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Mesothelioma in Man and Experimental Animals

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Asbestos has been established as the cause of most cases of diffuse malignant mesothelioma occurring in the industrialized world. The morphology of mesothelioma may be complex, and the employment of chemical, histochemical and ultrastructural studies are often helpful in identification. Diagnostic difficulties may to some degree blur the extent of its prevalence and reliance on exposure history may not reveal its association with asbestos. Reference panels can be useful in assessing the former and analysis of lung tissue asbestos content may help to clarify the latter, especially in the low dose range. Electron microscopy may prove to be of assistance in this respect, possibly with particular attention to the peripheral areas of the lung. Animal experimentation has supported epidemiologic conclusions and revealed the phenomenon of fiber carcinogenesis. The morphology of mesothelioma in experimental animals is very similar to that in humans, including ultrastructural and biochemical features.

The predominant association of mesothelioma with exposure to asbestos and the failure to demonstrate another epidemiologically consequential etiologic agent, in the industrialized world, give this tumor unique significance (*1*). Other neoplasms of increased prevalence among asbestos workers have one or more known or suspected causal factors that act upon the general population (*2*). The one known exception to the singular role of asbestos in relation to mesothelioma is confined to an area of Turkey. Here endemic mesothelioma has been related to zeolites. These resemble asbestos, in that they are fibrous hydrated silicates but differ chemically and structurally (*3*).

The term, mesothelioma, used in the context of asbestos exposure in man means diffuse malignant mesothelioma of the pleura and peritoneum. The localized, usually benign, primary tumors of the pleura and the very rare malignant mesotheliomas of the pericardium and tunica vaginalis have not been shown to have any association with asbestos.

A brief summary of features of the morphology of human diffuse malignant mesothelioma may be desirable. The term diffuse is significant. Although possibly limited in its earliest phases, when mesothelioma is symptomatic, it involves both the parietal and visceral serous layers entirely or at least very extensively. Fluid is usually present in any residual space of the involved pleural or peritoneal cavity. Pleural mesothelioma is more common than peritoneal except in certain heavily exposed occupational cohorts (*4*). Invasion of included organs and extension to adjacent tissues are frequent. Metastasis to lymph nodes and to various organs, such as the opposite lung, liver, adrenals, bone, thyroid, and brain occur in about half of the cases (*5, 6*). It should be pointed out that, although the gross pathology of mesothelioma is characteristic, it is not specific and can be closely simulated by and indistinguishable from metastasis of other tumors to the serous membranes.

The microscopic features also create diagnostic problems because of their diversity, varying from epithelial forms resembling carcinoma, on the one hand, to mesenchymal or sarcomatoid tumors, on the other. A multiplicity of cytoarchitectural types occur, including pleomorphic, anaplastic forms. Certain varieties are more characteristic in that they are better differentiated and more frequent. Epithelial cell types are in the majority; pure sarcomatoid forms are the least common (*6*).

These various expressions are attributable to the multipotentiality of the mesothelial cells, retained from the primitive mesenchyme from which they

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develop (*7*). The coincidence of epithelial and mesenchymal differentiation, the so-called mixed or biphasic form, may serve as a clue to diagnosis in about one-fourth of the cases but these must be distinguished from other tumors of mixed histology.

A feature that is of basic biologic interest, as well as of diagnostic utility in many cases, is the capacity of mesothelial cells to secrete the acid mucopolysaccharide, hyaluronic acid. This substance is not produced by tumors of intrinsically epithelial derivation, and its demonstration in effusion fluids and in tissues by chemical or histochemical methods can be decisive in diagnosis. Conversely, the presence of neutral mucin as produced by native epithelial cells and adenocarcinomas and not by mesotheliomas excludes the diagnosis of the latter (*8*).

Another technique bearing on theoretical as well as practical considerations is electron microscopy. It demonstrates certain characteristic features of mesothelioma cells of epithelial type but, perhaps even more significant, it reveals epithelial qualities in tumors that appear entirely spindle celled or sarcomatous by light microscopy (*9*).

