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# Ménétrier's Disease

## *A Trivalent Gastropathy*

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Current conceptions of Ménétrier's disease only obliquely resemble those originally described. Bona-fide cases are so uncommon that, of 125 cases diagnosed as Ménétrier's disease, hypertrophic gastritis, or protein-losing gastropathy treated at the Massachusetts General Hospital during the 26-year period of 1962–1987, only six cases merited an unequivocal anatomic diagnosis. Two other cases previously described proved on review to be nondiagnostic in one instance and *Campylobacter pylori* gastritis in the other. Because abnormalities in the secretion of gastric acid and in the loss of protein from the stomach may coexist, a representation of each case in semiquantitative terms can be described on triaxial coordinates. Three patients had a hypercoagulable state, one in association with gastric carcinoma. One other case of gastric carcinoma and one of esophageal carcinoma coexistent with Ménétrier's disease were identified. Administration of subcutaneous heparin during the perioperative period to patients with Ménétrier's disease is appropriate regardless of whether or not hypercoagulation or carcinoma is manifest. If treatment with anticholinergic drugs and inhibitors of gastric acid secretion fails, total gastrectomy is the best solution, because it stops protein loss, eliminates hyperchlorhydria, prevents development of gastric carcinoma, and permits anastomotic reconstruction between normal esophagus and normal small bowel.

**F**OUR CLASSES OF STIMULI potentially affect the mass and function of the enteric mucosa<sup>1</sup>: 1) intraluminal substances, such as nutrients, secretions from the proximal intestinal tract, growth factors, and products of inflammatory reactions,<sup>2–5</sup> 2) tropic factors—hormonal, locally transmitted, or infectious,<sup>6,7</sup> 3) neural factors,<sup>7,8</sup> and 4) immunologic phenomena.<sup>9</sup> Similar kinds of influences probably modulate gastric mass and function.<sup>6</sup>

In Ménétrier's disease\*<sup>10</sup> (hypertrophic gastropathy),

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\* Despite various patterns of accent marks applied to his name in the Anglo-Saxon literature, Pierre E. Ménétrier (1859–1935) spelled his name with two accent marks. Professor André Monsaingeon informs us that a *ménétrier* is a person who plays the violin (a *ménéstral*, or *minstrel* in English). The *s* in *ménéstral* interdicts the second acute accent.

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the gastric mucosal hypertrophy is so great that the rugae can look like convolutions of the brain. Although this gross appearance is common to all cases of Ménétrier's disease, as the eponymic diagnosis is usually used, in a single case, either the gastric glandular elements or the superficial epithelial elements may predominate; acid secretion may be high, normal, or low; and hypoproteinemia may or may not be present. There is no consensus about which of these features define the disease.<sup>11–20</sup>

Because the mucosal histology, level of acid secretion, and serum albumin levels are semiquantifiable along three graphic axes, we suggest describing the cardinal abnormalities of Ménétrier's disease under the rubric *trivalent gastropathy*. An interplay of the agents influencing gastric mucosal structure and function could be the determinants of the phenotypic state.

### Materials and Methods

From a retrospective analysis of 127 cases during the period of 1962 through early 1987 with diagnoses of Ménétrier's disease, hypertrophic gastritis, or protein-losing enteropathy, only six cases had clinical presentations, radiologic and endoscopic features, and pathologic findings compatible with a diagnosis of Ménétrier's disease. Pathologic material from each of these was reanalyzed. On review, one case previously considered classic Ménétrier's disease was reclassified as *Campylobacter pylori* gastritis. In another case, a biopsy specimen deep enough to allow certain diagnosis was not taken.

### Case Reports

**Case 1.** In 1973, a 62-year-old man with a 25-year history of recurrent gastrointestinal (G.I.) bleeding was observed. Previous barium-contrast,

endoscopic, and angiographic examinations had been normal, except for a question of a jejunal vascular malformation. The patient's serum albumin level was 3.8 g/dl. No acid-secretion studies were performed, and serum gastric levels were not checked.

The patient was readmitted with recurrent hematemesis. A "string test" localized the bleeding to the stomach. Laparotomy disclosed multiple, small angiomatous malformations of the small intestine, and gastrotomy revealed hypertrophic gastritis. A 70% distal subtotal gastrectomy was performed, together with oversewing of the vascular malformations. At the time of microscopic examination of the surgical specimen, diffuse hyperplasia of both the superficial compartment (foveolar region), and glandular compartment of the gastric body mucosa were present.

Over the ensuing years, the patient was admitted several times with recurrent bleeding. The range of serum albumin levels was 3.4–4.9 g/dl. No gastric acid-secretion studies were done, and serum gastrin levels were not measured. Although endoscopy was not helpful initially, with time, the patient developed hypertrophic folds in the gastric stump and bleeding from the gastrojejunostomy.

Thirteen years after his initial admission, the gastrojejunostomy was resected for the treatment of massive, recurrent bleeding. Hamartomatous polyps of the colon were resected. Mesenteric ischemia during the post-operative period resulted in death.

The surgical specimen showed a large polypoid mass at the gastrojejunostomy, with the typical histologic features of gastritis cystica polyposa (Fig. 1).<sup>21</sup> The polyp was composed of cystic, greatly dilated gastric pits and glands within an abundant edematous and acutely inflamed stroma. Dilated glands at the base of the polyp herniated through the splayed muscularis mucosae to invade the submucosa focally. Some of the cysts contained collections of neutrophils. The transition between the polyp and the surrounding, normal-appearing gastric mucosa was abrupt.

**Case 2.** In 1977, evaluation of a 28-year-old man at another hospital who had had a long history of abdominal pain and intermittent upper G.I. bleeding disclosed giant folds in the body and fundus of the stomach.<sup>22</sup> A random serum gastrin level was minimally elevated, but the calcium-stimulated gastrin level was normal. No acid-secretion studies were performed. A full-thickness biopsy of the gastric body mucosa showed pit hyperplasia and glandular atrophy consistent with Ménétrier's disease.

