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Malignant Giant Cell Tumor of Bone

Fine Structure and Localization of Acid Phosphatase*

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Summary. The fine structure of the different cell types constituting a primary malignant giant cell tumor of bone has been studied and the localization of acid phosphatase in relation to the subcellular organelles been demonstrated. Three distinct cell types with characteristic ultrastructural features were observed: giant cells, fibroblast-like cells, and cells with abundant lipid inclusions and mitochondria. Certain differences were noted between these three cell types and their counterparts in benign giant cell tumors of bone (described in a separate report). The enzyme histochemical and morphological data suggested that the giant cells in the malignant tumor might possess a more active and expansive lysosomal apparatus than corresponding cells in the benign variant.

Key words: Giant cell tumor — Ultrastructure — Acid phosphatase — Lysosomes — Bone tumors.

Giant cell tumor of bone is usually a benign condition. However, in approximately 10% of the cases manifestations of malignancy occur (Meary et al., 1975; Spjut et al., 1971). Most of these malignant cases represent giant cell tumors that have undergone radiotherapy. Another much smaller group of cases is constituted by tumors which show a histologically benign appearance, yet give rise to distant metastases (Jewell and Bush, 1959; Pan et al., 1964). These malignancies usually manifest themselves after repeated curettage. Finally, there are a small number of tumors having frankly malignant characteristics both histologically and clinically ("primary malignant cases"). This latter group of primary

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malignant giant cell tumors constitutes 2–4% of all giant cell tumors of bone (Coley et al., 1958; Dahlin et al., 1970; Meary et al., 1975).

The fine structure of benign giant cell tumors of bone is now beginning to be explored in great detail (Aparisi et al., 1977a; 1978), but, information on the ultrastructural appearance of primary malignant tumors is lacking. In the course of our studies on bone tumors, we recently had the opportunity to examine such a case. It is the purpose of this paper to relate the fine structural appearance of the tumor tissue in this case. Included is an analysis of the ultrastructural localization of acid phosphatase in order to elucidate the lysosomal apparatus in the different cells constituting the tumor. Lysosomes and related structures are of special interest in this type of tumor, since the lesion is of a lytic nature and characteristic appearance of the lysosomal vacuome has been reported in cases of benign giant cell tumor of bone (Aparisi et al., 1977a and b; 1978).

Materials and Methods

For diagnostic, clinico-pathologic purposes, small pieces of tumor tissue were fixed in buffered 4% formaldehyde solution, dehydrated, and embedded in paraffin. Sections cut at 3–5 μm were stained with H & E and the van Giesen connective tissue stain.

For electron microscopy, small pieces of tumor tissue were excised and immersed in glutaraldehyde solution for fixation (3% glutaraldehyde buffered with 0.1 M sodium cacodylate, pH 7.2, and containing 0.1 M sucrose) (Helminen and Ericsson, 1970). Fixation time was 24 h. Postfixation in *s*-collidine buffered OsO_4 was always performed for 1–2 h. After dehydration and embedding in Epon 812, approximately 1 μm thick sections were prepared on glass knives, stained with alkaline toluidine blue and examined for orientation in the blocks. After selecting a suitable area of the embedded material, thin sections were cut using diamond knives, and were subsequently stained with lead citrate. Examination of the material was carried out in a Jeol 100C electron microscope.

Histochemistry

Fixation was performed by immersing tumor tissue samples in the glutaraldehyde solution for 24 h. They were subsequently transferred to 0.1 M cacodylate buffer containing 0.1 M sucrose. Approximately 12 h before cutting, the material was immersed in a solution of 0.1 M cacodylate buffer and 0.1 sucrose with 10% dimethylsulfoxide (Göthlin and Ericsson, 1973; Helminen and Ericsson, 1970).

Sections cut at approximately 50 μm were then prepared on a freezing microtome (Leitz) and incubated in a sodium β-glycerophosphate medium for the demonstration of acid phosphatase using lead as capture ion. Control incubations were performed in a medium containing the enzyme inhibitors sodium fluoride or sodium-L-tartrate, and also in a medium lacking substrate. Incubation times varied between 10 and 60 min.

Following incubation, the sections were rinsed several times in 0.1 M cacodylate buffer with 0.1 M sucrose and were then postfixed in 2% OSO_4 buffered with *s*-collidine. Dehydration was performed in alcohol solution and the material was embedded in Epon and treated as mentioned previously (see above).

Case History

A 42 year old woman presented with progressive painful swelling of the lateral malleolus of the right ankle without preceding trauma. X-ray examination revealed an approximately 10 cm long destruction – mainly osteolytic – of the distal portion of the fibula. Some reactive periostal bone

formation was noted. A biopsy was performed and the histopathological findings were interpreted as indicative of malignant giant cell tumor (see below). The patient was operated and local resection of the tumor in the fibula with arthrodesis of the talocrural joint was carried out.

Results

A. Light Microscopy

Examination of the paraffin-embedded, routinely stained, surgical specimens (biopsy and resected tumor) confirmed the diagnosis of malignant giant cell tumor of bone (Figs. 1 and 2).[1] The tumor was composed of cell-rich areas with fibroblast-like polymorphous cells showing numerous atypical mitoses and infiltrative-destructive growth. In addition, there were moderate numbers of comparatively small giant cells with variable numbers of nuclei lacking obvious atypicality, and relatively large regions containing numerous lipid rich cells resembling xanthoma cells or foam cells with abundant, finely granular cytoplasm.

B. Fine Structure of Tumor Cells

Specimens both from the biopsy and the resected tumor were studied. Three distinct, easily recognizable cell types were observed: giant cells, fibroblast-like cells, and cells with abundant lipid inclusions and mitochondria. In addition, a small number of cells, which did not clearly fit any of the categories mentioned above, were observed; at least some of these might represent immature or intermediary forms. These will not be further commented on.

1. Giant Cells. These cells occurred frequently and had a highly variable number of nuclei. Individual nuclei differed greatly in size – in the plane of the section – and usually had a markedly irregular outline. The chromatin material was fairly evenly distributed throughout the nucleoplasm, although there was a tendency toward margination. Nucleoli (as a rule 1 or 2 in any given section) were irregular and varied greatly in size.

The cytoplasm was dominated by numerous rather small mitochondria. These organelles were roughly evenly distributed throughout the cell.

The endoplasmic reticulum was almost exclusively of the rough surfaced variety forming long, meandering, slender, sometimes branching units. Although rough surfaced endoplasmic reticulum occurred in any position of the cytoplasm of the cells, some concentration was often noted in the periphery and in some instances parallel stacks were encountered.

Golgi regions, mainly consisting of stacks of smooth surfaced cisternae, were rather small and were often located in a juxtanuclear position.

