PERNICIOUS ANEMIA IN CHILDHOOD

REPORT OF CASE IN SIX YEAR OLD GIRL RESPONDING TO REFINED LIVER EXTRACT, FOLIC ACID AND VITAMIN B₁₂ IN SUCCESSIVE RELAPSES

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The purpose of this paper is to present an unusual case of megaloblastic anemia in relapse in a 6 year old child who was treated successfully with vitamin B₁₂. This case is of particular interest because the patient had exhibited similar responses to parenteral administration of refined liver extract and folic acid during previous relapses.

"Megaloblastic anemia of infancy" has recently been defined by Zeulzer and Ogden. These investigators reserved this term for that group of children under 2 years of age who showed bone marrow changes identical with pernicious anemia and recovered either spontaneously or after a single course of liver or folic acid therapy.

Only a few cases of megaloblastic anemia in children requiring continuous treatment with antipernicious anemia factor have been reported. Jonsson² listed only 7 cases in addition to 2 of his own that he felt met the requirements, and Peterson and Dunn³ accepted only 3. These cases have been amply reviewed by Jonsson, Peterson and Dunn and by Benjamin.⁴ An additional case representing the same disease complex has been reported by Waagstein.⁵ Prompt response followed administration of liver extract or folic acid in these cases, but response to vitamin B₁₂ in such patients has not yet been reported.

Vitamin B₁₂, a pure crystalline antipernicious anemia factor, isolated from liver, was announced in a series of three papers⁶⁻⁸ published in April 1948 in this country and by Smith⁹ in England at about the same time. Spies¹⁰⁻¹⁵ and associates demonstrated the effectiveness of vitamin B₁₂ in cases of pernicious anemia in adults, macrocytic nutritional anemia, tropical sprue and non-tropical sprue. Berk et al.¹³ reported that vitamin B₁₂ was effective in the treatment of the neurologic manifestations in pernicious anemia. Hall and Campbell,¹⁴,¹⁵ after treating 11 patients with pernicious anemia, state that vitamin B₁₂ was as effective as liver extract in managing the hematologic and neurologic aspects of the disease. Luhby¹⁶ reported that vitamin B₁₂ alone was ineffective in the treatment of megaloblastic anemia of infancy, but when small amounts of folic acid were added a response was obtained. He concluded that vitamin B₁₂ alone could not catalyze nucleoprotein metabolism to the complete stage necessary for red blood cell formation.

Bethell and his associates¹⁷ have shown that B₁₂ is present in the feces of patients.
with pernicious anemia in relapse in approximately the same quantities as in normal individuals. Fecal extracts from a patient with pernicious anemia in relapse when given intramuscularly to an untreated case of pernicious anemia, produced significant hematologic and clinical response. Bethell states, however, that vitamin B₁₂ is ineffective in macrocytic anemia of pregnancy and the puerperium. It appears that vitamin B₁₂ may be the principal anti-pernicious anemia factor in liver, although information thus far accumulated is not conclusive.

**Report of Case**

M. D., unit 189660, was born in Rochester Municipal Hospital on 4/4/42 following 9 months gestation period and a normal labor. The birth weight was 3400 grams. The cord blood Wassermann was negative. The neonatorium was not remarkable; no cyanosis, jaundice, or pallor was noted. There were 4 normal siblings ages 14, 10, 8 and 3 years. The father and mother were in good health and of Sicilian extraction.

The child did well and showed no abnormalities in growth and development until the age of 16 months. In the fall of 1943, she was admitted to the Strong Memorial Hospital on three occasions because of progressive irritability, anorexia, pallor and weight loss. On each occasion marked anemia with red blood counts as low as 1.68 million and hemoglobin as low as 4.4 grams per cent were found. She was treated symptomatically and given several small whole blood transfusions. No definite diagnosis was made.

**Fourth Hospital Admission on 1/20/44**

**Interval History:** The patient during the six weeks between the third and fourth admissions was moderately improved for about one week, after which there was progressive return of symptoms. Lassitude and drowsiness were noted for two weeks prior to admission and edema around the eyes was noted for several days before admission.

