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Relationship Between Diseases of the Pancreas and Hyperplasia of Brunner's Glands

M. Stolte, H. Schwabe, and H. Prestele

Pathology Institute (Director: Prof. V. Becker) and the Institute for Medical Statistics and Documentation (Director: Prof. L. Horbach) of the University of Erlangen-Nürnberg, Krankenhausstrasse 8–10, D-8520 Erlangen, Federal Republic of Germany

Summary. Examination of 105 duodeno-pancreatectomy specimens showed that 75.7% of the cases of chronic pancreatitis ($n=74$) manifested diffuse hyperplasia of Brunner's glands. In pancreatitis involving part of the pancreas in the presence of ducts of the embryonic type ($n=6$), in segmental pancreatitis ($n=16$), and in pancreatic cancer ($n=23$), no significant difference in the thickness of the layer of Brunner's glands was found as compared with normal specimens.

There was no statistically significant correlation between the degree of hyperplasia of Brunner's glands and the degree of scarring of the exocrine pancreatic parenchyma. Nor was there any correlation between existence and extent of scarring of the duodenal wall, inflammatory infiltration of the duodenal mucosa, duration of disease, consumption of alcohol and history of gall stones and ulcers in patients with and without hyperplasia of Brunner's glands. Diffuse hyperplasia of the duodenal glands is probably an adaptive reaction to the exocrine insufficiency of the pancreas or the changes in gastric function (hyperacidity, accelerated emptying of the stomach) caused by chronic pancreatitis. A fact which supports this statement is that the inhibitor hormone urogastrone – an inhibitor of gastric acid secretion – is formed in Brunner's glands. The question is also discussed whether chronic pancreatitis and hyperplasia of Brunner's glands might not also develop simultaneously in the presence of disturbances of the gastrointestinal hormones, themselves either primary or due to alcohol consumption.

Key words: Chronic pancreatitis – Pancreatic cancer – Brunner's glands

Introduction

The "glandulae duodeni" which were described by Brunner (1683, 1687, 1715) and later named after him, were first mentioned almost 200 years after this

Send offprint requests to: M. Stolte at the above address

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first anatomical description (Cruveilhier 1835; Salvioli 1876). Although numerous case reports on tumours and hyperplasia of the duodenal glands have been made, there have been few systematic studies of the diseases and adaptive reactions of these glands. In particular, there have been no studies of the question as to whether and how these glands are affected by pancreatic diseases. Therefore, our examination of duodeno-pancreatectomy specimens was intended to show whether diseases of the pancreas can induce changes in Brunner's glands.

Material and Methods

A total of 105 surgical duodeno-pancreatectomy specimens were examined with the following pathology: Chronic pancreatitis ($n=74$); "divisum pancreatitis", i.e. chronic pancreatitis in only one of the two drainage areas in cases with an embryonic type of duct ($n=6$); carcinomas of the terminal common bile duct ($n=3$), of the papilla of Vater ($n=1$), and the head of the pancreas ($n=19$). In addition there were two specimens in which there was scarring only in the pancreatic area, localized mainly in the region of the common bile duct and without chronic pancreatitis (termed "normal specimens" in the following report).

Methods of Examination

Fixation was by perfusion through the common bile duct and the pancreatic duct and x-ray examination of the ducts in operative specimens was performed. The pancreatic duct system and the lateral part of the duodenum were dissected longitudinally. Histological examination was performed on various sections of the pancreas, the papilla of Vater and of five sections of the duodenum between the duodenal bulb and the major papilla. The stains used were haematoxylin and eosin, Elastica-van-Gieson, Masson-Goldner and PAS-alcian blue.

Hyperplasia of Brunner's gland was graded subjectively (slight, moderate, marked). The thickness of the layer of Brunner's glands (using the average of the measurements of five sections of the duodenum) and the duodenal mucosa was measured with a "Periplan" device manufactured by Leitz. Chronic pancreatitis was classified in accordance with the extent of scarring: Grade I = slight scarring, Grade II = moderate scarring, Grade III = marked scarring, and Grade IV = complete replacement of the exocrine parenchyma. The group of cases with pancreatitis largely or exclusively confined to certain segments ($n=16$) was examined separately. In addition, the cases with postpancreatic pseudocysts ($n=22$) were evaluated irrespective of the degree of scarring of the exocrine tissue. Gradation of scarring of the duodenal wall (slight, moderate, marked); grading of the duodenitis in three degrees of severity in accordance with Maratka et al. (1977).

