Salivary secretion in duodenal ulcer disease¹

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SUMMARY Salivary response to stimulation with citric acid was higher in patients with duodenal ulcer disease than in patients with other diseases of the upper gastrointestinal tract. This increase was proportional to an increase of histamine-stimulated gastric acid secretion. In duodenal ulcer disease, the increase in parietal cell mass may therefore be associated with the growth of other exocrine organs such as the salivary glands.

The only consistent and persisting changes in duodenal ulcer disease, apart from the ulcer and its scar, are thought to be an enlargement of the parietal cell mass and an increase in gastric secretion (Grossman, 1960). In the present study it is shown that in ulcer patients the secretion rate of the salivary glands is increased in proportion to the rate of gastric acid secretion. It is suggested that duodenal ulcer disease is characterized by an enlargement of several exocrine glands, such as the parietal cell system, salivary glands, and pancreas while only the enlargement of one gland—the stomach—is related to ulcer symptoms.

Material and Methods

PATIENTS

Seventy hospitalized male veterans who were scheduled for gastric analysis in 1969 and 1970 fulfilled the following criteria: (1) A barium meal had been interpreted independently by two examiners. (2) A disease of the upper gastrointestinal tract was the only major pathological finding at the time of study. Specifically excluded from this study were patients with complications of ulcer disease, such as bleeding and obstruction. (3) No gastric surgery had been performed except in three patients who had previously undergone simple suture for perforated duodenal ulcer. For at least one week before secretion tests the patients had not received anti-

cholinergics and other drugs which might have a lasting effect on gastric or salivary secretion.

Patients with duodenal ulcer disease, including four in whom ulcer was inactive at the time of admission, formed the duodenal ulcer group. All other patients formed the control group. In patients with gastric ulcer and gastric cancer diagnosis was confirmed by gastroscopy and/or surgery at a later date. Patients with gastroesophageal reflux had heartburn, reflux of barium following a barium meal, and abnormal histology in an oesophageal biopsy.

In patients with functional disorders, at least two barium meals were performed. Small sliding hiatal hernias were seen in four patients. No abnormal findings were seen in five patients. In all nine patients, epigastric discomfort was nonspecific, and a cholecystogram, a barium enema, and oesophageal histology were normal.

PROCEDURES

Tests were performed eight $\pm$ 1.3 days (mean $\pm$ SEM) after hospital admission in duodenal ulcer patients and eight $\pm$ 1.5 days after admission in control patients respectively. Salivary secretion tests were started at 8.00 am after a 12-hour fast and were followed by gastric secretion tests.

Salivary secretion

For mechanical stimulation the subject was asked to exercise the muscles of the cheek and tongue against the teeth and squeeze the saliva out before voiding it into a preweighed beaker. The process was continued for 10 minutes at the end of which the bottle was weighed again and salivary flow calculated by difference.

For chemical stimulation the subject emptied from the mouth all salivary remnants. At zero time,

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0.3 ml of citric acid solution was delivered on the anterior surface of the tongue and tasted by rolling movements of the tongue. At the 30th second, 5 ml of distilled water was delivered rapidly below the tongue. Between the 45th and 60th seconds the patient forcefully emptied the contents of the mouth into a preweighed beaker. The test was performed three times at three to four minute intervals. Salivary flow was calculated by subtracting 5.3 g from the increase in beaker weight.

The response to chemical stimulation was obtained by subtracting from the observed flow rate due to chemical stimulation the flow rate due to mechanical stimulation.

Further details of collection techniques have been reported in previous studies (Blum and Makhlof, 1971; Makhlof and Blum, 1971).

Gastric secretion

A 14 Fr radioopaque nasogastric tube was positioned in the antrum under fluoroscopic control. During the test the patient was recumbent, usually on his left side. Fasting juice was aspirated manually with a syringe. For further collections, suction pulses of 40 to 45 mm Hg were applied by a modified Gomco intermittent suction apparatus. Every five minutes, patency of the tube was checked by injecting 5 ml of air. Basal secretion was collected for 60 minutes. At the 30th minute, 20 mg of Benadryl (Parke Davis & Co) was injected into the deltoid muscle. At the 60th minute, histamine phosphate (Lilly) was injected subcutaneously at a dose of 40 µg/kg body weight. Stimulated secretion was collected for 60 minutes. During the entire test cotton rolls were inserted into the sulci of the cheeks and under the tongue in order to prevent contamination of gastric juice by saliva. In each 15-minute sample acidity was measured by titration with 0.1 N NaOH to pH 7 in an automatic titrator (Radiometer, Copenhagen). Unstimulated and stimulated acid output were calculated by adding 15-minute outputs during the pre- and post-histamine hour respectively.