**Physical Examination:** She was afebrile but pale, irritable and appeared chronically ill. The liver and spleen were not palpable and the neurologic examination was not remarkable. The examination was otherwise entirely negative.

**Laboratory:** Figure 1.

**Course:** Three days after admission, therapy with refined liver extract* was started, 1 cc. (15 units) weekly for 5 injections. A maximum reticulocyte response of 35 per cent was obtained on the fifth day of treatment. She was discharged on the thirtieth hospital day when the red blood cell count was 4.4 million and hemoglobin was 12.5 Gm.

The child was followed in the Out-Patient Department for four months during which time she received two injections of refined liver extract. There were no complaints and the child gained 6 pounds in weight during this interval. She failed to return and was not seen for nine months until April 1945 when her symptoms recurred and it was found that the hemoglobin had fallen to 7.8 Gm. per cent. A course of six weekly injections of refined liver extract was started and in June, 1945, she had no complaints, was cheerful and eating well and the hemoglobin was 13.6 Gm. per cent. She again failed to return for observation and therapy.

**Fifth Hospital Admission on 4/19/45**

**Interval History:** Patient did well for about five months following the liver therapy of the previous spring. Over the five months preceding the present admission, she showed a gradual return of symptoms.

**Physical Examination:** The patient appeared chronically ill, was irritable and showed a yellowish salivary color to the skin. The liver was palpable two fingerbreadths below the costal margin but the spleen was not felt. Except for a soft blowing apical systolic murmur, the remainder of the physical examination was negative.

**Laboratory:** Laboratory findings not included in table 1 were as follows: Vitamin A absorption and glucose tolerance tests were normal. Duodenal drainage revealed normal juices. G. I. series showed a probable deficiency pattern. The electrophoretic pattern was normal. Sickling tests were negative.

* Reticulogen—Eli Lilly and Company.
TABLE I—Laboratory Findings in Child with Pernicious Anemia

<table>
<thead>
<tr>
<th></th>
<th>4th Admission</th>
<th>5th Admission</th>
<th>6th Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cells in millions per cu. mm.</td>
<td>1.38</td>
<td>1.62</td>
<td>2.08</td>
</tr>
<tr>
<td>White blood cells in thousands per cu. mm.</td>
<td>9.100</td>
<td>5.900</td>
<td>4.400</td>
</tr>
<tr>
<td>Hemoglobin in Gm. %</td>
<td>5.5</td>
<td>6.8</td>
<td>6.9</td>
</tr>
<tr>
<td>Segmented neutrophils, %</td>
<td>16</td>
<td>57</td>
<td>61</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>72</td>
<td>40</td>
<td>31.5</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>alb. +</td>
<td>alb. + +</td>
<td>alb. + +</td>
</tr>
<tr>
<td>Stool examinations for blood and parasites</td>
<td>negative</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>Serum bilirubin mg. %</td>
<td>—</td>
<td>—</td>
<td>0.5 mg.</td>
</tr>
<tr>
<td>Icterus index, units</td>
<td>5 units</td>
<td>11 units</td>
<td>—</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>14</td>
<td>17</td>
<td>13.5</td>
</tr>
<tr>
<td>Color index</td>
<td>1.37</td>
<td>1.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Gastric analysis</td>
<td>19.8 free acid present</td>
<td>free acid present</td>
<td>11.6 free acid present only after histamine</td>
</tr>
<tr>
<td>Osmotic fragility</td>
<td>normal</td>
<td>normal</td>
<td>—</td>
</tr>
<tr>
<td>Reticulocytes, %</td>
<td>1.8</td>
<td>1.9</td>
<td>0</td>
</tr>
<tr>
<td>Platelets, %</td>
<td>normal</td>
<td>low</td>
<td>normal</td>
</tr>
</tbody>
</table>

**Course:** Patient was given 5 mg. of folic acid orally every other day. A maximum reticulocyte response of 35 per cent was obtained on the seventh day and she was discharged on the seventeenth hospital day, at which time the red blood count was 4.2 million per cubic mm. and the hemoglobin was 13.5 Gm. per cent.

