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Clinica del Lavoro « L. Devoto » of the University of Milan

ENRICO C. VIGLIANI

Professor and Chairman

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ENRICO C. VIGLIANI
Professor and Chairman

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The problem of the cause of the fibrogenic response to the inhalation of asbestos dust can be dealt with by considering the following three questions:

— What is fibrogenic?
— How is it fibrogenic?
— Why is it fibrogenic?

Let us start with the first question:

WHAT IS FIBROGENIC?

This question can be sub-divided into five parts:

1) Importance of fibre length;
2) Importance of the ultramicroscopic fibres;
3) Importance of the non-fibrous asbestos dust particles;
4) Importance of asbestos bodies in fibrogenesis;
5) Fibrogenic response to different types of asbestos.

1) *Importance of fibre length*: Whether short asbestos fibres are as fibrogenic as the long ones has been debated since 1937. GARDNER exposed guinea pigs to the inhalation of asbestos fibres ground in a steel ball mill until pratically none more than 3 microns in length were left. The response to 4 times the concentration of a much finer dust was less pronounced than that obtained with the long fibres. He concluded that the long fibres were more fibrogenic than the short ones. KING et al. (1951) saw that long fibres produced interstitial and focal fibrosis with alveolar collapse; the short fibres produced only slight peribronchial fibrosis. In 1951 VORWALD, DURKAN and PRATT, working with chrysotile, showed that only fibres longer than 3 microns were fibrogenic. This statement was considered for a long time as the basis for the mechanical theory of the pathogenesis of asbestosis. However, HOLT, MILLS and YOUNG observed a widespread fibrosis in the lungs of animals treated with a very finely divided dust and concluded that

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very small dust particles are at least as lethal as the long fibres. According to KLOSTERKÖTTER, long fibres are more fibrogenic for a given mass than short ones (1965, personal communication to GILSON). WEBSTER (1965) exposed laboratory animals to crocidolite, amosite and chrysotile in order to determine whether fibres or small particles of asbestos dust, or both, are fibrogenic: the long fibres produced fibrosis, whereas the small particles remained in the alveolar macrophages.

TABLE I - *Importance of fibre length.*

GARDNER (1937)	Long fibres are more fibrogenic.
Mac LEAN & KING (1951)	Long fibres → moderate interstitial and patchy fibrosis. Short fibres → slight peribronchial fibrosis.
VORWALD et al. (1951)	Only fibres > 3 μ are fibrogenic.
HOLT et al. (1965)	Short fibres are as lethal as long ones.
KLOSTERKÖTTER (1965)	Long fibres are more fibrogenic.
WEBSTER (1965)	Long fibres are fibrogenic; small particles remain in macrophages.

We must conclude that the question of the importance of particle length on the development of fibrosis is still not solved. As GILSON pointed out (1966), we need experiments of the type KING and NAGELSCHMIDT developed to study the effect of mass, surface area and number in experimental silicosis.

2) *Importance of the ultramicroscopic fibres*: As KÜHN had already observed in 1941, and as HOLT and DAVIS have recently shown, the lungs of workers and animals with asbestosis contain a very large number of very minute fibres which are not visible with the optical microscope but which are visible with the electron microscope. The ultramicroscopic fibres are scattered thoughout the lung and seem to be much more numerous than the visible ones. What is the relevance of these invisible fibres? Are they as fibrogenic as the visible ones? This is yet an unanswered problem, the relevance of which should be considered also in relation to the prevention of asbestosis.

3) *Importance of non-fibrous asbestos dust particles*: Asbestos dust is composed of fibres and non-fibrous particles made of serpentine, iron compounds and other minerals. Are these non-fibrous particles totally harmless? The Russian KOGAN (1966) found serpentine dust fibrogenic, though to a lesser extent than chrysotile fibres, and concluded that the fibrogenic reaction to asbestos is due more to its topo-chemical composition than to its mechanical properties. WEBSTER pointed out that asbestosis is similar to the type of fibrosis found in nepheline workers (BARRIER and GOSSELIN). As nepheline is a feldspar albite with nepheline syenite and is made of sodium, potassium and aluminium silicate, in his view asbestosis should be considered as a kind of silicatosis. However, the case published by BARRIER and GOSSELIN seems different from asbestosis insofar as the almost inert dust of nepheline rock produced negligible structural lesions, besides a lymphatic block; the progressive massive fibrosis of that case being probably due to a superimposed infection. The prevalent belief is that fibres are by far more fibrogenic than non-fibrous asbestos particles.