Because of continued gastric bleeding, the patient was transferred. His serum albumin level was 3.3 g/dl. A 1-hour gastric aspiration produced 236 ml of fluid with a pH of 1.5 and 14.6 mEq of (hydrochloric acid) HCl. The basal acid output was markedly elevated, and the response to pentagastrin was high.

A total gastrectomy was performed because of hypersecretion, recurrent bleeding, hypoalbuminemia, and the patient's peripatetic habits. A segment of the Roux-en-Y loop needed to be resected before being used because of rapidly developing thrombosis in the mesenteric veins. The surgical resection specimen contained massive rugae of the gastric body and fundus with sparing of the antrum (Fig. 2). At the time of microscopic examination, marked foveolar hyperplasia and body glandular atrophy were seen (Fig. 3). Cystic dilatation of both greatly expanded pits and atrophic glands was present in multiple foci. No malignancy was identified. After the gastrectomy, the patient's serum albumin rose to normal levels. The patient remains well.

**Case 3.** In 1977, a 42-year-old man with a history of alcoholism presented himself with peripheral edema and ascites. The serum bilirubin level, serum glutamic oxaloacetic transaminase activity, and prothrombin time were normal, but the serum albumin level was 2.3 g/dl. No gastric-acid studies were performed. A barium-contrast upper G.I. series disclosed nodular thickening of the rugae in the proximal stomach. No ulcers were present, and the gastric wall was pliable. Gastroscopy confirmed these findings. An endoscopic biopsy of the gastric body showed elongation of gastric pits, focal mucinous metaplasia of chief cells, and cystically dilated glands consistent with Ménétrier's disease.

Acral ischemia secondary to right innominate and subclavian artery thrombosis precipitated admission 2.5 years later. The serum albumin

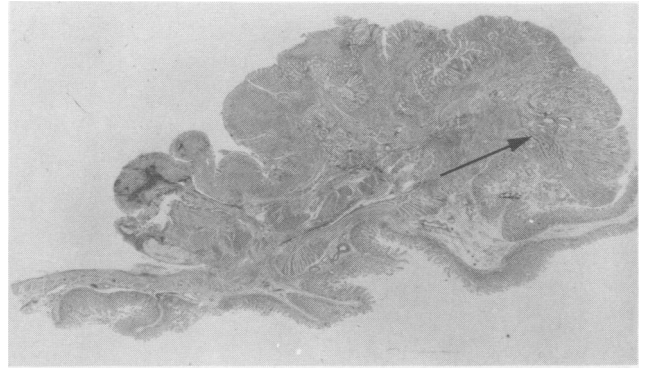


FIG. 1. Low-power photomicrographs of gastritis cystica polyposa. A large discrete polypoid mass is seen on the gastric aspect of the gastrojejunostomy anastomosis site. The greatly expanded and branched gastric pits show focal cystic dilation (arrow). The process resembles a localized Ménétrier's disease.

level was 1.3 g/dl. Several months after vascular reconstruction, the patient returned with G.I. bleeding. Gastroscopy again demonstrated prominent rugae, but this time with focal rigidity. Total gastrectomy was performed.

The specimen showed marked foveolar hyperplasia and atrophy of subjacent glands throughout the gastric fundus and body. The average mucosal thickness of the fundus was 4 cm, whereas the antral mucosal folds were no more than 1 cm high. Within the hypertrophic mucosa of the posterior gastric body, a 4.5 × 3.5 cm indurated ulcer was present;

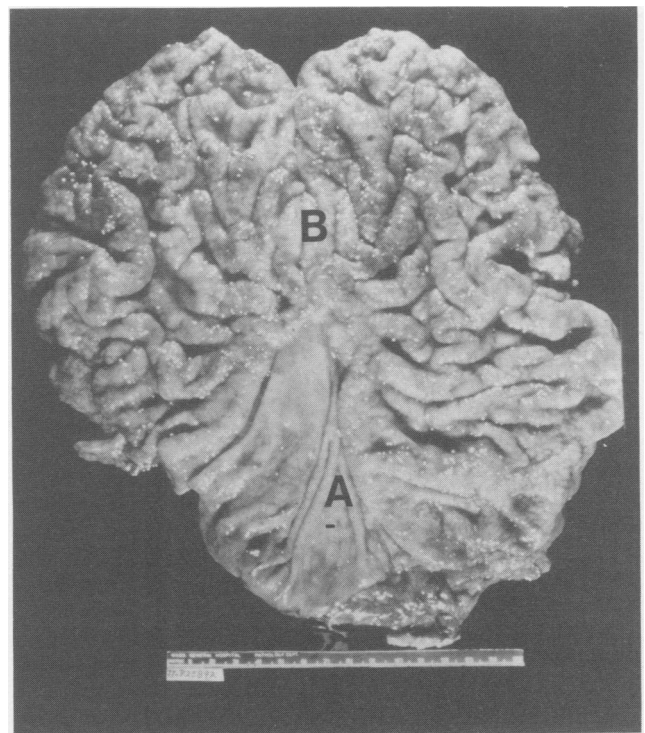


FIG. 2. Ménétrier's disease: gastric resection specimen. The typical distribution of gastric mucosal hypertrophy in Ménétrier's disease is seen. Fundus and body mucosa (B) show greatly enlarged folds and the mucosa has a finely nodular (cobblestone) appearance. The antrum (A) is relatively spared and appears smooth and comparatively flat.

