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Giant Cell Tumor of Bone

Variations in Patterns of Appearance of Different Cell Types

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Summary. Eleven benign giant cell tumors of bone were studied in the electron microscope, and the fine structural localization of acid phosphatase was elucidated. Three distinct cell types are always present in these tumors: stromal cells type 1; stromal cells type 2; and multinucleated giant cells. Small mononuclear cells may also occur, but are not likely to be actively participating in the neoplastic process.

The range of variability in the fine structure of the different cell types constituting this tumor has been established. Variations in appearances include: a) presence of nuclear pseudoinclusions in stromal cells type 1 and multinucleated giant cells; b) aberrations in the structure of the rough surfaced endoplasmic reticulum in the same cell types; c) occurrence of ruffled borders, ectoplasmic layers and cytoplasmic labyrinths containing acid phosphatase in the giant cells. Some giant cells show evidence of marked phagocytic activity and contain large and numerous residual bodies carrying acid phosphatase.

The significance of the interrelations between the different cell types are discussed and the possible role of stromal cells type 2 in immunological mechanisms directed against the tumor cells are mentioned.

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

Introduction

We have recently described the basic fine structural appearance and localization of acid phosphatase in three different cell types of a genuine benign giant cell tumor of bone (Aparisi et al., 1977a, b). In a subsequent report (Aparisi et al., 1978), the ultrastructure of the malignant counterpart of this type of tumor was elucidated and compared with that in the benign tumor. Although the observations suggested that similar populations of cells occurred in both

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tumors, definitive differences were noted in each of the 3 types of cells which constitute the tumor tissue – or at least the bulk of this tissue.

In the case of benign giant cell tumors of bone, electron microscopic studies by others (Boquist, 1976; Hanaoka et al., 1970; Steiner et al., 1972; le Charpentier et al., 1975) have suggested that a certain variation in the appearance of different cell components may occur – perhaps at least in part dependent upon the localization of the tumor (Steiner et al., 1972).

In order to broaden our knowledge of the variability in the fine structure of giant cell tumors of bone, we have studied 11 cases with different localization in the skeleton, all benign. The peculiarities in structural characteristics of the cells composing these tumors are described in the present report, using the appearance of the tumor previously described by us in detail (Aparisi et al., 1977a, b) as the guide-line.

Materials and Methods

Small pieces of tumor tissue, approximately $1 \times 1 \times 1$ mm, were excised for fixation which was carried out in 2% highly purified glutaraldehyde, containing 0.1 M cacodylate buffer and 0.1 M sucrose (pH 7.2) (Helminen and Ericsson, 1970); fixation times varied between 4 and 24 h. Postfixation was performed in 2% osmium tetroxide (OsO_4) in *s*-collidine buffer. After fixation in OsO_4, the tissue samples were dehydrated in ethyl alcohol solutions of increasing strength (70%–100%). Uranyl acetate was included in the 100% alcohol solution to obtain en bloc staining. Embedding was performed in Epon 812. Approximately 1 µm thick sections stained with alkaline toluidine blue were examined for orientation in the Epon blocks. Suitable areas were trimmed out, and thin sections were cut on an LKB Ultratome using diamond knives. After staining with lead citrate, the sections were examined in a Jeol 100 C electron microscope. When decalcification was needed the tissues were immersed in isotonic, neutral 4.13% solution of ethylene diaminetetra-acetate (EDTA).

Histochemistry

Fixation was performed by immersing pieces of tumor tissue in the aforementioned glutaraldehyde solution for 4–24 h. The material was subsequently washed and stored at +4° C in 0.1 M cacodylate buffer containing 0.1 M sucrose. Approximately 12 h prior to cutting, the tissues were immersed in a solution of 0.1 M cacodylate buffer and 0.1 M sucrose with 10% dimethyl-sulfoxide (Göthlin and Ericsson, 1973). 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 (Göthlin and Ericsson, 1973). Control incubations were performed in a medium lacking the substrate or in a complete medium containing 0.01 M sodium fluoride or sodium-L-tartrate as enzyme inhibitors. 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 with *s*-collidine buffer. Dehydration was performed in alcohol (see above), and the material was embedded in Epon and treated as mentioned previously for electron microscopy.

Case Histories

Eleven tumors were investigated, none of which was malignant. The tumors occurred in 4 males and 7 females of widely different age (17–62 years). All tumors arose in sites typical of giant cell tumors of bone except one which was located in the second metatarsal bone and one in

Table 1

Case no.	Pat.	Age	Sex	Location	Initital treatment	Histologic type	Local recurrence	Treatment of recurrence	Specimen obtained from	Follow up after last procedure
1	SG	62	F	Sacrum	Resection of sacrum	Jaffe 2[a]			Primary	4 years
2	GB	34	M	Distal femur	Curettage	Jaffe 2	1st aft 1 y 2nd aft 2 ys	Knee endo-prosthesis	1st and 2nd recurrence	2 years
3	MA	17	F	2nd meta-tarsal bone	Curettage	Jaffe 1	after 9 months	Local resection	Primary	1 year
4	CJ	28	F	Proximal tibia	Curettage	Jaffe 2	after 6 months	Curettage	1st recurrence	11 months
5	EA	25	F	Distal ulna	Curettage	Jaffe 2			Primary	1 year
6	JH	31	M	Distal radius	Curettage	Jaffe 2	1st aft 6 m 2nd aft 3 m	Curettage	2nd recurrence	6 months
7	IA	41	F	Distal femur	Homotransplant. hemijoint	Jaffe 1			Primary	4 years
8	ST	33	F	Distal humerus	Curettage	Jaffe 1	after 6 months	Curettage	Primary and 1st recurrence	2 years
9	SA	25	M	Distal ulna	Curettage	Jaffe 2	after 4 years	Resection of ulna	Recurrence	4 years
10	LS	33	F	Th 11	Extirp. of the body of Th 11	Unclassified (not malignant)			Primary	3 years
11	TJ	47	M	Proximal tibia	Curettage	Jaffe 2			Primary	6 months

[a] Jaffe et al. (1940)

the 11th vertebral body. A summary of the cases is presented in Table 1. Some of the patients were referred to the department of orthopedic surgery after previous diagnostic procedures, and – in some instances – treatment in another hospital.

Results

For survey light and electron micrographs of the common appearance of the cells constituting the tumor tissue, the reader is referred to a previous paper (Aparisi et al., 1977a).

By light microscopy, all the tumors studied were typical giant cell tumors of bone lacking morphologic signs of malignancy. Clinically and roentgenologically, there were no signs of hyperparathyroidism or Paget's disease of bone.

The fine structural analysis revealed the occurrence – in all the tumors – of three basic cell types, as previously described, viz, stromal cells type 1, stromal cells type 2, and multinucleated giant cells. In addition, occasional tumors contained small, mononuclear cells and certain intermediate forms – some of which were binucleated. The fine structure of the different cell types is described below. In the cases of the three commonly occurring cells, their appearance is put in relation to that previously analyzed in detail in the initial ("model") study (Aparisi et al., 1977a, b).

A. Stromal Cells Type 1

Common Features

As in the initital study, these cells were of fibroblast-like appearance with an irregular outline of both nuclei and cell borders. Rough surfaced endoplasmic reticulum was abundant and Golgi regions were large and well developed. Mitochondria varied in number, while lysosomes usually were small and inconspicuous. Endocytic vesicles and vacuoles were few. The cytoplasmic ground substance contained particulate glycogen, a well developed system of microfilaments, and sparse "free" ribosomes. The stromal cells type 1 of all tumors were dominated by cells with the features previously described.

Variations in Appearance

Two modifications in the fine structure were observed in some cells of many of the tumors. These cells occurred either singly or in groups with a highly variable frequency. The modifications consisted in (1) extreme folding and irregularity of nuclear membranes with occurrence of nuclear pseudoinclusions (Fig. 1); and (2) marked predominance of rough surfaced endoplasmic reticulum over other cytoplasmic organelles (Fig. 13).