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[1] The histopathological diagnosis was made by senior pathologists at Karolinska Hospital, representing internationally recognized expertise in bone tumor pathology (Professor Gunnar Moberger and Dr. Gunnar Söderberg)

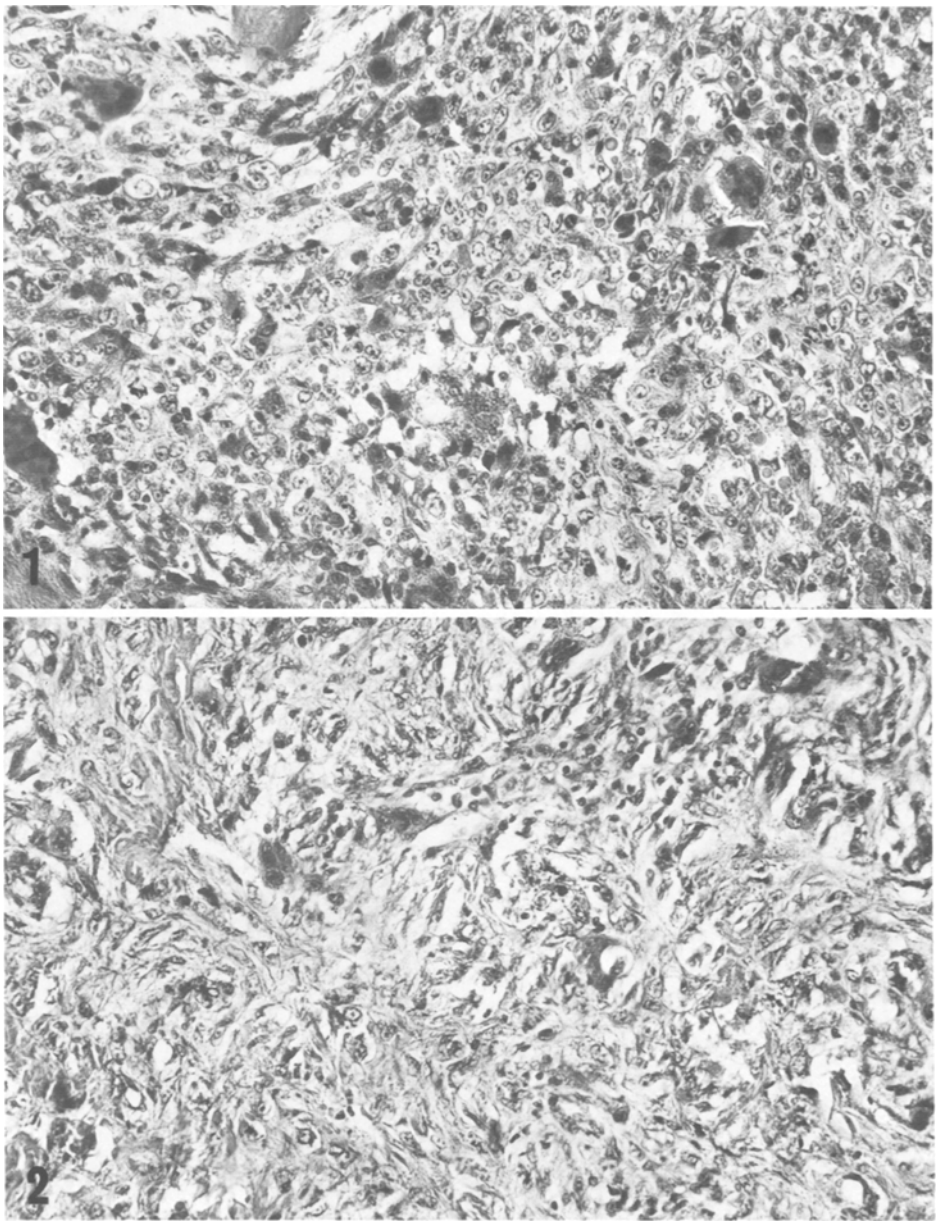


Fig. 1. Light microscopic picture of portion of malignant giant cell tumor with abundant polymorphous stromal cells containing large, irregular nuclei with prominent nucleoli. Giant cells vary considerably in size and are rather frequent. Paraffin; H & E. ×250

Fig. 2. Light microscopic picture from the same tissue as in Figure 1 with irregular bands of collagenous stroma. Although stromal cells are less frequent than in the area illustrated in Figure 1, they show a similar appearance. Multinucleated giant cells occur in great numbers and show a more pronounced variation in size and shape than those depicted in Figure 1. Paraffin; H & E ×250

Lysosome-like elements were usually inconspicuous. In most instances, they were rather small, with a dense, irregular or granular matrix. Although they might be observed in any position of the cell, they often tended to be gathered in the vicinity of the Golgi apparatus. An occasional large lysosome might be seen, and also large heterophagic vacuoles.

Vacuolar elements were evenly disposed and often occurred in clusters subjacent to the plasma membrane (Fig. 3) and in the vicinity of the Golgi apparatus. Some appeared to be attenuated and formed oblong or tubular structures (Fig. 3). They often contained a moderately electron dense, finely granular material, and some also showed presence of membrane fragments in their lumen.

Smooth-surfaced, ring-shaped structures (Fig. 12) were rather frequent.

The cytoplasmic ground substance was composed of free ribosomes, microfilaments and occasional microtubules except in certain areas subjacent to the plasma membrane where thick focal condensations of microfilaments resembling the ectoplasmic layer in osteoclasts were found (Figs. 3 and 4). Particulate glycogen was absent from the cytoplasmic ground substance. Likewise, lipid droplets were never encountered.

Usually, the plasma membrane was very irregular with formation of large, blunt extrusions, numerous – often long and slender – microvilli, and deep excavations. Formation of a distinct brush border was not observed.

2. *Fibroblast-Like Cells.* These cells are commonly encountered in the tumor tissue, although in some areas the cells with abundant lipid inclusions and mitochondria predominate. The fibroblast-like cells vary considerably in shape, some being slender and elongated, others rounded, ovoid or completely irregular with centrally or excentrically located nucleus. Blunt extrusions, microvilli, and invaginations of the plasma membrane are commonly seen (Figs. 6, 7 and 8).

