

Spontaneous achlorhydria with atrophic gastritis in the Zollinger-Ellison syndrome

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SUMMARY This case report describes the occurrence of spontaneous, persistent achlorhydria in a patient with markedly raised basal acid secretion and diarrhoea for over two years (Zollinger-Ellison syndrome). Achlorhydria was due to the rapid development of severe atrophic gastritis in a gastric mucosa that had previously shown markedly increased numbers of parietal cells.

Non-beta cell tumours of the islet of Langerhans are known to cause two syndromes: first the Zollinger-Ellison syndrome characterized by markedly increased basal gastric acid secretion, recurrent peptic ulceration, and/or chronic diarrhoea (Zollinger and Ellison, 1955; Zollinger and Grant, 1964). The manifestations of this syndrome are due to the constant secretion of a hormone, gastrin, by primary and metastatic tumour cells (Gregory, Tracy, French, and Sircus, 1960; Hallenbeck, Code, and Kennedy, 1963; Gregory, Grossman, Tracy, and Bentley, 1967). About 260 cases of the Zollinger-Ellison syndrome were reported up to 1964 (Ellison and Wilson, 1964). The second syndrome is 'pancreatic cholera', characterized by watery diarrhoea, profound hypokalaemia, and hypo- or achlorhydria (Brown, Neville, and Hazard, 1950; Verner and Morrison, 1958; Cheers, Thompson, Huteheson, and Patterson, 1960; Murray, Paton, and Pope, 1961; Telling and Smiddy, 1961; Espiner and Beaven, 1962; Brown and Crile, 1964; Matsumoto, Peter, Schultze, Hakim, and Franck, 1966). The manifestations of this syndrome probably result from secretion of an unknown hormone (gastrin excluded) interfering with the fluid and electrolyte transfer in the small bowel (Hindle, McBrien, and Creamer, 1964). Sixteen such cases have been reported up to 1966 (Matsumoto *et al.*, 1966).

This report is of a patient with markedly raised basal acid secretion (without peptic ulceration), watery diarrhoea, steatorrhoea, and loss of weight observed over a period of two years followed by spontaneous, persistent achlorhydria, remission of diarrhoea, and gain in weight. To our knowledge, spontaneous achlorhydria with severe atrophic gastritis in a patient with the Zollinger-Ellison syndrome has not previously been reported.

CASE REPORT

The patient, a man aged 53 years, was first seen in June 1966 with symptoms of frequency of stool (4 to 5/day) without blood and mucus for about one and a half years. His weight had fallen from 48 to 34 kg during the same period. The stools were watery, moderate in quantity, and not offensive. The patient denied any recent or past history of pain in the abdomen or back, heartburn, vomiting, or haematemesis. Gastric function tests showed a high basal acid secretion consistent with the diagnosis of Zollinger-Ellison syndrome (Table I). On large doses of oral antacid and anticholinergic drugs throughout the waking hours, neither the diarrhoea nor the weight improved significantly though parenteral anticholinergic treatment effectively reduced acid output (Table II). Laparotomy was performed in June 1967 with a view to detect and remove any localized pancreatic tumour. A thorough exploration failed to reveal any tumour in the pancreas or duodenum (not opened) or any enlargement of abdominal lymph nodes. The abdomen was closed (as planned) without performing total gastrectomy or blind distal pancreatectomy. High basal acid secretions were again observed in July 1967, and in April and May 1968. From January 1968 he passed one or two semisolid stools a day and his weight was 44 kg in April 1968. Since May 1968, he has passed one solid stool a day and his weight is increasing (46 kg, November 1968; 48 kg, January 1969). Achlorhydria after adequate histamine stimulation was noted for the first time in November 1968 and subsequently in January 1969 (Table I). The patient is now asymptomatic.

FAMILY HISTORY The patient's father died of accidental injury at the age of 35 years and the mother at the age of 55 years (the cause is not known). His sister died at the age of 45 years of pulmonary tuberculosis, one brother died at the age of 65 years (cause unknown), and the other (62 years) is living and healthy.

INVESTIGATIONS On examination, the findings were:

