The absorption of radioactive vitamin $B_{12}$ and the secretion of hydrochloric acid in patients with atrophic gastritis

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EDITORIAL SYNOPSIS This paper correlates the absorption of vitamin $B_{12}$ with the gastric acidity and with the histological changes in the stomach of patients with simple atrophic gastritis who have no family history of pernicious anaemia. It demonstrates marked impairment of absorption of vitamin $B_{12}$ in some of them. There is a good but by no means complete correlation between the severity of the gastric atrophy and the depression of gastric function. The bearing of this work on the pathogenesis of Addisonian pernicious anaemia is discussed.

It is now well known that chronic atrophic gastritis may occur in patients who do not have Addisonian pernicious anaemia, and that the histological appearance of the gastric mucosa in patients with and without pernicious anaemia may be indistinguishable. In fact there is no pathognomonic histological gastric lesion in pernicious anaemia (Magnus, 1958; Williams, Coghill, and Edwards, 1958). Furthermore defective absorption of vitamin $B_{12}$ has been found in some patients with atrophic gastritis when there was no overt haematological evidence of Addisonian pernicious anaemia (Badenoch, 1954; Callender and Denborough, 1957; Mollin, Booth, and Baker, 1957; Siurala and Nyberg, 1957; Glass, Speer, Nieburgs, Ishimori, Jones, Baker, Schwartz, and Smith, 1960). However, some of these patients were either suffering from early Addisonian pernicious anaemia or were from families of patients with pernicious anaemia (Callender and Denborough, 1957; Siurala and Nyberg, 1957). In them factors other than gastric atrophy may contribute to diminished ability to secrete intrinsic factor (McIntyre, Hahn, Conley, and Glass, 1959).

During the course of an investigation into the histological appearances of the gastric mucosa, patients were found with atrophic gastritis unassociated with clinical or haematological evidence of Addisonian pernicious anaemia, and with no certain family history of pernicious anaemia. They have provided the basis for a study of the relationship between chronic inflammation and atrophy of the gastric mucosa on the one hand, and the secretion of intrinsic factor and hydrochloric acid on the other. The results are reported in this paper.

MATERIALS AND METHODS

PATIENTS STUDIED Using the flexible suction biopsy tube of Wood, Doig, Motteram, and Hughes (1949), modified by Coghill and Williams (1955), one or more gastric biopsy specimens were obtained from 124 patients with atrophic gastritis who suffered from non-ulcer dyspepsia (48), 'idiopathic' hypochromic anaemia (39), various gastric operations (13), acute gastric ulcer (7), gastroscope gastric atrophy (4), myxoedema (2), or other miscellaneous medical disorders (11). One patient (case 14, Table IV) in the last group suffered from megaloblastic anaemia due to treatment with phenobarbitone; her serum $B_{12}$ concentration was 175 $\mu$g per ml and the condition responded to treatment with folic acid.

Non-anaemic patients with atrophic gastritis who had macrocytes in the peripheral blood smear, early megaloblastic change in the marrow, serum $B_{12}$ levels within the range found in pernicious anaemia, i.e., less than 100 $\mu$g per ml, and a subnormal $B_{12}$ absorption, were considered to be suffering from early pernicious anaemia and were excluded. However, patients were included if a subnormal serum $B_{12}$ level was the only abnormality present.

The studies we report in patients with hypochromic anaemia, gastric ulcer, and myxoedema were performed after these disorders had been cured by medical treatment.
The family history was investigated in 106 patients, 61 with atrophic gastritis and 45 with superficial or mixed gastritis. In only one (case 39) of the 18 patients (11 with atrophic gastritis) in whom a family history was not obtained was radiovitamin B₁₂ absorption impaired, and in her it was entirely normal after Carbachol. There was a possible history of pernicious anaemia in the mother of one patient with superficial gastritis and in the grandmother of another with atrophic gastritis. There was a doubtful history of pernicious anaemia in the sister of another patient with atrophic gastritis. In all the patients with a possible family history of pernicious anaemia the absorption of radioactive B₁₂ was entirely within normal limits. There was no family history suggestive of pernicious anaemia in any of the patients who absorbed abnormally small amounts of radioactive B₁₂.

**Classification of Patients** The patients were grouped on the basis of the histological findings in their gastric biopsy specimens which were classified as follows (Williams, Edwards, Lewis, and Coghill, 1957):

- **Chronic superficial gastritis** There is atrophy of the glands in their superficial part and infiltration of the stroma with inflammatory cells, mainly plasma cells and lymphocytes.
- **Chronic atrophic gastritis** Glandular atrophy is complete or almost so and there is a variable amount of infiltration of the stroma with inflammatory cells. Intestinal metaplasia and pyloric gland heterotopia are common.
- **Gastric atrophy** The mucosal changes are the same as in atrophic gastritis, but inflammatory cells are inconspicuous. In our experience this condition is rarely seen. It was found in only six of 44 patients with pernicious anaemia (Williams et al., 1958), and only once in this series of patients. Perhaps it should be regarded as a variant of atrophic gastritis, for the degree of inflammatory change in many examples of chronic atrophic gastritis is slight.
- Abnormalities in the gastric mucosa, too slight to allow classification into any of these groups, were found in some of the biopsy specimens from some patients with gastritis and were classified under the heading of miscellaneous minor mucosal changes (Williams et al., 1957).

The patients were divided into three groups. The first was made up of 52 patients with superficial or 'mixed' gastritis whose several biopsy specimens showed either chronic superficial gastritis, or chronic superficial gastritis in some and chronic atrophic gastritis or miscellaneous minor changes or normal mucosa in others; or atrophic gastritis in some with miscellaneous minor changes or normal mucosa in others. The second group comprised 57 patients from whom two or more biopsy specimens were obtained, all of which showed chronic atrophic gastritis. The third group consisted of 15 patients from whom only one biopsy was obtained, showing atrophic gastritis in 14 and gastric atrophy in one. Patients in this group were regarded as cases of atrophic gastritis rather than of mixed gastritis because of the likelihood that the single biopsy specimens were, eight or nine times out of 10, representative of the whole gastric mucosa (Williams et al., 1957).