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4) *Importance of asbestos bodies in fibrogenesis*: The formation of asbestos bodies is considered by some as a defence mechanism of the organism against the irritating and inflammatory properties of asbestos fibres. Others have advanced the opposite view, namely that the disintegrating asbestos bodies constitute the fibrogenic stimulus. In dealing with this problem, one has to consider that collagen fibre formation precedes the appearance of asbestos bodies and that fibrosis occurs also in animals which do not produce asbestos bodies and in sites where asbestos bodies are not formed as, for instance, in asbestos warts. It must, however, be considered that if asbestos bodies do actually disintegrate, the disintegration products being phagocytized might exert an additional fibrogenic stimulus.

5) *Fibrogenic response to different types of asbestos*: The experience gained by half a century of clinical and pathological observation of human asbestosis seems to indicate that all types of asbestos are fibrogenic if inhaled in sufficient concentrations over a long period of time. However, it is felt by many that some types of asbestos and especially some amphiboles are more fibrogenic than chrysotile. WAGNER and his colleagues [1] (1965) and MORRIS et al. [2] (1966) observed that chrysotile produces less fibrosis than amosite or crocidolite for the same dose on inhalation. They refer this to the much more rapid elimination of chrysotile. Contrary to this, in the past the hypothesis was put forward that chrysotile was more fibrogenic than other asbestos types because, being more soluble in body fluids, it can release more silicic acid. This hypothesis derived from a statement by SUNDIUS and BYGDEN, who saw only amosite and no chrysotile in the lungs of asbestos workers. Then the idea was advanced that chrysotile produced fibrosis through its dissolution and amphyboles produced the asbestos bodies.

Experiments reported by HOLT at the New York meeting on asbestosis showed no difference in fibrogenic response to 4 types of asbestos tested in animals, i.e., chrysotile, crocidolite, amosite and anthophyllite. Some facts, however, indicate that there are differences in the cellular response to the different types of asbestos: for instance, the cytotoxicity for macrophages and the haemolytic activity varies considerably for the different types of asbestos, as PERNIS has pointed out; pleural plaques and calcification seem to be more frequent among people exposed to anthophyllite.

The question as to whether one type of asbestos is more fibrogenic than other types is still open and requires careful examination; it may even be possible that differences exist between different sources of the same type of asbestos, as SELIKOFF has pointed out.

HOW ASBESTOS IS FIBROGENIC

The possible pathways of the fibrogenic activity of asbestos are summarized in the following table:

Main fibrogenic pathways	— Direct stimulation of fibroblasts — Conversion of macrophages and giant cells into fibroblasts — Release of a fibrogenic factor from macrophages — Appearance of giant cells (and epithelioid cells?) and release of a fibrogenic factor from them

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Additional factors { — Chronic interstitial oedema and red cell diapedesis; — Infections; — Immunological reactions }

Main fibrogenic pathways

Direct stimulation of fibroblasts: From experiments made at the Clinica del Lavoro it has been shown that mouse L-strain fibroblasts cultivated « in vitro » take up crocidolite fibres actively: the dust particles and the short fibres are collected in cytoplasmic vacuoles. The amount of collagen produced after 8 days by the cell cultures plus asbestos and by the control cultures was calculated by measuring the hydroxyproline production per mg of the protein of the culture. It was seen that the amount of collagen produced by the fibroblasts plus asbestos was significantly higher than that produced by the fibroblasts alone. The conclusion was drawn that a direct effect of asbestos dust on the fibroblasts should be seriously considered. However, the above mentioned experiment was only a preliminary one and is open to criticism: it should be repeated with fibroblasts in the stationary phase with different asbestos types and also with other dust types, cytotoxic as well as inert.

Conversion of macrophages and giant cells into fibroblasts: This seems to be a very simple and attractive explanation for the fibrogenic action of asbestos. J. DAVIS has studied the ultrastructural changes occurring in the lung of experimental and human asbestosis and by maintaining fragments of lung in organ cultures for 8-10 days; he observed a cellular pattern strongly suggesting conversion of macrophages and giant cells into fibroblasts; the obvious conclusion was that asbestos dust causes fibrosis by direct fibrogenic action on macrophages. The problem of the cytogenesis of the fibroblasts in the inflammatory tissue belongs to the field of general histology and pathology and has been very nicely dealt with by COHN and by GOLDBERG, so I do not need to comment on it. I would only like to remind you of the view of BAIRATI, JACOBY and other histologists, who maintain that fully mature mammalian macrophages are post-mitotic forms bearing a definite function and a set of organelles and that it seems unlikely that they can convert into other cells whose function is completely different. CURRAN (1964), following the fibrogenic response to egg-white and agar implants in the peritoneal cavity of the rat, found that after 72 hours the macrophages fuse to form a syncytium, and the cells furthest from the implant elongate and become fibroblast-like. He points out that the fibroblasts are apparently derived from the round mononuclear cells already present by the end of the second day, since many transitional (ovoid) forms are seen. He concludes that macrophages and fibroblasts almost certainly arise from the large mononuclear cells and that some of them are relatively undifferentiated stem cells. BAIRATI thinks that the fibroblasts in asbestosis are more likely to derive from the multipotential, undifferentiated stem cells; but he admits that in the intermediate stage of differentiation from precursor cells into macrophages or into fibroblasts, it is often very difficult to decide whether a cell is going to become a fibroblast or a macrophage. Moreover, a young fibroblast can exhibit moderate phagocytic activity.

