

Ultrastructure of an Anaplastic Giant Cell Tumor of the Thyroid

YUJI MIZUKAMI, TAKATOSHI MICHIGISHI*, AKITAKA NONOMURA,
TAKUMA HASHIMOTO**, MASAKUNI NOGUCHI***,
SHINOBU NAKAMURA**** AND FUJITSUGU MATSUBARA

*Pathology Section, *Nuclear Medicine, **Laboratory Medicine,
Surgery, and *Internal Medicine, Kanazawa University Hospital, 13-1,
Takara-machi, Kanazawa, 920, Japan*

Abstract

A case of anaplastic, multinucleated giant cell tumor of the thyroid was studied by light and electron microscopy. The coexistence of anaplastic sarcomatous tumor and well differentiated follicular carcinoma, and the presence of desmosomes among the mononuclear cells suggested that this tumor originates in thyroid follicular cells. The multinucleated giant cells, which characterize this thyroid tumor, appeared to be formed by fusion of follicular carcinoma cells and mononuclear epithelial cells, and not by nuclear division without cytoplasmic division.

Anaplastic, multinucleated giant cell tumor of the thyroid, a relatively rare tumor, is one of the most aggressive neoplasms known to occur in humans. The microscopic and ultrastructural appearances of this tumor have been described previously (Cibull and Gray, 1978; Esmaili *et al.*, 1983; Fisher *et al.*, 1974; Gaal *et al.*, 1975; Graham and Daniel, 1974; Jao and Gould, 1975; Newland *et al.*, 1981; Silverberg and DeGiorgi, 1973) and at present, this tumor is generally regarded as an epithelial derivation. On the other hand, the origin of multinucleated giant cells, which characterize this thyroid tumor, remains unclear: they may be formed by fusion of the mononuclear cells or by nuclear division without cytoplasmic division. The present report describes the ultrastructure of this type of thyroid tumor

and discusses the origin of the multinucleated giant cells.

Case Reports

An 84-year-old woman presented with a swelling of 5 years' duration in the left neck. The mass had grown rapidly over the preceding 2 months, and at the time of admission she had dysphagia and dyspnea. Physical examination revealed a hard mass 7 cm in diameter in the left neck, which appeared to be within the thyroid gland. Local lymph nodes were not enlarged. A scintiscan showed a "cold" area in the left lobe of the thyroid. A chest roentgenogram disclosed several dense shadows in both lung lobes, suggestive of metastatic tumors. There was no involvement of the skeletal systems. Routine laboratory studies, including thyroid function

tests, were within normal ranges. The serum thyroxine was 6.4 $\mu\text{g/dl}$ (normal range, 4.6–11.0 $\mu\text{g/dl}$), and serum triiodothyronine was 96 ng/dl (95–200 ng/dl). Aspiration biopsy was performed and a diagnosis of anaplastic carcinoma of the thyroid was made. Total thyroidectomy was performed. The left lobe was replaced by a tumor mass that was adherent to the adjacent neck structures. Postoperatively, the patient received irradiation and chemotherapy, but this treatment failed to induce remission of the neoplasm, and the patient died 3 months after surgery from local invasive tumor, generalized skin metastases, and numerous pulmonary metastases. An autopsy could not be performed.

Materials and Methods

The resected thyroid gland weighed 105 gm. The cut surface of the left lobe revealed nearly complete replacement by a grayish firm tumor with a large necrotic area, measuring approximately 7×5×5 cm.

For light microscopy, tissues removed during the operation were fixed in 10% formalin, processed in the conventional manner, and stained

with hematoxylin and eosine as well as with periodic acid-Schiff reagent. For immunohistochemistry, deparaffinized sections were treated with anti-lysozyme serum (Dako Co., Santa Barbara, CA.), or anti-thyroglobulin serum (Dako Co.), followed by swine anti-rabbit serum and rabbit peroxidase-antiperoxidase (PAP) complexes. For electron microscopy, tissues were fixed in cold 2.5% glutaraldehyde buffered with 0.1 M cacodylate buffer for 1 hour. They were then post-fixed in 1% osmium tetroxide for 1 hour, dehydrated in graded ethanol and embedded in epoxy resin. The sections were cut with a glass knife on an ultramicrotome, stained with uranyl acetate and lead citrate, and examined under a Hitachi HU-11DS electron microscope.

