HISTOLOGICAL AND ELECTRON MICROSCOPIC OBSERVATION ON THE ADENOMATOUS HYPERPLASIA OF THE ALVEOLAR EPITHELIAL CELL IN THE HUMAN LUNG

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INTRODUCTION

The rising incidence of lung cancer in recent years has stimulated a search for the site of origin. While studying the histogenesis of lung cancer, Rössle[20] (1943) and Lüders et al.[12] (1954) found that it was possible to relate many peripheral lung cancers to previous scarring. Their observation has received further confirmation by many other investigators (Gelzer[5] (1956), Reaburn et al.[19] (1957), Kambara et al.[8] (1960), Oboshi[15] (1960), Carroll[4] (1962), Okada et al.[17] (1967)).

Most people who had studied lung cancer believed that lung scar cancers originate from the proliferation, especially from the adenomatous hyperplasia of epithelial cells associated with scaring in the peripheral lung tissue (Berkheiser[1][2] (1959, '63), King[10] (1964)). Lung cancers which seem to arise in scars are frequently associated with adenomatous hyperplasia. Sixty to ninety per cent. of lung scar cancers are adenocarcinoma, and the histological appearance resembles that of the adenomatous hyperplasia in the peripheral lung tissue. These facts indicate there may be causal relationship between lung scar cancer and adenomatous hyperplasia.

The origin of these epithelial cells proliferating in the alveolar area has not been clearly established. The purpose of this study is to ascertain histological and electron microscopic structure of the adenomatous hyperplasia in the alveolar area, and to prove the histogenesis of the adenomatous hyperplasia in the human lung.

HISTOLOGY OF THE ADENOMATOUS HYPERPLASIA

In the area of the adenomatous hyperplasia in the human lung, low columnar or cuboid cells proliferate and line continuously the alveolar septa, thickened with large amount of fibrous tissue. A single layer of hyperplastic epithelial cells lines

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narrow alveolar lumen to form gland-like spaces as shown in Figs. 1 and 2.

In Fig. 3 epithelial proliferation can be seen on the surface of the hypertrophic alveolar septum. In this case, the amount of fibrous tissue in the alveolar septum is less than that in Fig. 1.

The case shown in Fig. 4 is suggestive of the early stage of adenomatous hyperplasia in the alveolar area. Cuboid or low columnar cells are densely scattered on alveolar septa associated with slight fibrosis, and they aggregate to line continuously the alveolar septum in a portion of the alveolar area.

Even in the healthy lung, such cuboid cells are occasionally found on the alveolar septum as shown in Fig. 5.

From the above mentioned histological findings, it is supposed that cuboid cells in the adenomatous hyperplasia originate from pre-existing lining cells of the alveoli. Adenomatous hyperplasia is probably a nonspecific response of the epithelial cell associated with fibrosis induced by inflammation or other stimuli occuring in the alveolar area.

ELECTRON MICROSCOPY OF THE ADENOMATOUS HYPERPLASIA

According to the electron microscopy of the healthy lung tissue, two kinds of epithelial cell are found in the alveolar area as shown in Fig. 6. One is cuboid in form and called "alveolar wall cell" (or type B epithelial cell or large alveolar cell), and the other is flat and is called "alveolar epithelial cell" (or type A epithelial cell or small alveolar dell) (Nagaishi et al.[13] (1964)). It is suggestive that the cuboid cell in the adenomatous hyperplasia corresponds to the alveolar wall cell.

Electron microscopic observations on the adenomatous hyperplastic portion in the human lung revealed that thick connective tissue is lined continuously with cuboid cells resembling alveolar wall cell in the fine structure.

The individual cell has numerous microvilli on the luminal surface, and a basement membrane below the cell membrane facing the connective tissue as shown in Figs. 7 and 8. Terminal bars are found between cells. All of these cuboid cells contain osmiophilic lamellar bodies in their cytoplasm as shown in Fig. 9. Microvilli, basement membrane and terminal bar indicate that these cells are epithelial in origin. Osmiophilic lamellar bodies are characteristic of the alveolar wall cell (tyep B epithelial cell) and the fact that they are found in cells of adenomatous hyperplasia suggest that hyperplastic cells originate from the alveolar wall cell.

