Part II In megaloblastic anaemia

EDITORIAL SYNOPSIS There is a relatively high incidence of atrophic gastritis in patients in the Punjab with megaloblastic anaemia. No correlation was found with age, degree of anaemia, steatorrhoea, iron deficiency, or response to vitamin B_{12} and folic acid.

Nutritional deficiency, secondary to inadequate diet or conditioned by structural or functional disease of the small intestine, is the chief cause of the megaloblastic anaemias seen in the Punjab. It was therefore decided to examine the gastric mucosa of patients with megaloblastic anaemia (excluding that associated with pregnancy or the puerperium) in order to establish the incidence of atrophic gastritis in these cases, and to see if gastric atrophy, without marked cellular infiltration, occurred in this type of anaemia.

MATERIAL AND METHODS

Gastric mucosal biopsies were obtained from 30 patients with megaloblastic anaemia; there were 17 males and 13 females and their clinical data and laboratory findings are set out in Tables I and II.

DIET An assessment of the diets of the patients was made on the basis of the amount of meat, milk, wheat, pulses, and vegetables consumed.

NUTRITIONAL DEFICIENCY SIGNS Each patient was examined for koilonychia, glossitis, and abnormal pigmentation of the skin. This is frequently seen in patients who have other stigmata of nutritional deficiency, and consists of dark brown pigmentation of the hands, particularly over the interphalangeal joints. Baker, Ignatius, Johnson, and Vaish (1963) described this type of brown pigmentation of the skin in South Indian patients who had vitamin B_{12} deficiency.

BLOOD LOSS Particular attention was paid to any history of blood loss; proctoscopy was performed to exclude haemorrhoids, and pelvic examinations were done in all parous women.

STOOL EXAMINATIONS The stools were examined on several occasions for occult blood and the ova of hookworm.

FAECAL FAT EXCRETION This was estimated in every case, using the method of van de Kamer, ten Bokkel Huinink, and Weyers (1949). The tests were performed on a three-day collection of stool, while the fat content of the diet was 50-100 g. per day. The results were expressed as a daily average, and steatorrhoea was considered to be present when the daily excretion exceeded 7 g.

RADIOLOGY Active pulmonary tuberculosis was excluded by fluoroscopy in all patients, and barium studies of the small intestine were done in the 15 patients who had gastrointestinal symptoms, which ranged from vague central abdominal discomfort to colicky pain suggestive of subacute obstruction in one case.

HAEMATOLOGY Standard haematological techniques were employed (Dacie, 1956). The diagnosis of megaloblastic anaemia was established on the basis of a macrocytic peripheral blood and a megaloblastic bone marrow. Peripheral blood films were carefully scrutinized for the presence of hypochromia of the red cells.

SERUM IRON This was estimated in seven instances only, using Ramsay's method (1957).
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GASTRIC ACID Gastric acidity was determined by means of the augmented histamine test (Kay, 1953), with the minor modifications of Bock, Richards, and Witts (1963), using 50 mg. of pheniramine maleate to counteract the effect of the large dose of histamine. The gastric juice was obtained by means of continuous hand suction, and the acidity expressed as the number of milliequivalents of HCl secreted in one hour following the administration of histamine (0·04 mg. per kilogram of body weight).

GASTRIC MUCOSA Gastric mucosal biopsies were obtained in all of the 30 patients by means of Wood's flexible peroral suction biopsy tube (Wood, Doig, Motteram, and Hughes, 1949), and in many cases two biopsies were taken from each patient. The sections were examined independently by two pathologists, neither of whom was aware of the haemoglobin level or acid output of the patients. Not only was there almost complete agreement between the observers with regard to the degree of gastritis present, but, where two biopsies were taken from the same patient, similar findings were present in approximately 90% of the cases. The classification of Bock, Arapakis, Witts, and Richards (1963) was used to determine the presence of gastritis.

RESULTS

These are set out in Tables I and II.

GASTRIC MUCOSA This was abnormal in 23 of the 30 patients (76·6%). Superficial gastritis was present in nine (30%), and atrophic gastritis in 14 (46·6%). The atrophic gastritis was of a moderate degree in eight patients and severe in six. In every case of atrophic gastritis the glandular atrophy was accompanied by marked cellular infiltration, that is, true gastric atrophy with little or no cellular infiltration was not encountered in the study.