The following information and clinical data were taken from the case histories available for this evaluation, and related to the degree of hyperplasia of Brunner's glands: (1) alcohol consumption, (2) duration of symptoms, (3) history of gallstones and (4) history of gastric or duodenal ulcers.

Statistical Methods

The Kruskal-Wallis-test was used for the statistical comparison of the separate groups with respect to the existence and extent of hyperplasia in Brunner's glands. Afterwards comparison of the individual groups was made in pairs by the Wilcoxon-test for random samples.

Results

1. Subjective Grading of Hyperplasia in Brunner's Glands

In the two normal cases, the cases of divisum pancreatitis and in the cases of cancer, no hyperplasia of Brunner's glands was ever evident, whereas it

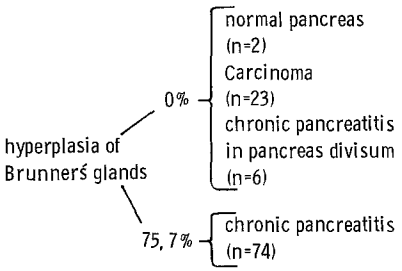

Fig. 1. Schematic summary of the results of the examination of 105 duodeno-pancreatectomy specimens

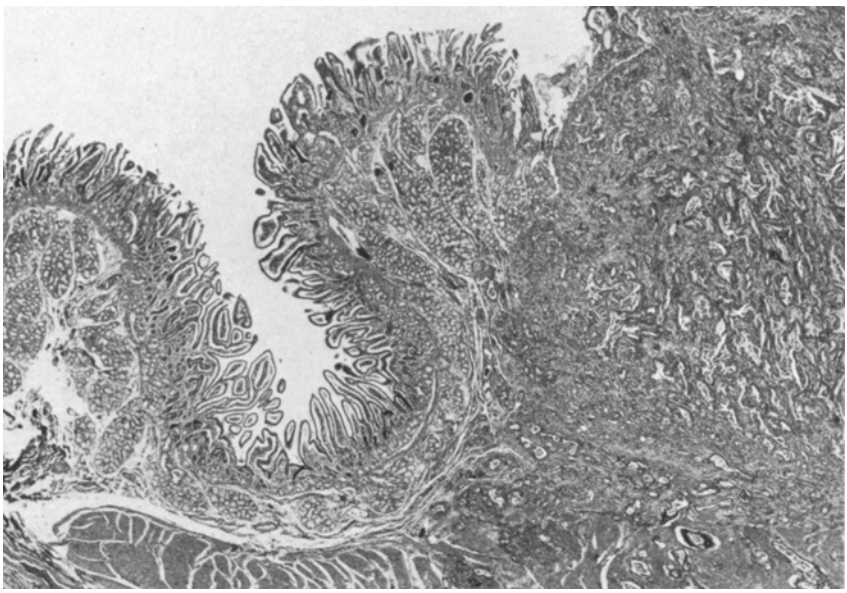

Fig. 2. Carcinoma of the pancreatic head with infiltration of the duodenal wall (on the right), no hyperplasia of Brunner's glands (H & E, magnif. 10 ×)

occurred in 75.7% of the cases of chronic pancreatitis (including segmental pancreatitis) (see Figs. 1 and 2). In 23% of the cases of chronic pancreatitis a slight degree in hyperplasia was seen, in 30% a medium degree and in 32.4% there was extreme hyperplasia (see Figs. 3 and 4). In all cases the hyperplasia was distributed diffusely from the duodenal bulb to the papilla of Vater. No circumscribed nodular or adenomatous hyperplasia was evident.

2. Morphometry and Statistics

The measurement of the thickness of the layer containing Brunner's glands shows that they manifest no hyperplasia in cases of cancer or divisum pancreatitis (see Table 1). In segmental pancreatitis the layer is, on average slightly, but not significantly, wider than normal.

