SPANDIDOS PUBLICATIONS

Pathophysiology and modern treatment of ulcer disease (Review)

G.E. HOLLE

Gastrointestinal Research Laboratory, University Policlinic,
Pettenkoferstrasse 8a, D-80336 Munich, Germany

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Abstract. This is an overview of the pathophysiological abnormalities of gastroduodenal (GD) ulcers [duodenal ulcer (DU), gastric ulcer (GU) and Dragstedt ulcers (combined DU and GD)], as well as the effects of the different treatments (surgical, medicinal and physiological) described since the introduction of stomach resections. The intention is to demonstrate whether the peptic ulcer diseases are a homogeneous entity with a characteristic pathophysiology or whether they represent the final expression of many heterogeneous causes including impairment of upper gastrointestinal motility. The review also asks whether DU and GU have a common or different pathogenesis and whether ulcers in the stomach might be predominantly due to impaired mucosal resistance and the DU to gastric hypersecretion. The symptoms of both diseases are also compared with the findings in the normal controls.

Contents

1. Introduction

In recent years the hospitalization rate for duodenal ulcer (DU) has decreased by 43%, that for gastric ulcer (GU) by 8% and mortality by ca. 62%. At first sight these figures might suggest that the disease as such is dying out. This is an illusion based to some extent on improvements in diagnosis, therapy and control of complications (1).

Direct incidence studies in the USA and Denmark show that ulcer occurrence is unchanged, i.e., 10% of men and ca. 5% of women in the Caucasian western population are expected to have some form of ulcer disease during their lifetime. This unchanged trend is genetically programmed: 30-59% of ulcer patients have a positive family history in contrast to 5-15% of control persons (2-5). DU and GU follow separate genetic pathways. We owe this information almost entirely to the teams attached to the Center for Ulcer Research and Education of the University of California, Los Angeles, CA (1). Irrespective of the nature of the triggering noxa the leading symptom of ulcer disease, the lesions of the mucosa, is always preceded by a change in the permeability of the mucosal epithelium, which, with a lowering of the transepithelial electric potential difference (PD) and resistance (R), allows re-diffusion of H^+ ions in damaging concentration. The extent and course of the lesions are linear functions of the concentration and duration of the noxious effect (4,5).

In 1977 Silen (6), showed that the instillation of 120 mM acid over 30 min or a pH of 2.25 for 6 h in the gastrointestinal lumen led in 100% of tests to serious exulceration. The same amount of acid produced by stimulation led to an exulceration rate of only 10%. Silen compared the first trial condition to the interdigestive motility state in DU (7). This suggests that in ulcer disease several factors have to occur together in order to trigger a recurrence of the peptic lesion. On the one hand there are aggresors such as pepsin and acid, on the other the mucosal resistance (8). Equally important are the mechanisms that bring about the exposure necessary for damage to occur (9).

What are the changes brought about by stimulation that protect the gastric mucosa? It normally activates epithelial mucus and bicarbonate production. This is pronounced in ulcer patients, particularly in gastroduedenal (GD) type. However, in these patients the genetically induced changes in the gastrointestinal motility (9) and also the alterations in the chemical composition of the mucus with the increased low-molecular glycoproteins are pathological (10), as proteolytic decomposition from the lumen and H^+-ion rediffusion are favored.

Stimulation normally influences gastric blood flow. It is known that no necrosis develops when there is a 4-fold

Correspondence to: Dr G.E. Holle, Gastrointestinal Reseach Laboratory, University Policlinic, Petterkoferstasse 8a, D-80336 Munich, Germany
E-mail: hollegresearch@aol.com

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increase in flow or when the mucous membrane is perfused with pure O^2 (11). In comparison, when the mucosal blood flow is reduced subliminal noxae cause an increase in H^+-ion rediffusion and extreme damage to the mucosa (11). There is, however, no ulcer without acid (7,12,13). In DU and GU the lower limit of acid stimulation is 10 mEq/h. Some 50-70% of DU are hyperacidic with a 50% increase in the maximal acid output MAO. The cephalic phase also brings an increase in secretion response of 50-70% (13).