TABLE I
RESULTS OF GASTRIC FUNCTION TESTS IN A PATIENT WITH ZOLLINGER-ELLISON SYNDROME FOR THREE YEARS

Date	Secretion				Basal: Stimulated		Method
	Basal		Stimulated		Concentration	Acid Output	
	Volume (ml/hr)	Acid Output (m-equiv/hr)	Volume (ml/hr)	Acid Output (m-equiv/hr)			
July 1966	400	42.4	535	60.0	0.87	0.70	Histamine infusion test (2.0 mg/hr)
July 1966	435	49.6	620	76.9	0.89	0.64	Subcutaneous histamine test (2.4 mg)
July 1967	440	55.4	650	85.9	0.90	0.64	Subcutaneous histamine test (2.4 mg)
July 1967	400	54.4	610	81.4	0.98	0.67	Subcutaneous histamine test (2.0 mg)
April 1968	460	48.0	450	51.5	0.82	0.93	Subcutaneous histamine test (2.4 mg)
April 1968	460	39.0	400	35.7	0.89	1.15	Histalog (125 mg) intramuscularly
May 1968	460	45.2	410	40.2	0.89	1.12	Pentagastrin (200 Ug) intramuscularly
Nov 1968 ¹	64	1.0	46	0.8	0.89	1.25	Subcutaneous histamine test (2.0 mg)
Jan 1969 ¹	65	0.6	45	0.4	0.83	1.5	Subcutaneous histamine test (2.4 mg)

¹pH = 5.5 (basal and stimulated)

TABLE II

THE EFFECT OF PARENTERAL ATROPINE ON BASAL ACID SECRETION IN THE ZOLLINGER-ELLISON SYNDROME

Time (min)	Volume/15 min (ml)	Concentration (m-equiv/l)	Acid Output (m-equiv/15 min)
Basal	120	100	12.0
1-15 ¹	110	108	11.88
16-30	65	100	6.5
31-45	43	112	5.82
46-60	38	96	3.65
61-75	46	116	5.34
76-90	65	100	6.5
91-105	50	100	5.0
106-120	62	98	6.08

¹Injection atropine 1/100 gr intramuscularly.

weight 34 kg, generalized wasting of muscles, nails pink, no clubbing; pulse 78/min; blood pressure 110/70 mm of Hg; no oedema of feet, no jaundice, no enlargement of thyroid or lymph nodes. Examination of different systems was negative. Investigations showed haemoglobin 14.0 g/100 ml; peripheral smear normal; total and differential white blood count normal; erythrocyte sedimentation rate 10 mm/hr; bone marrow normoblastic. A urine and stool examination was normal. A chest radiograph was normal. SGOT was 12 units, SGPT 6 units; total proteins 3.45 g/100 ml (albumin 2.2 g/100 ml, globulins 1.25 g/100 ml and L1 = 0.12, L2 = 0.29, B = 0.36, r = 0.48); thymol turbidity 0.3 units, serum alkaline phosphatase 6.1 (1967) and 6.0 (1969) Bodansky units; serum calcium 11.6, 12.0 (1967), and 10.4 (1969) mg/100 ml; serum phosphorus 2.2, 1.3 (1967), and 4.7 (1969) mg/100 ml; serum sodium 141.0 m-equiv/l; serum potassium 4.9 m-equiv/l; serum chloride 96.8 m-equiv/l. A skull radiograph was normal; radiographs of the spine and limbs showed generalized mild osteomalacia. An electrocardiogram was normal. Fasting blood sugar was 105 mg/100 ml; D-xylose excretion 4.0 g/day (5 g dose). The average daily faecal fat excretion was 16.6-45.8 g (August 1966) and 10.0 g (February 1969); ⁵⁸Co-vitamin B₁₂ absorption 41% on faecal excretion (1966), 15% on Schilling's test (1969). A jejunal biopsy showed leaves (dissecting microscope) and normal villous height (light microscope). Culture of small intestinal fluid

showed no organisms and the pH of the content of the first loop of jejunum was 1. A gastric biopsy (Fig. 1, 1966) showed markedly increased glandular structure with an increased number of parietal cells (Fig. 2, 1969), and severe atrophic gastritis with dense infiltration of lymphocytes and moderate numbers of plasma and polymorphonuclear cells but no parietal cells. A barium meal and follow through (1966) showed markedly hypertrophic gastric and duodenal folds (Fig. 3); the mucosal pattern of upper loops of the jejunum was distorted. There was flocculation in the jejunum and rapid transit through the small intestine Fig. 4 (1969), and gastric and duodenal folds were prominent. Gastric analysis (Tables I and II) showed no circulating intrinsic factor antibodies in serum (1969).

DISCUSSION

Gastric function tests in our patient repeatedly showed markedly raised basal acid output and the ratios of the basal acid output (BAO) to the maximal acid output (MAO) and basal acid concentration (BAC) to maximal acid concentration (MAC) were always greater than 0.6. Such characteristic findings on gastric analysis have been reported only in the Zollinger-Ellison syndrome (Marks, Selzer, Louw, and Bank, 1961; Aoyagi and Summerskill, 1966; Ruppert, Greenberger, Boman, and McCullough, 1967) or excluded the gastric antrum in a post-operative condition (Scobie, McGill, Priestley, and Rovelstad, 1964). In our patient the consistently high basal acid secretion observed for over two years, the characteristic radiological findings in the stomach and duodenum, and marked hyperplasia of parietal cells on gastric biopsy should be considered adequate for the diagnosis of the Zollinger-Ellison syndrome. A negative exploration in our patient does not exclude the diagnosis of the Zollinger-Ellison syndrome as the tumour may be extremely small or aberrant pancreatic tissue may be in the duodenum (Ober-

