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Fibrogenesis

by J. S. Harington*

A review of fibrogenesis by asbestos fibers is given. There is nothing to indicate that the fibrogenic effects of inhaled asbestos fibers should differ in any way from those of ingested asbestos. Recently, ingestion has assumed some importance concerning human exposure. Three sections dealing with the process of fibrogenesis are covered: the first deals with *in vitro* fibrogenesis, in particular the interrelation of macrophages damaged by dusts and the subsequent laying down of collagen by fibroblasts in culture; the second deals with *in vivo* fibrogenesis after the inoculation of extracts of silica-treated macrophages into various animals, and the third, with the fibrogenicity of a wide variety of mineral fibers in man and experimental animals.

Recent studies described in the first section of the present review appear to offer a better understanding of the effects of macrophages on fibroblasts after tissue damage of various kinds has occurred.

Introduction

Fibrogenesis (or collagenesis) is the term used to describe the laying down of collagen in normal or abnormal conditions by fibroblasts. Collagen normally serves as a structural or repair protein and its metabolic turnover is therefore slow. In abnormal circumstances, such as silicosis and asbestosis, fibrogenesis may continue progressively, long after the inhalation of excessive dust particles or fibers by man or animal has stopped. The fibrosis which results from such exposures may be nodular in character (as in silicosis) or diffuse (as in asbestosis) though whatever the case, the progressive accumulation of such deposits of collagen eventually harms pulmonary function.

The biolchemical events in fibrogenesis are essentially the same whether asbestos fibers are ingested or inhaled; collagen is laid down whenever enough biologically active fibers are present in the tissues. With this in mind then, the treatment of the subject in this paper concerns the fibrogenic action of both ingested and inhaled asbestos.

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In Vitro Fibrogenesis

It is now generally accepted that the toxic effect of fibers on macrophages precedes fibrogenesis, and in this respect, work on various forms of silica has been instructive. Here there are two types of cytotoxicity, an early one due to the action of fibers on the plasma membrane of the macrophage, and a delayed effect after the fibers have been taken up by these cells *(1)*. This last-named action is the principal one in the pathogenesis of both silicosis and asbestosis.

There is a parallel between the cytotoxicity of different forms of silica to macrophages and fibrogenesis in experimental animals. All but one crystalline form of silica (tridymite, quartz, coesite, cristobalite) are toxic to macrophages and subsequently fibrogenic. The exception is a rare type known as stishovite which crystallizes under conditions of high temperature and pressure. This mineral and other particles such as crystalline titanium dioxide (rutile, anatase) or diamond dust, of comparable size and surface area, are not toxic to macrophages and do not seem to stimulate the formation of collagen.

Most *in vitro* studies have been made with macrophages in culture *(2)* because the main in-

teraction of silica particles and asbestos fibers *in vivo* occurs with these cells (Table 1). The mode of action of silica on the macrophage and on the phagosomes formed in the cytoplasm after phagocytosis, and the prevention of these toxic effects by certain polymers, has been well worked out *(3)*. The mode of action is shown schematically in Figure 1. Recent studies on the effects of asbestos on macrophages show that of all types of fibers, the greatest toxicity is shown by chrysotile (Fig. 2). This is true of both early and late cytotoxicity. Other forms show some toxic effects, but in general these are weak. The technique of hemolysis has been useful in predicting the toxic effects of various forms of asbestos *(6)* and correlations between the hemolytic and cytotoxic activities of a fairly wide range of mineral fibers (and various forms of silica) have been well established. In the case of asbestos, there are certain interesting exceptions, such as crocidolite and amosite, although their hemolytic activity can be enhanced by complement *(7)*.

The death of the macrophage is a prerequisite to the subsequent fibrogenesis although the biochemical steps between these two major processes have not yet been worked out. All forms of asbestos fibers can stimulate the production of collagen in experimental animals. The fact that glass fibers and other nonasbestos fibers can also do this emphasizes the importance of the fibrous nature of the material rather than its chemical composition, although oversimplification in ascribing such effects exclusively to a pure physical action should be guarded against.