Basal hypersecretion of +110% is very important. There is no ulcer with basal achlorhydria. This, too, is hereditary, as is the hyperpepsinogenic production, which in both kinds of ulcers has a higher increase than the acid (14,15), with stimulation over 100% compared to the norm (16). The hypersensitivity of the chief and mucous neck cells is reflected in the requirement of only one-third of the normal pentagastrin dose for half-maximal response (D50). For acid the D50 requires three quaters of the normal dose and is pathological in only a few patients, indicating that every case of hyperacidity is accompanied by greatly increased pepsin and that many normosecretors still have high levels of pepsin. In 60% of DU hyperpepsinogenemia I is also present, which correlates closely with the acidity and is of autosomal dominant inhertance in the majority of cases. Secretion behavior is not dependent on age, onset or duration of the illness, family history or the activity and progress of the ulcer.

It is widely accepted that the hypersecretion is caused by an increase in the mucosal capacity to secrete acid and pepsinogen (17,18). Cox counted the parietal cells (PCs) in necropsy material and calculated this as 1.8 billion for the DU which represents a PC hyperplasia of 62%. The cell count for the smaller GU is 0.8 billion. We were able to show (19,20) that the density of the PC population is increased in both diseases: on average +44% in GU and +47% in DU, with hypersensitivity of pepsinogen and, to a lesser extent, acid production. Two factors play a role: enlargement of the secretory capacity and the numbers of the of PCs and chief cells with specific receptors, e.g., gastrin receptors (21-23), muscarinic-cholinergic receptors and receptors of the secretin group, e.g., VIP for pepsin (24). The basal serum gastrin levels are normal in ulcer patients. Possibly gastrin-17 has an effect here (25,26).

We found that gastrin immunoreactive cells were within the normal range in the antrum of 96% of DU and 84% of GU patients before every therapy (27,28). However, in some patients gastrin cells are hypersensitive to stimulants, particularly food.

In addition, in 70% of ulcer patients reduced inhibitory sensitivity of gastrin cells to luminal acid disturbs the autoregulation mechanism. This is particularly noticeable in the second part of the secretory response. In the majority of the patients this disturbance is also of autosomal dominant inheritance (5).

Chronic gastritis is a dynamic pathological process classified into three subtypes: A, B and AB. Type A also termed 'pernicious type', is an agetypical form with corpus gland atrophy and has autosomal dominant inheritance, as family history analyses show. In gastric carcinoma there are two genetically different etiopathological types. In carcinoma of the proximal stornach the gastrin cells are reduced by 20-70% in the antrum and the 5-HT (serotonin) - i.r., cells are drastically increased by 200-400% (normal range, 0.25-0.39% of the total cell count) (28).

In addition to the PC increase in the stornach fundus in peptic ulcer there is also a 20% reduction in the histamine-storing mast cells (29). Parallel to this, Lorenz *et al* demonstrated the reduction in histamine tissue and decreased histamine-methyltransferase activity (30).

Epidermal growth hormone, a natural cytoprotector, is secreted in large quantities in Brunner's glands and in salivary glands and their efferent ducts, is stable against all gastric juice proteolytic enzymes, and provides maximum stimulation for mucosal cell proliferation, while at the same time totally inhibiting acid secretion, irrespective of the kind of stimulation. It is the main physiological factor for restorative conservation of the epithelium. The same cells that produce epithelial growth hormone also synthesize the blood group antigen (31-33). Of the latter we know that in a high proportion of GU cases it is not produced at all. This is called 'non-secretor status' and, like the established frequency of blood group 0 in DU, is a hereditary symptom (5). In spite of the morphological link between the two factors, pathological deviations in synthesis and function of epithelial growth hormone in ulcer disease are not yet fully ascertained, although the clinical dysfunction of this hormone, non-inhibition of acid, is evident.