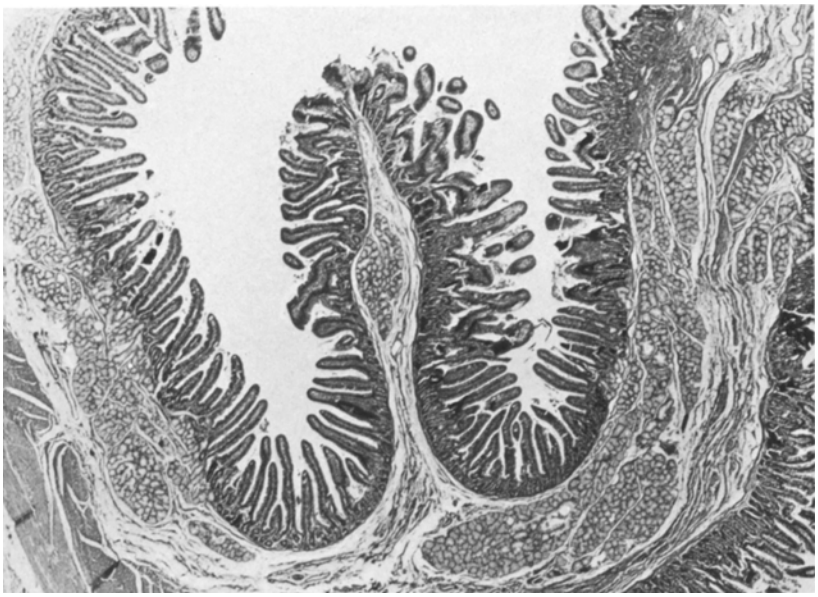

Fig. 3. Duodenum in chronic pancreatitis with slight hyperplasia of Brunner's glands (H & E, magnif. 10×)

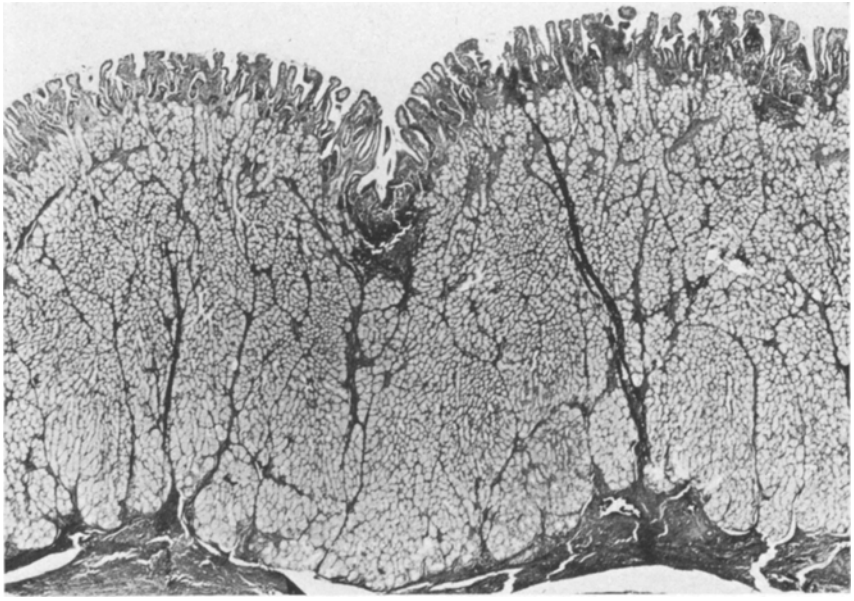

Fig. 4. Duodenum in chronic pancreatitis with extreme hyperplasia of Brunner's glands (H & E, magnif. 10×)

Table 1. Mean values ($\bar{x}$), variance ($s\pm$), minimum- (min) and maximum-values (max) for the thickness of the layer of Brunner's glands in mm

	n	$\bar{x}$	$s\pm$	min	max
Normal pancreas	2	0.42	0	0.42	0.42
Pancreatic cancer	23	0.43	0.19	0.23	0.98
Divisum-pancreatitis	6	0.50	0.20	0.33	0.82
Segmental pancreatitis	16	0.73	0.26	0.33	1.20
Chronic pancreatitis degree I	10	1.35	1.11	0.39	4.10
Chronic pancreatitis degree II	22	1.77	0.90	0.46	3.93
Chronic pancreatitis degree III	14	2.17	1.07	0.49	4.10
Chronic pancreatitis degree IV	9	1.29	0.88	0.33	2.62
Chbronic pancreatitis degree I+II	32	1.64	0.97	0.39	4.10
Chronic pancreatitis degree III+IV	23	1.82	1.07	0.33	4.10
Pseudocysts	22	1.28	0.92	0.33	4.10

