Family Study in Addisonian Pernicious Anemia

By S. ARDEMAN, I. CHANARIN, A. JACOBS AND LORRAINE GRIFFITHS

The familial incidence of Addisonian pernicious anemia is well established and has been reviewed by McIntyre, Hahn, Conley and Glass. Most of these studies have also noted an increase in the frequency of gastric achlorhydria and of gastric carcinoma among relatives of patients with pernicious anemia.

The introduction of vitamin B₁₂ absorption tests based on the use of isotopically labeled vitamin B₁₂ and of microbiological assay of vitamin B₁₂ in serum led to these important investigations being applied in the study of relatives of patients with pernicious anemia. Callender and Denborough carried out "Co-vitamin B₁₂ absorption tests in 52 relatives who had achlorhydria. In 10 the urinary excretion of vitamin B₁₂ was within the range found in pernicious anemia and in another 16 the result was less than the value found in controls.

McIntyre et al. carried out vitamin B₁₂ absorption tests on 106 relatives of 34 patients with pernicious anemia. A low excretion (less than 12.5 per cent of an 0.5 μg. oral dose) was found in 21 of these relatives, although only one fell in the so-called pernicious anemia range—i.e., less than 5 per cent. The majority of these subjects had hydrochloric acid in the gastric secretion.

The last few years have seen the introduction of acceptable methods for the detection of antibodies against gastric parietal cells and against gastric intrinsic factor. Further, the methods used for the detection of intrinsic factor antibodies are also applicable to the direct assay of the intrinsic factor content of gastric juice. Parietal cell antibodies are found in the sera of over 80 per cent of patients with pernicious anemia and intrinsic factor antibodies are found in over 55 per cent.

Te Velde et al. studied 220 relatives of patients with pernicious anemia. Parietal cell antibodies were found in 42 relatives, but in only 9 of 178 control...
subjects. Four relatives had intrinsic factor antibodies; three of these had the vitamin B₁₂ absorption pattern of Addisonian pernicious anemia. Vitamin B₁₂ absorption was normal in the fourth patient although she had gastric atrophy. It was suggested that the development of the parietal cell antibody was determined genetically.

The purpose of this paper is to describe a study of a family in whom at least 4 members were known to be receiving treatment for Addisonian pernicious anemia.

**Methods**

Hematologic methods were those described by Dacie. Serum vitamin B₁₂ levels were assayed using either Euglena gracilis or Lactobacillus leichmannii. Vitamin B₁₂ absorption tests were carried out using 1.0 μg doses of either ⁵⁷Co-vitamin B₁₂ or ⁵⁸Co-vitamin B₁₂ by the urinary excretion method. Intrinsic factor was either normal gastric juice containing 1500 units of intrinsic factor or a hog preparation (10 mg. of Lederle WES 818).

Parietal cell antibodies were detected by immunofluorescence.

Intrinsic factor antibodies were detected by the method of Ardeman and Chanarin. Gastric juice was collected through a Ryle’s tube for 1 hour before and 1 hour after a dose of 0.04 mg of histamine per kg. of body weight. Histamine was preceded by 10 to 20 mg of chlorpheniramine maleate. The pH, mEq. hydrochloric acid and the intrinsic factor content were measured. One unit of intrinsic factor has been defined as the amount that combines with 1 μg of Vitamin B₁₂.

Gastric biopsy was obtained using a Wood’s tube.

**The Family**

There were 53 living members of the family covering 3 generations. The propositus (I119) was admitted under Dr. A. W. Frankland to St. Mary’s Hospital for treatment of a respiratory tract infection. Her parents were both dead. The mother (II) was known to have received injections of liver and vitamin B₁₂ for pernicious anemia, was known to have relapsed on ceasing injections and to have recovered again on their resumption. She died from carcinoma of the stomach. The father (I12) died with neoplastic disease. The site of the primary is not known, nor was it possible to trace any of his relatives.

There were 9 siblings in generation II, 7 female and 2 male. Their ages ranged from 46 to 63; four were receiving vitamin B₁₂ injections for pernicious anemia (I13, I14, I16 and I110). Two siblings (II5 and II8) and their families were resident in Australia.

There were 19 members in generation III, 17 female and 2 male. Ten (including III29) were resident abroad and not available for study. Their ages ranged from 18 to 43.