Results

Characteristics such as age, body weight, and race, duration and type of subjective symptoms were similarly distributed among the two groups (Tables I and II). On palpation, the salivary gland area did not show abnormal findings in any patient.

In the first consecutive 25 subjects of this study (11 duodenal ulcer patients and 14 control subjects respectively) dose response curves were constructed by using the following concentrations of citric acid: 2.5%, 5%, 7.5%, 10%, and 20%. The response to 10% citric acid was a constant fraction of the

Characteristics	Duodenal Ulcer Group ¹ (38)	Control Group ¹ (32)	P Value
Age (yr, mean ± SEM)	49.2 ± 2.0	50.0 ± 2.1	> 0.05
Body weight (kg, mean ± SEM)	69.2 ± 1.4	66.9 ± 2.1	> 0.05
Race—Negroes	10 (26%)	6 (19%)	> 0.05
White collar workers	6 (16%)	4 (13%)	> 0.05
Duodenal ulcer	38 (100%)	0	
Gastric ulcer	7 (11%)	14 (44%)	
Gastroesophageal reflux	5 (5%)	8 (25%)	
Gastric cancer	0	1 (3%)	
Functional disorder		9 (28%)	

Table I Characteristics of patients

¹Nos. of patients in brackets.

Symptom	Duodenal Ulcer Group	Control Group	P Value
Past History			
Duration of symptoms (years, mean ± SEM)	10.4 ± 1.7	7.2 ± 2.3	> 0.05
Pain ¹ (n)	38 (100%)	32 (100%)	> 0.05
Water brash (n)	8 (21%)	6 (19%)	> 0.05
Dry mouth (n)	3 (8%)	4 (13%)	> 0.05
On Admission			
Pain ¹ (n)	34 (90%)	31 (97%)	> 0.05
Day of Study^a			
Pain ¹ (n)	2 (5%)	4 (13%)	> 0.05
Water brash (n)	0 (0%)	0 (0%)	> 0.05
Dry mouth (n)	5 (13%)	5 (16%)	> 0.05

Table II Subjective symptoms

¹Epigastric pain and/or heartburn; ^aafter ≥ 12 hr fasting; n = number of patients.

calculated maximal secretion rate ($64 \pm 2\%$ in duodenal ulcer patients and $63 \pm 2\%$ in control subjects respectively, mean ± SEM). These observations corresponded to values previously obtained in young healthy volunteers (Makhlof and Blum, 1971). In subsequent patients, therefore, the response to 10% citric acid was used as an estimate for the secretory capacity of the salivary glands.

Of the three consecutive salivary secretion tests with 10% citric acid, the response in the second and in the third test was $101 \pm 0.6\%$ and $99 \pm 0.6\%$ (mean ± SEM) of the first response respectively. This good reproducibility corresponds to observations in previous studies (Blum and Makhlof, 1971; Makhlof, 1971).

Results of secretion tests are summarized in Table III. Salivary secretion in response to citric acid

Type of Secretion	Duodenal Ulcer Group	Control Group
Gastric (m-equiv/hr)	27.7 ± 1.7	19.6 ± 2.2
Salivary (ml/min)	5.36 ± 0.32	4.00 ± 0.34

Table III Results of secretion tests¹

¹Data are given as mean ± SEM. Differences between duodenal ulcer group and control group are significant at 0.01 level.

Fig. 1 Gastric acid output during histamine stimulation (upper graph) and salivary output during stimulation with citric acid (lower graph). Results for patients below and above 50 years of age are given on left and right side of each graph respectively. Closed symbols represent patients of duodenal ulcer group and open symbols represent patients of control group. A small divided box indicates mean $\pm$ SEM.

in patients with duodenal ulcer was 34% higher than in controls, and gastric acid output in response to histamine was 41% higher.