1. Nuclear pseudoinclusions might be single or multiple and varied greatly in size. Some of these inclusions were composed of cytoplasmic organelles with an arrangement and appearance corresponding to that in the cytoplasm.

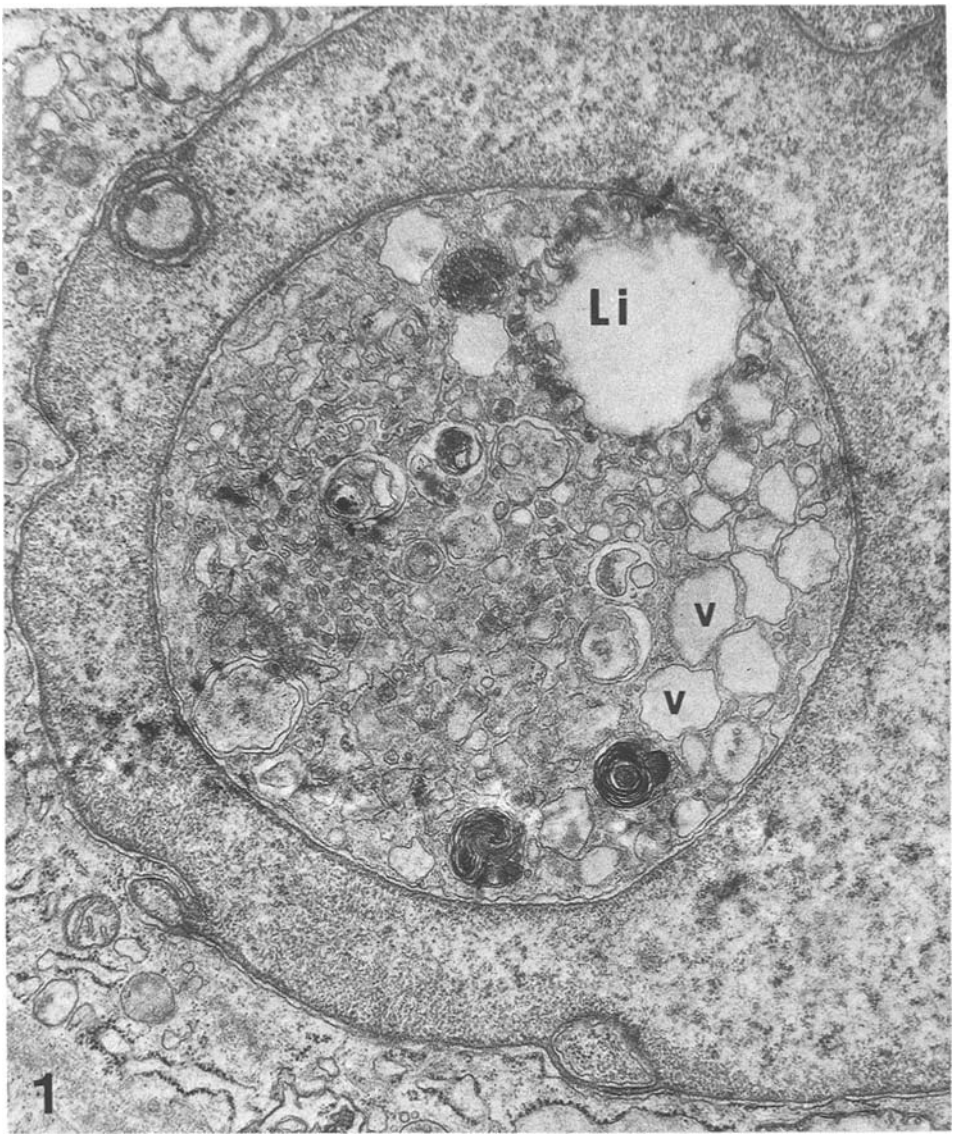

Fig. 1. Stromal cell type 1 with nuclear inclusion of cytoplasmic substance containing a lipid droplet (*Li*), smooth surfaced vacuoles (*v*) (Golgi associated ?), bodies with myelin figures, along with membranous and vesicular elements. Glutaraldehyde + OsO_4; lead citrate. × 19,800

2. Copious numbers of usually intercommunicating cisternae of rough surfaced endoplasmic reticulum were observed in some of the type 1 cells, where this organelle occupied almost the whole cytoplasm of the cells. The cisternae were often widely dilated and contained a moderately electron dense, finely granular and fibrillar ("proteinaceous") material.

In two cases, the cytoplasm in some of the type 1 stromal cells showed

presence of numerous large inclusion bodies with dense matrix containing lipid-like, membranous and granular material. Following incubation of the tissue for the demonstration of acid phosphatase, reaction product was deposited over these bodies indicating that they represented lysosomes.

B. Stromal Cells Type 2

Common Features

These are macrophage-like (Aparisi et al., 1977a, b) containing many mitochondria and lysosomes in their cytoplasm while the endoplasmic reticulum is inconspicuous (Fig. 13). Glycogen is lacking in the cytoplasm ground substance, and microfilaments are rather sparse. The cells are much fewer than stromal cells type 1.

Variations in Appearance

The range of variability was quite narrow with regard to different components of the cells. Hence, the cells constitute a well-defined easily recognizable entity present in all tumors and always are much fewer than stromal cells type 1.

C. Multinucleated Giant Cells

Common Features

These are large cells with multiple nuclei often containing one large, or moderately prominent, nucleolus. Folding of nuclear membranes is common. The cells vary considerably in size and shape. Mitochondria usually occur in abundance. In general, rough surfaced endoplasmic reticulum is sparse in central portions of the cells, but may be more prominent in the periphery where in some cells roughly parallel stacks of cisternae may be observed. Smooth-surfaced endoplasmic reticulum of conventional type is rarely encountered. The Golgi regions are large and often located perinuclearly. Vacuolar elements with tail-like expansions are frequently observed in the vicinity of the Golgi apparatus, as are also peculiar smooth surfaced tubular, sausage-, horse-shoe-, and ring-shaped structures. All these Golgi-associated organelles carry acid phosphatase. Evidence for the presence of this enzyme is also obtained in the Golgi apparatus proper, in conventional lysosomes, and in digestive vacuoles of apparent autophagic and heterophagic nature. The cytoplasm contains a fairly well developed system of microfilaments, while microtubules are sparse. Particulate glycogen is inconspicuous and rarely encountered. Condensation of microfilaments and/or ground cytoplasm to form a distinct, subplasmalemmally located "ectoplasmic layer" is usually not observed. The plasma membrane is commonly smooth or slightly wavy, forming microvillous-like projections in some areas.

