

UC Irvine

UC Irvine Previously Published Works

Title

Effect of Sucralfate on the Normal Human Gastric Mucosa. Endoscopic, Histologic, and Ultrastructural Assessment

Permalink

<https://escholarship.org/uc/item/5rg4k9xb>

Journal

Scandinavian Journal of Gastroenterology, 22(sup127)

ISSN

0036-5521

Authors

Taranwski, Andrzej

Hollander, Daniel

Stachure, Jerzy

et al.

Publication Date

1987

DOI

10.3109/00365528709090961

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at

<https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

Effect of Sucralfate on the Normal Human Gastric Mucosa. Endoscopic, Histologic, and Ultrastructural Assessment

ANDRZEJ TARNAWSKI, DANIEL HOLLANDER, JERZY STACHURA, TOMASZ MACH, and JOZEF BOGDAL

Division of Gastroenterology, Department of Medicine, University of California, Irvine;
Departments of Gastroenterology and Pathology, N. Copernicus Medical Academy,
Krakow, Poland

Tarnawski A., Hollander D., Stachura J., Mach T. and Bogdal J. Effect of Sucralfate on the normal human gastric mucosa. Endoscopic, histologic, and ultrastructural assessment. *Scand J Gastroent* 1987, 22, Suppl 127, 111–123.

Twelve healthy volunteers were given a single sucralfate tablet (1 gm) orally. For 60 min after ingestion they were examined endoscopically a) for the localization and disintegration of the tablet in the stomach, and b) biopsies were taken to determine the effect of sucralfate on the histology and ultrastructure of the normal gastric mucosa. After ingestion, the sucralfate tablet had disintegrated and firmly adhered to a relatively small mucosal area of the greater curvature covering 5 ± 2 and 7 ± 2 cm² at 15 and 30 minutes, and 9 ± 3 cm² at 60 minutes after drug ingestion. Histologic and ultrastructural examination of the mucosa in direct contact with sucralfate revealed distinct changes in the surface epithelial cells: mucus release, vacuolization, and exfoliation of some of the cells. Endoscopy offers a unique opportunity for the study of gastroduodenal effects and disposition of orally administered drugs.

Key words: endoscopy, histology, human gastric mucosa, sucralfate, ultrastructure.

Andrzej Tarnawski, MD, Gastroenterology Section (111G), Veterans Administration, Medical Center, 5901 E Seventh Street, Long Beach, CA 90822 USA

INTRODUCTION

Sucralfate is a non-systemic, effective drug for the treatment and prophylaxis of peptic ulcer disease.^{1–6} While the effect of sucralfate on eroded or ulcerated gastric mucosa has been reported in experimental animals^{7,8} and in humans,⁹ the distribution of the sucralfate tablet in the normal stomach and its effect on histology and ultrastructure of the normal human gastric mucosa are unknown.

Therefore, the aims of the present study were to determine: 1) the localization and distribution of

the sucralfate tablet in the stomach after its ingestion, and 2) the effect of sucralfate on the histology and ultrastructure of the normal human gastric mucosa.

METHODS

Subjects: Twenty volunteers (16 males and 4 females) aged 21 to 55 years were evaluated for this study. None of the volunteers had a history of chronic or excessive alcohol use, nor did they use alcohol or any medication for 14 days prior to

Results from this study were presented at the Annual Meeting of the American Society for Gastrointestinal Endoscopy, New Orleans, Louisiana, May 23, 1984, and published in abstract form in *Gastrointestinal Endoscopy* 1984;30:155.

evaluation. Twelve subjects met the inclusion criteria: 1) normal physical examination, 2) normal laboratory test results (complete and differential blood counts including platelets, prothrombin time, serum bilirubin, SGPT, alkaline

phosphatase, glucose, BUN, creatinine, total proteins, and albumin, Na^+ , K^+ , Ca^{++} , urine analysis, stool hemocult test), and 3) normal endoscopic appearance of the esophageal, gastric, and duodenal mucosa. The experimental protocol

