# Blocking of histamine H2 receptors enhances parietal cell degeneration in the mouse stomach

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**Summary.** The effects of the histamine H2 receptor antagonist, ranitidine, on parietal cell lineage was studied in the mouse stomach by using light and electron microscopy techniques. Mice were continuously infused for 15, 30, and 42 hr with ranitidine. Semithin sections examined under the light microscope revealed spherical light areas in the cytoplasm of parietal cells which in thin sections under the electron microscope appeared to be vacuoles. Cells were categorized as normal, altered and damaged. While altered cells were characterized by dilated canaliculi and vacuoles, the damaged cells showed signs of necrosis or apoptosis. In control mice, altered and damaged parietal cells were consistently few and only found in the pit or base regions of the epithelial units. After 15-hr-treatment with ranitidine, 40% of the parietal cells were altered. After 30 hr infusion, altered parietal cells became 53% of the examined population, and after 42 hr, 72% of the parietal cells were affected (42% altered and 30%, damaged). The gradual increase in parietal cell vacuolation was associated with an increase in the census of pre-parietal cells. Some mice were allowed to recover from treatment for 4 days. The appearance of normal parietal cells and disappearance of damaged cells was observed and the gastric glands became morphologically normal. In conclusion, inhibiting acid secretion by blocking the histamine H2 receptors, enhanced not only the degenerative elimination of parietal cells but also the production of pre-parietal cells and thus, the recovery of the population was prompt.

**Key words:** Gastric gland, H2 blockers, Acid secretion, Pre-parietal cells, Cell renewal

## Introduction

The epithelial lining of the body (corpus) of the mouse stomach is made of a single cell layer which invaginates into tubular units, composed of a pit continuous with a long gland (Helander, 1981; Karam and Leblond, 1992). The gland comprises three successive regions referred to as isthmus, neck and base. The isthmus region includes the epithelial pluripotent stem cells which give rise to all the cells of the pit-gland unit (Karam and Leblond, 1993, 1995). One of these cells is the "pre-parietal cell" which as the name indicates matures into the acid-secreting parietal cell. Newly produced parietal cells migrate from the isthmus in two directions: outward to the pit and inward to the neck and base (Karam, 1993) where they gradually lose their secretory activity (Karam et al., 1997). The life of parietal cells ends in the pit and base regions where they degenerate and are either extruded to the lumen, or phagocytosed by an epithelial cell neighbor or by an invading connective tissue macrophage. Such extrusion and phagocytosis are only infrequently observed in normal mice (Karam, 1993).

The secretion of acid by gastric parietal cells is triggered by several secretagogues including histamine, acetylcholine and gastrin (Soll and Berglindh, 1994). The binding of histamine to its H2 receptors (Ash and Schild, 1966) leads to the translocation of $H^+/K^+$-adenosine triphosphatase (ATPase) from cytoplasmic tubulovesicles to the apical secretory membranes of parietal cells (Forte and Soll, 1990). Accordingly, two different approaches are established to inhibit acid secretion: 1) blocking of the histamine H2 receptors with an antagonist (Black et al., 1972), such as ranitidine (Domschke et al., 1979; Brogden et al., 1982), and 2) blocking of the gastric ATPase by a substituted benzimidazole, such as omeprazole, which covalently binds to the enzyme leading to a potent long lasting inhibition of acid secretion (Wallmark et al., 1985; Sachs, 1994). These two approaches are being used worldwide for the treatment of peptic ulcer disease.

It has been recently shown that subcutaneous injection of rabbits every 12 hrs with omeprazole (1 mg/kg) for 5 days results not only in the inhibition of acid secretion but also in the enhancement of the degeneration of parietal cells, and their extrusion and phagocytosis become prominent (Karam and Forte, 1994). The question then arises whether the cell degeneration occurred due to decrease acid secretion in

general or specifically due to the covalent modification of the enzyme. In the hope of answering this question, parietal cells inhibited by another mechanism, that is blocking histamine H2 receptors have been examined.

To insure that the inhibition of acid secretion is maintained over a definite period of time, ranitidine has been administered to mice by continuous subcutaneous infusion. Such a method results in the alteration of many parietal cells, while their extrusion and phagocytosis become frequent. Moreover, the pre-parietal cells which are rare in normal mice become abundant. When the infusion of the H2 blocker is stopped, normal parietal cells reappear promptly.

## Materials and methods

### Continuous infusion of mice with ranitidine

A total of 16 C57BL/6 mice with an average age of 2 months and weight of 22 gm were subcutaneously infused with ranitidine (0.75 mg/gm body wt/day) for 15 hr (three mice), 30 hr (three mice) or 42 hr (ten mice). Infusion was through a 1 mm-diameter polyethylene tubing connected to an infusion pump, as described by Tsubouchi and Leblond (1979). For control, mice were infused with normal saline. Three of the 42-hr infused mice with their matched controls were allowed to recover for 4 days before sacrification.

### Tissue processing for light and electron microscopy

Mice were anaesthetized by pentobarbitone and sacrificed by perfusion of a mixture of 2% paraformaldehyde, 2.5% glutaraldehyde and 0.2% tannic acid in 0.1M sodium cacodylate buffer, pH = 7.4. After a 3-min perfusion, the upper left dorsal quarter of the corpus (body) region of the stomach was diced into 2 mm$^2$ pieces, which were immersed in the same fixative for an additional 2 hours. After three washes in cacodylate buffer the tissues were post-fixed in 1% osmium tetroxide for 1 hr at 4 °C. Subsequently, tissues were dehydrated in graded ethanol and embedded in Epon 812 or Araldite. Tissue blocks were oriented so that the sections were cut parallel to the long axis of the units (see Figs. 1, 2C). Three tissue blocks were examined for each animal. Toluidine blue-stained semithin (0.5 μm-thick) serial sections were examined under the light microscope (LM), whereas uranyl-lead-stained thin sections were viewed in the Phillips-400 or Joel-1200 electron microscopes (EM).

### Cell quantitation

Parietal and pre-parietal cells were quantified in semithin plastic sections cut parallel to the longitudinal axis of the pit-gland units using the x100 oil lens of the LM. In the control and each of the experimental conditions, cells were counted in three different animals. Cells exhibiting nuclei were only considered for quantitation. An average of 230 parietal cells were scored in three sections of three different tissue blocks for each animal and categorized as described in the results. In some cases, the categorization of the parietal cell had to be confirmed in adjacent serial thin section under the EM. The percentage of each form was determined out of the total scored parietal cells.

Regarding pre-parietal cells, one tissue block was selected for each animal in which the pit-gland axis was best oriented parallel to the cutting surface. Three toluidine blue-stained semithin sections were examined under the x100 oil lens of the LM to score pre-parietal cells. In some cases, the identity of a pre-parietal cell had to be confirmed in the adjacent thin section under the EM. In a total of 100 glands examined per block, pre-parietal cells were scored and their number was expressed per 20 glands.

