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A Light and Electron Microscopic Study of Endometrial Sarcomas of the Uterus*

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Summary. 38 endometrial sarcomas were studied light microscopically, 5 of them additionally with the electron microscope. According to their histological appearance these tumours were classified as homologous stromal sarcomas (13 cases), pure heterologous (4) and mixed mesodermal sarcomas (21). The ultrastructure is described with reference to the cytoplasmic differentiation of the tumour cells. A basic immature cell type was present in all endometrial sarcomas irrespective whether they were of pure homologous or of mixed type. In regard to the striking similarity between this cell and cells of the early proliferating endometrium an origin of all endometrial sarcomas from immature stromal cell is suggested. The mixed tumours contain a number of highly differentiated cells like smooth muscle cells, rhabdomyoblasts, fibroblasts etc. As there was a number of cells intermediate in cytoplasmic appearance between immature and differentiated end stages it seems likely that the latter develop from the former. Thus the undifferentiated cell represents the stem cell from which the differentiation processes of all cell lines take their origin. A transition from neoplastic epithelium to neoplastic mesenchyme could not be demonstrated in the 4 mixed mesodermal sarcomas analysed ultrastructurally. From these observations it is concluded that the mixed epithelial-mesenchymal endometrial tumours originate by a simultaneous malignant transformation of cells with a fixed differentiaton potency.

Introduction

Endometrial sarcomas comprise the structurally and cytologically most complex and heterogenous group of uterine tumours (Horlyck and Petri, 1964; Kempson and Bari, 1970; Laffargue *et al.*, 1966; Norris and Taylor, 1966; Norris *et al.*, 1966; Ober, 1955; Saksela *et al.*, 1973; Sternberg *et al.*, 1954). Although the histological appearance may vary considerably, there are now convincing data suggesting a common histogenesis of these tumours from the endometrium proper.

A problem in classifying tumours is to decide how finely subdivisions should be made (Sobin, 1974). Thus Obers' original classification, on a purely histologiacl basis provides no less than 16 clear, objectible and reproducible endpoints. This seems to us somewhat too complex for routine diagnostic use. By summarizing tumours with equal biological and therapeutic significance in the same subgroup a nomenclature, based primarily on histological-histogenetic principles, has evoked (Table 1) which comprises three major subgroups in the endometrial group: 1) pure homologous sarcomas 2) pure heterologous sarcomas 3) mixed mesodermal sarco-

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Table 1. Histological-histogenetic Classification of 79 Uterine Sarcomas

I. Leiomyosarcoma	35
II. Endometrial Sarcomas	
1. Pure homologous sarcomas (including 1 low grade sarcoma)	13
2. Pure heterologous sarcomas	4
3. Mixed mesodermal sarcomas with or without heterologous sarcomatous elements	21
III. Angiosarcomas (Hemangioendotheliomas and Hemangiopericytomas)	2
IV. Sarcoma unclassified	4

mas. For the diagnosis of these three lesions sufficient criteria are now available and are accepted by most pathologists. In the present study the material of 39 endometrial sarcomas was analysed; 1 case of pure stromal sarcoma and 4 cases of mixed mesodermal sarcomas were analysed electron microscopically. It is not the purpose of this paper to review the abundant literature on classification, clinic and prognosis of uterine sarcomas. Rather our intension here is to consider these tumours from their fine structural viewpoints and to provide additional information to the histogenesis of this tumour group.

Material and Methods

A material of 79 uterine sarcomas was collected from the files of three institutions.[1] All histological specimens were reanalysed and classified according to the classification in Table 1. Those cases with inadequate histological material for study were excluded from our analysis. From 5 tumours tissue for both light- and electron microscopy was obtained.

Tissue for light microscopic investigation[2] was fixed in formalin. Sections were stained with hematoxylin-eosin, van Gieson, Masson-Goldner, PAS and Gomori staines.

For electron microscopy small specimens were immersed a few minutes after resection in phosphate buffered 2.5% glutaraldehyde solution, pH 7.4. The tissue was fixed 2 hours, washed several times and postfixed with 1% OsO_4, dehydrated in ethanol and embedded in Epon 812 or Westopal W. Semithin sections were stained with toluidine blue. Fine sections were cut with diamond knives on a Reichert ultramicrotome mounted on uncoated grids and stained with uranyle acetate and lead citrate. The sections were examined with a Zeiss 9 A electron microscope.

Results

In regard to diagnostic and prognostic criteria of uterine sarcomas we may refer to previous publications (literature cited above). In this chapter only a short histological description of the three tumour groups of endometrial sarcomas is presented. Emphasis is given to some structural peculiarities and variations of some cell types found in our own material.

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Pure Homologous Stromal Sarcomas

These tumours appeared in two types: One which contained small poorly differentiated polygonal cells in a loose mesenchymal tumour tissue, that closely resembled the early proliferative phase during the menstrual cycle. The other variant consisted of closely packed larger cells with a round oval contour. The polymorphy of these tumour cells varied widely but was generally only slight to moderate. In one case a differentiation to smooth muscle cells was observed. Focal clustering of tumour cells around vessels may give the impression of an angiomatous tumour. One of the 13 cases was regarded as a low grade sarcoma as revealed by relative uniformity, lack of mitoses and presence of invasive growth.

Pure Heterologous Sarcomas

In our material 3 tumours were classified as pure rhabdomyosarcomas and one additional as chondrosarcoma. Structurally they bear resemblance to corresponging heterologous structures in mixed mesodermal sarcomas.

Mixed Mesodermal Sarcomas

All 21 tumours of this group were composed of both epithelial and mesenchymal elements. 5 of the neoplasms contained only homologous sarcomatous tissue while all others showed in addition heterologous sarcomatous components. Usually the carcinomatous elements were clearly separated from each other. Within a few tumours foci of an intimate intermingling of epithelium and mesenchyme suggested a transformation of one tissue into the other. The differentiation of epithelial elements generally corresponds to that described by previous authors (Ober, 1955; Sternberg *et al.*, 1954). In only one case were psammoma bodies found, both ovaries being free of tumour. The sarcomatous areas vary greatly from one area to the other, the frequency with which the different components are encountered being dependent somewhat on the actual number of slides analysed. Undifferentiated areas which closely resemble pure homologous sarcoma were found in all cases. Trichrome stains indicate that in 9 cases foci of fibroblastic or leiomyoblastic differentiation is present. Sometimes it is difficult or even impossible to distinguish between these two structures at light microscopic level. The most common heterologous elements were rhabdomyosarcoma (12 times) and chondrosarcoma (8 times). In addition to the classical tadpole- and racket-shaped rhabdomyoblasts two more rare types were encountered, the pseudoepithelial rhabdomyoblasts and ganglion-cell like rhabdomyoblasts. In the former a myxoid stroma with small aggregates of cells are sometimes seen which closely resemble and may be confused with carcinomatous elements. These cells possess an eosinophilic, granular or fibrillar cytoplasm and a nucleus with a prominent nucleolus. Often at the periphery of this cell a lighter cytoplasmic rim may be observed which helps to differentiate it from carcinomatous cell nests. The latter bears a resemblance to ganglion cells of ganglioneuroblastomas (Fig. 8) but ultrastructurally showes the typical myoblastic appearance.