There were 25 members in generation IV. Their ages ranged from a few months to 17 years. Only blood samples and sera were obtained from these subjects.

**Observations**

Blood counts and serum samples were obtained from 48 of the 53 members of the family. Thus the serum vitamin B₁₂ level was assayed in almost all the members of the family, and the sera were also tested for the presence of antibodies against gastric parietal cells, gastric intrinsic factor and against thyroid.

More detailed studies were carried out on 18 adults: all siblings in Generation II and 9 adults in Generation III. The other members of the family were either children or were in Australia. Studies in these 18 adults included study of the gastric juice after histamine, gastric biopsy and vitamin B₁₂ absorption tests.
The Incidence of Addisonian Pernicious Anemia

Six of the 9 siblings in generation II had Addisonian pernicious anemia (fig. 1). Four (II.3, II.4, II.6 and II.10) were receiving vitamin B₁₂ injections at the start of the study. The diagnosis was confirmed in these by demonstrating (a) absence of HCl and intrinsic factor from the gastric juice after an augmented dose of histamine, (b) gastric atrophy on biopsy, (c) failure to absorb vitamin B₁₂ except when given with intrinsic factor.

Subject II.7 had a hemoglobin concentration of 12.8 Gm. per 100 ml.; the stained blood film was macrocytic and the marrow showed megaloblastic hemopoiesis. The serum vitamin B₁₂ level was 110 μg. ml. and the diagnosis of pernicious anemia was confirmed on the same criteria as described.

Subject II.5 was resident in Australia and was studied while on holiday in the United Kingdom. Clinically she had a sore tongue which was smooth, and angular stomatitis. Her hemoglobin concentration was 13.0 Gm. per 100 ml.; the stained blood was macrocytic and the marrow was megaloblastic. The serum vitamin B₁₂ level was 140 μg. ml. and the diagnosis of pernicious anemia was established as in the other siblings.

All the subjects with pernicious anemia were females.

Observations on Blood or Sera

Blood Counts: The hemoglobin levels, packed cell volumes, white cell counts and stained blood films were normal in 44 of the 53 members of the family who were studied. Two had Addisonian pernicious anemia although the hemoglobin concentration was within the normal range (II.5 and II.7). Two others had iron-deficiency anemia (II.19 and II.21).
**Serum Vitamin B₁₂ Levels:** The serum vitamin B₁₂ level was estimated in all but 10 members of the family. Serum samples were not available from 6; the remaining 4 were receiving therapeutic doses of vitamin B₁₂. The serum vitamin B₁₂ level was abnormally low in subjects II5 and II7 (140 and 110 μg. per ml.). Both were thought to have pernicious anemia. The serum vitamin B₁₂ level was 180 μg. /ml. in subjects III15, and was normal in the remaining subjects.

**Parietal Cell Antibodies:** These were looked for in 48 of the 53 members of the family (fig. 2). Parietal cell antibodies were found in the sera from all 9 siblings in Generation II (age 46 to 63). Sera from 17 relatives in Generation III were tested and parietal cell antibodies were present in 10; an equivocal result was obtained in subject III17. Their ages ranged from 18 to 43. Twenty-two sera were tested from members of Generation IV aged 6 months to 17 years and an equivocal result was obtained with 3 sera.

**Intrinsic Factor Antibodies:** Demonstrable intrinsic factor antibodies were present in only 1 subject, II6, and was not detected in 44 other serum samples.

**Observations on 17 Adults**

These results are shown in Table 1.

**Histamine-Fast Achlorhydria:** Eighteen subjects were tested (fig. 3). Achlorhydria was found in 7 subjects with proved pernicious anemia and also in II8, II9 and III15.

**Intrinsic Factor Secretion:** The secretion of intrinsic factor over 1 hour following histamine was measured in 18 subjects. In the 6 subjects with pernicious anemia intrinsic factor was virtually absent from the gastric juice. The secretion of intrinsic factor was as low in the propositus (II9) as
ACHLORHYDRIA

Fig. 3.—Incidence of histamine-fast achlorhydria.

in the pernicious anemia group. The results of 3 tests in subject II9 are shown in Table 2.

The output of intrinsic factor was also reduced in subject II8 (500 units in the hourly resting secretion and 170 units per hour after histamine) and in subject II12 (700 units in 1 hour). In the other 9 subjects the intrinsic factor output ranged from 2100 units to 12,900 units.

