Gastric studies in Sjögren’s syndrome


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EDITORIAL COMMENT These studies demonstrate that deranged gastric secretion is a feature of Sjögren’s syndrome.

In 1943 Henrik Sjögren first described the syndrome which bears his name. It is generally recognized that the diagnosis can be made when any two of the following three features are present: xerostomia with or without salivary gland enlargement, keratoconjunctivitis sicca, and connective tissue disease, usually rheumatoid arthritis (Bunim, 1961; Bloch and Bunim, 1963). The xerostomia and keratoconjunctivitis sicca are due to reduced secretion by the salivary and lacrimal glands which are the seat of chronic inflammatory change. Impaired secretory function has been reported in many other sites, including the nose, pharynx, upper oesophagus, trachea and bronchi, vagina, skin, and pancreas (Gordon and Shanbrom, 1958; Fenster, Buchanan, Laster, and Bunim, 1964).

Reduced gastric acid secretion in Sjögren’s syndrome has been reported by several workers (Lutman and Favata, 1946; Godtfredsen, 1947; Behrman and Lee, 1950; Morgan and Raven, 1952; Gurling, 1953; MacLean and Robinson, 1954; Szanto, Farkas, and Gyulai, 1957; and Gordon and Shanbrom, 1958). The significance of these reports is uncertain since most are concerned with individual cases and augmented histamine stimulation was rarely used. Other workers have observed apparently normal gastric acid secretion and normal gastric histology has been reported (Ellman, Weber, and Goodier, 1951; Cardell and Gurling, 1954). However, Joske, Finckh, and Wood (1955) noted significant gastritis on histological examination of mucosal biopsies from five patients. In the present investigation, in a group of patients with Sjögren’s syndrome, gastric secretion, using augmented histamine stimulation, gastric mucosal histology, and gastric mucosal autoantibodies have been studied.

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MATERIALS AND METHODS

PATIENTS STUDIED The clinical findings in the six women studied are summarized in Table I. The diagnosis of Sjögren’s syndrome was made using the criteria described above (Bunim, 1961). Keratoconjunctivitis sicca was confirmed by diminished wetting of a filter paper strip during a five-minute Schirmer test for tear secretion, rose-bengal staining of the conjunctiva, and the finding of filamentary or punctate keratitis on slit-lamp examination. The severity of xerostomia was recorded as 0 to ++++, and past or present salivary gland enlargement was recorded. Patients were excluded when the clinical findings could be attributed to other causes, e.g., sarcoidosis, lymphoma, leukaemia, and macroglobulinaemia of Waldenström. A history of dyspepsia was sought in every patient, and, when present, barium meal examination was performed.

SEROLOGICAL STUDIES Antibody to the cytoplasm of gastric parietal cells was detected by an immunofluorescent ‘sandwich’ technique (Taylor, Roitt, Doniach, Couchman, and Shapland, 1962), using unfixed frozen sections of normal gastric body mucosa, and a serum dilution of 1 in 4. The following serological tests were also performed: tanned red cell haemagglutination tests for thyroglobulin auto-antibodies (Anderson, Buchanan, Goudie, and Gray, 1962), the Hyland latex agglutination test and sheep cell agglutination test (Ziff, Brown, Lospalluto, Badin, and McEwen, 1956), precipitin tests for antibodies to non-organ-specific cellular constituents (Anderson, Gray, Beck, Buchanan, and McElhinney, 1962), L.E. cell test and/or the Hyland latex agglutination test for antinucleoprotein, and fluorescent antibody studies for antinuclear factor (Beck, 1961). The results are set out in Table II. The morphological patterns of nuclear staining e.g., ‘homogeneous’, ‘speckled’, and ‘nucleolar’ produced by antinuclear autoantibodies were defined by the criteria described by Beck (1961, 1962, 1963).

Estimations and electrophoresis of the serum proteins were carried out as described by Buchanan, Koutras, Alexander, and Crooks (1962).