### Statistical analysis

Counts of pre-parietal cells and different forms of
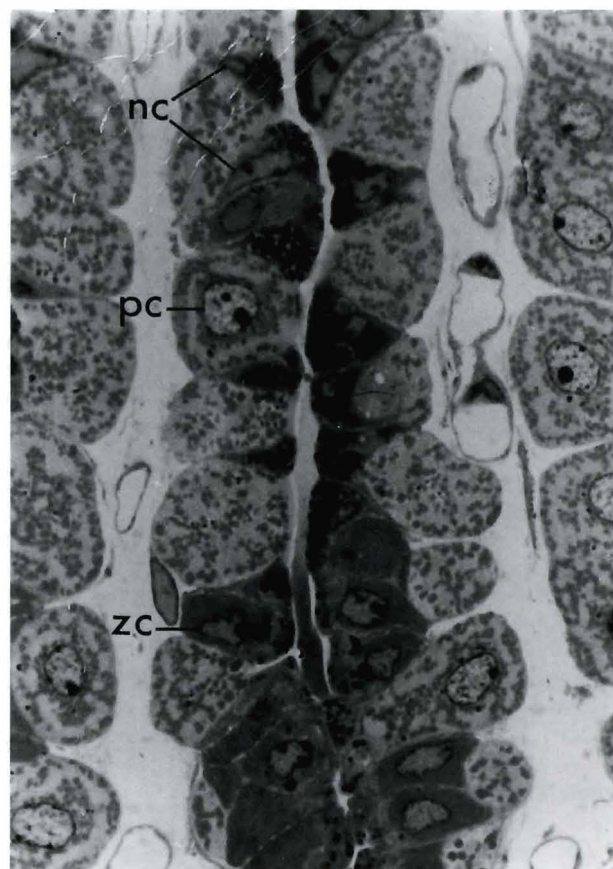


**Fig. 1.** Normal parietal cells as seen in a control mouse under the light microscope. In the middle is part of a gastric gland cut through it lumen. Parietal cells (pc) are scattered among the neck cells (nc) and zymogenic cells (zc). Parietal cell cytoplasm includes numerous moderately dense mitochondria, and grayish areas representing tubulovesicles and/or secretory canaliculi. x 1,000

mature parietal cells were averaged and standered of error (SE) was calculated. Student's t test was used to compare counts of normal vs. ranitidine-infused mice.

## Results

### *Light microscopic appearance of the parietal cell population*

In control mice, parietal cells examined under the LM appear as large pyramidal or round cells exhibiting cytoplasm dotted with mitochondria and the spaces in between represent secretory canaliculi (Fig. 1). After continuous infusion of ranitidine, progressive changes in the morphology of parietal cells are observed. Thus, after 15-hour-infusion, the canaliculular lumen recognized by its grayish border is slightly dilated, and small sharply outlined light spaces are found in the cytoplasm (Fig. 2A). (In an adjacent serial section examined under the EM, such spaces are found to represent vacuoles as shown below). These vacuolated cells are categorized as "altered parietal cells". After 30 hr infusion, altered parietal cells become more prominent (Fig. 2B). By 42 hr infusion, most parietal cells become affected and many of them exhibit pale cytoplasm with disrupted mitochondria to suggest death (Fig. 2C). These dead parietal cells may exhibit luminal cytoplasmic processes as an indication of extrusion to the gland lumen (Fig. 3A), or may even be seen free in the gland lumen (Fig. 3B) or in the process of being phagocytosed by a connective tissue macrophage (Fig. 3C).

Parietal cell counts revealed that the longer parietal cells are exposed to ranitidine, the more they become affected. Thus, after 15-hr-infusion altered parietal cells represent about 40% of the total population, while 4% are severely damaged to suggest death (Fig. 4). By 30 hr infusion, 53% of parietal cells become altered again with a few severely damaged cells (Fig. 4). In the 42 hr infused mice, most parietal cells are affected; 42% of
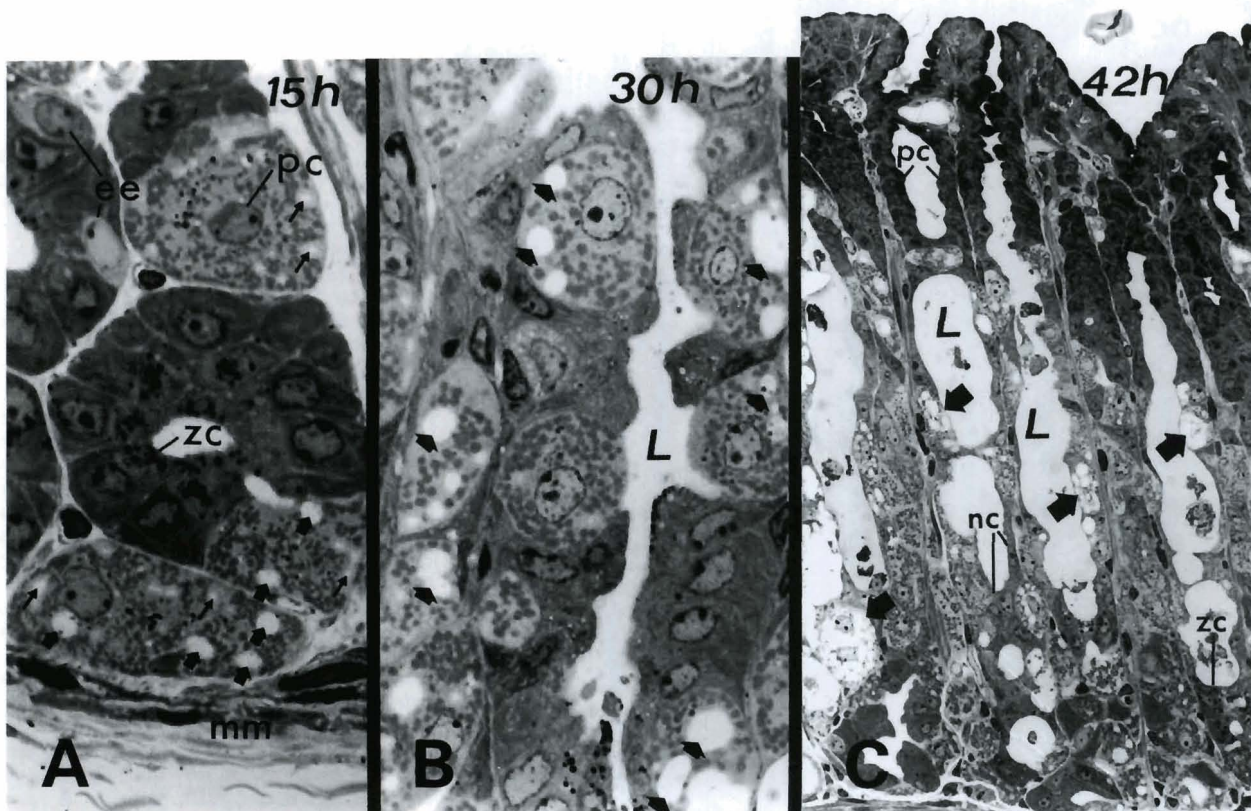


**Fig. 2.** Parietal cells as seen in mice subcutaneously infused with ranitidine for different time intervals. **A.** After 15-hr-infusion, some parietal cells (pc) show dilated canaliculi (small arrows). The two other parietal cells seen at the bottom next to the muscularis mucosa (mm) exhibit few dilated canaliculi (small arrows) and several light spaces (large arrows), interpreted as 'vacuoles'. These vacuoles have sharp outline, and may include small debris as seen in the lower left one. Several cytoplasmic dense lysosomal bodies are seen in all three parietal cells. ee: entero-endocrine cell; zc: zymogenic cell. x 1,000 **B.** After 30-hr-infusion, many parietal cells become vacuolated. A normal spherical parietal cell is seen in the middle facing the central lumen (L). All other parietal cells exhibit large vacuoles (arrows) which may include small particles as seen in the two cells along the right border. x 1,000. **C.** Pit-gland units as seen after 42-hr-infusion of ranitidine. There is massive vacuolation of many parietal cells (arrows) and dilatation of the units' lumen (L). On the other hand, pit cells (pc), neck cells (nc) and zymogenic cells (zc) appear fairly normal. x 275

them are altered and 30%, severely damaged (Fig. 4).