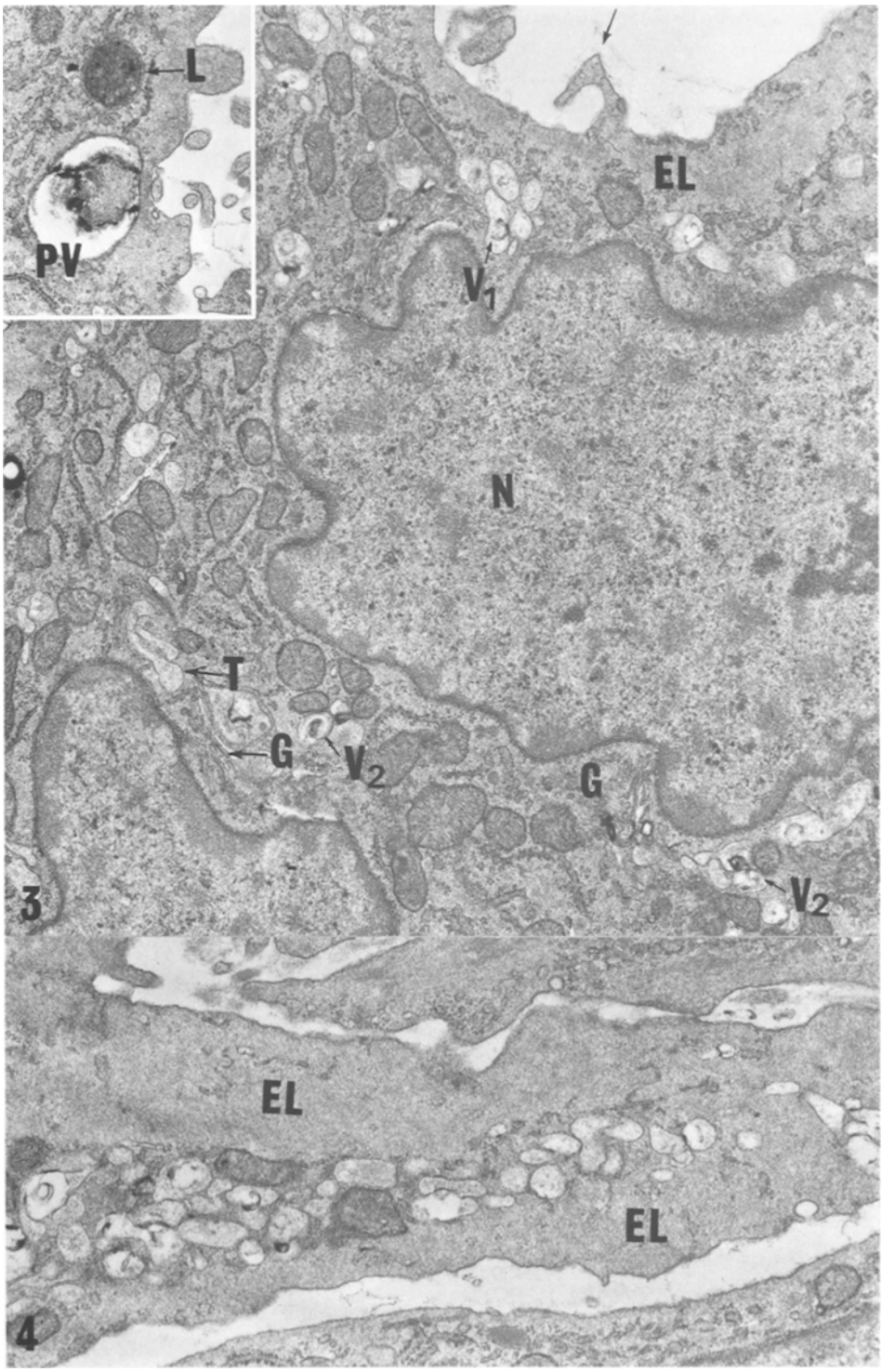
The nuclei are comparatively large, tend to follow the shape of the cells in their outline and contain 1–3 often irregular nucleoli (Fig. 6). The nuclear contour is usually slightly undulating with occasional irregular extrusions and infoldings. The chromatin material is fairly evenly distributed, but there is usually a tendency toward margination. Occasionally peculiar multivesicular (lipid containing) inclusions have been demonstrated in the nuclei.

The most conspicuous cytoplasmic organelle is the endoplasmic reticulum covering a large proportion of the extranuclear space in the cells. It is almost exclusively of the rough surfaced variety, with irregularly widened cisternae filled with a moderately dense, finely granular material. A great variability in the size and shape of individual cisternae is noted, and some cisternae seem to interconnect (Figs. 7 and 8).

The Golgi areas are small and inconspicuous in comparison with those of the giant cells.

Mitochondria are comparatively sparse and vary greatly in size and shape, some being slender and attenuated. Irregular dilatations of the cristae are frequently observed (Fig. 5).

Like the mitochondria, lysosomes are of infrequent occurrence. They are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small and of conventional type. Autophagic vacuoles are rarely encountered; the same applies to phagocytic and other types of vacuoles.

The cell sap is rich in free ribosomes, often arranged in small clusters. Subplasmalemmal bundles of microfilaments are often seen. Similar bundles are also observed in deeper portions of the cells. Microtubules are inconspicuous. Particulate glycogen and droplets of fat are not present in the cell sap.

The cells are regularly surrounded by wide, extracellular spaces containing bundles of collagen (Fig. 8).

3. Cells with Abundant Lipid Inclusions and Mitochondria. In the planes of the sections, these cells appear somewhat larger than the fibroblast-like cells. They are extremely irregular in shape forming numerous pseudopodia and blunt extrusions and having deeply infolded areas of their plasma membranes (Figs. 10 and 11).

The nuclei are – like the cellular outlines – irregular with folded and protruding nuclear membranes. The chromatin is evenly distributed and in general somewhat more compact and dense than in the nuclei of fibroblast-like cells. Nucleoli are sparse but when occurring they tend to be highly irregular and large.

Distinguishing cytoplasmic features of these cells are: presence of usually numerous, large, lipid-like "droplets" in the cytoplasmic matrix and in membrane-bordered organelles resembling lysosomes; abundance of mitochondria; occurrence of numerous large, lysosome-like organelles; and presence of large phagocytic vacuoles subjacent to the plasma membrane.

The droplets presumed to consist of neutral fat are homogeneous, pale or moderately electron dense (Figs. 5, 9, 10 and 11). They may encompass small membrane fragments and densities (Figs. 5 and 9). Droplets of similar type are also present in lysosome-like elements, which usually in addition contain irregular densities, granular material and membrane fragments in their matrix (Figs. 9 and 10). In many cells, the bulk of the cytoplasm is occupied by the droplets and droplet-filled lysosome-like bodies.

The mitochondria vary considerably in size and shape. They tend to be

Fig. 3. Portion of giant cell containing two nuclei (*N*). The cytoplasm is dominated by mitochondria with variable sizes and shapes and endoplasmic reticulum of the rough-surfaced variety forming slender meandering cisternal structures. The Golgi regions (*G*) are small and usually located in the vicinity of the nuclei. The plasma membrane forms slender protrusions (arrows). Subjacent to the plasma membranes there is an ectoplasmic layer of variable thickness (*EL*). Two types of vacuolar structures are present: those located near the plasma membrane (V_1) and those in the deeper portions of the cytoplasm (V_2). Note smooth surfaced tubular elements (*T*) with expanded end portions. *Inset.* Surface of cell with a phagocytic vacuole (*PV*) and a lysosome-like (*L*) dense body. ×15,000: *Inset* ×15,000

Fig. 4. Picture illustrating the appearance of a long, slender protrusion from a giant cell with thick ectoplasmic layers (*EL*) on both sides of the protrusion. The cytoplasm between the ectoplasmic layers is filled with vacuoles of variable sizes and appearances, and occasional mitochondria. ×17,500