Occasionally islets of chondrosarcoma were scattered throughout. These lesions were usually highly differentiated, the plumb cells containing large double nuclei. Usually chondroblastic areas merged with the adjacent undifferentiated stroma. In only one case did we find a focus of lipoblastic differentiation.

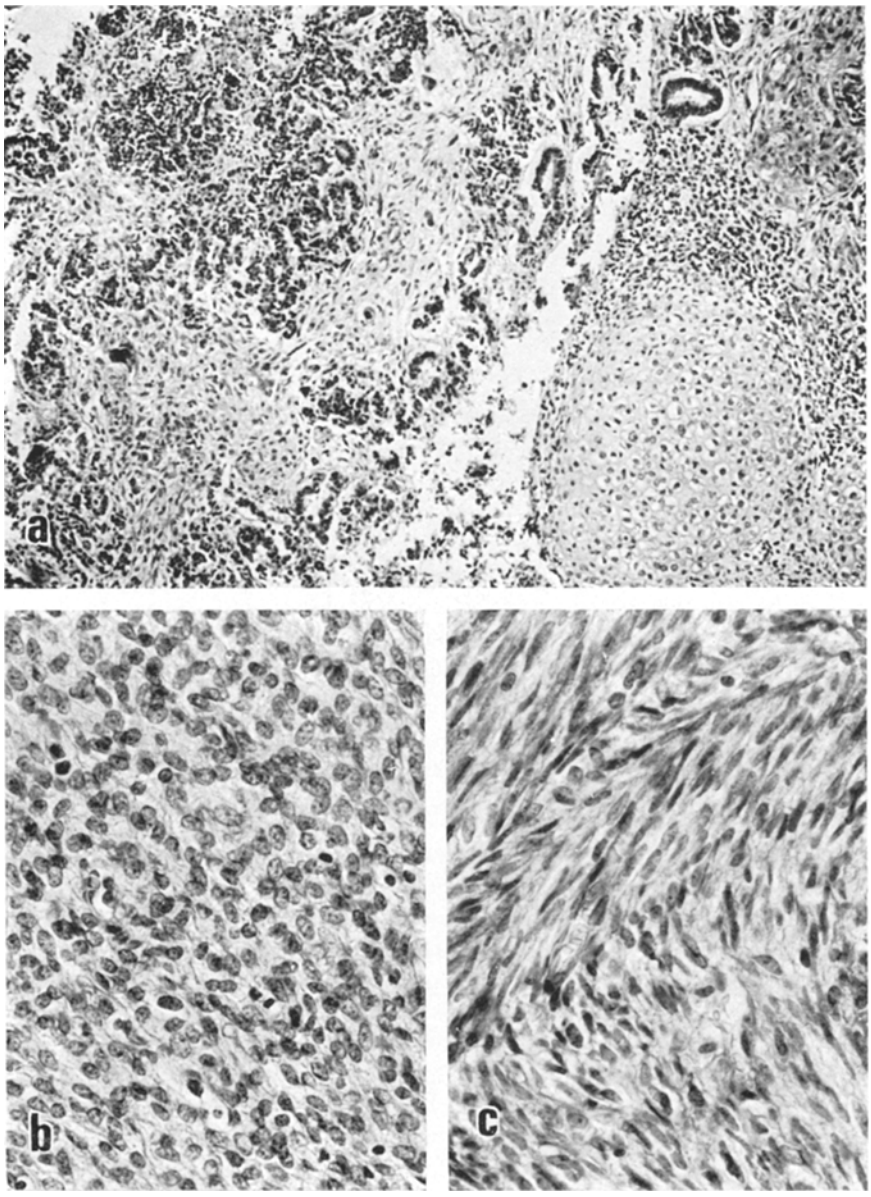

Fig. 1a—c. Mixed mesodermal tumour. (a) Close intermingling of carcinomatous and sarcomatous elements. Note well differentiated chondroid island (c). (b) Undifferentiated area with some mitoses. (c) Leiomyoblastic differentiation with fascicular arrangement of tumour cells

Electron Microscopic Examination

The ultrastructure of 1 homologous and 4 mixed mesodermal sarcomas was examined under the following aspects:

(1) cell configuration and cell relationship,

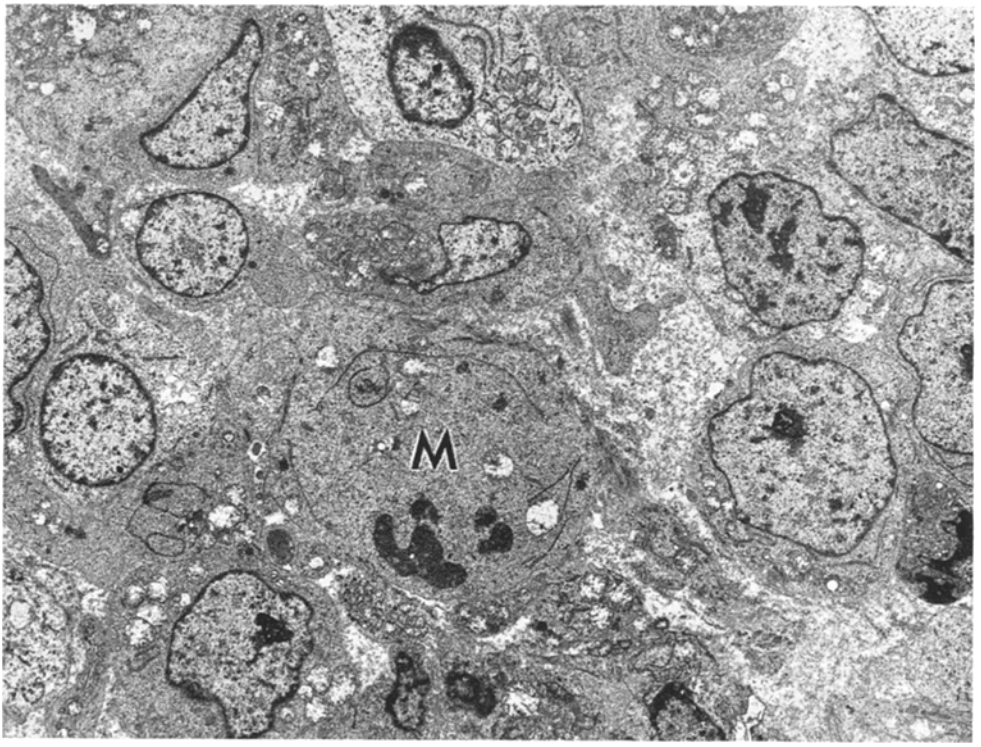

Fig. 2. Pure stromal sarcoma. The undifferentiated tumour cells show a cytoplasm with varying electron density and only few cell organelles. *M* mitosis. Magn. ×4000