Vitamin B₁₂ Absorption: The urinary excretion of labeled vitamin B₁₂ was tested in 18 subjects in Generations II and III. The result was abnormally low in the 6 subjects with pernicious anemia, as well as in the propositus (II9) and in II8. The results in the propositus are shown in Table 3. Subject II8 excreted 9.8 per cent of the dose. Subject III15 gave low urinary excretion values on 3 occasions (6.4, 8.2 and 8.8 per cent) but normal results were obtained when she was admitted to hospital for the test (20.5 and 23.0 per cent excretion). Subject III23 also excreted only 7.0 per cent of the dose of vitamin B₁₂, but since all other tests including gastric biopsy were normal this too was thought to be due to incomplete urine collection.

Gastric Biopsy: Gastric biopsies were obtained from 8 of the 9 siblings in Generation II and from 8 of the 19 subjects in Generation III (fig. 4). The biopsy appearance in the 8 siblings in Generation II aged 46 to 63 was similar with complete loss of parietal and chief cells, lymphocytic and plasma cell infiltration and marked intestinal metaplasia (gastric atrophy).

The biopsy in subjects III12, III15 and III16 showed well-marked atrophic
Table 1.—Data on Subjects in Generations I, II and III

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex/age</th>
<th>Hb</th>
<th>Serum G12 absorption</th>
<th>Bi2+</th>
<th>pH</th>
<th>Intrinsic factor units/hour</th>
<th>Gastric Juice</th>
<th>Antibody to</th>
<th>Gastric Biopsy</th>
<th>Parietal cell</th>
<th>Intrinsic factor</th>
<th>Thyroid</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>Dead; probable pernicious anemia</td>
</tr>
<tr>
<td>2</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>3</td>
<td>F/63</td>
<td>13.6</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td>Gastric atrophy</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>DEAD</td>
</tr>
<tr>
<td>4</td>
<td>F/62</td>
<td>13.5</td>
<td>7</td>
<td>8</td>
<td>20</td>
<td>Gastric atrophy</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>5</td>
<td>F/61</td>
<td>13.0</td>
<td>140</td>
<td>5.7</td>
<td>7.7</td>
<td>30</td>
<td>Gastric atrophy</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>6</td>
<td>F/59</td>
<td>14.5</td>
<td>*</td>
<td>6.6</td>
<td>7</td>
<td>Gastric atrophy</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>7</td>
<td>F/58</td>
<td>12.8</td>
<td>110</td>
<td>1.8</td>
<td>7.1</td>
<td>0</td>
<td>Gastric atrophy</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>8</td>
<td>M/54</td>
<td>14.7</td>
<td>525</td>
<td>9.8</td>
<td>7.0</td>
<td>170</td>
<td>Gastric atrophy</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>9</td>
<td>F/52</td>
<td>13.9</td>
<td>260</td>
<td>8.8</td>
<td>7.7</td>
<td>20</td>
<td>Gastric atrophy</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>10</td>
<td>F/51</td>
<td>13.8</td>
<td>*</td>
<td>1.0</td>
<td>7.6</td>
<td>0</td>
<td>Gastric atrophy</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>11</td>
<td>M/46</td>
<td>15.2</td>
<td>420</td>
<td>16.5</td>
<td>1.3</td>
<td>4800</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>12</td>
<td>F/43</td>
<td>12.8</td>
<td>370</td>
<td>20.3</td>
<td>3.6</td>
<td>700</td>
<td>Atrophic gastritis</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>13</td>
<td>F/41</td>
<td>14.4</td>
<td>400</td>
<td>14.0</td>
<td>1.4</td>
<td>6000</td>
<td>Normal</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>14</td>
<td>F/49</td>
<td>14.9</td>
<td>390</td>
<td>13.0</td>
<td>1.4</td>
<td>7700</td>
<td>Normal</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>15</td>
<td>F/47</td>
<td>13.6</td>
<td>180</td>
<td>20.5</td>
<td>5.8</td>
<td>2100</td>
<td>Atrophic gastritis</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>16</td>
<td>F/29</td>
<td>14.2</td>
<td>390</td>
<td>15.0</td>
<td>1.4</td>
<td>3300</td>
<td>Atrophic gastritis</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>17</td>
<td>F/21</td>
<td>13.8</td>
<td>765</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>doubt</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>18</td>
<td>F/26</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>19</td>
<td>F/35</td>
<td>8.9</td>
<td>625</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>20</td>
<td>F/22</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>21</td>
<td>F/31</td>
<td>8.7</td>
<td>325</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>22</td>
<td>M/35</td>
<td>17.4</td>
<td>310</td>
<td>13.2</td>
<td>1.4</td>
<td>12,100</td>
<td>Superficial gastritis</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>23</td>
<td>F/31</td>
<td>14.4</td>
<td>400</td>
<td>7.0</td>
<td>2.0</td>
<td>12,900</td>
<td>Normal</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>24</td>
<td>F/30</td>
<td>14.0</td>
<td>600</td>
<td>24.0</td>
<td>1.4</td>
<td>5000</td>
<td>Superficial gastritis</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>25</td>
<td>F/21</td>
<td>14.8</td>
<td>535</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>26</td>
<td>F/30</td>
<td>13.1</td>
<td>500</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>27</td>
<td>M/25</td>
<td>14.8</td>
<td>520</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>28</td>
<td>M/18</td>
<td>13.8</td>
<td>930</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>29</td>
<td>F/25</td>
<td>14.5</td>
<td>1000</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>doubt</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>30</td>
<td>F/22</td>
<td>15.4</td>
<td>320</td>
<td>17.9</td>
<td>1.2</td>
<td>11,800</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>
Table 2.—Intrinsic Factor Secretion in II9