We have also included for comparison studies of radioactive B₁₂ absorption in 84 patients with Addisonian pernicious anaemia and of the serum vitamin B₁₂ levels in a group of 222 apparently healthy young and middle-aged control subjects who have been reported in detail elsewhere (Mollin and Baker, 1955; Mollin et al., 1957; Mollin, 1962).

**Serum vitamin B₁₂ concentrations** These were measured by micro-biological assay, using either the bacillus or the z strain of Euglena gracilis as test organism (Ross, 1952; Hutner, Bach, and Ross, 1956). Concentrations in health range from 140 to 960 μg per ml. (Table I); patients with pernicious anaemia have levels of less than 100 μg per ml. (Mollin and Ross, 1954). The serum B₁₂ level was measured in all except one patient.

**Absorption of radioactive vitamin B₁₂** This was measured in 110 patients, using in most instances the faecal excretion technique described by Booth and Mollin (1956). The results of the faecal excretion test were confirmed in most cases by measuring the hepatic radioactivity. In a few patients the hepatic uptake method (Glass, Boyd, Gellin, and Stephanson, 1954) was used alone.

Oral test doses of 1·0 μg. of ⁵⁸Co-labelled B₁₂ were used. Young normal subjects usually absorb 0·5 μg. of this dose or more (Mollin, unpublished data). Control subjects (a group made up of normal people of various ages and convalescent hospital patients with no evidence of gastrointestinal disorder) absorb from 0·26 to 0·98 μg. They absorb more than 0·5 μg. if the dose of B₁₂ is accompanied by a subcutaneous injection of 0·25 mg. of carbamyl choline chloride (Carbachol) (Mollin et al., 1957). Patients with pernicious anaemia absorb from 0 to 0·28 μg., 83% absorbing less than 0·20 μg., and absorption is not improved by Carbachol.

Our patients were first given the oral dose alone. If less than 0·5 μg. was absorbed, a second dose was given, accompanied by an injection of 0·25 mg. of Carbachol. If the amount absorbed was still less than 0·5 μg., another dose was given with 40 mg. of a hog intrinsic factor concentrate (Batch 186, Lederle Laboratories Inc.)

**Aspiration of gastric juice after injection of histamine** Aspiration was performed in all but 11 patients. The gastric tube was manipulated by the method of Kay (1953) to ensure that the gastric juice was adequately sampled. In a few patients (including cases 27 and 35) the tube was placed in position under fluoroscopy. Histamine test meals were done more than once in many of the patients and in some were performed repeatedly.

In 22 patients 0·5 mg. of histamine was injected. In 36 patients injections of 0·5 or 1·0 mg. of histamine were given repeatedly in the same or different tests. Fifty-five patients, a group which included nearly all those with defective B₁₂ absorption, were given an augmented dose of histamine (Kay, 1953). As the full dose (100 mg.) of mepyramine maleate recommended in this test sometimes causes malaise, a dose of 75 mg. was used. This effectively abolished the unpleasant effects of histamine.
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The pH of the aspirated juice was measured electrometrically in all except one case in which it was titrated. For the purpose of this paper we have assumed that hydrochloric acid was present if the pH was 3·0 or less. Patients in whom the pH of the gastric juice remained above 3·0 after histamine stimulation were called 'achlorhydric' but, where appropriate, have been subdivided according to the final level of the pH.

Among the 55 patients who were given an augmented dose of histamine a group of 39 patients who were 'achlorhydric' after smaller doses. Twelve of these (31%) secreted HCl after maximal histamine stimulation. These results differ from those of Callender, Retief, and Witts (1960) who found that after failure with a small dose of histamine about 60% of their patients (excluding those with pernicious anaemia) secreted gastric HCl after an augmented dose. This discrepancy may have been due to the selected nature of our series of patients, or, in part, to misplacing of the gastric tube.

In five patients, with intact stomachs, who were unable to swallow a tube, a tubeless test was performed using an ion exchange resin containing azure A.1 The augmented dose of histamine was used.

HAEMATOLOGICAL METHODS Those described by Dacie (1956) were used throughout. The diagnosis of red blood cell macrocytosis was made by careful scrutiny of films of peripheral blood as well as by measurements of red cell volume.

RESULTS

SERUM VITAMIN B₁₂ CONCENTRATIONS The range and mean of the serum B₁₂ concentrations in the three groups of patients and in control subjects are shown in Table I. The distribution of the serum B₁₂ levels is shown in Figure 1.

The vitamin B₁₂ concentrations in the patients with superficial or mixed gastritis were not significantly different from those in control subjects. Only one patient had a level below the range found in the control subjects.

The B₁₂ levels in the patients with atrophic gastritis were significantly lower than those in control subjects or in the patients with superficial or mixed gastritis (P = < 0·001). However, none of the patients with atrophic gastritis had B₁₂ levels within the range found in Addisonian pernicious anaemia (less than 100 μg. per ml.), the lower mean B₁₂ concentrations being due to an increase in the proportion of patients with B₁₂ levels between 100 and 220 μg. per ml. The serum B₁₂ levels with within this range in 46% of the patients were atrophic gastritis compared with 14% of control subjects. In 2% of the patients with superficial gastritis.

TABLE I

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of Subjects</th>
<th>Serum B₁₂ Concentrations (μg. per ml.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>Mean ± S.E.</td>
</tr>
<tr>
<td>Control subjects</td>
<td>222</td>
<td>140-960</td>
</tr>
<tr>
<td>Superficial and mixed gastritis</td>
<td>52</td>
<td>135-635</td>
</tr>
<tr>
<td>a. Two or more biopsy specimens</td>
<td>56</td>
<td>100-610</td>
</tr>
<tr>
<td>Atrophic gastritis</td>
<td>15</td>
<td>115-490</td>
</tr>
<tr>
<td>b. One biopsy specimen</td>
<td>71</td>
<td>100-610</td>
</tr>
<tr>
<td>c. All cases (a + b)</td>
<td>56</td>
<td>100-610</td>
</tr>
</tbody>
</table>

FIG. 1. The distribution of the serum vitamin B₁₂ levels in 222 control subjects, in 52 patients with superficial or mixed gastritis, in 56 patients with atrophic gastritis established by two or more gastric biopsy specimens and, in 71 patients with atrophic gastritis established by one or more gastric biopsy specimens.
and mixed gastritis and in 17% of the patients with atrophic gastritis the levels were below 140 μg per ml., i.e., below the lower limit of the range found in control subjects.