Similar problems occur in connection with genetic dysfunction of the prostaglandins. We have long known that prostaglandin E_1 (PGE) inhibits gastric acid secretion, stimulated by histamine, gastrin, 2-deoxyglucose, carbachol and food in the dog. The mechanism of this inhibition has not been fully elucidated, but activity against a wide range of stimulants indicates an action of mucosal blood flow (32,33). Adenosin monophosphate (cyclic AMP) in contact with histamine may be involved. Despite this, it is believed that in ulcer pathogenesis prostaglandins act by regulating the blood flow. PGE reduces mucosal blood flow and inhibits acid secretion. Exogenically applied prostaglandins also do not confer cytoprotection, as Ito *et al* demonstrated (34). Genetic abnormalities are present in the transport functions of the upper gastrointestinal tract and pylorus (35,36).

Accelerated stomach emptying in DU has long been known. Changes in the pylorus in many DU patients makes the extent of the autosomal dominant hereditary disturbance difficult to calculate. The underlying cause is loss of the vago-vagal duodeno-antral inhibitory reflex, which in healthy people is activated by acidification of the duodenum and leads to a temporary cessation of contractile antral motility. In DU patients this loss results in the overacidified stomach contents being propelled into the duodenum (37-39). Another faulty mechanism is found in the interdigestive motility of the upper gastrointestinal tract. In DU maximum acid secretion also occurs in the interdigestive phase at night as weIl as during the day. The propulsive phase II is greatly prolonged at the expense of the resting phase I of the interdigestive complex, and shows irregular, intensified contractions (40-42). The already overacidified fasting secretion is thus emptied almost throughout the interdigestive period into the bulbus duodeni, which has the motor function of a reservoir. A rise

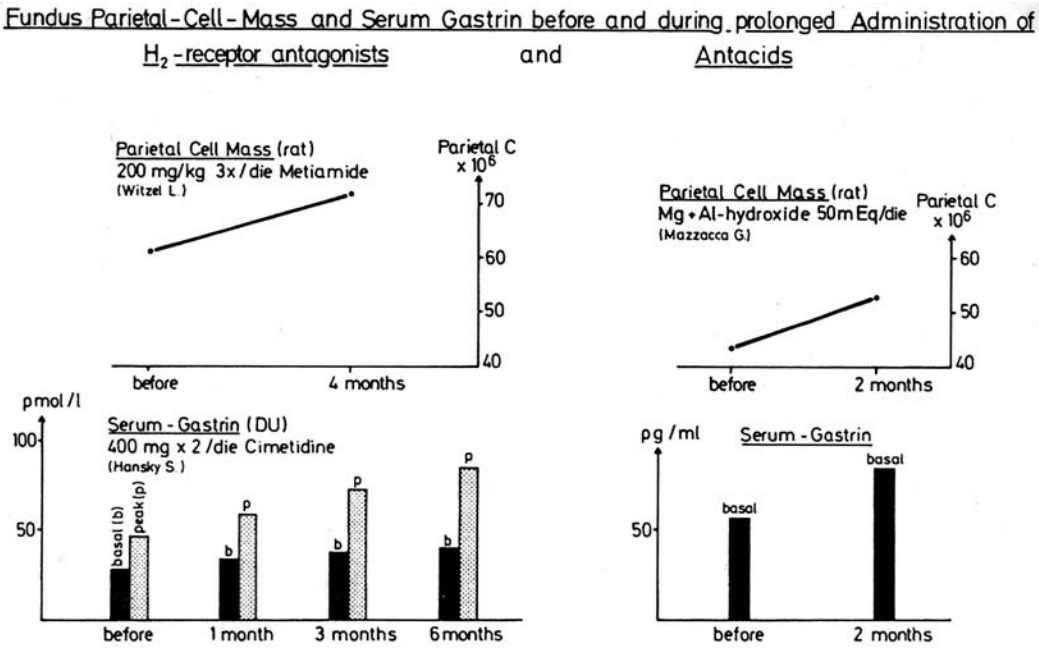

Figure 1. Fundus parietal cells combined with serum gastrin during prolonged medical administration: H_2-antagonists (left side) and antacids (right side) (85-87).