Light microscopy

The tumor was composed of spindle-shaped and rounded mononuclear cells and characteristic multinucleated giant cells. The multi-nucleated giant cells had strongly eosinophilic cytoplasm, which was occasionally vacuolated; some cells contained as many as 30 nuclei, but the average was 6 to 8. The nuclei of multinucleated giant cells tended to be slightly smaller and more regular in shape than those of mononuclear cells. The spindle-shaped and ovoid mononuclear cells had pale pink cytoplasm and indistinct cell borders, and they showed signs of marked nuclear pleomorphism (Fig. 1). Mitotic figures were present only in the mononuclear cells;

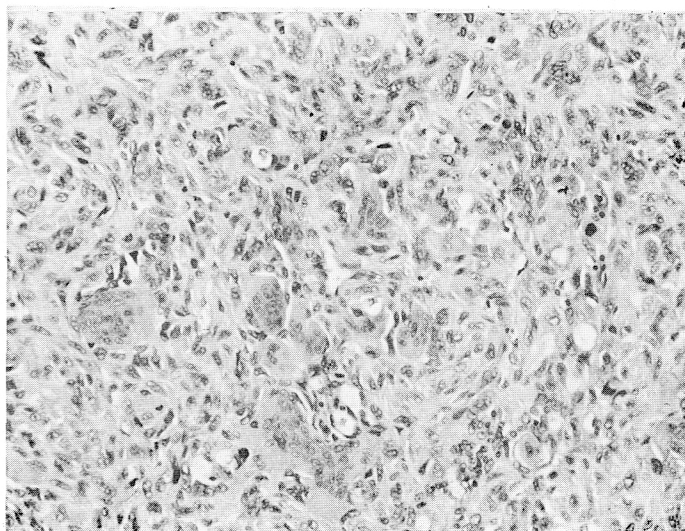


Fig. 1. Multinucleated giant cells surrounded by round or spindle-shaped mononuclear cell. (H&E, ×200)

none were present in the multinucleated giant cells. They averaged 2 per high power field. The tumor was not encapsulated but extended into the surrounding soft tissues. Large areas of necrosis and hemorrhage were present. Massive invasion into veins was a prominent feature. In some sections, foci of well differentiated follicular carcinoma forming small follicles were scattered within the anaplastic sarcomatous tumor. In one section, some microfollicles were arranged close to the multinucleated giant cells, indicating a transition from microfollicles to multinucleated giant cells (Fig. 2). Neither

lysozyme nor thyroglobulin was detected in the giant cells of mononuclear cells by the immunoperoxidase technique. Some infiltrating neutrophils were positive for lysozyme, and thyroglobulin was clearly positive in co-existing follicular carcinoma cells.

Electron microscopy

The mononuclear cells contained angulated and indented nuclei with coarsely clumped chromatin. The cytoplasm contained many vacuolated mitochondria and rough endoplasmic reticula (rER) with dilated cisternae. Free ribo-

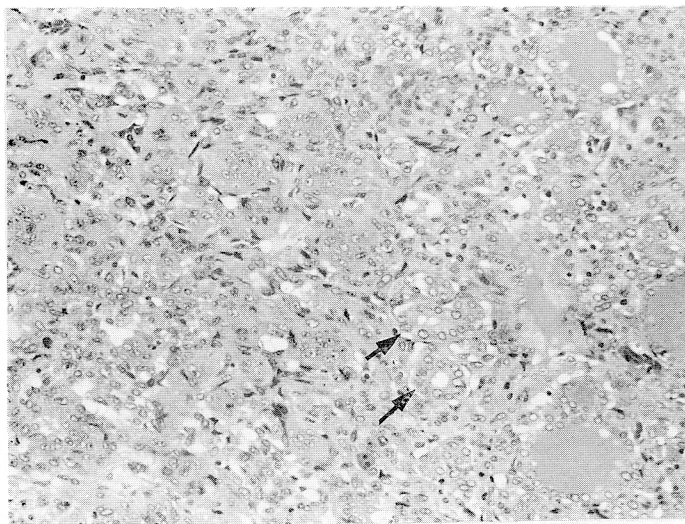


Fig. 2. Multinucleated giant cells are seen on the left part of the micrograph and the foci of follicular carcinoma on the right. The transition from microfollicle to giant cell can be seen (arrows). (H&E, $\times 200$)

