SEVERE MEDITERRANEAN ANEMIA (COOLEY'S ANEMIA)
IN A CHINESE CHILD

By Q. B. DeMarsh, M.D.

With the technical assistance of Susan Boyce

A HYPOCHROMIC microcytic anemia in children was first described by Cooley and Lee in 1915. Later, milder forms of this condition were recorded. The highest incidence of the disease has been shown to occur in persons of Mediterranean stock (Italians, Greeks, Syrians, and Armenians). However, cases have been reported in individuals of English, German, Spanish, Egyptian, Chinese, and Negro descent. Foster was apparently the first to describe a typical case of Cooley's anemia in a Chinese child. Of the 2 cases reported by Gardner, the mother of Case 1 did not have the stigmata of the minor form of the disease in her peripheral blood, which is contrary to all other reports. It is interesting that the father of this same patient, and two siblings, all showed microcytosis and hypochromia, without definite anemia. An error is suggested in Gardner's Case 2, in that the red blood cell count and hemoglobin indicate a normocytic anemia, though the smear reveals microcytosis. The serum bilirubin value and the x-ray films were consistent with a hemolytic process. Scott records the fourth case, in which the clinical and laboratory data are typical of the disease. This paper records the findings in what we believe to be the fifth reported case of Cooley’s anemia in a Chinese child.

It is important to recognize the disease clinically for several reasons: (1) It presents many of the findings of other types of hemolytic anemia, but splenectomy is usually of little or no value; (2) both forms of the disease resemble closely iron-deficiency anemia, but do not respond to iron therapy; (3) it is not a rare disease, as was first thought, since Neal and Valentine in a study of persons of Italian descent found one severe case in every 2,368 live births, and one case with the trait in every 2.5 persons studied (Smith found an even higher incidence in a study of sixteen Italian families); and (4) early recognition may prevent unnecessary treatment and permit a more accurate prognosis.

CASE REPORT

A 4 year old Chinese female was admitted to King County Hospital on February 27, 1948, with complaints of cough, fever and rhinorrhea of ten days' duration, complicating a chronic anemia. She was born on February 17, 1944, with a birth weight of 5 pounds culminating a full term uncomplicated pregnancy. She was breast fed for six months. Following this, she received a whole milk formula for one month, and then was placed on a soft general diet. On October 6, 1944, she made the first of several

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* Although Wang and Khoo reported cases which they considered to be Cooley's anemia, none of their cases fulfill the criteria for this disease, and they cannot be considered to be authentic.

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visits to the office of the referring pediatrician. At this time she weighed 12 pounds, 12 ounces. Physical examination was within normal limits. A routine hemoglobin estimation, however, was 9.1 grams per cent. She was given iron orally. She next returned on October 17, 1946, at the age of 14 years, when she weighed 11 pounds. Her mother stated that her skin had been yellow, she had failed to gain weight, and that she tired easily. Examination at this time revealed slight malnutrition, no icterus, a protuberant abdomen, marked hepatomegaly, and splenomegaly. A loud, harsh, systolic murmur was heard

* Dr. C. Scheer of Seattle.
### Table 1.—Family Findings before and after Iron Therapy

<table>
<thead>
<tr>
<th></th>
<th>Before Iron Therapy</th>
<th>After Iron Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name</strong></td>
<td>Mrs. W.</td>
<td>Mr. W.</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>37</td>
<td>42</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td><strong>Red Blood Cells, million</strong></td>
<td>5.90</td>
<td>5.93</td>
</tr>
<tr>
<td><strong>Hemoglobin in grams</strong></td>
<td>12.8</td>
<td>13.2</td>
</tr>
<tr>
<td><strong>Hematocrit %</strong></td>
<td>44</td>
<td>43</td>
</tr>
<tr>
<td><strong>Mean Corpuscular Hgb. (μm grams)</strong></td>
<td>21.7</td>
<td>23.1</td>
</tr>
<tr>
<td><strong>Mean Corpuscular Volume (cu. μ)</strong></td>
<td>74.5</td>
<td>72.5</td>
</tr>
<tr>
<td><strong>Mean Corpuscular Hgb. Concentration %</strong></td>
<td>29.0</td>
<td>31.0</td>
</tr>
<tr>
<td><strong>Reticulocytes %</strong></td>
<td>3.0</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Icterus Index</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Hypochromia</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Anisocytosis</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Poikilocytosis</strong></td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td><strong>Target Cells</strong></td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Basophilic Stippling</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Abnormal Shapes</strong></td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