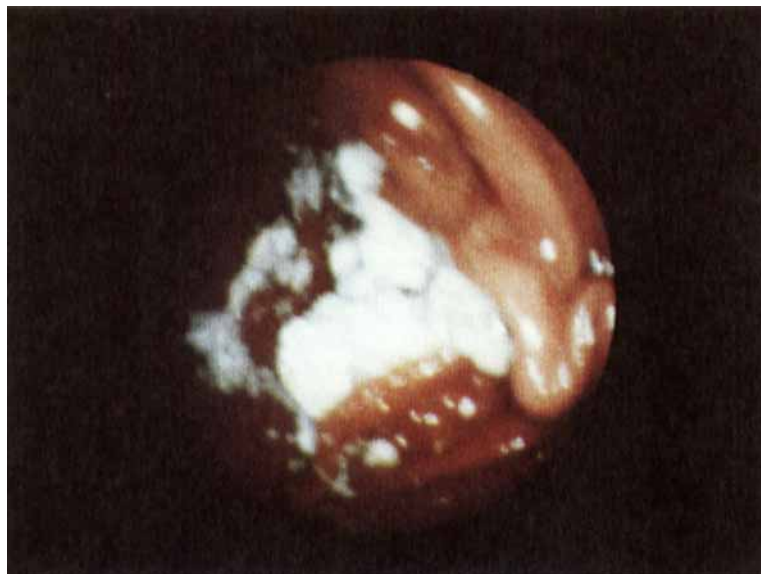


Fig. 1A

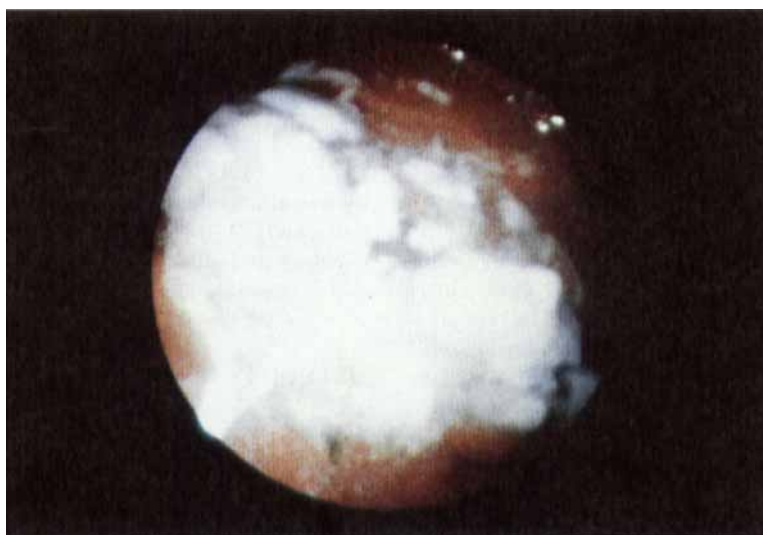


Fig. 1C

Figure 1. Appearance of sucralfate tablet in the stomach A) 15 minutes, B) 30 minutes, and C) 60 minutes after its ingestion. Partly disintegrated sucralfate tablet covers relatively small mucosal area. In subject with increased gastric peristalsis, the disintegrated sucralfate tablet is dispersed over a larger mucosal area on both greater and lesser curvatures (D).

was approved by the Institutional Human Research Committee. All evaluated volunteers gave informed consent.

Study Plan: Twelve subjects that met the entrance criteria were given 1 tablet (1 gm)

sucralfate orally with 100 ml water. One minute later, endoscopy was performed with an Olympus GIFQ endoscope. No premedication was given except local oropharyngeal lidocaine spray.

For one hour after administration of sucralfate,



Fig. 1B



Fig. 1D

two investigators observed the appearance of the gastric mucosa, and the localization and disintegration of the tablet. At 15, 30, and 60 minutes after ingestion, the area of sucralfate deposition was measured utilizing an open biopsy forceps as a reference.

Mucosal biopsies were obtained 60 minutes after sucralfate ingestion from 1) the area of direct contact between sucralfate and the mucosa, 2) 5 cm away, and 3) 10 cm away from the partly disintegrated sucralfate tablet. Mucosal specimens were prepared for light microscopy. Tissue was fixed in 10 % buffered formalin. Paraffin sections were stained with hematoxylin and eosin (H&E) and Alcian blue and periodic acid Schiff (AB+PAS). The microscopic slides were coded, and tissue sections were evaluated by two investigators.

For transmission electron microscopy, specimens were fixed for two hours in 3.5 % purified glutaraldehyde buffered in 0.1M phosphate (pH 7.4) at 4°C. Specimens were then washed with buffer and postfixed in 1 % osmium tetroxide at 4°C for one hour, dehydrated in a graded series of ethyl alcohol solutions, and embedded in a mixture of five parts Epon resin to four parts Spurr low-viscosity embedding resin (10, 11). Mucosal sections were stained with uranyl acetate and lead citrate and examined with a Tesla 50B and a Phillips 300 electron microscopes at 60 kV.

RESULTS

Endoscopy

Five minutes after ingestion, swollen and fragmented sucralfate tablet had adhered to the mucosa of the greater curvature of the mid corpus (Figure 1A). At 15 and 30 minutes after ingestion, the disintegrated sucralfate tablet was still seen at the same site, covering 5 ± 2 cm² and 7 ± 2 cm², respectively, of the mucosal area (Figure 1B). At 60 minutes after ingestion, sucralfate was still present in the region of initial contact with the mucosa, covering a relatively small area of the mucosa 9 ± 3 cm² (Figure 1C). The sucralfate material was firmly adherent to the mucosa and could not be removed or displaced even with vigorous saline washing with the Olympus washing tube.

In two subjects with increased gastric peristalsis, the disintegrated sucralfate tablet was dispersed over a large mucosal area, 25 ± 6 cm² of the corpus and antrum on both the greater and lesser curvatures (Figure 1D).

Histology and Ultrastructure

1. *Mucosa in direct contact with sucralfate.* The most distinct histologic and ultrastructural changes seen in the mucosa covered with sucralfate (compared to normal mucosa — Figures 2A and 3A) were: 1) discharge of the mucus granules from the surface epithelial cells (Figure 2B and 3B), 2) presence of a thick mucus layer covering the gastric mucosal surface, and 3) separation of some of the surface epithelial cells from the basal membrane and exfoliation (Figures 2C, 2D, 3C and 3D). In addition, the cytoplasm of surface epithelial cells had become vacuolized due to dilation of the endoplasmic reticulum (Figures 3C and 3D). Nuclei had become enlarged, displaying less euchromatin and an increase in heterochromatin (Figure 3B).
2. *Mucosa 5 cm distant from the sucralfate.* The surface epithelial cells displayed dilatation of intracellular spaces (Figure 4A) and were separated from the basal lamina (Figure 4B). Mucus discharge from these cells was no obvious (Figure 4B).
3. *Mucosa 10 cm distant from the sucralfate.* Cells were generally normal in appearance.

The changes described in 1, 2, and 3 were present in all subjects studied.