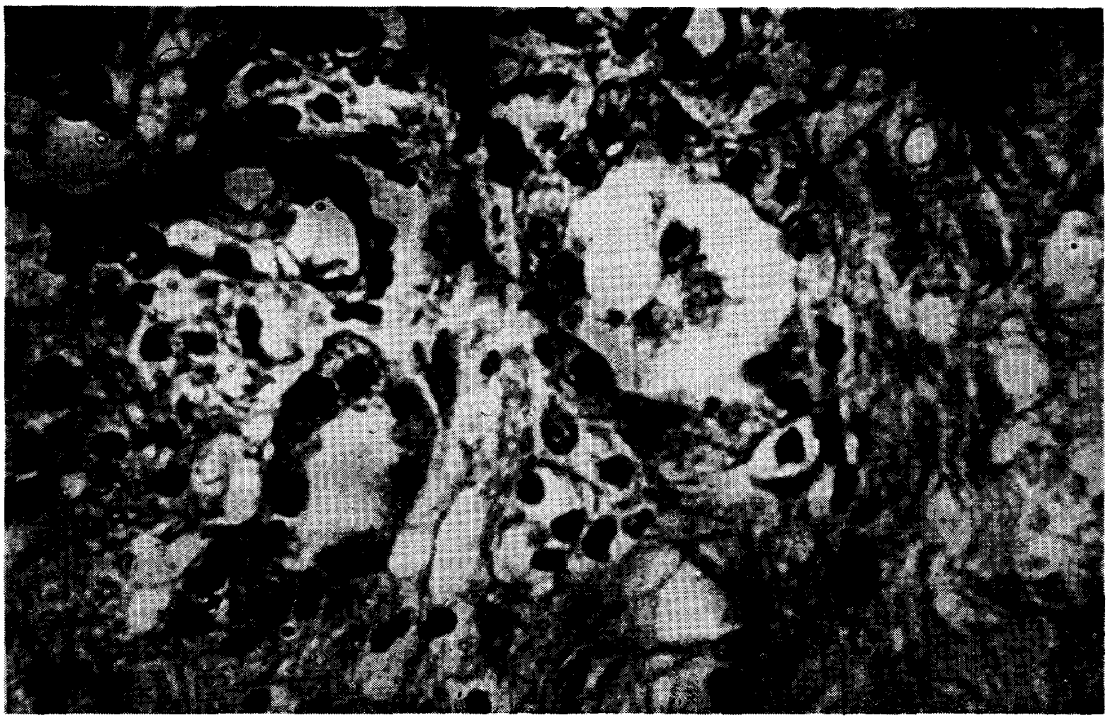

Fig. 1. Adenomatous hyperplasia of the alveolar epithelial cell.
Small gland-like spaces lined by cuboid cells are seen in the fibrous tissue.

