Virchows Arch. A Path. Anat. and Histol. 372, 287–297 (1977)

Virchows Archiv A

The Importance of Smooth Muscle Cells in the Development of Foam Cells in the Gastric Mucosa

An Electron Microscopic Study

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Summary. Foam cells in lipid islands of the stomach can develop from both histiocytes and smooth muscle cells. With increasing storage of lipid vacuoles in smooth muscle cells, loosening of the myofilament arrangement and decrease of the dense areas subjacent to the plasma membrane occurs. Endoplasmic reticulum and the cisternae of the Golgi-apparatus dilate, the cell organelles increase initially and the basement membrane of the smooth muscle cells is fragmentarily formed. Only in incompletely formed foam cells can the origin from smooth muscle cells be recognised, in their final state their histiogenesis is seldom apparent.

Key words: Stomach – Lipid islands – Smooth muscle cells – Foam cells – Electron microscopy.

Introduction

With the increasing use of gastroscopy and stomach biopsy more attention has been given to lipid islands in the stomach. They were initially described by Orth (1887) and later were investigated by Feyrter (1929) and Lubarsch and Borchardt (1929). During recent years reports have accumulated about lipid islands, but knowledge about their aetiology and pathogenesis is still incomplete. The islands are rare findings but their practical importance is that they may be mistaken for early cancer in a gastroscopic examination. Takebayashi (1970) has carried out the only previous ultrastructural study of lipid islands and suggested the derivation of the foam cells from histiocytes. Stimulated by other reports on the multipotency of smooth muscle cells in other tissues we wanted to investigate the problem of whether foam cells in lipid islands could develop from smooth muscle cells.

Material and Methods

Observations were made on excised gastric samples taken from a 69 year old female patient.

For light microscopy, some specimens were embedded in paraffin. For electron microscopy other samples were fixed for 2 h in 3% glutaraldehyde buffered at pH 7.3 with 0.1 M phosphate.

They were rinsed in 1% osmium tetroxide buffered with 0.1 M cacodylate at pH 7.4 for 1 h, dehydrated in graded alcohols and propylene oxide and embedded in EPON 812. For light microscopy sections 1–4 μm in thickness were cut and stained either with haematoxylin and eosin, periodic acid-Schiff or with alkaline methylene blue and azur II (Richardson, 1960). Thin sections were made with the LKB microtome, stained by uranyl acetate (Watson, 1958) and lead citrate (Venable and Coggeshall, 1965) and examined with a Siemens I electron microscope.

Results

I. Light Microscopy

Specimens from the pyloric antral mucosa showed a distinct chronic superficial gastritis. The lamina propria was clearly infiltrated by lymphocytes, plasma cells and eosinophilic granulocytes, but some neutrophilic granulocytes could also be seen. The crypts were elongated and the number of mucinsecreting cells was reduced.

Specimens taken from the gastric body showed fairly marked to distinct chronic superficial gastritis. Here and there intestinal metaplasia could be observed.

In several specimens from the body, the lamina propria was densely infiltrated with foam cells (Fig. 1). They were large, round or oval, sometimes polygonal with irregular surfaces. The cytoplasm was foamy or contained great numbers of small vacuoles. In some small granules PAS-reaction was positive and the content of the foam cells could not be stained with alcian blue. The nuclei of the foam cells were mostly round, and were situated towards the cell centre. Among the foam cells, groups of smooth muscle cells could be found, which showed some small vacuoles (Fig. 2). Infiltrates of lymphocytes, plasma cells and several granulocytes were scattered in the tissue, the mucosal surface looked clumpy because of the compact accumulations of foam cells. In general, this is the typical picture of lipid islands. Specimens taken from the greater curvature showed further similar lipid islands.

II. Electron Microscopy

1. Epithelium. The ultrastructure of the epithelial cells corresponded to the findings of Rubin et al. (1968), Ferguson (1969), Johnson and McMinn (1970) and Pfeiffer (1970, 1975), who investigated the epithelium in the body and antrum of the stomach. The superficial epithelium and the upper parts of the crypts showed distinct dilatation of the intercellular spaces. Here an interstitial edema was present. Erythrocytes were often found between the epithelial cells. Numerous small myelin figures could be seen both in and between epithelial cells (Fig. 7). Some pinocytotic vesicles were found at the lateral cell borders. In epithelial cells and in intercellular spaces there were no signs of lipid resorption or transport.