<table>
<thead>
<tr>
<th></th>
<th>Units in 1 Hour</th>
<th>Post-histamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting</td>
<td>200</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 3.—Absorption of Vitamin B₁₂ in the Propositus (II9)

<table>
<thead>
<tr>
<th></th>
<th>H₁₂ alone</th>
<th>With human intrinsic factor</th>
<th>With hog intrinsic factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per cent of oral dose of ²⁶Co-B₁₂</td>
<td>8.8, 9.5, 9.7</td>
<td>13.0, 11.3</td>
<td>9.2</td>
</tr>
</tbody>
</table>

changes with, however, residual parietal and chief cells (atrophic gastritis). Subjects II22 and II24 showed the changes of superficial gastritis.

Three biopsies (III13, III14 and III23) were normal.

Chromosome Study: Chromosomes in both peripheral blood and marrow of II5 were examined by Dr. Sylvia Lawler and found to be normal. Normal chromosome members were found in peripheral blood cultures from two other patients (II3 and II4).

Summary of the Data on the Propositus (II9): The propositus, aged 52, had a hemoglobin concentration of 13.9 Gm. 100 ml. The appearances of the stained blood film and the marrow were normal. There was a histamine-fast achlorhydria and a very low intrinsic factor secretion which was in the range found in Addisonian pernicious anemia. Gastric biopsy showed gastric atrophy with complete loss of specialized cells and marked intestinal metaplasia. Parietal cell antibodies only were present in her serum.

The serum vitamin B₁₂ levels were 260 and 290 μg. ml and, some months after a series of Schilling tests, 460 μg. ml. Three vitamin B₁₂ absorption tests gave values of 8.8, 9.5 and 9.7 per cent excretion. Two tests with the addition of normal gastric juice gave values of 11.3 and 13.0 per cent. However, with hog intrinsic factor the results were 7.0 and 9.7 per cent. Thus, this patient had the gastric lesion of Addisonian pernicious anemia. Nevertheless, she was still able to absorb sufficient vitamin B₁₂ to maintain a normal vitamin B₁₂ status.

Discussion

The Incidence of Gastric Atrophy

Study of the genetics of Addisonian pernicious anemia is a study of the failure of normal gastric function and of its morphologic accompaniment, the atrophic changes in the gastric mucosa. Changes in the mucosa are not uncommon while gastric function is still normal, and at this time a very high proportion of such patients have antibodies in serum against gastric parietal cells. If the presence of parietal cell antibodies is taken as evidence of gastric pathology, then this was present in at least 19 of the 28 members of Generations II and III.

The family study of McIntyre et al. suggested that in the adult-type of
Addisonian pernicious anemia intrinsic factor secretion may fail independently of acid production. No evidence in support of this was obtained in this family. Secretion of acid or intrinsic factor declined only as a consequence of loss of secreting cells from the gastric mucosa and there was no isolated decline of intrinsic factor secretion.