Table 1. Summary of conditions under which macrophages have been incubated with dusts in various experiments.

Species used	Stimulated (S) or unstimulated (U) macrophages	Medium with serum (+) or without serum (—)	Dust added with serum (+) or without serum (—)	Age of cell culture when dust added	Duration of incubation of cells with dust, hr	Dust Used
Mice	U	+	—	overnight	2–72	Quartz + amorphous silica
Golden hamster	U	+	+	5 days	72	Quartz + amorphous silica, UICC chrysotile amosite crocidolite
Rat	S	+	+	24 hr	3–4½	Silica (several forms), asbestos and other minerals
Rat	S	—	—	0–2 hr	0–1/3	Quartz, other minerals
Guinea pig	S	—	—	1 hr	2	DQ12 silica (quartz) and other silicas
Guinea pig	S	—	—	1 hr	2	UICC asbestos dusts
Guinea pig	S	—	—	2 hr	6	Quartz
Guinea pig	S	—	—	1 hr	¼–7	Tridymite, rutile, coal
Guinea pig	S	—	—	1 hr	¼–7	Tridymite, rutile, coal
Golden hamster	S	+	—	6 hr	4–60	Amorphous silica, rutile, UICC chrysotile, crocidolite, amosite, DQ12 silica (quartz), colloidal silica

[a] Data of Harington *(2)*.

Since most fibrogenic minerals inhaled into the lungs are ingested by macrophages, and since there is evidence that these cells seldom differentiate into collagen-synthesizing fibroblasts, it has long been held that fibrogenesis takes place by a two-stage mechanism *(1, 8)*. The interaction of the particle with the macrophage has been thought to liberate a factor which stimulates collagen synthesis by attendant fibroblasts. Apparent proof of this is contained in an interesting report by Heppleston and Styles *(9)* and later by Heppleston *(10, 11)*. Mouse macrophages exposed to silica particles were reported to release a factor into the surrounding medium which stimulated collagen synthesis by chick fibroblasts *in vitro*. Attempts to confirm this result, however, have not been entirely successful although there is now evidence that the state of cell or tissue culture during experiments may be a deciding factor as to whether stimulation or inhibition of collagen production takes place. Harington et al. *(12)* after an earlier study *(13)* had shown an efficient production of collagen by newborn hamster fibroblasts *in vitro* studied the effects of extracts of silica-treated macrophages on this process (Fig. 3). As before, collagen production was found to be considerable, provided proline, vitamin C and insulin (collagen stimulating medium) were present (Fig. 4).

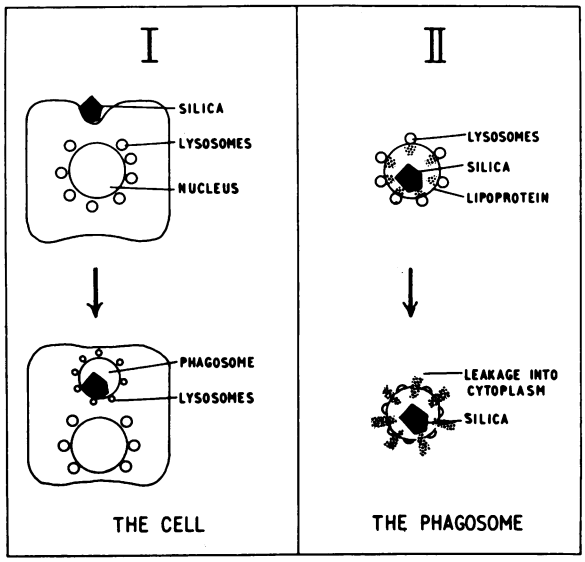

FIGURE 1. Diagram showing uptake of silica particle into a phagosome (I), release of lysosomal enzymes into the phagosome and subsequent leakage of these enzymes into the cytoplasm (II). From Harington and Allison *(4)*.