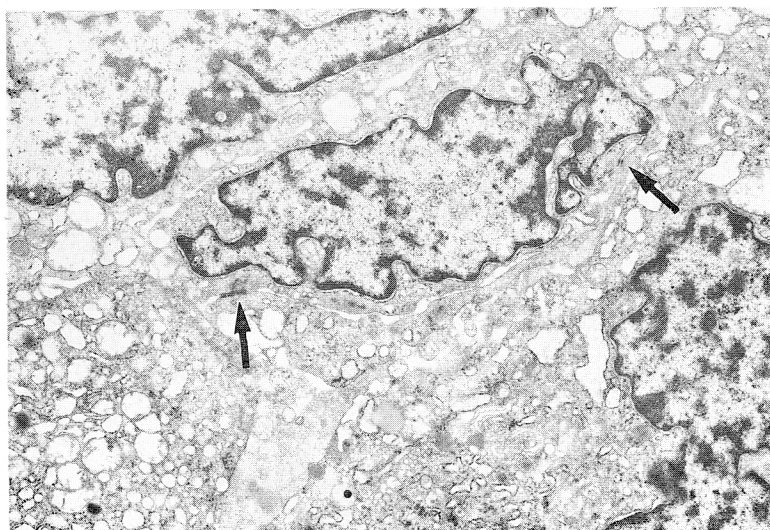


Fig. 3. Sheet of mononuclear cells. Note the presence of desmosomes (arrows). ($\times 6,100$)

somes and polysomes were increased in number and scattered in the cytoplasm. Some round dense lysosomal bodies were also seen in the cytoplasm. The cell surface was irregular, and desmosomal structures were occasionally seen between tumor cells (Fig. 3). The multinucleated giant cells varied considerably in size and configuration. Their cytoplasmic features, however, were fairly uniform and characterized by abundant, evenly disposed mitochondria (Fig. 4). Fragments of rER, occasional lysosomes, and

many small vacuoles were also observed in their cytoplasm. In spite of a meticulous search, neither residual plasma membranes nor desmosomal structures were recognized in their cytoplasm. In one ultrathin section, an extremely tiny neoplastic follicular structure, which was recognizable at the ultrastructural level, was observed (Fig. 5).

The follicle was composed of three neoplastic follicular cells. The nuclei of these cells were irregular and contained coarsely dispersed chro-

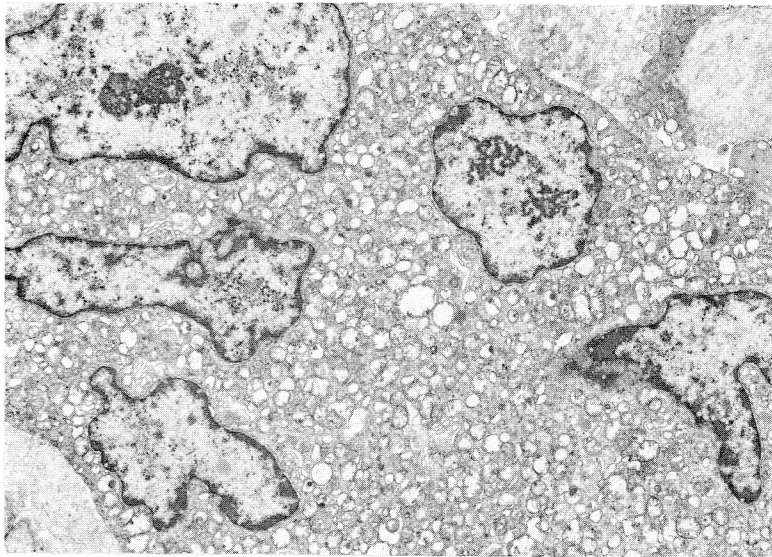


Fig. 4. A multinucleated giant cell. The nuclei are irregular with deep marginal invaginations and the cytoplasm is rich in mitochondria.