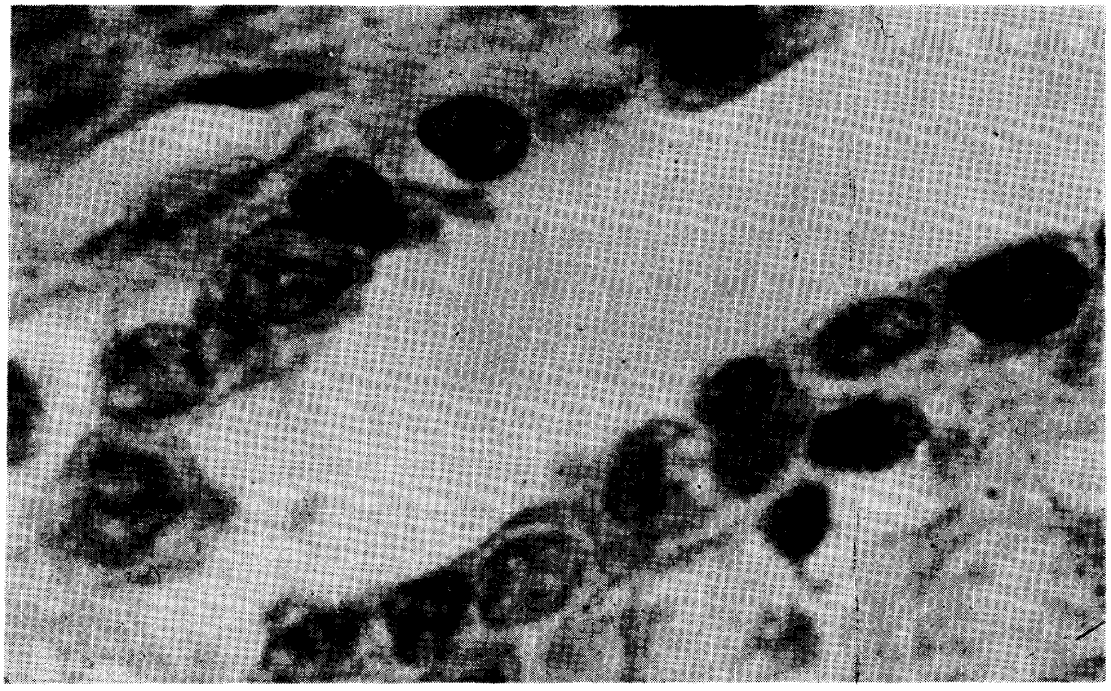

Fig. 2. Adenomatous hyperplasia of the alveolar epithelial cell.
Hyperplastic cuboid cells continuously line the alveolar lumen.

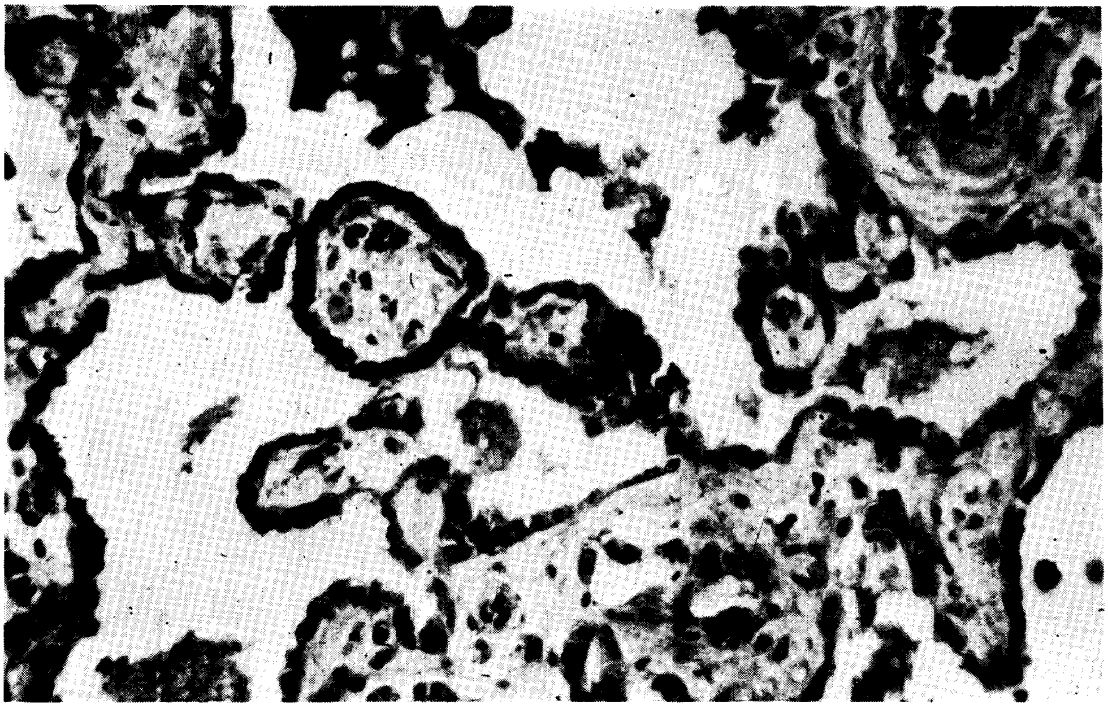

Fig. 3. Adenomatous hyperplasia of the alveolar epithelial cell.
Proliferation of cuboid epithelial cell is seen on the surface of the hypertrophic alveolar septum.