The alteration of mature parietal cells after infusing ranitidine is found to be associated with an increased production of pre-parietal cells. These cells are defined by their grayish apical border and an apical invagination representing an incipient canaliculus (Figs. 5, 6A). When pre-parietal cells are counted in semi-thin sections cut parallel to the units, they are found to be rare in control animals (one cell per 20 glands). After 15-hr-infusion of ranitidine, pre-parietal cell number becomes six cells per 20 glands, and after 30- or 42-hr-infusion periods, 14 cells per 20 glands (Fig. 4).

The recovery of parietal cells altered by continuous infusion of ranitidine for 42 hours has been examined in mice allowed to survive for some days. After 4-day recovery, the parietal cells appear morphologically normal as in control tissue shown in figure 1. Also, pre-

parietal cells are back to their normal frequency, about one pre-parietal cell per 20 glands (Fig. 4).

*Ultrastructural events taking place during degeneration of parietal cells*

To further confirm the morphological changes in parietal cells after ranitidine infusion, thin tissue sections were examined under the EM. The exposure of parietal cells to ranitidine leads to their characteristic resting morphology, that is, small canaliculi, and numerous tubulovesicles (Fig. 6B). Increasing the duration of ranitidine infusion, induces ultrastructural changes in parietal cells which can be divided into four stages. In stage 1, some profiles of the canalicular system become dilated (Fig. 7) and the lining microvilli appear shorter and thinner than in those which are merely inhibited,
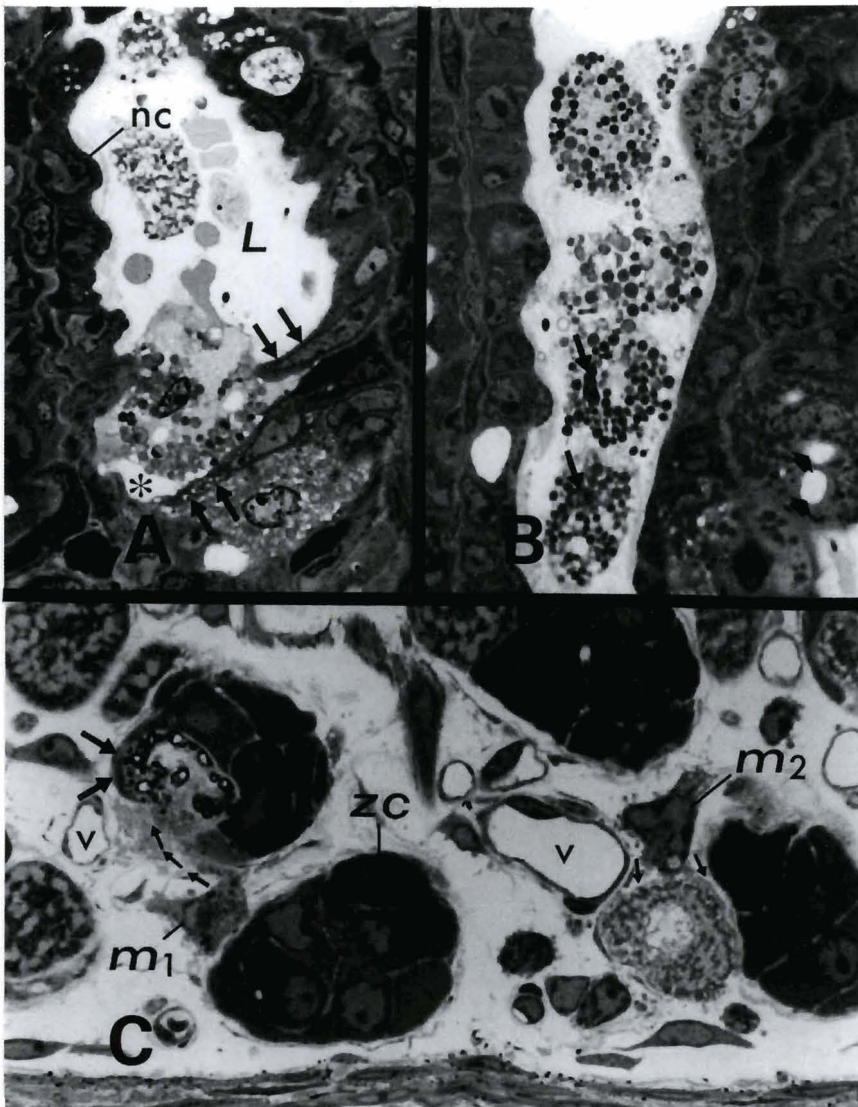


**Fig. 3.** Signs of parietal cell elimination in mice infused with ranitidine for 42 hour. **A.** A parietal cell caught during its extrusion into the gland lumen (L). The cell exhibits swollen mitochondria of variable densities and a condensed nucleus. While the apex of the cell is extending into the lumen, the basal surface is partially separated from the underlying connective tissue by a space (asterisk). The lumen appears dilated and lined with fairly normal neck cells (nc). Two neck cells (double arrows) are flattened to cover the denuded basement membrane. **B.** Four extruded parietal cells are seen free in the lumen of a gastric gland. All four cells exhibit swollen mitochondria with variable densities and pale cytosol. The nuclei of the lower two cells (long arrows) appear condensed. In the upper right is a fairly normal parietal cell facing the lumen, and in the lower right is a vacuolated one (short thick arrows). **C.** Macrophage invasion of parietal cells. Profiles of transversely cut basal portions of gastric glands showing many dark zymogenic cells (zc). The muscularis mucosa is seen at the bottom. In the left side, there is a shrunken "apoptotic" parietal cell with condensed mitochondria. It is partially included within the cytoplasm of a neighbor zymogenic cell (two large arrows). In the connective tissue, a large macrophage ($m_1$) with dense lysosomal bodies sends part of its abundant cytoplasm (a series of three small arrows) toward the dead cell, and is probably invading the unit. At the right side, is another parietal cell dying by "necrosis" as indicated from the paleness of the mitochondria (compare with the fairly normal parietal cell at the upper left corner) and the lysis of the central nucleus. The cell appears to be released into the connective tissue and the adjacent macrophage ($m_2$) extends cytoplasm (two small arrows) toward and around it. Several other connective tissue cells and small blood vessels (v) are visible around the two degenerated cells. x 1,000
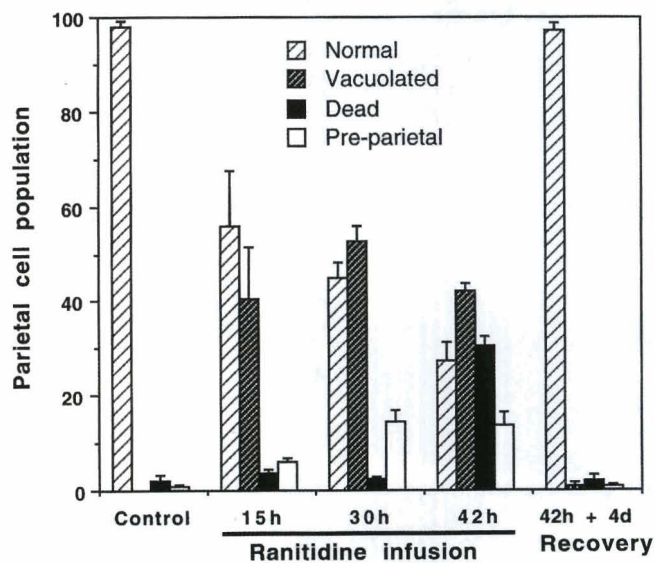
while some of the tubulovesicular elements become curled. Stage 2 is characterized by the presence of small vacuoles in the cytoplasm (Fig. 8). The dilated canaliculi are lined by microvilli which appear shorter and much fewer than at stage 1. Cells of stage 3 exhibit prominent vacuoles and almost all the elements of tubulovesicular system appear curled and form the concentric bodies of the "myelin figure" type (Fig. 9). Dense lysosomal bodies are abundant at this stage. Parietal cells of stage 4 (Fig. 10) show dissolution of much of the cytoplasm and nucleoplasm, degeneration of the mitochondria and lysis of cell membranes, all signs of cell death.