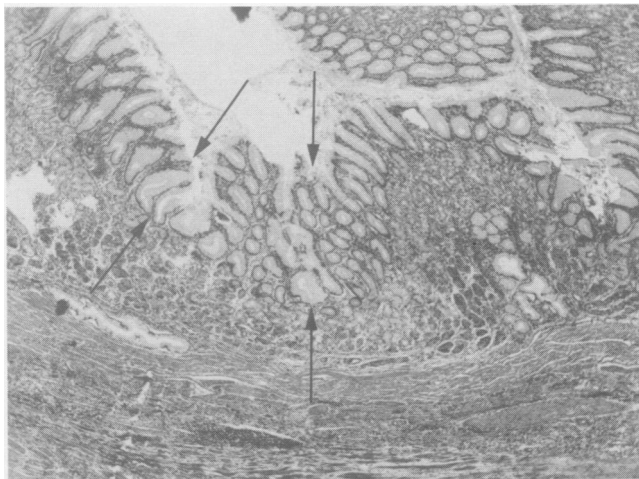


FIG. 3. Photomicrographs of gastric body mucosa in Ménétrier's disease. The mucosa shows disproportional expansion of the superficial compartment (pit region) (arrows) of the mucosa and atrophy of underlying glands.

at the time of microscopic examination, it proved to be a deeply invasive, poorly differentiated adenocarcinoma. The tumor penetrated the full thickness of the gastric wall and was metastatic to 16 lymph nodes. Death occurred within 3 months.

**Case 4.** In 1983, a 37-year-old woman with a 3-year history of abdominal distress and a recent 8.2 kg weight loss was evaluated. Her serum albumin was 2.5 g/dl, and a barium-contrast upper G.I. radiologic study showed enlarged rugae in the proximal stomach. Mild chronic gastritis was found at the time of endoscopic biopsy. No acid secretion studies were done.

Because both these studies and those performed at another hospital indicated the presence of Ménétrier's disease, a total gastrectomy was

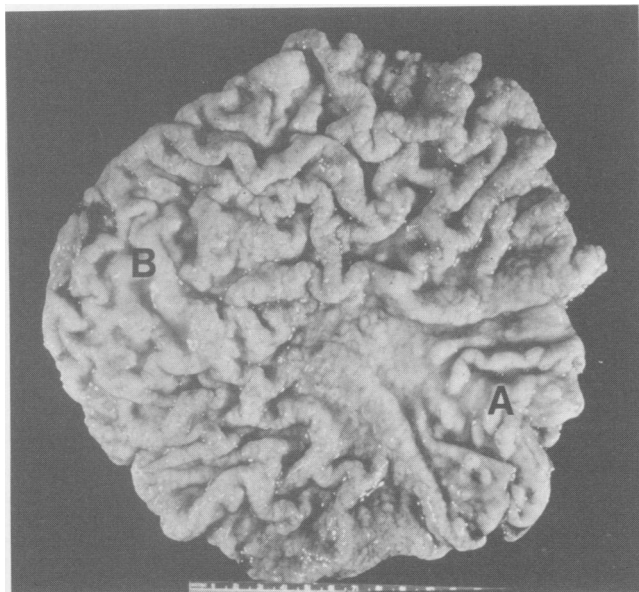


FIG. 4. Ménétrier's disease: gastric resection specimen. Expansion of mucosal folds is most marked in the body (B) and fundus. In this case the antrum (A) is also involved.

performed. The surgical resection specimen showed giant mucosal folds in the gastric body with incomplete sparing of the antrum (Fig. 4). At the time of microscopic examination, moderate to marked foveolar hyperplasia and moderate body glandular atrophy were present (Fig. 5). Within 1 week of surgery, the patient's serum albumin level rose to 3.3 g/dl and eventually became stable at a normal level. Her symptoms markedly improved, and her weight stabilized.

**Case 5.** In 1980, during evaluation for hematochezia and anemia, a 55-year-old man with a history of juvenile colonic polyps was found on upper G.I. series to have coarse nodularity of his gastric mucosa and a large mass along the greater curvature.<sup>24</sup> His symptoms included heartburn, bloating, and one tarry stool, but he had experienced no pain, weight loss, or anorexia. His hematocrit was 44% while he was taking iron supplements, and his serum albumin was 3.7 g/dl. His gastric acid output was 0.06 mEq per hour, rising to 4.0 mEq per hour (normal = 22 mEq per hour) with histamine simulation. Upper G.I. endoscopy disclosed hundreds of mucosal polyps. Random biopsies of the polyps performed over several years were intermittently interpreted as inflammatory (hyperplastic) or adenomatous polyps. A specimen obtained in 1986 showed carcinoma *in situ*.

A total gastrectomy was performed in 1987. The resection specimen showed cerebriform hypertrophic folds involving the body and fundus, predominantly along the greater curvature. The antrum was studded with numerous bulbous polyps as large as 3 cm.

At the time of microscopic examination, the giant folds showed foveolar hyperplasia and atrophy of the glands of the gastric body, with cystic dilatation of both expanded pits and shortened glands. The lamina propria was infiltrated with chronic inflammatory cells; focal mucinous metaplasia of the glands was present. A moderately to poorly differentiated adenocarcinoma was seen arising in a background of dysplastic surface epithelium near the lesser curvature. The tumor infiltrated the full thickness of the gastric mucosa, but did not penetrate the muscularis mucosae. The antral polyps differed markedly in appearance from the polypoid form of hypertrophic gastropathy in the proximal stomach. They were composed predominantly of greatly expanded and edematous stroma containing large numbers of eosinophils but devoid of smooth muscle. Widely spaced, cystically dilated gastric pits, and few antral glands were present, but the epithelial component of the polyps was far less conspicuous than the stroma. This histologic appearance was compatible with juvenile (hamartomatous) gastric polyps.