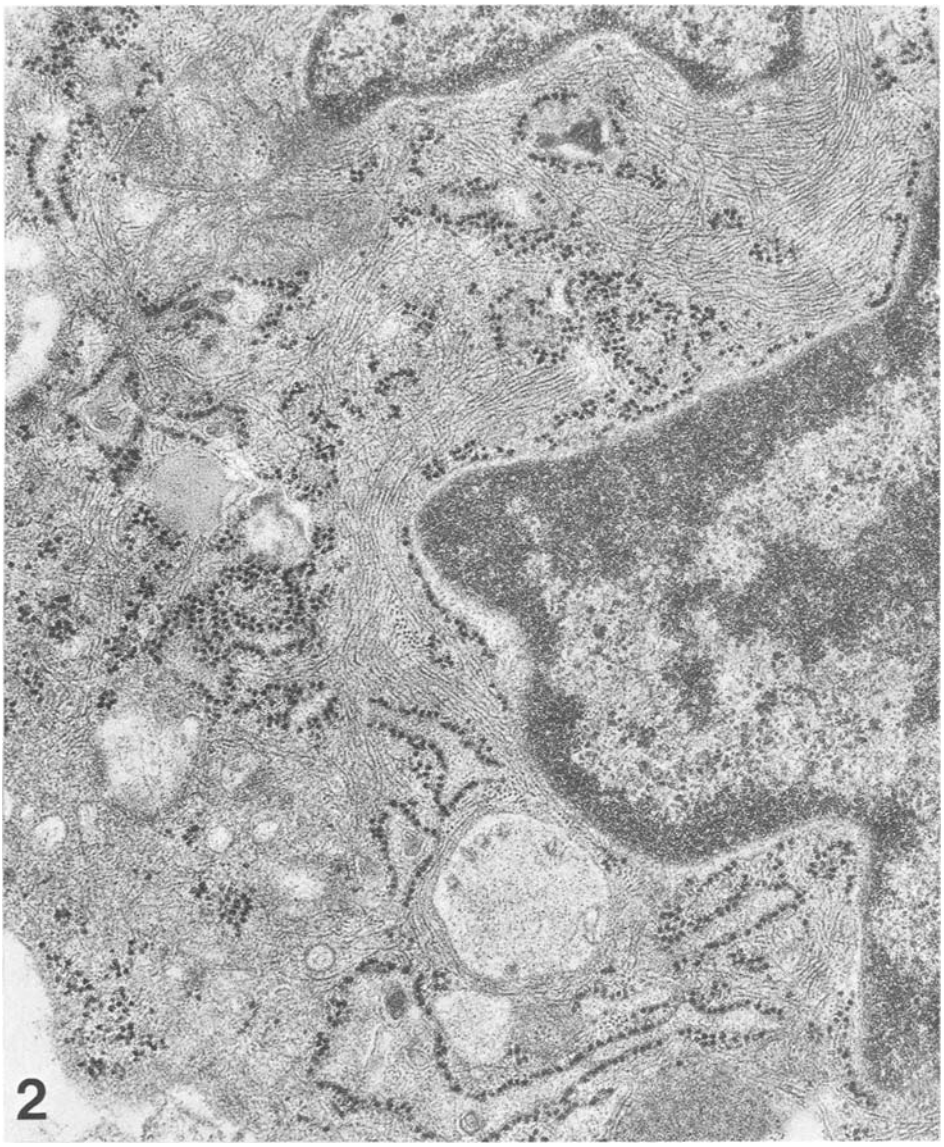

Fig. 2. Portion of binucleated cell. Note abundance of microfilaments forming irregular bundles in the cytoplasmic ground substance. Glutaraldehyde $+OsO_4$; lead citrate. $\times 39{,}000$

Variations in Appearance

1. Nuclear Pseudoinclusions. These appearances seem to be created by extensive folding of the nuclear membrane and generally resemble those already described in stromal cells type 1. In some instances, when the apparent stalk connecting the inclusion with the cytoplasm is located in another plane than the section,

nuclear material appears as a ring surrounding a large inclusion with smooth lining.

2. Bundles of Fibrils in the Nuclear Sap. These structures were occasionally observed and showed a fine morphology similar to that described by Le Charpentier et al. (1977) and Welsh and Meyer (1970). They were only identified in two cases.

3. Aberrations in the Arrangement and Structure of the Rough Surfaced Endoplasmic Reticulum. In some cells, the rough surfaced endoplasmic reticulum formed abundant interconnecting irregularly dilated cisternae and tubules filled with a finely granular moderately electron dense material (Fig. 6). In such areas, endoplasmic reticulum was the predominant cytoplasmic organelle and mitochondria were sparse. Other cells contained large areas of cytoplasm composed almost exclusively of wide spaces of ground cytoplasm with haphazardly dispersed, flattened, usually not interconnected tubules, or occasionally of narrow cisternae of meandering rough surfaced endoplasmic reticulum forming whorls (Fig. 5, inset).

4. Aggregations of Small Vacuoles. These aggregations are commonly located in subplasmalemmal regions (Fig. 4). The vacuoles are filled with a moderately electron dense finely granular, proteinaceous material. They do not seem to be associated with, or take their origin from, the rough surfaced endoplasmic reticulum.

5. Microvilli and Ruffled Border-Like Structure. Many cells showed a tendency at their free surfaces, to form microvilli of variable size and density. In some areas these microvilli were so high and tightly spaced as to form a true ruffled border, as depicted in Fig. 3. Vesicles or vacuoles were few or absent in the subjacent portions of the cytoplasm. However, a tendency toward formation of an ectoplasmic layer was sometimes noted (see also below).

6. Digestive Vacuoles and Residual Bodies. These structures were observed in many of the cases, although only in some cells. Digestive vacuoles might contain large bits of cytoplasm, like in Fig. 7. Lipofuscin-like and other residual bodies (Fig. 8) and large lysosomes were often present in cells with prominent digestive vacuoles. Fine structural evidence for the presence of acid phosphatase in the digestive vacuoles (Fig. 16), lysosomes and residual bodies has been obtained.

7. Cytoplasmic Labyrinths Containing Acid Phosphatase. These elements consist of elaborate systems of intercommunicating canals with focal expansions, often located subjacent to the cell surface (Fig. 17). The limiting membranes are smooth, and connections with the rough surfaced endoplasmic reticulum have not been observed. In some areas, the canals are spatially closely associated with digestive vacuoles carrying acid phosphatase (Fig. 16) and images suggesting continuity between the canals and lumens of the vacuoles can be obtained in fortuitous sections (Fig. 16).