2. Lamina propria. The lamina propria contained many of groups of foam cells which abutted on the epithelial basement membrane. Groups of smooth muscle cells were arranged between them, characterized by numerous intracyto-

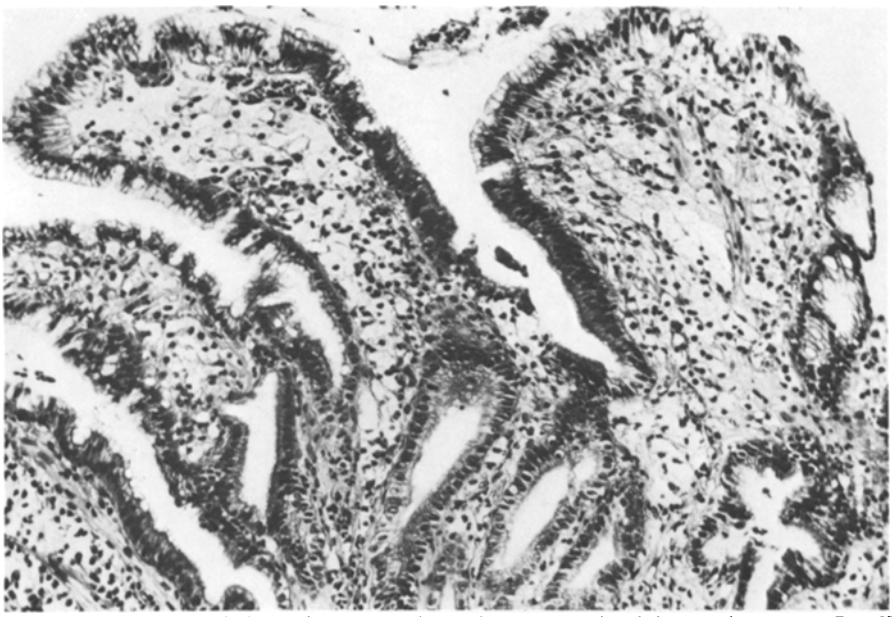
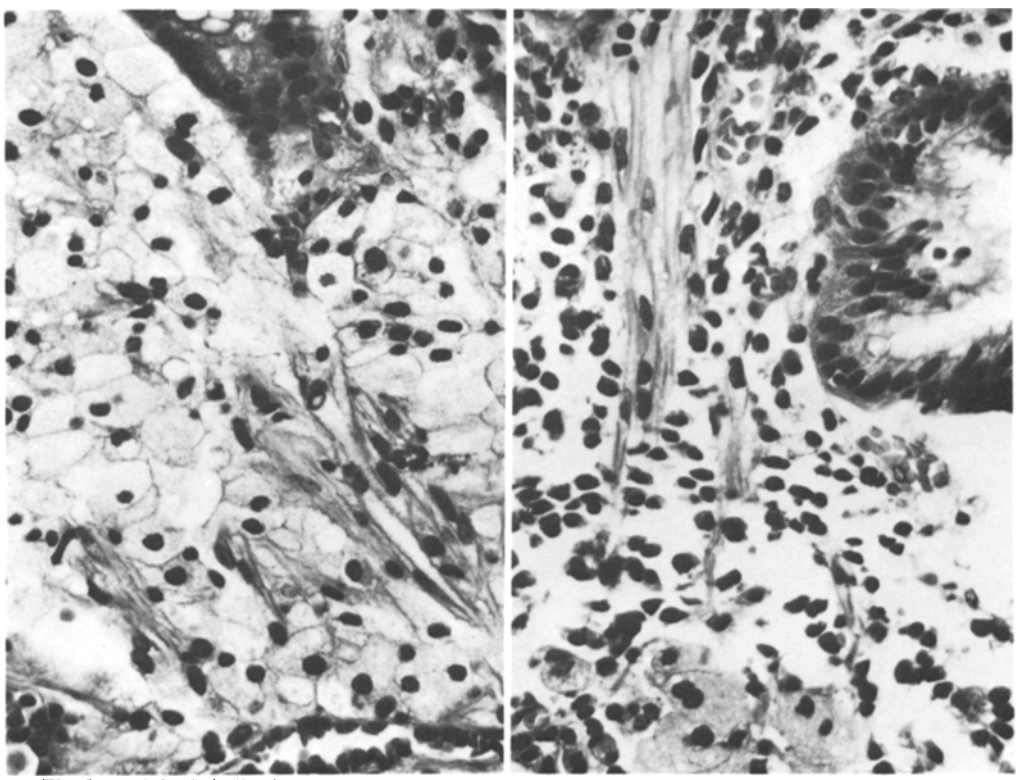