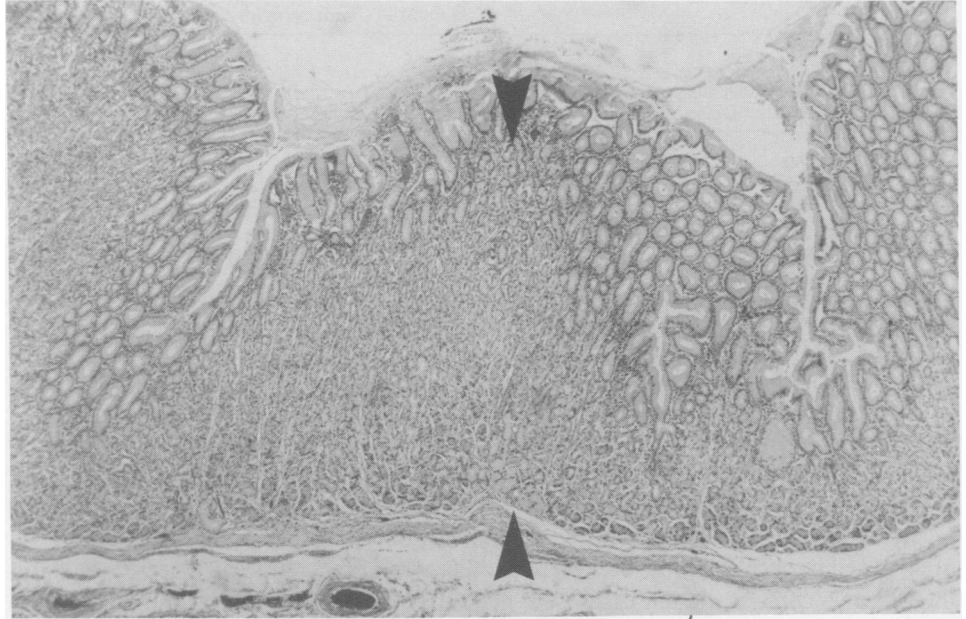
**Case 6.** In late 1987, an esophagogastrectomy was performed on a 60-year-old man because of symptoms of esophageal obstruction secondary to a squamous-cell carcinoma. The specimen of the stomach had gross and microscopic features diagnostic of Ménétrier's disease. The gastric fundus and body were more severely involved than the antrum of the stomach. Hyperplasia of the gastric pits and spotty glandular atrophy were present throughout the specimen. There was no pre-existing evidence of hypertrophic gastritis, of hyperchlorhydria, or of protein-losing gastropathy.

## Discussion

### Origins

Ménétrier did not formulate a syndrome.<sup>10</sup> He reported postmortem observations of two patients showing extraordinary gastric abnormalities that were associated with the development of gastric carcinoma. He acknowledged that he had been preceded in these discoveries by other observers, including Andral, who had remarked on the similarity of the large gastric folds to those of the third stomach of ruminants (the omasum).

FIG. 5. Photomicrograph of gastric body in Ménétrier's disease without glandular atrophy. The gastric pits are expanded and branched, but underlying glands (arrows) are not shortened, preserving normal proportions between the superficial and deep mucosal compartments.



Claire L. was a 52-year-old woman who died on January 5, 1887 of cerebral infarction and left hemiplegia. Although she had had no symptoms of gastric disease, along the greater curvature of her enlarged stomach there was a 4 × 8-cm area of sheetlike adenomatous growth 0.5–1.0 cm high, 9 cm proximal to the pylorus. A large amount of mucus was present, and an adenomatous polyp was identified in the antrum. Although greatly elongated gastric glands retained their rectilinearity, the basal aspects of the ducts were distorted and filled with mucus.

Barthelemy G. was a 38-year-old alcoholic building painter with lead colic, cramps in his arms and legs, shaky hands, a 2-month history of anorexia and nausea, and a 4-week history of diarrhea. He had ascites and peripheral edema. He died of cirrhosis on February 9, 1887. Tenacious mucus covered cerebriform folds, present not only in most of the stomach, but in the intestine (presumably the duodenum). The gastric hypertrophy stopped 3 cm distal to the cardia and did not involve the antrum. Raymond's microscopic examination disclosed rectilinear gastric glands 5–6 times that of normal height, but with the basal aspects of the glands filled with mucus.

Arterial ischemia, inflammation, alcoholism, and lead-poisoning were postulated as the causes of the disease. Palmer has translated the rest of Ménétrier's treatise.<sup>25</sup>

### Definition

From a description of the morbid anatomy that could have been responsible for G.I. distress in some few patients, Ménétrier's name has been applied to an ill-defined, broader syndrome characterized in every instance by large rugae in the body of the stomach, usually sparing the esophagocardiac area and the antrum. Here agreement ends. Several early studies of groups of patients with pathologic findings similar to those described by Ménétrier identified frequent hypoproteinemia<sup>11</sup> and hypochlorhydria.<sup>26,27</sup> Although many authors apply only the criterion of en-

larged gastric rugae that are not of neoplastic or granulomatous origin for the diagnosis of Ménétrier's disease,<sup>11,15,26–28</sup> others include hypoproteinemia,<sup>12,20,29</sup> normal or low gastric acid secretion,<sup>13,30</sup> or both.<sup>14,31–37</sup> There is disagreement among pathologists, as well, about diagnostic microscopic features of the condition. Ming defined three types of hypertrophic gastropathy: mucous cell type, glandular cell type, and mixed mucous-glandular type.<sup>16</sup> Although he did not identify any single type as diagnostic of Ménétrier's disease, he indicated that the patients reported by Ménétrier appeared to have the mixed type of hyperplasia. Nonetheless, others have suggested that only the mucous type of hyperplasia should be considered representative of Ménétrier's disease.<sup>17</sup>

Attempts to classify subgroups of hypertrophic gastropathies have been confusing and ambiguous; all possible combinations of the principal characteristics of the disease have been found. Cases exhibiting acid hypersecretion with either hypoalbuminemia<sup>18,22,33,37</sup> or normal serum albumin<sup>14</sup> have been reported, in addition to the more common cases demonstrating normal or low gastric acid associated with normal or low serum protein. A summary of these features present in each of the six cases we describe is presented in Table 1.