Neither achlorhydria nor vitamin B<sub>12</sub> absorption tests were satisfactory screening tests for gastric atrophy. Only three subjects other than those with pernicious anemia had a histamine-fast achlorhydria, although evidence of gastric pathology as judged by the incidence of parietal cell antibodies was present in at least 9 other subjects. Further, the difficulty of ensuring complete urine collection tends to cast doubt on the validity of abnormal vitamin B<sub>12</sub> absorption tests. Even when urine collection is complete, however, abnormal results are to be expected only when there has been almost complete loss of intrinsic factor secretion so that the Schilling test is not likely to be a sensitive guide to decline in intrinsic factor output. Vitamin B<sub>12</sub> “malabsorption” was found in 10 of the 18 subjects tested. Six of these had Addisonian pernicious anemia, two had gastric atrophy without pernicious anemia, and in 2 others there was incomplete urine collection. The possible significance of the result in the other subject with gastric atrophy is discussed below.

The great importance of age in this type of study is illustrated both by the frequency and character of the gastric lesion in Generations II, III and IV. The gastric lesion in the older generation (II) was that of gastric atrophy
in 8 of the 9 members. In Generation III secreting cells were still present in the biopsy (that is, this is the age group with developing atrophic gastritis) and the most severe lesions were present in the oldest members (III12, III15, and III16). In Generation IV only some rather equivocal reactions in the tests for parietal cell antibodies were found in 3 members.

The Absence of Demonstrable Intrinsic Factor Antibodies

Antibodies against human intrinsic factor were found in only one subject. This would suggest that such antibodies are of no importance in the development of Addisonian pernicious anemia. Nevertheless, there is some evidence that antibodies at cellular level are important rather than antibodies in serum. Thus hog intrinsic factor was found to be better than human intrinsic factor in promoting vitamin B₁₂ absorption in pernicious anemia even in those patients without a demonstrable antibody in the serum. High titer intrinsic factor antibodies may be present in the serum in patients with thyroid disease who have a normal vitamin B₁₂ absorption, suggesting that serum antibodies alone do not necessarily impede vitamin B₁₂ absorption. When the dose of vitamin B₁₂ is given orally to such patients with 10 ml. of their own serum, vitamin B₁₂ absorption is prevented.

The evidence concerning the possible role of intrinsic factor antibodies in pernicious anemia has been reviewed by Doniach and Roitt. The failure to demonstrate such antibodies in serum cannot be taken as excluding their presence at a cellular level. However, considerably more evidence is required on this point.

Intrinsic Factor Secretion and Vitamin B₁₂ Absorption

There was impaired vitamin B₁₂ absorption in two members of the family who did not have Addisonian pernicious anemia. Similar observations in relatives of patients with pernicious anemia were noted by Callender and Denborough and McIntyre et al. Most of the patients in this category studied by McIntyre and her colleagues had hydrochloric acid in the gastric juice and this makes it almost certain that these subjects also had adequate amounts of intrinsic factor. Thus the low vitamin B₁₂ excretion could not be due to lack of intrinsic factor.

On the other hand Te Velde and his colleagues found impaired vitamin B₁₂ absorption only in subjects with achlorhydria and severe gastric atrophy. In all Te Velde's patients the absorption was improved with intrinsic factor. Thus, whereas the cases reported by Te Velde and his colleagues appear to have the gastric lesion of pernicious anemia, this does not appear to be the case in the patients described by McIntyre and her colleagues.

We feel that the probable explanation for the apparently impaired vitamin B₁₂ absorption in the majority of relatives of patients with pernicious anemia is incomplete urine collection. Subject III15 indeed gave a low value in the Schilling test in 3 successive tests performed as an out-patient, despite an adequate intrinsic factor output in the gastric juice. On admission to the ward for assessment of small intestinal function, normal vitamin B₁₂ absorp-
tion results were obtained. Results for tests of fat absorption, jejunal biopsy etc., were all normal.