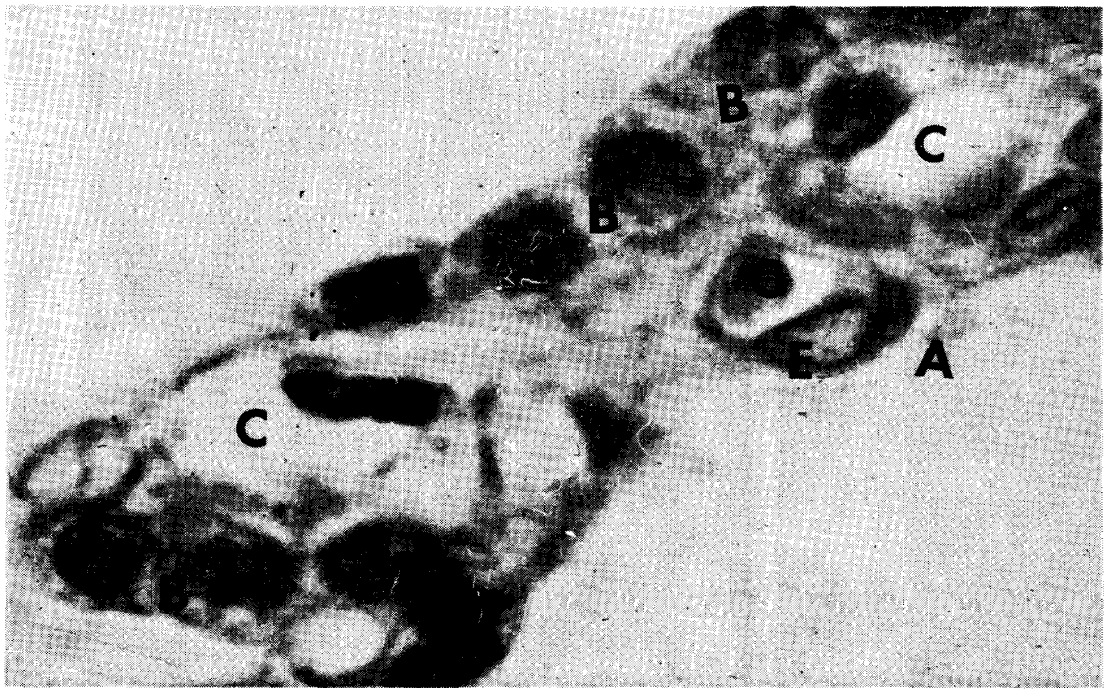

Fig. 4. Early stage of epithelial hyperplasia.
A: alveolar epithelial cell, B: alveolar wall cell, C: alveolar capillary, E: capillary endothelium.

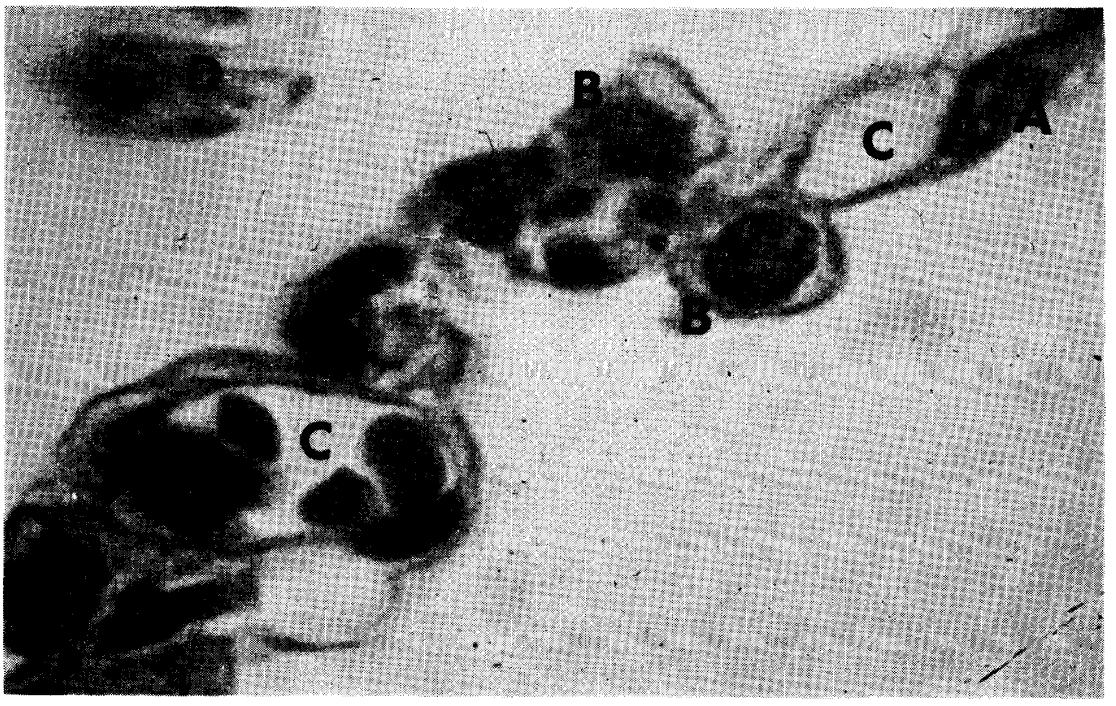

Fig. 5. Healthy alveolar area.
A: alveolar epithelial cell, B: alveolar wall cell, C: alveolar capillary, D: dust cell, E: capillary endothelium.