The EM study confirms that the degenerated parietal cells are eliminated by extrusion into the gland lumen



**Fig. 4.** Quantitation of the three different forms of parietal cells (normal, vacuolated, and dead) as well as pre-parietal cells in control, ranitidine-treated and recovered mice. Percentage of each parietal cell form is expressed as bars that represent average of three different mice ± SE. The bars of pre-parietal cells represent their average number per 20 glands in three mice ± SE. Except for the value of dead parietal cells after 30 hr treatment, counts of ranitidine-treated mice are significantly different (p < 0.01) comparing to control.
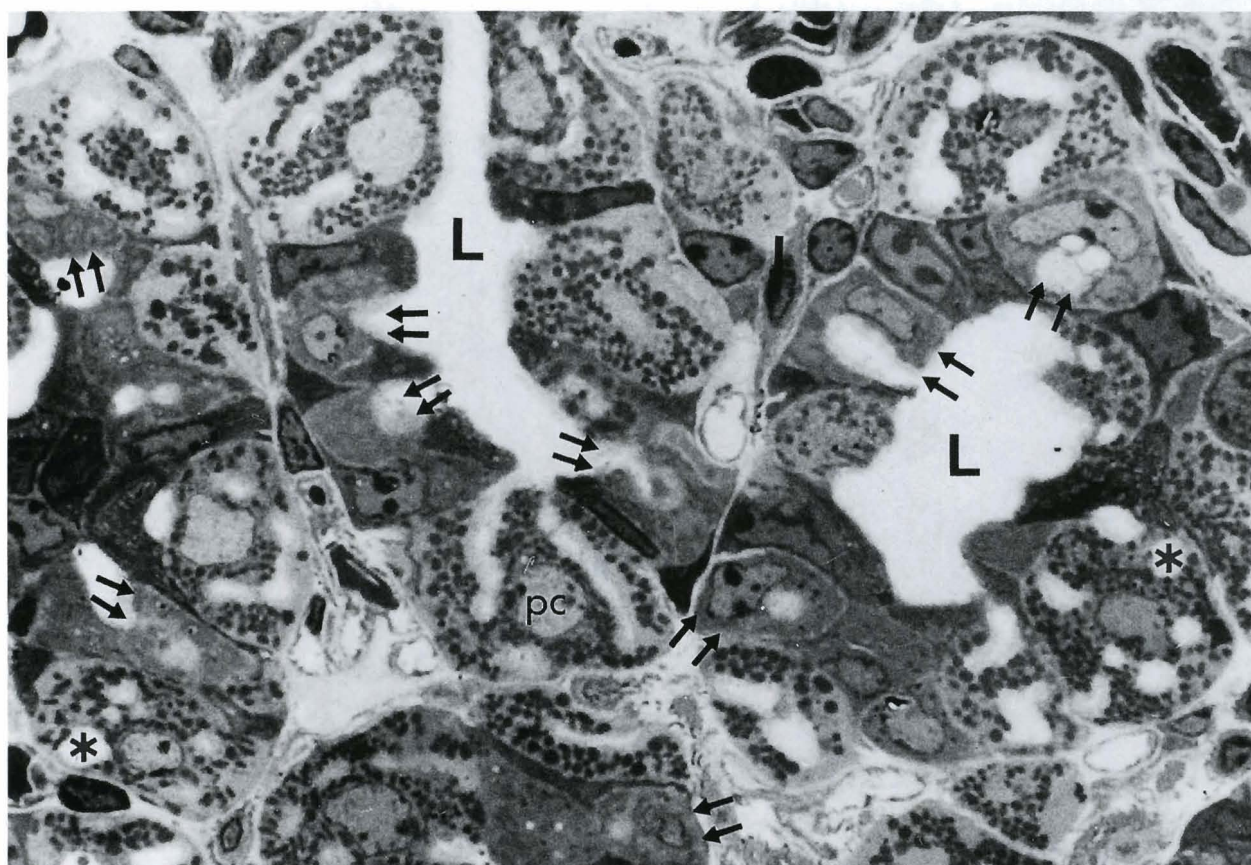


**Fig. 5.** Pre-parietal cells as seen in the isthmus regions of different gastric glands of the 30-hr-infused mouse. Pre-parietal cells (double arrows) exhibit incipient canaliculi which appear as an invagination of the apical surface. The mid profile has a typical parietal cell (pc) with a central nucleus, a slightly dilated canaliculi continuous with the lumen (L) and numerous large mitochondia. Few vacuolated parietal cells (asterisk) are also visible. x 1,300

