined in lungs from 27 workers in the asbestos-textile industry. The exposure time varied from 5 to 33 years, and the time interval between the last exposure to dust and death (survival time) was from less than 1 year to 21 years.

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... hilar region, and the ...as been determined in ... exposure time varied ...sure to dust and death

## ...ERAL CONTENT OF LUNGS AFTER ASBESTOS EXPOSURE

There was an indication that the mineral material found in the lungs increased ...amount as the exposure time lengthened. The amount so accumulated varied ...siderably from person to person. As the survival time increased, the mineral ...ent of the lung tended to decline but again at a very variable rate.

The severity of the asbestotic lesions in the lungs found at death was related ... to the mineral content but to the sum of the exposure and survival times.

The Directors of Turner Brothers Asbestos Company, Ltd., cooperated in this work and ... a grant toward the expenses of the study. Further assistance was rendered by pathologists ... personnel managers.

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