

DEVELOPMENT OF GASTRIC DYSFUNCTION IN DERMATITIS HERPETIFORMIS*

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Abstract. In order to study the development of atrophic gastritis, gastric secretory function was examined by a standard pentagastrin test 24 to 78 months after a previous examination (Ex I). The study included 12 patients with dermatitis herpetiformis (DH), 6 patients with functional signs of atrophic gastritis previously, and 8 healthy controls. The current examination (Ex II) also included microbiological culture of gastric juice and estimation of gastrin(s), parietal cell and thyroidal antibodies. Most of the controls had increased their maximum acidity and maximum acid output (MAO) between the examinations. This may indicate an altered potency of pentagastrin in recent years. Conversely, 5 of the 6 patients with atrophic gastritis showed a further reduction of maximum acidity and MAO, indicating progressive parietal cell atrophy. In the DH-group, two tendencies were observed: 6/12 patients had an increased MAO at Ex II. They had had lower mean age and higher mean MAO at Ex I, as compared with the remaining 6 patients who had a decreased MAO at Ex II. The latter group more often had parietal cell antibodies.

Key words: Dermatitis herpetiformis; Pentagastrin; Achlorhydria; Gastritis; Stomach

It is now well established that patients with dermatitis herpetiformis (DH) may have reduced gastric secretion of hydrochloric acid and intrinsic factor (1, 4, 5, 8). Recent studies indicate that such patients have atrophic gastritis of autoimmune pathogenesis similar to that in latent or manifest pernicious anaemia (8, 12). Furthermore, patients with concurrent DH and megaloblastic anaemia have been reported (3, 6, 8, 18).

The object of the present study was to gain further information about the time factor in development of the gastric lesion by repeatedly examining patients with DH, and comparing them with patients having atrophic gastritis without DH, and with healthy controls.

PATIENTS

Twelve patients with DH were studied (Table I). There were 6 women and 6 men aged 29 to 65 years (mean 49 years $\pm$ 4 S. E. M.). In all cases the diagnosis was based

on a typical clinical picture, skin biopsy findings and a therapeutic response to Dapsone. A gastroenterological examination had been carried out in all the patients, including pentagastrin stimulation test 24-66 months earlier (mean 55 ± 4 months). 8 patients have been described in previous studies (1, 12). 10 patients had jejunal biopsies done by means of a Watson capsule (Table I).

Six patients (5 females and 1 male) without DH were also included in the study. The age range of this group was 55-71 years (mean 62 ± 3). In earlier tests they had demonstrated a diminished ability to secrete HCl (MAO < 10 mEq/h; mean 5.0 ± 1.2 mEq/h), indicating a reduced functional parietal cell mass as in chronic atrophic gastritis (16). This group will be called "atrophic gastritis" in the following, though a histological examination of the body mucosa was not performed in all of them. The first examination of these patients was performed 29-78 months previously (mean 64 ± 8).

Eight persons (3 females, 5 males) aged 32-60 years (mean $44 \text{ years} \pm 3$) served as controls. They had undergone a pentagastrin stimulation test 25-60 months earlier (mean 52 ± 4), either as healthy volunteers in experimental studies or because of dyspeptic symptoms. Further investigations had not revealed any gastric disease, autoimmune condition or diabetes mellitus.

METHODS

The Pentagastrin test (6 $\mu\text{g/kg}$ body-weight subcutaneously) (described earlier, ref. 1) was carried out by the same laboratory nurse on both occasions, by applying an identical technique. Definitions of the terms BAO, MAO, and achlorhydria are given elsewhere (13).

Bacteria and fungi were cultivated at Ex II on the first portion of the basal secretion. Routine cultivations were carried out for bacteria, both aerobically and anaerobically. Estimation of the microbial growth was carried out semiquantitatively according to the following criteria: 0, no or extremely sparse growth; +, sparse growth; ++, moderate growth; +++, abundant growth. Moderately or abundantly growing microorganisms were typed.

