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Ultrastructural aspects of the histogenesis of diffuse and localized mesothelioma

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Summary. During an ultrastructural review of 30 diffuse and 10 localized mesotheliomas, it was apparent that some micrographs showed various stages in the developmental processes involved in the formation of histological patterns in diffuse mesotheliomas and a histogenetic link between diffuse and localized mesotheliomas. Cells in the stromal or sarcomatous regions of diffuse mesothelioma often show varying degrees of mesothelial differentiation and a gradual transition to cells with typical mesothelial characteristics that organize into structures recapitulating the surface layer of serosal membranes. Tumor cells in localized mesotheliomas had many similarities to the "stromal" cells in the diffuse counterpart including intercellular junctions, rare microvilli and occasional foci of basal lamina. It is postulated that diffuse and localized mesotheliomas share a common histogenetic origin as a result of neoplastic induction of specialized submesothelial cells. In this concept, tumor cells in diffuse mesotheliomas reflect stages in the differentiation and organization of normal serosal membranes and localized mesotheliomas mirror the earliest phases of this process.

Key words: Mesothelioma – Histogenesis – Ultrastructure

With the growing use of asbestos in this century, the incidence of mesothelial tumors has increased. The histological patterns of this tumor are diverse and frequently pose a diagnostic challenge. Localized serosal neoplasms also show considerable histological variation though the great majority are basically fibrous. Klemperer and Rabin in 1931 recognized the basic division of primary pleural neoplasms into localized and diffuse forms and stated

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that the diffuse tumors arose from mesothelium and that the localized variety originated from subpleural areolar tissue. Subsequently it has become generally accepted that diffuse serosal neoplasms, including purely fibrous ones, are mesothelial in origin but the histogenesis of the localized neoplasm has remained controversial. On the basis of tissue culture (Stout and Murray 1942) and ultrastructural observations (Kawai et al. 1978; Bolen and Thorning 1980; Briselli et al. 1981), it has been postulated that localized tumors are also derived from mesothelium and these tumors are often called localized (or solitary) mesothelioma. Other ultrastructural studies have appeared to support a submesothelial origin (Briselli et al. 1981; Hernandez and Fernandez 1974).

Ultrastructural examination of diffuse mesotheliomas has established the characteristic fine structural features of well differentiated neoplastic mesothelial cells (Bolen and Thorning 1980; Butler and Johnson 1980; Davis 1974; Stoebner et al. 1979; Suzuki et al. 1976; Wang 1973; Warhol et al. 1982). These include long branching microvilli, intracytoplasmic lumens, tonofilaments, desmosomes and basal lamina. In contrast, electron microscopy of localized fibrous tumors of pleura (Briselli et al. 1981; Hernandez and Fernandez 1974; Luse and Spjut 1964; Kay and Silverberg 1971; Wang 1973; Osamura 1977; Kawai et al. 1978; Benisch et al. 1981) has usually revealed less differentiated cells, which in some instances were thought suggestive of a fibroblastic neoplasm (Briselli et al. 1981; Hernandez and Fernandez 1974). However, in several studies spindle cells with intercellular junctions and an external lamina have been noted (Briselli et al. 1981; Kawai et al. 1978; Kay and Silverberg 1973). Microvilli have not been described in typical localized fibrous tumors, though they have been noted occasionally in tumors to which the appelation of "localized" has been applied loosely (Bolen and Thorning 1980).

A few authors have discussed the inter-relationship of tumor cell types in various types of mesothelioma (Suzuki et al. 1976; Bolen and Thorning 1980) and have suggested that there is a direct histogenetic relationship between surface and subsurface serosal cells.

During the course of an ultrastructural study of 40 serosal tumors (30 diffuse and 10 localized), we have noted fine structural features indicative of a histogenetic link between diffuse and localized mesothelioma. This report discusses developmental processes in mesotheliomas and the relationship between the two types of serosal tumors.

Materials and methods

Material for an ultrastructural study of mesotheliomas was obtained from the files of the Electron Microscope Unit of the Department of Pathology of the Toronto General Hospital and from the Canadian Tumour Reference Centre. Forty cases were available from 1974 to 1982. All cases had characteristic clinical features, X-ray findings and disease distribution based on staging, operative procedures or autopsy.

In each case, operative and surgical pathology reports were reviewed to establish the distribution and gross characteristics of the lesions. Tumors were designated as localized if they were attached to pleura, were solitary, and circumscribed. Some were pedunculated,

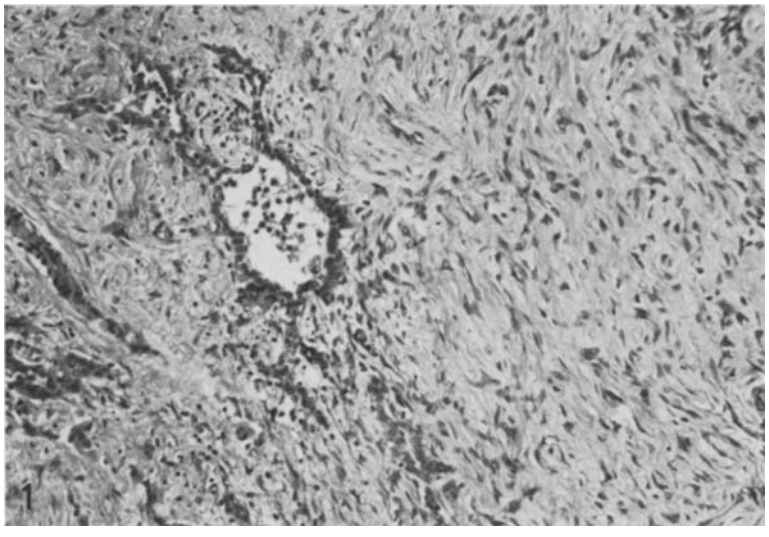

Fig. 1. Diffuse mesothelioma # 1. Regular cuboidal cells lining variably sized spaces. Linear cords and small clusters of similar epithelial-type cells are present within the spindle cell stroma (H and E, ×130)

some sessile. In the localized group, 9 lesions were classified as histologically benign and one as malignant.

Tissues were fixed in Karnovsky's solution, post-fixed in osmium tetroxide, dehydrated in graded alcohols and embedded in epon-araldite. After appropriate areas had been selected from toluidine blue stained semithin sections, thin sections were cut and double stained grids were examined with a Phillips EM 301 microscope.