DISCUSSION

Our knowledge of the disposition and local effect of orally ingested drugs on the gastroduodenal mucosa is very limited. Sucralfate is a non-systemic drug for the treatment and prophylaxis of gastroduodenal ulcers (1–6). Interaction of sucralfate with the ulcerated gastric mucosa has been reported in experimental animals (7, 8) and in man (9). This has been postulated as a major mechanism of its therapeutic actions (12, 13). The formation of a stable drug-protein complex on eroded or ulcerated mucosa (which prevents contact with, and further injury by H⁺, pepsin and bile salts) may indeed play a role in healing of ex-

isting ulcers or erosions (9, 12, 13). However, this postulated mechanism does not explain the ability of sucralfate: 1) to prevent stress ulcers in critically ill patients (14), 2) to prevent ulcer recurrence (4–6), and 3) to prevent or reduce experimental mucosal injury produced by necrotizing agents (15–19). In each of these instances, sucralfate is given prophylactically before the development of mucosal erosions, which suggests that sucralfate's major site of action may, in fact, be the normal, non-eroded mucosa. Direct evidence of sucralfate-induced actions on the normal, human, gastric mucosa has not yet been demonstrated.

The present study demonstrated that in the majority of studied subjects, ingested sucralfate tablets dispersed and adhered firmly to a relatively small mucosal area (5 to 9 cm²) in the region of initial contact with the gastric mucosa. This single dose of sucralfate produced striking histologic and ultrastructural changes in normal tissue. Some of the changes, such as mucus release, edema of the lamina propria, and vacuolization, disruption, and exfoliation of some surface epithelial cells, were similar to changes produced in normal human gastric mucosa by topically administered prostaglandin E₂ methyl analog (unpublished observation). It should also be pointed out that sucralfate exerts very similar action on the normal gastric mucosa of the rat (20). Similar changes are also seen in normal gastric mucosa of the rat after intragastric administration of arachidonic acid (prostaglandin precursor) (21), and antacid (22). Each of these is a gastric protective agent.

The release of mucus from the surface epithelial cells is a common effect of gastric "cytoprotective" drugs such as prostaglandins and antacids (22–24). Mucus secretion may play a role in mucosal defense (24).

Disruption and exfoliation of the surface epithelium is followed by prompt reepithelialization and is a normal feature of epithelial cell renewal (25). It is seen not only after topical application of gastric irritants such as alcohol or aspirin, but also after ingestion of food (25, 26, 27). The latter observation indicates that exfoliation of the surface epithelium only (without deeper mucosal damage) is not necessarily a sign of severe mucosal injury but occurs physiologically and most likely represents a stimulus for epithelial cell renewal. In addition, disruption of some of the surface epithelial cells by sucralfate may constitute a trophic stimulus for cell renewal and may result in the release of prostaglandin precursors (from membrane phospholipids) which themselves are mucosal protective agents (21).

In conclusion, sucralfate is a potent drug with topical action on the normal human gastric mucosa. Sucralfate-induced changes in the normal gastric mucosa, which are similar to those produced by "cytoprotective" drugs such as prostaglandins, may account for sucralfate's therapeutic and prophylactic efficacy.

Since our knowledge of the distribution and effects of orally ingested drugs on the upper gastroduodenal mucosa is limited, endoscopy offers a unique opportunity for direct study of the mucosal effects of orally administered drugs.