Two patients suffered from iron deficiency, shown by almost complete loss of the free iron stores in the bone marrow. Neither was anaemic at any time. In one (case 13, Table IV) the serum B₁₂ level ranged between 85 and 100 μg per ml before treatment with iron and at this time the bone marrow showed a very early megaloblastic change. After oral iron treatment the serum B₁₂ level rose to 125 μg per ml. Four months later, when her ability to absorb radioactive B₁₂ was tested, the serum B₁₂ level had fallen to an average of 100 μg per ml. In the other patient (case 22) the serum B₁₂ level was 100 μg per ml. when it was first measured and at that time there were possibly early megaloblastic changes in the bone marrow. The serum B₁₂ level rose spontaneously to 115 μg per ml. at which point the radioactive B₁₂ absorption tests were performed (Table IV). These two patients have been followed for nine years and neither has so far developed clinical pernicious anaemia.

**TABLE II**

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of Subjects</th>
<th>Amount of B₁₂ Absorbed (μg.)</th>
<th>Mean ± S.E.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects</td>
<td>58</td>
<td>0.26-0.98</td>
<td>0.60 ± 0.02</td>
</tr>
<tr>
<td>Superficial and/or mixed gastritis</td>
<td>44</td>
<td>0.19-0.90</td>
<td>0.54 ± 0.02</td>
</tr>
<tr>
<td>Atrophic gastritis</td>
<td>14</td>
<td>0.06-0.89</td>
<td>0.51 ± 0.07</td>
</tr>
<tr>
<td>Addisonian pernicious anaemia</td>
<td>66</td>
<td>0.06-0.89</td>
<td>0.47 ± 0.03</td>
</tr>
</tbody>
</table>

Three control subjects absorbed respectively 0.26, 0.30, and 0.30 μg. radioactive B₁₂. The first two had normal gastric mucosae on biopsy, and in the third HCl was present in resting gastric juice and radioactive B₁₂ absorption was normal after Carbachol.
Absorption of radioactive vitamin \( \text{B}_{12} \) and secretion of hydrochloric acid in patients with atrophic gastritis

Absorption of radioactive vitamin \( \text{B}_{12} \) after Carbachol

The effect of an injection of Carbachol on the absorption of radioactive \( \text{B}_{12} \) was studied in 11 of the 15 patients with superficial or mixed gastritis and in 33 of the 38 patients with atrophic gastritis, who absorbed less than 0.50 \( \mu \text{g} \) of the oral dose given alone. The results are shown in Figure 3 and summarized in Table III; details of individual patients are given in Table IV.

Absorption was significantly increased in both groups after Carbachol (\( P = 0.001 \) for each, Table III), reaching the normal range in a third to a half of all the patients tested (Figure 3 and Table IV). The increase was, however, significantly less in the case of patients with atrophic gastritis (0.05 > \( P > 0.02 \)). The mean absorption in both groups of patients given Carbachol was still significantly lower after the drug than the mean absorption in control subjects given the dose without Carbachol (0.60 \( \mu \text{g} \pm 0.02 \))(0.05 > \( P > 0.02 \) for superficial or mixed gastritis; \( P = < 0.001 \) for atrophic gastritis).

Vitamin \( \text{B}_{12} \) absorption before Carbachol was within, or bordering on, the range found in pernicious anaemia in four patients with superficial or mixed gastritis and in 20 patients with atrophic gastritis (Table IV). After Carbachol such severely depressed absorption was found in only 12 patients, 11 of whom had atrophic gastritis (cases 12-22), all except one (case 19) having a histamine-fast achlorhydria. The mean \( \text{B}_{12} \) absorption in these 12 patients (0.20 \( \mu \text{g.} \pm 0.02 \)) was, however, significantly greater than in patients with overt Addisonian pernicious anaemia (\( P = < 0.001 \)).

Effect of Intrinsic Factor

The results of administering intrinsic factor concentrate are given in Table IV. \( \text{B}_{12} \) absorption increased significantly in all except three patients (cases 6, 25, and 31), who absorbed between 0.38 and 0.50 \( \mu \text{g.} \) after Carbachol or when intrinsic factor concentrate was used; it is possible that absorption would have increased further with larger doses of intrinsic factor or if normal gastric juice had been used.

Relation between Serum Vitamin \( \text{B}_{12} \) Concentration and Absorption of Radioactive Vitamin \( \text{B}_{12} \)

This relationship was studied in patients with
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### TABLE III

THE EFFECT OF CARBACHOL ON THE ABSORPTION OF RADIOACTIVE $\text{B}_12$ IN PATIENTS WITH DIFFERENT FORMS OF GASTRITIS (ORAL DOSE: $1.0 \, \mu\text{g. of } ^{68}\text{CO-}\text{B}_12$).

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of Patients</th>
<th>Amount of Radioactive $\text{B}_12$ Absorbed (\mu g.)</th>
<th>Dose Alone</th>
<th>Dose with Carbachol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Range</td>
<td>Mean $\pm$ S.E.</td>
<td>Range</td>
</tr>
<tr>
<td>Superficial or mixed gastritis</td>
<td>11</td>
<td>0.19-0.44</td>
<td>0.34 $\pm$ 0.03</td>
<td>0.28-0.59</td>
</tr>
<tr>
<td>Atrophic gastritis</td>
<td>33</td>
<td>0.06-0.44</td>
<td>0.29 $\pm$ 0.02</td>
<td>0.08-0.77</td>
</tr>
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</table>

### TABLE IV

THE RESULTS OF RADIOACTIVE $\text{B}_12$ ABSORPTION TESTS AND ESTIMATION OF SERUM $\text{B}_12$ LEVELS IN DIFFERENT GROUPS OF INDIVIDUAL PATIENTS ALL OF WHOM ABSORBED LESS THAN 0.5 \mu g. OF AN ORAL DOSE OF $1.0 \, \mu\text{g. } ^{68}\text{CO-}\text{B}_12$