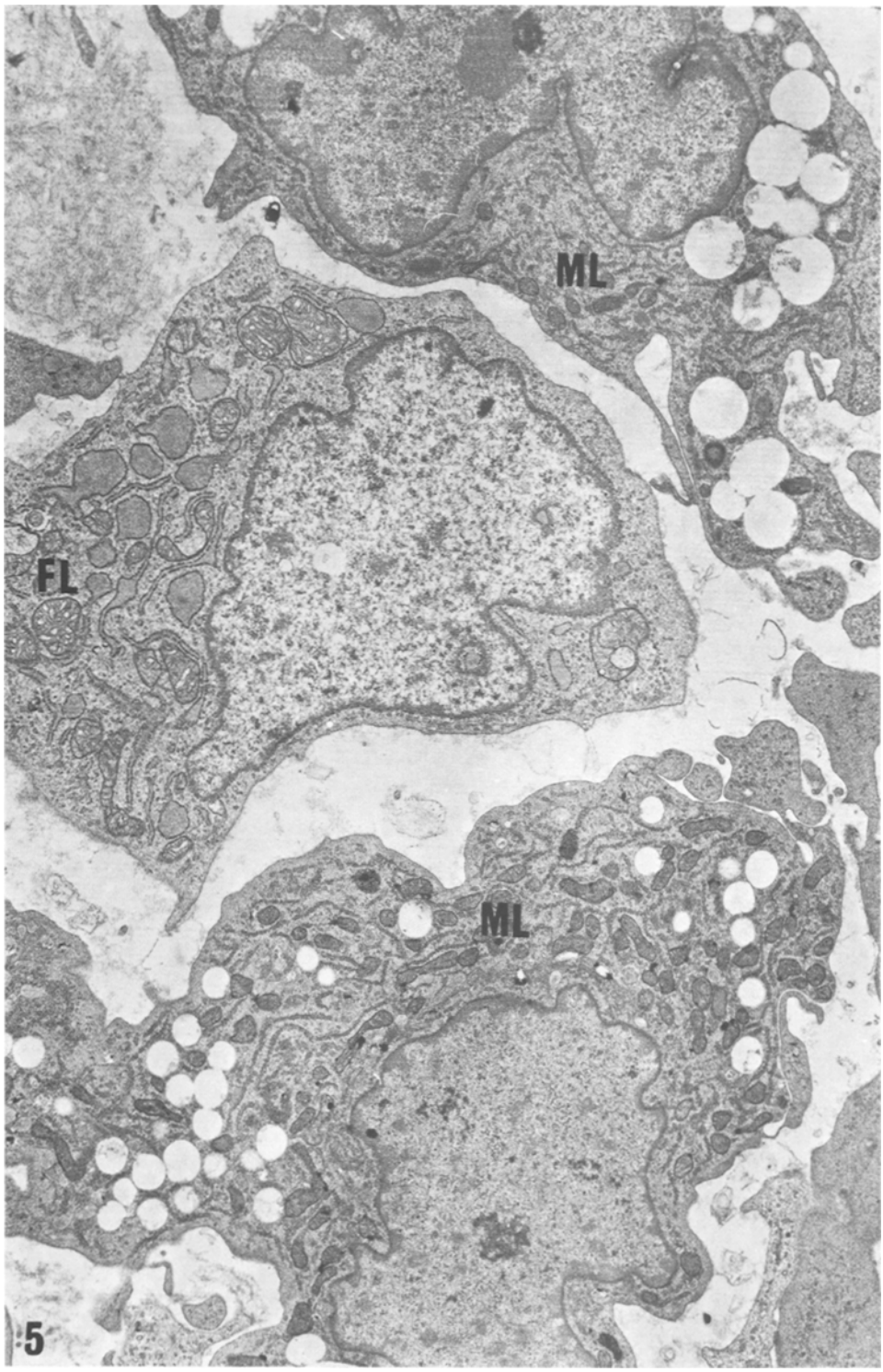

Fig. 5. Survey electron micrograph showing the appearance of one fibroblast-like cell (*FL*) and two cells (*ML*) containing abundant mitochondria and lipid droplets. Note irregular widening of the cisternae of rough surfaced endoplasmic reticulum in the fibroblast-like cell and also the irregular dilatations of mitochondrial cristae. Mitochondria are much larger in the fibroblast-like cells than in the other cells. No dilatation or expansion is seen in the rough surfaced endoplasmic reticulum of the cells rich in mitochondria and lipid. ×7500

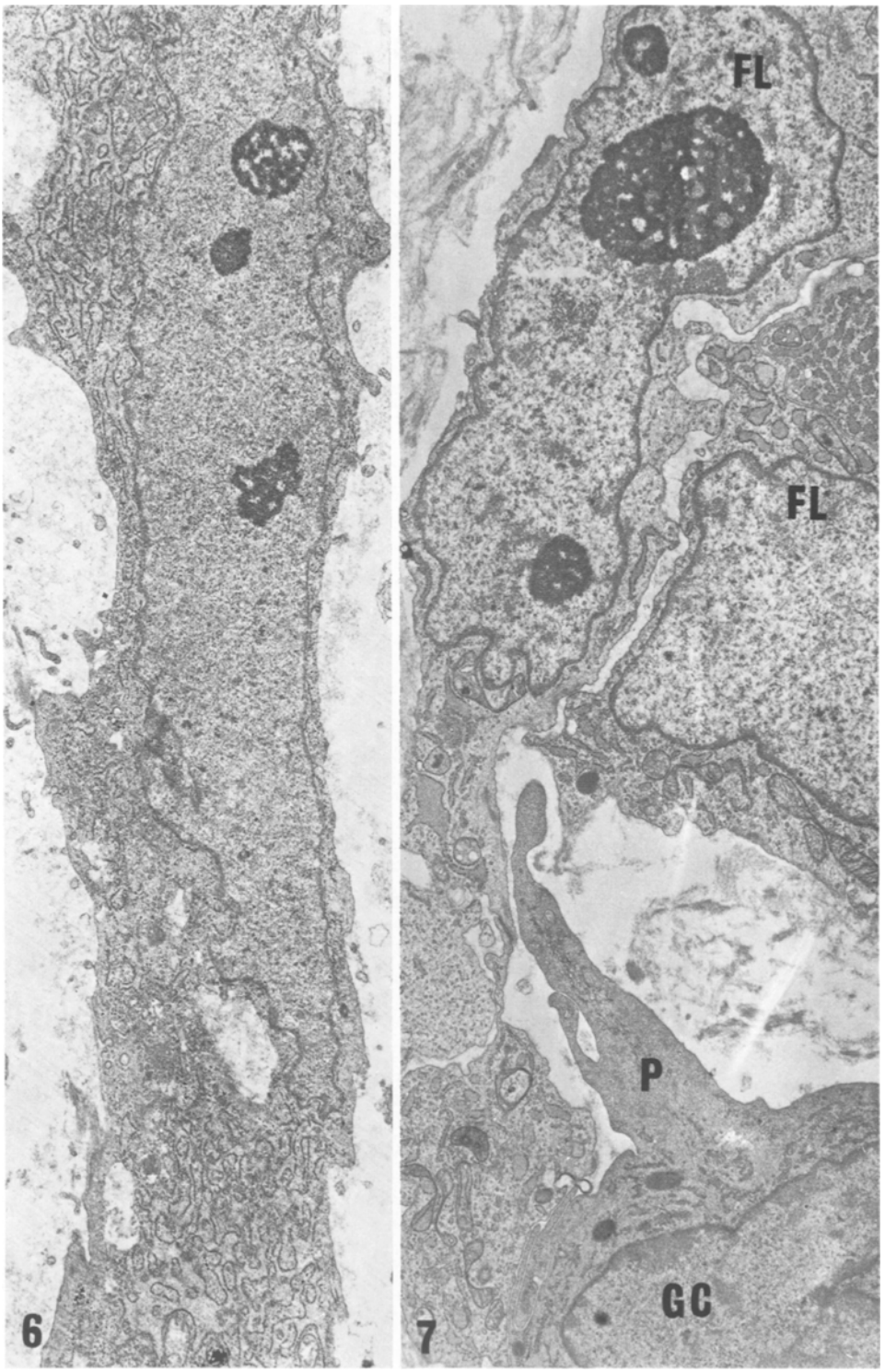

Fig. 6. Portion of a slender fibroblast-like cell with attenuated nucleus containing three irregular nucleoli. ×7800

Fig. 7. Portions of two fibroblast-like cells (*FL*) and a multinucleated giant cell (*GC*), the latter forming a thick protrusion (*P*) containing abundant ectoplasmic layers. Note the irregular shapes of the nuclei in the fibroblast-like cells, and the occurrence of three dense nucleoli in one of the latter. ×7500