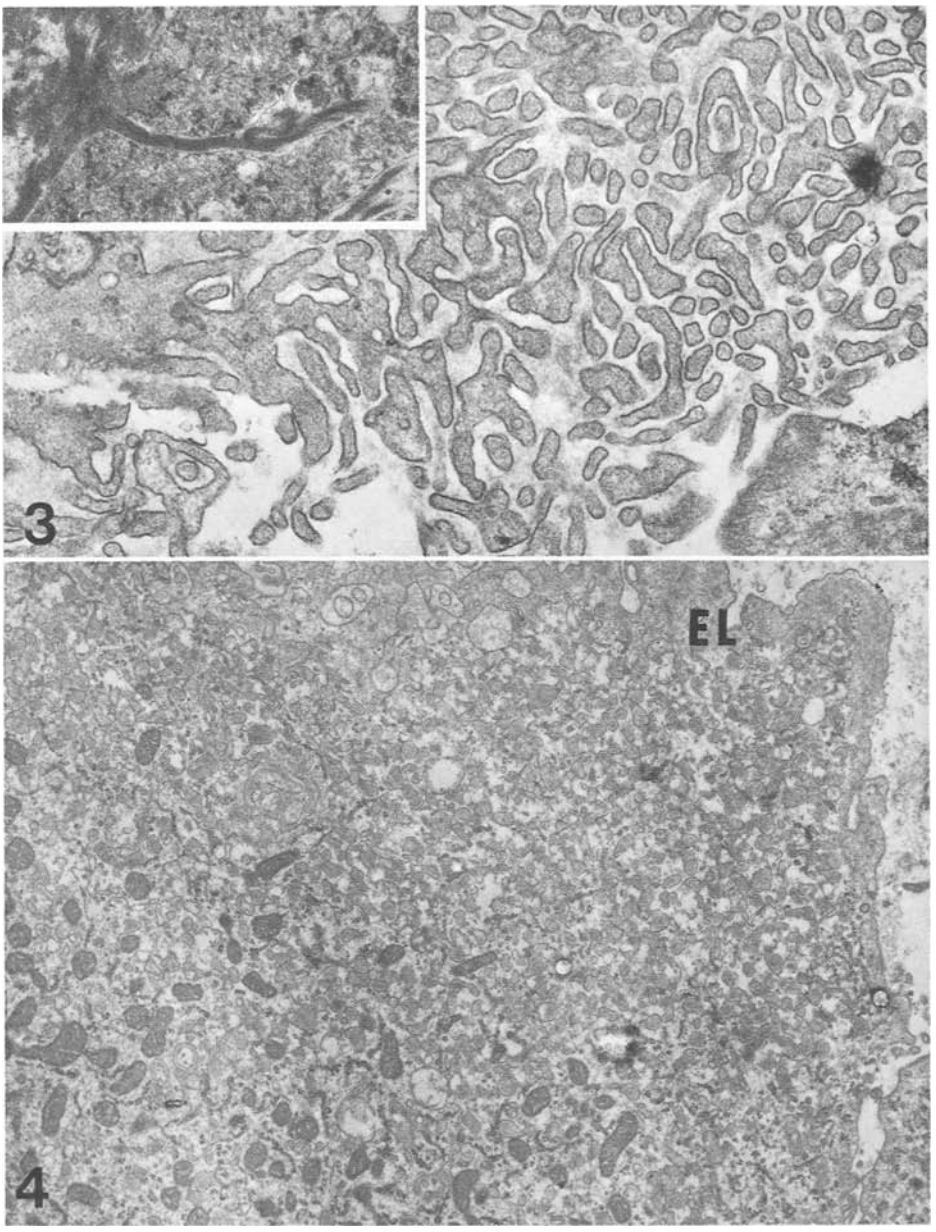

Fig. 3. Superficial area of giant cell with prominent ruffled border. *Inset* shows portion of other giant cell in the process of absorbing a strand of fibrin-like material. Glutaraldehyde + OsO_4; lead citrate. × 17,800; *Inset* × 13,000

Fig. 4. Portion of giant cell with numerous tightly packed vacuoles in the cytoplasm subjacent to the plasma membrane. The vacuoles are filled with a homogeneous, finely granular, moderately dense substance. Note thin ectoplasmic layer (*EL*). Glutareldehyde + OsO_4; lead citrate. × 8,600

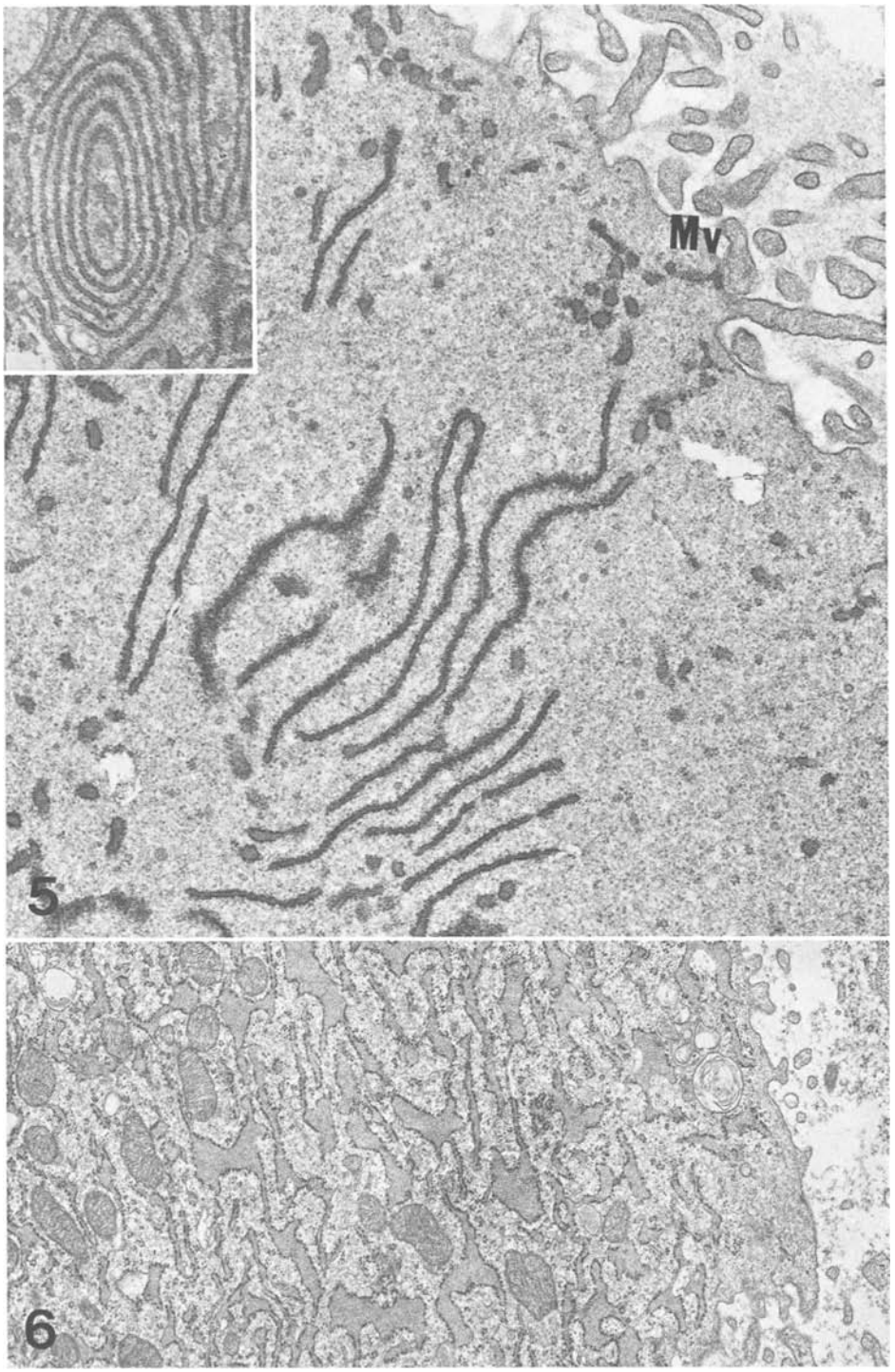

Fig. 5. Superficial area of giant cell with microvilli on the surface (*Mv*) and haphazardly distributed slender tubules or narrow cisternae of rough surfaced endoplasmic reticulum in a ground cytoplasm which is lacking other organelles and has a finely granular structure. *Inset* shows central portion of other giant cell with rough surfaced endoplasmic reticulum forming a fingerprint-like whorl. Glutaraldehyde + OsO_4; lead citrate. × 17,800; *Inset* × 13,000

Fig. 6. From a giant cell containing abundant rough surfaced endoplasmic reticulum with irregularly dilated intercommunicating cisternae filled with a homogeneous, finely granular material. Glutaraldehyde + OsO_4. × 13.000