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Release of a fibrogenic factor from macrophages: It is a well established fact that in silicosis the fibroblastic activity is secondary to the phagocytosis of silica particles by macrophages and seems to be induced and controlled by the damage inflicted upon them. When phagocytized, asbestos particles do not behave like an inert foreign body. It has been shown « in vitro » and « in vivo » that they may be highly cytotoxic. They can kill the macrophage or alter it, as experiments being made at present in our Institute have

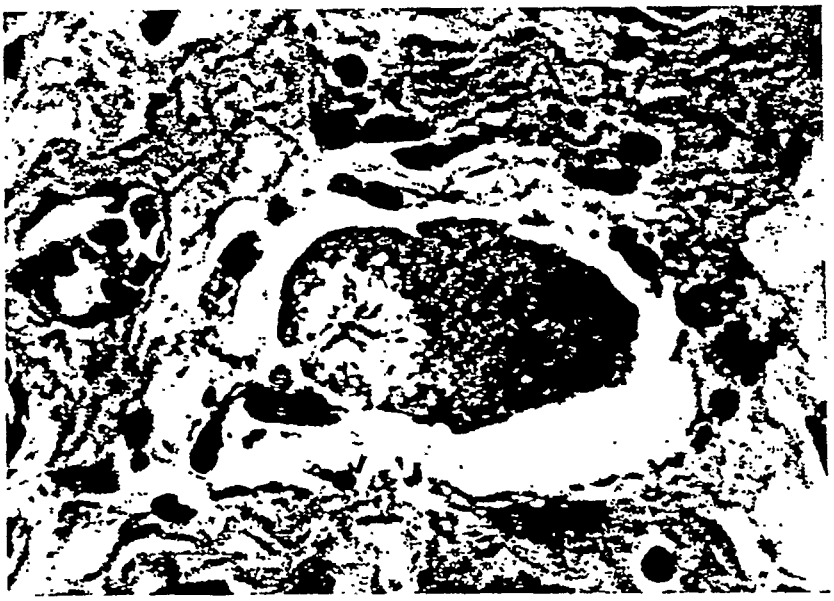

Fig. 1 - Human asbestos. Giant cell with asteroid body within an area of fibrosis. Near the cell, two small asbestos bodies are visible. (Magnification 650 ×).

shown, and the result of the death or damage can be the release of a fibrogenic factor similar to that found by HEPPLESTONE in the supernatant fluid of macrophage cultures treated with quartz. A proof that this factor is released also from the macrophages having ingested asbestos particles is, however, still lacking.

Conversion of macrophages into giant cells and possibly into epithelioid cells: Multinucleated, giant cells are a common finding in early as well as in advanced asbestosis. They are shown by DAVIS to be derived from macrophages having taken up asbestos particles. In granulomatous lesions such as sarcoidosis, berylliosis, tuberculosis, etc., giant cells are generally found surrounded by large, mononuclear cells called « epithelioid cells » and are considered to be derived from them. Although large mononuclear cells have been seen by several investigators in experimental as well as in human asbestosis, no mention of « epithelioid cells » has been made in this disease.

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BAIRATI studied with the electronmicroscope the effect on the rabbit popliteal lymph node of quartz dust or beryllium oxide or Freund's adjuvans injected into the footpad: after 7-15 days he observed epithelioid cells and multinucleated cells; as soon as regressive phenomena began to appear among phagocytic cells, fibroblasts and reticulin fibres became apparent and increased until the epithelioid node was fully replaced by fibrous tissue.