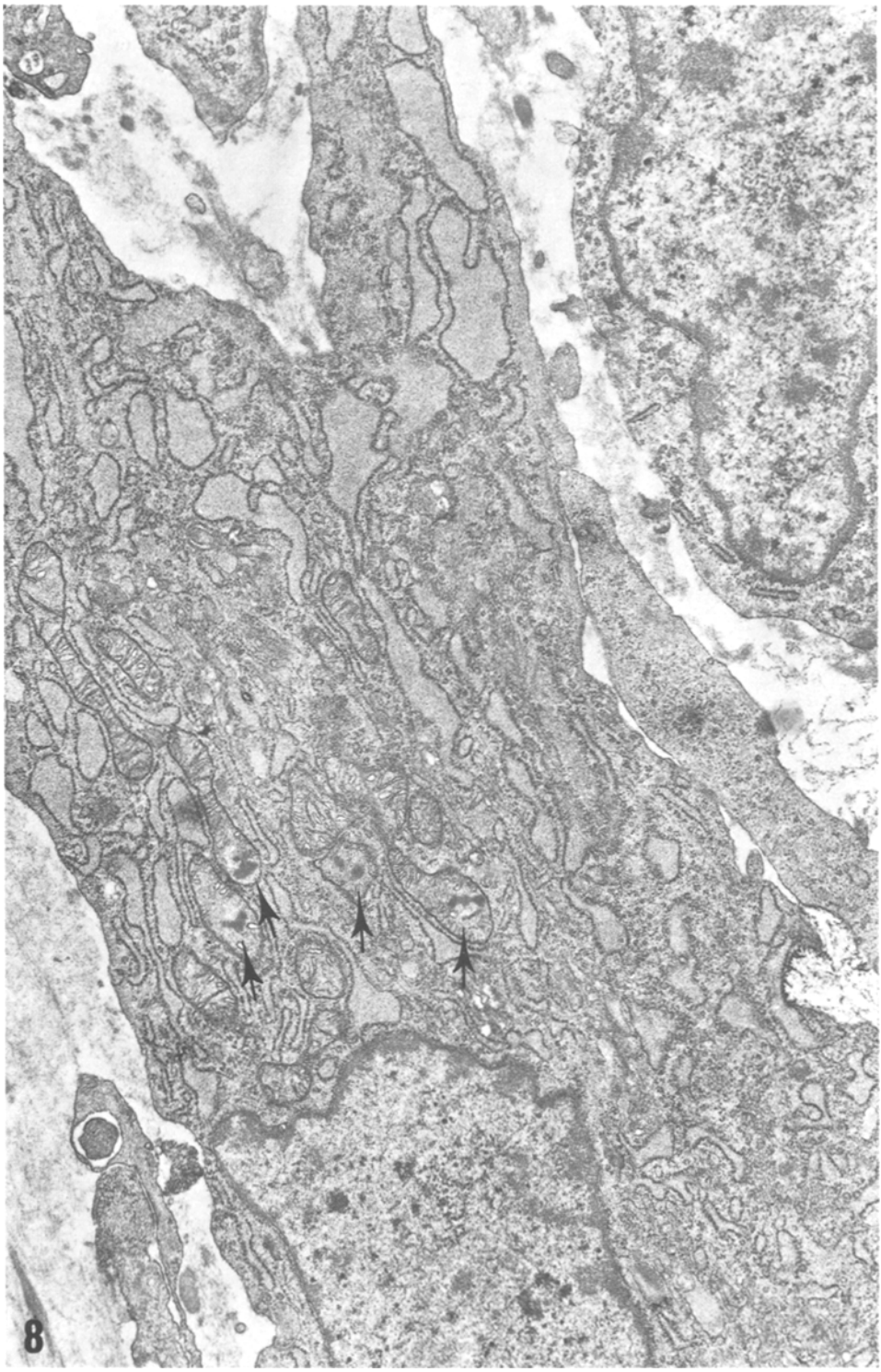

Fig. 8. Electron micrograph dominated by the cytoplasm of a large fibroblast-like cell with abundant rough surfaced endoplasmic reticulum forming highly irregular widened cisternae filled with a moderately electron dense finely granular material. Note tendency toward widening of intracristal spaces in the mitochondria and the presence of irregular densities in the matrix of the latter. Note also the irregular outline of this cell. ×13,500