Fig. 1. Compact accumulations of foam cells in the lamina propria of the gastric mucosa. Paraffin, HE, ×90



a b

Fig. 2a and b. Spindle-shaped cells (probably smooth muscle cells), partly containing vacuoles, in a group of foam cells (**a**), and in their neighbourhood (**b**). Paraffin, HE, ×360

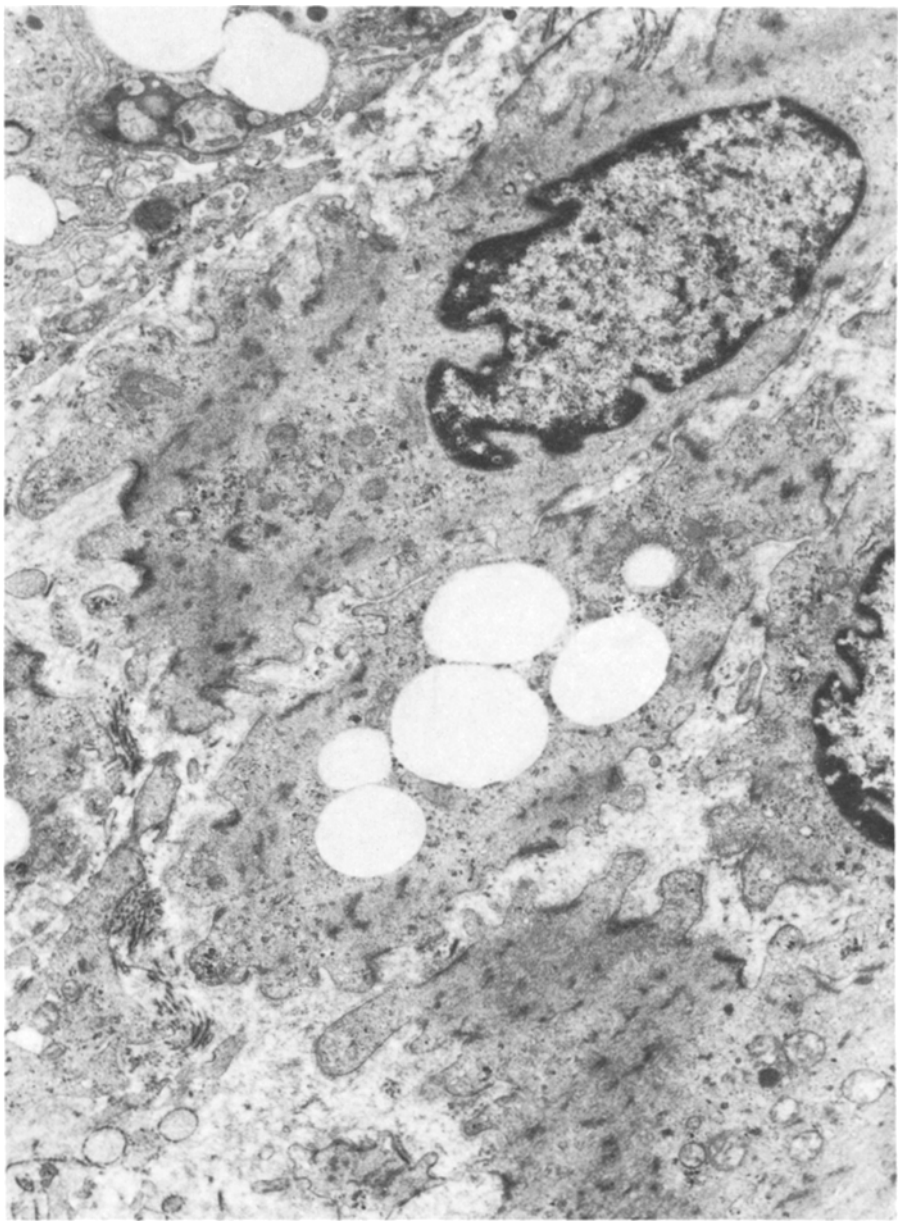


Fig. 3. Unchanged smooth muscle cells and others, which contain lipid vacuoles. ×13,000

plasmatic filaments, dense areas subjacent to the plasma membrane, a moderate endoplasmic reticulum, vesicles, glycogen granules and ribosomes. They were surrounded by a continuous basement membrane, measuring 500 Å.