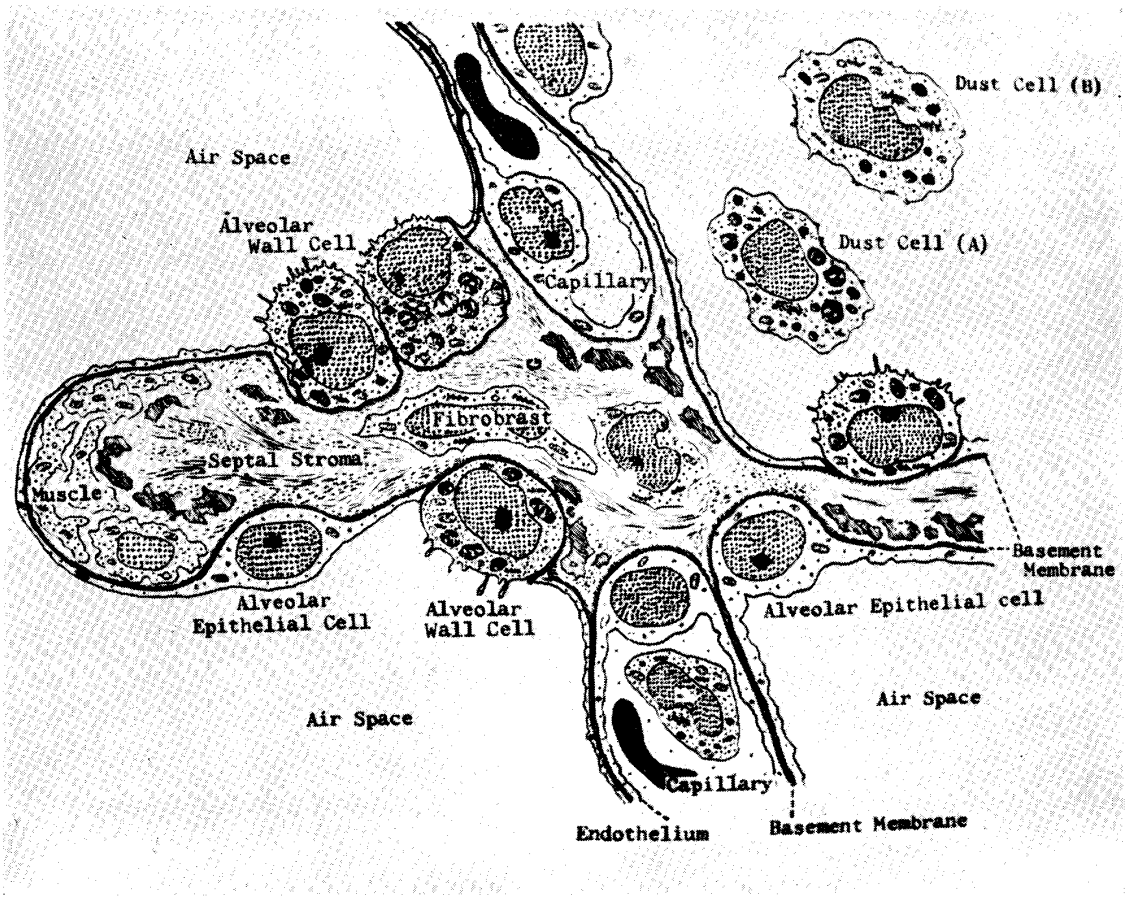

Fig. 6. Fine structure of the alveolar area (schema)