in pH is only possible in the following short phase III (MMC, migrating motor complex). At the same time, in DU the retrograde contractile activity in the middle section of the duodenum is abnormal, as the retropulsive peristaisis type 2 waves (up to 5 mmHg) are greatly reduced (41,42). This is precisely the motility that under normal conditions propels bicarbonate from the duodenum back into the bulbus, so neutralizing it. In DU the bulbus is permanently under-neutralized in the entire fasting period, although secretin and bicarbonate production is inceased (41,42).

In contrast, in GU the type 2 peristaltic waves in the middle duodenum are significantly increased. The intensified retrograde peristaisis with the weakened pyloric tone and reduced antral motility in UV leads to increased bilious and pancreatic reflux into the stomach (43). This, in association with the increased pepsin output has been postulated to be the key injurious factor causing gastric ulcer (43).

As seen from the multiple pathological symptoms in peptic ulcers, the disease is polygenetically programmed with inborn errors in the innervation of the gastrointestinal tract, where mucosal protection is also locally weakened and the stomach secretion faulty. Whatever form it takes, treatment must therefore be symptomatic, whereby precedence must be given to the best method of controlling the cardinal symptoms. In this disease not only are individual functions disturbed but they are also wrongly coordinated, and the system is incorrectly programmed, resulting in physiologically inappropriate patterns of secretion and motility. If one defect, e.g., gastric hypersecretion is corrected, the system spontaneously tries to compensate this, e.g., by continuously increasing G-cell mass over the years (Fig. 1).

The ultimate goals of peptic ulcer treatment are elimination of pain, healing of ulceration (mucosal inflammation and heartburn) and prevention of ulcer recurrence. Pharmacological intervention has been mainly directed at the suppression of peptic acid activity. Serious attempts have also recently been made to develop drugs to enhance mucosal resistance and to try to eliminate bacteria.

2. Antacids

Antacids - the first such agents were antacids (44-46). Postprandial acid output after antacid ingestion was significantly increased by an average of 16%; the level of gastric juice also rose (46). Other side effects were increase in gastrin release, gastric secretion, gastric emptying rate and duodenal acid load. Twenty-five percent of patients suffered from diarrhea, some from duodenogastric reflux (47-49). Multiple receptors showed interactions: H_2 receptor, gastrin and acetylcholine receptor and carbamyl-choline interact (49) and seem to sensitize cells like gastrin cells (Fig. 1). The goal of antacid treatment is to raise the pH to 3.0 as gastric content end-point, to reduce the load of acid delivered into the duodenum, and to reduce pepsin activity by lowering conversion of pepsinogen into pepsin. The bile-acid-binding properties in the duodenum increase gastric reflux and play a pathogenic role in GU. The four types of antacids: calcium, carbonate, and magnesium and aluminium hydroxide all require evaluation of the speed with which an antacid combines with acid. Alteration in bowel movement is frequently combined with constipation.

3. Pirenzepine

Anticholinergics (pirenzepine) (22,50). Based on the role of the vagus nerve in stimulating acid and pepsin secretion mediated by acetylcholine (51), pirenzepine a benzodiazepine with structural similarities to tricyclic compounds, but without activity on the central nervous system, was developed as a drug against peptic ulcer disease. Mucosal permeability to hydrogen ions and the gastric mucosal barrier are not affected by anticholinergic drugs (e.g., atropine).

Optimal dosage of pirenzepine inhibits basal and pentagastrin-stimulated gastric acid secetion by decreasing the total volume of secretion but with little change in the pH. Basal and nocturnal acid output are reduced by 40-50% and maximal acid output by 30-40% (52). A high dose is required to produce a significant delay in gastric emptying. Endogenous gastrin release in response to a meal is slightly increased by anticholinergics. This effect is not observed if the pH is maintained at a constant level. The bile-acid binding properties in the duodenum increase gastric reflux and play a pathogenic role in GU. After cessation of the treatment, gastric secretion returns to a control level after 48 h (53).