Ultrastructural observations

A. Diffuse mesothelioma

The ultrastructural survey of the 30 cases of diffuse mesothelioma revealed to a greater or lesser degree the cellular fine structural features considered typical of this kind of mesothelioma. Micrographs were chosen from 4 of these cases to illustrate what are interpreted as various stages in the evolution of the histological patterns seen in diffuse mesothelioma.

In one case, various sized luminal spaces were lined by relatively regular, cuboidal tumor cells (Fig. 1). In addition, narrow cords or small clusters of tumor cells with similar features and staining characteristics as judged by light microscopy lay in the broad expanses of spindle cell stroma (Fig. 1). It was the small groups of epithelium-type tumor cells with and without obvious lumens, and the surrounding spindle cells that were available for electron microscopy (Figs. 2 and 3). In Fig. 2, a group of polygonal tumor cells had become organized around a lumen-like space. The lateral aspects of these cells were closely apposed and displayed tonofilament-associated desmosomes. Their apical and lateral surfaces frequently bore numerous microvilli. Around the tumor cells with a distinctly epithelial appearance

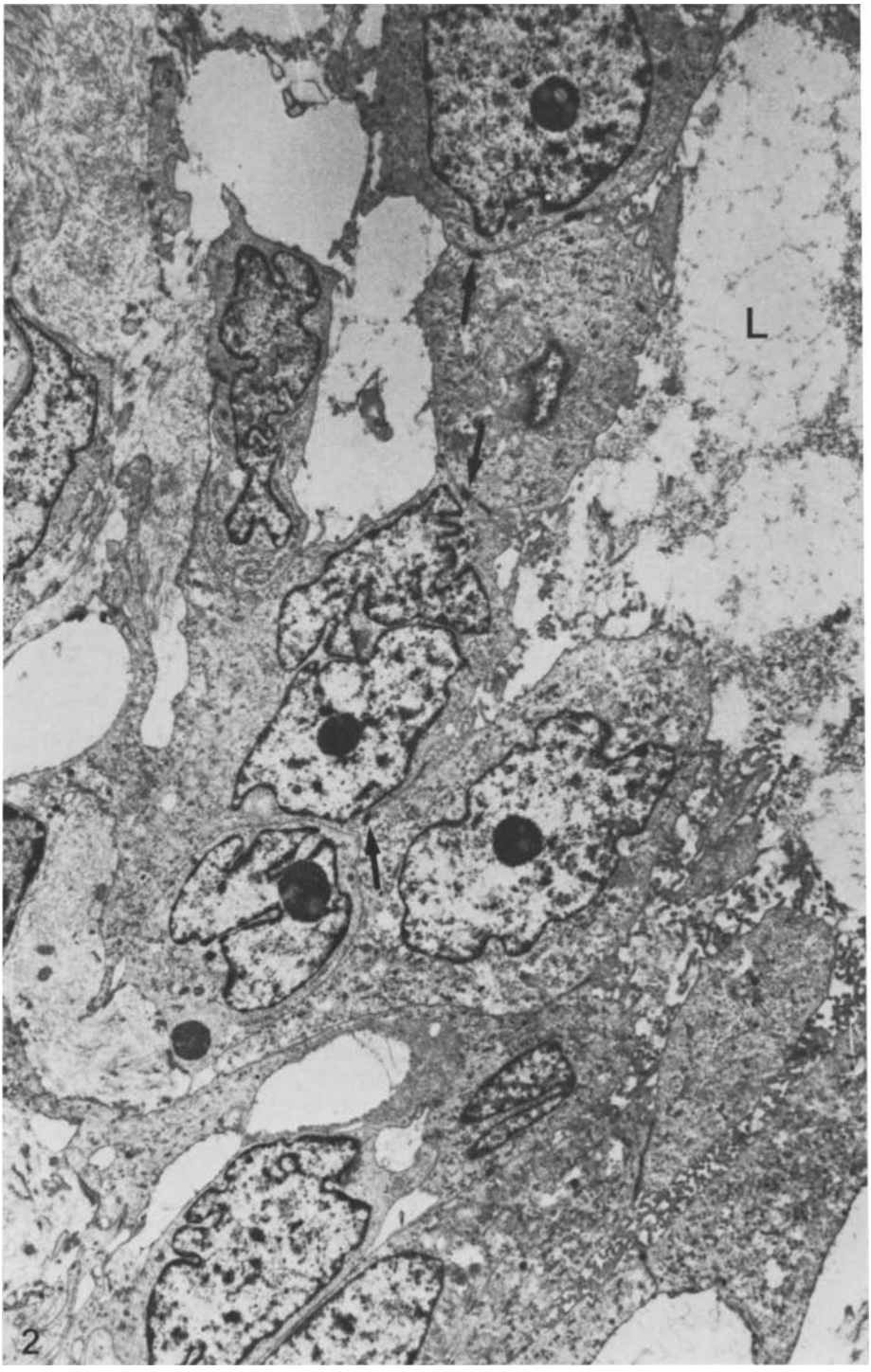

Fig. 2. Diffuse mesothelioma # 1. Polygonal, microvillus-bearing tumor cells border a lumen-like space (*L*) and are linked by desmosomes (*arrows*). Cells on the outer aspect of luminally oriented tumor cells lack microvilli and stream into the adjacent collagenized "stromal" tissue (×3,700)