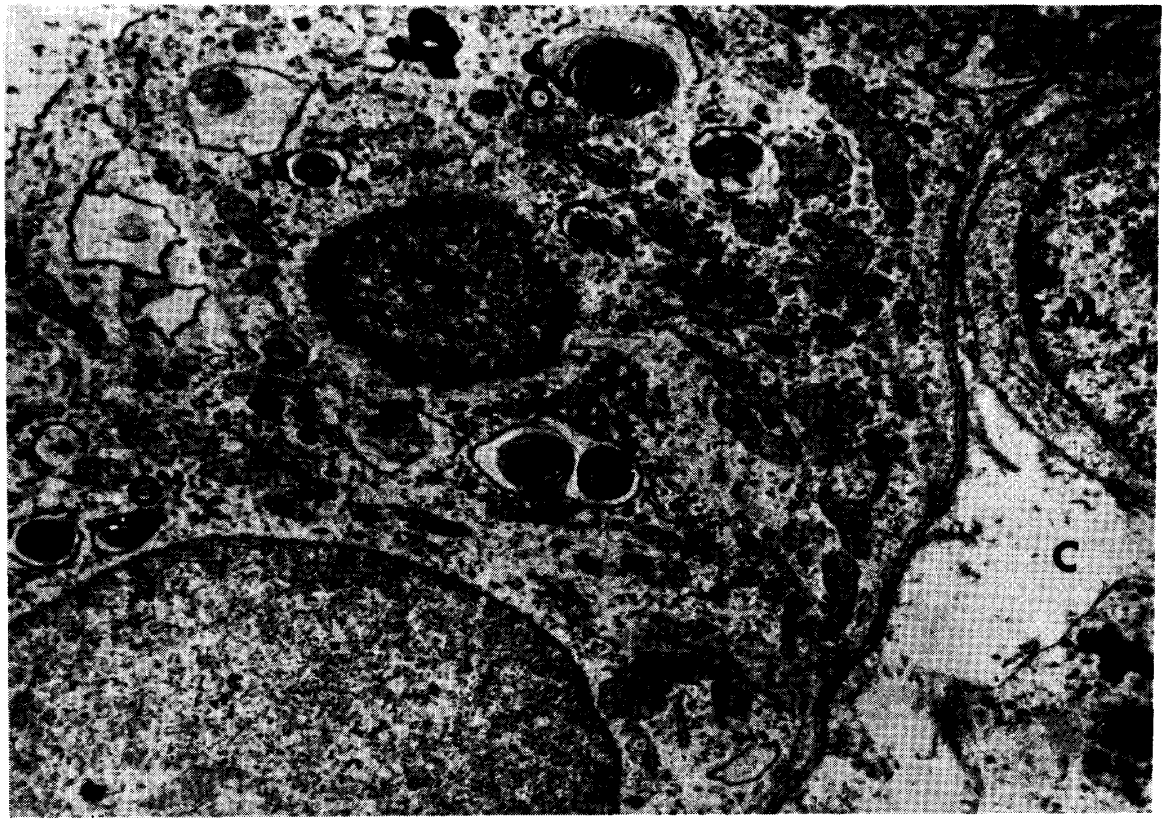

Fig. 7. Hyperplastic cells and basement membrane.
B: basement membrane, C: connective tissue, M: mesenchymal cell, N: nucleus, O: osmiophilic lamellar body.

DISCUSSION

Otsuka[18] (1959) in our laboratory observed experimentally produced atelectasis by the electron microscope and proved that the alveolar epithelial cell (type A epithelial cell) is extremely highly differentiated and when it falls into degeneration it cannot be replaced by other cells of its kind. He also reported that its defect seems to be repaired by the alveolar wall cell (type B epithelial cell), and concluded that the alveolar wall cell is presumed to be the reserve cell in the alveolar area like the basal cell in the bronchial epithelium.

The important role of the alveolar wall cell in the histogenesis of experimental adenoma of mice induced by urethane was emphasized by us (Okada et al.[16] (1962)) based on electron microscopic observation. Furthermore, Nagaishi and others[14] (1965) observed electron microscopically many cases of human lung cancer and occasionally found cancer cells containing osmiophilic lamellar bodies in their cytoplasm. They supposed that some cases of human lung cancer may originate from the alveolar wall cell.