**Fragility Test**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Hemolysis Began</th>
<th>Hemolysis Complete</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>.45%</td>
<td>.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td>.31%</td>
<td>.17</td>
</tr>
</tbody>
</table>

* This baby was not available for further study. I assume that the infant was developing the trait since it was on iron at the time and no other cause for anemia was apparent.
A presumptive diagnosis of Cooley’s anemia was made at this time. Progress was satisfactory until February 27, 1948, when the patient appeared to have marked anemia together with an upper respiratory infection. Hospitalization was advised. On admission to the King County Hospital, physical examination revealed mongoloid facies of marked degree. The conjunctivae were pale, both tympanic membranes were diffusely inflamed. The pharynx was moderately edematous and hyperemic. Coarse, moist rales were heard throughout both lungs. A harsh blowing systolic murmur was audible over the entire precordium, but was heard best in the mitral area. The abdomen was rounded and moderately enlarged, with prominent hepatomegaly and splenomegaly (fig. 3). The peripheral blood revealed a hypochromic, microcytic anemia with increased icterus index. The smear contained many target cells (fig. 4). The fecal urobilinogen was increased. Photographs of the roentgenograms are shown in figures 1 and 2. The cardiac silhouette was markedly enlarged. These findings were all considered compatible with a diagnosis of Cooley’s anemia.

Five blood transfusions of 100-155 cc. each were given in a period of two weeks, along with penicillin. There was a marked improvement in the general condition, although the blood specimen showed only 7.0 to 8.0 grams per cent of hemoglobin. She was followed in the hematology (outpatient) clinic, with little change until April 22, 1948, when she again presented symptoms of upper respiratory infection. At this time the red blood cell count was 1.9 million/cu. mm. with 4.3 grams per cent of hemoglobin. Again the patient was hospitalized and given one unit of blood, with much improvement. On May 17, 1948, the red cell count was 1.38 million, with 5.0 grams per cent of hemoglobin. On August 19, 1948, her hemoglobin was 5.5 grams per cent and she felt well. She was not seen again until February 7, 1949, at which time she was admitted to the hospital with complaints of fever and pain in her left upper quadrant. She had had fever and upper respiratory infection for three days previously. Five days preceding this she had apparently recovered from epidemic parotitis. She had vomited once with the sudden onset of the pain in her splenic area. Examination revealed extreme pallor with a mild icteric tinge to the sclerae. The abdomen was rounded, with exquisite tenderness over the enlarged spleen. The heart was enlarged and the systolic murmur present as previously. The lungs were clear to percussion and auscultation. Laboratory findings revealed hemoglobin to be 3.3 grams per cent with a hematocrit of 9.0 per cent. Red cell count was 1.46 million/cu. mm. and white blood cell count was 3,700 per cu. mm. with 53 per cent polymorphonuclears and 47 per cent lymphocytes. The reticulocyte count was 4.9 per cent. Urinalysis was normal.

X-ray of the chest revealed increased markings in both lung fields, especially in the right hilar region suggesting broncho-pneumonia. The bowel was markedly distended and low large bowel obstruction was thought to be present.

Despite parenteral fluids, penicillin, oxygen, and blood transfusion, the patient became progressively worse and expired about forty hours following admission.