($\times 4,700$)

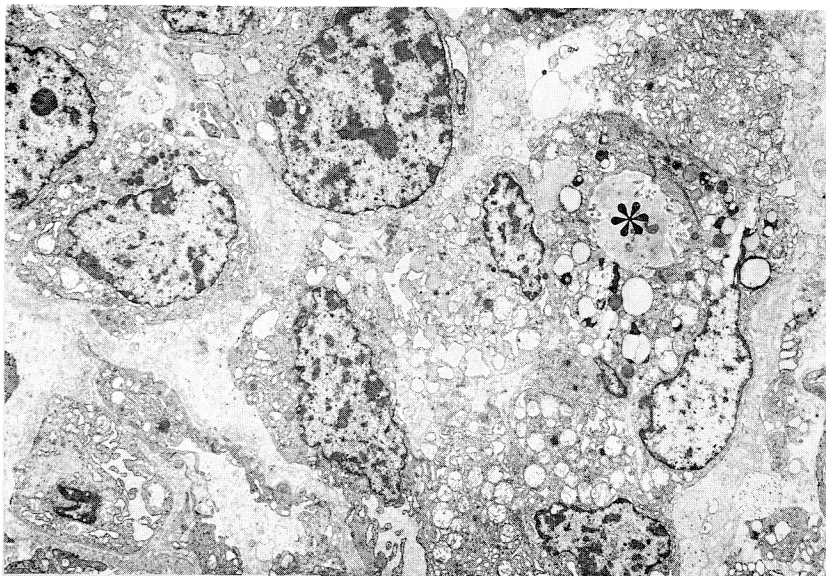


Fig. 5. A neoplastic midro-follicular structure (asterisk) and neighboring mononuclear cells are seen.

($\times 2,600$)

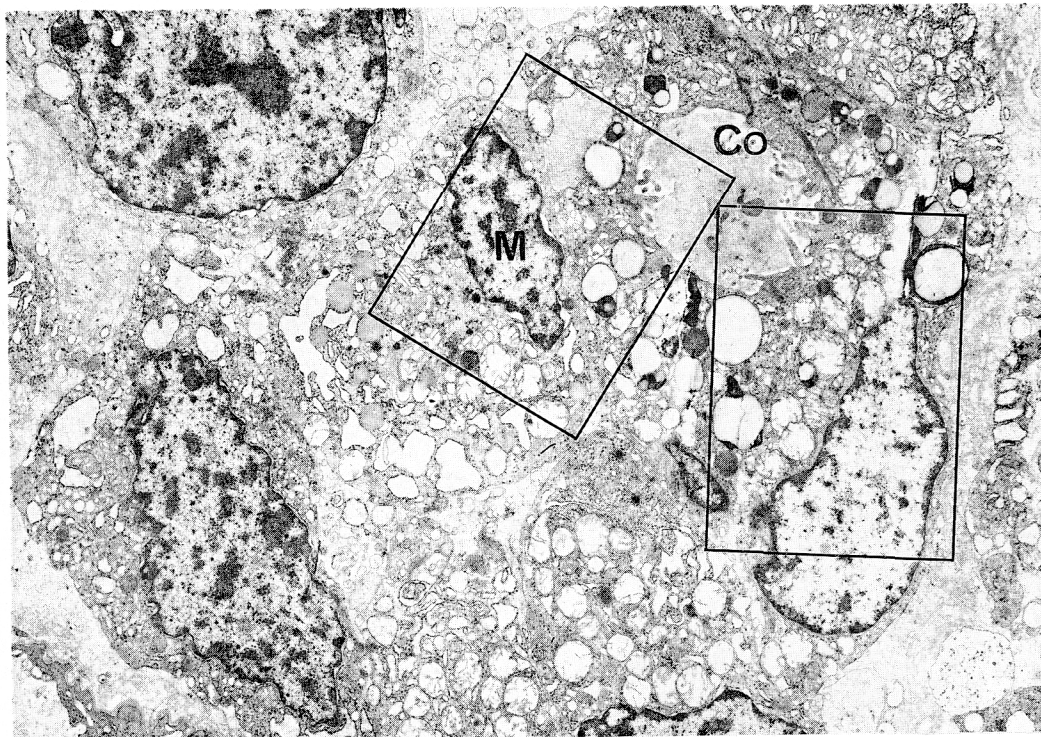
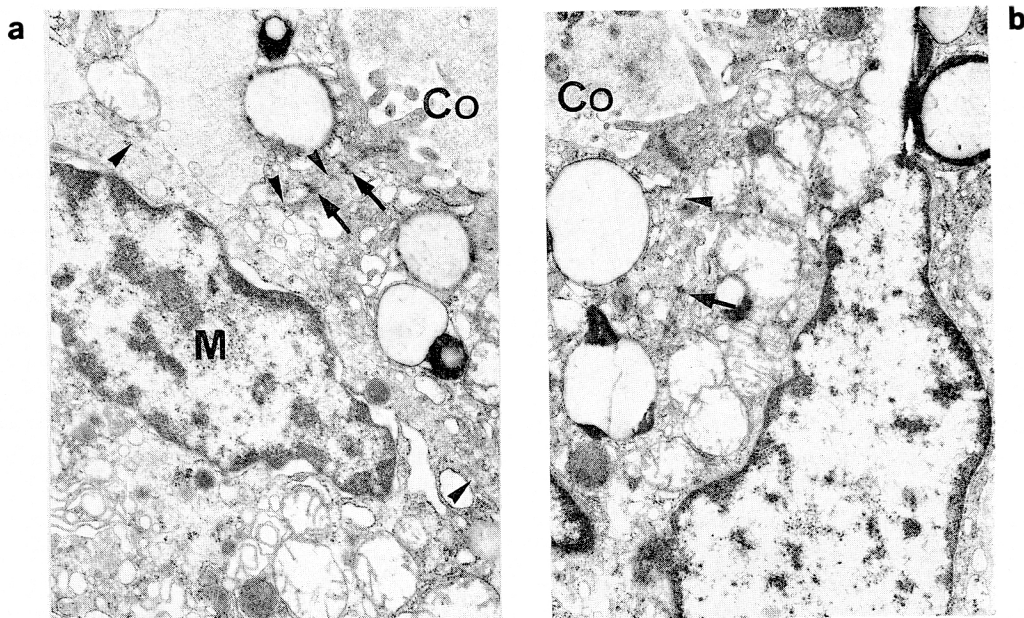