*Effects of ranitidine on parietal cells*
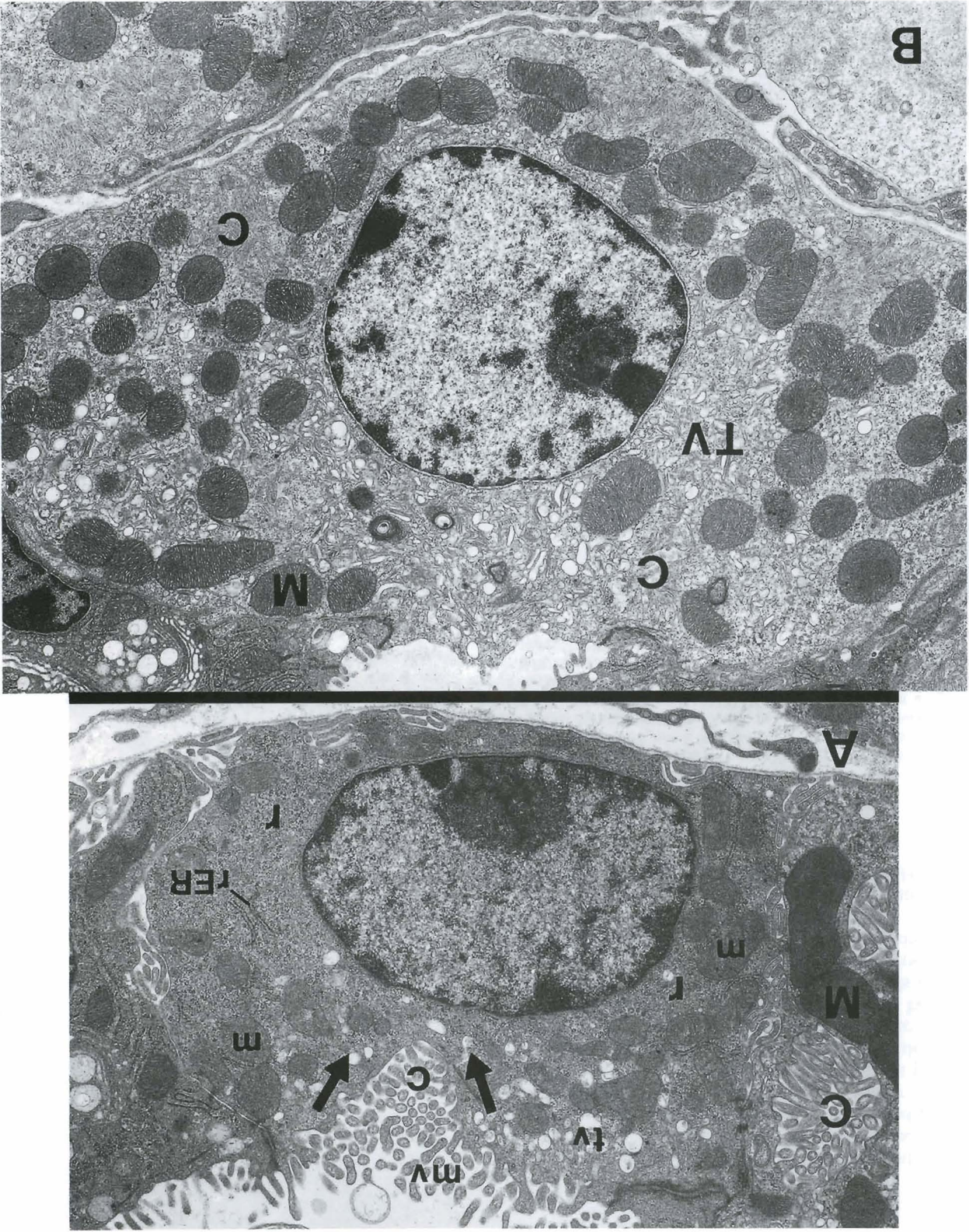


**Fig. 6.** Electron micrographs of pre-parietal and parietal cells in the 15-hr-infused mouse. **A.** A pre-parietal cell characterized by numerous microvilli at the apical surface which slightly invaginates (arrows) forming an incipient canaliculus (c). Several tubulovesicles (tv) are visible in the apical cytoplasm. While ribosomes (r) are abundant, the cisternae of rough endoplasmic reticulum (rER) are few. Note that the mitochondria (m) are slightly larger than those of the neighbor pre-neck cell at right but are much smaller than those of the parietal cell (M) on the left side which exhibits a canaliculus (C). **B.** A typical normal parietal cell showing the inhibited morphology after ranitidine treatment. The canaliculi (C) are small, and the apical microvilli are very few, but the elements of the tubulovesicular system (TV) are abundant. M: mitochondria. x 10,000

(Fig. 11) or phagocytosis by either a healthy neighbor cell, or a macrophage coming from the connective tissue (not shown). Examination of 57 cells undergoing elimination in the mucosa of the 42-hr-infused mouse has revealed that extrusion into the gland lumen is more common (68% of the eliminated cells) than phagocytosis by a neighbor cell (18%) or by an invading macrophage (14%).

## Discussion

During the course of this study several findings were elucidated regarding the effect of blocking H2 receptors on parietal cells, the mechanisms of their elimination from the gastric epithelium, and their recovery after affecting their steady state.

### Effects of blocking the histamine H2-receptors on parietal cells

Contradictory observations on the morphological appearance of parietal cells after inhibiting their secretory function by H2-blockers were reported. Ainge and Poynter (1981) found no morphological changes in canine parietal cells even after a one year treatment. On the other hand, following a 2-week administration of ranitidine (Helander and Mattsson, 1989), the presence of dilated canaliculi in rat parietal cells was reported. In another study, Helander et al. (1990) found some increase in degenerated parietal cells after ranitidine administration to rats. However, no degenerating forms of parietal cells were demonstrated.

In the present study, an apparent alteration and
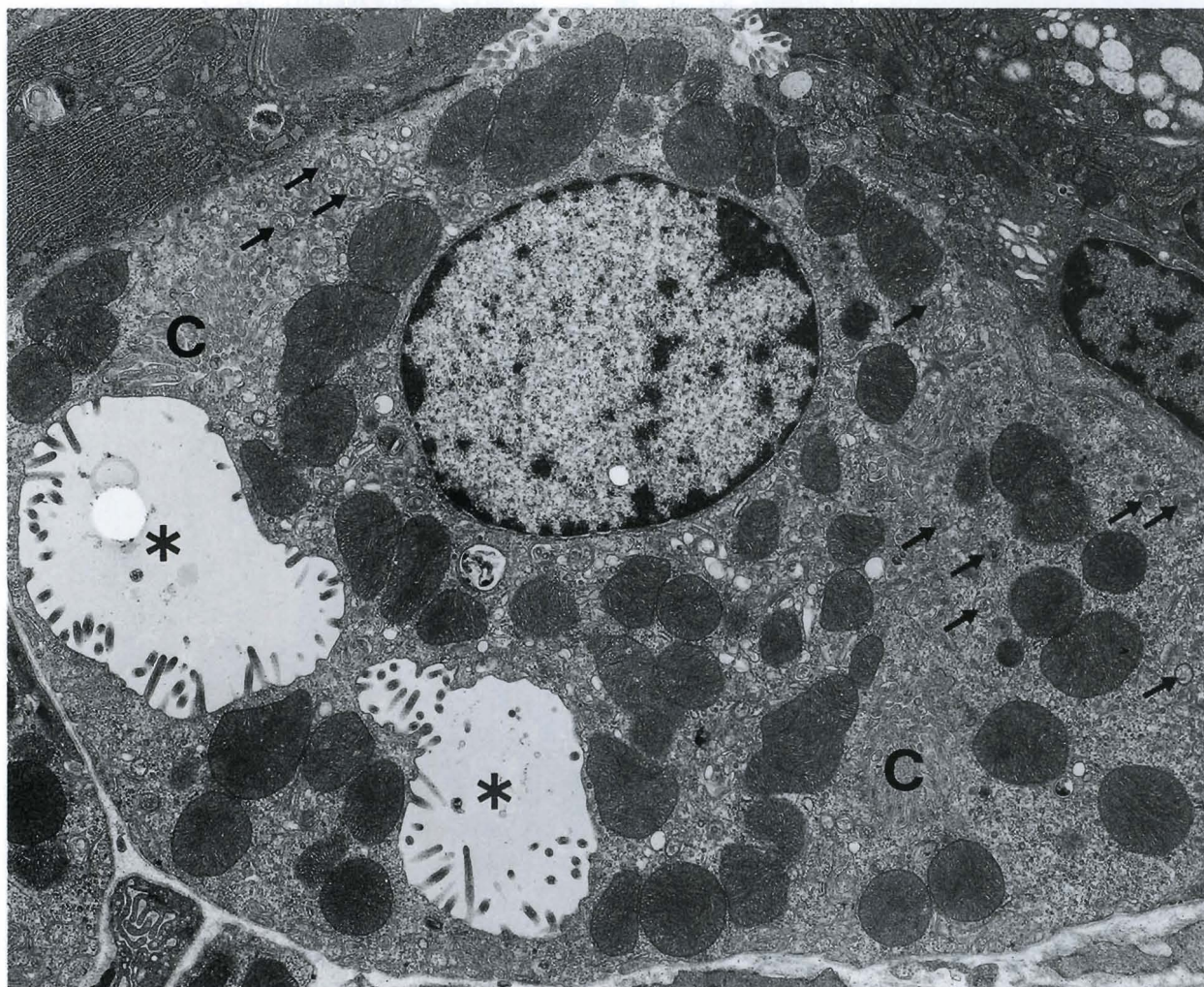