4. Histamine H_2-receptor antagonists

Cimetidine (54-56). This drug is equally effective against stimulation of acid output by histamine, pentagastrin and insulin. Pepsin output is reduced secondarily to reduction of volume and to reduction in acid. Both are similarly effective in GD and DU. Cimetidine is independent of or less sensitive to histamine. Gastrin release is enhanced during prolonged treatment and chronic pH changes. A dose of 300 mg reduced nocturnal acid output by about 80-90% for as long as 7 h (57-59). After long-term treatment with cimetidine there is an increase in antral pH and inhibition of acid feedback on gastrin release, and an increase in parietal cell hyperplasia. H_2-receptor antagonists increase transmucosal potential difference without affecting active transport of sodium or chloride (60,61).

At a very early date Domschke *et al* (62,63) described a drug called ranitidine. Ranitidine does not contain the imidazole nucleus of histamine, which was previously regarded as essential for the effect. The reduction of pepsin output is proportional to the reduction in gastric volume, as with cimetidine, but the action lasts longer than that of cimetidine.

Cimetidine 1.5 μg/kg/h intravenously and 100 mg/h in the second hour brings down basal acid-secretion to ~0. Blood-flow in the mucosa is reduced and pepsin significantly decreased.

Cimetidine is equally effective applied orally and absorbed from the small intestine (73%) with a peak blood level after 60-90 min. Acid output is reduced for 7 h by 300 mg nocturnal application.

5. *Helicobacter pylori*

Several years ago interest was centered on a spiral gram-negative bacterium. It has unique cellular fatty acid output and an ultrastructure different from other campylobacters (64). It colonizes the mucosa of the upper gastrointestinal tract of >84% of the human population. This bacterium was named *Helicobacter pylori* because it is also observed in the minority of people suffering from peptic ulcer disease with inflammation of the duodenal and gastric mucosa which predisposes to peptic ulceration at those sites, produces powered urease enzymes, which tolerate acid secretion, and large amounts of extracellular catalase. It is also believed to cause metaplasia in gastritis and implies a high risk for gastric cancer (65-68).

The majority of the *Helicobacter pylori* bacteria live freely in colonized hosts, but ~20% are believed to bind gastric epithelial cells. This colonization is highly specific *in vivo* when it overlays islands of gastric metaplasia (69). The interaction of these bacteria with the epithelial cells plays an important role in the pathogenesis of cancer risk. Loci have been identified the mucosa in which people harboring particular alleles which have different risk of disease, and *Helicobacter pylori* should have the capacity to interact with those molecules that induce epithelial response with carcinogenic potential. *Helicobacter pylori* is well characterized as determining the 'cag' pathogenicity island (cag PAI), a multigene locus.

It induces gastritis augmenting the risk for atrophie gastritis and distal gastric cancer. In most people, however, it remains asymptomatic. It would be useful to identify a few people with high risk, because they could serve as a paradigm for the chronie role of inflammation in the genesis of malignancies that arise in the gastrointestinal tract.

Helicobacter pylori is not the only organism that is believed to cause active chronie gastritis in man. Other infections with spiral organisms have been described (70,71). Antibody to *Helicobacter pylori* was measured by ELISA in sera of patients and in gastric biopsy specimens (72,73). Colloidal bismuth subcitrate (CBS) combined with tinidazole in patients sensitive to nitroimidazole eradicates most *Helicobacter pylori* organisms. Ulcers recur less often than in patients who retain *Helicobacter pylori* in the upper gastrointestinal tract over 12 months. The US Food and Drug Administration has approved the first two combination therapies to eradicate *Helicobacter* (66) (Table I).