(2) cellular differentiation processes with special attention given to specific cytoplasmic structures,

(3) classification of cell populations (cell linings like fibroblasts etc.).

I. Pure Homologous Sarcoma

The characteristic cells of this tumour are shown in Fig. 2. Two poorly differentiated cell types could easily be distinguished: One round to oval cell with a moderately dense cytoplasm and a nucleus with several indentations. The cytoplasm contained numerous ribosomes and some tubules of granular endoplasmic reticulum. The mitochondria were round to oval and were concentrated in small clusters. A small Golgi apparatus was located near the nucleus.

The other cell type was of similar size but the cytoplasm contained fewer cell organelles and was less electron dense. The nucleus had a more smooth contour and surface specializations like desmosomes were absent. The intercellular space contained some amorphous material but generally lacked collageneous fibrils. Mitoses were often seen.

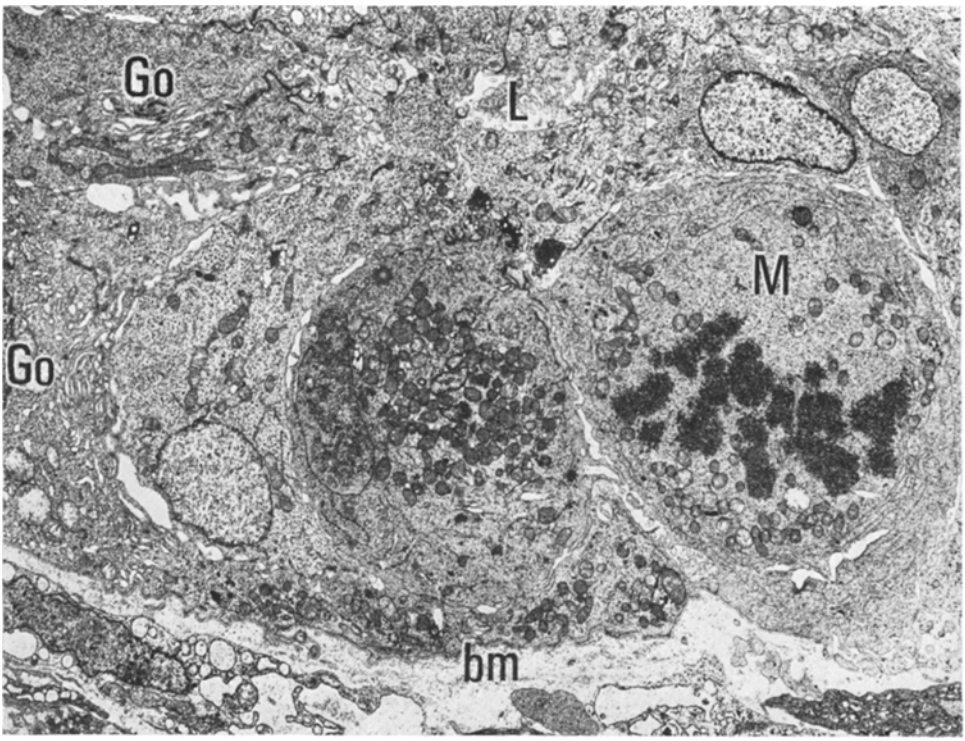

Fig. 3. Mixed mesodermal tumour. Carcinomatous component with a central lumen (*L*) and a well defined basement membrane (*bm*). Note cells with hyperplastic Golgi fields (*Go*) and one cell with numerous mitochondria. *M* mitosis. Magn. ×7300

II. Mixed Mesodermal Sarcomas

Sampling is probably the major prime limitation of electron microscopy of mixed mesodermal sarcomas, since the limited volume in the tissue usually prevents an adequate ultrastructural appraisal of these neoplasms. From our 4 cases in only two could we study both epithelial and mesenchymal tissues while in one case there was either carcinoma or sarcoma present. Otherwise these tumours showed similar features, therefore they will be described conjointly.

Carcinoma. The carcinomatous areas varied from well differentiated columnar cells to undifferentiated solid sheets or cords of cells. Electronmicroscopically a transformation of epithelial into mesenchymal tissue and vice versa could not be detected. The neoplastic glands were separated from sarcoma by a well defined basement membrane (Fig. 3), although loss of coherence of carcinoma cells and disruptions of the basement membrane by cytoplasmic projections, which invaded the stroma, could be seen occasionally. Two principal cell types were observed, which according to their electron density were designated as light and dark cells. Both usually contained one nucleus of various size and identations of various depth. In some cells heavily lobulated nuclei were seen. More differentiated tumour