In addition to these totally unchanged smooth muscle cells there were others which contained large vacuoles measuring 0.8–2.5 μm. Endoplasmic reticulum and the cisterna of the Golgi apparatus were dilated (Fig. 3), the mitochondria

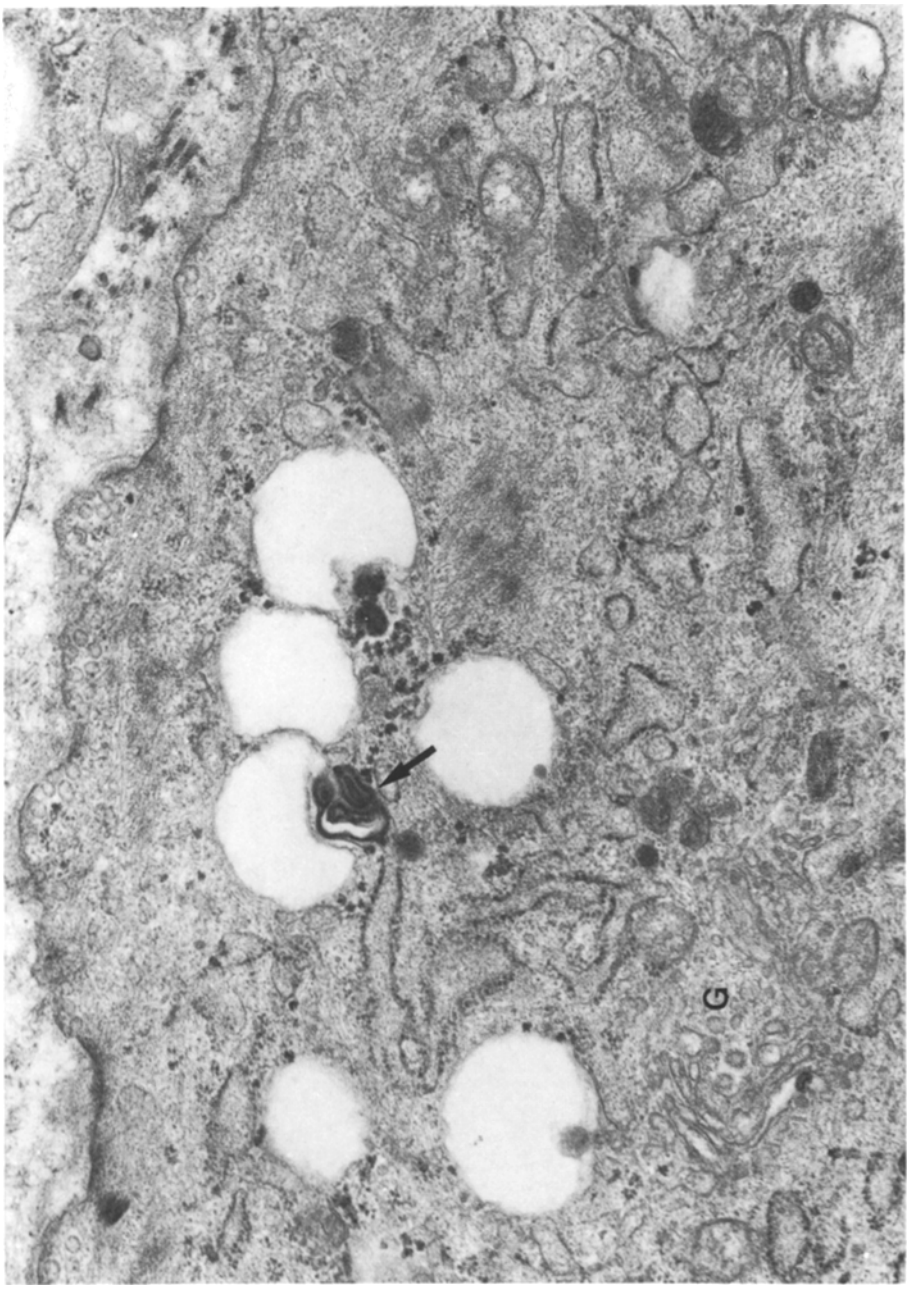


Fig. 4. Smooth muscle cells containing lipid vacuoles and myelin figures (→). Dilatation of the rough surfaced and smooth surfaced endoplasmic reticulum and the cisterna of the Golgi apparatus (*G*). ×25,000