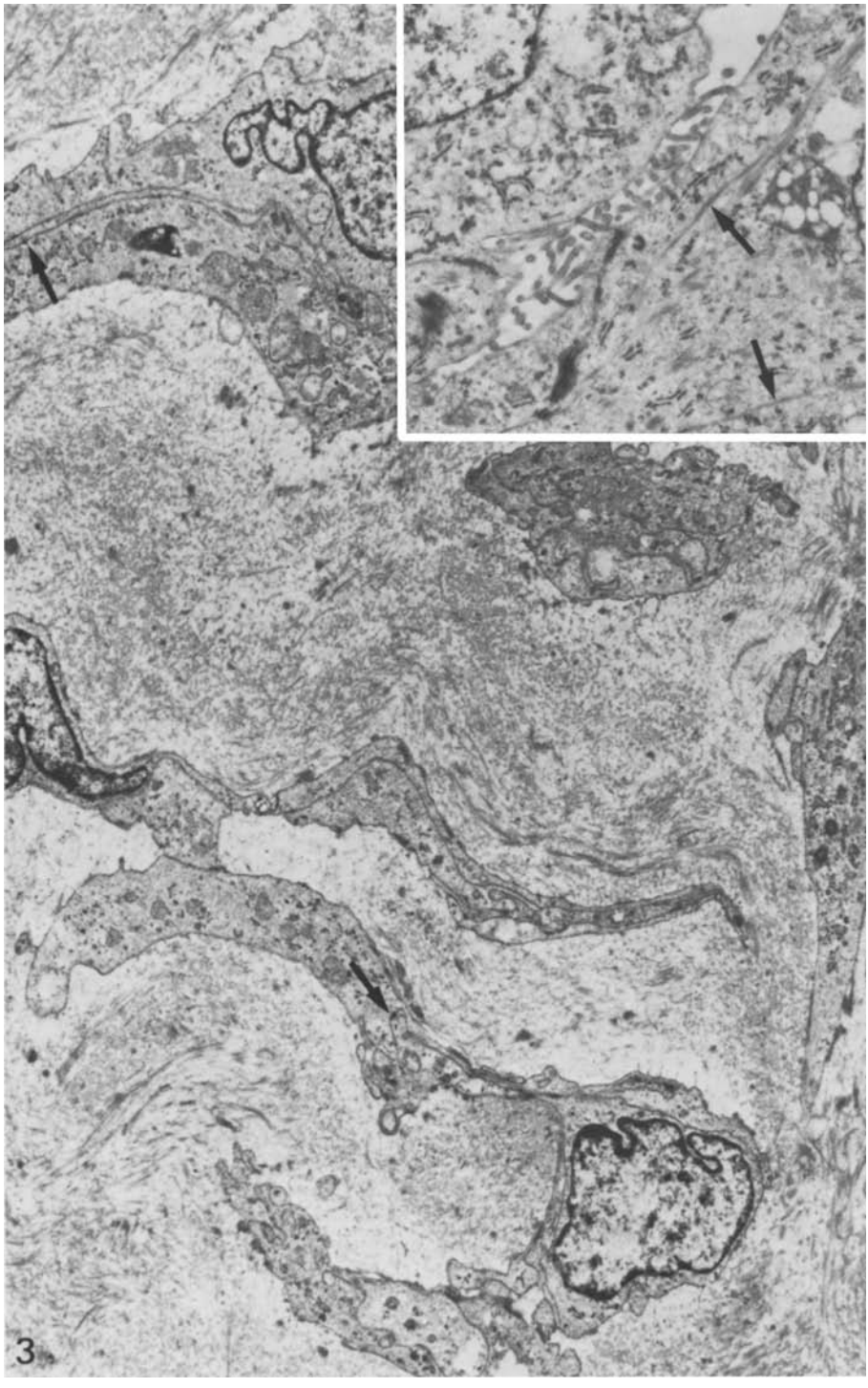

Fig. 3. Diffuse mesotheioma # 1. Portions of "stromal" tissue noted in Figure 1 contain groups of narrow tumor cells that show a considerable degree of organization maintained through elongated cytoplasmic processes and small desmosome-like junctions (arrows) (× 5,600). *Inset*. Spindle cells occasionally demonstrated tonofilament-associated desmosomes, focal microvilli and intracytoplasmic filaments (arrows) (× 9,000)

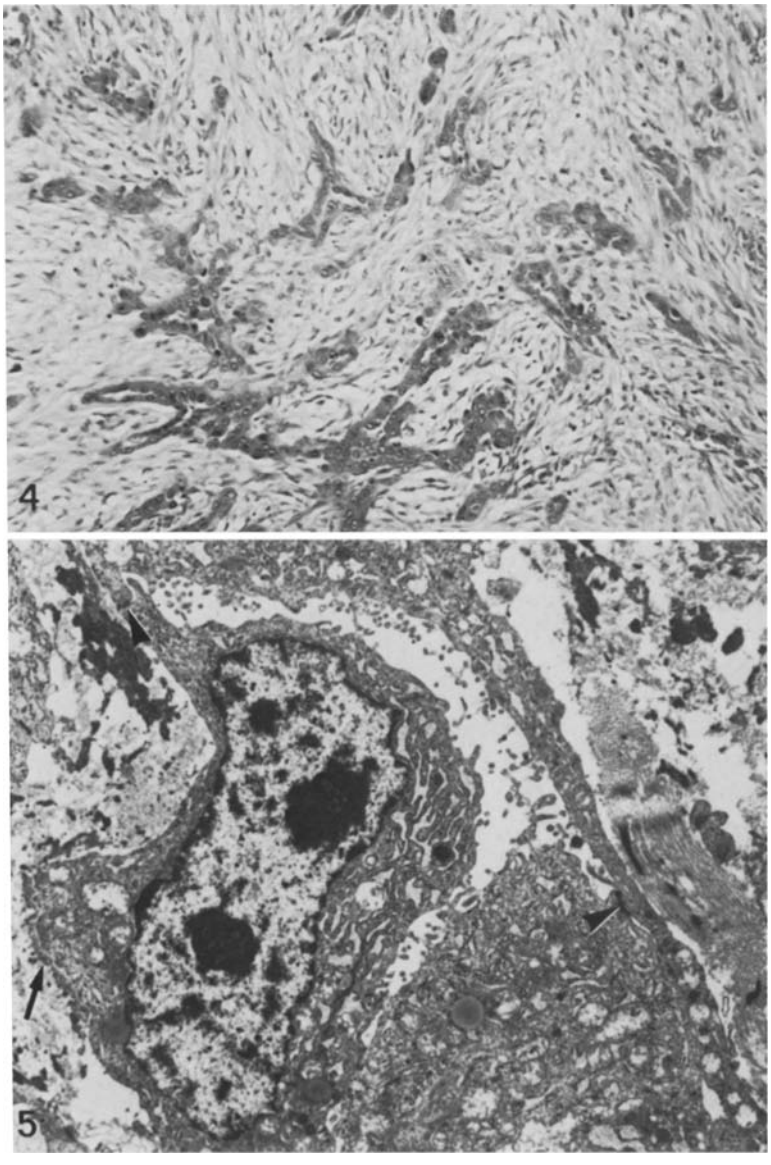

Fig. 4. Diffuse mesothelioma # 2. Narrow anastomosing cords of tumor cells with slit-like lumens are separated by a desmoplastic stromal tissue (H and E, ×130)