GASTRIC ACIDITY In seven instances out of a total of 14, atrophic gastritis was associated with complete achlorhydria or marked hypochlorhydria of less than 1 mEq. of HCl following maximal histamine stimulation. In five others the maximal acid output ranged from 1·2 to 2·1 mEq. and in the remaining two, whose glandular atrophy was of a moderate degree, the maximal acid output was 8·6 and 7·6 mEq. Achlorhydria was not found in any of the 16 patients who had a normal gastric mucosa or superficial gastritis; only one had hypochlorhydria (2 mEq.) while in the remaining 15 the maximal acid output ranged from 4·2 to 19·1 mEq. The relationship of the acid output to the histology of the gastric mucosa is shown in Table III.

The results of similar investigations performed on 29 normal subjects and 18 duodenal ulcer patients, together with the results obtained in the iron-deficiency study and in the present group of 30 patients, are set out in Table IV. Atrophic gastritis

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**Table I**

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Diet</th>
<th>Duration Diarrhoea</th>
<th>'Deficiency' Signs</th>
<th>Haemoglobin (g. %)</th>
<th>Serum Iron (mg. per 100 ml.)</th>
<th>Folic Acid</th>
<th>B12</th>
<th>Maximal Acid Output (mEq. per hr.)</th>
<th>Gastric Mucosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26</td>
<td>Fair</td>
<td>4 mth.</td>
<td>-</td>
<td>7·4</td>
<td>26·8</td>
<td>+</td>
<td>5·7</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>Poor</td>
<td></td>
<td>-</td>
<td>8·6</td>
<td>23·4</td>
<td>+</td>
<td>10·7</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Very poor</td>
<td></td>
<td>None</td>
<td>-</td>
<td>5·9</td>
<td>4·4</td>
<td>+</td>
<td>6·2</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Fair</td>
<td>4 mth.</td>
<td></td>
<td>+</td>
<td>8·5</td>
<td>23·4</td>
<td>+</td>
<td>19·1</td>
<td>Superficial gastritis</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>Fair</td>
<td>3 mth.</td>
<td>+</td>
<td>6·8</td>
<td>13·9</td>
<td>+</td>
<td>10·4</td>
<td>Superficial gastritis</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>Very poor</td>
<td>3 mth.</td>
<td>+</td>
<td>5·7</td>
<td>21·9</td>
<td>+</td>
<td>2·0</td>
<td>Superficial gastritis</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>53</td>
<td>Very poor</td>
<td>3 mth.</td>
<td>+</td>
<td>7·6</td>
<td>47</td>
<td>6·0</td>
<td>7·6</td>
<td>Superficial gastritis</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>Fair</td>
<td>2 yr.</td>
<td>+</td>
<td>7·7</td>
<td>30</td>
<td>13·0</td>
<td>8·7</td>
<td>Moderate atrophic gastritis</td>
<td>(Gluten-free diet)</td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>Fair</td>
<td></td>
<td>-</td>
<td>8·0</td>
<td>6·0</td>
<td>+</td>
<td>0·0</td>
<td>Moderate atrophic gastritis</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>14</td>
<td>Good</td>
<td>12 yr.</td>
<td>+</td>
<td>7·0</td>
<td>30</td>
<td>13·0</td>
<td>+</td>
<td>Moderate atrophic gastritis</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>21</td>
<td>Very poor</td>
<td>None</td>
<td>+</td>
<td>4·7</td>
<td>7·6</td>
<td>+</td>
<td>2·1</td>
<td>Moderate atrophic gastritis</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>24</td>
<td>Poor</td>
<td></td>
<td>-</td>
<td>10·0</td>
<td>29·8</td>
<td>+</td>
<td>1·2</td>
<td>Moderate atrophic gastritis</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>47</td>
<td>Poor</td>
<td>2 mth.</td>
<td>-</td>
<td>4·4</td>
<td>16·4</td>
<td>+</td>
<td>0·0</td>
<td>Moderate atrophic gastritis</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>45</td>
<td>Fair</td>
<td>10 days</td>
<td>-</td>
<td>5·9</td>
<td>30</td>
<td>11·8</td>
<td>2·0</td>
<td>Severe atrophic gastritis</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>18</td>
<td>Poor</td>
<td></td>
<td>-</td>
<td>4·3</td>
<td>5·0</td>
<td>Uncertain</td>
<td>2·0</td>
<td>Severe atrophic gastritis</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>35</td>
<td>Very poor</td>
<td>None</td>
<td>+</td>
<td>2·9</td>
<td>4·3</td>
<td>+</td>
<td>0·7</td>
<td>Severe atrophic gastritis</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>80</td>
<td>Very poor</td>
<td>None</td>
<td>+</td>
<td>4·0</td>
<td>28</td>
<td>4·5</td>
<td>+</td>
<td>Severe atrophic gastritis</td>
<td></td>
</tr>
</tbody>
</table>
was not found in any normal subject or duodenal ulcer patient. The incidence of atrophic gastritis in megaloblastic anaemia and 'idiopathic' iron-deficiency anaemia was approximately equal and significantly greater than in post-haemorrhagic iron-deficiency anaemia.