Epithelioid cells possess a strong polarity; part of the cytoplasm contains a well developed endoplasmic reticulum, and part contains lysosomes, vacuoles and Golgi zones; the cell membrane has many processes which are intimately intertwined with those of the adjacent cells. Fibroblasts and collagen fibrils are frequently seen close to epithelioid cells. These, and the multinucleated cells, are said to be no longer phagocytic, but often contain particles phagocytized at an early stage, as well as residual bodies.

In asbestosis, large mononuclear cells, multinucleated and giant cells (Fig. 1), and cells with remnants of phagocytosis and with well developed endoplasmic reticulum, are a common feature. It would be interesting to see whether cells which could be called epithelioid also occur, as they are invariably followed by the appearance of a fibrous tissue.

Summarizing this long discussion about the cytogenesis of fibroblasts in the asbestotic lesion, two main possibilities are offered: the first and less probable is that phagocytes convert directly into fibroblasts and start fibrogenesis; the second and more probable is that the differentiation of fibroblasts and their activity are controlled by macrophages or giant or epithelioid cells through some active substances released by them.

Additional fibrogenic factors

Oedema and congestion: A factor which may have some importance is represented by a condition of chronic oedema of the interstitial lung tissue secondary to the chronic inflammatory and irritating properties of asbestos dust. Experimental studies have shown that congestion with diapedesis of some erythrocytes and a slight oedema are among the first changes due to the inhalation of asbestos and that these changes can persist over a long period. The iron that accumulates very quickly in the macrophages can come either from disintegrated red cells or from the transferrin contained in the plasma exudate. HAYWARD and POKORNY et al. suggest that prolonged interstitial oedema and congestion can contribute to the onset and development of diffuse interstitial fibrosis of the lung; this can, perhaps, be taken into consideration as an additional fibrogenic factor in asbestosis.

Infections: The importance of infections should not be underestimated in asbestosis, although asbestosis does not predispose to tuberculosis as does silicosis. The patchy areas of fibrosis seen in advanced asbestosis might well be the result of a superimposed infection. Experimental evidence of the enhancing effect of bacterial endotoxin on collagen formation has been given by JACKSON: the rate of synthesis of collagen in implanted Ivalon sponges is greatly increased by the intraperitoneal injection of a single dose of a few microgrammes of bacterial endotoxin; the maximum collagen content is reached in 12 days, as compared to 20 days for the control animals.

Rôle of immunological factors: The rôle played by the immunological

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reaction in the development of the silicotic nodule is well established. A preliminary proof of the situation in asbestosis conducted with methods similar to those employed in silicosis led to negative results. In two cases of human asbestosis, where the lungs could be examined fairly soon after death, no gamma globulins were found in the fibrous tissue by the immunofluorescence technique and by the indirect complement fixation test. Nor has it been possible to induce in the plasma of rabbits rheumatoid-like factors by injecting intratracheally 200 mg of asbestos fibres, in contrast to the rapid appearance of these factors after injection of quartz (PERNIS, VIGLIANI et al.). It appears from these negative findings that asbestos dust does not possess the ability to adsorb and denature the rabbit's own gamma globulins in such a way as to render them autoantigenic. It seems, therefore, that within the limits of the work carried out so far, no clear-out evidence in favour of immunological reactions in the pathogenesis of asbestosis has been found. It should be pointed out, however, that the field of possible investigation has by no means been exhausted: for example, the possibility of hypersensitivity reactions of the delayed type remains to be investigated.

WHY ASBESTOS IS FIBROGENIC

The theories on the pathogenetic mechanism of asbestosis have been as numerous as those put forward to explain silicosis. It would be too long to tell the story of the development of the various theories and experiments on which they have been based. The best I can do is to try to summarize the various theories in a table and to comment on it very briefly.

TABLE 2 - *Theories on the pathogenesis of asbestosis.*

I Mechanical Theory
Irritation and microwounds produced by the fibres.
Implications: 1) Long fibres are more fibrogenic than short ones. 2) Phagocytosis protects the surrounding tissue. 3) Asbestosis is more severe in the more mobile parts of the lung. 4) Fibrogenesis is not caused by dissolution of the fibres. 5) Asbestos bodies are harmless.

The *mechanical theory* was strongly supported by GARDNER, SUNDIUS and BYGDEN, BEHRENS, VORWALD and KING. According to this theory, asbestos fibres penetrate everywhere in the lung tissue and mechanically irritate it. Microwounds can be inflicted on cells and capillary walls. Arguments in favour of a mechanical action of asbestos are mainly three:

1) Long fibres seem to be more fibrogenic than short fibres and non-fibrous dust particles;

2) Asbestosis develops in mobile organs and especially in the more mobile parts of the lung, where friction of the fibres against the tissue is more likely to occur;

3) Asbestosis can develop with very resistant types of fibres (crocidolite), and without the formation of asbestos bodies.