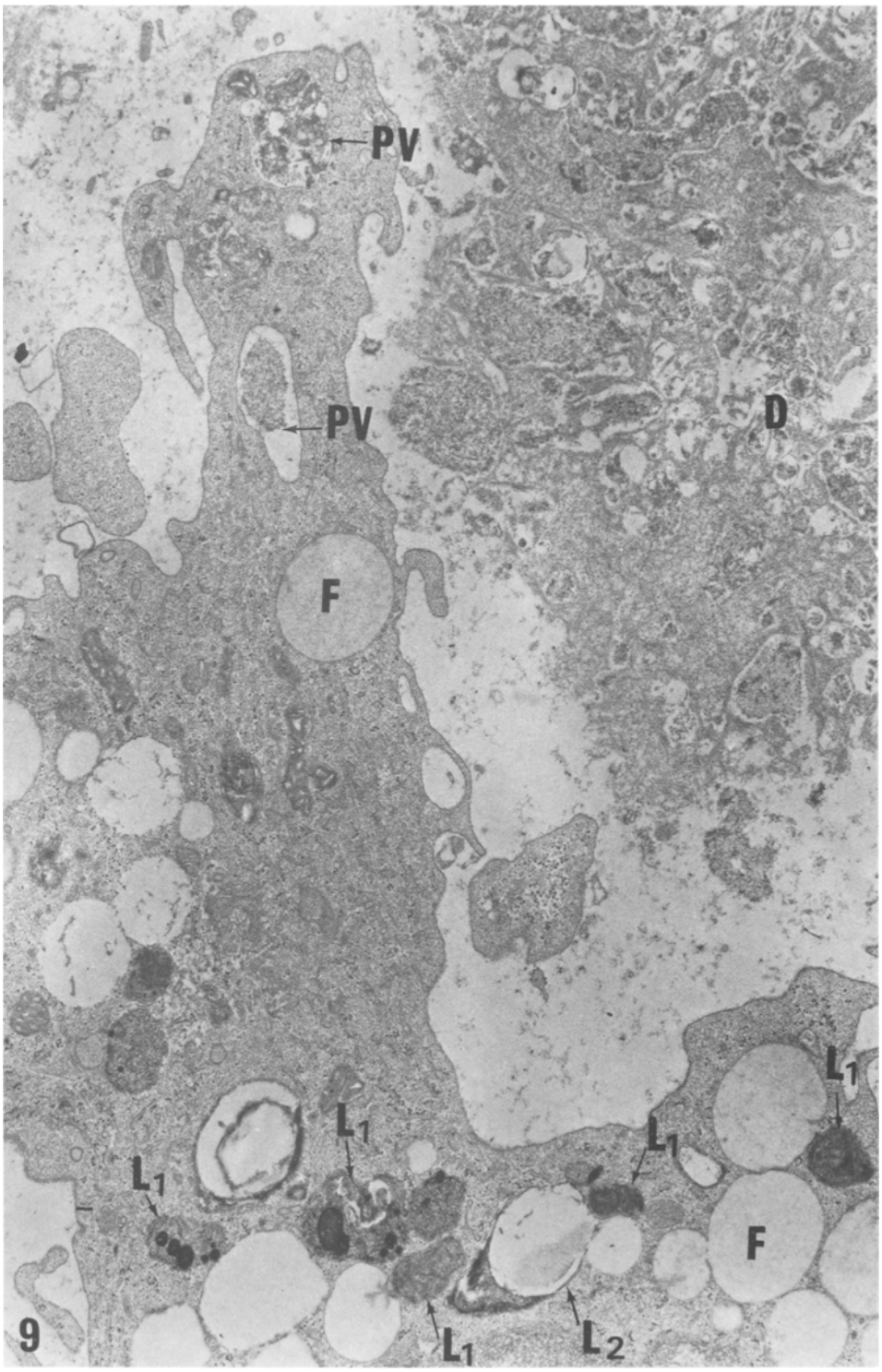

Fig. 9. Portion of a cell of the type containing numerous mitochondria and lipid droplets lying close to an area with debris (*D*). Fat droplets (*F*) are numerous. The cytoplasm also contains many lipid-like bodies (*L*1). At least one of the lysosome-like bodies seems to contain lipid (*L*2). Note the occurrence of the two phagocytic vacuoles (*PV*) in a large protrusion close to the debris. Note also the very irregular outline of the cell, which forms occasional narrow villous-like protrusions. ×14,500

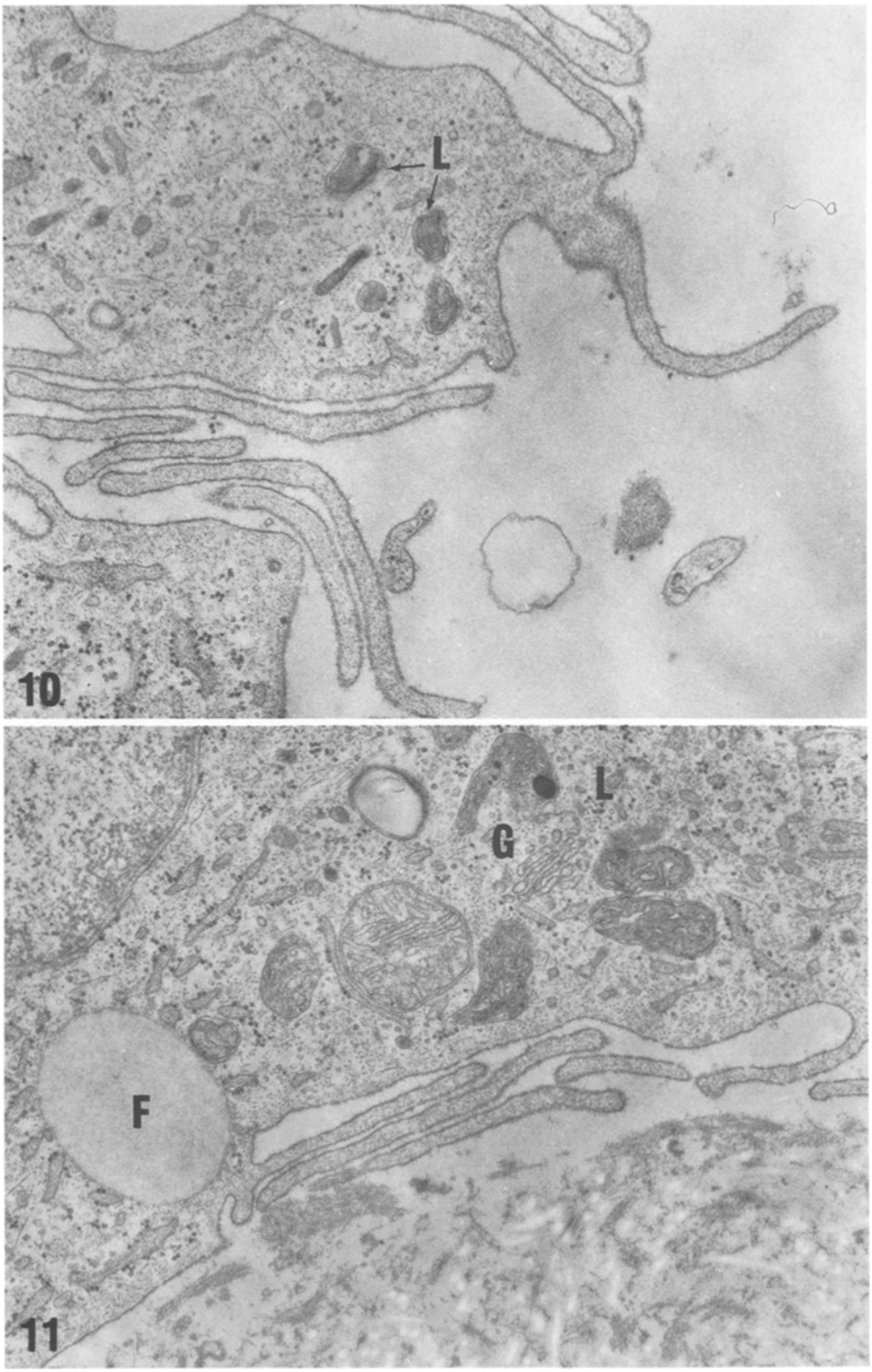

Fig. 10. Superficial areas of adjacent mitochondria and lipid-rich cells forming abundant narrow microvillous-like protrusions. The cytoplasm contains scattered, glycogen-like particles in the matrix. There are some small lysosome-like bodies (*L*) present, and also small dense tubular and vesicular structures, possibly related to lysosomes or GERL. ×33,000

Fig. 11. Superficial portion of a similar cell as in Figure 10. Microvillous-like protrusions lie parallel to the surface. *F*, fat droplets; *G*, Golgi apparatus; *L*, lysosome-like bodies. ×30,000