The bacillus is sensitive to penicillin, erythromycin, cephalosporins, gentamycin, tetracycline and bismuth citrate (74,75). Ranitidine has been combined with bismuth citrate (RBC), clarithromycin or amoxycillin. In 70% of patients the peptic ulcer healed within 4 weeks, but only 41-48% of the *Helicobacter* organism were eradicated. In a randomized study of 900 patients with peptic complaints an average of 75% of those given the combination of omeprazole plus clarithromycin, had *Helicobacter* eradication, but at 6 months 30% in one study and 52% in another had ulcer recurrence. In a third study at final analyses after 4-6 weeks 50-70% of ulcers had not healed (66). In Germany, recently the therapy has consisted of a combination of pantoprazol for acidity and heartburn, amoxycillin and clarithromycin as antibiotics to eradicate the *Helicobacter pylori*. If the ulcer does not heal promptly, pantoprazol alone can be continued. The healing rate of around 40-50% in duodenal ulcers at 1 year after discontinuation of treatment is similar to that in all the conservative regimes.

The healing time may be shortened with multiple drug combinations and when *Helicobacter pylori* is completely eradicated. However, there is no influence with respect to peptic ulcer relapse or the different types of mucosal inflammation or recurrence. The side effects of combined drug regimens are those of all the individual drugs, but this topic is not discussed here.

Table I. Therapeutic efficacy in medical and surgical treatment of duodenal ulcer (DU).

	Healing rate in (%)						
	Natural history (%)	Placebo (%)	Antacids Al-Mg (144 mEq of buffering)	Anticholinergics pirenzipine (75 mg/die) (100-150 mg/die)[a] (%)	H_2-receptor antagonists cimetidine (3x200-400 mg/die) ranitidine (200-300 mg/die)	*H. pylori* 0-100% bismuth RBC 400 mg/ 2x daily omeprazol 40 mg clarithromyzine 500 mg 3x/day-4 weeks	Surgery SPV+ pyloroplasty with/without ulcus exc. (%)
4-6 weeks		30-60	~70% no loss of pain diarrhea	55 70-87	70-85% cimetidine 80-92% ranitidine	70% healed *H. pylori* ~82% eradicate	~97.6
1 year and more under treatment		37-42		63	~75% cimetidine ~80% ranitidine	RBC + 2x/day 1-2 antibiotics ~30-60%	
1 year discontinuation of treatment	40-50	40-50	40-50	40-50	40-50	40-50% Hp. eradicate?	97.6
Refs.	Bardam (61) Malmros and Hierton (56)		Peterson *et al* (46) Ippoliti *et al* (47) Ström *et al* (48)	Sonnenberg *et al* (52) Bianchi-Porro *et al* (51)[a]	Binder *et al* (54) Brogden *et al* (55) Korman *et al* (62) Hetzel *et al* (57)	Barnett (66) Marshall *et al* (68)	Holle and Holle (76) Holle (27)

Medical treatment of peptic ulcer aims to decrease acid secretion and in parallel increase parietal and gastrin cells in DU and GU. Surgical treatment (SPV+pyloroplasty) durably decrease acid secretion and decline parietal cells in DU+GU.