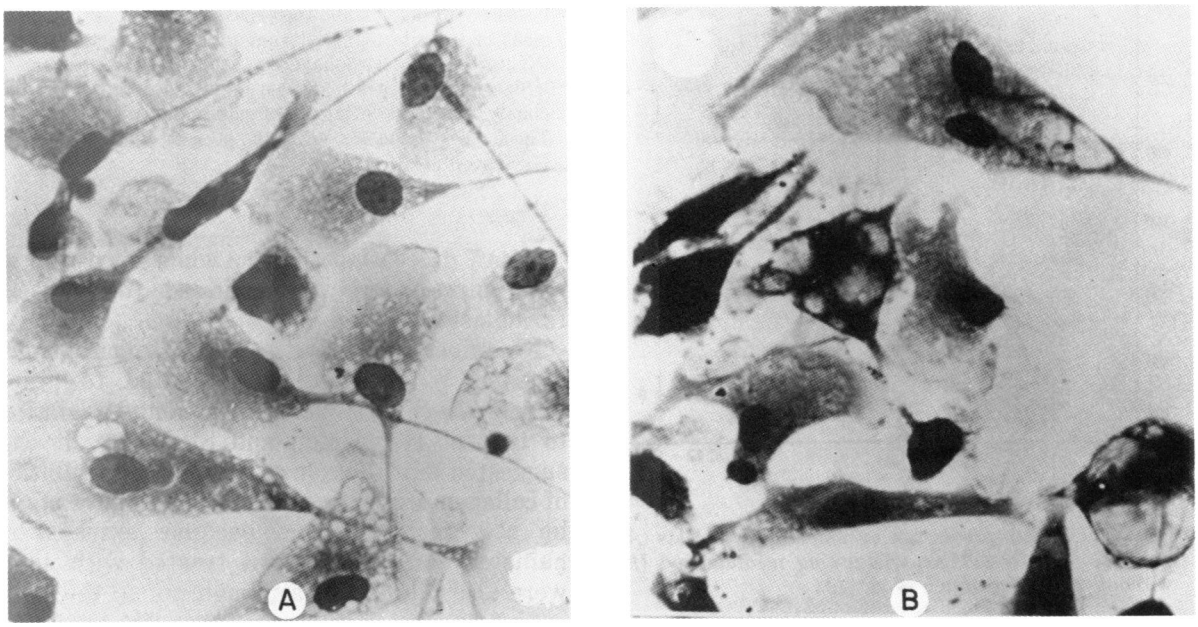

FIGURE 2. Hamster peritoneal macrophages fixed and stained with hematoxylin: *(A)* untreated cells on 6th day of culture; *(B)* cells treated with UICC chrysotile (72 μg/5×10^5 cells), on the 5th day of culture. Photographed 4 hr after administration of dust. Note pronounced cytotoxic effects. 374×. Data of Bey and Harington *(5)*.

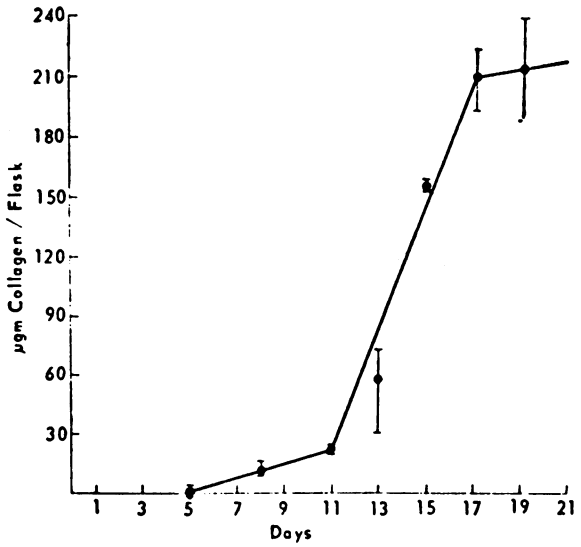

FIGURE 3. Composite curve of collagen synthesis by fibroblasts from explants from three newborn hamsters. From Harington et al. *(13)*.