The patient was not seen until five months later when she returned because of pallor, anorexia and listlessness. The hemoglobin was 8 grams per cent. She was treated as an out patient with weekly injections of liver. A remission of symptoms was obtained and the hemoglobin one month later was 14.2 grams per cent.

The patient failed to return to the clinic and was not seen until November 1, 1948.

**Sixth Hospital Admission on 11/2/48**

**Internal History:** Three months prior to admission her symptoms had begun to recur and she had lost 10 pounds in weight.

**Physical Examination:** Temperature 37 C. Blood pressure 108/66. The patient was a well developed and well nourished child in no acute distress. The skin had a sallow color and both skin and mucous membranes were pale. There was no lymph node enlargement and the liver and spleen were not palpable. The remainder of the examination was not remarkable.

**Laboratory:** Laboratory findings not included in table 1 were as follows: Serum iron: 89 gamma per cent. Erythrocyte protoporphyrin: 2.18 gamma per cent. Vitamin A absorption curve: fasting: 55 μ/100 ml., 4 hr: 133 μ/100 ml., 7 hr: 30 μ/100 ml. Carotene: 374 μ/100 ml. Xanthophyl: 53 μ/100 ml. Total serum protein: 7.5 mg. per cent. Albumin: 6.1 and globulin: 1.4 grams per cent. An intravenous pyelogram revealed normal appearing kidney, ureters and bladder.

**Course:** After studies were complete, the patient was given 12.5 micrograms of vitamin B₁₂* intramuscularly daily for six days. A maximal reticulocyte response of 21.5 per cent was obtained on the sixth day of treatment. Bone marrow aspirations from the lumbar spinous processes were performed before treatment and at 14, 38 and 120 hours after treatment. The serial changes in erythroid elements present

* Supplied through the courtesy of Merck and Company, Rahway, New Jersey.
in the bone marrow are shown in figure 1. She was discharged on the fourteenth hospital day with red blood cell count of 3.7 million and hemoglobin of 12 grams per cent.

The patient is currently receiving 15 units of refined liver extract every three weeks. Clinical and laboratory findings are normal at the time of this writing.

**DISCUSSION**

The similar responses to refined liver extract, folic acid and vitamin B₁₂ are illustrated in the upper three graphs of figure 1. Maturation of erythroid elements

![Graphs showing hematologic response to therapy with liver, folic acid, and vitamin B₁₂.](image)

in the marrow following administration of B₁₂ is also shown graphically in figure 1 and photomicrographs of the maturing erythroid cells are shown in figure 2. The need for continuous therapy to prevent relapse is apparent in view of the five relapses that have occurred during the four years of observation.

The criteria necessary for the diagnosis of pernicious anemia in childhood according to Peterson and Dunn³ are: (1) macrocytic anemia; (2) arrest of maturation of bone marrow at the megaloblastic level; (3) specific response, i.e., reticulocytosis after liver therapy; (4) need for continuous therapy to maintain a continuous remission; (5) histamine resistant achlorhydria.

There is general agreement concerning the first four of these criteria, but other
authors are of the opinion that the diagnosis can be made in an occasional case in which achlorhydria is not present. We believe that the case described is one of true pernicious anemia although free hydrochloric acid was found in the gastric secretions. The future course of the patient will be followed with interest, especially as regards gastric acidity.

![Image of bone marrow aspiration smears]

**Summary**

A case of megaloblastic anemia without specific neurologic complications in a 6 year old girl is presented as an example of pernicious anemia in childhood despite
the fact that a small amount of free hydrochloric acid was present in the gastric juice after injection of histamine. Prompt hematologic response was obtained following administration of refined liver extract, folic acid and vitamin B₁₂ in successive relapses.

REFERENCES

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