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DATE January 14, 1975

TO G. B. Meyers

C. C.

ASBESTOSIS

The attached is for your information in the event you have not already seen the article.

H. A. Sinclaire, M.D.

HAS:sm
Attach.

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C.C Dr. H. A. Sinclaire - New York

ASBESTOSIS

I am attaching a very interesting article that appeared in THE NEW ENGLAND MEDICAL JOURNAL this past week. The article casts some doubt on previously held opinions regarding asbestosis. One of the points that has been taken as fundamental in the pathology of asbestosis in the past has been that the size of the particles must be large enough to form a block in the smaller divisions of the pulmonary tree and by so doing, begin the pathophysiology of asbestosis. Unlike particles of silica that have been injurious because of their minute size, the opposite has been held to be true for asbestos, where particles greater than 5 microns in length were used to define an asbestos fiber and were also thought to be the size that was important in causing the clinical disease. Those fibers that were smaller than 5 microns were thought to be innocous because an efficient pulmonary toilet could cough these up and clear the lung of them. However, this article raises some doubts in this area and by the use of electron microscopy, it has now been shown that the lung does retain some microscopic particles of asbestos and some doubt is being raised that these are innocous. As the article points out, they may be incriminating in causing asbestosis. While the article makes some mention of sub-microscopic particles of silica in African gold miners, this is nothing really new as far as the knowledge of silica and the size of silica particles in the etiology of silicosis is concerned.

I would like you to read the article because I do believe it is timely and it does open up a new vista of thought and one that we should be following relative to the problem of particle size versus clinical disease when it comes to asbestosis.

Robert J. Potts, M. D.

RJP/t
Attachment

Susan
Pls. make a copy of article & sent to GBM. "For his information in case he hasn't seen." Then pls. circulate article only to N.Y. M.D's + R.N's.
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tubular necrosis have a high prevalence of potentially fatal infectious complications. Consequently, stringent precautions must be employed to minimize this risk. Foley catheters, central-venous-pressure lines and other indwelling devices should be used with extreme caution and only when there is a commanding indication.

Prognosis

In the 1940's, the mortality rate in unselected patients with acute tubular necrosis was as high as 90 per cent. The introduction of antibiotics, the recognition that salt and water restriction was essential, the availability of effective treatment of hyperkalemia and the development of effective dialysis procedures resulted in a dramatic decline in mortality to approximately 50 per cent by the early 1960's. Surprisingly little improvement in the crude mortality rate has occurred subsequently. It is clear that, at present, death during an episode of acute tubular necrosis is usually due, not to the absence of renal excretory function per se, but rather to complications of the underlying disease. Further improvement in mortality rate appears likely to occur only with improved ability to prevent, or to reverse more promptly, the conditions in which acute tubular necrosis is now such a frequent and ominous complication.

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"NONSPECIFIC" INTERSTITIAL PULMONARY FIBROSIS

Association with Asbestos Fibers Detected by Electron Microscopy

ALBERT MILLER, M.D.,
ARTHUR M. LANGER, PH.D.,
ALVIN S. TEIRSTEIN, M.D.,
AND IRVING J. SELIKOFF, M.D.

ELECTRON microscopy has only recently been applied to "idiopathic" interstitial pulmonary reactions. In 1971, we described a patient with interstitial granulomas and fibrosis indistinguishable from sarcoidosis.[1] A history of occupational exposure impelled electron microscopy and x-ray diffraction studies, which revealed talc crystals in his lungs. For the patient described below, we examined lung tissue that had shown severe interstitial fibrosis, with no evidence of mineral particles, on light microscopy. Although the patient had had no exposure to known pathogenic dusts, electron microscopy demonstrated ubiquitous fibrils of chrysotile asbestos, averaging 27.5 nm (275Å) in width and less than 100 nm (1000Å, or 0.1 μm) in length — well below the resolution of a light optical system.