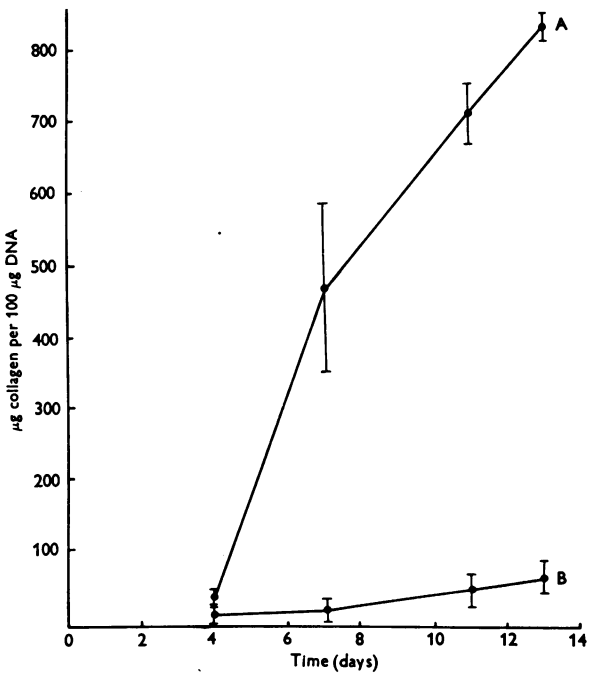

FIGURE 4. Collagen production by hamster fibroblasts (*A*) in medium with collagen-stimulating medium and (*B*) without. From Harington et al. *(12)*.

When suspensions of silica-treated hamster macrophages (at 5–100% concentrations) were added to hamster fibroblasts in culture, a marked inhibition of collagen production (60–80%) occurred over an 11-day period (Fig. 5).

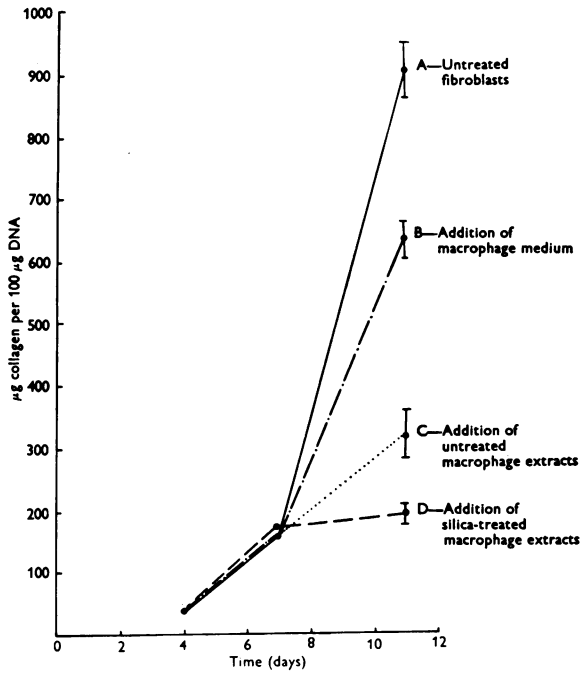

FIGURE 5. Collagen production by (*A*) untreated (normal hamster fibroblasts and the effects on this of 50% suspensions of (*D*) silica-treated hamster macrophage extracts, (*C*) untreated macrophage extracts, and (*B*) medium in which macrophages had been maintained for 24 hr. For clarity, standard deviations of values at day 7 are omitted. These are: (*A*)±40; (*B*)±40; (*C*)±33; (*D*)±37. From Harington et al. *(12)*.

A 44% decrease was found when silica-treated rat macrophages were added to hamster fibroblasts (Fig. 6).

No effect was found when rat macrophages treated with silica were added to chick fibroblasts (Fig. 7). This experiment was similar to that of Heppleston and Styles *(9)*. It was suggested that the role of silica in the inhibition of collagen production as described above might be a synergistic one, because extracts of hamster macrophages not treated with silica were also inhibitory, although not to the same extent as when silica was present. The potent inhibitor reported by Harington and his associates may reflect the lack of response of the hamster to the development of fibrotic lesions when silica *(14)* or asbestos *(15)* is administered.