<table>
<thead>
<tr>
<th>Type of Gastritis</th>
<th>Case No.</th>
<th>Amount of Radioactive $\text{B}_12$ Absorbed (\mu g.)</th>
<th>Serum $\text{B}_12$ Level (\mu g./ml.)</th>
<th>Dose Alone</th>
<th>Dose with Carbachol</th>
<th>Dose with Intrinsic Factor</th>
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<tbody>
<tr>
<td></td>
<td>(1)</td>
<td>(2) Dose Alone</td>
<td>(3) Dose with Carbachol</td>
<td>(4) Dose with Intrinsic Factor</td>
<td>(5)</td>
<td></td>
</tr>
<tr>
<td>Group 1: Superficial or mixed</td>
<td>1</td>
<td>0.29</td>
<td>0.28</td>
<td>0.64</td>
<td>260</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.19</td>
<td>0.39</td>
<td>0.45</td>
<td>230</td>
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<tr>
<td>3 (GE + V)</td>
<td>0.21</td>
<td>0.39</td>
<td>0.50</td>
<td>450</td>
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<tr>
<td>4</td>
<td>0.34</td>
<td>0.44</td>
<td>0.37</td>
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<tr>
<td>5</td>
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<td>0.38</td>
<td>0.60</td>
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<tr>
<td>6</td>
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<td>0.69</td>
<td>0.53</td>
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<td>7</td>
<td>0.36</td>
<td>0.62</td>
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<td>9</td>
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<tr>
<td>10</td>
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<td>11</td>
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<td>Group 2: Atrophic</td>
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<td>0.31</td>
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<td>13</td>
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<td>0.59</td>
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<td>0.48</td>
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<td>0.30</td>
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<td>0.49</td>
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<td>36</td>
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<td>0.58</td>
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<td>37</td>
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<td>0.57</td>
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<td>38</td>
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<td>0.63</td>
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<td>0.63</td>
<td>0.58</td>
<td>135</td>
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<tr>
<td>40</td>
<td>0.35</td>
<td>0.60</td>
<td>0.58</td>
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<td>0.68</td>
<td>0.58</td>
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<td>0.58</td>
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<td>0.58</td>
<td>135</td>
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<tr>
<td>44</td>
<td>0.44</td>
<td>0.50</td>
<td>0.58</td>
<td>135</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*0.23 \mu g. one year later. This patient subsequently developed clinical pernicious anaemia.

Absorption of radioactive vitamin B₁₂ and secretion of hydrochloric acid in patients with atrophic gastritis

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superficial and mixed gastritis and in those with atrophic gastritis.

Patients with superficial and mixed gastritis The mean serum B₁₂ concentrations were not significantly different from those in control subjects and in some patients there was no correlation between the serum B₁₂ level and the B₁₂ absorption (for example, case 1 Table IV).

Patients with atrophic gastritis In this group there was a relationship between the serum B₁₂ concentration and the amount of B₁₂ absorbed. The mean serum B₁₂ concentration (220 ± 35 μg./ml) was significantly lower in 14 patients who absorbed less than 0.29 μg. than the concentration (263 ± 26 μg./ml.) in 23 of those who absorbed 0.29 μg. or more (0.02 > P > 0.01). Most of the patients with subnormal serum B₁₂ levels absorbed less than 0.50 μg. B₁₂ and the serum B₁₂ levels were less than 200 μg. per ml. in most patients who absorbed less than 0.29 μg. when the dose was given with Carbachol. However in individual patients there was often little correlation between the serum B₁₂ level and the amount of B₁₂ absorbed (Table IV). Thus B₁₂ absorption was within the range found in pernicious anaemia, even after Carbachol, in six patients whose serum B₁₂ levels were normal; in contrast, of 12 patients with subnormal serum B₁₂ levels, two absorbed normal amounts of B₁₂ (0-50 μg. or more), a third did so after Carbachol, and the rest all absorbed more B₁₂ than patients with pernicious anaemia.

Relation of gastric acidity to absorption of radioactive vitamin B₁₂ ‘Achlorhydria’ was much commoner in patients with atrophic gastritis. On maximal histamine stimulation the gastric juice pH remained above 6.0 in 25 out of 31 ‘achlorhydric’ patients with atrophic gastritis. In 15 of these patients the pH increased after the augmented dose of histamine. Scanty parietal cells were present in the gastric mucosa of seven of these. Callender et al. (1960) observed a rise in the gastric juice pH after maximal histamine stimulation in most of their patients with pernicious anaemia, a phenomenon also observed, but not commented upon, by Williams et al. (1958) in 10 out of 44 patients with this condition; in four of these 10 patients a few parietal cells were present in the gastric mucosa.

In patients secreting gastric hydrochloric acid The mean radioactive B₁₂ absorption and the mean serum B₁₂ concentrations in patients who secreted hydrochloric acid after doses of 0.5 to 1.0 mg. of histamine were identical with those found in control subjects and 70% absorbed entirely normal amounts of B₁₂. The mean B₁₂ absorption (0.51 ± 0.05 μg. in 18 cases) and the mean serum B₁₂ level (297 ± 22 μg./ml. in 21 cases) in patients secreting hydrochloric acid after an augmented dose of histamine (a selected group because many had previously been ‘achlorhydric’ with smaller doses of histamine) were slightly but significantly lower than the levels in either the controls or the patients secreting HCl after smaller doses of histamine (0.05 > P > 0.02). In this group only 50% absorbed entirely normal amounts of B₁₂ and in two absorption was within the range found in pernicious anaemia (cases 2 and 25, Table IV) and borderline in a third (case 19). However after Carbachol a further 25% absorbed entirely normal amounts of B₁₂ and in only one patient did absorption then remain within the range found in pernicious anaemia (case 19).

In patients with ‘achlorhydria’ after any dose of histamine The mean absorption of radioactive B₁₂ (0.44 ± 0.06 μg. in 15 cases tested with 0.5 ± 1.0 mg. histamine; 0.40 ± 0.03 μg. in 39 cases receiving a maximal histamine stimulus) was lower in these patients than in control subjects or patients who secreted hydrochloric acid (P = < 0.001). Only 37% of the ‘achlorhydric’ patients absorbed entirely normal amounts of B₁₂ when the dose was given alone. Absorption was within the range found in pernicious anaemia in 15 of the 54 ‘achlorhydric’ patients and was borderline in seven others (Figure 4).