Correlation between pathologic and clinical findings is imprecise as well. Fieber and Rickert<sup>19</sup> analyzed 50 cases of "hypertrophic gastropathy," including only those cases with: 1) giant rugae meeting radiologic and gastroscopic criteria, 2) full-thickness samples of gastric mucosa permitting classification according to Ming's criteria,<sup>16</sup> 3) available clinical data, and 4) no concurrent peptic ulcer or gastric neoplasm. Although it would be logical to expect hypoproteinemia in patients with increased numbers of

TABLE 1. Characteristics of Patients

Case	Radiologically Compatible Diagnosis	Full-Thickness Biopsy	Mucosal Histology	Acid Level	Serum Protein Level	Thrombosis
1	Yes	Yes	High glands, deep pits	N/A	Low	Yes
2	Yes	Yes	Low glands, deep pits	High	Low	Yes
3	Yes	Yes	Low glands, high pits	N/A	Low	Yes
4	Yes	Yes	Low glands, deep pits	N/A	Normal	No
5	Yes	Yes	Low glands, deep pits	Normal	Normal	No
6	Indeterminate	Yes	Low glands, deep pits	N/A	Normal	No

Measurements of serum gastrin levels in Cases 2 and 6 were normal.

Gastric carcinoma was present in Cases 3 and 5. Esophageal carcinoma was present in Case 6.

mucous cells and hyperchlorhydria in those with increased glandular components,<sup>14,31</sup> Fieber and Rickert found hypoalbuminemia in 60% of cases demonstrating glandular hyperplasia (n = 10), rising only to 73% in those with mucous cell hyperplasia (n = 30). Hyperacidity was identified in only 50% of the ten cases with glandular hyperplasia, but in none of the cases of mucous cell hyperplasia.

The dilemma presented by attempts to define Ménétrier's disease and to subclassify the other hypertrophic gastropathies may be resolved by focusing on the clinical hallmarks of each case, not on historically assigned labels. In all cases of hypertrophic gastric fold disease, the following studies are mandatory: serum albumin levels, serum gastrin levels, gastric acid secretion studies, and full-thickness gastric biopsy. In Ménétrier's disease, serum levels should be normal or only mildly increased. Very high serum gastrin levels should raise the possibility of the Zollinger-Ellison syndrome, which also produces gastric mucosal hypertrophy and increased acid output. The proliferative state of the gastric mucosa, the serum protein levels, and the degree of acid secretion are the cardinal features of this disease, but they vary among individual cases. They may also vary with time during the course of the disease.

We suggest the name *trivalent gastropathy* so that each of these variables may be represented graphically on a three-dimensional scale (Figs. 6 and 7). This convention offers a uniform method of displaying the manifestations of the disease within a framework that does not arbitrarily imply relationships among the separate aspects, while emphasizing the importance of defining all three characteristics in each case.

Although one can only speculate on factors influencing these features, the manifestations observed seem to be the product of a dynamic equilibrium between opposing forces. This compromise is not to deny the previously defined associations, such as the common coincidence of glandular hyperplasia and hyperacidity or the rarity of hypoalbuminemia with hyperchlorhydria. Rather, it permits a more inductive approach to the analysis of this disease or group of diseases. Searcy and Malagelada iden-

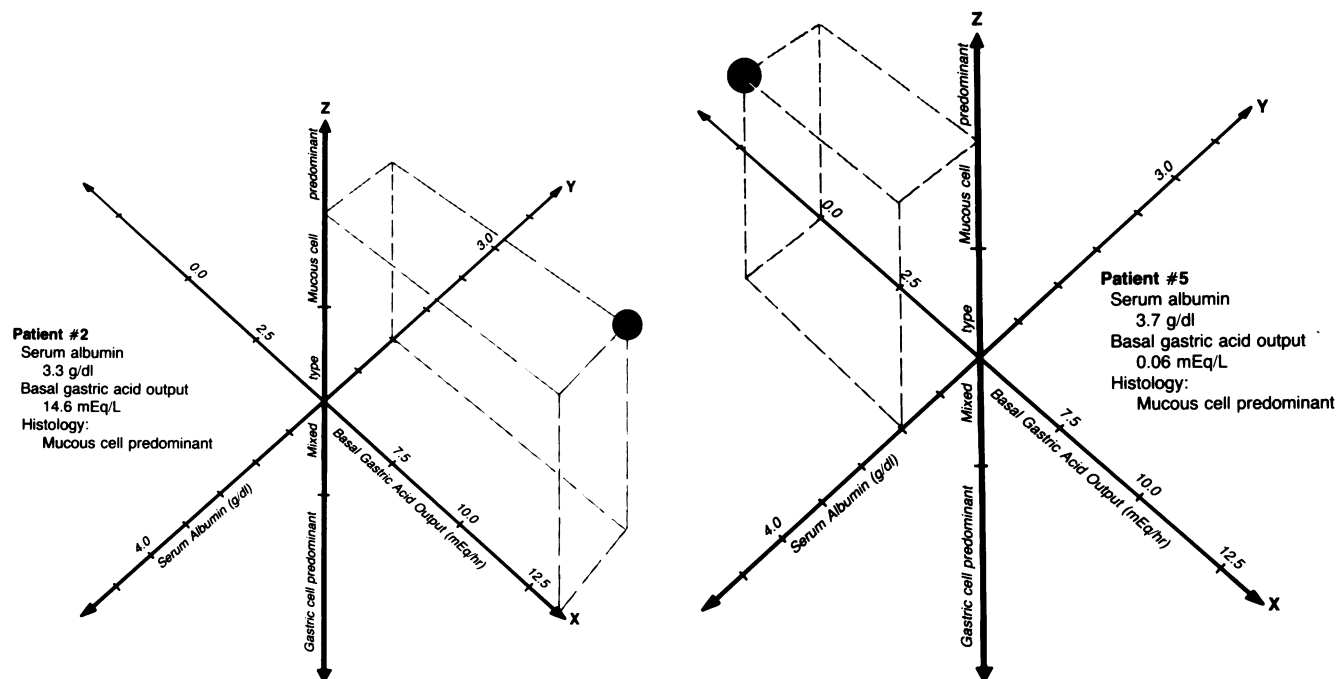
tified markedly increased risks of recurrent infection, vascular disorders, and pulmonary edema in patients with hypertrophic gastropathy associated with hypoalbuminemia.<sup>12</sup> Unfortunately, neither the mucosal histology nor the acid secretory status of these patients was identified. Perhaps these risks are limited to a subgroup of patients that could be further defined by these criteria. Other subgroups with distinctive natural histories or etiologies may become apparent, as well.