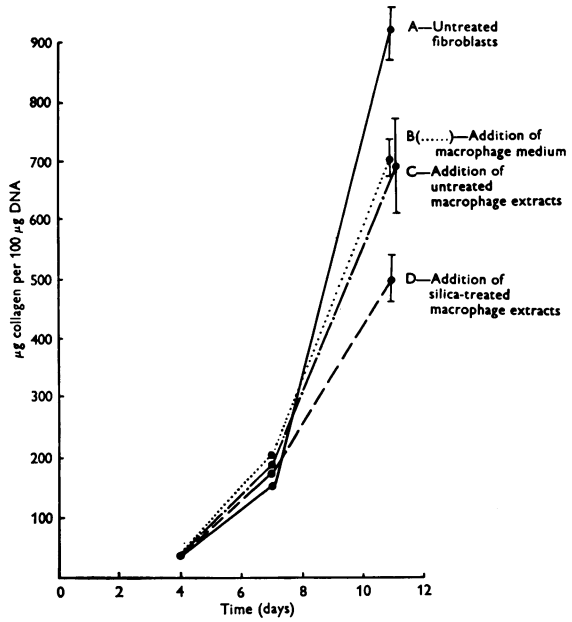

FIGURE 6. Collagen production by (*A*) untreated normal hamster fibroblasts and the effects on this of (*D*) silica-treated rat macrophage extracts, (*C*) untreated rat macrophage extracts, and medium in which macrophages had been maintained (*B*) for 24 hr. For clarity, standard deviations for values at day 7 are omitted. These are: (*A*)±40; (*B*)±48; (*C*)±28; (*D*)±34. From Harington et al *(12)*.

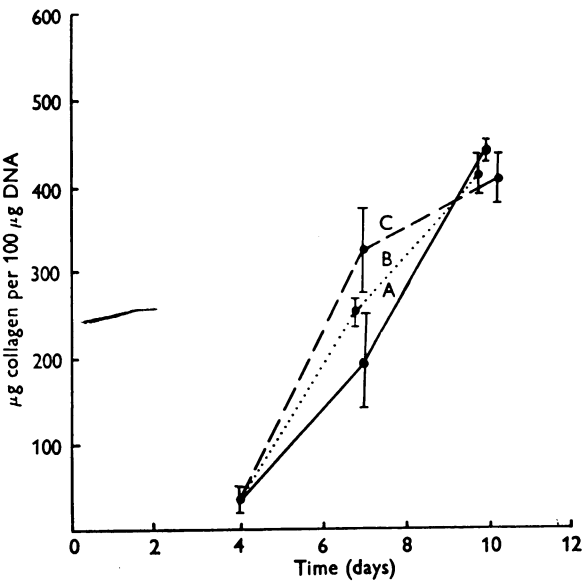

FIGURE 7. Collagen production by (*A*) untreated normal chick fibroblasts and the effects on this of (*C*) silica-treated rat macrophage extracts and (*B*) untreated rat macrophage extracts. From Harington et al. *(12)*.

Burrell and Anderson *(16)* working with normal rabbit alveolar macrophages and WI–38 fibroblasts obtained results similar to those of Heppleston and Styles *(9)* although whether the fibroblasts used were in a confluent or non-confluent state is not known. This is important because Nourse et al. *(17)* have recently found that silica-treated macrophages inhibit collagen synthesis provided the fibroblasts are no longer dividing. When they are still capable of dividing, that is, when they are not fully prepared for collagen synthesis (in this case, the cells would not yet be confluent), a factor is produced which increases collagen synthesis. This factor does not seem to act by increasing the rate of fibroblast proliferation nor the rate of collagen synthesis but by causing fibroblasts incapable of synthesizing collagen to do so. This study may to a certain extent reconcile the apparently divergent results of Heppleston and Styles *(9)* and Harington and his associates *(12)*.