The effect of Carbachol on the absorption of B₁₂ in 33 ‘achlorhydric’ patients who absorbed less than 0.5 μg. is shown in Table IV and Figure 4. When the radioactive B₁₂ was given alone absorption in two-thirds of them was within the range found in pernicious anaemia or just above its upper limit (cases 1, 3, 7, 12-18, 20, 22-24, 26, 27, 34-38, Table IV). After Carbachol, one third absorbed entirely normal amounts of B₁₂ but absorption remained within the range found in pernicious anaemia in 10 (cases 1, 12-18, 20 and 21) and was borderline in two others (cases 22 and 23).

The mean serum B₁₂ level (275 ± 29 μg./ml. in 20 cases tested with 0.5-1.0 mg. histamine; 232 ± 19 μg./ml. in 39 cases receiving a maximal histamine stimulus) was lower in the ‘achlorhydric’ patients and in 13 (22%) the levels were below the range found in normal subjects.

In patients with ‘achlorhydria’ on maximal histamine stimulation The 39 patients in this group incorporated two important categories. 1 There were 30 patients in whom the gastric juice pH remained above 6.0; after histamine there was an increase in the pH in 15 and no change in six; when a fall occurred it never exceeded 0.5. In 16 of these patients absorption of B₁₂ was within, or bordering on, the range found in pernicious anaemia. The gastric juice pH remained
unchanged, or even rose, in 14 of these 16 patients and in eight of the 14 absorption of B₁₂ after Carbachol was within the pernicious anaemia range (cases 12-18, and 20). 2 There was another group of seven patients in whom the gastric juice pH remained between 4-0 and 6-0. In all but one of these the pH fell by more than 1·0 after histamine. None of them absorbed as little B₁₂ as did patients with pernicious anaemia. Three absorbed B₁₂ entirely normally, and two others did so when Carbachol was given.

Eight (27%) of the patients whose gastric juice pH remained above 6·0 after maximal histamine stimulation had subnormal serum B₁₂ levels.

**GASTRIC HISTOLOGICAL APPEARANCES AND ABNORMALITY OF FUNCTION**  The patients were grouped into those with defective absorption of B₁₂ and those with atrophic gastritis.

**In patients with defective absorption of B₁₂** The patients were grouped according to the manner in which they absorbed radioactive B₁₂. Group 1 contained seven patients whose absorption, before and after Carbachol, was within the range found in pernicious anaemia. Group 2 contained six patients whose absorption either before or after Carbachol was just outside the range found in pernicious anaemia. In group 3 there were nine patients whose absorption of B₁₂ was within or at the upper limit of the range found in pernicious anaemia when the dose was given alone, but in whom absorption was well above this range when the dose was given with Carbachol.

One of us (A.W.W.) examined the gastric biopsy specimens from these patients without any knowledge of the data on vitamin B₁₂ absorption or gastric acidity. The severity of the atrophic changes...
Absorption of radioactive vitamin B₁₂ and secretion of hydrochloric acid in patients with atrophic gastritis

**TABLE V**

The serum level of vitamin B₁₂, and the amount absorbed of an oral dose of 1·0 μg. of radioactive B₁₂ in patients graded in order of severity of gastric mucosal atrophy.

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Percentage Secreting Gastric HCl</th>
<th>Serum B₁₂ (μg./ml.)</th>
<th>Radioactive Vitamin B₁₂ Absorption (μg.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± S.E.</td>
<td>Percentage &lt; 140 μg./ml.</td>
<td>Mean ± S.E.</td>
</tr>
<tr>
<td>Severe</td>
<td>32</td>
<td>271 ± 24 (32)</td>
<td>0·43 ± 0·05 (30)</td>
</tr>
<tr>
<td>Moderate</td>
<td>19</td>
<td>257 ± 25 (19)</td>
<td>0·46 ± 0·05 (18)</td>
</tr>
<tr>
<td>Relatively mild</td>
<td>21</td>
<td>260 ± 25 (20)</td>
<td>0·53 ± 0·56 (18)</td>
</tr>
<tr>
<td>All atrophic gastritis cases</td>
<td>72</td>
<td>264 ± 145 (71)</td>
<td>0·47 ± 0·03 (66)</td>
</tr>
</tbody>
</table>

*The figures in parentheses refer to the number of patients studied.

in the mucosa paralleled the severity of the absorptive defect. Histologically group 1 was the most homogeneous and contained cases with the most severe mucosal atrophy. In group 3 mucosal changes were heterogeneous, atrophy being less severe than in patients in group 2. Parietal cells were scanty or absent in group 1; present in appreciable numbers in the biopsy specimens from only one patient in group 2, and were more commonly found in biopsy specimens from patients in group 3; even in this group, however, they were absent in three patients. Severity of gastric histological defect related to function in patients with atrophic gastritis. The patients with atrophic gastritis were divided into three groups by one of us (A.W.W.) as before, according to the degree of atrophy of the body glands (Table V): 'severe' (parietal cells absent in 16 patients, very scanty in 10, scanty in four, and present + in two), 'moderately severe' (parietal cells very scanty in one, scanty in five, present + in 12, and + + in one), and 'relatively mild' (parietal cells present + in three, + + in 17, and +++ in one). Table V compares the absorption of radioactive B₁₂, the serum B₁₂ levels and the secretion of gastric acid in these three groups. The results may be compared with those found in patients with superficial or mixed gastritis (Tables I and II).

There was a correlation between the degree of atrophy and the severity of the defect in gastric function. Ability to secrete HCl steadily declined as atrophy increased. Seven of the group of 12 whose absorption was within or near the pernicious anaemia range had severe atrophy. The mean serum B₁₂ level was essentially the same in all three groups but a notably large number of patients with severe atrophy had levels of less than 140 μg. per ml.

There was, therefore, good correlation in most patients between the biopsy findings and the results of gastric function tests. But there were exceptions. Thus case 1 had only superficial gastritis (with mild atrophy) yet his ability to secrete intrinsic factor and HCl was markedly depressed. The gastric mucosa in cases 36, 40, and 48 was severely atrophic (Figs. 5–7), and none secreted gastric HCl on maximal histamine stimulation. Yet case 48 absorbed 0·42 μg. radioactive B₁₂ when the dose was given alone and in cases 36 and 40, although B₁₂ absorption was reduced (being in the pernicious anaemia range in case 36 when the dose was given alone), it was normal in both with Carbachol.