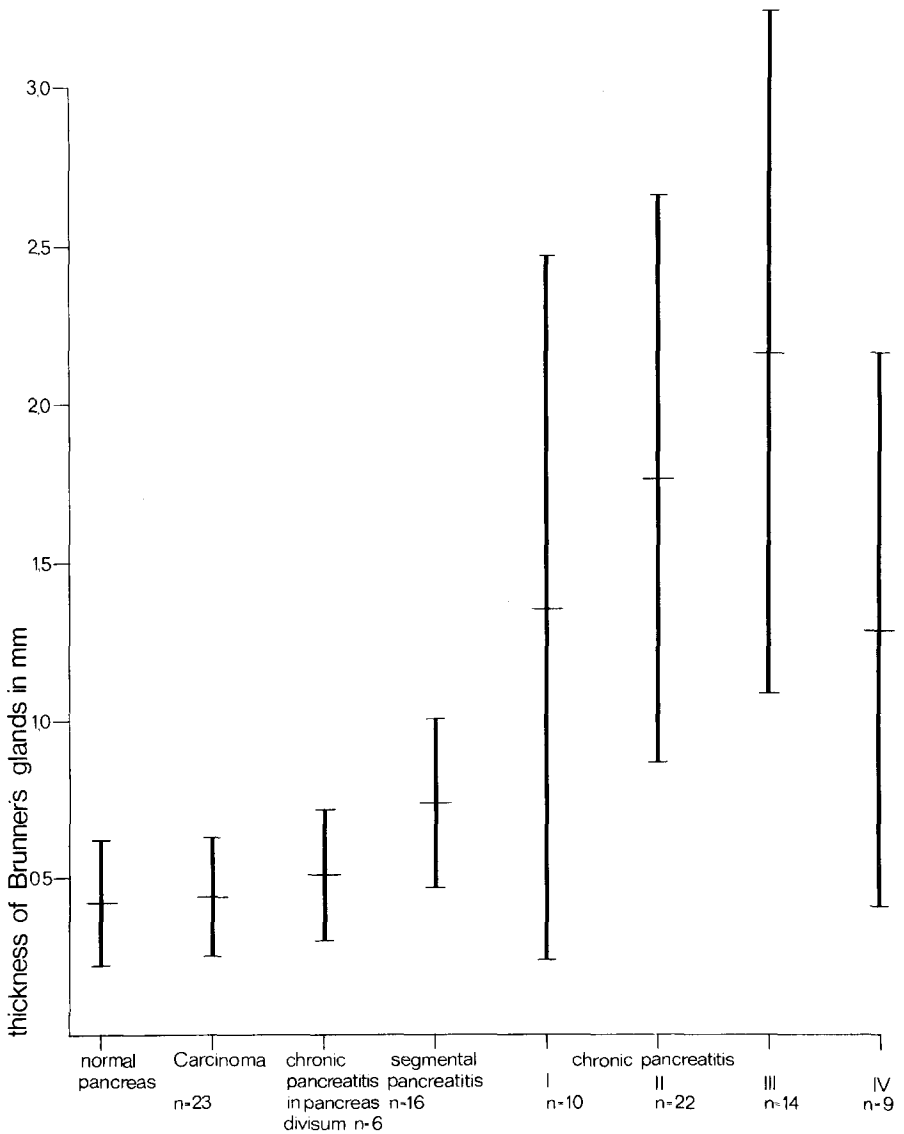

Fig. 5. Thickness of layers of Brunner's glands with median values listed for the individual groups