The propositus (II9) had the gastric lesion of pernicious anemia—i.e., gastric atrophy with no HCl and minimal amounts of intrinsic factor that were in the range seen in pernicious anemia. Nevertheless, she was able to absorb adequate, although reduced, amounts of vitamin B₁₂. We have encountered a similar situation in a number of other patients with gastric atrophy without pernicious anemia.² We have not found any change in the vitamin B₁₂ absorption tests over 1 year and her serum vitamin B₁₂ level remains normal. Although she appears to have no more intrinsic factor in her gastric juice than many patients with Addisonian pernicious anemia, it is possible that she is able to maintain an adequate vitamin B₁₂ absorption because she lacks antibodies against intrinsic factor. On this hypothesis the development of such antibodies is required to produce a final failure of vitamin B₁₂ absorption. In this subject human intrinsic factor was superior to hog intrinsic factor in improving vitamin B₁₂ absorption. The contrary is generally true in pernicious anemia—i.e., hog intrinsic factor is better than human intrinsic factor in potentiating vitamin B₁₂ absorption.

One of the difficulties in interpreting the data in this family is that no information is available concerning the father (II). We were unable to find any history of pernicious anemia in that side of the family but we were also unable to trace any of his living relatives. Thus it is uncertain whether the high incidence of pernicious anemia is due to a contribution from both sides of the family or whether the tendency was transmitted only via the mother (II).

The high frequency of gastric atrophy in the members of this family suggests that this process is determined by a dominant mode of inheritance. We are in agreement with the views expressed by Doniach and Roitt,¹⁰ and Te Velde and his colleagues¹¹ that these subjects react to the normal frequent episodes of superficial gastric damage by forming antibodies to various gastric antigens. The most frequent antibody formed is that detected in the usual test for parietal cell antibodies; far less frequently the antibody is directed against intrinsic factor. Intrinsic factor antibodies are only capable of exerting an effect where they are able to come into contact with the antigen—i.e., in the stomach and in the small gut—and there is some evidence to suggest that this is the case. In the stomach the antibodies prevent normal regeneration of gastric mucosa leading to gastric atrophy. In the gut they may interfere with intrinsic factor mediated vitamin B₁₂ absorption, presumably by reacting with the intrinsic factor-vitamin B₁₂ complex in the region of the brush border of the epithelial cell lining the villus. Failure of vitamin B₁₂ absorption in turn leads to deficiency of the vitamin and ultimately to the hematologic and neurologic features of Addisonian pernicious anemia.

**Summary**

Addisonian pernicious anemia was present in 6 of 9 siblings (Generation II). All 9 siblings had evidence of gastric pathology as judged by the pres-
ence of antibodies against parietal cells, abnormalities in the gastric biopsy, and diminution of secretion of acid and intrinsic factor.

Parietal cell antibodies were present in 10 of 17 offspring of these 9 siblings who were available for study. Gastric biopsy in the older members of this generation (III) showed atrophic gastritis; some of the younger members showed superficial gastritis.

Loss of intrinsic factor was always accompanied by loss of gastric secreting cells and there was no evidence that decline of intrinsic factor secretion occurred independently of hydrochloric acid.

**Summario in Interlingua**

Anemia perniciosa de Addison esseva presente in 6 de 9 fraternos (del generation II). Omne le 9 fraternos exhibiva evidentia de pathologia gastric in le forma del presentia de anticorpore anti cellularas parietal, de anormalitates in le biopsia gastric, e del diminution del secretion de acido e factor intrinsec.

Anticorpore anti cellularas parietal esseva presente in 10 del 17 accessibile proles del 9 fraternos. Biopsia gastric in le membros plus avantiates in etate de 9fraternos monstrovava gastritis atrophic. Certes del membros plus juvence de 9fraternos monstrovava gastritis superficial.

Perdita de factor intrinsec esseva accompaniate in omne cases per perdita in secernente cellularas gastric. Esseva trovate nulle evidentia que un declino del secretion de factor intrinsec occurreva independentemente ab acido hydrochloric.

**ACKNOWLEDGMENT**

We are indebted to Dr. Deborah Doniach and Dr. I. Roitt for testing sera for the presence of thyroid antibodies and for permitting us to record these results, to Dr. Sylvia Lawler for carrying out the chromosome study, to Dr. T. Wilkinson and Dr. J. D. Reid for carrying out blood counts and forwarding samples of sera from the Australian members of the family and to Dr. S. Whittingham for allowing us to publish his data on one of the members of the family.

**REFERENCES**


Family Study in Addisonian Pernicious Anemia

S. ARDEMAN, I. CHANARIN, A. JACOBS and LORRAINE GRIFFITHS