Fig. 6. Higher magnification of the micro-follicular structure. The follicle is composed of three neoplastic follicular cells. One mononuclear cell (M) is attached to the follicular cell. Co; colloid ($\times 6,400$)



Figs. 7a and 7b. Higher magnification of boxed areas. The left boxed area (Fig. 7a) shows fusion between a follicular cell and a mononuclear cell (M). Right boxed area (Fig. 7b) shows fusion between neighboring follicular cells. Merging plasma membrane (arrowheads) and residual desmosomal structures (arrows) are observed. Co; colloid ($\times 11,000$: $\times 12,000$)

matin. The apical cell membrane formed microvilli, and the cells were linked to each other by desmosomes and terminal bars (Fig. 6). These ultrastructural features resembled were similar to those of well differentiated follicular carcinoma. Furthermore, this follicle was surrounded by several mononuclear neoplastic cells, and appeared to be undergoing fusion with them, since only fragments of plasma membrane and desmosomes were observed between these structures. In addition, neighboring follicular cells also appeared to be in the process of cell fusion (Figs. 7a and 7b). These findings suggested a transition from the follicular structure to the multinucleated giant cell at the ultrastructural level, and the size and the number of nuclei of the multinucleated giant cell seemed to increase by merging with additional mononuclear cells.

Discussion

Since the first electron microscopic observation of giant cell tumor of the thyroid was made by Fisher *et al.* (1974), several reports have appeared (Cibull and Gray, 1978; Esmaili *et al.*, 1983; Gaal *et al.*, 1975; Graham and Daniel, 1974; Jao and Gould, 1975; Newland *et al.*, 1981). Most authors suggested that giant cell tumor of the thyroid is of epithelial cell origin, i.e. originating in follicular epithelial cells. On the other hand, Cibull and Gray (1978) reported that this tumor is of mesenchymal origin, because tumor cells possess no morphological characteristics of epithelial cells.

In our study, the presence of desmosomal structures between adjacent mononuclear cells suggests the epithelial origin of this tumor. Moreover, the association of this tumor with follicular carcinoma noted under the light microscope suggests that this tumor originates in follicular epithelial cells. In the present case, thyroglobulin was not detected immunohistochemically in the mononuclear cells or giant cells. However, recent immunohistochemical studies sug-

gested that some of these tumors may stain positively for thyroglobulin (Albores-Saavedra *et al.*, 1983; Carcangiu *et al.*, 1985; Hurlimann *et al.*, 1987; LiVolsi *et al.*, 1987). These reports support this hypothesis about the origin of giant cell tumor of the thyroid.