**Fig. 7.** Stage I altered parietal cell in the 15-hr-infused mouse. In addition to the signs of inhibited morphology (numerous tubulovesicles and small canaliculi, C), some canalicular profiles are abnormally dilated (asterisks). They are lined by fewer and thinner microvilli in comparison to those of normal canaliculi. Some elements of the tubulovesicular system appear curled (arrows). x 10,000

degeneration of parietal cells after ranitidine treatment are demonstrated in mice. The half-μm-thick plastic sections examined under the LM showed some cytoplasmic changes in comparison to normal control tissue. Along the length of the pit-gland unit, the parietal cells exhibited spherical light areas in their cytoplasm. These areas were different from the secretory canaliculi which were abnormally dilated in many of the cells. The ill-defined microvilli characterizing the canaliculi were lacking from the light cytoplasmic areas. In addition, these areas usually included small dense particles. After examining thin tissue sections under the EM, it became apparent that these areas were actually vacuoles. Such vacuoles did not exist in parietal cells of normal control tissues.

The use of the continuous infusion method for an increasing periods of time made it possible to demonstrate the ultrastructural changes leading to progressive alteration and degeneration of parietal cells after blocking their function. First, the gradual dilatation of the canaliculi, the decrease in the size and number of microvilli (stage 1), and the formation of vacuoles (stage 2) were demonstrated. Inhibiting the activity of the proton pump by omeprazole induced similar canalicular dilatation and vacuole formation in rabbits (Karam and Forte, 1994). Second, elements of the tubulovesicular system gradually became curled until they formed concentric bodies (stage 3). Similar myelinic transformation of tubulovesicles was previously described in parietal cells of rats treated with the
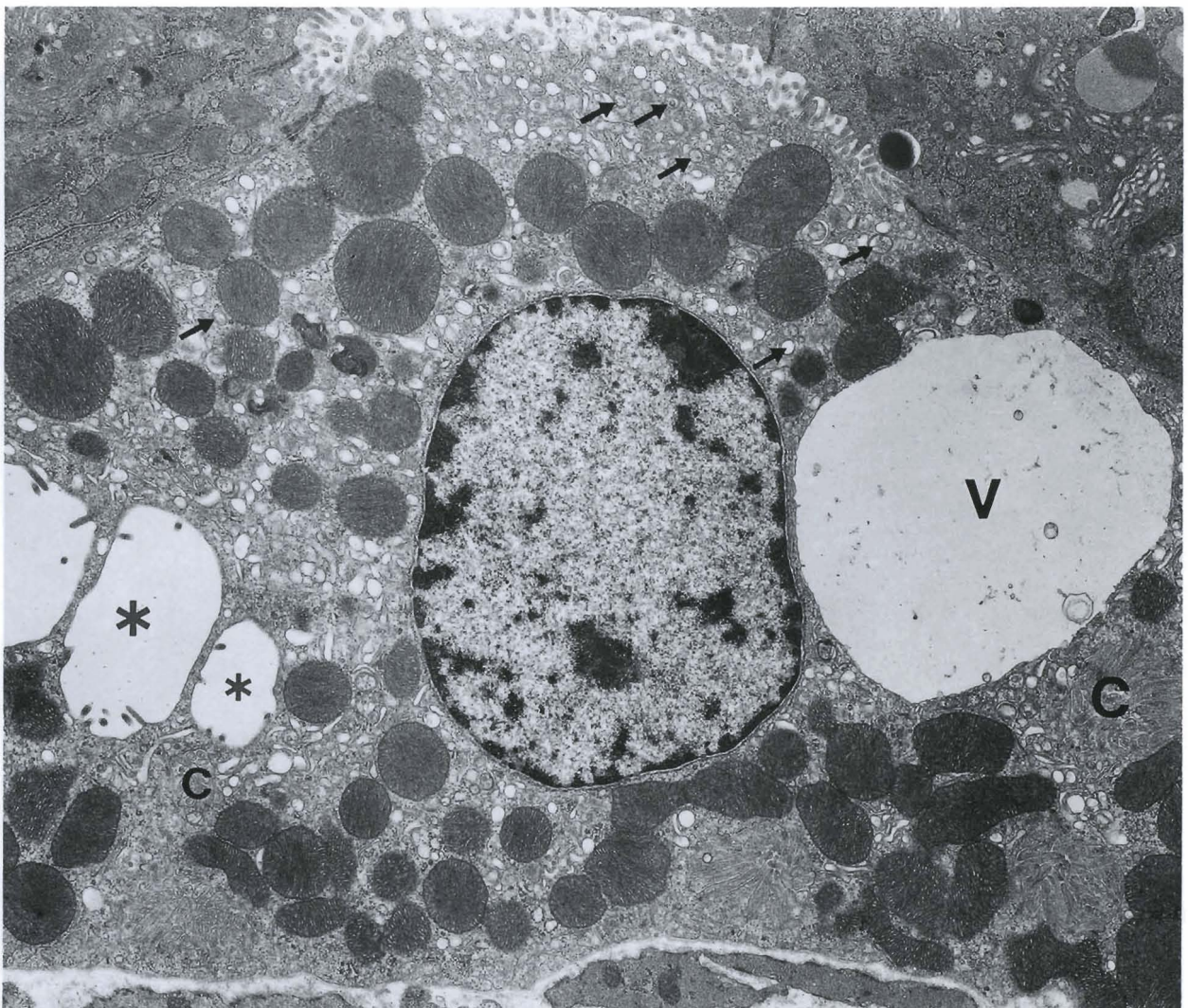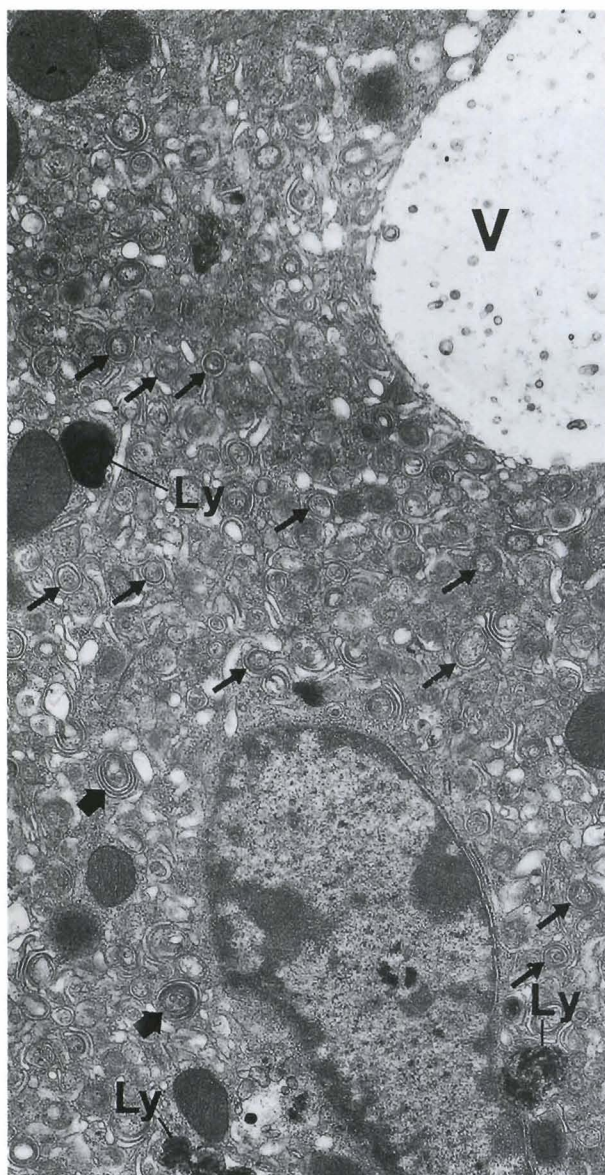