The effect of age on secretion rate is shown in

Figures 1 and 2. A reduction of salivary secretion with old age was seen in controls, but not in patients with duodenal ulcer. In an analysis of covariance, both age and duodenal ulcer were significantly

Characteristics	Rate of Salivary Secretion (ml/min)			
	Duodenal Ulcer Group		Control Group	
	<50 Years	≥50 Years	<50 Years	≥50 Years
All patients	5.40 ± 0.40 (n = 20)	5.31 ± 0.51 (n = 18)	4.95 ± 0.55 (n = 15)	3.17 ± 0.32 (n = 17)
Smoking	5.38 ± 0.41 (n = 15)	5.21 ± 0.59 (n = 11)	4.73 ± 0.55 (n = 14)	3.33 ± 0.31 (n = 13)
Drinking	5.45 ± 0.38 (n = 7)	4.89 ± 0.65 (n = 5)	4.82 ± 0.59 (n = 9)	3.25 ± 0.29 (n = 10)
Dentures	5.01 ± 0.65 (n = 6)	5.40 ± 0.61 (n = 10)	5.37 ± 1.47 (n = 4)	2.91 ± 0.40 (n = 11)
Gastric ulcer	5.61 ± 0.72 (n = 5)	5.60 (n = 2)	5.11 ± 0.69 (n = 5)	3.13 ± 0.40 (n = 9)
Gastroesophageal reflux	6.72 (n = 1)	5.80 (n = 1)	5.30 (n = 2)	3.27 ± 0.59 (n = 6)

Table IV Rate of stimulated salivary secretion¹

¹mean $\pm$ SEM, n = number of patients.

Fig. 2 Linear relation between salivary secretion (y) and gastric secretion (x). Each symbol represents the mean of a 10-year age group: 30-39 years ($\circ, \bullet$), 40-49 ($\square, \blacksquare$), 50-59 ($\nabla, \blacktriangledown$), and ≥ 60 ($\triangle, \blacktriangle$). Closed symbols represent patients with duodenal ulcer and open symbols represent patients of control group.

($P < 0.01$) correlated with rate of salivary secretion. Thus, the difference between duodenal ulcer and control group was most marked in old age. A similar tendency was seen for gastric secretion. In Fig. 2, rate of stimulated salivary secretion in each 10-year age group is plotted against the rate of stimulated gastric secretion. A linear regression could be fitted to these data. On the average, therefore, salivary secretion rate changed in proportion to gastric secretion rate.

Other factors which might have an effect on salivary secretion are listed in Table IV. They include local irritants such as dentures, smoking (one or more cigarettes per day), and drinking (two or more cocktails per week), and diagnosis such as gastric ulcer and gastroesophageal reflux. Salivary and gastric secretion of patients with these characteristics were similar to the rates of age-matched patients without these findings.

Discussion

The results of the present study demonstrate that patients with duodenal ulcer disease have a higher rate of salivary secretion than matched control patients without duodenal ulcer. This difference in secretion rate is not due to habits such as smoking

and drinking or to other factors such as wearing of dentures but it appears to be related to the rate of gastric acid secretion. It could be shown that in duodenal ulcer disease the rate of salivary secretion was increased in proportion to the rate of gastric secretion. Furthermore, the fall in secretion rate of exocrine glands which usually occurs beyond the age of 50 (Garrett, 1962; Baron, 1963a and b; Waterhouse, 1963; Blackman, Lambert, and Thayer, 1970) was not observed in patients with duodenal ulcer. The rate of both gastric and salivary secretion remained high in older ulcer patients. This observation confirms previous studies on this subject (Baron, 1963b; Blackman *et al*, 1970). It is well established that the rate of gastric secretion is related to the parietal cell mass and that both gland size and secretion rate depend upon body weight (Boyd, 1941; Brody, 1945; Card and Marks, 1960; Crean, 1967; 1969; Blackman *et al*, 1970). In duodenal ulcer disease, an increase in gastric secretion is caused by an increase in parietal cell mass. It is likely therefore that the parallel increase in salivary secretion is caused by an increase in salivary gland mass. This postulate is supported by our previous observation of a relationship between salivary secretion and body weight (Blum and Makhoul, 1971) and by the well established relationship between salivary gland size and body weight (Boyd, 1941). In this context it is interesting to note that pancreatic secretion is also increased in duodenal ulcer disease (Petersen, 1970). It may well be that duodenal ulcer disease is characterized by an enlargement of several exocrine glands such as the parietal cell system, salivary glands, and pancreas while only the enlargement of one gland—the stomach—is related to ulcer symptoms.

Increased salivary secretion in patients with duodenal ulcer might be of some practical importance. The value of gastric secretion tests for the diagnosis of duodenal ulcer disease is low since there is a broad overlap of secretion rates between duodenal ulcer and control populations (Baron, 1963a and b; Blackman *et al*, 1970). The results of the present study suggest that combined tests of gastric and salivary secretion might improve diagnostic accuracy—at minimal additional costs of time and discomfort.

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