A recent study by McGee, O'Hare, and Patrick *(18)* shows that collagen formation is increased fourfold when extracts of the livers of mice (poisoned with carbon tetrachloride after intubation into the stomachs) are added to fibroblasts in culture. Here, potent stimulators are obviously at work. It proved possible to isolate at least three active components from the original extract. Harington and Corfield however, found a complete shut-off of collagen synthesis when extracts of rat liver poisoned with carbon tetrachloride (as well as extracts of "normal" rat liver) were added to hamster fibroblasts in culture (unpublished results). This finding agrees with their earlier one on the effect of silica-treated macrophage extracts on collagen production by hamster fibroblast *(12)*. It would appear, therefore that these cells do not seem at all amenable to stimulation by factors released by macrophages damaged by silica nor by hepatic cells damaged by carbon tetrachloride. It will be necessary to determine whether similar results are obtained when hamster fibroblasts have not yet reached confluence in culture, particularly in view of the results obtained by Nourse and his associates *(17)*.

There appear to be active stimulatory factors in extracts of chick and guinea pig macrophages damaged by silica provided, it seems, that these extracts are added to fibroblasts which have not yet reached confluence in culture *(17, 19)*. After confluence, collagen production is markedly in-

hibited *(12, 17)*. Damage to liver cells by carbon tetrachloride (CFLP mouse cells on L–929 mouse fibroblasts) stimulates collagen production *(18)* though extracts of rat liver poisoned with carbon tetrachloride are totally inhibitory to collagen formation by hamster fibroblasts (Harington and Corfield, unpublished data). Table 2 summarizes results so far obtained.

Further investigations of different combinations of extracts and source of fibroblasts should be useful in determining whether the stimulatory or inhibitory factors which have been reported are different chemical materials or the same or whether they act at different times of tissue or cell activity, such as at confluence or nonconfluence, or whether they occur in some animals (the rat) and not in others (the hamster). There are three possibilities to consider. (a) Dead or dying macrophages under appropriate conditions release a factor which stimulates fibroblasts to produce collagen. There need not be any marked increase in number of fibroblasts present, but more collagen would be formed around the site of macrophage death or damage by a comparatively fixed number of fibroblasts *(17, 19)*. (b) Dead or dying macrophages do not release any stimulatory factor but are attended by a rapidly increasing number of fibroblasts making constant amounts of collagen. This would also allow for more collagen to be deposited where it is needed. The process would be a chemotactic one in which fibroblasts migrate to areas of cell damage. The response would not be specific to silica but a general one to any damaged cells or tissues. (c) There may be a combination of both mechanisms (a) and (b).

The possibility that mineral fibers might stimulate fibroblasts directly should also be considered. Richards et al. *(20, 21)* exposed cultures of rabbit lung fibroblasts to Rhodesian chrysotile asbestos, glass fiber, coal, and quartz. Chrysotile significantly increased the amount of collagen in the cell mat and concentrations of DNA in control and treated cultures were not significantly different. When interpreting these results, however, it is worth recalling that the synthesis and laying down of collagen *in vitro* is a complex process which can be affected by many variables including the composition of the medium, the rate of growth of the cells, the proportion of collagen synthesized that is bound

Table 2. Summary of results obtained after extracts of silica-treated macrophages are added to fibroblasts in culture.[a]

No.	Agent used	Cells used		State of fibroblasts in culture	Effect of macrophage extract on collagen production	Reference
		Macrophages	Fibroblasts			
1	Quartz (Dörentrup)	Rat peritoneal	Chick embryo	Not stated	Stimulation (in cell layer, 3–15 fold)	Heppleston and Styles *(9)*
2	Quartz	Rabbit alveolar	Human (WI-38)	Not stated	Stimulation (in medium, 4–16 fold); no effect on cell layer	Burrell and Anderson *(16)*
3	Quartz	Guinea pig alveolar	Guinea pig embryo lung	Nonconfluent Confluent	Stimulation (60%) No effect, or inhibition (30–70%)	Nourse et al. *(17)*
4	Silica (Fransil)	Hamster peritoneal	Hamster skin	Confluent	Inhibition (80%)	Harington et al. *(18)*
1	Carbon tetrachloride	Intact mouse liver	Mouse L–929	Not stated	Stimulation (4-fold)	McGee et al. *(18)*
2	Carbon tetrachloride and control	Intact rat liver	Hamster skin	Confluent	Inhibition (100%)	Harington and Corfield (unpublished)

[a] The results of the two experiments with carbon tetrachloride are included because of relevance.

within the cell mat and the breakdown of collagen itself. There can also be a considerable release of collagen into the culture medium. Although the results of Richards and his colleagues raise the possibility that the *in vivo* fibrogenic effects of asbestos might be exerted directly on fibroblasts without the intervention of macrophages, this conclusion cannot yet be taken as established.*(1)*.