Fig. 5. Diffuse mesothelioma # 2. The lumen-forming cords of tumor cells in Fig. 4 have apical microvilli and zonula occludens-type junctions (*arrowheads*) and occasional foci of basal lamina (*arrow*). Dilated rough endoplasmic reticulum is prominent (×6,400)

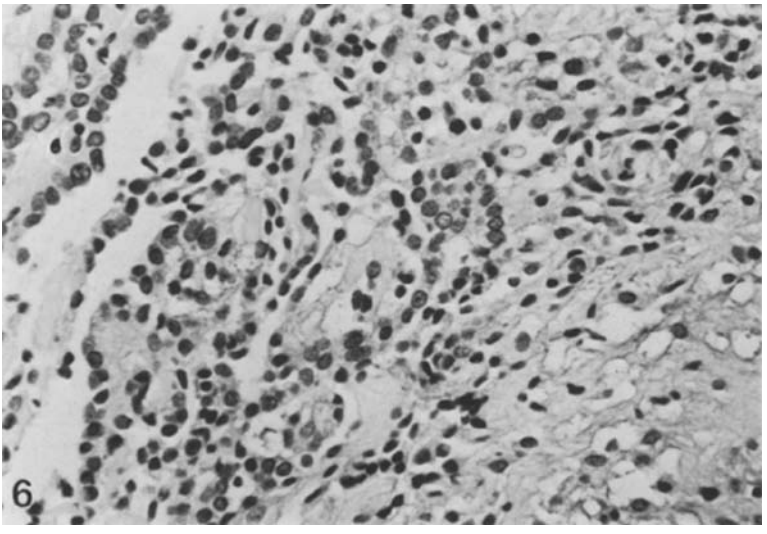

Fig. 6. Diffuse mesothelioma # 3. Polygonal cells in the "stromal" regions are closely associated or even in direct continuity with tumor cells lining the numerous cleft-like spaces (H and E, × 320)

were groups of more fusiform, irregularly elongated tumor cells (Fig. 2). These cells were intimately associated with each other and with the adjacent epithelium-like cells. This intimate cellular relationship was maintained as narrow columns or small groups of spindle cells streamed into the large quantities of stromal collagenous matrix (Fig. 3). Even when tumor cells were widely separated, frequent cell-to-cell contacts were maintained, and small intercellular junctions were evident (Fig. 3). Occasional groups of spindle cells revealed well developed desomosomes, focal microvillous formation, and bundles of filaments within the cytoplasm (Fig. 3).

Figure 4 shows another example of a pleural mesothelioma of epithelial type with marked desmoplasia. Epithelium-type cell clusters with slit-like lumens seen in Fig. 4 were examined by electron microscopy (Fig. 5). A group of plump tumor cells joined by blunt or elongated cytoplasmic processes and poorly developed junctions formed a narrow irregularly shaped lumen. The tumor cells possessed apical microvilli, prominent dilated rough endoplasmic reticulum and intracytoplasmic filaments but no basal lamina. Near the nests of epithelium-like cells were spindle-shaped tumor cells similar to those in Fig. 3. They had a similar distribution of nuclear chromatin and abundant rough endoplasmic reticulum compared to the epithelial component (Fig. 5), and intercellular junctions and intracytoplasmic filaments. In the more desmoplastic regions, despite increasing separation by collagenous matrix, tumor cells maintained these fine structural features, and intercellular junctions persisted.

Figure 6 illustrates a third diffuse mesothelioma of biphasic type in which gland-like spaces lined by regular, cuboidal tumor cells were surrounded