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Dr. Langer is the recipient of a career award (ES44812), and Drs. Langer and Selikoff recipients of a University Center grant (ES00928) from the National Institute of Environmental Health Sciences, National Institutes of Health, and Dr. Miller the recipient of a grant from the Jack Martin Fund.

Case Report

A 63-year-old man was admitted to the Mount Sinai Hospital, New York City, on March 30, 1971, because of breathlessness of six years' duration. Clubbing had been present since 1958. He was a clerk in the civil service; his hobby had been refinishing wood furniture. Physical examination revealed tachypnea, cyanosis, clubbing, fine rales, and signs of right ventricular failure. The hemoglobin was 19.2 g per 100 ml, and the hematocrit 57 per cent. One of two antinuclear-antibody determinations was positive, but lupus preparations, latex fixation, Venereal Disease Research Laboratory test and serum electrophoresis were within normal limits.

A roentgenogram of the chest showed moderate enlargement of the heart, preserved lung volume and diffuse honeycombing. Lung volumes, air flow and maximum voluntary ventilation were normal, severe hypoxemia and compensated respiratory alkalosis were present. The wedge pressure was 10 mm Hg, pulmonary-artery pressure 75/35 mm Hg, with a mean of 50 mm Hg, right ventricular pressure 70/8 mm Hg, and mean right atrial pressure 7 mm Hg, with a prominent A wave. There was no evidence of intracardiac shunt by angiocardiography. The patient died of respiratory failure two months after admission.

Lung tissue obtained at open biopsy of the right middle lobe was examined by light microscopy. No mineral particles or asbestos bodies were observed. The alveoli were filled with iron-containing macrophages that lined up along the thickened septa and were seen within the septa as well. In some areas, macrophages, lymphocytes and fibroblasts obliterated the alveoli. The histologic diagnosis was "interstitial inflammation and fibrosis."

The lung tissue was cut into 5-μm sections and prepared by carbon extraction for electron microscopy.[2] At magnifications beyond 10,000 times, numerous small fibers were seen. At 20,000 to 31,000 times, these were identified by their morphology as chrysotile fibers that filled all fields of view (Fig. 1). Most striking were the large number of particles, their uniformity and their minute size.

Particles were measured and counted in three 6-μm^2 areas. Two thirds (238 of 361) were fibers and fibrils of chrysotile asbestos, and 95 per cent (226) of these were fibrils. Only 88 (37 per cent) of the 238 fibers and fibrils were longer than 100 nm (1000Å, or 0.1 μm), averaging 145 nm (1450Å) in length and 27.5

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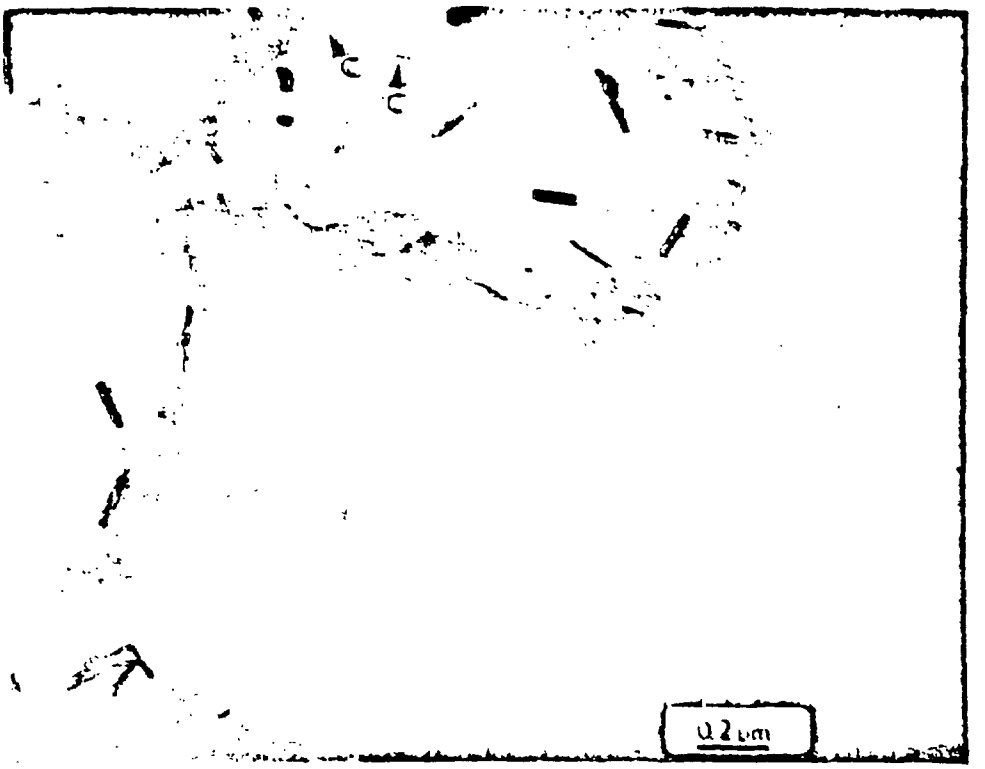