**SEX** There was no correlation between the sex of the patients and the incidence of atrophic gastritis which was found in nine of the 17 male patients, and in five of the 13 females.

**TABLE III**

### RELATIONSHIP BETWEEN THE ACID OUTPUT AND THE HISTOLOGY OF GASTRIC MUCOSA

<table>
<thead>
<tr>
<th>Histology</th>
<th>No. of Cases</th>
<th>Acid following Maximal Histamine Stimulation (mEq./hr.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>7</td>
<td>6-8</td>
</tr>
<tr>
<td>Superficial gastritis</td>
<td>9</td>
<td>7-9</td>
</tr>
<tr>
<td>Atrophic gastritis</td>
<td>8</td>
<td>2-7</td>
</tr>
<tr>
<td>Severe atrophic gastritis</td>
<td>6</td>
<td>0-83</td>
</tr>
</tbody>
</table>

**AGE** There was no evidence that the incidence of atrophic gastritis increased with increasing age, as none of the 19 who were under 40 years of age and five of the 11 who were over 40 years had atrophic gastritis.

**DEGREE OF ANAEMIA** This was assessed as follows:

- **Haemoglobin** The haemoglobin levels ranged from 1·6 g.% to 10 g.% (average 6·2 g.%). There was no correlation between the degree of anaemia and the incidence of atrophic gastritis, since the average haemoglobin level of those with atrophic gastritis (5·4 g.%) was only slightly lower than that of the remainder (6·9 g.%). who had normal gastric mucosa or superficial gastritis.

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**TABLE IV**

### INCIDENCE OF ATROPHIC GASTRITIS IN NORMAL AND DUODENAL ULCER SUBJECTS, AND IN IRON-DEFICIENCY AND MEGALOBLASTIC ANAEMIA

<table>
<thead>
<tr>
<th>No. Acid following Maximal Histamine Stimulation (mEq./hr.)</th>
<th>No. with Atrophic Gastritis</th>
<th>% Incidence of Atrophic Gastritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td>29</td>
<td>12-0</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>18</td>
<td>19-0</td>
</tr>
<tr>
<td>Iron-deficiency anaemia (blood loss)</td>
<td>47</td>
<td>7-7</td>
</tr>
<tr>
<td>Iron-deficiency anaemia (idiopathic)</td>
<td>23</td>
<td>4-3</td>
</tr>
<tr>
<td>Megaloblastic anaemia</td>
<td>30</td>
<td>4-8</td>
</tr>
</tbody>
</table>

**Serum Iron** This was low in each of the seven patients in whom it was estimated (range 18 to 47 μg. per 100 ml., average 30 μg. per 100 ml.).

**Stool examinations** A few hookworm ova were present in the stools of two male and two female patients; none was heavily infested with hookworm.

**MALABSORPTION** Malabsorption was assessed by a history of diarrhoea and steatorrhoea and radiologically.

- **History of diarrhoea** Atrophic gastritis was found in six of the 17 patients who had a history of diarrhoea of duration ranging from 10 days to 12 years, and in eight of the 13 who had no diarrhoea.

- **Steatorrhoea** The incidence of atrophic gastritis was practically the same whether steatorrhoea was present or not. Fourteen patients had steatorrhoea, and their daily excretion of fat ranged from 11·6 to 29·8 g. (average 17·1 g.). Twelve of the 14 had a history of diarrhoea, while the other two, who excreted 23·4 g. and 29·6 g. of fat daily, had no diarrhoea.
Radiology  In four patients the mucosal pattern of the small intestine was altered. In the other patients investigated these studies contributed nothing, possibly because non-flocculating barium was unfortunately not used. The patient who had colicky abdominal pain had abnormal radiological appearances consistent with the findings, at laparotomy, of multiple tuberculous strictures of the ileum, with dilatation of the gut proximal to each stricture (no. 2, Table I).

Assessment of nutritional status  Diet and nutritional status were examined.