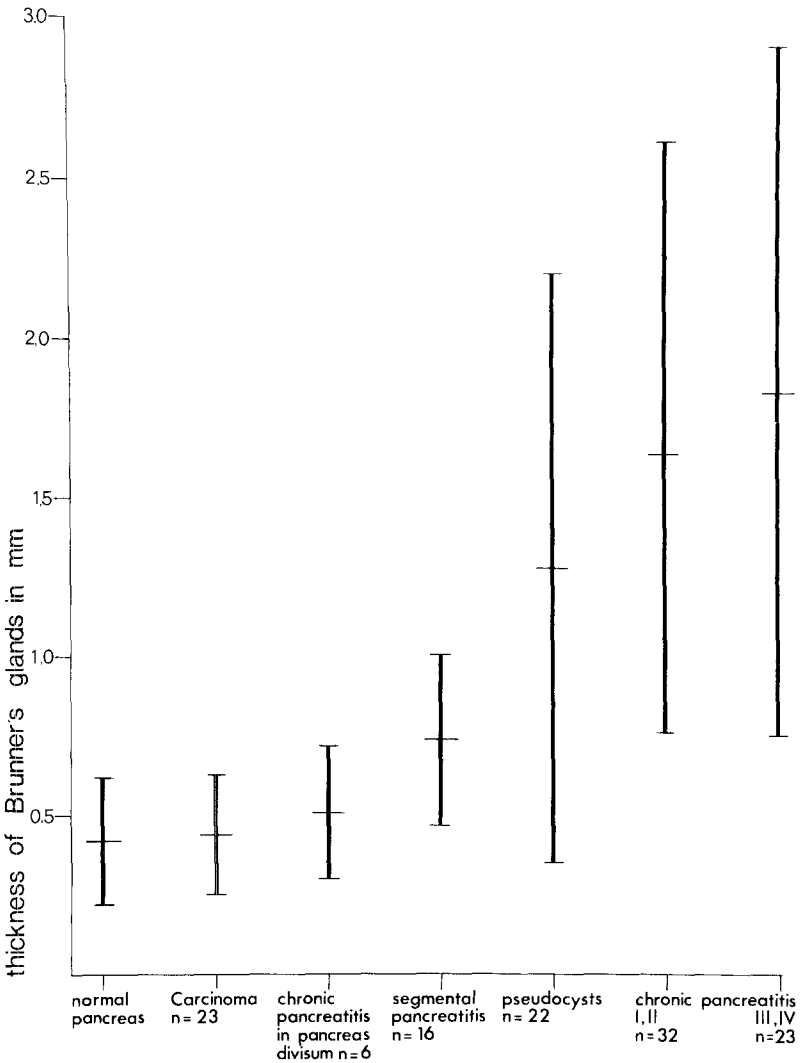

Fig. 6. Significant differences in the thickness of the layer of Brunner's glands existed in the following groups: Normal, carcinoma, divisum-pancreatitis and segmental pancreatitis as compared with chronic pancreatitis grades I–IV and with the postpancreatic pseudocysts

In chronic pancreatitis the mean measurements were clearly above normal, in individual cases the thickness of the layer being increased to ten times the normal. The mean value increases with the degree of parenchymal scarring (see Fig. 5), but in stage IV it is lower again at 1.29 mm. The cases with postpancreatic pseudocysts seen in the group with chronic pancreatitis also showed only moderate hyperplasia of Brunner's glands (see Fig. 6).

The results of the Kruskal-Wallis-test in a comparison of four pancreatitis groups were not significant. The groups of chronic pancreatitis grades I and II and grades III and IV were therefore combined (see Fig. 6). Comparison of these two groups with normal, cancer, divisum pancreatitis and segmental

Table 2. Duodenal wall scarring and duodenitis in several diseases of the pancreas (0=no pathological findings, + =slight degree, + + =medium degree, + + + =high degree)

Duodenal wall scarring	0	+	+ +	+ + +
Normal pancreas Divisum-pancreatitis Segmental pancreatitis Pancreatic cancer	28	10	5	4
Chronic pancreatitis				
a) without hyperplasia of Brunner's glands	2	3	8	4
b) with hyperplasia of Brunner's glands	1	10	15	12
Duodenitis	**0**	**+**	**+ +**	**+ + +**
Normal pancreas Divisum-pancreatitis Segmental pancreatitis Pancreatic cancer	43	3	0	1
Chronic pancreatitis				
a) without hyperplasia of Brunner's glands	13	3	1	0
b) with hyperplasia of Brunner's glands	21	8	3	6

pancreatitis specimens, using the Kruskal-Wallis-test, revealed a statistically significant difference with regard to the degree of hyperplasia of Brunner's glands ($p < 0.01$). In order to specify these difference more precisely, the Wilcoxon-test was done on all pairs of groups. This test also showed a statistically significant difference with respect to the extent of hyperplasia of Brunner's glands between the groups of normal specimens, carcinomas, divisum pancreatitis and segmentary pancreatitis and the groups of cases with varying degrees of chronic pancreatitis ($p < 0.01$).