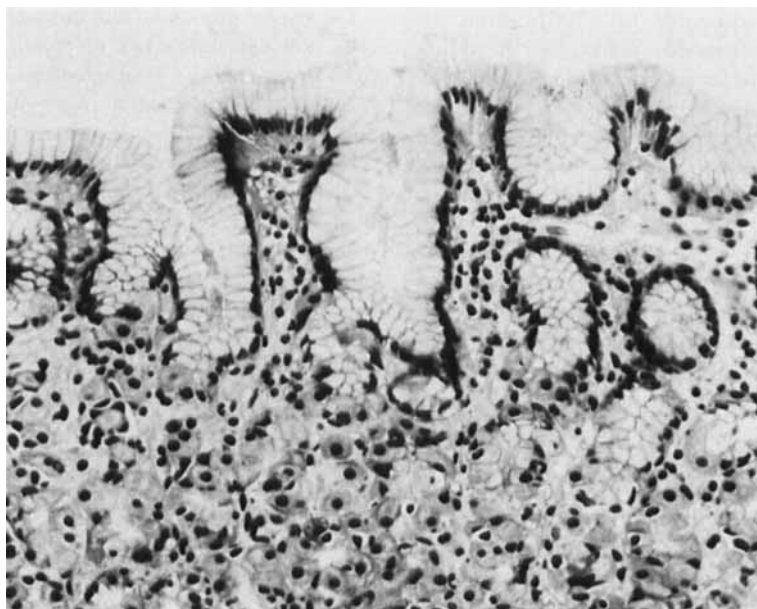


Fig. 2A

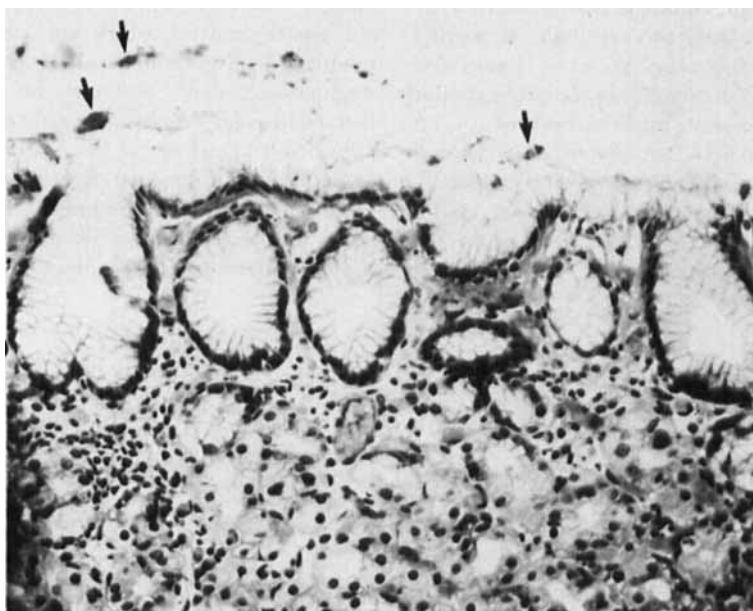


Fig. 2B

Figure 2. Histologic pictures of the gastric mucosa: A) normal, nontreated (H & E stain; 200X). B, C & D mucosa in direct contact with sucralfate particles (arrows in B; pink material in C and D) Some of the surface epithelial cells are damaged and exfoliated (Figures 2B,C & D). Release of mucus granules and separation of the cells from basal lamina propria are also present (B). (H & E stain, B-200x; C-400x; D-1000x original magnification).