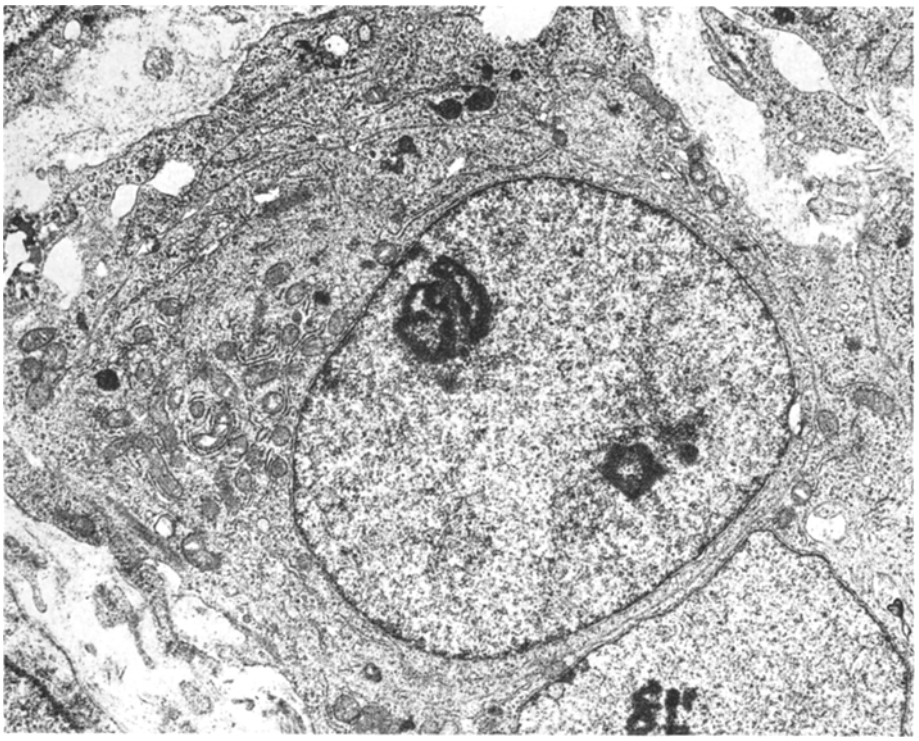

Fig. 4. Undifferentiated mesenchymal cell of a mixed mesodermal tumour with only few cytoplasmic organelles. Magn. ×9900

cells showed microvilli at their luminal surface. Desmosomes were usually conspicuous. Granular endoplasmic reticulum, Golgi fields and mitochondria were hyperplastic in some cells while they were nearly lacking in others. Where mitochondria were abundant they usually collected in some portion of the cell. Occasionally dehiscence of the cell membrane of adjacent cells could be seen producing intercellular spaces that at times had short microvilli projections.

Sarcoma. Ultrastructurally the mesenchymal part of mixed mesodermal sarcomas with its various differentiation processes showed a tremendous variety of different cell types and structures. According to their counterparts in normal tissues these cells could be recognized on the basis of their general ultrastructure, shape and especially of their specific cytoplasmic organelles like myofibrils etc. In the following description the cells are referred to as undifferentiated, fibroblastic and leiomyoblastic cells and as rhabdomyoblasts.

Undifferentiated Cell (Fig. 4). The cells to a certain degree resembled those found in homologous stromal sarcoma. They had scant cytoplasm and were round to polygonal in shape. The main cytoplasmic feature were ribosomes and polyribosomes. Few mitochondria and some profiles of endoplasmic reticulum were scattered throughout the cytoplasm. The nucleus contained one or two prominent nucleoli. Contrary to the pure sarcoma only one undifferentiated cell type could be

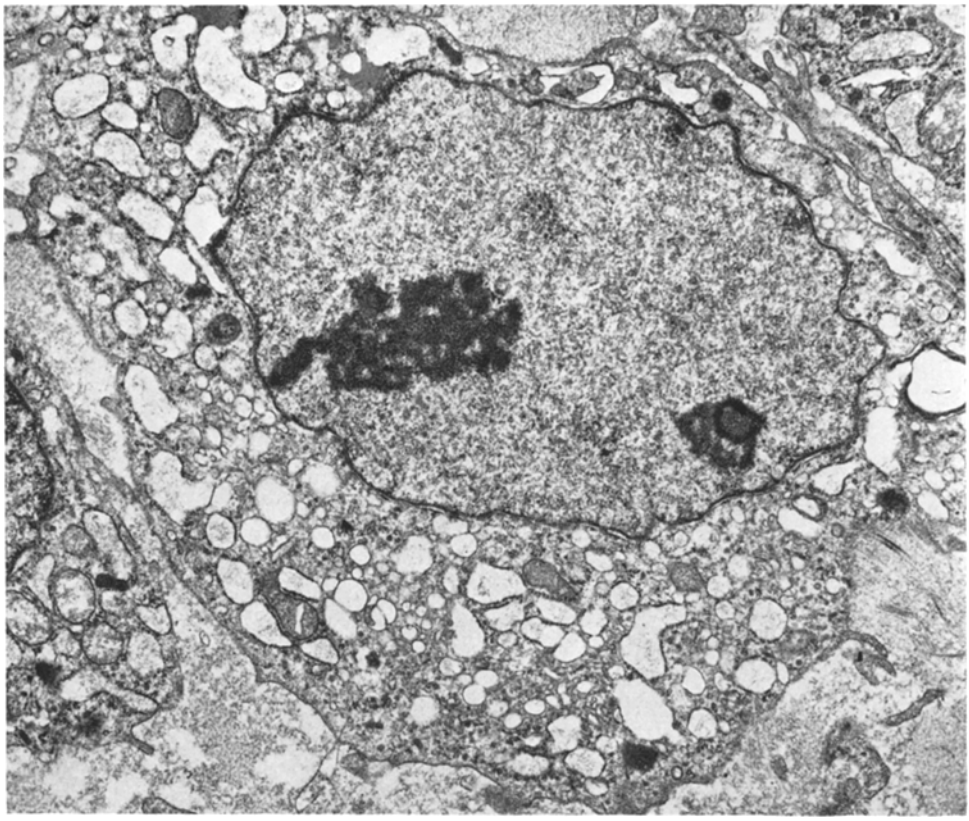

Fig. 5

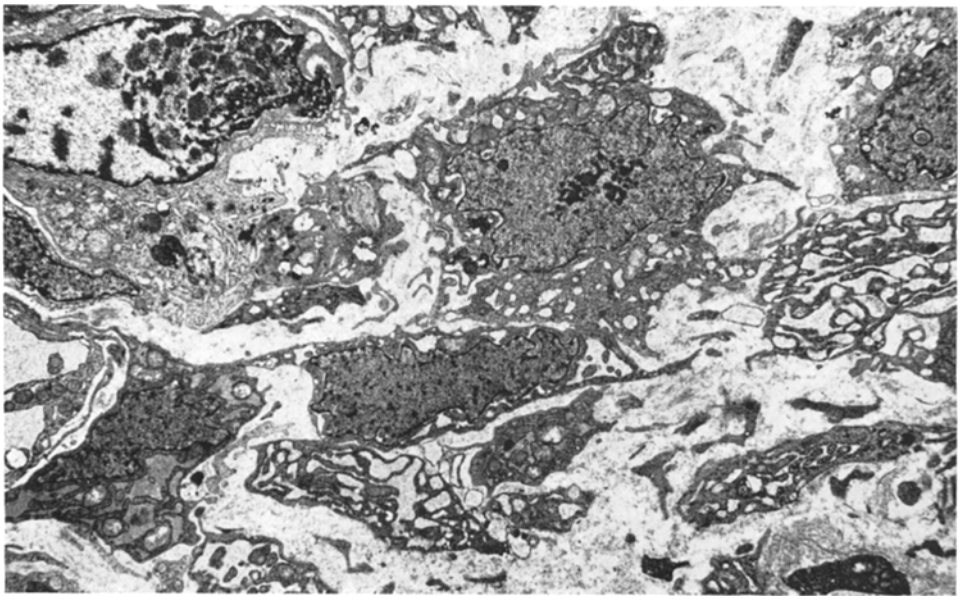

Fig. 6

visualized. A number of cell types intermediate in cytoplasmic appearance were found between these immature cells and the following cell types.