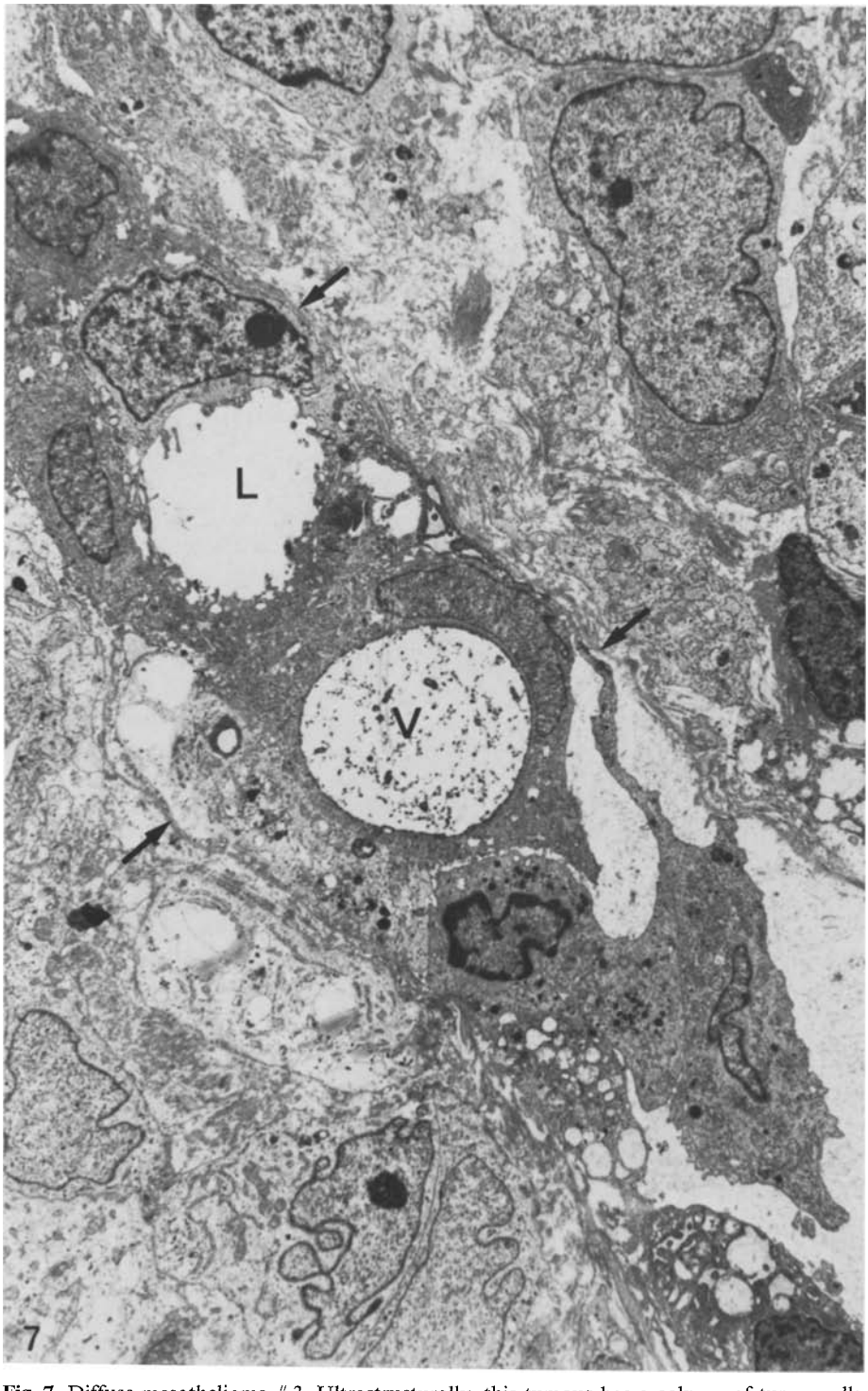

Fig. 7. Diffuse mesothelioma # 3. Ultrastructurally, this tumour has a column of tumor cells, one of which has an intracytoplasmic lumen (*L*) and another a large vacuole (*V*). Focal basal lamina (*arrows*) separates the column of cells from surrounding "stromal" cells whose cellular features and arrangement closely resemble tumor cells in Figs. 2 and 3 ($\times$ 4,000)

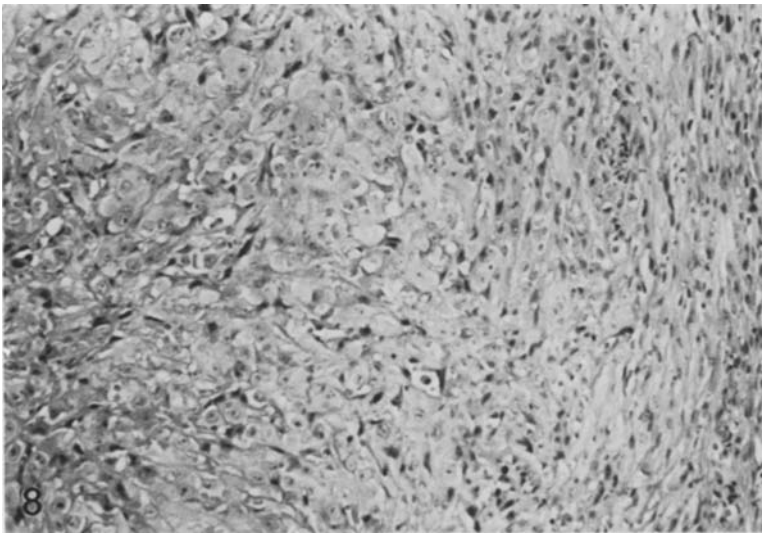

Fig. 8. Diffuse mesothelioma # 4. Sheets of polygonal tumor cells on the left gradually blend with the spindle cell component in this pleural mesothelioma with an undifferentiated growth pattern (H and E, ×130)

by stromal cells that were usually spindle-shaped, but often became more compact and plumper. Some of the more epithelioid cells in the stroma were associated with or in continuity with narrow, tubular spaces lined by tumor cells (Fig. 6), a feature confirmed in electron micrographs from such regions. What appeared to be an early stage in the formation of the epithelial component in this mesothelioma is shown in Fig. 7. A narrow, partially basal lamina delimited, column of tumor cells exhibited early intercellular lumen formation and was surrounded by intimately associated tumor cells lacking the features of fibroblasts. These latter cells (Fig. 7), were similar to the stromal cells shown in Fig. 2 and 3, though intercellular junctions were infrequent. In other regions of this case, the formation of the epithelial component was noted to be more advanced, with tumor cells forming a distinct microvillous bordered lumen separated from underlying and surrounding stromal-type cells by a well-defined, narrow basal lamina. Despite some features that suggested a fibroblastic differentiation of stromal cells, such as abundant rough endoplasmic reticulum and lyosomal granules, these cells often maintained contact via cytoplasmic processes that occasionally involved definite intercellular junctions (Fig. 7). Spindle-shaped stromal cells also formed focal basal lamina.

The fourth case was a diffuse mesothelioma with an undifferentiated growth pattern, showing a transition from polygonal to spindle shaped tumor cells (Fig. 8). Material available for ultrastructural studies was mainly of the spindle cells component. It revealed irregularly contoured, fusiform tumor cells in a highly collagenized matrix (Fig. 9). The cells had considerable numbers of microvilli that varied in distribution from focal to almost