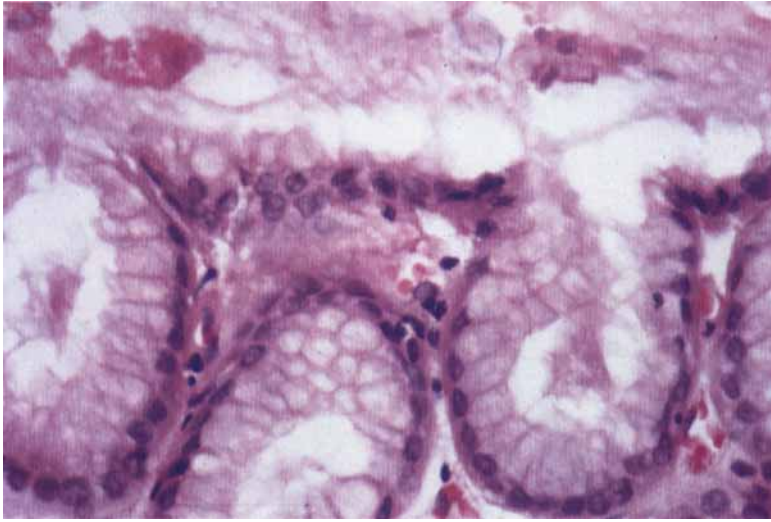


Fig. 2C

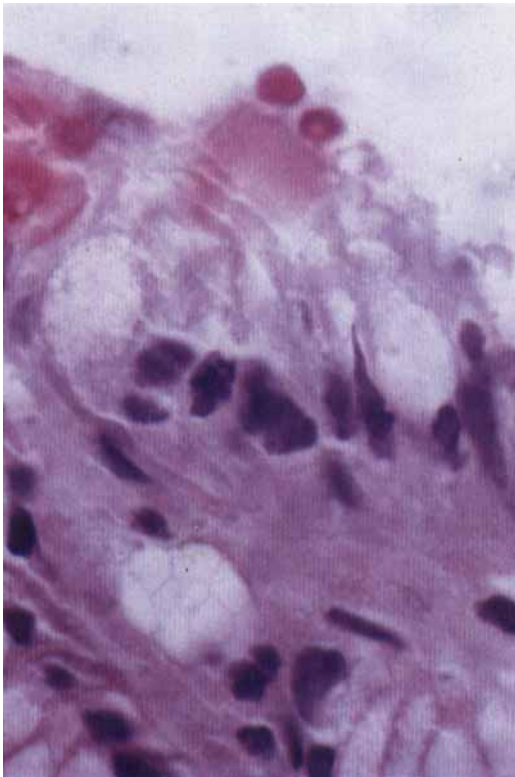


Fig. 2D

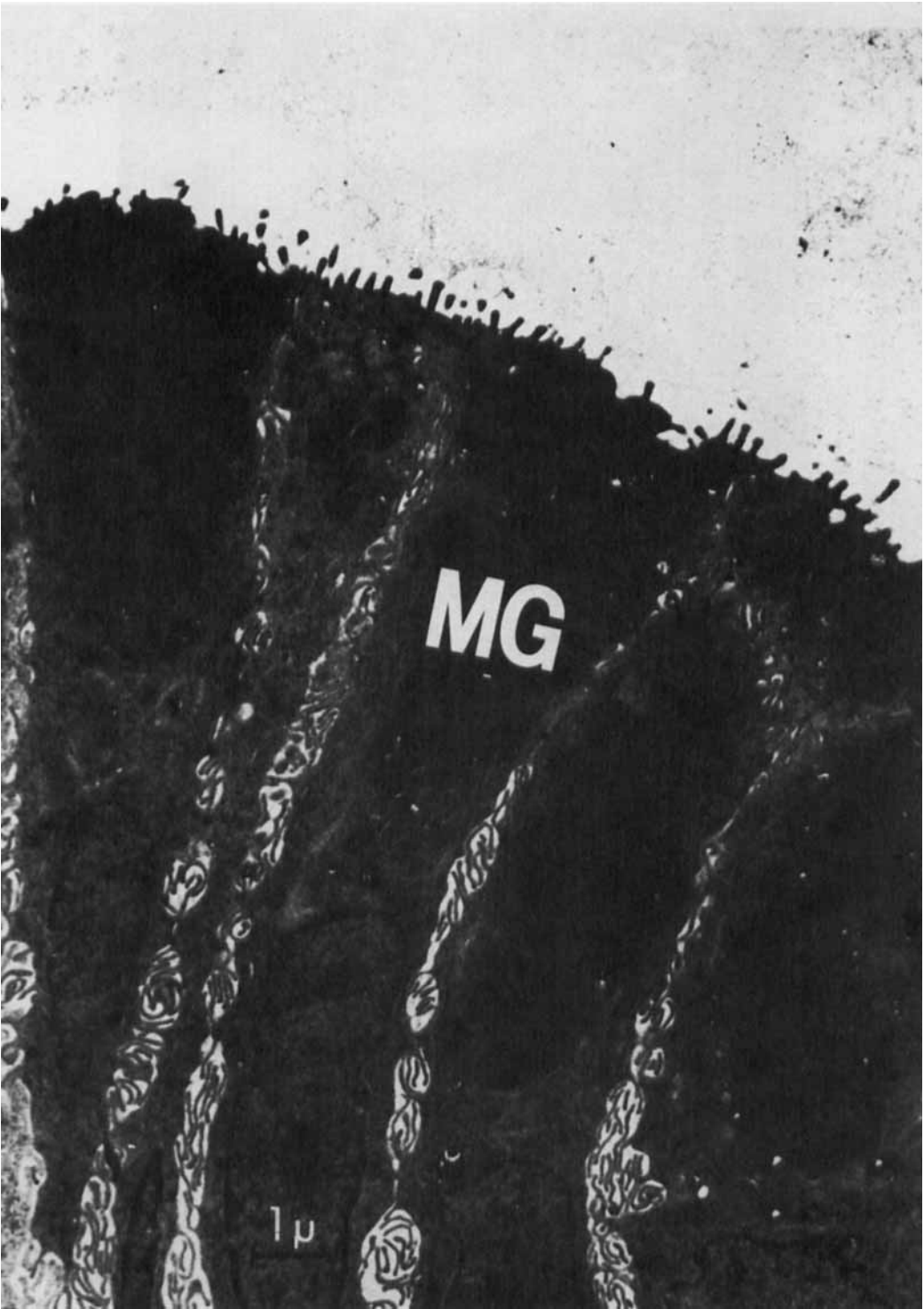


Fig. 3A

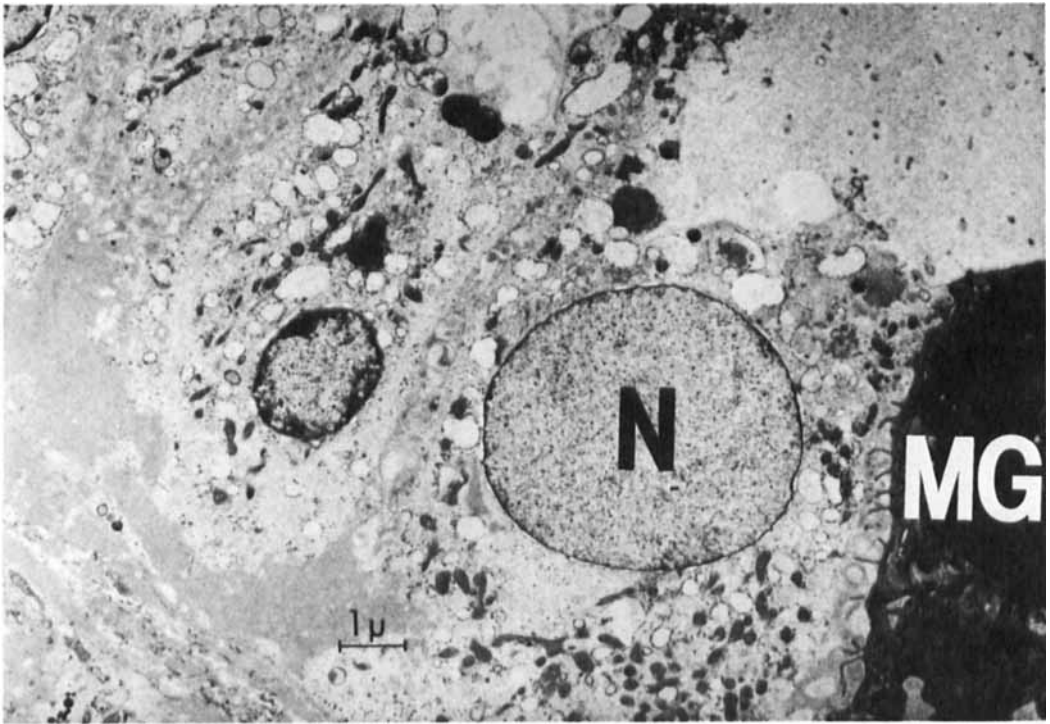


Fig. 3B

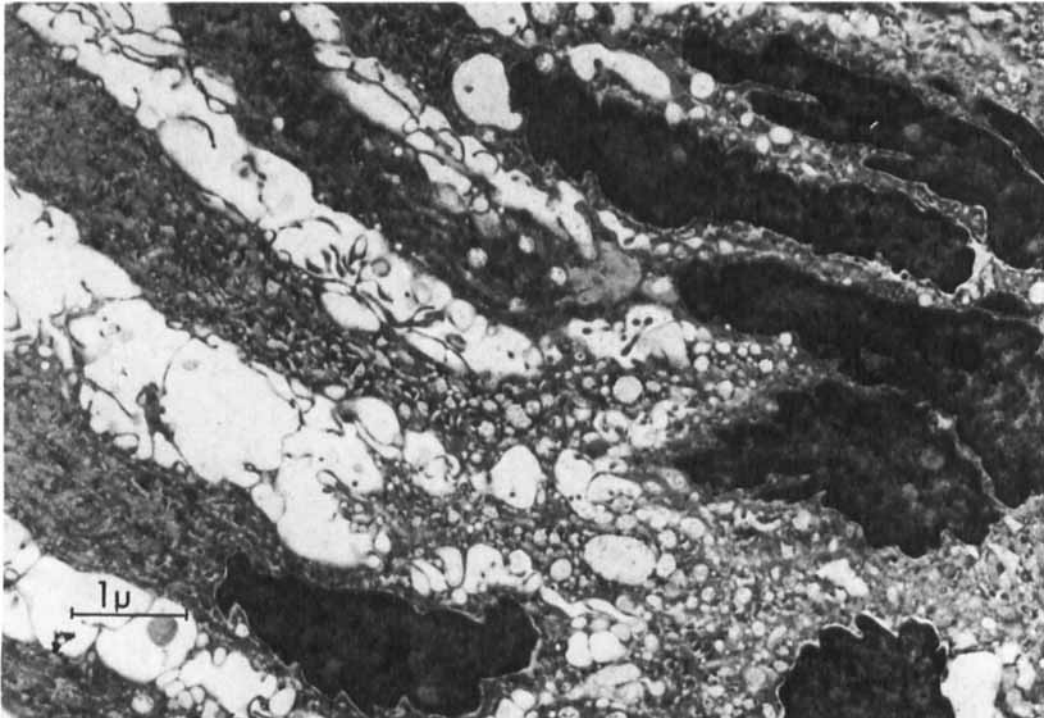


Fig. 3C

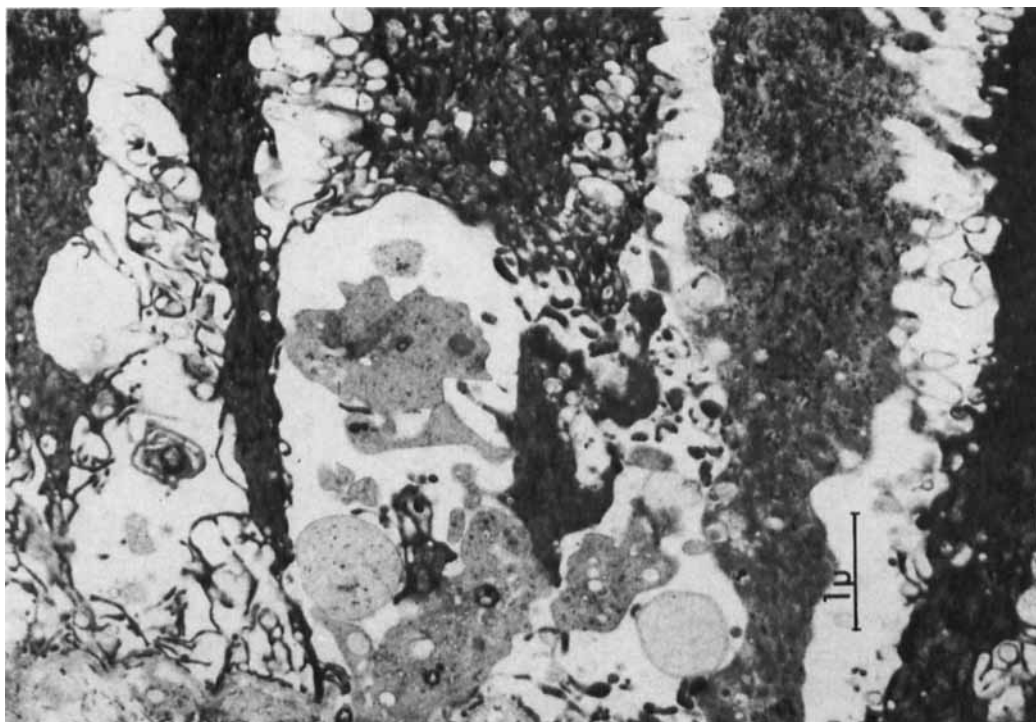


Fig. 3D

Figure 3. Transmission electron micrographs of: A) Normal gastric mucosa. Apical portion of the surface epithelial cells contains a concentration of mucus granules (MG). B) Mucosa in contact with sucralfate. One surface epithelial cell has preserved mucus granules (MG) but mucus granules were discharged from other cells. Round enlarged nucleus (N) with decreased heterochromatin. C) and D) Mucosa in contact with sucralfate. The surface epithelial cells are separated by prominent edema of lamina propria and devoid of mucus granules. Due to the prominent dilation of endoplasmic reticulum, the cytoplasm of these cells is vacuolized. (N=surface epithelial cell nuclei.)