Fibroblastic Cell (Figs. 5 and 6). The fully differentiated fibroblasts were characterized by their polygonal shape with multiple cytoplasmic processes and numerous cisterns of dilated granular endoplasmic reticulum. Many cisterns contained a fibrillar-floccular material. At the surface of these cells occasional margins of condensations were seen often in the very vicinity of intercellular collageneous fibrils.

Smooth Muscle Cell (Fig. 7). Ultrastructurally cells were found which in their cytoplasmic features and shape closely resembled those found in uterine leiomyosarcomas (Böcker and Strecker, 1975). Cell types could be distinguished, being regarded as representing different stages of development toward smooth muscle. The more immature of these cells showed an excentrically located nucleus with smooth contours in an elongated cytoplasmic body. The cytoplasm contained a number of ribosomes and polyribosomes, well developed Golgi fields, a moderate number of mitochondria and only rew tubules of rough endoplasmic reticulum. Additionally bundles of microfilaments were encountered.

The most differentiated cells resembled strikingly smooth muscle cells. The bulk of the cytoplasm was occupied by myofilaments with few oval to fusiform dense areas. Long slender mitochondria, few elements of granular endoplasmic reticulum and free ribosomes were interpersed among tracts of myofilaments. Small vesicular inpocketings and cellular vesicles were likewise rare when compared with the counterparts in leiomyosarcomas. A surface coat was also generally lacking. In addition to the specific elements occasional dense bodies, suggested to be lysosomes could be traced.

Rhabdomyoblasts (Figs. 8 and 9). The differentiation of striated rhabdomyoblasts from primitive mesenchymal cells has been described in previous papers (Boram *et al.*, 1972; Böcker and Stegner, 1975; Overbeck, 1967). Ultrastructurally the rhabdomyoblasts showed similar cytoplasmic and nuclear appearance irrespective of their shapes and cellular arrangements. The nucleus was round and had a smooth contour. There was at least one ball like nucleolus. Contrary to the light-microscopic appearance the chromatin was evenly distributed throughout the nucleus without clumping at the nuclear membrane. The bulk of the cytoplasm was usually filled with myofibrils, which were seldom oriented in a regular sarcomeric pattern. Usually a small rim at the periphery of the cell was sparse of myofibril formation. Small Golgi bodies were seldom encountered. Other cell organell esincluded mitochondria, lipid bodies, and scant endoplasmic reticulum.

Fig. 5. Mixed mesodermal tumour. A sarcoma cell which closely resembles cells of the endometrial cycle of about the 15th to 20th day. Note dilated cisterns of rough endoplasmic reticulum, numerous small vesicles, and an area of condensation with associated collageneous fibrils. Magn. ×12900

Fig. 6. Well differentiated fibroblastic area of a mixed mesodermal tumor. Magn. ×4900