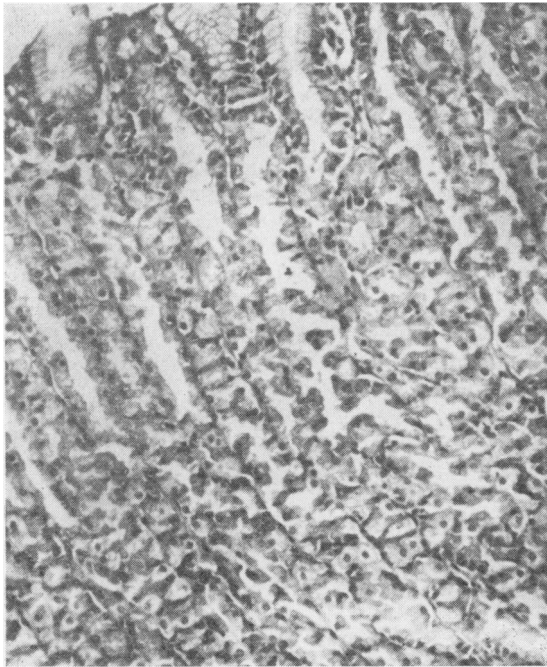


FIG. 1. *Gastric biopsy showing markedly increased glandular structure in 1966.*

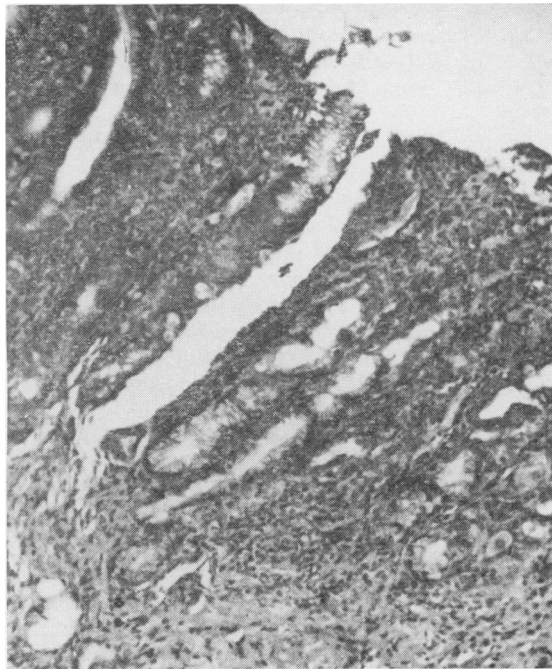


FIG. 2. *Gastric biopsy showing severe atrophic gastritis with infiltration of lymphocyte and plasma cells in 1969.*

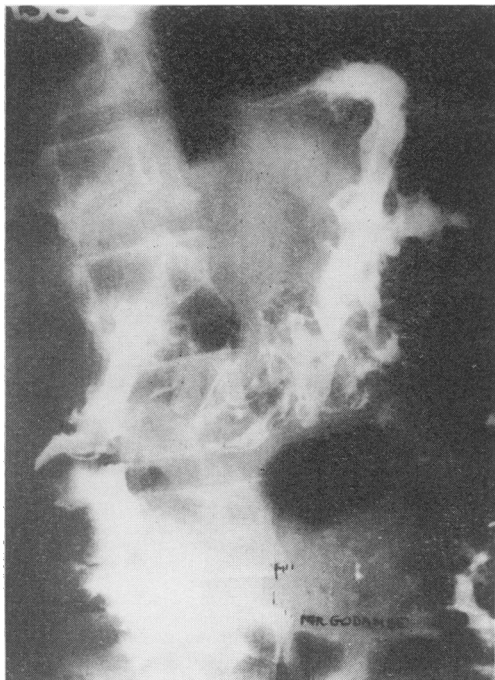


FIG. 3.

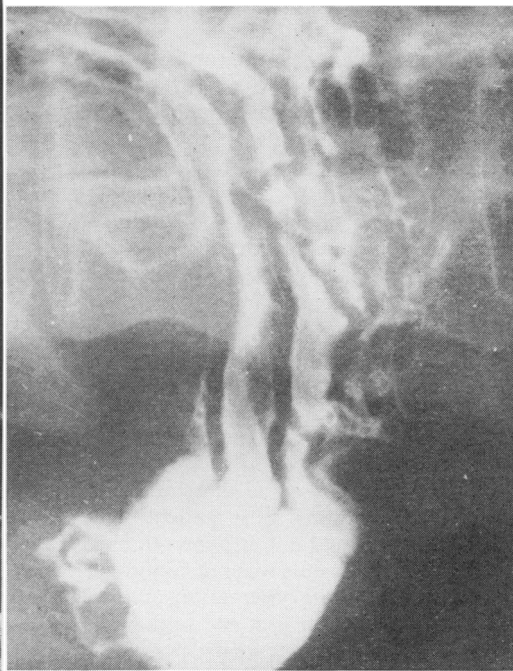


FIG. 4.