Diet  With one exception, all the patients were drawn from the poorer social classes. On the basis of the amount of meat, milk, wheat, pulses, and vegetables consumed, the diet was classified as ‘good’ (one patient), ‘fair’ (12), ‘poor’ (7), and ‘very poor’ (10). Four of the last group could only afford to eat wheat for a few weeks following harvest each year, and generally ate chappattis ( unleavened bread cakes) made from maize flour, with a little vegetable, taking no milk, meat, or first-class protein. The only patient whose diet was ‘good’ was considered to have coeliac disease on the basis of a long history of diarrhoea, steatorrhoea, and a good response to a gluten-free diet (no. 10, Table I). This patient, together with four of the 12 whose diets were ‘fair’, and nine of the 17 whose diets were ‘poor’ or ‘very poor’, had atrophic gastritis. These results are inadequate for statistical analysis, but the fact that six of the 10 whose diets were ‘very poor’ (including three of the four who could only afford to eat maize) had atrophic gastritis, suggests that the incidence of the gastric mucosal lesion might very well be greater in severe dietary deficiency. The biopsies of the three maize eaters showed the most marked degrees of glandular atrophy and intestinal metaplasia encountered in the study.

Nutritional deficiency signs  The incidence of atrophic gastritis was approximately the same whether koilonychia or glossitis were present or not. Eight of the 12 patients who had koilonychia and eight of the 15 who had glossitis had atrophic gastritis. Abnormal brown pigmentation of the skin was present in nine patients. In six this consisted of dark brown pigmentation of the skin of the dorsum of the hands, particularly over the interphalangeal joints, while in three, all of whom were maize eaters, there were the symmetrical pigmented skin lesions of the wrists and ankles which are typical of pellagra. One of these (no. 11, Table I) was admitted in coma which responded to nicotinic acid. Six of the nine patients who had abnormal pigmentation, including the three who had pellagra, had atrophic gastritis. Again these figures are too small for adequate statistical evaluation, but suggest a tendency for atrophic gastritis to occur more frequently in patients who show this particular sign of nutritional deficiency.

Response to therapy  Thirteen patients responded to folic acid, four to vitamin B12 (three of these had achlorhydria), and 10 required both folic acid and vitamin B12. Three patients left the hospital before an adequate response had been obtained. Oral iron was given to every patient when a repeat bone marrow showed normoblastic erythropoiesis. No conclusions can be drawn from the relationship of the incidence of atrophic gastritis and response to therapy since, in only a very few cases was it possible to determine whether the anaemia was due to deficiency of folic acid or vitamin B12, on the basis of a complete haematological response to small doses of either vitamin (100 μg. of folic acid or 5 μg. of vitamin B12). Some severely anaemic patients were given blood transfusions on admission, or were treated with 10 to 20 mg. of folic acid daily from the outset. Others were unwilling or unable for economic reasons to remain in hospital after subjective improvement had begun, and only a few returned for adequate follow up.

Discussion  The gastric mucosal lesion in chronic atrophic gastritis is apparently non-specific and the aetiology almost certain multifactorial (Coghill, 1960). Age, malabsorption, iron deficiency, nutritional deficiency, and disturbance of immune tolerance have all been suggested as causal factors in the pathogenesis of the gastric mucosal lesion.

It has been suggested that it occurs as part of the aging process in otherwise normal people, but this has not been clearly demonstrated so far (Coghill and Williams, 1958). The high incidence of atrophic gastritis in our group of 30 patients with megaloblastic anaemia, 14 of whom had varying degrees of gastric glandular atrophy, did not appear to be related to age. In our previous study of 70 patients with hypochromic anaemia, moreover, there was also no real correlation between the age of the patients and the incidence of atrophic gastritis, and one of us Joseph (1963) did not find a single instance of achlorhydria during the course of a survey of 100 normal Punjabi males, of whom there were 25 in each of four age groups ranging from 20 to 59 years.