In the last decade the role of the alveolar wall cell in secretion of alveolar

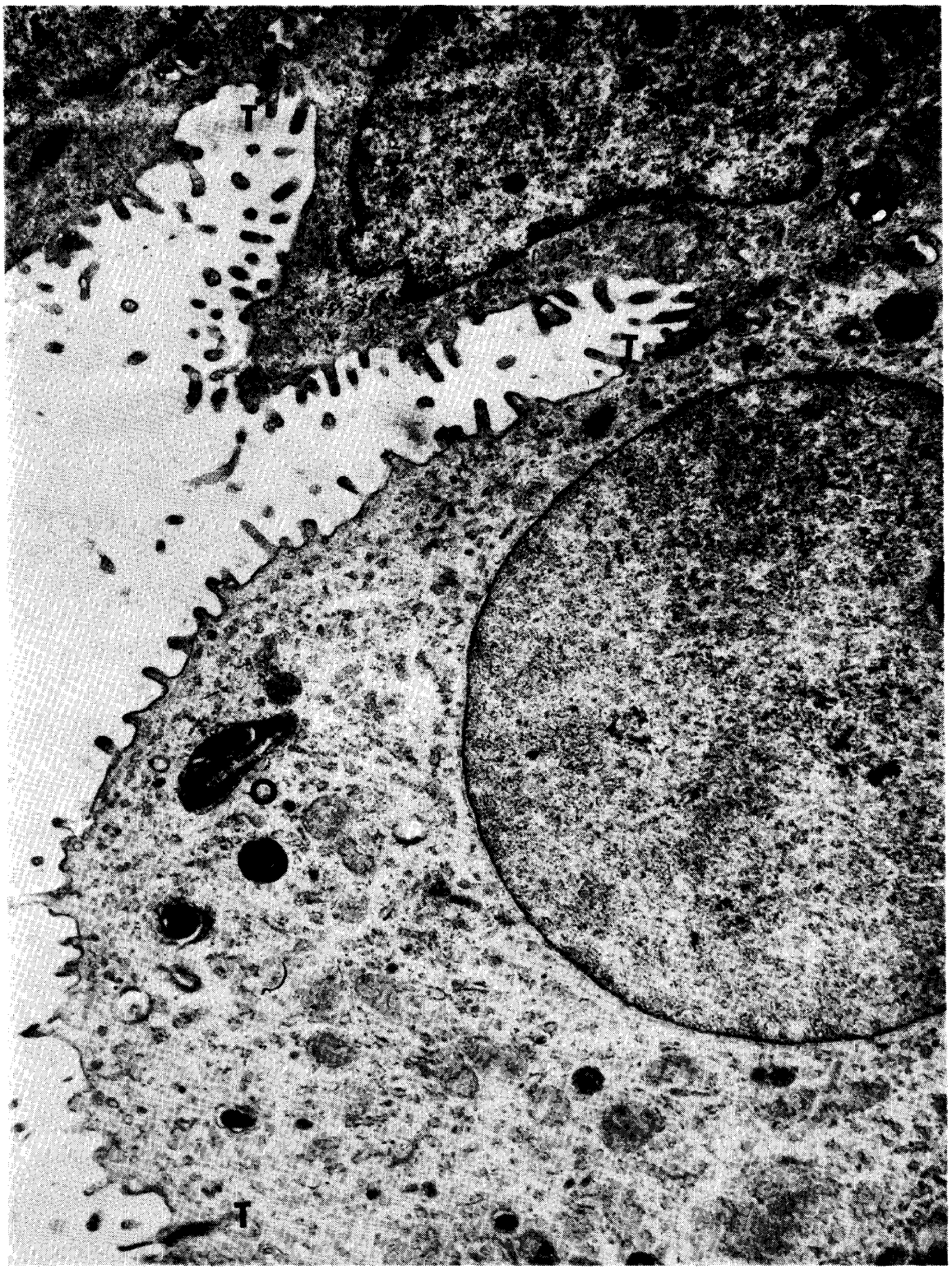

Fig. 8. Hyperplastic cell. Terminal bars (T) and numerous microvilli are seen.
O: osmiophilic lamellar body.