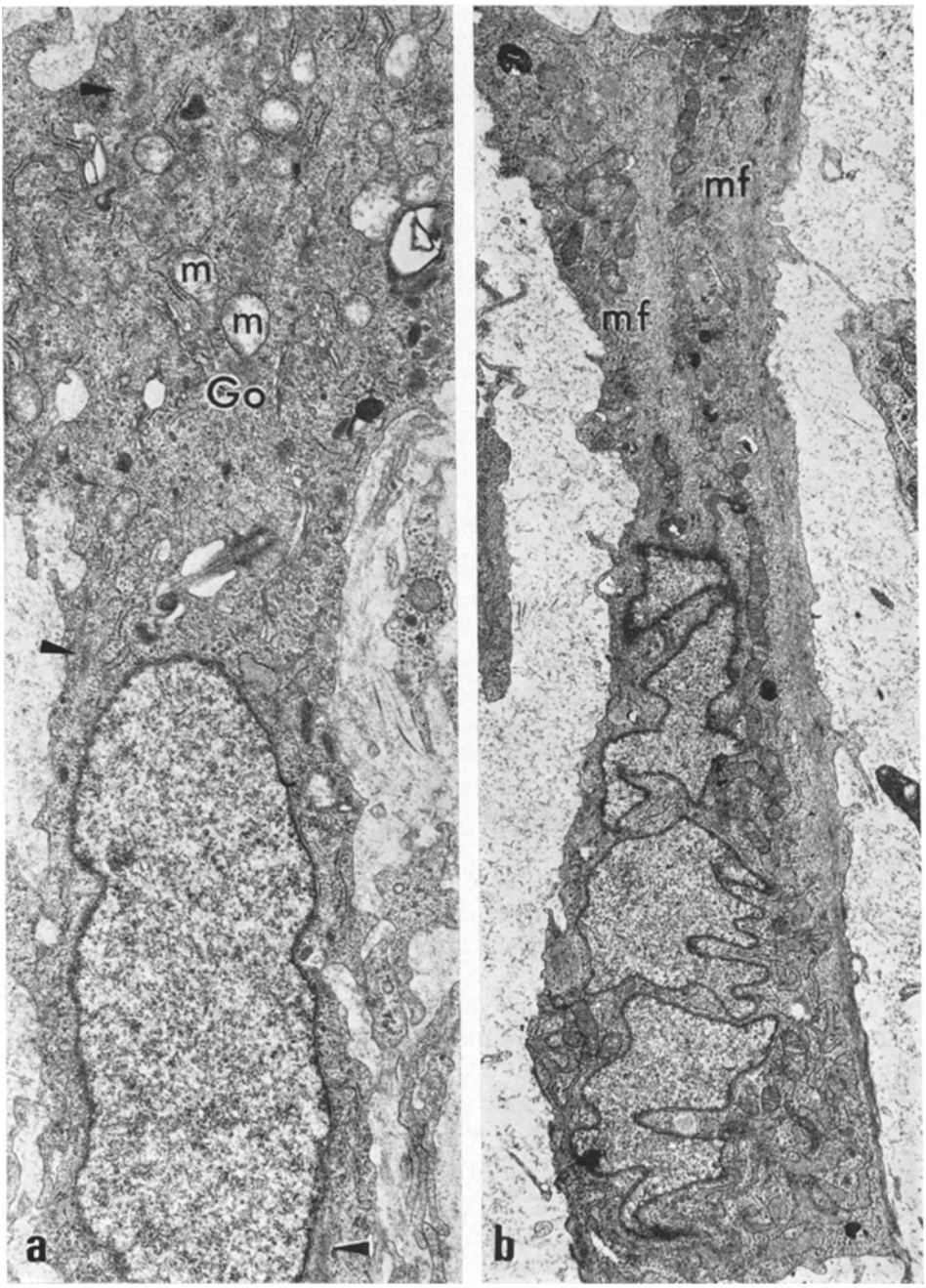

Fig. 7a and b. Leiomyoblastic differentiation in a mixed mesodermal tumour. (a) Immature leiomyoblast with numerous free ribosomes, a well developed Golgi field (*Go*), scattered mitochondria (*m*) and scattered bundles of microfilaments (arrows). Magn. ×9100 (b) Smooth muscle cell with typical myofilaments (*mf*). Magn. ×9900

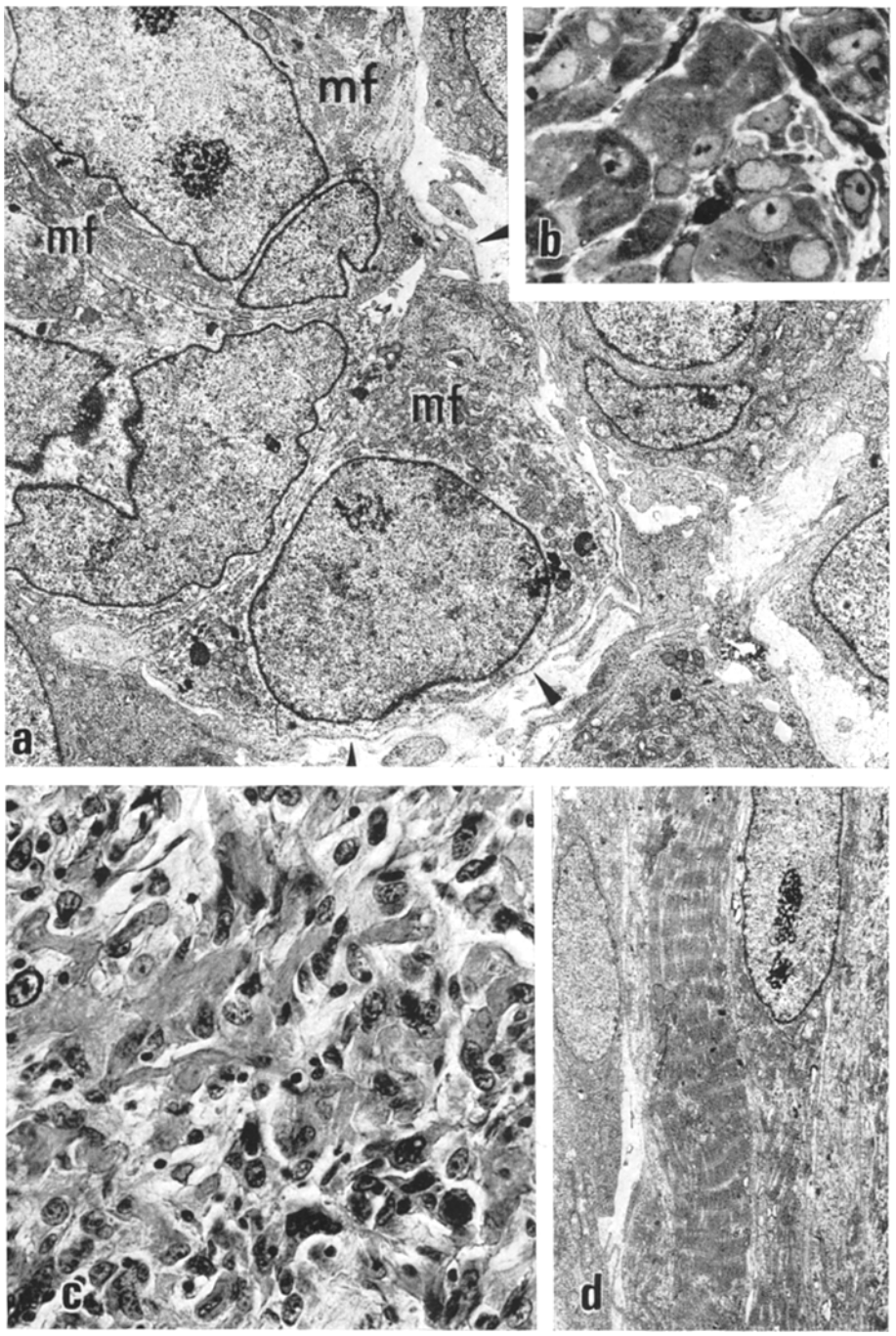

Fig. 8a—d. Rhabdomyoblasts of a mixed mesodermal tumour. (a and b) pseudoepithelial arrangement of rhabdomyoblasts, which are partly limited by a basement membrane (arrows). *mf* myofibrils. Magn. in (b) ×7200. (c and d) typical strap like rhabdomyoblasts. Note sarcomeric pattern of myofibrils in d. Magn. ×4300

Discussion

Endometrial sarcomas show a wide variety of histological patterns which have been analysed in numerous studies during recent years (literature see above). On the basis of morphology and biologic behavior it seems appropriate to distinguish between three subgroups:

1) pure endometrial stromal sarcomas,

2) pure heterologeous sarcomas, most commonly rhabdomyosarcomas and chondrosarcomas,

3) mixed mesodermal sarcomas with or without heterologeous sarcomatous elements.