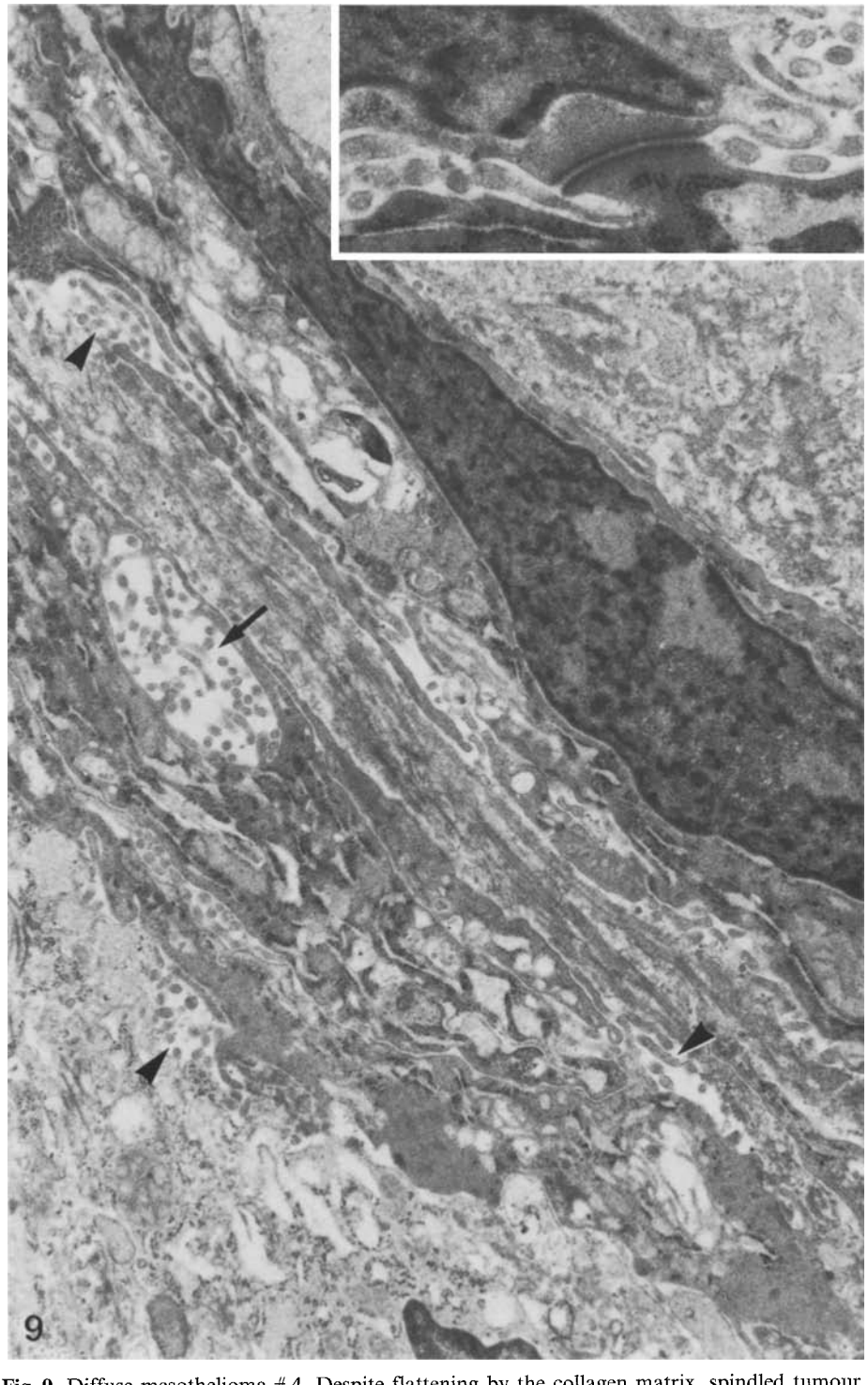

Fig. 9. Diffuse mesothelioma # 4. Despite flattening by the collagen matrix, spindled tumour cells retain surface microvilli (*arrowheads*) and have small intracytoplasmic lumens (*arrow*) and intercellular junctions (× 10,800; inset, × 18,900)

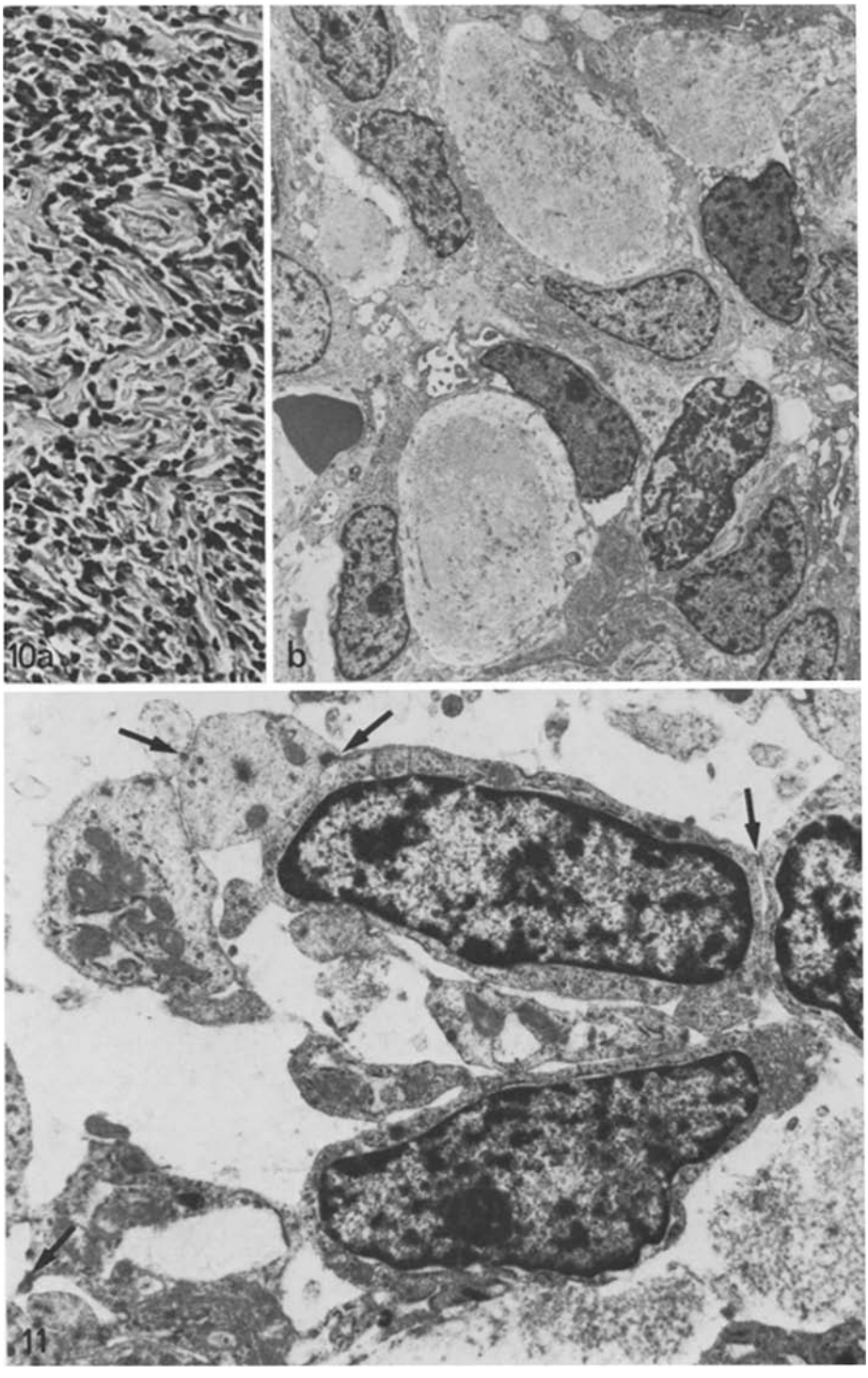

Fig. 10a, b. Localized mesothelioma # 1. **a** Flattened, spindle cells are separated by wavy strands of compact collagenous stroma. **b** Elongated and polygonal tumor cells form an intricate anastomosing network around compact bundles of collagen fibers. Except for varying amounts of RER, many tumor cells contain few organelles. Tumor cells are intimately associated and occasionally joined by inconspicuous junctions (**a**, ×250; **b**, ×2,300)