The diagnosis of mesothelioma can be very difficult, and this may have epidemiologic repercussions. The question of the accuracy of mesothelioma ascertainment is still not entirely settled. One aspect is the correctness of the diagnosis of mesothelioma by the original physicians, including the primary pathologist. Reviews over the years by panels of experts in this area have resulted in rejection of varying but meaningful numbers of cases (*10*). Another sizeable group may fall into an indeterminate category, sometimes because of intrinsic complexities but often as a result of deficiencies in available information as to clinical or gross pathologic presentation or of material for histological examination (*11*). A recent study in the United States with an experienced diagnostic panel as compared with some earlier reports indicates that the average pathologist has become increasingly sophisticated in the diagnosis of mesothelioma (*12*). Of submitted cases, 70% were accepted as definite or probable; only 14% were entirely rejected. In another 16%, the panel itself could arrive at a consensus of merely possible mesothelioma, and in more than half of these latter cases there was a divergence of opinion among the panel members. Another recent report from Europe discusses panel impediments and the value of panel meetings and discussions to improve agreement (*13*). A possibly more important aspect is that of missed cases, those that are attributed to some other origin. Retrospective studies relying merely on diagnostic indices may fail to detect such cases. No definitive study of this problem has been reported.

The proof of the etiologic association of mesothelioma and asbestos has rested largely on a history of occupational or environmental exposure. A positive history has ranged in various series from 22% (*14*) to almost 100% (*15*). To be significant a negative occupational and environmental history must be, of course, virtually life-long and intensive. A complicating feature is the long latent period between first exposure and onset of symptoms. This is almost invariably more than 20 years and averages 35 to 40 years.

Another problematic aspect is the occurrence of cases with a history of very brief or low dose exposure (*2*). The first does not necessitate the latter but there are cases of mesothelioma with evidence of having received only a very small amount of asbestos. This leads to the subject of the dose-response phenomenon. There is, in occupational studies, evidence of an increase in the rate of mesothelioma occurrence with increasing intensity and duration of exposure (*16, 17*). The variation in the dose required to induce mesothelioma down to seemingly minimal quantities effective in some cases may be attributable to differences in individual genetic tissue susceptibility.

Efforts to arrive at a more definite and quantitative index of asbestos association with the various asbestos-related diseases including mesothelioma have led to the study of the concentration of particles in lung tissue. Pooley compared groups of mesothelioma and random autopsy non-mesothelioma cases by electron microscopy of lung tissue (*18*). He found that 92% of the mesothelioma cases were positive for asbestos and over half were in the higher four of six categories of fiber content. Of the non-mesothelioma cases, over half showed no asbestos, and more than 90% fell into the lower two fiber content categories.

Recently Whitwell et al. (*17*), using a tissue digestion procedure and phase microscopy, determined the number of asbestos fibers per gram of dried lung tissue. They established that 78% of patients with mesothelioma had more than 100,000 fibers, whereas 71% in a control series contained less than 20,000. The majority of mesothelioma cases had over 500,000 fibers per gram, but none of the control cases approached that level.

In the investigation of lung tissue in an individual case the complexity of the method required will vary. If parenchymal asbestosis is present, there will usually be asbestos bodies, often in large number, and readily seen in routine 5 μm sections. However, a considerable proportion of cases of mesothelioma are patients without asbestosis, especially those with indirect occupational or nonoccupational exposure. Here, a more intense search for asbestos fibers, coated or uncoated, must be undertaken, particu-

larly where a quantitative estimation is desired.

There are a number of techniques for concentrating asbestos bodies and fibers from lung tissue. These vary from the use of ashed thick paraffin sections to digested tissue filtrates viewed by phase microscopy to electron microscopy. Asbestos body counting appears to be, in general, easier than uncoated fiber demonstration. The number of asbestos bodies above general population levels has been shown to be related to occupation even in those occultly exposed (*19*). However, uncoated fibers are 30 to 200 times as numerous as asbestos bodies (*20*). Phase microscopy will disclose fibers more than 0.36 μm in diameter but finer, suboptical fibers must be sought by electron microscopy. In one study (*21*), only 12 to 30% of fibers could be seen by phase microscopy as compared with electron microscopy. A recent investigation (*22*) found that in two groups of occupationally exposed patients, one heavily exposed and the other less so, the mean proportions of optically visible fibers were 10% and less than 1%, respectively, of the total fiber content. The authors make the point that optical microscopy can be used for screening but is unsuitable for a dose-effect relationship determination in asbestos-associated carcinogenesis, for which electron microscopy is necessary.