#### Etiology

Although neural influences modulate intestinal epithelial cell proliferation,<sup>7,8</sup> even maximal stimulation of gastric nerves is unlikely to produce mucosal hyperplasia and would not be expected to produce low acid secretion. Nevertheless, truncal vagotomy sometimes improves clinical symptoms in Ménétrier's disease.<sup>14,29</sup>

In human beings, secretory products of the salivary glands, the oropharynx, and the esophagus are not known to have tropic effects on the stomach. In the male mouse, however, stimulated secretion of the submandibular gland causes outpouring of its stores of epidermal growth factor (EGF), nerve growth factor, and other substances, and is dramatically tropic for the stomach, the small intestine, and, to a lesser extent, the colon.<sup>5,38</sup> EGF alone stimulates growth of oxyntic gland mucosa while inhibiting gastric acid secretion. The human submandibular gland and duodenal Brunner's glands contain EGF, and EGF can be detected in gastric secretions.<sup>39-41</sup>

Reports of hypertrophic gastropathy thought to be related to exposure to allergens<sup>20-35</sup> or found to be associated with autoantibodies to gastric parietal cells<sup>15</sup> suggest that the abnormalities in Ménétrier's disease may be related to immunologic phenomena. Indeed, in a murine model, protein-losing hypertrophic gastropathy is produced after neonatal thymectomy.<sup>9</sup> A self-limited protein-losing hypertrophic gastropathy in children has been attributed to an allergic phenomenon because peripheral eosinophilia occurs concomitantly,<sup>42</sup> but it may or may not be the same as Ménétrier's disease.



FIGS. 6 and 7. Triaxial representation of the abnormalities in Ménétrier's disease.

The potential influence of local inflammatory factors as postulated by Ménétrier's is exemplified by Type II ostertagiosis in cattle (a nematode infecting the fourth stomach, the abomasum), which causes a protein-losing gastropathy, hypoproteinemia, anemia, gastric mucosal inflammation, mucous cell hyperplasia, and abnormally high gastric pH.<sup>43,44</sup> The Drentse Patrijs dog seems particularly susceptible to a hypertrophic gastritis like Ménétrier's disease.<sup>45</sup> Cytomegalovirus infection has been identified in cases of pediatric hypertrophic gastropathy.<sup>42</sup>

### Treatment

The patient is indifferent to his gastric anatomy. He wants freedom from pain (present in over 80% of cases), blood loss (34%), and symptoms of hypoproteinemia (40%).<sup>19</sup> Treatment is directed to these goals. If the disease is the kind likely to remit spontaneously, such as the allergic hypertrophic gastropathies, anticholinergics should be prescribed because they diminish acid secretion and have the potentiality of tightening gastric cell junctions,<sup>46</sup> limiting protein losses by this route. Histamine-H<sub>2</sub> receptor-blockers have many of the same effects and should be tried if the response to anticholinergics is suboptimal or if their side effects are troublesome.<sup>47</sup> Treatment with cimetidine or ranitidine sometimes decreases protein losses.<sup>47,48</sup> Combination therapy with these two agents or administration of omeprazole might also be useful, perhaps in conjunction with parenteral nutrition.<sup>49</sup>

If pharmacologic therapy fails, surgery is appropriate.

Although distal subtotal gastrectomy with a Billroth II reconstruction should limit gastric acid secretion by removing gastrin-secreting antral cells and indirectly decrease the loss of albumin as pH rises, it entails anastomosis of thick, abnormal, proximal stomach to normal intestine. The risk of leakage and obstruction is great. In fact, the majority of postoperative deaths that occur after resections for Ménétrier's disease are attributed to anastomotic leaks.<sup>13</sup> A Billroth I anastomosis is even more susceptible to these problems. Pyloroplasty and vagotomy have the technical advantage of avoiding a difficult anastomosis, but have no physiologic advantage over a distal gastrectomy, since the potential complications of abolishing pyloric function are nearly the same. Proximal vagotomy is probably no more efficacious than treatment with an H<sub>2</sub>-receptor blocker. Perhaps even more disturbing is that the risk of gastric carcinoma known to be associated with Ménétrier's disease is not addressed by these approaches, and the efficacy of surveillance endoscopy has not been proved.

Total gastrectomy is the best therapeutic solution to Ménétrier's disease and is generally well-tolerated.<sup>34</sup> Reconstruction with a Roux-en-Y loop of jejunum is sufficient,<sup>50-52</sup> although debated.<sup>53</sup> By definition, all abnormalities are corrected, reflux esophagitis is prevented, and the risk of malignant complications is obviated. Patients whose cases have been reported (a preselected group) have gained weight; technical problems posed by distal gastrectomy are avoided. Indeed, the hazards of esophagojejunal anastomosis may sometimes be avoided if there

is enough normal stomach below the esophagus to permit union of two serosalized organs.

In addition to parochial problems of the stomach, patients with Ménétrier's disease may be afflicted by the development of a hypercoagulable state.<sup>12,14,54-56</sup> The cause of the hypercoagulability disease may sometimes be a consequence of occult gastric malignancy. Hypercoagulability is a well-known complication of mucin-producing adenocarcinomas of the G.I. tract. In experimental pancreatic adenocarcinoma, vascular permeability and interstitial deposition of fibrinogen has been suggested as an antecedent event in the production of thrombosis.<sup>57</sup> We recommend preoperative subcutaneous administration of heparin for patients with Ménétrier's disease, whether or not gastric carcinoma is present. Anticoagulation with warfarin in ambulatory, untreated patients would be dangerous, however, because of the risk of recurrent gastric hemorrhage.