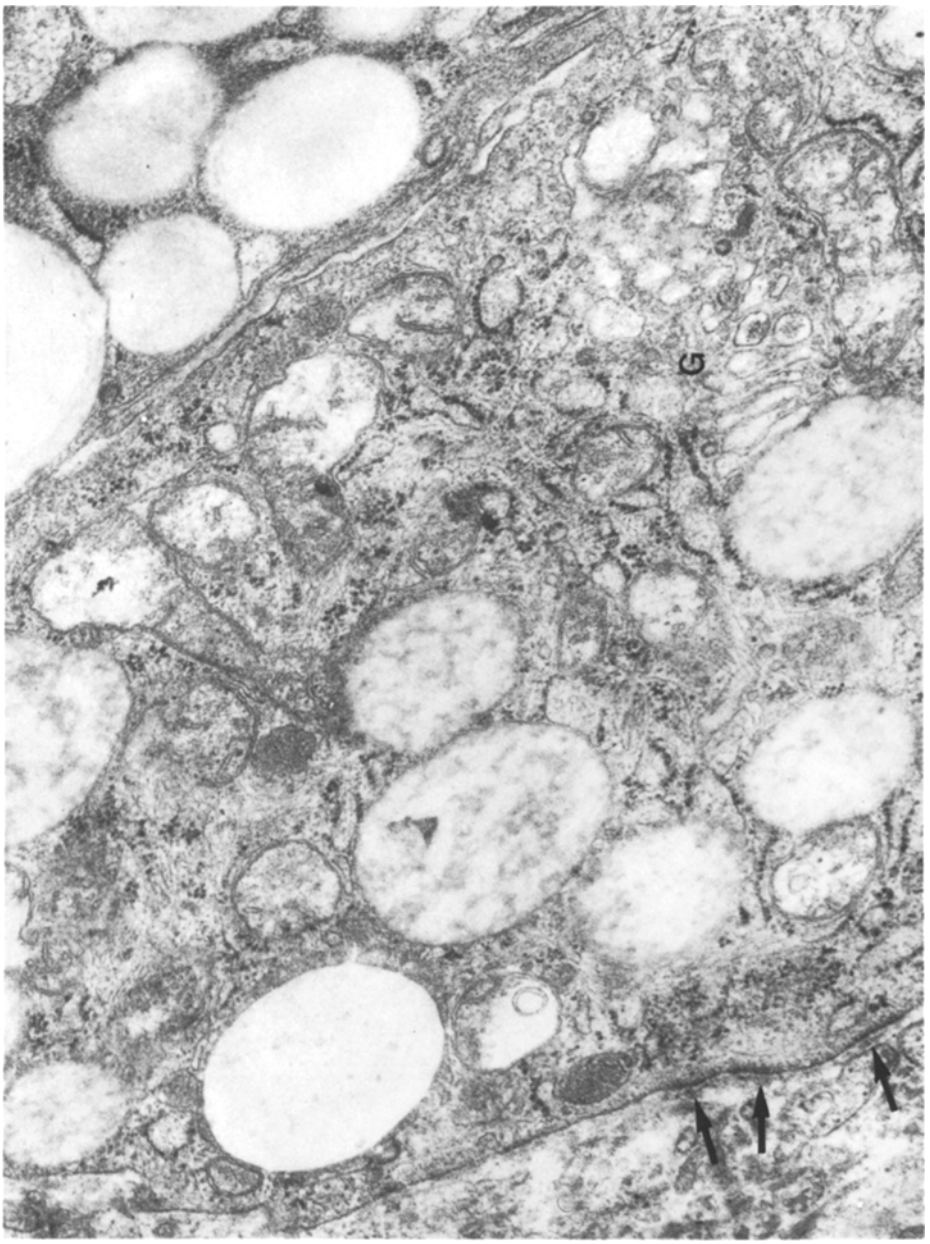


Fig. 5. Loosening of the myofilament arrangement. The basement membrane is hardly recognizable and several dense areas may be seen (→). Dilatation of the endoplasmic reticulum and the cisterna of the Golgi apparatus (*G*). × 25,000

were slightly swollen and sporadic myelin figures appeared (Fig. 4). Because of the tight arrangement of the intracytoplasmatic filaments, the dense areas subjacent to the plasma membrane and almost continuous basement membrane, these cells could still be identified as smooth muscle cells. As the storage of lipid vacuoles increased, the myofilament arrangement loosened up, the quantity and extent of the dense areas diminished and the basement membrane was