**Fig. 8.** Stage II altered parietal cell in the 30-hr ranitidine-treated mouse. As in the previous two figures, the cell has resting morphology (abundant tubulovesicles, and small canaliculi, C). At this stage the cell is characterized by large cytoplasmic vacuole (V) in addition to the dilated canaliculi (asterisks). The dilated canaliculi have fewer and shorter microvilli than those of the previous stage. Numerous elements of the tubulovesicular system become curled (arrows). x 10,000

anticholinergic acid inhibitor, atropine (Lehy and Dubrasquet, 1972). The vacuolation and myelin-like transformation of tubulovesicles were probably followed by release of hydrolytic enzymes and dissolution of cytosol and nucleoplasm (stage 4). Once the cells reached this point of no return, death would be their destiny.

*Mechanisms of parietal cell elimination from the gastric epithelium*

Dead parietal cells were eliminated by several ways,



**Fig. 9.** Stage III altered parietal cell in the 42-hr-infused mouse. The cell is characterized by abundant curled tubulovesicles, myelin-like figures (arrows) and large vacuoles (V). Ly: lysosome. x 10,000

most commonly by extrusion into the gland lumen. The accumulation of several extruded parietal cells into the gland lumen was frequently observed and was associated with some lumen dilatation and flattening of the lining cells (Fig. 3B). Few cases were observed in which the gland was extremely dilated to form a cyst-like structure (not shown). In such cases, an aggregate of extruded cells were probably blocking the pit opening with the gastric lumen. In other few cases, expansion of the connective tissue space in between the epithelial units was observed. Similar changes were reported by Lacy et al. (1990) in rats treated with 50 mg/kg cimetidine, an H2 blocker, and interpreted as an increase in the interstitial fluid or edema. This microscopic edema was associated with stretching of the interfoveolar mucus-secreting cells. In addition to cell extrusion, some dead parietal cells undergo phagocytosis by a neighbor pit or zymogenic cell or even by an invading connective tissue macrophage (Fig. 3C).

Several reports in the literature suggested that the inhibition of acid secretion might cause pathological changes in the gastric mucosa. A case of gastric erosion was developed in a patient receiving cimetidine treatment (Webster et al., 1978). Another case of focal gland atrophy in Zollinger-Ellison syndrome patient receiving omeprazole was also reported (Caruana et al., 1992). In the present study, both focal damage of the pit-gland unit and gastric erosion were occasionally observed after inhibiting acid secretion by ranitidine (not shown). Macrophage invasion of several degenerated parietal cells in one epithelial unit could affect its integrity and might lead to degeneration and atrophy of the whole unit. If this process occurs in several adjacent units, one might expect a case of gastric erosion.

The inhibition-induced alteration of a cell population is not unique for the parietal cells. Similar conditions in other systems of the body were previously reported. In the respiratory passages, the inhibition of Clara cells' activity by a compound called 4-ipomeanole specifically induced their degeneration and death (Witschi, 1987).

*Recovery of the gastric epithelium after cessation of ranitidine*

In this study, a rapid recovery of the gastric epithelium after termination of ranitidine infusion was observed. This recovery could be attributed to four main factors. 1) The ability of the gastric epithelial cells to restitute by extending lamillopodia to cover denuded basement membrane (Lacy and Ito, 1984). 2) Hypergastrinemia which occurs due to inhibition of acid secretion (Ryberg et al., 1990) and leads to trophic effects in the gastric mucosa (Hakanson and Sundler, 1991). 3) The increase in pre-parietal cell production which with the cessation of treatment rapidly transformed into new parietal cells. In an electron microscopic study combined with radioautography, the time required for the production of pre-parietal cells was found to be 1-2 days and within an additional day a new

parietal cell could be formed (Karam, 1993). Thus, the prompt recovery of parietal cells found in the present study is not unexpected. 4) The possible return of parietal cells exhibiting dilated canaliculi and relatively few vacuoles (stages 1 and 2) to their normal morphology.