Figure 1. Transmission Electron Micrograph of Carbon-Extracted Lung Tissue.
Fibrous particles are clearly visible; fibrils marked C (arrows) show the characteristic capillary of chrysotile. Histologic structures are outlined as electron-dense relict tissues.

nm (275 Å) in width. All were considerably below 500 nm (0.5 µm or 5000 Å) in greatest dimension. Mean length of the smaller fibrils was 70 nm (700 Å), and mean width was again 27.5 nm (275 Å). Some fibrils were as small as 25 nm (250 Å) long and 5 nm (50 Å) wide. For comparison, amosite asbestos fibers in the lungs of exposed workers average 350 nm (0.35 µm, or 3500 Å) in width,[3] which is several times the length of the present fibrils. The 123 other particles averaged 80 nm (800 Å) in greatest dimension. They were mainly chrysotile fragments, some were clay or talc.

The asbestos content of the patient's lungs was calculated to be a minimum of 0.45 g. This amount, finely divided, may have a surface area of more than 30 m².

Discussion

Several questions are raised by this patient's illness. The vital capacity was 109 per cent of the predicted value, and the total lung capacity 97 per cent. Normal lung volumes are unusual in pulmonary fibrosis, especially when long standing clubbing and cor pulmonale are present. Reduction in vital capacity is a reliable indicator of pulmonary fibrosis in asbestosis and precedes roentgenographic and clinical evidence of disease.[4]

The source of dust was not identified. The minimum content of 0.45 g of chrysotile in the patient's lungs is consistent with a low-level occupational exposure.[5]

The small size of the fibrils may have resulted from their fragmentation before they were inhaled or from their degradation in vivo.[6,7] The fibrils were different from "mineralogic specimens", their central capillaries were discontinuous, their walls thin, and their ends irregular. In biologic environments chrysotile fibers are chemically unstable. Magnesium is lost from the surface, exposing the silica layer to chemical reaction.

Most investigations of the relation between the size of respirable mineral particles and the frequency and severity of pulmonary disease have been based on light microscopy, thus overlooking the role of submicroscopical particles. However, electron microscopy has shown that up to 97 per cent of the particles in the lungs of South African gold miners with severe silicosis were less than 200 nm (0.2 µm) in diameter,[8] and silica fume particles, with an average size of 20 nm (0.02 µm), have produced silicosis in animals.[9] As particles range down in size to 200 nm (0.2 µm) and below, alveolar retention and tissue reactivity both increase.[8,10]

Evidence for the pathogenicity of submicroscopical asbestos fibers comes from experimental instillation into animal lungs.[11] Uncoated, small fibers were observed in lungs long after experimental inhalation and caused progressive tissue alterations. Examinations at our laboratory, and in Great Britain, have demonstrated submicroscopical particles in the lungs of workers exposed to asbestos fibers.[12-14]

Because it is readily demonstrated by light microscopy, the diagnostic importance of the "asbestos body" has been exaggerated. In human disease, tissue fibrosis is not related to the number of asbestos bodies. As in experimental asbestosis, it is likely that the smallest, uncoated fibers are the most fibrogenic.[14] They may be present without asbestos bodies or other evidence of asbestosis.