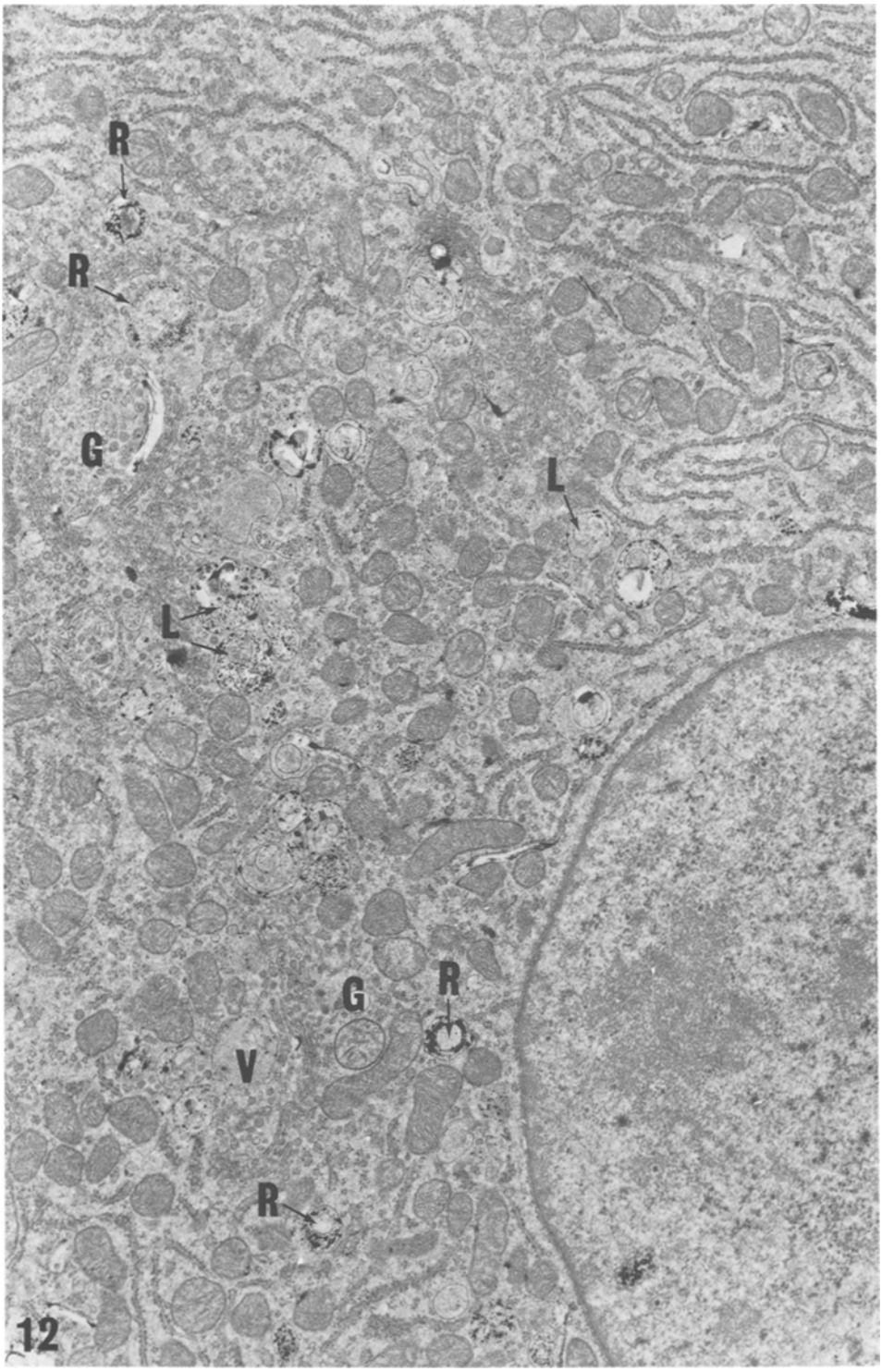

Fig. 12. Central portion of multinucleated giant cell from tissue incubated for the demonstration of acid phosphatase. Reaction product is deposited over lysosome-like bodies (*L*) and ring-shaped structures (*R*) with smooth surfaced limiting membranes. Scattered deposits are also present over Golgi cisternae (*G*) and a Golgi-associated vacuole (*V*). ×14,000

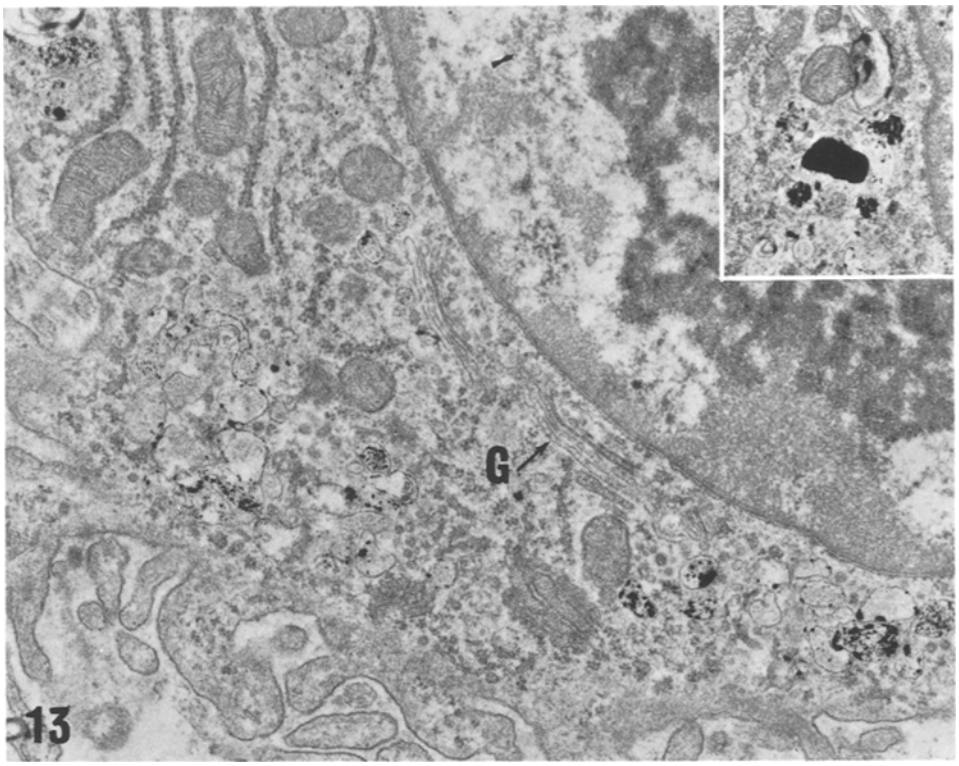

Fig. 13. From tissue incubated for the demonstration of acid phosphatase. Superficial area of multinucleated giant cell showing presence of reaction product over numerous vacuoles subjacent to the plasma membrane. There is no reaction in the Golgi apparatus (*G*) in this cell. *Inset* shows deposits of reaction product in conventional lysosomes. ×19,500; *Inset* ×15,000

diffusely distributed over the cytoplasm. Dilatations of cristae or other special features are not noted.

In addition to bodies containing lipid inclusions, lysosome-like structures filled with dense, membranous and granular materials are often encountered. Although, in general, these bodies are large, they come in all sizes.

Vacuoles of endocytic (phagocytic) type are commonly observed subjacent to the plasma membrane (Fig. 9). Such vacuoles are particularly numerous in cells lying adjacent to necrotic or severely damaged cells.

The endoplasmic reticulum is moderately well developed consisting almost entirely of slender, meandering and branching rough surfaced cisternae with closely apposed bordering membranes (Fig. 5). Expanded or dilated portions have not been observed.

Golgi regions are inconspicuous. Particulate glycogen in the cell sap has not been observed. While present in moderate numbers, microfilaments and microtubules do not show any characteristic features with regard to distribution or organization.

Localization of Acid Phosphatase

1. Giant Cells. Reaction product (lead phosphate precipitate) was deposited over lysosomes of conventional types and one or several of the cisternae making up the Golgi apparatus. In addition, small vacuoles located in the vicinity of the Golgi apparatus showed presence of final product. Precipitate was further deposited over smooth surfaced tubular elements, often with ring-shaped ("tire-like") appearance (Figs. 12 and 13).

2. Fibroblast-Like Cells. Sites with reaction product were sparse and limited to small conventional lysosomes.

3. Cells with Abundant Lipid-Inclusions and Mitochondria. Deposits of reaction product were confined to the different types of lysosome-like bodies described in section 1 A.

4. Controls. No precipitates were observed in tissues incubated in media containing sodium fluoride or L-tartrate, or lacking the substrate.