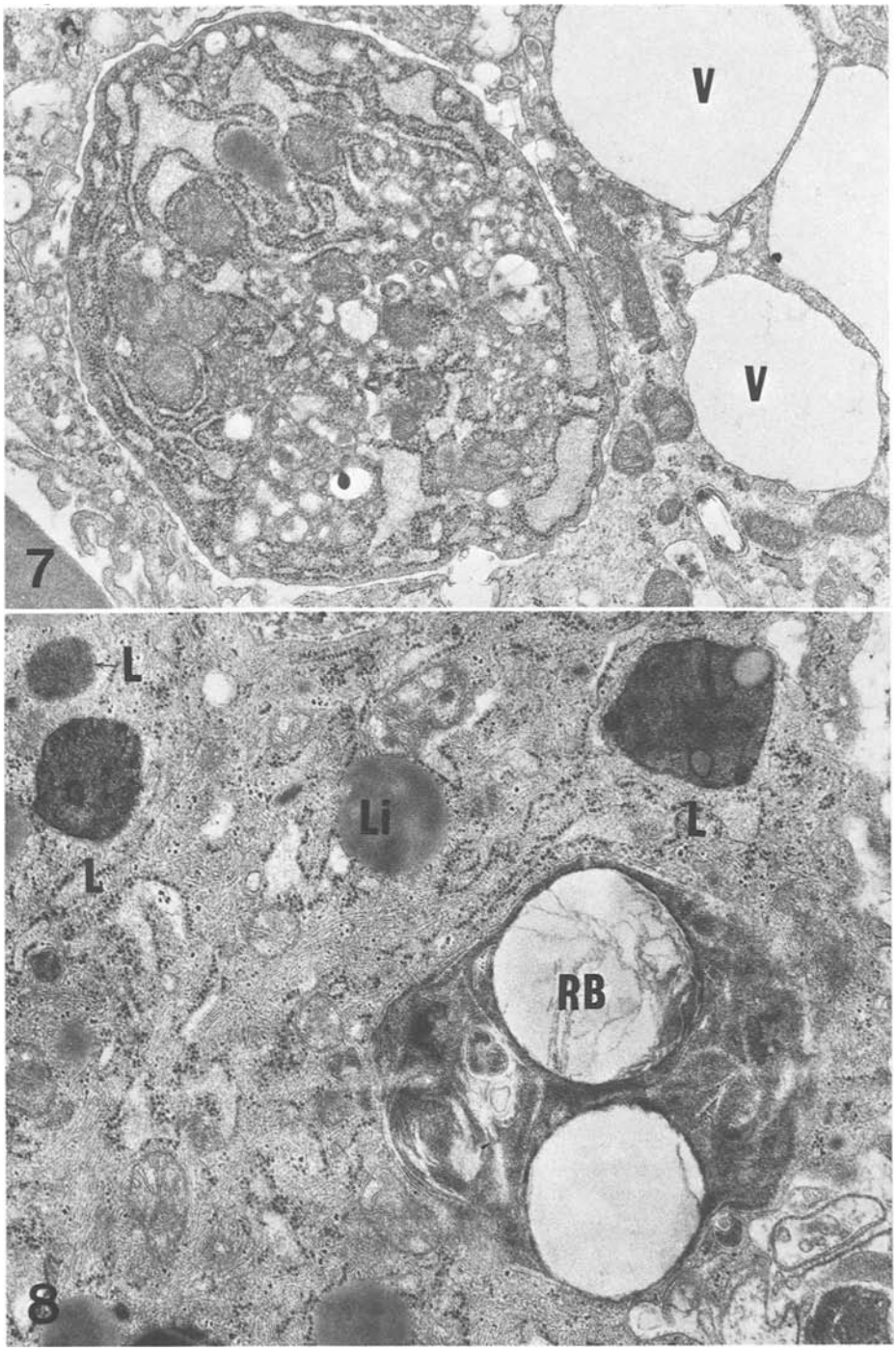

Fig. 7. Superficial portion of giant cell with a large, apparently phagocytotic, vacuole and a couple of empty vacuoles (*V*). Glutaraldehyde + OsO_4. ×17,150

Fig. 8. Area of giant cell with large residual body-like structure (*RB*) and three lysosomes (*L*). *Li*, lipid droplet. Note abundance of microfilaments in the cytoplasmic ground substance. Glutaraldehyde + OsO_4. ×24,000

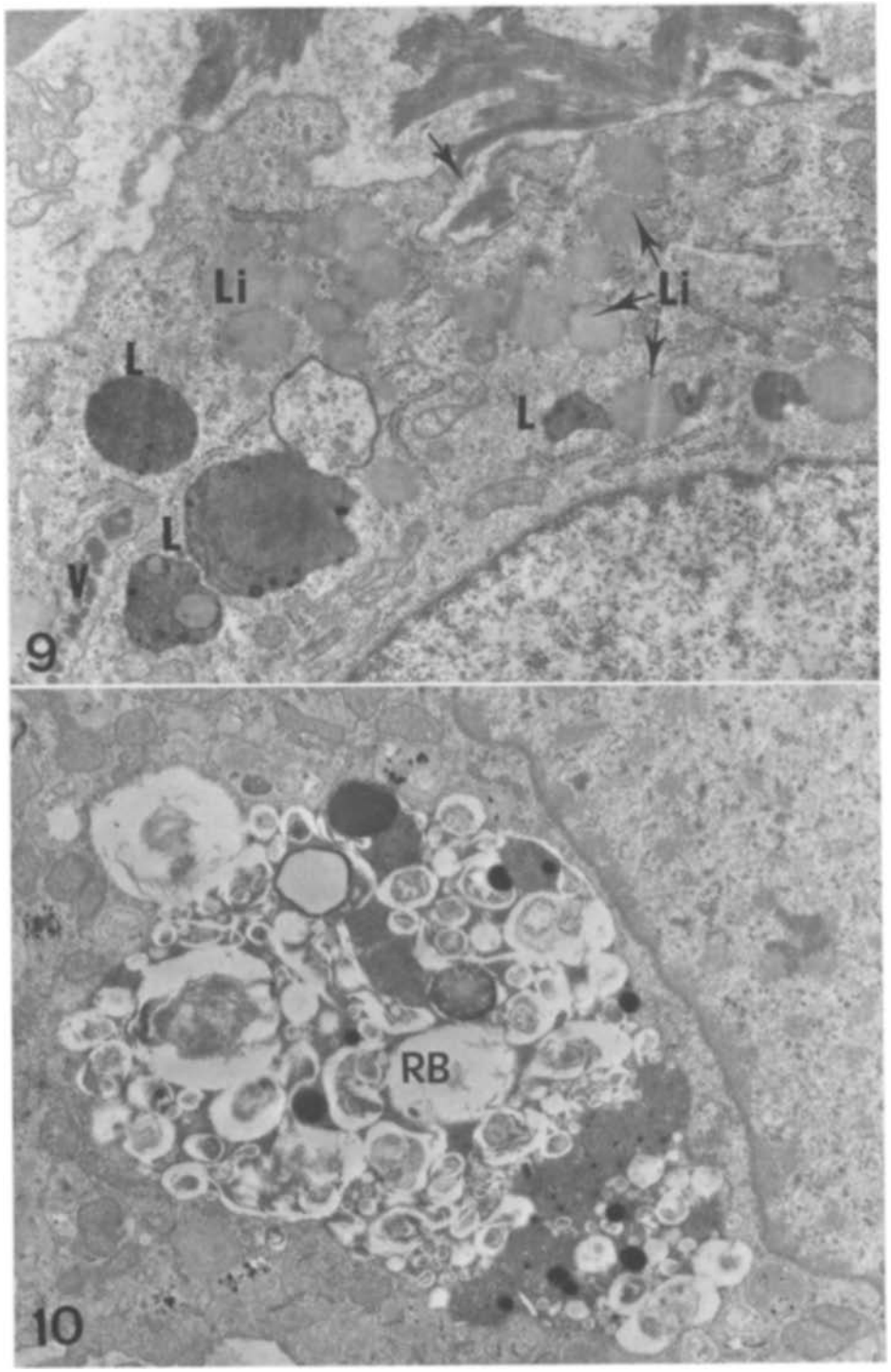

Fig. 9. Superficial area of giant cell appearing to absorb strands of fibrin-like material (*arrow*). The cytoplasm contains numerous lipid droplets (*Li*) and large, dense lysosomes (*L*). Fibrils in the cytoplasmic ground substance are prominent. *V,* vacuole containing dense, proteinaceous material, possibly fibrin. Glutaraldehyde + OsO_4; lead citrate. × 13,500

Fig. 10. Large residual body in giant cell, from tissue incubated for the demonstration of acid phosphatase. Dense deposits of reaction product are present in the residual body (*RB*). Glutaraldehyde; incubated 15 min in the Gomori-type medium; postfixed in OsO_4; lead citrate. × 15,600