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scopy. This characteristic is especially true of chrysotile, the most common form of asbestos used in the United States, which tends to fragment in tissue.

The submicroscopical chrysotile fibers found in the lungs of 80% of the populations of New York City and London[9,13] are much less numerous than those in our patient. A recent investigation at this laboratory showed only occasional fibers after carbon extraction, as compared with the ubiquitous fibrils in our patient. Total asbestos content in the "normal" lungs was in the range of 0.1 μg to 0.5 mg — three to four orders of magnitude less.

The case reported above documents the association of submicroscopical chrysotile fibrils with severe pulmonary fibrosis, in the absence of fibers demonstrable by light microscopy. Together with the case of talc pneumoconiosis previously reported,[1] this case raises a question concerning the diagnosis of "idiopathic" interstitial fibrosis. Gaensler, Carrington and Coutu have stated that cases "may be erroneously classified [as idiopathic] if dust particles are overlooked."[15] We suggest that lung tissue showing alterations diagnosed as "usual interstitial pneumonia," "fibrosing alveolitis" or "idiopathic pulmonary fibrosis" be examined by electron microscopy. It is likely that other cases will prove to be pneumoconioses by yielding evidence of mineral dusts.

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NOTES OF A BIOLOGY-WATCHER

The Deacon's Masterpiece

LEWIS THOMAS, M.D.

THE brightest and most optimistic of my presentiments about the future of human health always seems to arouse a curious mixture of resentment and dismay among some very intelligent listeners. It is as though I'd said something bad about the future. Actually, all I claim, partly on faith and partly from spotty but unmistakable bits of evidence out of the past century of biomedical science, is that mankind will someday be able to think his way around the finite list of major diseases that now close off life prematurely or cause prolonged incapacitation and pain. In short, we will someday be a disease-free species.

Except for gaining a precise insight into the nature of human consciousness (which may elude us for a very long time, perhaps forever, because of a variant of the indeterminacy principle, which may cause it to blur and twitch away, or even explode, when we succeed in focusing on it closely enough), I cannot imagine any other limits to the profundity of our understanding of living things. It may happen within the next few centuries, maybe longer, but when it does it will bring along, inevitably, the most detailed sorts of explanations for human disease mechanisms. It is an article of faith with me that we will then know how to intervene directly, to turn them around or prevent them.

Something like this has already happened for most of the major infections. Even though we are still in a primitive, earliest stage in the emergence of biology, as compared, say, to physics, we have accomplished enough basic science to permit the development of specific antimicrobial antiserums, and an impressive list of safe, rational viral vaccines. Within 50 years after the recognition of bacteria as pathogens we had classified them and learned enough of their metabolic intricacies so that the field was ready for antibiotics. In the years since the late 1940's the first great revolution in technology in all the long history of medicine has occurred, and infectious diseases that used to devastate whole families have now been almost forgotten.

Events moved rapidly in the field of infection, and this may have represented abnormally good luck. For some of the others — heart disease, cancer, stroke, the senile psychoses, diabetes, schizophrenia, emphysema, hypertension, arthritis, tropical parasitism and the like — we may be in for a longer, more difficult pull, but maybe not. With the pace of research having increased so rapidly in the last two decades, and the remarkable new young brains enlisted for the work of biology, we could be in for surprises at almost any time. Anyway, sooner or later, they will all become non-mysteries, accountable and controllable.

These prospects seem to me exciting and heartening,

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