Case 27 was admitted to hospital with peripheral neuritis. He and case 35 were found to have achlorhydria on maximal histamine stimulation (gastric tube screened into position). Both had severe atrophic gastritis. Indeed case 27 was the solitary example in this series of gastric atrophy without inflammation. In them also B₁₂ absorption, within, or bordering on, the pernicious anaemia range when the dose was given alone, improved after Carbachol (Table IV). Absorption of B₁₂ was very defective in case 34, yet his gastric juice pH fell from 6·0 to 3·1 after 1·0 mg. histamine and he was, therefore, classed as achlorhydric. The pH might well have fallen below 3·0 after maximal histamine stimulation. In view of his probable ability to secrete small amounts of gastric HCl it was not surprising that when the dose of B₁₂ was given with Carbachol absorption became normal.

**IRON-DEFICIENCY ANAEMIA AND THE GASTRIC DEFECT**

Forty-nine patients with gastritis had suffered, in the past, from iron deficiency. Thirty-nine of these had hypochromic anaemia at the time the gastric biopsy was taken and 10 others were authenticated cases of previous iron deficiency. Approximately the same proportion of patients with atrophic gastritis, or with superficial or mixed
FIG. 5. Gastric biopsy specimen from case 36. The mucosa is thin. No body glands are present. There is marked intestinal metaplasia with numerous goblet cells, and small intestinal-like 'villi'. Paneth cells are present. There are many inflammatory cells in the stroma (× 56).

FIG. 6. Gastric biopsy specimen from case 40. The normal body glands have been lost as completely as in case 36 but there has been greater replacement by simple glands. Intestinal metaplasia is marked and Paneth cells are present. Inflammatory cells are numerous. The muscularis mucosae is thickened (× 56).

FIG. 7. Gastric biopsy specimen from case 48. There has been an almost complete loss of normal body glands although a few parietal cells remain. The numerous glands present are simple. There is no intestinal metaplasia and inflammatory cells are less numerous than in cases 36 and 40 (× 42).
gastritis, gave a history of iron-deficiency anaemia. In patients with superficial or mixed gastritis there was no difference in the results in the iron-deficient and non-iron-deficient groups. In patients with atrophic gastritis the mean absorption of $B_{12}$ and the mean serum $B_{12}$ levels were lower, but not significantly so, in the patients with a history of iron-deficiency anaemia ($0.1 > P > 0.05$). However, of the 10 patients whose absorption of $B_{12}$ was within the pernicious anaemia range after Carbachol (cases 12-21, Table IV), there was a history of hypochromic atrophic gastritis in six (cases 12, 15, 16, 18, 20, and 21), and of iron deficiency without anaemia in one other (case 13).

AGE AND SEX The average age of the patients with superficial and mixed gastritis was 51.8 years and of patients with atrophic gastritis 52.6 years. The scatter was wider in the patients with atrophic gastritis, two being respectively 16 and 20 years old and three being over 70 years. However, whereas among the patients with superficial and mixed gastritis the ten-year age group 41-50 years contained the largest number of patients (35%), the largest number of patients with atrophic gastritis (39%) was in the 51-60 years group. There were 66 male and 58 female patients. There were equal numbers (26) of male and female patients with superficial and mixed gastritis. There were 40 males and 32 females with atrophic gastritis.

Although patients with atrophic gastritis tended to be older than those with milder forms of gastritis there was no correlation between age and sex on the one hand and the serum $B_{12}$ level, the absorption of $B_{12}$, and secretion of gastric $HCl$ on the other.

**DISCUSSION**

**INTRINSIC FACTOR SECRETION** The primary purpose of this study was to assess the ability of patients with atrophic lesions of the stomach, but with no family history of pernicious anemia, to secrete intrinsic factor. The results are essentially similar to those obtained by Siurala, Erämäa, and Nyberg (1960). Any divergences are due to differences in the methods of classifying biopsy findings, to the fact that those authors included a number of patients whom we would have excluded as suffering from early Addisonian pernicious anemia, and because, in contrast to this series, an appreciable number of their patients had relatives with pernicious anemia.

The results reported here and elsewhere (Mollin et al., 1957; Siurala and Nyberg, 1957; and Siurala et al., 1960) indicate that patients with atrophic gastritis can be divided into the following groups on the basis of their ability to absorb radioactive $B_{12}$:—

1. Patients who absorb normal amounts of radioactive $B_{12}$. 2. Patients who, when given the oral dose alone, absorb less $B_{12}$ than normal subjects but more than patients with overt pernicious anemia, and absorb normal amounts when the dose is given with Carbachol. 3. Patients in whom absorption is similar to those in group 2 except that absorption does not become normal with Carbachol. 4. Patients whose absorption of $B_{12}$ is within the range found in patients with pernicious anemia when the dose is given alone but increases to normal or intermediate levels when the dose is given with Carbachol. 5. Patients whose absorption of $B_{12}$ is within the range found in pernicious anemia when the dose is given alone or with Carbachol.

In general the severity of the histological lesion in our patients ran parallel with the severity of the absorptive defect. There was a fairly close relationship between the degree of atrophy, the number of parietal cells present in the section, the power of the stomach to secrete $HCl$, and the ability to absorb vitamin $B_{12}$. There was a less notable correlation between atrophy and serum $B_{12}$ level.