Because Ménétrier's disease is rare and has never been studied prospectively, the prevalence of gastric carcinoma is unknown. Nevertheless, gastric carcinoma has been associated with approximately 10-15% of the reported cases of Ménétrier's disease. The increased cell proliferation essential for carcinogenesis in most epithelial systems might be expected to create a fertile field for the development of carcinoma in hyperplastic gastric mucosa.<sup>58,59</sup> In two of the six cases reported here, gastric carcinoma developed years after their initial diagnosis of Ménétrier's disease, and in Case 5, the full spectrum of preneoplastic to malignant epithelial changes was seen. Our sixth patient had a co-existing esophageal squamous cell carcinoma. Another patient with gastric carcinoma superimposed on Ménétrier's disease was seen while this manuscript was in press. Scharschmidt found that the incidence of adenocarcinoma developing in Ménétrier's disease followed for more than 1 year was 12% (n = 26).<sup>13</sup> Although the degree of risk cannot be precisely determined, the association makes the argument for total gastrectomy stronger.

### References

1. Appleton DR, Sunter JP, Watson AJ, eds. Cell Proliferation in the Gastrointestinal Tract. Tunbridge Wells, Pitman Medical. 1980.
2. Williamson RCN. Intestinal adaptation. I. Structural, functional, and cytokinetic changes. *N Engl J Med* 1978; 298:1393-1402.
3. Williamson RCN. Intestinal adaptation. II. Mechanisms of control. *New Engl J Med* 1978; 298:1444-1450.
4. Williamson RCN, Malt RA. Humoral modulation of compensatory intestinal hyperplasia. In Robinson JW, Dowling RH, Riecken E-O, eds., *Mechanisms of Intestinal Adaptation*, Falk Symposium 30. Lancaster: MTP Press, 1982; 215-226.
5. Li AKC, Schattenkerk ME, Huffman RG, et al. Hypersecretion of submandibular saliva in male mice: trophic response in small intestine. *Gastroenterology* 1983; 84:949-955.
6. Johnson LR. The trophic action of gastrointestinal hormones. *Gastroenterology* 1976; 70:278-288.
7. Tutton PJM, Barkla DH. Biogenic amines as regulators of the proliferative activity of normal and neoplastic intestinal epithelial cells, review. *Anticancer Res* 1987; 7:1-12.
8. Tutton PJM, Barkla DH. Neural control of cell proliferation in colonic carcinogenesis. In Malt RA, Williamson RCN, eds. *Colonic Carcinogenesis*, Falk Symposium 31, Lancaster: MTP Press, 1982; 283-295.
9. Kubota H, Taguchi O, Suzuki Y, Matsuyama M, Nishizuka Y. Hypertrophic gastritis with hypergastrinemia and protein loss after neonatal thymectomy in mice. *Gastroenterol Jpn* 1986; 21:122-128.
10. Ménétrier P. Des polyadénomes gastriques et de leurs rapports avec le cancer de l'estomac. *Arch Physiol Norm Path* (4th ser.) 1888; 1:32-55, 236-262.
11. Reese DF, Hodgson JR, Dockerty MB. Giant hypertrophy of the gastric mucosa (Ménétrier's disease): a correlation of the roentgenographic, pathologic and clinical findings. *Am J Roentgenol* 1962; 88:619-626.
12. Searcy RM, Malagelada J-R. Ménétrier's disease and idiopathic hypertrophic gastropathy. *Ann Int Med* 1984; 100:565-570.
13. Scharschmidt BF. The natural history of hypertrophic gastropathy (Menetrier's disease): report of a case with 16 year follow-up and review of 120 cases from the literature. *Am J Med* 1977; 63:644-652.
14. Stempien SJ, Dagradi AE, Reingold IM, et al. Hypertrophic hypersecretory gastropathy: analysis of 15 cases and a review of the pertinent literature. *Am J Dig Dis* 1964; 9:471-493.
15. Berenson MM, Sannella J, Freston JW. Ménétrier's disease: serial morphological, secretory, and serological observations. *Gastroenterology* 1976; 70:257-263.
16. Ming SC. Tumors and tumor-like lesions of entodermal origin. In *Tumors of the Esophagus and Stomach*. Washington: Armed Forces Inst Pathol, Fasc 7 1973; 115-119, 153-154.
17. Appelman HD. Localized and extensive expansions of the gastric mucosa: mucosal polyps and giant folds. In HD Appelman, ed. *Pathology of the Esophagus, Stomach and Duodenum*. New York: Churchill Livingstone, 1984; 79-119.
18. Kristensen M, Nilsson T. Mucus secretion in hypertrophic, hypersecretory, protein-losing gastropathy. *Am J Gastroenterol* 1985; 80:77-81.
19. Fieber SS, Rickert RR. Hyperplastic gastropathy: analysis of 50 selected cases from 1955-1980. *Am J Gastroenterol* 1981; 76:321-329.
20. Lesser PB, Falchuk KR, Singer M, Isselbacher KJ. Ménétrier's disease: report of a case with transient and reversible findings. *Gastroenterology* 1975; 68:1598-1601.
21. Koga S, Watanabe H, Enjoji M. Stomal polypoid hypertrophic gastritis: a polypoid lesion at gastroenterostomy site. *Cancer* 1979; 43:647-657.
22. Maynard EP III, Vickery AL Jr. Case records of the Massachusetts General Hospital. Case 41—1978. *N Engl J Med* 1978; 299:878-884.
23. Schapiro RH, Vickery AL Jr. Case records of the Massachusetts General Hospital. Case 38—1980. *N Engl J Med* 1980; 303:744-750.
24. Podolsky DP, Compton CC. Case records of the Massachusetts General Hospital. Case 2—1988. *N Engl J Med* 1988; 318:100-109.
25. Palmer ED. What Menetrier really said. *Gastrointest Endosc* 1968; 15:83-109.
26. Kenney FD, Dockerty MB, Waugh JM. Giant hypertrophy of gastric mucosa: a clinical and pathological study. *Cancer* 1954; 7:671-681.
27. Butz WC. Giant hypertrophic gastritis. *Gastroenterology* 1960; 39:183-190.
28. Jones EA, Young WB, Morson BC, Dawson AM. A study of six patients with hypertrophy of the gastric mucosa with particular reference to albumin metabolism. *Gut* 1972; 13:270-277.
29. Russell IJ, Smith J, Dozois RR, et al. Ménétrier's disease: effect of medical and surgical vagotomy. *Mayo Clin Proc* 1977; 52:91-96.
30. Smith RL, Powell DW. Prolonged treatment of Menetrier's disease with an oral anticholinergic drug. *Gastroenterology* 1978; 74:903-906.
31. Albo RJ, Peters HE, Williams RR. Giant hypertrophic gastritis. *Am J Surg* 1973; 126:229-234.