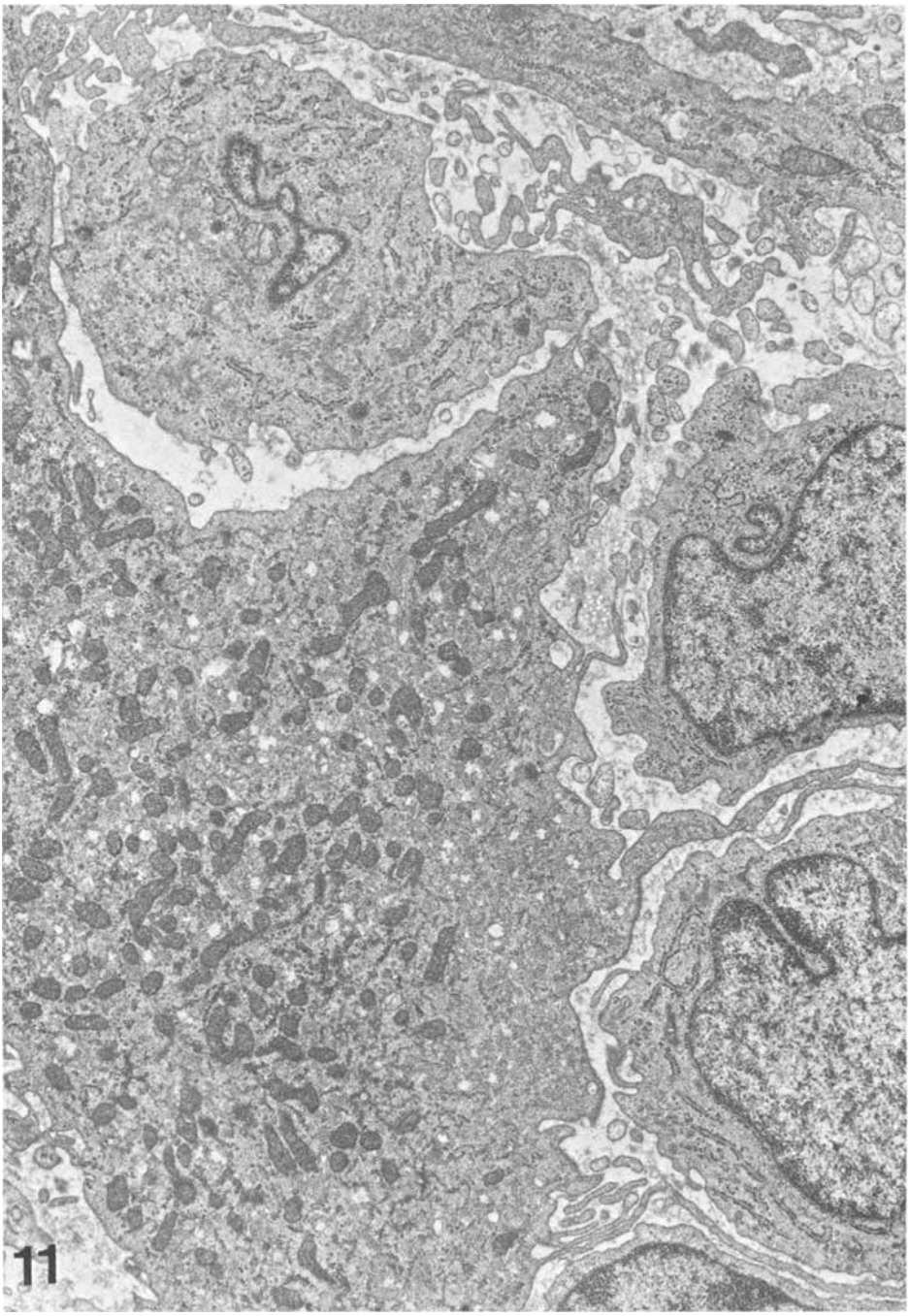

Fig. 11. Overview of giant cell forming protrusions and slender projections which tend to embrace three adjacent type 1 stromal cells. Glutaraldehyde + OsO_4; lead citrate. × 7,550

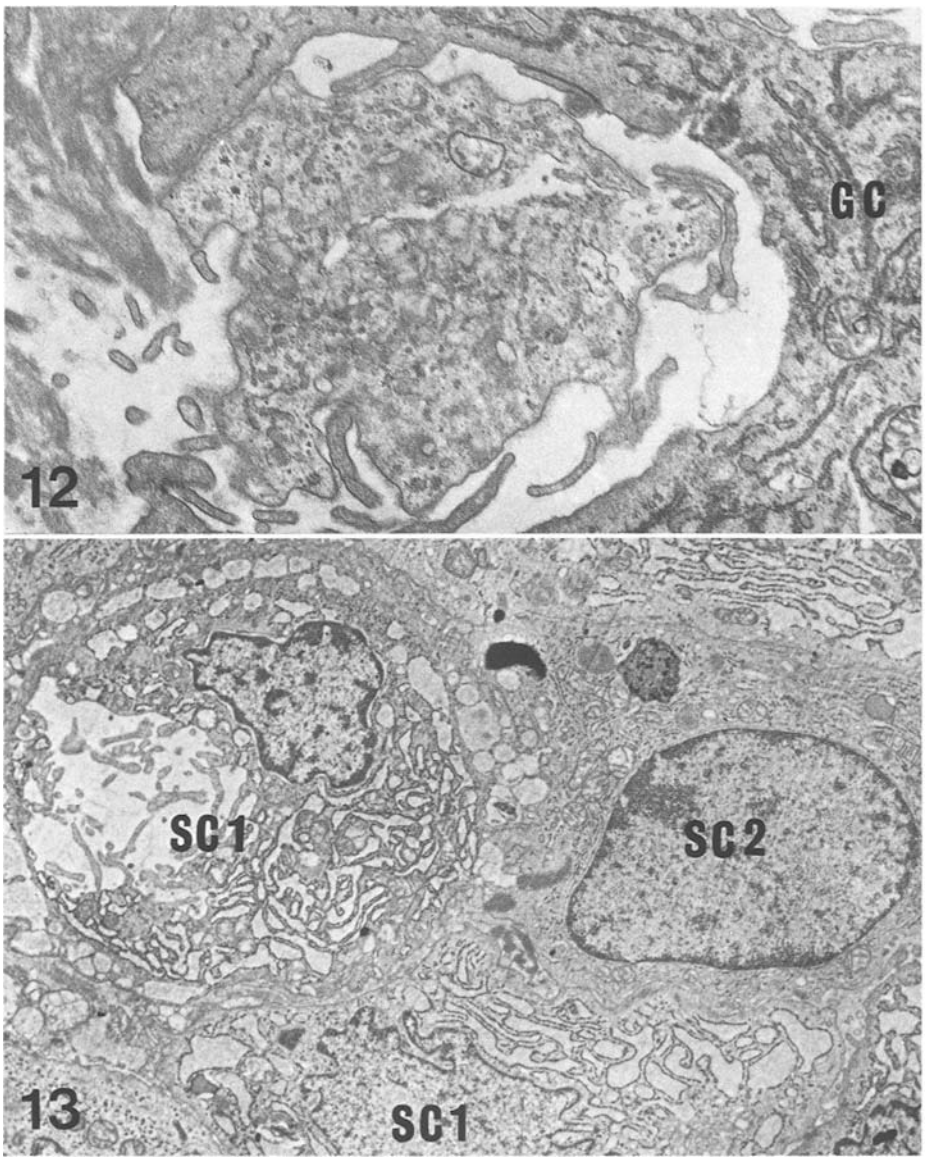

Fig. 12. Portions of a cell partly surrounded by projections and protrusions from a giant cell, *GC*. Glutaraldehyde + OsO_4; lead citrate. × 15,000

Fig. 13. Portions of three adjacent stromal cells, two of which represent type 1 (*SC 1*) and one type 2 (*SC 2*). Note prominent rough surfaced endoplasmic reticulum with widened cisternae in the type 1 cells. Glutaraldehyde + OsO_4; lead citrate. × 6,700