Serum gastrin was estimated by a radioimmunoassay technique, as described previously (13). Antigastrin

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Table 1. Clinical and laboratory data for 12 patients with dermatitis herpetiformis

PCA=parietal cell antibody, STVA=subtotal villous atrophy, GFD=gluten-free diet, Thyr=antibody against cytoplasmic thyroid antigen, TVA=total villous atrophy, ANF=antinuclear factor, ND=not done

Ref. value	Sex	Age (y.) Ex I	Duration of DH (y.) Ex I	Interval (y.) Ex I-Ex II	Therapy dapsone mg/d		Antibodies		Gastric bact. Ex II	Gastric fungi Ex II
					Ex I	Ex II	Ex I	Ex II		
LB	M	47	20	4 9/12	660 ^a	660 ^a	ANF 1/25	ANF 1/25 PCA 1/25	++	Neg
EH	F	59	7	5	—	—	PCA 1/32	PCA 1/25	Neg	+
GJ	F	62	6	2 6/12	50	50	Neg	PCA 1/10	++	+
AL	F	59	2	5 6/12	—	—	Neg	Thyr 1/200	Neg	Neg
BL	M	26	6/12	3 9/12	—	100	Neg	Neg	+	Neg
RM	M	31	3/12	5 4/12	—	100	Neg	Neg	Neg	Neg
BO	M	36	3	5 1/12	50	100	Neg	Neg	++	+++
AA	F	38	4	5 4/12	50	10	Neg	Neg	Neg	Neg
HS	F	57	37	5 6/12	50	50	PCA 1/25	PCA 1/100	Neg	++
BA	F	24	7	4 10/12	150	100	Neg	PCA 1/10	+	+
LE	M	40	10	5 3/12	50	10	Neg	Thyr 1/25	ND	ND
LJ	M	50	9	2	50 ^a	50 ^a	Neg	Neg	+	+

^a Aldesulfone sodium.

(2604-8) was kindly supplied by Professor Jens Rehfeld, Århus, Denmark.

Autoantibodies against cytoplasmic thyroid antigen, smooth muscle, renal glomeruli, mitochondria and gastric parietal cells were examined by an immunofluorescence technique at Ex II. Antibodies against thyroglobulin were examined by an indirect haemagglutination technique. The immunological analyses were done at the State Bacteriological Laboratory, Stockholm. The sera of 10 of the 12 patients with DH had also been analysed with respect to antibodies to thyroid antigen and parietal cells at Ex I.

Statistical methods

Calculations were made of the mean (*M*) and the standard error of the mean (*S.E.M.*). The significance of differences between the means was estimated with Student's *t*-test. A difference was considered significant when the corresponding level of probability was $p < 0.05$.

RESULTS

HCl secretion

The alteration of the several variables of the HCl secretion between Ex I and Ex II is shown in Fig. 1 for each group. The mean and *S.E.M.* of variables BAO, stimulated volume, maximal acidity and

MAO for each group of patients at both examinations are given in Table II, where the significance of the alterations is also indicated.

In the controls, 5/8 persons had an elevated MAO at Ex II, compared with Ex I, 1/8 had unchanged MAO and 2/8 showed a minor decrease. For the group as a whole there was a non-significant increase in stimulated volume and a significant increase in maximum acidity, resulting together in a significant increase in MAO of about 40%.

The results of the DH group are given in Table II-III. The figures indicate that DH patients with low acid output at Ex I are older, have a greater tendency to a reduced functional parietal cell mass and have a higher frequency of autoantibodies than DH patients with normal acid output.

Microbiological findings

In Table IV the microbiological results are shown for the patients and controls in relation to the acid secretion capacity. At quantification, the highest concentrations of microbes were found in the achlorhydric patients. The bacteria encountered were those normally inhabiting the mouth and throat.

Gastrin pmol/l Ex II	Jejunal biopsy	Remarks
<55		
14	Normal	Gastric carcinoma in both parents
18	Normal	Gastric carcinoma in both parents
1293	Diffuse inflamm.	Diab. mell., hypertonia, myocard. infarction
114	STVA	Hyperlipaemia
53	ND	Diab. mell. c. amaurose
36	TVA	
87	Normal	Ulcus duodeni earlier
<7	Normal	Mother has goitre
209	STVA	Intestinal reticulum cell sarcoma (2)
39	STVA before GFD	
14	1970 TVA 1973 on GFD normal	Coeliac disease, hepatitis, ulcerative colitis, GFD since 1971
7	ND	

Table I. They had a mean value of 158 pmol/l $\pm$ 105. 9 patients with MAO < 10 mEq/h at Ex II: mean 199 pmol/l $\pm$ 139; 3 patients with MAO > 10 mEq/h at Ex II: mean 34 pmol/l $\pm$ 11. This difference was not statistically significant. In 5/12 patients, the value exceeded the upper reference value and 2/3 patients with achlorhydria belonged to this subgroup. In the achlorhydric patients with a normal serum gastrin value, biopsy disclosed an atrophic gastritis of the antral area (Prof. Lennart Angervall, Göteborg).