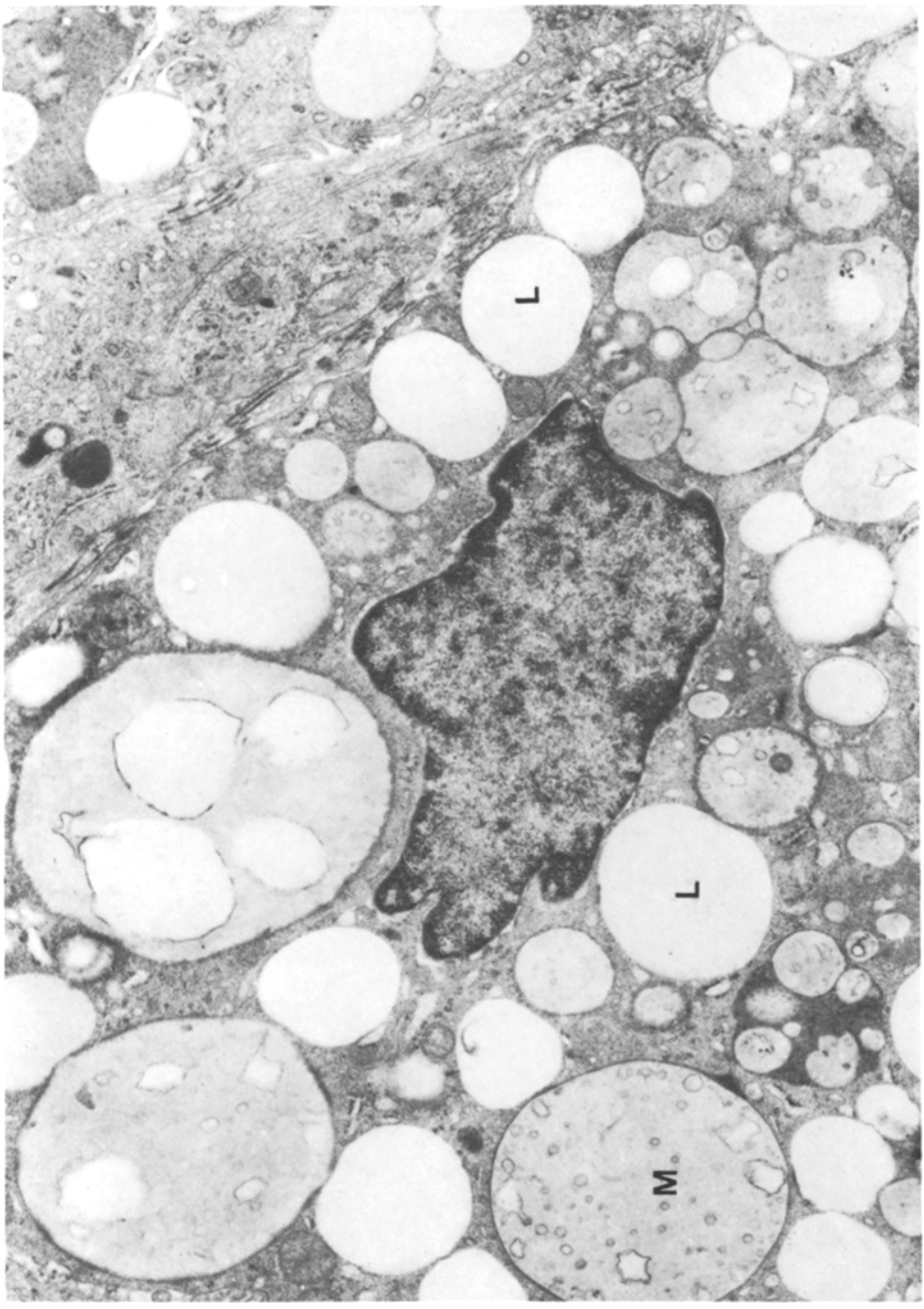


Fig. 6. Typical foam cells with numerous lipid vacuoles (*L*), multivesicular bodies (*M*) and a distinct fine granulation of the cytoplasma. ×13,000