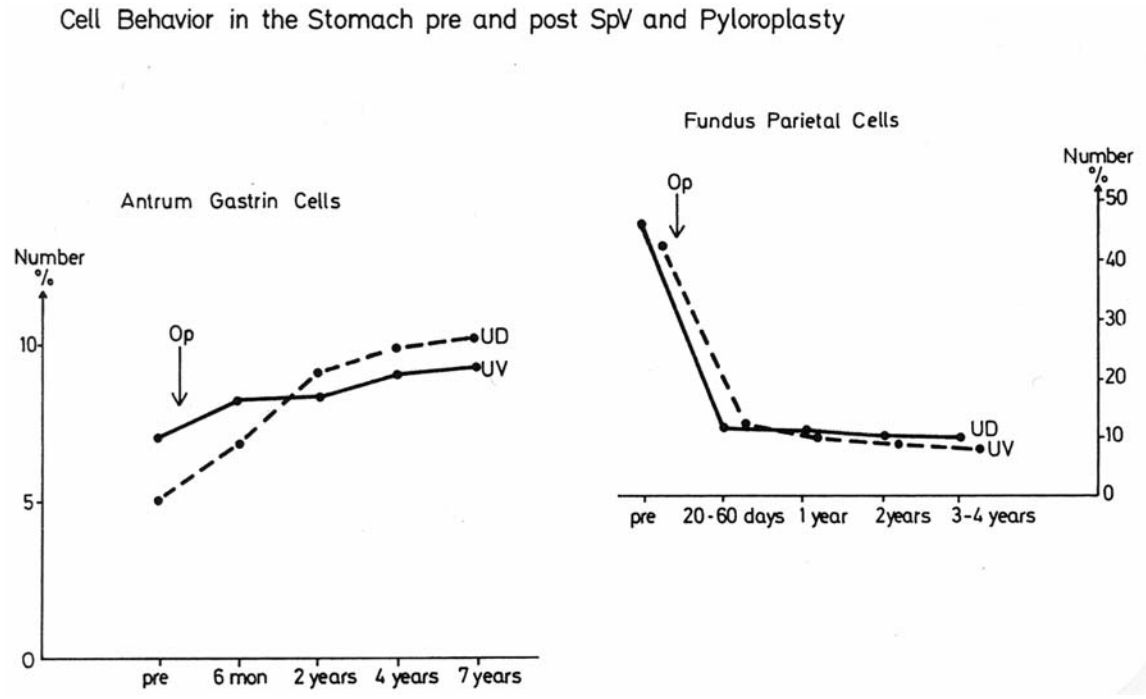

Figure 2. Cell behavior in the stomach pre and longterm post-SPV and pyloroplasty in gastrin-cell count in the antrum and and parietal-cell count in the fundus in GU and DU.

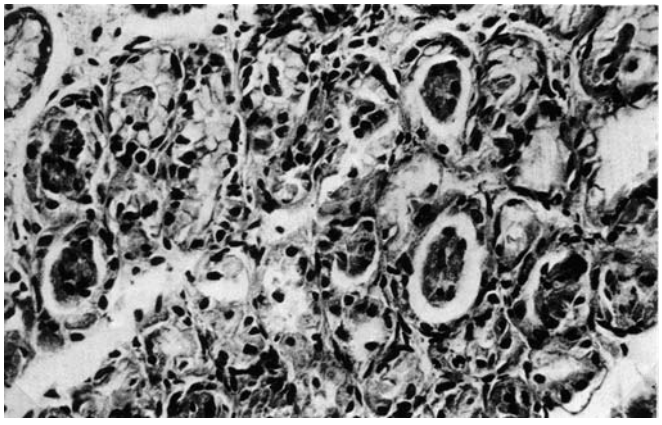

Figure 3. Parietal cell detritus and whole parietal cells in fundic glandular lumina in DU early after SPV and pyloroplastic. (Stain/HE).

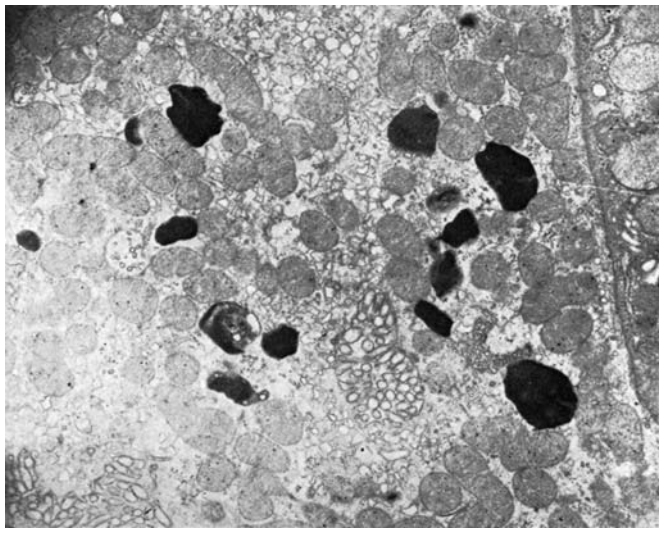

Figure 4. Parietal-cell with fat droplets in the degenerated cytoplasm in DU after SPV and pyloroplasty. (Prof. F. Miller, Inst. f. Zellbiol.).