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The *solubility theory* derives from the solubility theory of silicosis. According to this theory, the asbestos fibres or the asbestos bodies dissolve in the tissue and a fibrogenic substance, generally considered to be silicic acid, is released. This theory was first advanced by STEWART Mc DONALD (1927) and then, with minor changes concerning the rôle of the asbestos bodies, developed by BEGER, KOPPENHÖFER, HOLT, BEATTIE, and more re-

TABLE 3 - *Theories on the pathogenesis of ashestosis.*

II Chemical Theory	
Asbestos fibres dissolve, liberating fibrogenic compounds (silicic acid).	
Variants:	*a*) Asbestos fibres dissolve. *b*) Asbestos bodies break down, releasing fibrogenic substances.
Implications:	1) Short fibres are as fibrogenic as long ones. 2) Inverse relationship between the amount of asbestos in the lung and the severity of the fibrosis. 3) The more soluble the asbestos, the more fibrogenic. 4) Asbestos bodies can be fibrogenic.

cently by NAGELSCHMIDT (1965). This theory is founded on the following points:

1) The relative solubility of chrysotile in the body fluids;

2) Pattern of asbestos bodies suggesting their breakdown:

3) There is no difference in fibrogenicity between long and short fibres (HOLT, 1964);

4) Very little asbestos has been found in the lung in severe cases of asbestosis, as compared with the amount of asbestos found in cases of moderate or slight asbestosis, or even in cases of exposure to asbestos without asbestosis (NAGELSCHMIDT, 1965).

Should the solubility theory be valid, then fibrosis is due to what has disappeared from the lung: dissolved silicic acid should be fibrogenic; chrysotile should be more fibrogenic than any other asbestos type, a finding which is not supported by human or experimental evidence. BEATTIE, who defended this theory in 1961, does not seem now to be so enthusiastic and he doubts whether an asbestos fibre really breaks up in the lung, releasing fibrogenic silica.

The « *surface theory* » derives either from the new findings on the cytotoxic action of quartz, or from the experience gained from implants of inert matter in the peritoneal or subcutaneous tissue. According to this theory, the surface of asbestos possesses some special feature which renders it cytotoxic to macrophages or capable of inducing an inflammatory state.

The first possibility is that asbestos acts like quartz in being cytotoxic for macrophages. The toxicity may not be as strong as that of quartz, but nevertheless could be such as to inflict an irreversible change in the macrophages with the release of a fibrogenic factor similar to that released by macrophages treated with quartz (HEPPLESTONE).

The second possibility is that asbestos may act in the same way as implants of an inert foreign material. OPPENHEIMER and many others have shown that implants of inert material such as plastic films and metal discs.

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TABLE 4 - *Theories on the pathogenesis of asbestosis.*

III Surface Theory
The surface and shape of asbestos is such as to make it fibrogenic.
1st Variant: Asbestos surface is cytotoxic for macrophages.
Implications: 1) Phagocytosis is necessary. 2) The more asbestos is cytotoxic, the more it is fibrogenic. 3) Release of a fibrogenic factor from macrophages, or conversion of macrophages into fibroblasts.
2nd Variant: Foreign body reaction, similar to that of implants of foreign inert material having a particular physical shape.
Implications: 1) Inflammatory response with presence of macrophages is necessary. 2) Mesothelioma of the pleura as an Oppenheimer effect.

or of harmless material which can be digested - egg-white, gelatin, fibrin (CURRAN), causes the appearance of a fibrosis of the tissue surrounding the implant. The reason for this fibrosis is not yet fully understood, although it seems that it is secondary to and controlled by a phagocytic response (CURRAN, 1964). But whether the macrophages must be damaged in order to induce a fibrogenic response is not yet established.

The importance of the physical shape of the foreign substance in the induction of the fibrosis and specially of the subsequent tumour development has been demonstrated, and it is a fact that the same substance which induces a tumour when implanted as a film or as a disc is without effect when embedded in the form of powders or fibres. But asbestos might be an exception to this rule just because of its peculiar surface properties. Although HARINGTON (1967) is against the hypothesis that carcinogenesis due to asbestos could be related to the « Oppenheimer effect », the relationship between fibrogenic and cancerogenic response to asbestos and to plastic or metal foreign bodies deserves serious consideration.

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Prof. ENRICO C. VIGLIANI

Clinica del Lavoro Università di Milano

8 Via S. Barnaba - Milano

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