3. Changes in the Duodenal Wall and Hyperplasia of Brunner's Glands

The existence and extent of duodenal wall scarring and the presence and degree of severity of the inflammatory infiltration of the duodenal mucosa, had no effect on the degree of hyperplasia of Brunner's glands (see Table 2). In the combined group of normal, cancer, divisum pancreatitis and segmental pancreatitis specimens, scarring of the duodenal wall was much less frequent and when present, was only of a lesser degree. The thickness of the duodenal mucosa varied from 0.57 mm to 1.78 mm both in the chronic pancreatitis groups with and without hyperplasia of Brunner's glands, and in the other groups. With regard to these values there were also no statistically significant differences between the individual groups.

4. Clinical Findings

Reliable information on alcohol consumption was available for 102 of the cases. 70.2% of the patients with intact pancreatic parenchyma, divisum pancreatitis, segmental pancreatitis and cancer had a daily alcohol consumption that varied

Table 3. Alcohol consumption of 102 patient with different diseases of the pancreas with and without hyperplasia of Brunner's glands

Alcohol consumption/day	0–80 g	80–160 g	< 160 g
Normal pancreas Divisum-pancreatitis Segmental pancreatitis Pancreatic cancer	33	9	5
Chronic pancreatitis			
a) without hyperplasia of Brunner's glands	9	2	6
b) with hyperplasia of Brunner's glands	24	5	9

between 0 and 80 g. In the group with chronic pancreatitis without hyperplasia of Brunner's glands the percentage was lower at 53.9 (9 out of 17) and in the group of cases with chronic pancreatitis with hyperplasia of Brunner's glands it was 63.1 (24 out of 38). It was not possible to establish a statistically significant difference between these three groups with regard to the intake of alcohol (see Table 3).

There was also no difference between patients with and without hyperplasia of Brunner's glands with respect to duration of the disease, gall stone history and history of ulcers. No information was available about gastric acid secretion, emptying time of the stomach or pancreatic secretion analyses.

Discussion

In man Brunner's glands are located almost exclusively between the pylorus and the papilla of Vater, being found only sporadically distal to the papilla (Robertson 1941; Landboe-Cristensen 1944). They are disseminated within the submucosa, which has a mean thickness of 0.42 mm (Jirko et al. 1974).

The secretion of Brunner's glands contains only small amounts of amylase, peptidase and enterokinase. It is highly viscous, having a mucin content of 0.5%, and less alkaline than pancreatic secretion with a Na_2CO_3 level of 0.09–0.15% (Babkin 1928; Davenport 1971). Thus the secretion of the glands cannot neutralize the acid chyme to any extent and has hardly any digestive capacity. The main function of Brunner's glands is rather, via the mucus they produce, to protect the surface of the mucous membrane of the first part of the duodenum against the acid gastric contents (Florey and Harding 1933, 1935; Landboe-Cristensen 1944; Grossman 1958; Davenport 1971). Recently, however, the glands have also been shown to have an endocrine function. They produce the substance urogastrone, which inhibits the secretion of gastric acid (Heitz et al. 1978).

Brunner's glands are stimulated or inhibited by neural, hormonal and luminal influences. Wright et al. (1939, 1940) found that Brunner's glands are stimulated via the vagus, by severing the splanchnic nerves or preganglionic nerve fibers, and by the administration of eserine (physostigmine). They are inhibited by

atropine and various anaesthetics. Sonnenschein et al. (1947) observed an increase in secretion after meals and following the administration of secretin and intestinal mucosa extract.

Stening and Grossman (1969) found that secretin, gastrin, CCK-PZ, caerulein and histamine brought about hormonal stimulation. Jones and Hall (1969) described the stimulating effect of glucagon and Wormsley (1970, 1978) the same effect by acid perfusion of the duodenum or jejunum and of accelerated emptying of the stomach. The inhibiting effect of somatostatin was described by Hanssen (1977).