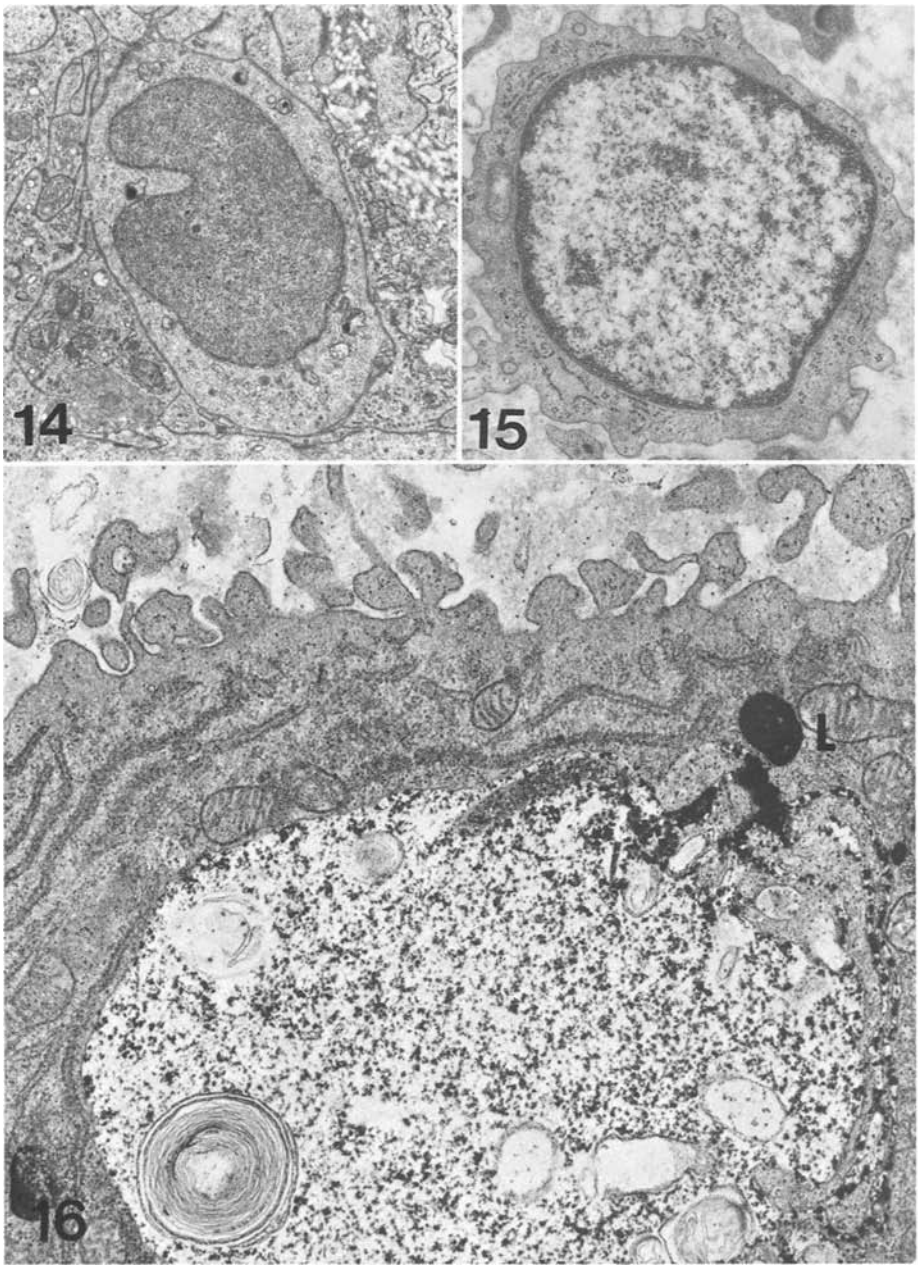

Fig. 14. A small mononuclear cell with scanty cytoplasm and kidney-shaped nucleus. The organelles present appear to mainly represent lysosomes. Glutaraldehyde + OsO_4; lead citrate. × 5,800

Fig. 15. Mononuclear cell with scanty cytoplasm and rounded nucleus. The cytoplasm contains a small mitochondrion, sparse rough surfaced endoplasmic reticulum, and occasional vesicles. Glutaraldehyde + OsO_4; lead citrate. × 11,500

Fig. 16. A huge vacuole containing fragments of mitochondria along with myelin figure-like structures shows presence of reaction product. Lead phosphate precipitate is also deposited over long slender tubular images in the vicinity of the vacuole (right hand side of the picture) and also in a body of conventional lysosomal appearance (*L*). Postfixation in OsO_4; lead citrate. × 20,000

Note: Figs. 16 and 17 are from tissues incubated for the demonstration of acid phosphatase following fixation in glutaraldehyde. All pictures show portions of giant cells

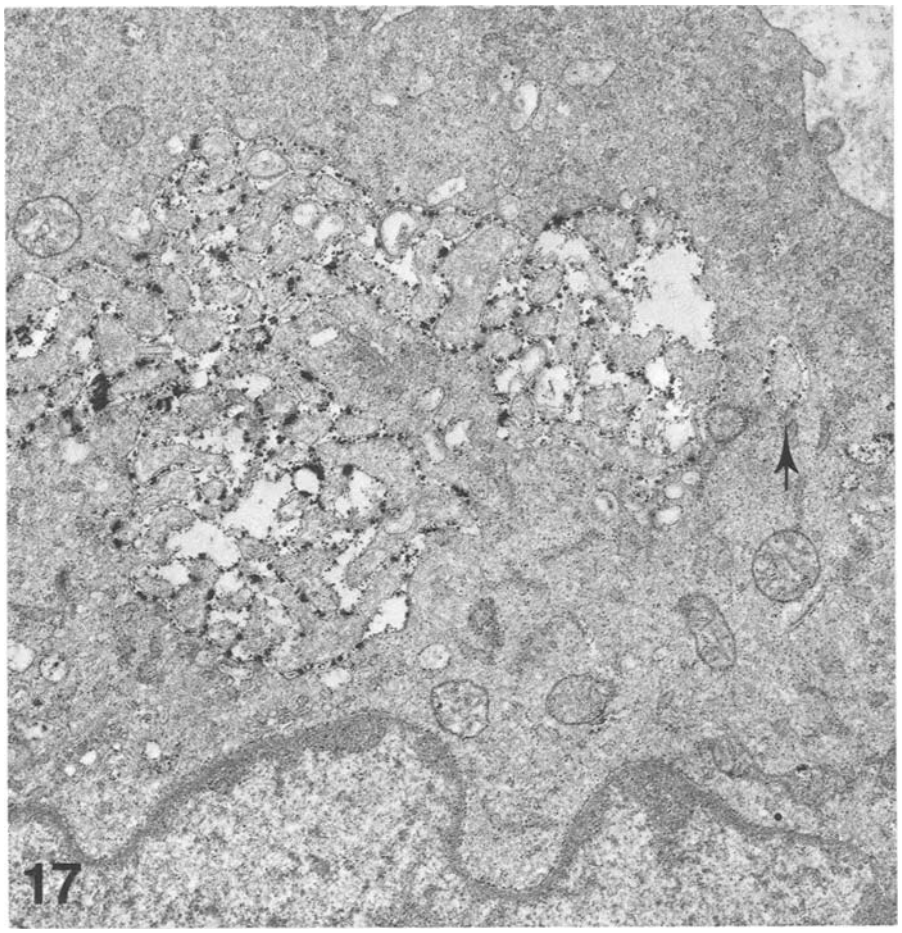

Fig. 17. Superficial and intermediate portion of cell containing numerous, partly intercommunicating, focally dilated tubular and cisternal structures with deposits of final product. Note the ring-shaped image (arrow) which also shows evidence of presence of acid phosphatase. Postfixation in OsO_4; lead citrate. ×14,500

8. Phagocytic Activity. Some cells appeared to be very active in phagocytizing various materials, such as fibrin (Fig. 3, inset) or bits of cytoplasm (Fig. 12). In the latter case, large flaps of cytoplasm seemed to "float" around the material apparently destined for phagocytosis, and the cells formed deep invaginations in such areas.