In all except one (case 1) of the patients whose absorption remained within or bordering on the pernicious anemia range after an injection of Carbachol the histological lesion was about as severe as that seen in overt pernicious anemia. However, the correlation between the severity of the histological lesion and the defect in $B_{12}$ absorption was not complete. Some patients with superficial or mixed gastritis in whom parietal cells were present in fair numbers absorbed subnormal amounts of $B_{12}$ even after Carbachol, and in one such patient absorption bordered on the pernicious anemia range (case 1). Other patients with severe atrophic gastritis absorbed normal amounts of $B_{12}$. A similar general, but not complete, correlation between the histological findings and the results of the $B_{12}$ absorption tests was noted by Siurala et al. (1960) and by Callender et al. (1960). In our series the exceptions to the general rule were sufficiently numerous to indicate that the finding of severe atrophic gastritis, or even gastric atrophy, is not conclusive evidence of Addisonian pernicious anemia (Doig, Motteram, Robertson, and Wood, 1950). Small numbers of parietal cells were present in most of the biopsy specimens from the groups with the most severe atrophic gastritis. However, these cells may be found in as many as 30% of patients with pernicious anemia (Williams et al., 1958) and were present even in patients in whom the gastric juice $pH$ rose after maximal histamine stimulation.
Relationship between achlorhydria and ability to secrete intrinsic factor. The patients whose gastric juice pH was above 3-0 after an augmented histamine test fell into two groups: those with the pH between 4-0 and 6-0 and those with the pH above 6-0. There was a significant fall in pH after histamine in all but one of the first group. The pH of the second group either increased, remained unchanged, or fell less than 0-5 after histamine. This group therefore was suffering from achlorhydria indistinguishable from that seen in pernicious anaemia, and in general the atrophic gastritis in its members was the most severe and the absorption of B₁₂ lowest.

It has been suggested that progressive gastric atrophy results in the loss of the ability to secrete acid, pepsin, and intrinsic factor in that order (Witts, 1932; Poliner and Spiro, 1958). This view is supported by the observations of Callender et al. (1960) who found that, although 50% of patients who were completely achlorhydric after an augmented histamine test absorbed as little B₁₂ as patients with pernicious anaemia, the remainder absorbed normally. They point out, however, that they were studying a special sample, and that this sequence might not necessarily be true in other groups. Thus McIntyre et al. (1959) noted subnormal absorption of B₁₂ among relatives of patients with pernicious anaemia who secreted gastric HCl. Furthermore, in relatives of patients with juvenile pernicious anaemia the secretion of intrinsic factor is depressed while the ability to secrete gastric HCl is retained and the gastric mucosa is histologically normal (Mollin, Baker, and Doniach, 1955; Waters and Murphy, 1963). In the present series, although subnormal radioactive B₁₂ absorption was commoner and usually more severe in patients with achlorhydria, about one third of those who secreted gastric HCl also absorbed subnormal amounts of vitamin B₁₂ (Table IV, Fig. 4), and this number would probably have been higher had the augmented dose of histamine been used in every case or if the gastric tube had more often been placed under fluoroscopy. In 24% of patients who secreted gastric HCl absorption remained subnormal after Carbachol, but in only one of these was it then within the range found in pernicious anaemia.

Our results, therefore, indicate that in adult patients with atrophic gastritis but no family history of pernicious anaemia the loss of one gastric function is not necessarily related to the loss of another, that different functions may be lost at different rates, and that loss of intrinsic factor may not be directly related to atrophy of parietal and chief cells of the stomach. These results are best explained by assuming that the ability to secrete HCl and intrinsic factor are both reduced as the gastric mucosa atrophies, but that these different functions are lost at different rates in different patients. In most patients the ability to secrete at least some intrinsic factor persists longer than the ability to secrete acid. In this series some patients with achlorhydria on maximal histamine stimulation absorbed almost normal amounts of radio-vitamin B₁₂ when the dose was given alone.

Serum B₁₂ levels in atrophic gastritis. These fell in parallel with reduction in both B₁₂ absorption and gastric HCl secretion.

Serum B₁₂ levels within the range found in overt pernicious anaemia were found in a considerable number of the patients with severe atrophic gastritis described by Siurala, et al. (1960) and Callender et al. (1960). Only one patient in our series (case 13, Table IV) had a serum B₁₂ level within this range as found with the Euglena gracilis assay (Mollin and Ross, 1956). This difference is presumably due to the fact that we excluded from our study non-anemic patients with definite haematological signs of B₁₂ deficiency.

Subnormal serum B₁₂ levels, i.e., less than 140 µµµg. per ml., were, however, found in 12 patients in whom B₁₂ absorption tests were performed. In the patients who absorbed subnormal amounts of B₁₂ these low levels presumably reflect some degree of tissue depletion. This suggestion is supported by the observation that in two patients (cases 13 and 22, Table IV) the serum B₁₂ level fell to 85 and 100 µµµg. per ml. respectively and evidence of mild megaloblastic change appeared in the bone marrow in association with iron deficiency. Some of the patients with subnormal serum levels in whom there was marked depression of B₁₂ absorption have been studied for periods of up to nine years without significant change in the serum B₁₂ level or their clinical state. In such patients it evidently takes many years to deplete tissue stores to the very low levels found in pernicious anaemia. However, more than half of the patients with subnormal B₁₂ levels absorbed normal or intermediate amounts of B₁₂ when the dose was given alone or with Carbachol and the cause and significance of this finding are not clear. Defective absorption of B₁₂ is unlikely to be the sole cause. There was no reason to suppose that there was an increased requirement for vitamin B₁₂. They may, like similar patients reported by Callender et al. (1960), have been eating a poor diet.

The serum B₁₂ levels in a significantly increased proportion of patients with atrophic gastritis were within the lower part of the normal range (140-220 µµµg. per ml., Fig.1). Almost all of these patients
Absorption of radioactive vitamin $B_{12}$ and secretion of hydrochloric acid in patients with atrophic gastritis

Absorbed less than 0.5 μg $B_{12}$. The significance of these low normal blood levels is also uncertain but they may reflect a less severe depletion of tissue $B_{12}$ stores.

**ATROPHIC GASTRITIS AND PERNICIOUS ANAEMIA**

The cause of the gastric atrophic process in these patients is a matter for speculation. A number of factors have been suggested as causes of gastritis and the subject has been reviewed by Coghill (1960) and Taylor (1961).

Severe atrophic gastritis or gastric atrophy, associated with achyia gastrica, is characteristic (but not pathognomonic) of the adult form of pernicious anaemia (Magnus, 1958; Williams, et al., 1958). Some of our patients with atrophic gastritis, like those of Mollin et al. (1957) and Siurala and Nyberg (1957), had the defects of gastric secretory function found in Addisonian pernicious anaemia. The precise relationship of the condition in these patients to that in clinical pernicious anaemia is uncertain. Similar findings have been described in members of families of patients with pernicious anaemia (Callender and Denborough, 1957; Siurala et al., 1960) and the condition is thought to be pre-pernicious anaemia by Callender et al. (1960). This may be so, particularly in subjects with a family history of pernicious anaemia. It certainly seems likely that clinical pernicious anaemia will develop in our cases 12 and 14 if they live long enough, for their ability to absorb $B_{12}$ is well within the range found in severe pernicious anaemia.