The electron microscopic study discloses a wide spectrum of different cell types. The most immature of these cells occur in pure stromal sarcomas (see also Komorowski *et al.*, 1970) and in undifferentiated areas of mixed mesodermal sarcomas. The cytoplasm of these tumours is poorly differentiated with myriads of ribosomes, small clusters of mitochondria, only a small Golgi field and few tubules of granular endoplasmic reticulum. Desmosomes were neither detectable in the pure homologous sarcoma (contrary to the findings of Komorowski *et al.*, 1970) nor in sarcomatous areas of mixed tumours. It is interesting that cells closely resembling the undifferentiated elements in our 5 tumours have been described in the early proliferative endometrium of menstruating woman (literature see Cavazos and Lucas, 1973; Wienke *et al.*, 1968). Thus it may be concluded that these primitive tumour cells have their origin in endometrial stromal cells. During the course of our study it became evident that it is impossible to determine the exact nature of each mesenchymal cell. Nevertheless, we were able to clarify the the developmental stages of at least some mesenchymal "cell lines" on the basis of specific cytoplasmic proteins and of the general ultrastructure and on the relationship of the cells to each other. The most simple and somewhat "physiologic" differentiation that may be seen in pure and mixed sarcomas is the development of fibroblasts and of cell elements that closely resemble those of the mid-endometrial cycle. Both these cells contain cytoplasmic organelles and specializations of the cell surface which are directed toward a synthesis of collagen. The second homologous element is the leiomyoblast which, when fully differentiated, contains many tracts of longitudinally oriented myofilaments. Ryan *et al.* (1974) in an ultrastructural study have described the development of typical intracytoplasmic myofilaments in fibroblasts of granulation tissue which he called myofibroblast. Although a similar cytoplasmic differentiation from fibroblasts in our tumour cannot be excluded, it seems to us more likely that the typical neoplastic leiomyoblasts arise directly from the undifferentiated tumour stem cells.

Contrary to the homologous elements described above the heterologous tissues are only encountered in pure heterologous and in mixed sarcomas. These tissues have led to many concepts of histogenesis of mixed mesodermal sarcomas like those of the embryonal cell rests etc. However most of these hypotheses have been discarded and it is now generally believed that the endometrium proper—or in a more common sense the Müllerian mesodermal blastema—is the tissue of origin. Ultrastructural studies tend to support that contention, as indicated by the wide spectrum of intermediate forms of neoplastic cells, which by almost imperceptible steps range from immature to highly differentiated cells. Thus Silverberg (1971) in his study could demonstrate the development of neoplastic cartilage

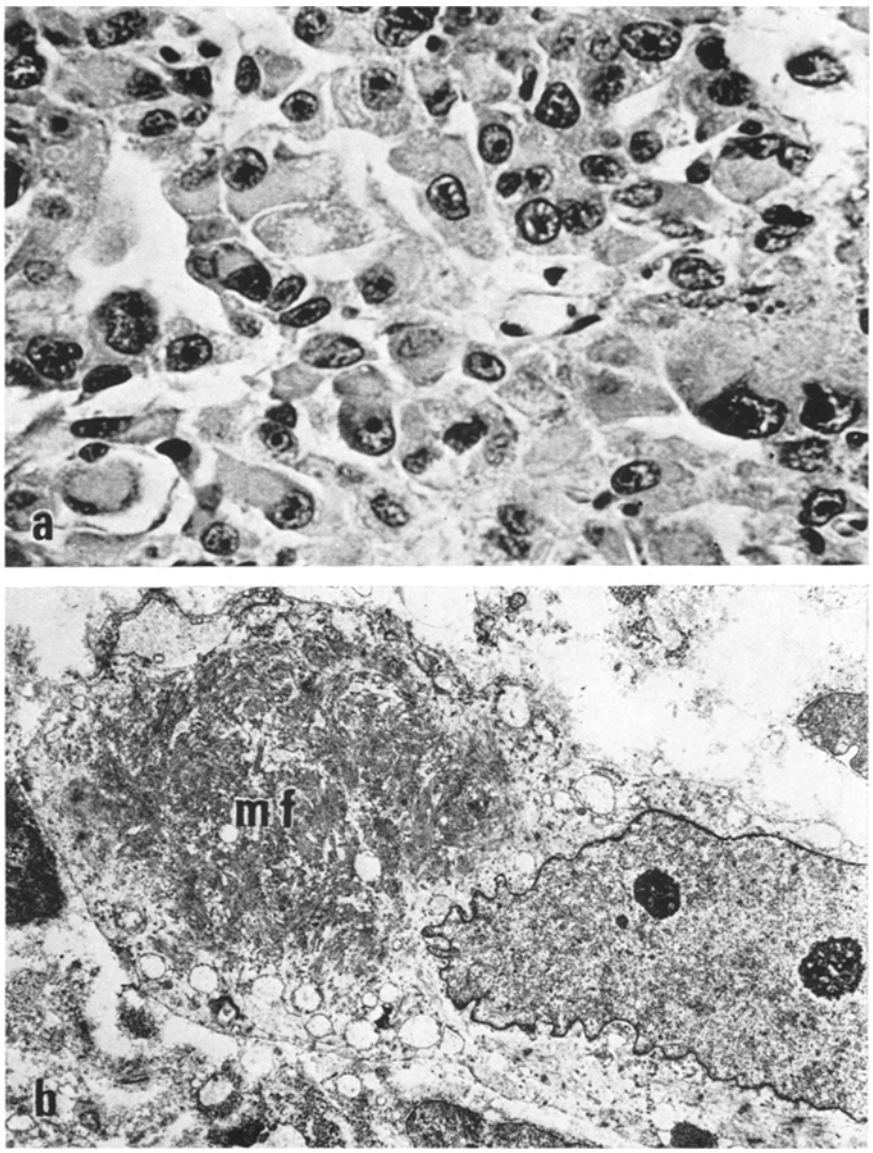

Fig. 9. Rhabdomyoblasts which at light microscopic level bear some resemblance to ganglion cells. In electron micrographs these cells show irregularly arranged myofibrils (*mf*) in their cytoplasm. Note prominent nucleoli. Magn. ×5900

from "basic stromal cells" and Boram *et al.* (1972) showed in a similar extensive study the developmental process of rhabdomyoblasts. From a comparison of the most undifferentiated cell elements in our analysis with those of the above cited authors it seems that their basic stromal cell already represents one of the first stages in the differentiation process of either chondroblasts or rhabdomyoblasts. At least the cytoplasm of their "stem cells" shows already a very complex cytoplasm with cytoplasmic filaments and other cell organelles.