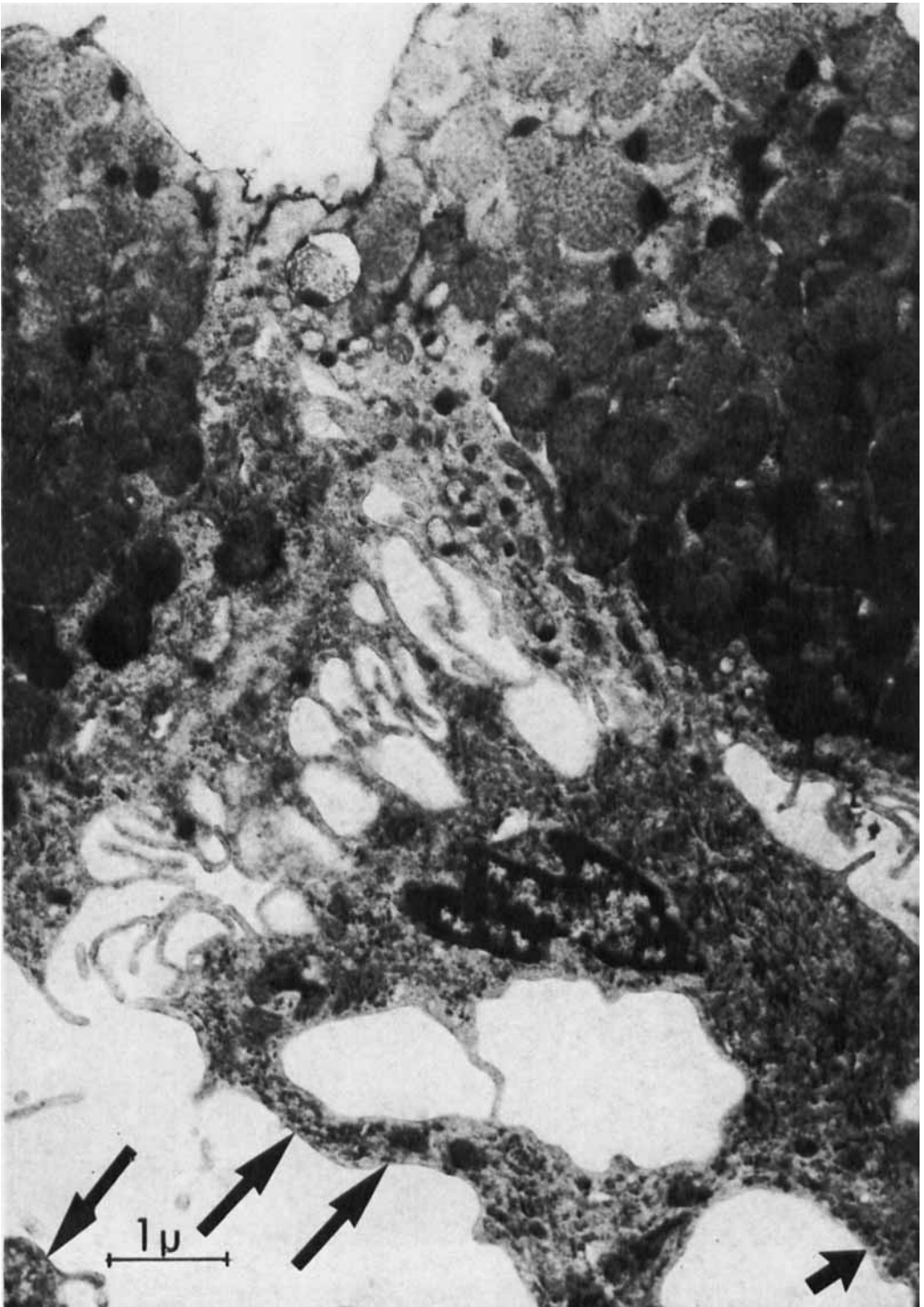


Fig. 4A

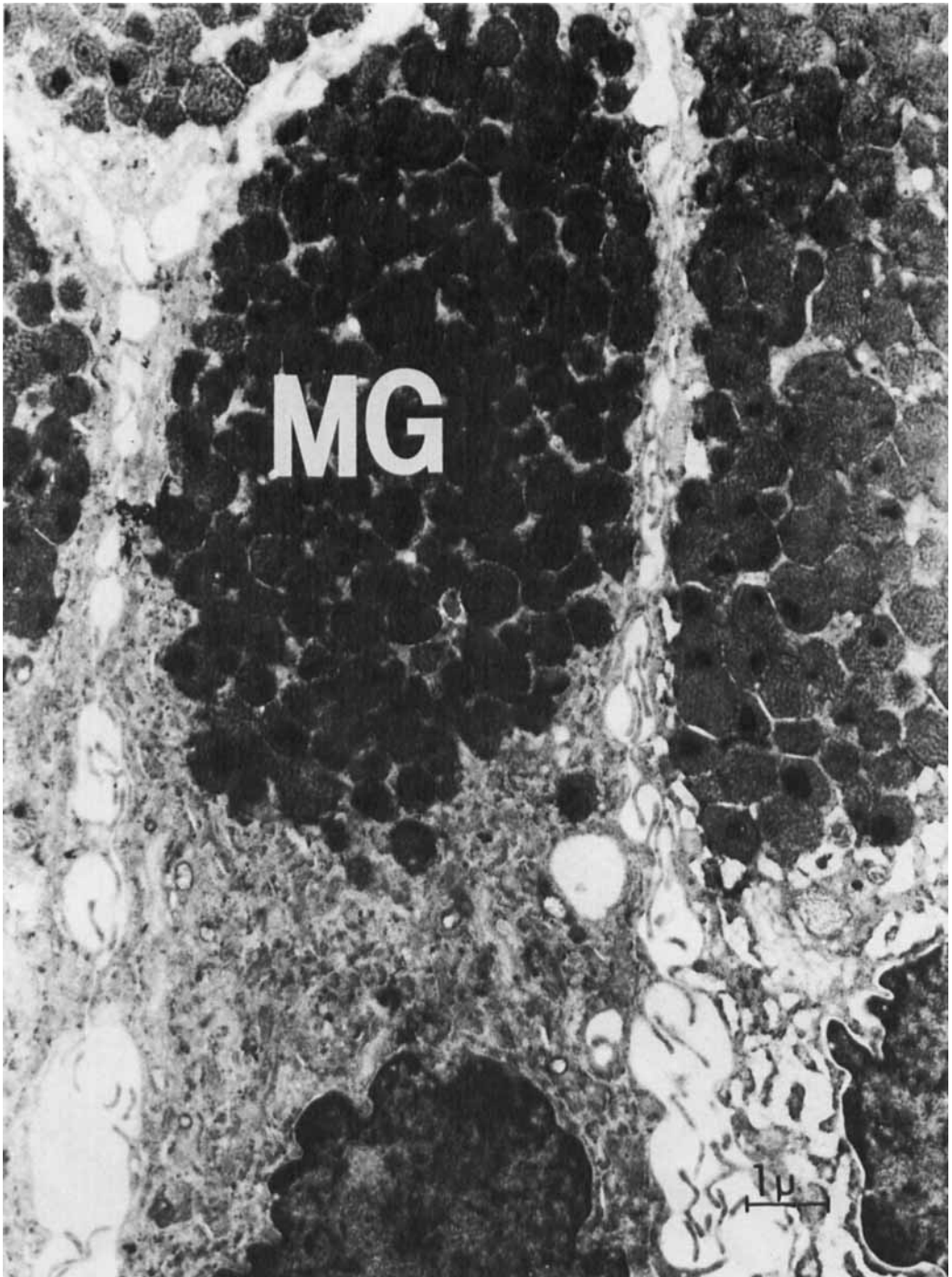


Fig. 4B

Figure 4. Transmission electron micrographs of the mucosa 5 cm distant from sucralfate. A) Dilation of intercellular spaces (arrows) between surface epithelial cells and B) separation of the cells from the basal lamina (arrows). mucus discharge did not occur.

REFERENCES

1. Hollander D. *J Clin Gastroenterol* 1981, 3 (suppl 2), 153-157
2. McHardy GG. *J Clin Gastroenterol* 1981, 3 (suppl 2), 147-152
3. Ishimori A, Arakawa H. In Caspary WF ed. Duodenal Ulcer, Gastric Ulcer: Sucralfate. A New Therapeutic Concept, Sucralfate Symposium, 11th International Congress of Gastroenterology Hamburg, Jun 1980. Urban & Schwarzenberg. Munich. 1981, pp. 93-100
4. Miyake T, Ariyoshi J, Suzaki T, Oishi M, Sakai M, Ueda S. *Dig Dis Sci* 1980, 25, 1-7
5. Classen M, Bethge H, Brunner G, et al. *Scand J Gastroenterol* 1982, 18 (suppl 83), 61-68
6. Libeskind M. *Scand J Gastroenterol* 1982, 18 (suppl 83), 69-70
7. Nagashima R, Hirano T. *Arzneimittelforsch* 1980, 30, 80-83
8. Steiner K, Garbe A. In Caspary WF ed. Duodenal Ulcer, Gastric Ulcer: Sucralfate. A New Therapeutic Concept, Sucralfate Symposium, 11th International Congress of Gastroenterology, Hamburg, Jun 1980. Urban & Schwarzenberg. Munich. 1981, pp 19-21
9. Nakazawa S, Nagashima R, Samloff IM. *Dig Dis Sci* 1981, 26, 297-300
10. Luft J. *J Biophy Biochem Cytol* 1961, 9, 409-414
11. Spurr A. *J Ultrastruct Res* 1969, 26, 31-35