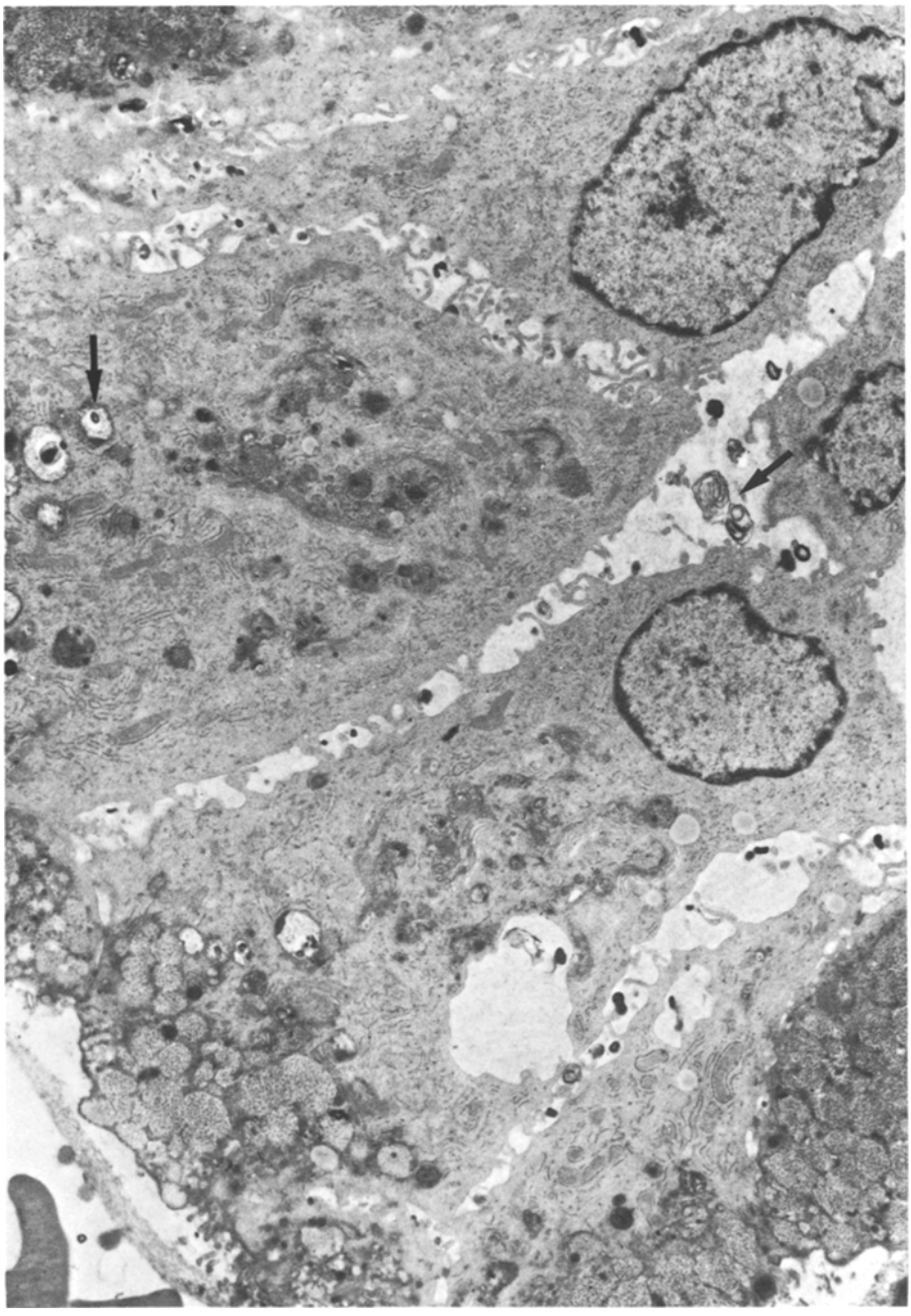


Fig. 7. Epithelial layer, which shows an intercellular edema and numerous myelin figures (→). ×6000

hardly recognizable (Fig. 5). In this phase the endoplasmic reticulum and the cisterna of the Golgi apparatus were distinctly dilated and the number of mitochondria and ribosomes increased. The initially elongated smooth muscle cells rounded off and formed typical foam cells.