The serum gastrin value in patients with atrophic gastritis without DH was 94 pmol/l $\pm$ 28. 4/6 values were above the upper reference value.

Autoantibodies

Of the controls, 1 out of 8 had thyreoglobulin antibodies (titre 1/1 600). Other antibodies did not occur. 7/12 patients with DH had autoantibodies as shown in Table I, among them 2/3 patients who developed achlorhydria. The difference between controls and DH patients in this respect was not significant. No autoantibodies could be found in subjects having atrophic gastritis but lacking DH.

DISCUSSION

No follow-up study on the gastric secretion over a period longer than 48 months and performed by an adequate and identical method has been reported hitherto, as far as we know, for normal subjects or patients with gastric disease (17).

The present study shows that nearly all control

Serum gastrin

In the controls the mean value for serum gastrin was 18.2 pmol/l ($\pm$ 4.9). No individual value exceeded the laboratory's upper reference value of 52 pmol/l (13).

The results for patients with DH are shown in

Table II. Means and standard errors of BAO, stimulated volume, maximal acidity and MAO in the patients and controls at Ex I and Ex II

	Dermatitis herpeti- formis (n = 12)		Atrophic gastritis (n = 6)		Controls (n = 8)	
	Ex I	Ex II	Ex I	Ex II	Ex I	Ex II
BAO (mEq/h)	0.96 $\pm$ 0.40	1.16 $\pm$ 0.58	0.29 $\pm$ 0.13	0.40 $\pm$ 0.17	2.31 $\pm$ 0.60	2.53 $\pm$ 0.66
	n.s.		n.s.		n.s.	
Stimulated volume (ml/h)	105.3 $\pm$ 21.2	117.2 $\pm$ 26.0	77.5 $\pm$ 18.1	78.2 $\pm$ 12.7	225.6 $\pm$ 17.5	258.3 $\pm$ 27.4
	n.s.		n.s.		n.s.	
Maximal acidity (mEq/l)	66.4 $\pm$ 12.1	62.3 $\pm$ 15.2	74.5 $\pm$ 12.3	63.0 $\pm$ 12.1	93.5 $\pm$ 7.7	113.8 $\pm$ 5.5
	n.s.		n.s.		p < 0.05	
MAO (mEq/h)	8.10 $\pm$ 2.46	9.47 $\pm$ 3.08	5.00 $\pm$ 1.16	3.88 $\pm$ 0.59	19.55 $\pm$ 2.54	27.39 3.58
	n.s.		n.s.		p < 0.05	