*General conclusion*

In the mouse gastric epithelium, the normal life history of parietal cells includes their production and differentiation in the isthmus region and their bi-directional migration toward the pit and base regions. The cells are programmed to have a limited, even though long, life span of 54 days. Old parietal cells in the pit and base undergo necrosis or apoptosis and are finally eliminated from the epithelium. In the present study we found that the physiological degeneration of parietal cells is enhanced by inhibiting their secretion using a H2-receptor antagonist. In previous studies (Karasawa et al., 1988; Inokuchi et al., 1992; Karam and Forte, 1994), it was shown that the inhibition of parietal cells by blocking their major protein (ATPase) using omeprazole also enhances their degeneration. Furthermore, blocking the muscarinic receptors also induced degeneration of parietal cells (Lehy and Dudrasquent, 1972). Thus, it seems that the ATPase-mediated as well as the receptor-mediated inhibition of parietal cells would change their dynamics to make them die early and grow fast.
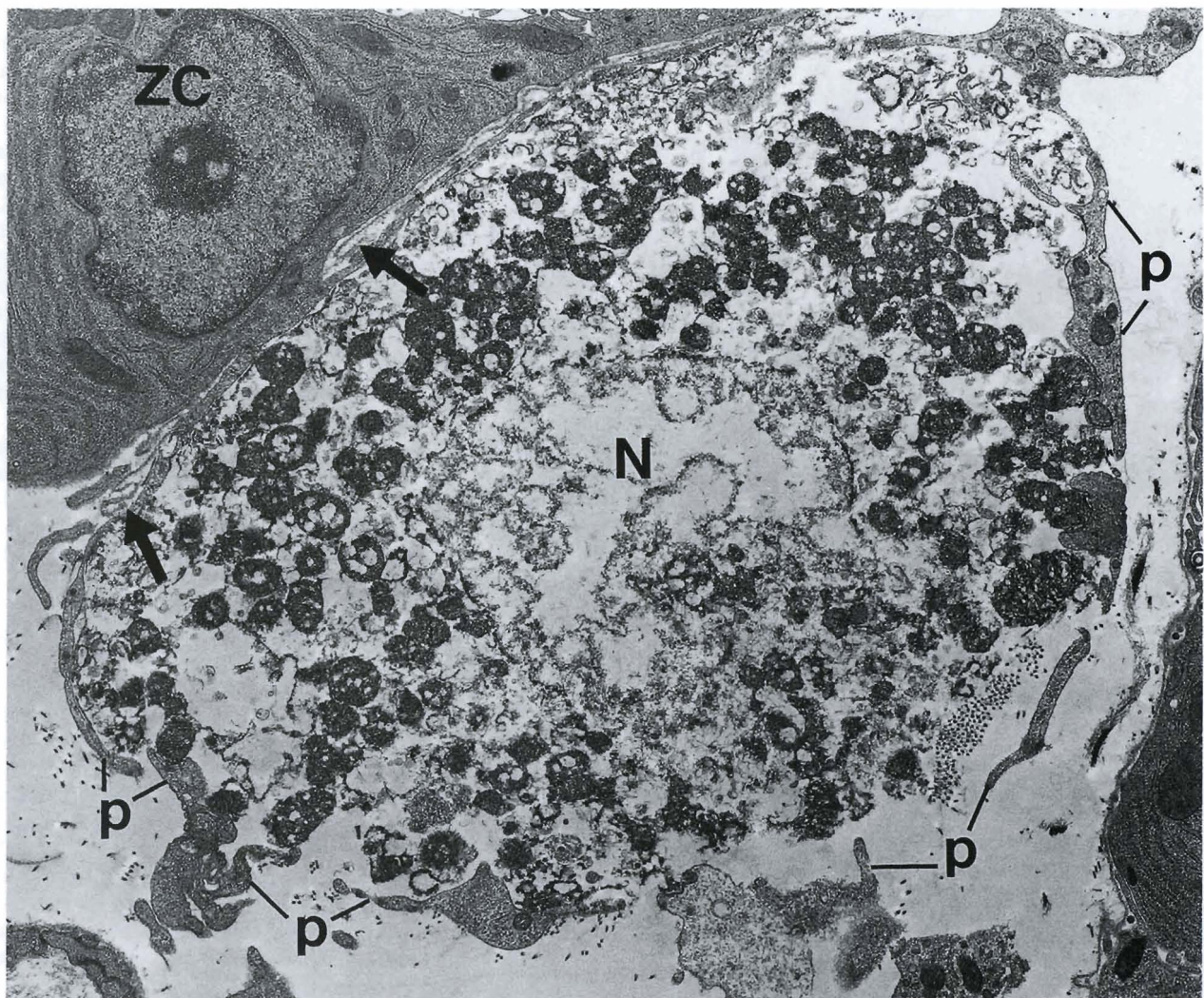


**Fig. 10.** A necrotic parietal cell as seen in the 42-hour-ranitidine-infused mice. The cell is characterized by dissolution of the cytosol and nucleoplasm and lysis of most of the cell membranes. The basement membrane around the cell has also been lysed and its two broken ends are visible at the arrows. Several cytoplasmic processes (P), probably of a connective tissue macrophage, surround the necrotic cell. In the upper left corner is a normal zymogenic cell (ZC). x 9,000
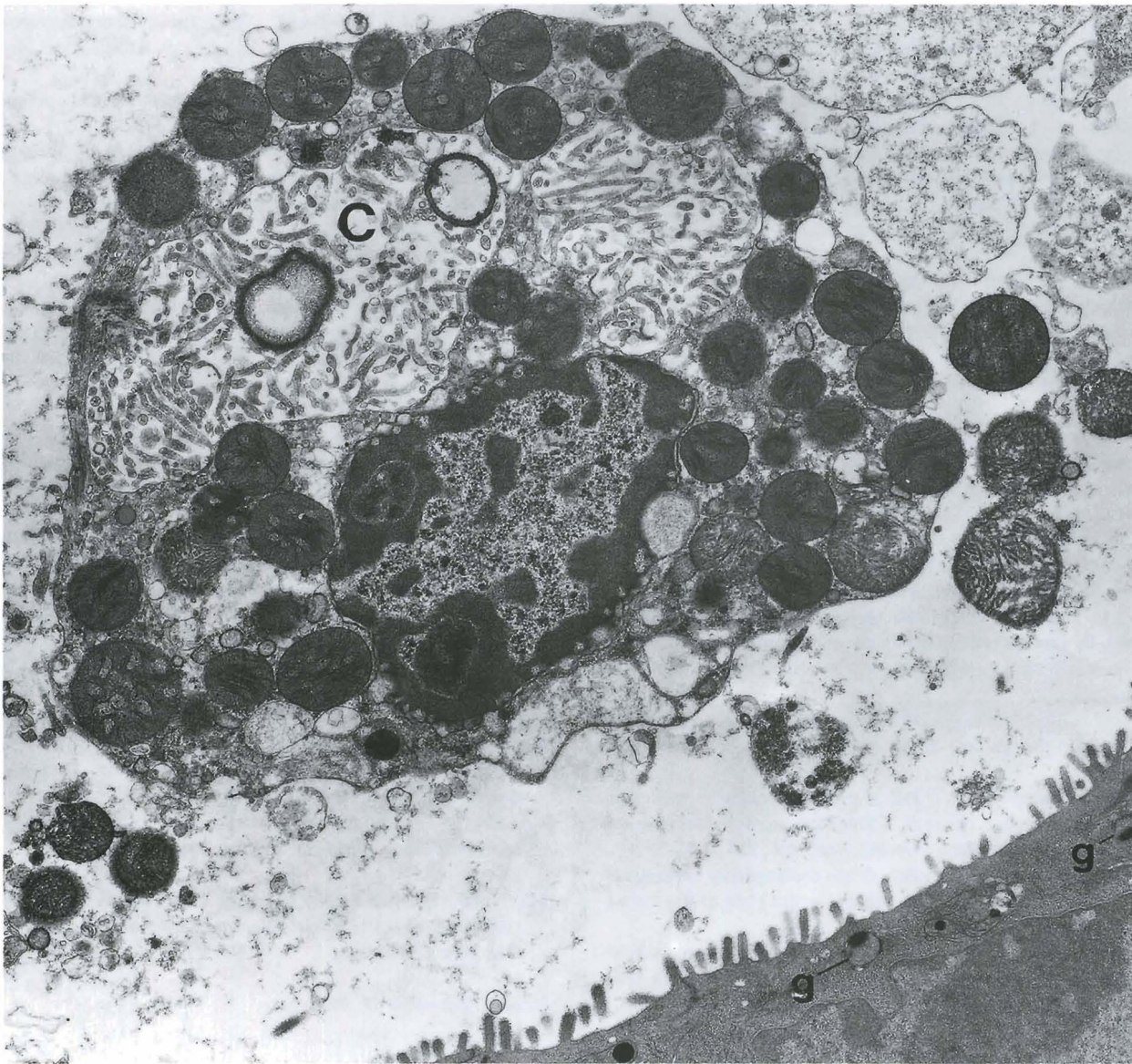
**Fig. 11.** Extruded dead parietal cell as seen free in the gland lumen of the 42-hr-infused mouse. The cell shows signs of apoptosis: condensation of the nucleus seen in the center and of the mitochondria. The canaliculus (C) exhibit thin microvilli and dense spherical membrane remnants. Note the pre-neck cell with a few cored granules (g) seen in the lower right. x 9,000

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