351
TABLE I

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Keratoconjunctivitis</th>
<th>Xerostomia</th>
<th>Duration of Sicca Components (years)</th>
<th>Salivary Gland Enlargement</th>
<th>Dyspepsia</th>
<th>Associated Diseases</th>
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<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>F</td>
<td>+</td>
<td>+</td>
<td>2</td>
<td>+</td>
<td>-</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>F</td>
<td>+</td>
<td>+ + + +</td>
<td>12</td>
<td>+</td>
<td>—</td>
<td>Raynaud's phenomenon</td>
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<tr>
<td>3</td>
<td>70</td>
<td>F</td>
<td>+</td>
<td>+</td>
<td>5</td>
<td>+</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>F</td>
<td>+</td>
<td>+ + + +</td>
<td>9</td>
<td>—</td>
<td>—</td>
<td>Raynaud's phenomenon</td>
</tr>
<tr>
<td>5</td>
<td>71</td>
<td>F</td>
<td>+</td>
<td>+</td>
<td>2</td>
<td>+</td>
<td>+ ¹</td>
<td>Progressive systemic sclerosis</td>
</tr>
<tr>
<td>6</td>
<td>73</td>
<td>F</td>
<td>+</td>
<td>+ + + +</td>
<td>5</td>
<td>—</td>
<td>+ ¹</td>
<td>Raynaud's phenomenon</td>
</tr>
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</table>

¹No abnormality in stomach or duodenum detected on barium meal examination.

TABLE II

<table>
<thead>
<tr>
<th>Patient</th>
<th>γ-Globulin1 (g/100 ml.)</th>
<th>S.S.C.A. Test</th>
<th>Hyland R.A. Test</th>
<th>L.E. Test</th>
<th>A.N.F. Testa</th>
<th>Sjögren Precipitating Testb</th>
<th>T.R.C. Testc</th>
<th>W.B.C. (cells/cmm.)</th>
<th>E.S.R. (mm. in first hr.)</th>
<th>Hb %</th>
<th>M.C.H.C. (%)</th>
<th>Serum B12 (µg./ml.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1·1</td>
<td>ve</td>
<td>+ ve</td>
<td>- ve</td>
<td>- ve</td>
<td>- ve</td>
<td>ve</td>
<td>5,300</td>
<td>5</td>
<td>94</td>
<td>30·0</td>
<td>292</td>
</tr>
<tr>
<td>2</td>
<td>1·2</td>
<td>+ ve</td>
<td>+ ve</td>
<td>- ve</td>
<td>+ ve</td>
<td>- ve</td>
<td>+ ve</td>
<td>(1:4,000) 6,000</td>
<td>15</td>
<td>80</td>
<td>31·5</td>
<td>234</td>
</tr>
<tr>
<td>3</td>
<td>1·1</td>
<td>+ ve</td>
<td>+ ve</td>
<td>- ve</td>
<td>- ve</td>
<td>- ve</td>
<td>+ ve</td>
<td>4,400</td>
<td>19</td>
<td>92</td>
<td>33·3</td>
<td>128</td>
</tr>
<tr>
<td>4</td>
<td>0·9</td>
<td>- ve</td>
<td>+ ve</td>
<td>- ve</td>
<td>+ ve</td>
<td>- ve</td>
<td>- ve</td>
<td>1,800</td>
<td>8</td>
<td>61</td>
<td>30·1</td>
<td>460</td>
</tr>
<tr>
<td>5</td>
<td>1·3</td>
<td>- ve</td>
<td>+ ve</td>
<td>+ ve</td>
<td>+ ve</td>
<td>+ ve</td>
<td>- ve</td>
<td>6,900</td>
<td>30</td>
<td>92</td>
<td>30·2</td>
<td>366</td>
</tr>
<tr>
<td>6</td>
<td>0·8</td>
<td>+ ve</td>
<td>+ ve</td>
<td>- ve</td>
<td>- ve</td>
<td>(1·64)</td>
<td>- ve</td>
<td>6,300</td>
<td>16</td>
<td>86</td>
<td>31·0</td>
<td>520</td>
</tr>
</tbody>
</table>

1γ-globulin normal <1·0 g./100 ml. 
S.S.C.A. = sensitized sheep cell agglutination test for rheumatoid factor, diagnostic titre 1·32 or greater
2A.N.F. = antinuclear factor. H = homogeneous staining. S = speckled staining. N = nucleolar staining, diagnostic titre 1·16 or greater.

*Precipitating autoantibodies to non-organ specific tissue components, diagnostic titre 1·1. 
*T.R.C. test = thyroglobulin tanned red cell test, diagnostic titre 1·16 or greater.