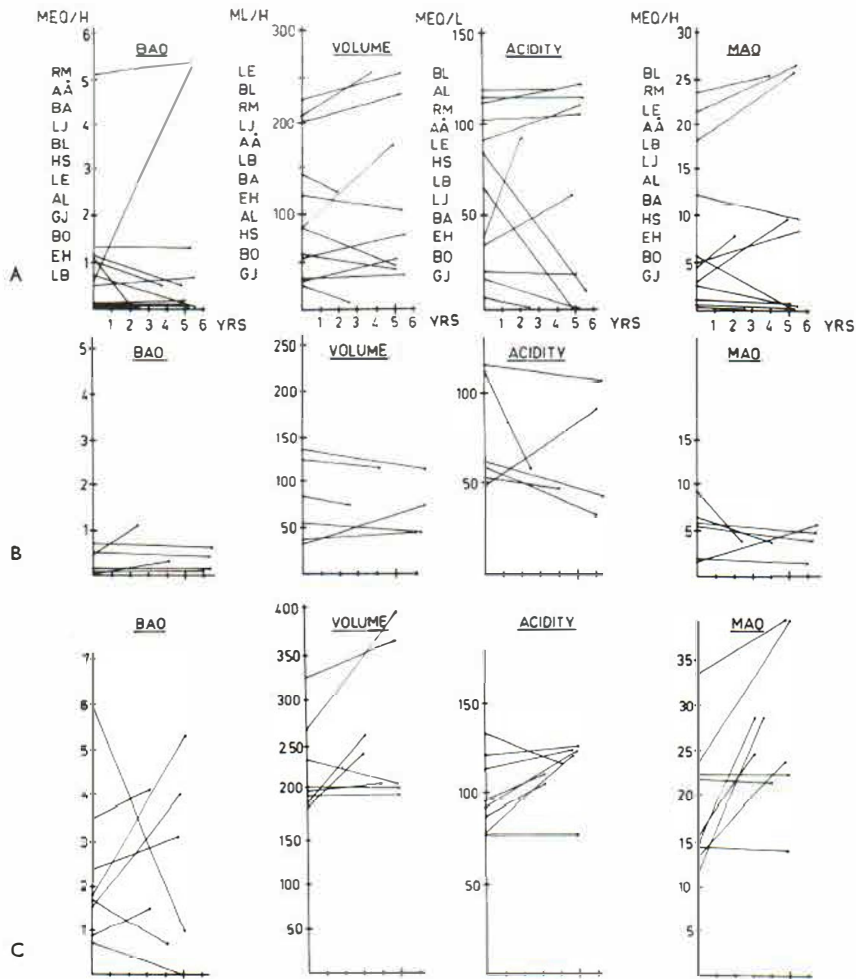


Fig. 1. Changes in gastric secretion from examination I to II in 12 patients with dermatitis herpetiformis (A), 6 patients with atrophic gastritis (B) and 8 controls (C). The order of the starting points on the ordinate in each diagram for the DH group is indicated by the sequence of patients' initials

persons had an increased MAO, whereas patients with functional signs of atrophic gastritis had further diminished acid output between the examinations. Among the patients with DH, there were two tendencies: Most patients with a low initial secretion experienced a further reduction and 3 of them now have total achlorhydria, whereas most of the patients with a normal initial secretion showed an increase, as did the control subjects.

The 40% increase in mean MAO in the group of controls was surprising. Theoretically, there could be several explanations.

1. An increase in the functional parietal cell mass in five out of eight healthy individuals selected at random: such an increase would probably also have resulted in an increase of BAO, and have led to a larger volume rather than a higher acidity.

2. A systematic error in measuring the hydrogen

Table III. Alterations in MAO and frequency of autoantibodies in patients with DH, according to their previous value of MAO

MAO at Ex I	Mean age	Increasing MAO Ex I → Ex II	Decreasing MAO Ex I → Ex II	All anti-bodies	PCA
MAO > 10 mEq/h (n = 4)	38 ± 4	3/4	1/4	1/4	0/4
MAO ≤ 10 mEq/h (n = 8)	54 ± 5	3/8	5/8	6/8	5/8

Table IV. Concentrations of bacteria and fungi in gastric juice according to the MAO in patients and controls (semiquantitative estimation as described above)

MAO at Ex II	Bacteria				Fungi			
	0	+	++	+++	0	+	++	+++
MAO > 10 mEq/h (n=9)	6	3			8	1		
MAO < 10 mEq/h (n=15)	9	2	4		4	7	3	1

ion concentration: this is improbable as all apparatus is checked routinely with standard buffer solutions. Nor would a systematic error of measurement have produced differences of from -17 mEq/l to +44 mEq/l.

3. Increased potency of the stimulating penta-gastrin: this would fit in well with the observation of increased frequency of adverse reactions against pentagastrin seen in our laboratory over the last 2 years (14). If this hypothesis is correct, the increased activity of pentagastrin affects the ion secretion rather than the volume secreted. Whatever the correct explanation, the increased secretion in the control subjects contrasts against the reduction of the HCl secretion in the patients with atrophic gastritis at the initial examination (whether they have DH or not). This reduction may indicate progress of the parietal cell atrophy during the observation period and agrees with earlier histological findings demonstrating that gastritis in many instances has a tendency to progress (9, 11).

The age factor in the development of atrophic gastritis has been discussed (10). In the present study the age of the controls is similar to that of those patients with DH who had increased secretion. On the other hand, the mean age of the patients with DH who had reduced secretion is close to that of the non-DH-patients with atrophic gastritis. The established opinion that atrophic gastritis is more common in advanced age thus also seems fairly correct for the atrophic gastritis in patients with DH. It is still not certain, however, whether all patients with DH gradually will develop atrophic gastritis or if there are two subpopulations of patients, one of which has a tendency to develop atrophic gastritis. The latter hypothesis is supported by the fact that 4/6 patients with reduced acidity have parietal cell antibodies (PCA)—among

these are 2/3 patients with total achlorhydria—whereas only 1/6 patients with increased secretion had PCA (and in a low titre at that). Further longitudinal studies are required to resolve this problem.

The occurrence of PCA is characteristic of an antrum-sparing atrophic gastritis (13, 15). Hypergastrinaemia is also found in this condition (13, 15). The mean serum gastrin value was significantly elevated in DH patients with MAO lower than 10 mEq/h. This indicates that the atrophic gastritis in DH is similar to that in pernicious anaemia (12). A few of the controls had a sparse growth of bacteria and fungi whereas a majority of the patients with atrophic gastritis, with or without DH, had moderate to heavy growth. This accords with the findings of Heading et al. (5) concerning the bacterial flora in the upper jejunum in DH. The similarity of the microorganisms to those of the mouth and throat makes it probable that they reach the stomach by normal swallowing of saliva. Their chances of surviving are then obviously better in the milieu created by an atrophic gastritis.