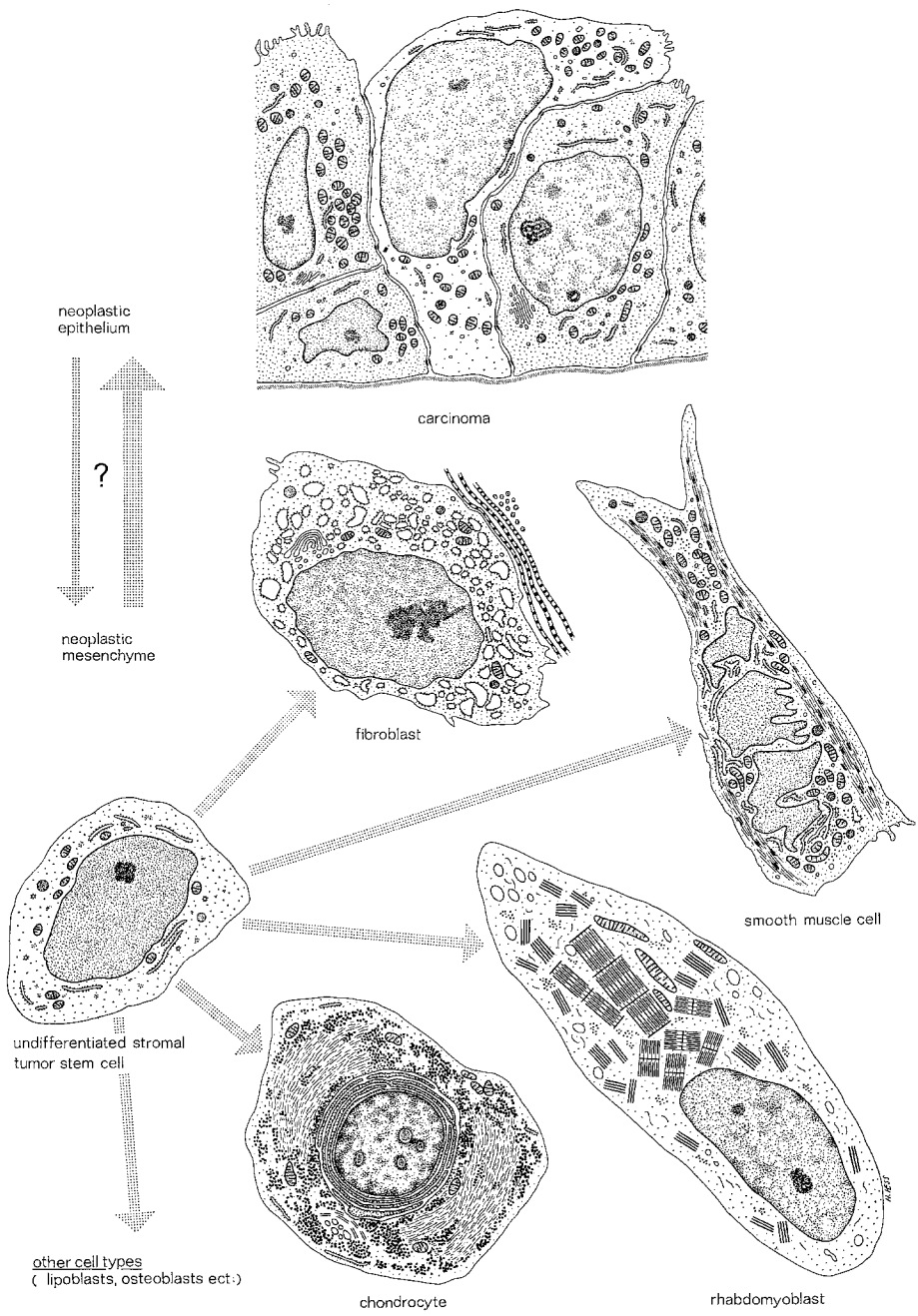

Fig. 10. A semischematic diagram to show the differentiation of various cell types from the undifferentiated tumour stem cell

Whether the presence of heterologous tissue elements is an important indication of the biologic behaviour of this tumour is at this time unknown (Chuang *et al.*, 1970; Norris and Taylor, 1972) but will determine to what extent the third group of endometrial sarcomas has to be further subclassified. For this reason it is important to know exactly the morphology of the heterologous tissue elements, especially that of rhabdomyoblasts. There are three basic histological pictures presented by rhabdomyoblastic growth: The best known resembles embryologic rhabdomyosarcoma elsewhere (see WHO Classification of Soft Tissue Tumours, 1969). The second growth pattern may be designated as pseudoepithelial with regard to the cellular arrangement of the tumour cells whereas the third picture is one of clusters of rhabdomyoblasts within the same range of development. Light microscopically the latter cells may be confused with ganglion cells but always disclose the typical cytoplasmic features of rhabdomyoblasts at electron microscopic level. Moreover, with regard to the normal development of the peripheral nervous system from the embryonic ectoderm it seems to us unlikely that nerve cells represent as an integrated part of mixed mesodermal tumours. The epithelial components in our 4 cases of mixed sarcomas consisted of more or less differentiated adenocarcinomas and were ultrastructurally similar to adenocarcinomas which have been reported in the literature (Cavazos and Lucas, 1973; Fasske *et al.*, 1965; Nilsson, 1962). Although it was not possible light microscopically to distinguish clearly beween epithelium and mesenchyme in all areas we were not able to find transitional forms between the two tissues at electron microscopic level (see also Komorowski *et al.*, 1970). Nevertheless it must be stated that the most undifferentiated cells within epithelium and mesenchyme at least disclose some striking similarities in their ultrastructural morphology.

Summing up the above discussion it seems reasonable to assume (Fig. 10):

(1) The neoplastic stromal cell (tumour stem cell) has a multifold mesenchymal (mesodermal) differentiation potency which is especially realized in mixed mesodermal tumours. The tumour stem cell may give origin to one or the other of the varieties of mesenchymal tissue cells (that means fibroblasts, chondroblast, rhabdomyoblast etc.). To some extent the line of differentiation may be due to positional or environmental factors. Contrary to the mesenchymal elements the epithelial components strictly retain their Müllerian character (Sternberg *et al.*, 1954).

(2) The pure homologous sarcoma may in account of its cellular features be regarded as "stem cell sarcoma" with occasional differentiation into fibroblastic and smooth muscle tissue.

(3) The pure heterologous sarcomas are tumours, in which only one differentiation line is realized.

(4) Mixed mesodermal sarcomas are the most complex mesenchymal neoplasms, usually with an additional epithelial component. From our own results a metaplasia of Müllerian duct epithelium (carcinoma) from neoplastic mesenchyme seems unlikely. Rather we suggest a simultaneous neoplastic transformation of morphologically immature cells each with a fixed potency to differentiate either into epithelium or into mesenchyme. It cannot be said conclusively whether these tumour stem cells originate exclusively from either endometrial glands or endometrial stroma—the latter being suggested by many authors—or from both

tissues. The factors which lead to the development of uterine sarcomas and the factors which influence the direction of the differentiation processes are to date completely unknown.

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