32. Frank BW, Kern F Jr. Menetrier's disease. *Gastroenterology* 1967; 53:953-960.
33. Brooks AM, Isenberg J, Goldstein M. Giant thickening of the gastric mucosa with acid hypersecretion and protein-losing gastropathy. *Gastroenterology* 1970; 58:73-79.
34. Scott HW Jr, Shull HJ, Law DH IV, Burko H, Page DL. Surgical management of Menetrier's disease with protein-losing gastropathy. *Ann Surg* 1975; 181:765-777.
35. Walker FB IV. Spontaneous remission in hypertrophic gastropathy (Menetrier's disease). *South Med J* 1981; 74:1273-1276.
36. Editorial: Menetrier's disease. *Br Med J* 1979; 1:150.
37. Overholt BF, Jeffries GH. Hypertrophic, hypersecretory, protein-losing gastropathy. *Gastroenterology* 1970; 58:80-87.
38. Li AKC, Schattenkerk ME, deVries JE, Ross JS, Malt RA. Saliva as a modifier of dimethylhydrazine-induced colorectal cancer. In: Malt RA, Williamson RCN, eds. *Colonic Carcinogenesis*, Falk Symposium 31, MTP Press: Lancaster, 1982, 261-274.
39. Heitz PU, Kasper M, Van Noorden S, Polak JM, Gregory H, Pearse AGE. Immunohistochemical localization of urogastrone to human duodenal and submandibular glands. *Gut* 1978; 19:408-413.
40. Elder JB, Williams G, Lacey E, Gregory H. Cellular localisation of human urogastrone/epidermal growth factor. *Nature* 1978; 271:466-467.
41. Gregory H, Walsh S, Hopkins CR. The identification of urogastrone in serum, saliva, and gastric juice. *Gastroenterology* 1979; 77:313-318.
42. Marks MP, Lanza MV, Kahlstrom EJ, et al. Pediatric hypertrophic gastropathy. *Am J Roentgenol* 1986; 147:1031-1034.
43. Snider TG III, Ochoa R, Williams JC. Menetrier's disease: pre-type II and type II ostertagiosis in cattle. *Am J Pathol* 1983; 113:410-412.
44. McKellar Q, Duncan JL, Armour J, et al. Further studies on the response to transplanted *Ostertagia ostertagi* in calves. *Res Vet Sci* 1987; 42:29-34.
45. van der Gaag I. Hypertrophic gastritis in 21 dogs. *Zbl Vet Med A* 1984; 31:161-173.
46. Kelly DG, Miller LJ, Malagelada J-R, et al. Giant hypertrophic gastropathy (Ménétrier's disease): pharmacologic effects on protein leakage and mucosal ultrastructure. *Gastroenterology* 1982; 83:581-589.
47. Krag E, Frederiksen H-J, Olsen N, Henriksen JH. Cimetidine treatment of protein-losing gastropathy (Ménétrier's disease). *Scand J Gastroenterol* 1978; 13:635-639.
48. Reinhart WH, Weigand K, Kappeler M, et al. Comparison of gastrointestinal loss of alpha-1-antitrypsin and chromium-51-albumin in Ménétrier's disease and the influence of ranitidine. *Digestion* 1983; 26:192-196.
49. Krol TC, Isenberg JI. Remission in a patient with Menetrier's disease: spontaneous or induced by treatment? *J Clin Gastroenterol* 1985; 7:161-168.
50. Gustavsson S, Kelly KA. Total gastrectomy for benign disease. *Surg Clin NA* 1987; 67:539-550.
51. Herfarth C, Schlag P, Buhl K. Surgical procedures for gastric substitution. *World J Surg* 1987; 11:689-698.
52. Olbe L, Lundell L. Intestinal function after total gastrectomy and possible consequences of gastric replacement. *World J Surg* 1987; 11:713-719.
53. Troidl H, Kusche J, Vestweber K-H, et al. Pouch versus esophagojejunostomy after total gastrectomy: a randomized clinical trial. *World J Surg* 1987; 11:699-711.
54. Wijngaards G, Jespersen J. Fibrinolytic activity of the gastric mucosa in Ménétrier's disease. *Eur J Clin Invest* 1983; 13:347-350.
55. McDermott VG, Connolly CE, Finnegan P, O'Gorman T. Menetrier's disease presenting with deep venous thrombosis, iron deficiency anaemia, and early evolution to atrophic gastritis. *Irish J Med Sci* 1986; 155:53-54.
56. Polga JP, Spencer RP. Menetrier's disease with occlusion of splenic and brachial arteries. *Clin Nucl Med* 1982; 7:526-527.
57. Brown LF, Chester JF, Malt RA, Dvorak HF. Fibrin deposition in autochthonous Syrian hamster pancreatic adenocarcinomas induced by the chemical carcinogen N-nitroso-bis(2-oxopropyl)amine. *J Natl Canc Inst* 1987; 78:979-986.
58. Rotstein J, Sarma DSR, Farber E. Sequential alterations in growth control and cell dynamics of rat hepatocytes in early precancerous steps in hepatocarcinogenesis. *Cancer Res* 1986; 46:2377-2385.
59. Pozhariski KM. The significance of nonspecific injury for colon carcinogenesis in rats. *Cancer Res* 1975; 35:3824-3830.