Fig. 11. Localized mesothelioma # 2. Short rows and small groups of tumor cells with minimal cytoplasm and sparse cytoplasmic organelles are closely associated and connected by small, poorly formed intercellular junctions (*arrows*) (×6,000)

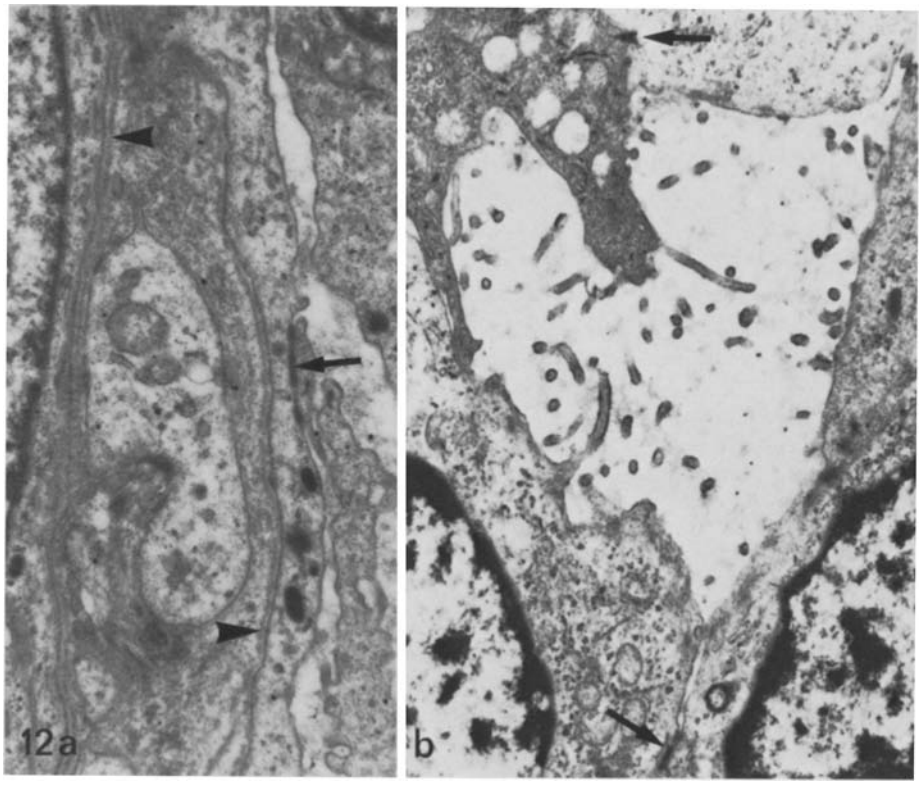

Fig. 12a, b. Two other examples of localized mesotheliomas in which (**a**) many tumor cells were partially enveloped by a narrow well defined basal lamina (arrowheads) and joined by maculae occludentes (*arrow*) and (**b**) very occasional microvilli and macula adherens-type junctions (arrows) were formed (**a**, ×15,600; **b**, ×10,000)

circumferential. Even when cells were compressed and flattened by the extensive collagenous matrix, small numbers of surface microvilli, intracytoplasmic lumens and intercellular junctions could still be discerned (Fig. 9).

B. Localized mesothelioma

The typical histology of a pleural localized mesothelioma is illustrated in Fig. 10a. In this subgroup of serosal lesions, a recurring growth pattern that was consistently present in at least some portion of each of the 10 tumors examined ultrastructurally is evident in Fig. 10b. Elongated and polygonal tumor cells were closely associated in cord-like arrays, separated by orderly columns of closely packed collagen fibers producing a repetitive pattern. Even in regions of another example of a localized mesothelioma in which the tumor cells were widely dispersed in the collagenous stroma (Fig. 11), many tumor cells continued to form compact groups and continuous columns.

Some tumor cells in the 10 localized mesotheliomas contained segments of dilated rough endoplasmic reticulum (Fig. 10b), but the majority did not. In fact, they were relatively devoid of organelles (Figs. 10b, 11). Generally, the fine structure of tumor cells in localized mesothelioma closely resembled that of stromal tumor cells in many of the diffuse mesotheliomas (Figs. 2, 3 and 7). Despite an appearance of elongation by light microscopy, most of the tumor cells in the localized mesotheliomas were cuboidal or polygonal. These cellular features, the relatively high nuclear to cytoplasmic ratio, the manner in which tumor cells contact each other and their arrangement in groups (Fig. 11) are not typical of fibroblastic differentiation.

In the majority of localized cases, intercellular junctions were evident, although in some instances this required a careful search. The junctions varied from maculae occludentes (Fig. 12a) to small maculae adherentes (Fig. 12b) but the former were always more frequent. Additional features included foci of basal lamina, (Fig. 12a) but only very infrequently, microvilli (Fig. 12b).

Discussion

Within certain limitations, morphological investigations can provide information about and insights into histogenetic aspects and developmental processes of neoplasms. Fine structural observations of the serosal tumors presented in this report provide observations important to the understanding of such processes in mesotheliomas, whether diffuse or localized. One of the more important observations is that "mesenchymal" cells in the stromal or sarcomatous areas of diffuse mesotheliomas are often not fibroblastic, but show various degrees of mesothelial differentiation. There is evidence of a gradual transition between such "mesenchymal" cells and distinctly epithelium-like cells, with classical mesothelial characteristics. As part of this sequence there is a gradual differentiation and organization of epithelium-type cells into structures reminiscent of the surface layer of serosal membranes with eventual separation from underlying cells by basal lamina. Localized mesotheliomas reveal evidence of similar features and various stages of the cellular organization noted in diffuse mesotheliomas.