6. SPV and pyroloplasty

Between 1964 and 1982 at Munich Surgical Clinic we treated 1407 duodenal and 308 gastric ulcers, by non-resecting means, with selective proximal vagotomy (SPV) and pyloroplasty of form and function either submucous or open or with resection, and if necessary, with ulcer excision (76). The following results were achieved over a period of 5-7 years postoperative1y by examination combined with endoscopy and biopsy from the fundus and antrum, preoperatively, and then postoperatively, at 11 days, 45 days and from then on annually. Clinically 89% of the patients showed reduction of the basal acid output (BAO) by 90%, of maximal acid output (MAO) by 75%, and a decrease in the mucosal postoperative diameter of 21% despite a significant increase in chief cells. There was amelioration of pain in 90% of cases, weight increase in 75% (from 1 to 15 kg), dumping in 1.8%, diarrhea in 2%, recurrence in 2.7% of DU, and 7.3% of GU, and mortality was 0.5% (76) (Fig. 2). Biopsy specimens from fundus and antrum mucosa were examined preoperatively and postoperatively (77,78): chief cells (CH), parietal cells (PC), mucus neck cells (MNC), enterochromaffin cells (EC), gastrin cells (GC), and somatostatin i.r., D-cells (DC) were differentially stained and counted in the Leitz Ortholux II microprojector, outlined and determined in areas of a total of ~8000 gland cells (24,27). The preoperatively increased PCs by 30-60% over normal levels, in peptic ulcers decreased in

 postoperatively: in DU by 74.2% and in GU by (19,20). The energy metabolism of the PC mitochondria, as measured by absorption photometry of succinate-dehydrogenase activity with TNBT (Nachlass), was also significantly reduced postoperatively (79). Early after operation, increased PC detritus and whole PC were seen in the lumen of the glands (Fig. 3) and fatty droplets, showing degeneration, were visible in the cell plasma on electronmicroscopy (Fig. 4). Accompaning our cell count results, Lehy *et al* (80,81) investigated PC cell kinetics.

Following SPV and pyloroplasty the GC in the stomach antrum increased by up to 10% in DU and up to 16% in GU (Fig. 2), preoperative maximum 7% GC, and the peptic cells (chief cells and not MNC) in the stomach also increased continuously during the following years after surgery.

The inflammation seen preoperatively in the fundus ventriculi was not seen postoperatively in either DU or GU. The patients were mostly without drug medication post-operatively.

Despite the morphological changes after SPV plus pyloro-plasty as sole treatment, the acid secretion remains greatly reduced over the following years, and the fate of recurrence of uncomplicated DU and GU is low at 2.4%, over 4 years. Pharmacological intervention is usually not necessary. The complication rate of the SPV operation is zero. Motility disturbancies were without serious clinical signs (35). The outcome of this therapy depends on the skill of the surgeon.

Knowledge of the gastrointestinal system, particularly its innervation, has been greatly extended in recent decades and it has become clear that not only the vagus nerve and its sympathetic counterpart are responsible for the multiple deficiencies in motility and metabolism seen in peptic ulcer disease. These may also be triggered by extrinsic, intramural and serotoninergic, purinergic and various peptidergic transmitters (82). Together, these represent a kind of 'vegetative brain' (83), which regulates the gut functions. We do not know the underlying neurogenic causes of the frequent hereditary failures today, but they may extend back as far as to the neural crest (84). Our therapeutic efforts in the case of multifactorial polygenetic disorders, such as peptic ulcers, can only be directed against the various individual symptoms which are certainly not based on a simple infection which is expressed in the pathophysiology of the disease.

Acknowledgements

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