On the other hand the mean absorption of radioactive $B_{12}$ in all our patients whose absorption was within the range found in pernicious anaemia was significantly higher than in most patients with overt pernicious anaemia. It was, in fact, similar to that found in patients after partial gastrectomy (Lous and Schwartz, 1959; Mollin, 1962). Such patients not infrequently develop defective absorption of $B_{12}$ within 10 years of operation (Deller, Richards, and Witts, 1962). Nevertheless they rarely develop severe megaloblastic anaemia and their mean $B_{12}$ absorption is greater than that in patients with pernicious anaemia (Mollin, 1962). Our patients with atrophic gastritis and depressed $B_{12}$ absorption were, at the time of study, already within the age group in which pernicious anaemia is most commonly found. It therefore seems unlikely that most of the patients in our series will develop clinical pernicious anaemia.

It may well be that patients with atrophic gastritis only develop clinical pernicious anaemia if severe atrophy is present at an early age, or if some additional factor causing depression of intrinsic factor secretion, such as removal of gastric mucosa by operation, is also present. For example, a low serum $B_{12}$ level is more likely to be found after partial gastrectomy in patients who already have atrophic gastritis (Deller and Witts, 1962) and such patients may develop severe megaloblastic anaemia (Maclean, 1957). So far only one of our patients (case 21) has developed clinical pernicious anaemia. Perhaps significantly she had undergone partial gastrectomy seven years previously for a gastric ulcer. Others have been followed for upwards of nine years without developing this disorder. In classical Addisonian pernicious anaemia the additional factor which precipitates the clinical disorder may be an inherited tendency to defective secretion of intrinsic factor (McIntyre et al., 1959). If such a patient develops atrophy of the gastric mucosa depression of $B_{12}$ absorption might be expected to be severe and to develop early.

We started with the observation that there was no pathognomonic gastric histological lesion in pernicious anaemia. We end by observing that neither is there a single pathognomonic functional change. Patients with atrophic gastritis but not pernicious anaemia have been found with achlorhydria on maximal histamine stimulation (Card and Sircus, 1958). Patients with pernicious anaemia fall into the last of the five categories of $B_{12}$ absorption mentioned at the beginning of this discussion but so do some of our patients with simple atrophic gastritis who have not so far developed pernicious anaemia. Nevertheless 80% of patients with this disorder absorb less $B_{12}$ than most cases of simple atrophic gastritis, and the use of Carbachol to elevate $B_{12}$ absorption distinguishes many patients with simple atrophic gastritis in whom absorption of $B_{12}$ is impaired when the dose is given alone.

Thus it is clear that early adult Addisonian pernicious anaemia cannot be diagnosed unless the serum $B_{12}$ level is below 100 μg./ml.; HCl is absent from the gastric juice after maximal histamine stimulation; there is severe atrophic gastritis; and there is inability to absorb more than 0.28 μg. of a 1-0 μg. dose of radioactive vitamin $B_{12}$ given with Carbachol. But patients with all these abnormalities may yet not have clinical Addisonian pernicious anaemia. On the other hand a patient who is clinically well but who absorbs subnormal amounts of radioactive $B_{12}$, the absorption improving with Carbachol, probably has gastric mucosal atrophy.

**SUMMARY**

Fifty-two patients with superficial or mixed gastritis and 72 patients with atrophic gastritis, in none of whom was there a certain family history of pernicious anaemia.
anaemia or haematological evidence of this disease, were investigated in respect of their ability to secrete gastric HCl, and to absorb radioactive vitamin B12. Their serum vitamin B12 levels were measured.

Approximately one third of the patients with superficial or mixed gastritis absorbed subnormal amounts of B12 and in 7% the absorption was within the range found in pernicious anaemia. There was significant improvement in absorption when the dose was given with Carbachol but the absorption remained subnormal in about 15% and within the range found in pernicious anaemia in one patient.

More than half the patients with atrophic gastritis absorbed subnormal amounts of Bi and in 21% absorption was within the range found in pernicious anaemia. After Carbachol absorption was normal in one third of the patients who absorbed subnormally when the dose was given alone; there was, however, no improvement in half the patients whose absorption had been within the pernicious anaemia range, but the mean B12 absorption in these patients was significantly greater than that usually found in pernicious anaemia.

All except one of the patients whose absorption was within the range found in pernicious anaemia after Carbachol had 'achlorhydria', and in general there was a fair correlation between 'achlorhydria' and defective B12 absorption. However, hydrochloric acid was present in the gastric juice of a number of patients who absorbed subnormal amounts of Bi. The results suggest that the ability to secrete HCl and intrinsic factor are both reduced as the gastric mucosa atrophies, but that these functions may be lost at different rates. In most patients the ability to secrete at least some intrinsic factor persists longer than the ability to secrete HCl.

The serum B12 levels in patients with superficial or mixed gastritis were similar to those found in control subjects. The levels in patients with atrophic gastritis were significantly lower: none was within the range found in pernicious anaemia, but subnormal concentrations (below 140 μg/ml) were present in 17%. Such levels were usually found in patients who absorbed subnormal amounts of Bi, but in some the results of the Bi absorption tests were normal. Entirely normal B12 levels were found in some patients who absorbed grossly subnormal amounts of Bi.

There was a good but by no means complete correlation between the severity of the histological lesion and the depression of gastric function. There was severe depression of secretion of intrinsic factor and of acid in a few patients in whom the biopsy showed only moderately severe atrophy.

It was concluded that there is no single histological nor functional lesion of the stomach that is pathog- nomonic of pernicious anaemia. The exact relationship between atrophic gastritis and Addisonian pernicious anaemia is not yet clear but it is probable that for pernicious anaemia to develop the atrophic process must be of very long duration or some additional factor such as gastrectomy or a family trait must be present. The light that this work throws on the pathogenesis of pernicious anaemia is discussed.

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