Foam cells contained not only numerous membrane-bounded empty vacuoles measuring 1–4 μm, but also multivesicular bodies (Fig. 6) and dense osmiophilic particles measuring 0.2–2 μm (which may be lysosomes). The size of the vacuoles could not be related to the position within the lamina propria. Foam cells with a moderate content of lipid vacuoles showed a well developed Golgi apparatus with numerous vesicles, mitochondria, free ribosomes and a smooth-surfaced and rough-surfaced endoplasmic reticulum. Although scattered intracytoplasmic filaments could be observed, these cells had lost almost all characteristics of smooth muscle cells. On the other hand several foam cells showed fragments of a basement membrane and dense areas subjacent to the plasma membrane. Slender microvilli were observed here and there on the cell surface, whereas pinocytotic vesicles occurred rarely. With the increase of pale lipid vacuoles the content of osmiophilic particles and cell organelles diminished. The cytoplasm of these cells revealed a distinct fine granulation. Directly under the epithelium the foam cells were destroyed and the epithelial basement membrane could not be seen here. The contents of the foam cells (mainly pale lipid vacuoles but also parts of the endoplasmic reticulum and mitochondria) entered the dilated intercellular spaces of the epithelium.

In the lamina propria, fibroblasts, pericytes and plasma cells all contained a few vacuoles, but we never observed transformation into foam cells. On the other hand histiocytes could frequently be seen which, with an increasing content of lipid vacuoles, developed into foam cells.

Discussion

Our knowledge of the aetiology of lipid islands is incomplete (Feyrter, 1929; Lubarsch and Borchardt, 1929; Kimura et al., 1969; McCaffery jr., 1975).

It is probable that the formation of lipid islands accompanies pathological changes in the mucosa of the stomach. Lubarsch and Borchardt (1929) have already emphasized that lipid islands often appear in the "ill stomach". Tannhauser (1958) considered that cell degeneration in chronic gastritis and phagocytosis of cell detritus are important for the development of lipid islands.

We observed some changes in the mucosa. The superficial epithelium showed an intercellular edema, moreover myelin figures could be seen resembling those which Otto (1970) described in chronic atrophic gastritis (Fig. 7). Microvilli, which occur on the surface of the epithelium of the antral mucosa, indicate that these cells are capable of resorption. In our specimens there was no indication of either lipid resorption and transport or lipid droplets in the intercellular spaces as described by Rubin et al. (1967) in intestinal metaplasia, by Cardell et al. (1967) in triglycerid absorption in the small intestine or by Partin and Schubert (1969) in cholesterol storage disease in the small intestine.

There are few observations on the genesis of lipid islands. Kimura et al.

(1969) observed mature phagocytes next to immature ones, which were oval in shape and contained few vacuoles and a basophilic cytoplasm. Takebayashi (1970), Heilmann (1973) and Kraft and Heilmann (1975) described foam cells as being transformed histiocytes. With respect to cholesterol storage disease in the small intestine Partin and Schubert (1969) pointed out that smooth muscle cells, fibrocytes and pericytes have a limited capacity to release cholesterol and thus store it. They did not observe a transformation to foam cells.

Our examination confirms the observations of Takebayashi (1970) and Kraft and Heilmann (1975) who described how foam cells could develop from histiocytes. Apart from this, however, we have shown that they may originate from the smooth muscle cells of the lamina propria. This findings can be compared with observations on foam cells made by Knieriem (1970) in the intima of sclerotic arteries. He also showed a gradual transformation of smooth muscle cells to foam cells.

This transformation can be divided into different stages: In the *first phase* muscle cells show few lipid vacuoles, while the endoplasmic reticulum and the cisterna of the Golgi apparatus are dilated (Figs. 3, 4). With the increasing storage of lipid vacuoles in the *second phase* the myofilament arrangement loosens, the dense areas diminish and the basement membrane is only partly recognizable (Fig. 5). Initially the number of organells increases, later, with an increasing number of lipid vacuoles, they decrease. In the *third phase* necrosis of foam cells can be seen in areas immediately beneath the epithelial basement membrane. It is possible that the distinct fine granulation in the cytoplasm of foam cells may indicate the beginning of cell necrosis. Several studies have shown that vacuoles in foam cells may store lipids as variable compounds, and our electron microscopic findings support this. We have also shown that in lipid islands foam cells originate from two sources, histiocytes and smooth muscle cells. It is not possible to say what proportion of mature foam cells originate from each of these precursors. However, our findings show that origin from smooth muscle cells is common.

The authors are grateful to H. Gerdes for leaving the specimens and to R. Naumann and H. Staubitz for technical and photographic assistance.

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Received August 17, 1976