12. Bighley LD, Giesing D. in Caspary WF ed. Duodenal Ulcer, Gastric Ulcer: Sucralfate. A New Therapeutic Concept, Sucralfate Symposium, 11th International Congress of Gastroenterology, Hamburg, Jun 1980. Urban & Schwarzenberg. Munich. 1981, pp 3-12
13. Nagashima R. *J Clin Gastroenterol* 1981, 3 (suppl 2), 117-127
14. Borrero E, Margolis IB, Bank S, Shulman N, Char-davoyne R. *Am J Surgery* 1984, 148, 809-812
15. Harrington SJ, Schlegel JF, Code CF. *J Clin Gastroenterol* 1981, 3 (suppl 2), 129-134
16. Tarnawski A, Hollander D, Gergely H, Stachura J. *Am J Med* 1985, 79(2c), 19-23
17. Hollander D, Tarnawski A, Gergely H, Zipser RD. *Scand J Gastroenterol* 1984, 19 (suppl 101), 97-102
18. Ligumsky M, Karmeli F, Rachmilewitz D. *Gastroenterology* 1984, 86, 1164
19. Hollander D, Tarnawski A, Krause WJ, Gergely H. *Gastroenterology* 1985, 88, 366-374
20. Tarnawski A, Hollander D, Krause WJ, Zipser RD, Stachura J, Gergely H. *Gastroenterology* 1986, 90, 893-905.
21. Hollander D, Tarnawski A, Ivey KJ, et al. *J Lab Clin Med* 1982, 100, 296-308
22. Tarnawski A, Hollander D, Cummings D, Krause WJ, Gergely H, Zipser RD. *Gastroenterology* 1984, 86, 1276 (Abstract)
23. Stachura J, Tarnawski A, Ivey KJ, Mach T, Bigaj M. *Gastroenterology* 1981, 80, 1291 (Abstract)
24. Kauffman GL, Jr. *J Clin Gastroenterol* 1981, 3 (suppl 2), 45-50
25. Grant R. *Canad M A J* 1944, 51, 577-579
26. Grant R, Grossman MI, Ivy AC. *Gastroenterology* 1953, 25, 218-231
27. Willems G. *Digestion* 1972, 6, 46-63