The significance of atrophic gastritis in patients with malabsorption is far from clear, and it has been suggested that it may occur as an extension of the disease process from elsewhere in the alimentary tract, as in tropical sprue (Delamore and Shearman,
1965). Floch and Thomassen (1963) reported a 40% incidence in cases of tropical sprue, but found no correlation between the type and severity of the gastric mucosal lesion and age, anaemia, or results of absorption studies. Hansky and Shiner (1963) found atrophic gastritis in six of 15 patients (40%) with idiopathic steatorrhoea, and felt that the high incidence was somehow related to the intestinal lesion. In the present study of patients with megaloblastic anaemia we have found a similar incidence (46.6%) of atrophic gastritis, but this was not related to steatorrhoea. Specific malabsorption of folic acid or vitamin B12 without malabsorption of fat might have been responsible for the megaloblastic anaemia in those patients who did not have steatorrhoea, but the diets of all but four in this group were poor and only fair in the remainder. It is more likely, therefore, that the aetiology of the megaloblastic anaemia in their case was primary dietary deficiency, and there was a tendency for atrophic gastritis to occur more frequently in those patients whose diets were most deficient. The effect of malabsorption and primary nutritional deficiency, however, cannot be logically separated, and the incidence of megaloblastic anaemia in primary dietary deficiency is unlikely to be significantly greater than in the secondary nutritional deficiency states which result from prolonged untreated malabsorption. It may be, therefore, that secondary nutritional deficiency is an important aetiological factor in the pathogenesis of atrophic gastritis in cases of idiopathic steatorrhoea or tropical sprue, while primary nutritional deficiency may be responsible for a similar incidence of atrophic gastritis in patients who do not have malabsorption, but whose diet is quite inadequate.

From the results of our study of 70 patients with hypochromic anaemia, nutritional deficiency appears to be more important than iron deficiency in the pathogenesis of chronic atrophic gastritis, since the incidence was significantly greater in patients whose anaemia was 'idiopathic' than in others whose anaemia was due to blood loss. It is interesting to find, in support of the importance of nutritional deficiency, a still greater incidence of atrophic gastritis in the present study of patients with megaloblastic anaemia who had evidence of multiple nutritional deficiencies Moreover, the patients who had pellagra and had the greatest number of stigmata of nutritional deficiency, had the severest degrees of gastric glandular atrophy encountered in the study.

Coghill (1960) found that atrophic gastritis occurred more frequently in patients with 'idiopathic' hypochromic anaemia than in anaemia due to blood loss, but has made no suggestion as to the cause of the anaemia in this idiopathic group. Recently Delamore and Shearman (1965) have put forward an interesting hypothesis which might explain Coghills findings. They suggest that the atrophic gastritis found in Coghills idiopathic group represented a disorder of immune tolerance, and that the gastritis was a primary lesion. We have suggested, however, that nutritional deficiency, due either to dietary deficiency or malabsorption of iron, was responsible for the anaemia in our idiopathic group and that, while they presented with iron-deficiency anaemia they appeared to be deficient in other nutrients as well. The approximately equal incidence of atrophic gastritis in megaloblastic anaemia and nutritional deficiency normoblastic anaemia strongly suggests a common basis of nutritional deficiency in each. A search for parietal cell antibodies in our patients would be interesting. If, however, the atrophic gastritis found in these patients was due to autoimmune disease and could be expected to progress to gastric atrophy and clinically overt pernicious anaemia, we should expect to find such cases of complete gastric atrophy and instances of neuropathy secondary to deficiency of intrinsic factor, particularly in an area where patients seldom continue adequate maintenance therapy. This type of gastric mucosal lesion has never been found by us, and the neuropathy is rarely, if ever, seen. During the three-year period ending 31 December 1964, when at least 70 cases of megaloblastic anaemia were treated in the hospital, no case of subacute combined degeneration of the cord was encountered.

The high incidence of the gastric mucosal abnormality in the present study suggests that nutritional deficiency is a very important causal factor whether it is simply due to poor diet or conditioned in people whose diets are only marginally adequate, by disordered structure or function of the small intestine.

**SUMMARY**

The results of gastric mucosal biopsies taken from 30 patients suffering from megaloblastic anaemia are reported. The mucosa was abnormal in 23 (76.6%), superficial gastritis was present in nine (30%), and atrophic gastritis in 14 (46.6%). Gastric atrophy without inflammatory cellular infiltration was not encountered in any biopsy specimen. The incidence tended to be greater and the degree of glandular infiltration more severe in patients who showed abnormal pigmentation of the skin, in some cases amounting to frank pellagra. Age, the degree of anaemia, iron deficiency, or the presence of malabsorption, as judged by steatorrhoea, did not appear to influence the incidence of atrophic gastritis, and it is suggested that nutritional de-
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... deficiency, either from inadequate diet alone, or conditioned by disease of the small intestine, may be an important factor in the pathogenesis of chronic atrophic gastritis.

We are grateful to Professor A. A. Brash and Dr. D. N. Wysham for permission to study their patients, to the staff of the Department of Pathology of Brown Memorial Hospital for their assistance with the histological diagnosis, to Mr. A. A. Jenkins for the photographs, and to Mr. Lalit Kumar Lal for technical assistance. We are indebted to Hoechst Pharmaceuticals, New Delhi, who kindly donated the pheniramine maleate used in the study.

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