Some types of chronic atrophic gastritis are now regarded as an autoimmune disease (15). It has been suggested that in these cases immunosuppressives may normalize the gastric mucosa and partially restore its function (7). None of the patients or controls whose secretory capacity increased had been so treated. It should be noted, however, that one of the three patients with DH, who had an initially reduced MAO but which later increased, had been treated with a gluten-free diet (GFD). GFD is known to normalize the intestinal mucosa but its effect on gastric mucosa is, to the best of our knowledge, unknown. A study of the influence of GFD on gastric function in DH is now in progress.

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REFERENCES

- Andersson, H., Dotevall, G. & Mobacken, H.: Gastric secretion of acid and intrinsic factor in dermatitis herpetiformis. *Scand J Gastroent* 6: 411, 1971.
- Andersson, H., Dotevall, G. & Mobacken, H.: Malignant mesenteric lymphoma in a patient with dermatitis herpetiformis, hypochlorhydria and small-bowel abnormalities. *Scand J Gastroent* 6: 397, 1971.

3. Cream, J. J. & Scott, G. L.: Anaemia in dermatitis herpetiformis. *Br J Dermatol* 82: 333, 1970.
4. Fausa, O., Larsen, T. E., Husby, G. & Thune, P.: Gastrointestinal investigations in dermatitis herpetiformis. *Acta Dermatovener (Stockholm)* 55: 203, 1975.
5. Heading, R. C., Parkin, D. M., Barnetson, R. St. C., McClelland, D. Bl. & Shearman, D. J. C.: Small-intestinal bacterial flora in dermatitis herpetiformis. *Am J Dig Dis* 19: 704, 1974.
6. Ilyas, M.: Malabsorption with dermatitis herpetiformis. *Lancet* i: 248, 1968.
7. Jeffries, G. H., Todd, J. E. & Sleisenger, M. H.: The effect of prednisolone on gastric mucosal histology, gastric secretion and vitamin B₁₂-absorption in patients with pernicious anaemia. *J Clin Invest* 45: 803, 1966.
8. O'Donoghue, D. P., Lancaster-Smith, M., Johnson, G. P. & Kumar, P. J.: Gastric lesion in dermatitis herpetiformis. *Gut* 17: 185, 1976.
9. Rösch, W., Demling, L. & Elster, K.: Is chronic gastritis a reversible process? Follow-up study of gastritis by step-wise biopsy. *Acta Hepato-Gastroenterol* 22: 252, 1975.
10. Siurala, M., Isokoski, M., Varis, K. & Kekki, M.: Prevalence of gastritis in a rural population. Bioptic study of subjects selected at random. *Scand J Gastroent* 3: 211, 1968.
11. Siurala, M. & Salmi, H. J.: Long-term follow-up of subjects with superficial gastritis or a normal gastric mucosa. *Scand J Gastroent* 6: 459, 1971.
12. Stockbrügger, R., Andersson, H., Gillberg, R., Kastrup, W., Lundqvist, G. & Mobacken, H.: Auto-immune atrophic gastritis in patients with dermatitis herpetiformis. *Acta Dermatovener (Stockholm)* 56: 111, 1976.
13. Stockbrügger, R.: Aspects of chronic atrophic gastritis—with special reference to serum gastrin and antral gastrin cells. Thesis, Gothenburg, 1976.
14. Stockbrügger, R. & Dotevall, G.: Potency and side effects of pentagastrin. Personal communication.
15. Strickland, R. G. & Mackay, I. R.: A reappraisal of the nature and significance of chronic atrophic gastritis. *Amer J Dig Dis* 18: 426, 1973.
16. Vilardell, F. *In* Gastroenterology (ed. H. L. Bockus). W. B. Saunders Company, Philadelphia, London and Toronto, 1974.
17. Walan, A.: Studies on peptic ulcer disease—with special reference to the effect of l-hyoscyamine. *Acta Med Scand, Suppl.* 516, 1970.
18. Webster, A. B. D.: Spirillum hepatitis in "acquired" hypogammaglobulinaemia with thyroiditis, pernicious anaemia and possible dermatitis herpetiformis. *Proc R Soc Med* 66: 1126, 1973.

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