The first detailed morphological differentiation of hyperplasia of Brunner's glands was undertaken by Feyrter (1934). He distinguished three forms: hyperplasia diffusa et nodosa, hyperplasia nodularis circumscripta and hyperplasia adenomatosa. In 2800 autopsies Feyrter found hyperplasia of Brunner's glands in only 0.85%, particular in patients with renal insufficiency, and therefore considered the possibility that in the presence of uremia Brunner's glands might secrete substances normally excreted in the urine. However, he did not provide any information on pancreatic changes in his 14 cases of hyperplasia. Kocianova et al. (1974) registered the surprisingly high frequency of hyperplasia of Brunner's glands of 16% autopsy material. Most of patients involved had indicated epigastric pain in their case histories. However, these authors also failed to provide any information on coexistent afflictions of the pancreas. In contrast, the clinical diagnosis of hyperplasia of Brunner's glands is established only rarely and predominantly in polypoid forms (Kaplan et al. 1968). A connection with hyperacidity of the gastric juice is often discussed (Erb and Johnson 1940; Epstein and Cole 1954; Griffith and Harkins 195 ; Goldberg et al. 1959; Tanaka and Sakogushy 1974). However, Kaplan et al. (1968) found hyperchlorhydria in only 45% of their patients with predominantly polypoid hyperplasia of Brunner's glands. Thus, the pathogenesis of hyperplasia remains for the most part unexplained. The cases of circumscribed adenomatous hyperplasia (Deren and Henry 1956) might possibly be hamartomas (Goldman 1963).

The hyperplasia of Brunner's glands we found in 75.7% the chronic pancreatitis cases was exclusively of the diffuse type. The layer containing the glands is uniformly thickened from the duodenal bulb to the papilla of Vater. Our first hypothesis in the search for a cause of hyperplasia in chronic pancreatitis was that, as a result of the exocrine insufficiency of the pancreas, the glands were stimulated not only functionally, but also trophically. A factor supporting this hypothesis is that there was no hyperplasia in normal specimens, in cancer or divisum pancreatitis – that is in cases with chronic scarring in only one of the two separate areas of pancreatic juice outflow, the other remaining functionally and morphologically intact. Also in the segmental pancreatitis group there was no statistically significant thickening of the layer of Brunner's glands. Therefore, we assumed that the hyperplasia of Brunner's glands must be more marked, the more severe the exocrine insufficiency of the pancreas. A comparison of the degree of scarring of the exocrine parenchyma with the degree of hyperplasia of Brunner's glands, revealed no statistically significant correlation. Nor did the existence and extent of scarring of the duodenal wall in chronic pancreatitis or of inflammatory infiltration of the duodenal mucosa have any influence

on the existence and degree of hyperplasia of Brunner's glands. The same was also true for the duration of the disease, consumption of alcohol and history of gallstones or ulcers in patients with and without hyperplasia of the duodenal glands. We had no information on gastric acid secretion or stomach emptying times.