FIG. 3. *Prominent gastric and duodenal folds on barium meal study in 1966.*

FIG. 4. *Barium meal study still shows prominent gastric folds in 1969.*

heman, Nelsen, Johnson, and Dragstedt, 1961; Shay, Chey, Koide, and Burnett, 1962) or hyperplasia of islet cells may be the only abnormality (Zollinger and McPherson, 1958; Summerskill, 1959).

In the Zollinger-Ellison syndrome with peptic ulceration (Ellison and Wilson, 1964; Zollinger and Grant, 1964) chronic diarrhoea occurs in about 30 to 40% of patients and it may precede peptic ulceration by one to six years (Zollinger and Ellison, 1955; Summerskill, 1959). About 7 to 10% of patients with the Zollinger-Ellison syndrome suffer from diarrhoea (and gastric hypersecretion) only and peptic ulceration does not occur (Ellison and Wilson, 1964). Furthermore, hypokalaemia is observed in more than 50% of patients with chronic diarrhoea and the Zollinger-Ellison syndrome (Ellison and Wilson, 1964). These observations show that chronic diarrhoea and hypokalaemia are features not only of 'pancreatic cholera' but also of the Zollinger-Ellison syndrome. The important distinguishing features of the two syndromes of non-beta islet cell tumours are high basal acid secretion with peptic ulceration in the Zollinger-Ellison syndrome whereas in 'pancreatic cholera' there is hypo- or achlorhydria, watery diarrhoea, and no peptic ulceration. In our patient high basal acid secretion without peptic ulceration for more than two years followed by spontaneous, persistent achlorhydria showed that hypersecretion and subsequent achlorhydria could occur in the same individual over the course of time. It is not unreasonable to suggest that some patients with non-beta cell pancreatic tumour, chronic diarrhoea, and achlorhydria (or low acid secretion) reported in the literature might have the same high basal acid secretion earlier in the illness as was observed in our patient.

Three cases in some respects similar to our patient are reported. Lawrie, Williamson, and Hunt (1962) observed markedly raised acid output (58 m-equiv/15 min) on a test meal in a patient with the Zollinger-Ellison syndrome and achlorhydria was noted five months after stopping treatment with poldine methyl methosulphate (an anticholinergic agent). The authors attributed achlorhydria in their patient to the 'dramatic response to intensive medical treatment'. It may be assumed that achlorhydria had occurred spontaneously as anticholinergic drugs do not depress gastric acid secretion permanently. Maynard and Point (1958) observed diarrhoea and achlorhydria on two occasions in a patient who subsequently showed high acid output. Even though achlorhydria in these two patients was not confirmed with histamine stimulation these observations suggest that in a patient with non-beta islet cell tumour of the pancreas, if followed for some years, both high

basal acid secretion and achlorhydria could be detected. Melnyk, Krippaehna, Benson, and Dunphy (1965) reported markedly diminished basal acid secretion after removal of a small lymph node from the abdomen of a patient suffering from an extensive unresectable non-beta islet cell pancreatic carcinoma. Furthermore, unexplained marked regression of primary and metastatic islet cell tumours of the Zollinger-Ellison syndrome a few years after total gastrectomy has been reported (Friesen, 1967).

Achlorhydria in our patient has obviously resulted from anatomical damage to parietal cells, as gastric biopsy in 1969 showed severe, atrophic gastritis and the absence of parietal cells. Marked infiltration with lymphocytes, plasma, and polymorphonuclear cells suggest that perhaps some inflammatory or immunological process is involved in causing atrophic gastritis. Specific antibodies were detected in rabbits after injection of C-terminal tetrapeptide amide of gastrin conjugated with gamma globulin (McGuigan, 1967). Since antibodies against C-terminal tetrapeptide react specifically with human gastrin, porcine gastrin, or cholecystokinin-pancreozymin (McGuigan, 1968), antibodies (if formed) against pentagastrin may neutralize the action of circulating gastrin. Our patient, secreting large amounts of acid for more than two years, developed achlorhydria within a few months after an injection of pentagastrin (Table I). Whether this sequence of events was accidental or resulted from the formation of specific antibodies against pentagastrin (a foreign substance) is not clear. Would it not be worthwhile to inject pentagastrin (? conjugated with gamma globulin) repeatedly in patients with the Zollinger-Ellison syndrome with a view to forming antibodies and thus provide an effective medical treatment for this serious disease?

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