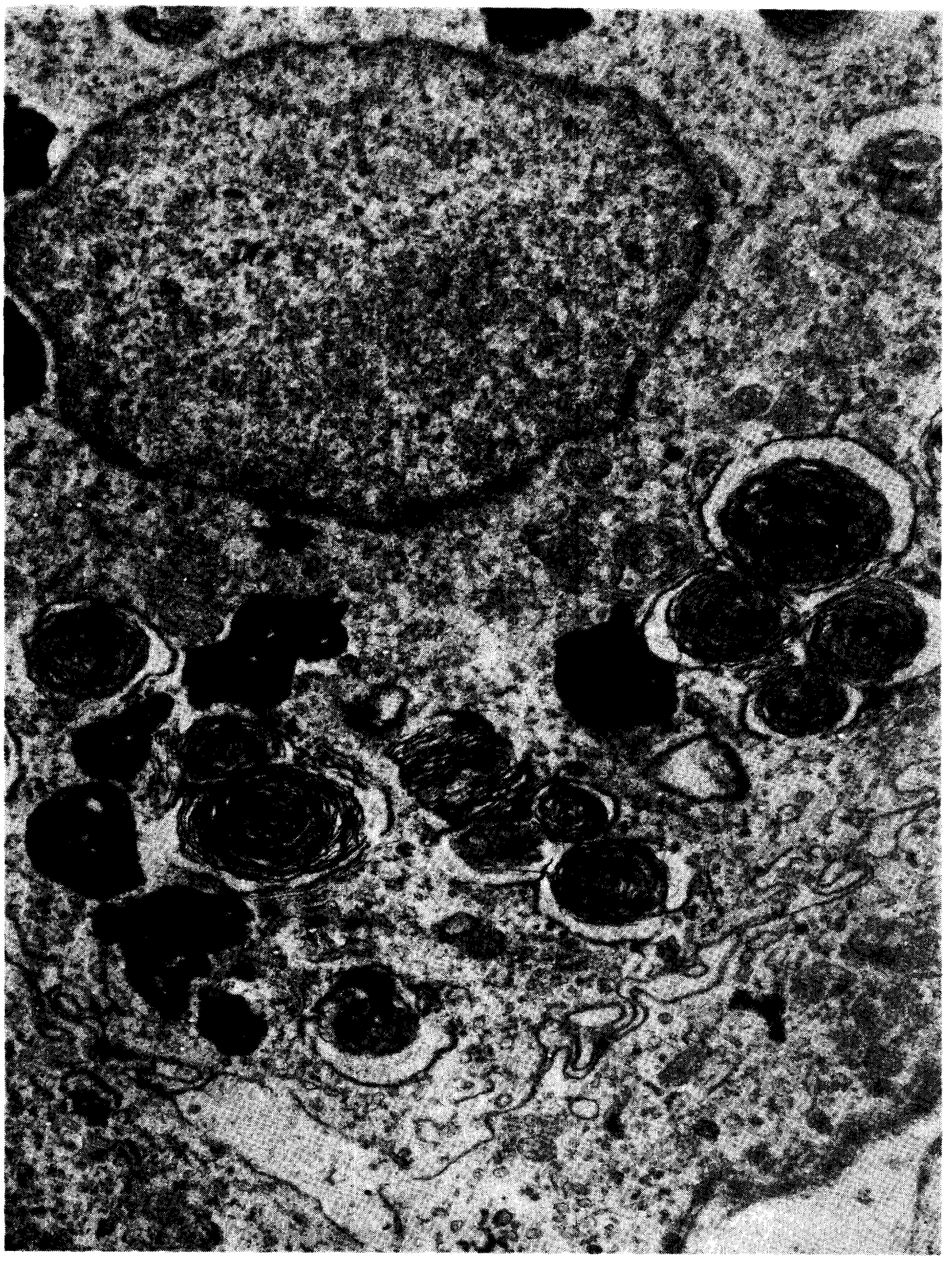

Fig. 9. Osmiophilic lamellar bodies in hyperplastic cell.

surfactant has been mentioned by some investigators (Klaus et al.[11] (1962), Hackney et al.[7] (1963), Groniowski et al.[6] (1964), Kikkawa et al.[9] (1965), Buckingham et al.[3] (1966)) and this cell has attracted attention from the physiological point of view. From the results of our observation, it must be emphasized that the alveolar wall cell can proliferate in response to pathogenic stimuli, and in some cases, grow to form adenomatous hyperplasia in the alveolar area. Furthermore, it is suggested that the alveolar wall cell might play an important role in the carcinogenesis of some peripheral lung cancer.

SUMMARY

Histological observation suggests that the cuboid cell of adenomatous hyperplasia originates from pre-existing lining cell of the healthy alveolus. The resemblance in the fine structure of the cuboid cell to that of the alveolar wall cell (type B epithelial cell) provides strong evidence that the alveolar wall cell proliferates in response to pathogenic stimuli and forms the adenomatous hyperplasia in the alveolar area. Furthermore, it is suggested that the alveolar wall cell might play an improtant role in the carcinogenesis of some peripheral lung cancer.

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