Even though no correlation between the degree of scarring of the pancreatic tissue and the hyperplasia of Brunner's glands can be demonstrated, it must still be assumed that hyperplasia is primarily an adaptive reaction to exocrine insufficiency of the pancreas in chronic pancreatitis. In analogy with the activation of enzymes in the mucosa of the small intestine in chronic pancreatitis (Caspary et al. 1975) the term of "endocrinopathia" might be appropriate, ergo a causality in the sense of a complex of symptoms (Günther 1948). Although this "secondary pancreas" (Brunner 1687) cannot wholly compensate the pancreatic insufficiency, it can apparently partially compensate for the loss of pancreatic alkaline protection by an increased production of mucus and alkali. In the search for the causes of hyperplasia of Brunner's glands, however, it must be kept in mind that the intermeshed regulatory systems in the upper abdominal area offer a multidude of possibilities. We have tried to summarize the various stimulating and inhibiting influences on Brunner's glands schematically (see Fig. 7). If one looks for a connecting link between chronic pancreatitis and hyperplasia of Brunner's glands, several possibilities present themselves. In experimental elimination of the pancreas by creation of a fistula, an increase in duodenal ulcers and a rise in gastric acid secretion have been observed (Elman and Hartmann 1931; Dragstedt 1943; Greenlees et al. 1959; Landor and Adams 1962; Kraetz and Spiro 1965). There have also been reports of an increased occurrence of peptic ulcers (Warren and Cattell 1959; Howard and Jordan 1960; Fitzgerald 1963; Drelling and Negavi 1969), and hyperacidity of the gastric juice together with accelerated stomach emptying (Wormsley 1978) in patients with chronic pancreatitis. Kalk et al. (1976) found a significant rise in immune reactive glucagon, and Harvey et al. (1973) found a sharp rise in the serum level of cholecystokinin-pancreozymin in patients with chronic pancreatitis. Perhaps CCK-PZ is a hormone not only with a highly trophic effect on the pancreas (Petersen et al. 1976), but also on Brunner's glands. On the other hand, secretin release and half life in patients with chronic pancreatitis do not differ from those of normal subjects (Pelletier et al. 1976). The discovery that the hormone urogastrone, which inhibits gastric acid secretion, is produced in Brunner's glands (Heitz et al. 1978) also supports the theory of an adaptative mechanism in chronic pancreatitis and hyperacidity of the gastric juice or accelerated stomach emptying.

One could also speculate as to whether a disturbance in the interplay of the gastrointestinal hormones – whether primary or due to alcohol consumption – might not play a role in the pathogenesis of chronic pancreatitis as well as hyperplasia of Brunner's glands. Evidence supporting this theory has been presented by Sarles et al. (1978), who reported that animals treated with alcohol showed a sharp rise in gastrin and cholecystokinin-pancreozymin production after meals rich in protein and fat. Thus, it might be possible that hyperplasia of Brunner's glands and chronic pancreatitis arise simultaneously as a result

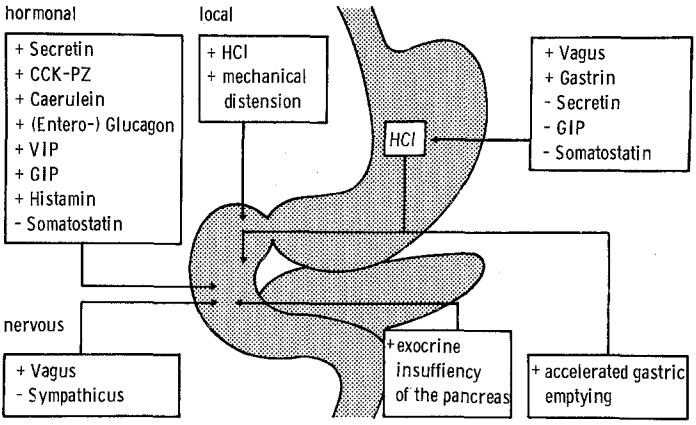

Fig. 7. Luminal, hormonal and neural possibilities of stimulating and inhibiting the secretion of Brunner's glands

of primary or secondary hormonal disturbances. A number of cases with marked hyperplasia of Brunner's glands and only slight chronic fibrotic pancreatitis in our study might speak for this hypothesis.

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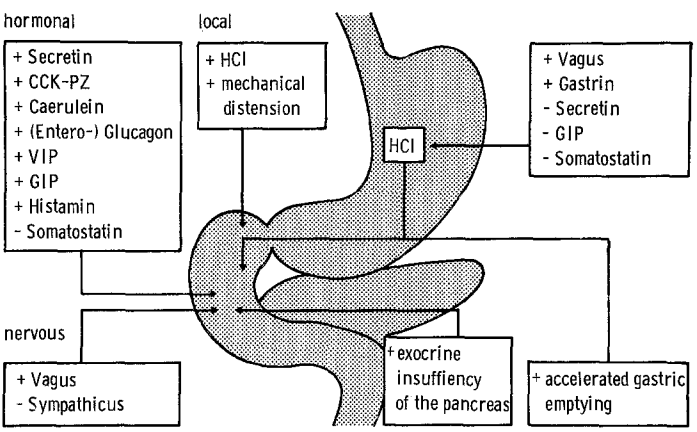

Fig. 7. Luminal, hormonal and neural possibilities of stimulating and inhibiting the secretion of Brunner's glands

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