9. Relationships With Other Cells. Some giant cells were closely surrounded by other cells (mainly stromal cells type 1, but also type 2 cells). In some instances these cells were located in invaginations of the giant cells (Fig. 11) and might be partially surrounded by flaps and pseudopods ejecting from the surface of the giant cells.

D. Possible Intermediate Forms

Clearly identifiable transitional forms between type 1 and type 2 cells have not been observed. Occasionally, binucleate cell forms occurred (Fig. 2). These were characterized by rather abundant rough surfaced endoplasmic reticulum and prominent microfilaments in the ground cytoplasm. Mitochondria as a rule occurred in moderate numbers. Lysosomes were not large or prominent. From the morphologic point of view these cells have more features in common with type 1 than type 2 cells. The specific features of multinucleated giant cells (ruffled border, intracytoplasmic tubular systems, ectoplasmic layer) are lacking.

E. Other Cell Types

Small mononuclear cells are seen in many – but not all – of the tumors examined. Examples of the appearance of these cells are given in Figures 14 and 15. They have rounded or kidney-shaped nuclei, often lacking a clearly identifiable nucleolus. The cytoplasm is scanty, containing few organelles.

Discussion

Differing views prevail concerning the types of cells which constitute genuine benign giant cell tumors of bone (Hanaoka et al., 1970; Horie et al., 1961; Iwashita, 1965; Steiner et al., 1972). The results of the present study show that three distinct cell types always are present in these tumors: stromal cells type 1; stromal cells type 2; and multinucleated giant cells. Small mononuclear cells may also occur but evidently cannot be considered to be actively participating in the neoplastic process. Their origin is enigmatic. At least some of them may emanate from the blood or the reticuloendothelial system (cf. Fig. 15).

Steiner et al. (1972) in a study of four genuine giant cell tumors of bone suggested that certain differences in the fine structural appearance between such tumors might exist, depending on the site of the tumor. We were unable to find support for this notion.

Nuclear pseudoinclusions were noted rather frequently both in stromal cells type 1 and giant cells. On the other hand, they were never observed in stromal cells type 2. Our reason for terming these appearances pseudoinclusions is that – in many instances – they appeared to be in connection with the cytoplasm through a "stalk". They were evidently created by the marked tendency of the nuclear membrane to fold and wrinkle. Typical nuclear pseudoinclusions in giant cell tumors have not been described previously by others, although the irregularity of the nuclear membrane has been commented on (Steiner et al., 1972). Folding of nuclear membranes and occurrence of pseudoinclusions characteristically occurs in tumor cells. Thus, our findings agree with the notion that the stromal cells type 1 and giant cells represent true tumor cells.

Stromal cells type 2 form a very monomorphic and homogeneous group of cells. The structure of their nuclei and lack of remarkable variability among the different components of the cytoplasm suggests that they are not very actively

proliferating or multiplying. Their participation in the neoplastic process may therefore be questioned (Aparisi et al., 1977a). These cells have a morphology resembling that of macrophages or histiocytes. The latter cells are known to actively participate in immunological reactions which may be directed against tumor cells and represent a host response against such cells. It is interesting in this connection to speculate that stromal cells type 2 may have a function in the immunological balance in the giant cell tumor.

Dilatation, irregularity and increased overall size of the rough surfaced endoplasmic reticulum has by some been considered to be a sign of malignancy (Ghadially, 1970). On the other hand, similar appearances have been noted in cells that clearly were non-neoplastic (Brown et al., 1974; Cooper et al., 1973). Whatever the significance of the appearance of the rough surfaced endoplasmic reticulum may be, increased size evidently is an indication of augmented protein synthesis in the cells. Aberrations from the conventional structure of the rough surfaced endoplasmic reticulum were noted in stromal cells type 1 and giant cells. These aberrations were most pronounced in the giant cells. The changes occurring in the stromal cells type 1 were mainly represented by increased size with dilatations of the cisternae. A similar appearance was also noted in the giant cells which – in addition – might show presence of whorl formations and thin, flattened widely dispersed cisternae lacking connections with one another. This variability in the structure of the rough surfaced endoplasmic reticulum is believed to signify a considerable plasticity of this organelle presumably reflecting a capacity for adaptation to different functional states.

Microvillous protrusions of the plasma membranes of giant cells were often observed, and in some cells these protrusions were so high and tightly spaced as to give the impression of a genuine ruffled border. This feature and the presence, in some cells, of a subplasmalemmal condensation of finely fibrillar material to a structure resembling the ectoplasmic layer (Göthlin and Ericsson, 1976) strengthens the morphologic kinship between some tumor giant cells and osteoclasts. The observations suggest that the tendency toward this structural differentiation is highly variable among the giant cells, and many of these cells evidently lack the property completely. The findings evidently raise the question whether or not there exist two populations of multinucleated cells in giant cell tumors of bone: true osteoclasts (Schulz et al., 1977) and tumor giant cells. If so, osteoclasts are much less common than tumor giant cells and do not occur in all tumors. It is interesting in this connection to note that Schajowicz (1977) – on the basis of DNA measurements – claimed the occurrence of two types of multinucleated cells in osteogenic sarcomas. The alternative would be that there is only one population of multinucleated giant cells showing highly variable structural differentiation.

Ruffled (brush) borders and abundant microvilli are hallmarks of cells active in absorptive functions. Pertinent examples of such cells are the surface cells in the gut and the cells of proximal convoluted tubules in the mammalian kidney. In these cells, transport of solutes and macromolecules occurs by transmembranous or bulk passage (endocytosis). The fine structural evidence obtained in the present study suggested that some of the giant cells in certain tumors were active in the bulk absorption of macromolecules. It would also appear

that the cells were able to phagocytize bits of cytoplasm of adjacent cells, and perhaps whole cells (although we have not demonstrated nuclei within phagocytic vacuoles). Possible early stages in the uptake of whole cells are illustrated in Fig. 11 and 12. The appearances in these figures do not suggest that the cells surrounding the giant cells are about to fuse with the latter. It remains to be clarified if, indeed, heterophagocytosis of whole cells does occur, and – if so – the role played by immunological mechanisms.

Occurrence of large inclusion bodies and residual bodies in the cytoplasm of some giant cells evidently is a reflection of their capacity for phagocytosis. These bodies are to be classified as lysosomes, since they show ultrahistochemical evidence of presence of acid phosphatase. It is possible that some of them may have been created by way of phagocytosis.

A striking feature of some giant cells was the cytoplasmic labyrinths. These elements were best revealed and separated from other organelles in tissues incubated for the demonstration of acid phosphatase, since reaction product marking the sites of enzyme was distinctly deposited in the narrow lumens of the labyrinths. These labyrinths show a rather striking resemblance to tubular systems demonstrated in osteoclasts (Göthlin and Ericsson, 1976), and believed to connect with the cellular surface. In the osteoclasts, these structures probably represent devices for the secretion of lysosomal enzymes to the extracellular space (Göthlin and Ericsson, 1976; Lucht, 1971). In the cases of the giant cells, we have so far not been able to demonstrate a direct connection between the labyrinth and the cell surface.

Microfilaments are particularly abundant in stromal cells type 1. They show a fairly wide distribution and frequency in the ground cytoplasm of the giant cells while they are rather inconspicuous in stromal cells type 2. In possible transitional forms, microfilaments have been demonstrated to be quite common. Convincing morphologic evidence for the transition of either stromal cells type 1 or type 2 by fusion to form giant cells has not been obtained, however.

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Addendum

After this manuscript was finished a paper by Wood et al. has been published supporting the notion that the giant cells in giant cell tumors of bone are derived from cells other than macrophages. The giant cells were found to lack the IgGFc and C3 receptors typical of macrophages, while such receptors were present on macrophages derived from the tumor tissue.

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