On the basis of these findings, it can be postulated that the histological patterns of diffuse mesotheliomas result from a neoplastic proliferation of cells with the capacity to differentiate either to the surface or the subsurface component of normal serosal membrane. In this concept, localized serosal tumors can be assumed to mirror the early stages of the differentiation of specialized subsurface cells. Such a hypothesis would not preclude some diffuse mesotheliomas arising as a result of neoplastic induction of mesothelium.

It has been suggested (Klemperer and Rabin 1931; Dalton et al. 1979) that separate precursor cell types were responsible for diffuse and localized serosal neoplasms, surface mesothelial cells in the former and subsurface mesenchymal cells in the latter. Classification of mesotheliomas and the histogenesis of this tumor class have thus been thought to reflect the struc-

tural organization of normal serosal tissues. Experimental studies of mesothelial regeneration (Raftery 1973 a, b) and recent ultrastructural evidence (Suzuki et al. 1976; Suzuki 1980; Bolen and Thorning 1981) challenge this concept and suggest a different histogenetic pathway for serosal tumors, namely that the precursor cell for all types of serosal tumor, whether epithelial or sarcomatoid, resides in the submesothelial compartment.

On the basis of experimental work, regeneration of mesothelium has been attributed to deposition of mononuclear cells on denuded serosal surfaces (Watters and Buck 1972; Ryan et al. 1973), or to migration and differentiation of committed submesothelial cells to reconstitute the serosa following incisional injury or asbestos exposure (Raftery 1973a, b; Davis 1974). In the present context, the latter theory is of particular interest and suggests a potential for induction of specialized but undifferentiated submesothelial cells that might be a precursor for both fibrous and epithelial mesotheliomas. If such a hypothesis has relevance to mesotheliomas, it might be expected that transitional forms or cell types might occur between the two classical subtypes of mesothelial tumors. Recently, tumor cells with ultrastructural characteristics intermediate between classical epithelial and fibroblastic appearing cells in epithelial and biphasic mesotheliomas have been demonstrated (Suzuki 1980; Bolen and Thorning 1980; Suzuki et al. 1976). Based on the ultrastructural findings of their comparative study, Bolen and Thorning (1980) concluded that there is "a direct histogenetic relationship between the epithelial-appearing cells and the mesenchymal-appearing cells of human mesothelial neoplasms". It is also notable that pleural tumors sometimes occur whose gross characteristics are intermediate between the classical diffuse and localized forms (McCaughey 1965).

The ultrastructural aspects of both the epithelium-type and fibrous-appearing serosal tumors detailed in this report provide further evidence for the concept advanced by Bolen and Thorning (1980). Our observations suggest again that the "non-epithelial" component of diffuse epithelial mesotheliomas, that is usually designated as their "fibrous or sarcomatous" stroma, is an integral part of the tumors with many of the stromal cells showing evidence of mesothelial differentiation. If this interpretation is correct, it has important implications for the classification of serosal tumors, and will clarify their histogenesis, explaining the variety of histological patterns in mesotheliomas. The true nature of the "fibrous" portion of epithelial mesotheliomas, and the presence of transitional cells in these tumors can be recognized in routine histological sections (Suzuki et al. 1976), and may be useful in the differential diagnosis between metastatic carcinoma of the pleura and mesothelioma.

The position of localized fibrous tumors within the spectrum of mesotheliomas is becoming established. Despite a number of reports indicating that localized mesotheliomas do not show mesothelial differentiation (Foster and Ackerman 1960; Hernandez and Fernandez 1974; Klemperer and Rabin 1931; Luse and Spjut 1964; Osamura 1977; Scharifker and Krancko 1979; Dalton et al. 1979), some ultrastructural studies of localized pleural lesions suggest at least minimal mesothelial differentiation (Kawai et al. 1978; Briselli et al. 1981). Indeed, if one reviews previous electron microscopic studies

of mesothelioma reported as localized tumors (Briselli et al. 1981; Hernandez and Fernandez 1974; Luse and Spjut 1964; Kay and Silverberg 1973; Osamura 1977; Kawai et al. 1978; Benisch et al. 1981; Bolen and Thorning 1980), 16 of 19 reported cases reveal features indicative of mesothelial differentiation such as cell-to-cell relationship, intercellular junctions, foci of external lamina and rarely, microvilli. Only 3 tumors appear to be purely of fibroblastic origin. A fusiform appearance and prominent development of rough endoplasmic reticulum are insufficient evidence to dismiss mesothelial differentiation. The latter organelle is prominent in well-differentiated epithelial cells in diffuse mesothelioma, and more important than the shape of tumor cells is their cell-to-cell relationship; typical fibroblasts are usually well separated and infrequently contact each other. However, as noted by Briselli et al. (1981), and also evident in our Figures 10b and 11, tumor cells in localized tumors are intimately related, display intercellular junctions, basal lamina and infrequently, microvillous formation. Similar characteristics are evident in mesenchymal-appearing cells of epithelial and biphasic mesotheliomas (Suzuki et al. 1976; Bolen and Thorning 1980; Suzuki 1980).

Localized and diffuse mesotheliomas clearly behave differently. Diffuse tumors are malignant while localized tumors usually are benign. Diffuse mesotheliomas are often caused by exposure to asbestos, but no such relationship has been shown for localized tumors.

In spite of these distinctions, and the different gross appearance of these two neoplasms, both seem to arise from mesothelial cells. There are, of course, many cells in the body which give rise to more than one kind of neoplasm.

It can be hypothesized that mesotheliomas recapitulate the pattern of differentiation of normal serosal tissues. In mesotheliomas, subsurface cells, very like mesenchymal cells morphologically, gradually acquire the features of mesothelium and finally evolve to fully differentiated, and surface-oriented mesothelial cells organized over a specialized submesothelial component. Diffuse epithelial mesotheliomas can harbor cells mimicking all stages of normal serosal tissue embryogenesis and regeneration, while localized fibrous mesotheliomas show only the earlier stages of development. However, this does not imply that individual cases of mesothelioma progress sequentially through all stages of this process or necessarily exhibit the full spectrum of normal developmental pathways.

This pattern of histogenesis explains the diverse histology of mesotheliomas. Pathologists are beginning to appreciate the heterogeneity of many tumors, the wide variety of their cells, their differing degrees of differentiation, their various secretory products and the heterogeneity of their organization (Finchk 1981; Henson 1982). Mesotheliomas are a case in point.

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