Discussion

The differentiation between malignant giant cell neoplasms and other malignant giant cell containing tumors of bone—especially osteosarcomas—is difficult. This is particularly true in cases where benign features of the giant cell tumors are lacking. The presence of bone, osteoid, cartilage, chondroid, and pleomorphic giant cells showing numerous mitoses make a diagnosis of malignant giant cell tumor unlikely, although there are no absolute morphologic criteria available for the differential diagnosis. Clinical features, such as age and localization, and also the X-ray changes, have to be taken into consideration. In the case studied in the present report, the histopathological, clinical or roentgenological data all supported the contention that the tumor was indeed a genuine malignant giant cell tumor of bone.

We have recently studied the fine structure of 11 benign giant cell tumors of bone (Aparisi et al., 1977a; 1978). The tissue in the latter tumors was made up of giant cells, and stromal cells type 1 (fibroblast-like) and type 2 (macrophage-like). In the malignant counterpart, giant cells and fibroblast-like cells were easily distinguishable but differed in certain respects from corresponding cells in the benign giant cell tumor. The third type of cells in the malignant tumor (rich in lipid droplets and mitochondria) carried some features in common with type 2 (macrophage-like) cells but also showed distinct differences in their appearance.

Schajowicz (1961) studied the light microscopic localization of acid phosphatase in 85 giant cell tumors of bone, 6 of which were considered to be malignant. The multinucleated giant cells were shown to exhibit evidence of strong acid phosphatase activity, whereas the apparent activity in the mononu-

cleated stromal cells was weak. Nothing was mentioned about differences in activity between benign and malignant giant cell tumors of bone.

In comparison with the giant cells in benign giant cell tumors, the corresponding cells in the malignant tumor contained more abundant vacuoles with lysosomal enzyme. There also appeared to be more numerous ring-shaped smooth-surfaced enzyme-containing structures in the giant cells of the malignant tumor. Although the nature of the latter organelle is not completely clear, it appears most likely that it represents a portion of GERL, since transitional curved tubular elements reminiscent of dilated sacs of endoplasmic reticulum are also encountered. Taken together, the enzyme histochemical and morphological data suggest that the giant cells in the malignant tumor may have a more active and expansive lysosomal apparatus than in the benign counterpart. The evidence thus seems to indicate that phagocytic and lytic properties of giant cells become accentuated in malignancy. However, there is no fine structural indication that the giant cells themselves have malignant properties. The irregular configuration of the surface of the giant cells in the present tumor may reflect their ability of extensive endocytosis. Formation of flaps and protrusions can perhaps be looked upon as the cell's way of compensating for the loss of the highly differentiated and organized ruffled border sometimes present in the cells of the benign variant (Aparisi et al., 1978).

The overall appearance of the fibroblast-like cells fits well with the notion that these cells are malignant in nature. By light microscopy they show presence of numerous mitoses and their fine structure is pleomorphic with marked irregularities of shape and disposition of cytoplasmic organelles, especially the endoplasmic reticulum. Comparison with the corresponding cells in benign giant cell tumors (Aparisi et al., 1977a; 1978) suggests that the fibroblast-like cells in the malignant tumor differ in their metabolism in that they appear to lack particulate glycogen in their cytoplasm. This may be explained by a very rapid and complete utilization of available glycogen or a profound change in the metabolic pathways of the cells.

The nature of the cells with abundant lipid inclusions and mitochondria is somewhat enigmatic. They differ from the macrophage-like cells in the benign giant cell tumors by being more numerous and having large numbers of fat-droplets in the cell sap and in the lysosomes. Furthermore, mitochondria appear to be more frequent and the cytoplasmic surface larger. These differences evidently do not exclude that they represent modified macrophages or histiocytes. The extensive accumulation of fat could possibly be explained by the location of the tumor in the skeleton: invasive growth in bone marrow would expose large quantities of fat to the ingrowing tumor cells. A raised metabolic activity of the cells would result in proliferation of mitochondria and occurrence of large and numerous lysosomes. We therefore conclude that these cells represent macrophages, which have modified their structure in response to the environment in which they live. There is no indication that these cells are neoplastic in nature.

Comparisons between the findings in the present study and those in investigations of benign giant cell tumors of bone have revealed certain differences in the fine structure between the two types of tumor. The limits and forms of the

structural variations in benign tumors have been defined and elucidated (Aparisi et al., 1978). Malignant giant tumors of bone are rarely encountered. Until more cases have been diagnosed and documented ultrastructurally, the variability in the appearance of the cells constituting such tumors remains obscure. It may be significant, however, that some of the features described in the malignant tumor were not observed in any of the benign forms.

It is interesting to note in this connection that the tumor studied by us shares certain ultrastructural characteristics with a giant cell tumor of soft parts recently described by van Haelst and de Haas van Dorsser (1976).

The findings in the present study suggest that each separate population of cells in benign and primary malignant giant cell tumor of bone is derived from similar stem cells.

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References

Aparisi, T., Arborgh, B., Ericsson, J.L.E.: Giant cell tumor of bone. Detailed fine structural analysis of different cell components. Virchows Arch., Abt. A, **376**, 273–298 (1977a)

Aparisi, T., Arborgh, B., Ericsson, J.L.E.: Giant cell tumor of bone. Fine structural localization of acid phosphatase. Virchows Arch., A, **376**, 299–308 (1977b)

Aparisi, T., Ericsson, J.L.E., Arborgh, B.: Giant cell tumor of bone. Variations in patterns of appearance of different cell types. (In manuscript) 1978

Coley, B.L., Higinbotham, N.L., Kogure, T.: Giant cell tumor of bone. Amer. J. of Surg. **96**, 479–491 (1958)

Dahlin, D.C., Cupps, R.E., Johnson, E.W., Jr.: Giant cell tumor of bone: A study of 195 cases. Cancer **25**, 1061–1070 (1970)

Göthlin, G., Ericsson, J.L.E.: Fine structural localization of acid phosphomonoesterase in the osteoblasts and osteocytes of fracture callus. Histochemie **35**, 81–91 (1973)

Helminen, H., Ericsson, J.L.E.: On the mechanisms of lysosomal enzyme secretion. Electron microscopic and histochemical studies on epithelial cells of the rat's ventral prostate lobe. J. Ultrastruct. Res. **33**, 528–549 (1970)

Jewell, J.H., Bush, L.F.: "Benign" giant-cell tumor of bone with a solitary pulmonary metastasis. A case report. J. Bone Jt. Surg. **41-A**, 895–904 (1959)

Meary, R., d'Aubigné, M.R., Tomeno, B., Sedel, L.: Tumeurs à cellules géantes. 85 observations suivies. Revue de Chir. Orthopedique **61**, 391–413 (1975)

Pan, P., Dahlin, D.C., Lipscomb, P.R., Bernatz, P.E.: "Benign" giant cell tumor of the radius with pulmonary metastasis. Mayo Clin. Proc. **39**, 344–349 (1964)

Schajowicz, F.: Giant cell tumor of bone. A histochemical study. J. Bone Jt. Surg. **43-A**, 1–29 (1961)

Spjut, H.J., Dorfman, H.D., Fechner, R.E., Ackerman, L.V.: Tumors of bone and cartilage. In Atlas of Tumor Pathology, Series 2. Fasc. 5. Washington DC, Armed Forces Institute of Pathology, 1971

Ueno, K.: Electron microscopic observations of giant cell tumors of bone. J. Jap. Orthop. Ass. **38**, 724–725 (1964)

van Haelst, U.J.G.M., de Haas van Dorsser, A.H.: Giant cell tumor of soft parts. An ultrastructural study. Virchows Arch. A, Path. Anat. and Histol. **371**, 199–217 (1976)

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