In Vivo Fibrogenesis

Subcutaneous Injection of Macrophage Extracts

A few studies have been done on the effects of extracts of silica-treated macrophages after these have been injected subcutaneously into various animals but there are inconsistencies in the results. It has been claimed that the lipid fraction of such macrophages is fibrogenic *(8)*, that defatted extracts are active *(22)*, and that fractions of whole macrophages treated with silica are fibrogenic after injection *(23)*. A systematic extension of these studies should provide valuable links between *in vitro* and *in vivo* fibrogenicity.

Fibrogenic Effects of Administered Minerals and Fibers

Other *in vivo* studies concern the fibrogenic effects of various mineral fibers on man and experimental animals *(1)*. In summing up the experience gained by many investigators using different animals, dusts and techniques over a long period of time, Vigliani emphasized *(24)* that most types of asbestos tested are fibrogenic and that long fibers very often act differently to short. This is borne out by the work of Davis *(25)*. Studies of cytotoxicity have also been illuminating, although it is still not clear exactly what properties of mineral fibers cause the severe tissue damage and the eventual fibrosis; there is some evidence *(26–28)* that, as in the pathogenesis of silicosis, lysosomal and phagosomal damage is involved. *(1)*.

Davis *(25)* found the following mineral dusts or fibers to be fibrogenic when injected into the pleural cavity of mice: Mineral fibers (chrysotile, short, <1 μm long, and normal, 1–200 μm long; and short synthetic fibers, fibrous brucite, silica fiber) glass fiber, man-made insulation fibers; other minerals (chlorite, chromite, forsterite, magnetite, olivine, pyroxene, serpentine and talc). All produced granulomas in the pleural cavities although there was great variation in magnitude of cell responses. Davis concluded that all the materials injected stimulated the production of a certain amount of collagen. Long-fiber samples quickly produced large cellular granulomas which were eventually replaced by large amounts of fibrous tissue while short-fiber samples or nonfibrous and finely ground dusts stimulated much less reaction *(1, 24)*.

Recent studies support the contention that longer fibers are more fibrogenic than shorter because the long ones are less well phagocytosed and transported away. Also, in experiments where the pleural cavity has been used, the fibers are artifically deposited in a confined space. In the lung, long fibers would be difficult to mobilize, whereas short ones can be phagocytosed by macrophages and suitably carried away *(25)*. Short fibers would also penetrate more efficiently to the lower parts of the lung. (Davis points out that long fibers could cause considerable irritation during constant respiratory movements while short ones would be aggregated into compact masses and probably encapsulated soon afterwards.) Thus, longer fibers are probably more effective than shorter ones in the production of asbestosis in experimental animals.

Fiber diameter has received considerable attention and seems to play an important part in deciding how deeply penetration into the lung can occur *(29, 30)* and whether some types of fiber may induce mesotheliomas in man or not *(31)*.

Finally, mention should be made of the extensive studies of Heppleston and his colleagues on the pathogenesis of silicosis with particular regard to mechanisms of fibrogenesis at the cellular and tissue level *(10, 11, 19, 32–35)*. These papers, although out of scope of the present review, throw much light on the subject.

Summary

The process of fibrogenesis by asbestos fibers has been briefly reviewed. There is nothing to indicate that the fibrogenic effects of inhaled asbestos differ in any way from those of ingested asbestos although ingestion has recently assumed some importance with regard to

human exposure. Fibrogenesis has been reviewed under three separate headings: *in vitro* fibrogenesis (in particular the inter-relation of macrophages damaged by dusts and the laying down of collagen by fibroblasts in culture), *in vivo* fibrogenesis after the inoculation of extracts of silica-treated macrophages into various animals, and the fibrogenicity of a wide variety of mineral fibers in man and experimental animals.

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