On the other hand, the origin of multinucleated giant cells, which characterize this thyroid tumor, remains unclear. Ultrastructural findings in this case suggested that multinucleated giant cells are formed by fusion of neoplastic follicular cells and that the number of nuclei increases by merger with neighboring mononuclear epithelial cells. On the other hand, most mature giant cells had no ultrastructural features suggesting follicular epithelial cell origin, such as an intracytoplasmic luminal structure or abundant phagolysosomes containing thyroglobulin. It has been shown *in vitro* that cell fusion proceeds rapidly and that the cytoplasmic structure of giant cells may be readily modified in accordance with environmental conditions (Sutton and Weiss, 1966). Therefore, the differences between the cytoplasmic features of mature multinucleated giant cells and follicular epithelial cells do not exclude the possibility that giant cells are formed by fusion of follicular epithelial cells.

Gaal *et al.* (1975) reported one case of giant cell tumor of the thyroid which ultrastructurally exhibited virus-like particles. Cell fusion is known to be induced by some viruses such as Sendai virus (Hosaka and Koshi, 1968). Therefore, viruses may be involved in the pathogenesis of this tumor. In our case, however, no viral particles were found in the tumor cells.

In conclusion, we support the concept that this tumor is an epithelial lesion arising from thyroid follicular cells. Moreover, the multinucleated giant cells appeared to be formed by cell fusion, and not by nuclear division without cytoplasmic division. Further studies are needed to clarify the

pathogenesis of this rare thyroid tumor.

Acknowledgments

The authors thank Mrs. Sanae Itoh for assistance in the preparation of this article.

References

- Albores-Saavedra, J., M. Nadji, F. Civantos and A. R. Morales (1983). Thyroglobulin in carcinoma of the thyroid. An immunohistochemical study. *Human Pathol.* 14, 62-66.
- Carcangiu, M. L., T. Steeper, G. Zampi and J. Rosai (1985). Anaplastic thyroid carcinoma. A study of 70 cases. *Am. J. Clin. Pathol.* 83, 135-158.
- Cibull, M. L. and G. F. Gray (1978). Ultrastructure of osteoclastoma-like giant cell tumor of thyroid. *Am. J. Surg. Pathol.* 2, 401-405.
- Esmaili, J. H., G. R. Hafez and T. F. C. S. Warner (1983). Anaplastic carcinoma of the thyroid with osteoclast-like giant cells. *Cancer* 52, 2122-2128.
- Fisher, E. R., R. Gregorio, R. Shoemaker, B. Horvat and C. Hubay (1974). The derivation of so-called "giant-cell" and "spindle-cell" undifferentiated thyroid neoplasms. *Am. J. Clin. Pathol.* 61, 680-689.
- Gaal, J. M., E. Horvath and K. Kovacs (1975). Ultrastructure of two cases of anaplastic giant cell tumor of the human thyroid gland. *Cancer* 35, 1273-1279.
- Graham, H. and C. Daniel (1974). Ultrastructure of an anaplastic carcinoma of the thyroid. *Am. J. Clin. Pathol.* 61, 690-696.
- Hosaka, Y. and Y. Koshi (1968). Electron microscopic study of cell fusion by HVJ virions. *Virology* 34, 419-434.
- Hurlimann, J., D. Gardiol and B. Scazziga (1987). Immunohistology of anaplastic thyroid carcinoma. A study of 43 cases. *Histopathology* 11, 567-580.
- Jao, W. and V. E. Gould (1975). Ultrastructure of anaplastic (spindle and giant cell) carcinoma of the thyroid. *Cancer* 35, 1280-1292.
- Livolsi, V. A., J. J. Brooks and B. Arendash-Durand (1987). Anaplastic thyroid tumors: Immunohistology. *Am. J. Clin. Pathol.* 87, 434-442.
- Newland, J. R., B. Mackay, C. S. Hill, Jr. and R. C. Hickey (1981). Anaplastic thyroid carcinoma: An ultrastructural study of 10 cases. *Ultrastruct. Pathol.* 2, 121-129.
- Silverberg, S. G. and L. S. DeGiorgi (1973). Osteoclastoma-like giant cell tumor of the thyroid. Report a case with prolonged survival following partial excision and radiotherapy. *Cancer* 31, 621-625.
- Sutton, J. S. and L. Weiss (1966). Transformation of monocytes in tissue culture into macrophages, epithelioid cells, and multi-nucleated giant cells: an electron microscopic study. *J. Cell Biol.* 28, 303-332.