RESULTS

The results of tests for gastric parietal cell antibodies, augmented histamine tests, and gastric mucosal histology are summarized in Table III.

Four of the six patients had no acid in the basal and histamine-stimulated gastric juice. In three of these the volume of gastric secretion was very low, antibodies to parietal cells were demonstrated, and the mucosal biopsy showed severe gastritis, with metaplasia to intestinal type of gland in one case. Although the fourth of these patients was achlorhydric, the volume of secretion was moderately large, the test for parietal cell antibodies was negative, and histology failed to reveal gastritis.
The remaining two patients secreted larger volumes of gastric juice with acid after histamine stimulation, but in one the basal secretions were anac. Both showed gastritis but parietal cell antibodies were absent.

In the four patients with histamine-fast achlorhydria the xerostomia was more severe and the sicca component of longer duration than in the two with an acid gastric juice. There was no obvious relation between the results of the gastric studies and the results of other laboratory investigations, including measurement of haemoglobin and serum vitamin B₁₂ concentration.

**DISCUSSION**

The number of patients studied is relatively small, but the frequency of abnormalities is striking and suggests that deranged gastric function is a real component of Sjögren's syndrome. The proportion of patients with achlorhydria is large, even allowing for the fact that patients were middle-aged or elderly women. There are few 'normal' data for this section of the population but Grossman, Kirs, and Gillespie (1963) reported the incidence of achlorhydria to be only about 10% in patients over 60 years old. In most of our cases, the achlorhydria was associated with severe gastritis which accords with the demonstration that the amount of acid secreted is correlated with the histological appearances of the gastric mucosa (Bock, Richards and Witts, 1963). The presence of parietal cell auto-antibodies in three of the six patients corresponds with the observations of Adams, Glen, Kennedy, Mackenzie, Morrow, Anderson, Gray, and Middleton (1964) that there is an association between these antibodies and gastric mucosal abnormalities. Parietal cell antibodies have been found in 61% of patients with biopsy-proved atrophic gastritis (Doniach and Roitt, 1964) and in 11 of 33 iron-deficient patients with histamine-fast achlorhydria (Dagg, Goldberg, Anderson, Beck, and Gray, 1964).

Various aspects of gastric function have been described in patients with Sjögren's syndrome but the present investigation is the first to utilize the augmented histamine test, gastric biopsy, and tests for gastric autoantibodies in a group of such patients. Previous reports of the absence of gastric abnormalities may be due partly to incomplete investigations and partly to differences in duration and severity of the sicca component of the disease.

The histological similarities between the lacrimal and salivary glands and the gastric mucosa suggest that the same basic defect may be present in all these organs, resulting in the sicca component which is such a characteristic feature of Sjögren's syndrome. This syndrome is associated with a high incidence of immunological abnormalities, and the finding of gastric autoantibodies in some of our patients is further evidence in favour of an autoimmune reaction. However, it is also possible that the gastric auto-antibodies are secondary to pathological changes since secretory abnormalities are found in Sjögren's syndrome in many organs including the pancreas (Fenster et al., 1964).

**SUMMARY**

Gastric function has been studied in six patients with Sjögren's syndrome. There was a high incidence of histamine-fast achlorhydria, histologically proven gastritis, and autoantibodies to parietal cells. There
appeared to be a relation between these abnormalities and the involvement of the salivary and lacrimal glands. It is concluded that deranged gastric function is a feature of Sjögren’s syndrome.

We are indebted to Professor Sir Edward Wayne and Professor Andrew W. Kay for advice and criticism.

ADDENDUM

Recently, Walker, Doniach, Roitt, and Sherlock (1965) have described a non-organ-specific antibody which probably reacts with a mitochondrial antigen in the serum of patients with primary biliary cirrhosis and occasionally in patients with connective tissue disease. By reacting particularly with cell types rich in mitochondria, e.g., gastric parietal cells, this antibody is capable of giving false-positive reactions in immuno-fluorescence tests for organ-specific autoantibodies. Accordingly, we have now performed tests for this antibody, and have obtained negative results with the four sera giving positive immuno-fluorescence tests for gastric antibody in the present paper. It is concluded that these four sera contain organ-specific gastric parietal cell antibody.

REFERENCES