The same investigators determined the topographical distribution of fibers in the lung. They compared numbers, sizes, and types of fibers centrally and peripherally in both upper and lower lobes. By light (phase) microscopy there were a great many more fibers, especially in the lower lobe peripherally in heavily exposed cases with fibrosis than in less exposed cases without fibrosis. However, with electron microscopy, suboptical fibers were in the same numerical range for both groups; 70 to 90% of fibers were shorter than 5 μm. In the less heavily exposed category, values for total fibers, optically and suboptically visible, showed no significant difference between upper and lower lobes and there was an accumulation of fibers in peripheral areas. The authors came to the conclusion that the number of fibers reaching the pleura may be more or less similar whatever the asbestos content of the lung. The fibers encountered in the pleura were frequently fragmented chrysotile and were very short. This preferential localization of asbestos fibers in the pleura with a small amount of dust in the lungs, they suggest, may explain the occurrence of nonoccupational pleural mesothelioma with moderate or low asbestos exposure.

It is conceded that there must be causes of mesothelioma other than the fibrous silicates, but these others must be responsible for only a small minority of cases in areas where the possibility of exposure to asbestos is considerable. In the work of Whitwell et al. (*17*) previously referred to, seven of the 100 cases of mesothelioma studied were regarded as spontaneous (i.e., not associated with asbestos). These cases had negative histories, no pleural plaques and low fiber counts. However, only an optical counting method was employed, and the question arises as to what electron microscopy might have shown. In the zone of overlap of lung asbestos content of mesothelioma and control cases, it would seem difficult to draw a sharp line between coincidence and unusual tissue susceptibility in attributing or denying causation to asbestos in an individual case. In any case, they estimate that in the geographical area from which their cases came — an industrial and shipyard district with many sources of occupational exposure to asbestos — about 15% of cases of mesothelioma are spontaneous.

A small number of cases of mesothelioma have occurred in children (*23*), where age was less than the latency period required for asbestos effect. Several case reports have attributed a mesothelioma to radiation (*24, 25*).

A few spontaneous (that is, nonexperimental) mesotheliomas have been reported in animals: in dogs, cattle, a goat, horses, rats, and Syrian hamsters. In the last (*26*), type C-virus particles were present and increased when the tumor was transplanted. These virus particles have been seen also in a study of asbestos-induced tumors in hamsters (*27*).

The reported induction of mesothelioma in chickens by MC 29 avian leukosis virus (*28*) raises another possible cause or causal factor. A number of nonfibrous chemicals other than asbestos and the fibrous nonasbestos materials (see below) have been found to produce mesotheliomas experimentally. These include malignant uterine mesotheliomas in squirrel monkeys after prolonged treatment with diethylstilbestrol (*29*) and peritoneal mesothelioma in rats following the administration of 1-nitroso-5,6-dihydrouracil (*30*). A metabolite of molds, sterigmatocystin, injected into the peritoneal cavity of rats, caused mesotheliomas (*31*). This material and a closely related material both formed needle-like crystals; however, only the sterigmatocystin produced mesotheliomas. The author suggests that the presence of a double bond in the terminal furan ring rather than the physical form of the material is responsible for the carcinogenicity.

The cause-effect association of asbestos and mesothelioma has been amply confirmed by animal experimentation (*32, 33*). This line of investigation has also established that all commercial varieties of asbestos can produce mesotheliomas. Intrapleural and intraperitoneal inoculation of a variety of animals, especially rats and hamsters, has been the

most frequently used technique. Inhalation and intratracheal injection have also been employed. Although direct introduction of asbestos into the serous cavities has been acknowledged as inconsistent with the situation in humans, it has permitted investigation and clarification of a number of questions that might not have been feasible with the inhalation method. By treating the asbestos fibers with a solvent before inoculation, the possibility of a contaminating hydrocarbon as the essential carcinogen or cocarcinogen was eliminated (*33*). Further it was shown that the addition of the polycyclic hydrocarbon carcinogen, benzo(a)pyrene, had no effect on the incidence or histological types of mesothelioma induced by asbestos (*34*). Trace metals were similarly not demonstrated to have any effect on mesothelioma induction. Dose-response effect was demonstrated with asbestos (*35*).

A significant approach to the mechanism of mesothelioma causation was accomplished by Stanton (*36*) who applied pledgets containing a variety of materials to the pleura of rats. These substances — asbestos, glass fibers, and aluminum oxide — had in common a fibrous form. Not only did each produce mesotheliomas, but as the nonasbestos fibers approached the size range of asbestos they became increasingly carcinogenic. Pott et al. (*37*) showed that chemically similar but nonfibrous material yielded few or no tumors. Thus it seems probable that it is the physical form and not the chemical constitution or the molecular structure that is responsible for the tumorigenic effect of these substances on the serous membranes.

Much work has been applied to the question of the most carcinogenic fiber dimensions. Fine fibers, with diameters of less than 0.5 μm have been considered significant (*35*). However, there have been contradictory findings regarding length, especially of fibers less than 10 μm. Although most investigators appear to use standard UICC preparations, characterized by Timbrell (*38*), differences produced by milling and other variations in technique complicate comparison of results. Wagner et al. (*35*) found UICC crocidolite samples the most carcinogenic of these preparations, but ground, superfine UICC chrysotile proved highly carcinogenic. Chrysotile fibers tend to fragment longitudinally in lung fluids; amphiboles do not.

Inhalation experiments, allowing for species differences between man and laboratory animals, approach more nearly the circumstances of human exposure and all the pathogenic effects of asbestos on the lung, including mesothelioma, have been reproduced using this route (*39*). In these inhalation experiments of Wagner et al. an interesting feature was the occurrence of two mesotheliomas after only one day's exposure to asbestos, out of 11 mesotheliomas in rats exposed for varying periods up to 24 months. Chrysotile proved as carcinogenic and fibrogenic as the amphiboles. The complexities of dose calculation have recently been discussed by Davis (*40*).

Experiments were performed by Bryks and Bertalanffy (*41*) in which natural chrysotile was administered intratracheally to rats injected with tritiated thymidine. Over 7 days there was a marked increase in the labeling index of the visceral pleural mesothelium, indicating a high degree of sensitivity to chrysotile, even when administered by the tracheal route. Experiments with ingestion of asbestos have provided no conclusive evidence as to a role for this route in carcinogenesis (*2*).

It has generally been accepted that diffuse mesotheliomas arise from the surface mesothelium. Using intraperitoneal inoculation of rats and mice, Davis (*42*) followed the response through a granulomatous and then a fibrotic phase. The earliest neoplastic stage consisted of a proliferation of pleomorphic connective tissue cells beneath a surface layer of epithelial cells similar to mesothelium. Often the tumor then spread in sheets with a continuation of pleomorphic connective tissue cells beneath surface epithelial cells. In some instances the cells became spindled and invasive. The ultrastructure of the different tumor cell types showed only slight differences. Davis suggests that these tumors arose from the submesothelial mesenchyme rather than the surface cells. This histogenesis has proponents in relation to human localized pleural tumors — the so-called localized mesotheliomas (*7, 43*). The reports describing apparently early human diffuse mesothelioma and our personal experience suggest a proliferation of surface cells and apparent invasion by these well-differentiated epithelial type cells into the fibrous layer (*44, 45*). The problem is occasionally one of differentiation of mesothelioma from hyperplasia. Pott et al. (*37*) from their experiments do not regard fibrosis as an initiating phase of mesothelioma and, indeed, that is true also of the human cases, seen in a relatively early stage.

Descriptions of inoculation mesothelioma suggest grossly in many a less diffuse character than those in humans. Wagner found multiple masses in the large majority of his cases, in some instances few and small. In other cases, however, there were large masses, some enveloping the lung (*46*). Davis, as mentioned, describes the tumor in the peritoneum as often spreading over the surface as a uniform sheet.

Histologically, the tumors resemble essentially the forms seen in humans. Wagner lists tubulopapillary, mixed, and spindle-celled, the mixed being most frequent. However, spindle cells predominated in the mixed cases, and many authors describe in

animals a predominance of sarcomatous tumors (*27, 37, 47*). Nevertheless, some epithelial mesotheliomas identical with those in humans have been seen in hamsters.

The ultrastructure of experimental mesothelioma in animals also corresponds to the features described in man (*27, 42*). Microvilli, epithelial junctions, basal laminae, and cytoplasmic filaments have been identified and are best developed in the epithelial types.

As with their human prototypes, animal mesotheliomas produce hyaluronic acid (*46, 48*), indicating similar mesenchyme-derived cell function.

The tumor mesothelioma has provided a strikingly identifiable example of the hazards to man resulting from his own assault on the environment. The ability to reproduce the tumor in animals has advanced understanding of a number of mechanisms. The revelation of fiber carcinogenesis has opened a new dimension in the comprehension of neoplastic processes. A wide range of scientific theory and techniques is being applied to persisting enigmas.

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