Autopsy Report.* The essential gross autopsy findings were as follows: Both lungs were increased in weight; the dorsal portion of the left and lower lobe of the right lung were atelectatic. The heart was enlarged (weight 190 grams) with the pericardial sac containing about 50 cc. of clear yellow fluid. The mesentery contained many firm, gray, discrete lymph nodes varying in size from 0.5 to 1.5 cm. The liver weighed 850 grams and extended 3.0 cm. below the right subcostal margin. The spleen weighed 420 grams and extended inferiorty to the iliac crest. There was an area of apparent infarction on the antero-lateral surface, which was evident on gross section of this area. The calvarium in the frontal area appeared abnormally thick (0.8 to 1.0 cm.). The brain weighed 1150 grams. The leptomeninges were diffusely red with fine red vascular striae. The bone marrow was obviously hyperplastic. The epiphysis and metaphysis of the tibia were almost solid red, with the cortex in the shaft appearing abnormally thin, and the epiphyseal line, a narrow gray strip. The microscopic findings were as follows: There was considerable atelectasis, with striking engorgement of the capillaries of the alveolar wall. In some areas there was free hemorrhage within the alveoli themselves. In the spleen there was a subcapsular hemorrhagic infarction as suggested by gross examination. The sinusoids were prominent and engorged with blood. There was evidence of erythroblastic hyperplasia in the sinusoids. Erythropoiesis was apparent in the lymph nodes, which also revealed in-
crease in size of the capillaries. The hepatic cells appeared normal except that many of them contained dark golden brown pigment, which with appropriate stains proved to be iron. The sinusoids of the liver were more prominent than usual, with thickening of the walls. There was no absolute evidence of erythropoiesis. Bone marrow was squeezed from a rib. These preparations revealed no fat, hypercellularity, and increased erythropoiesis. Many mature and immature normoblasts were largely responsible for the increased cellularity. In routine stains of the sections taken from the brain there was a haphazardly irregular degree of intense capillary hyperemia. Around some of the small blood vessels there was an unstained zone, as if from edema, but it was difficult to distinguish from artefacts of fixation. However, in one of the sections there were at least two small vessels with a perivascular cuff of lymphocytes. There were no distinct degenerative changes, but special stains were not applied in an effort to demonstrate possible mild degeneration.

Discussion

In general, the anatomic findings were consistent with those usually described in Cooley’s anemia. These include diffuse erythropoietic hyperplasia in the bone marrow, spleen and lymph nodes, with splenomegaly, hepatomegaly, slight icterus, and recent subcapsular infarction of the spleen. All of these findings, as well as the general underdevelopment of the body as a whole, have been described by others in anatomic studies upon such cases. The general cardiac enlargement was regarded as a consequence of the chronic anemia with its chronic acceleration of cardiac output. Erythropoiesis was not noted in the liver in this case, which would seem to be exceptional. The changes in the brain were interpreted as those of a low-grade or early encephalitis, compatible with the type of encephalitis sometimes following epidemic parotitis. Inasmuch as this patient had epidemic parotitis approximately two weeks before death, the acute encephalitis may be regarded as a consequence of this; hence the changes in the brain may not be directly relatable to the anemia.

The familial nature of this disease has been well established. In this case both parents showed the Cooley’s trait (table 1). Of special interest is the fact that all of the siblings also demonstrated similar hematologic abnormalities, leading one to suspect that the incidence of the disease is more common in Chinese than has heretofore been assumed.

The parents had both come to the United States recently from China. They have no knowledge of the cause of death of grandparents or of any familial diseases. They deny the possibility of admixture of other races or of being interrelated. All members of the family portrayed typical Chinese characteristics; i.e., small features, a broad oval face, high cheek bones, yellow skin, straight black hair, scant facial hair, dark eyes, and well-developed epicanthic folds.

The family, other than the subject of this report, has no signs or symptoms of anemia or jaundice. Splenomegaly was not demonstrable. All members of the family were placed on ferrous sulfate, 0.2 Gm. two times daily, to rule out the possibility of iron deficiency as a factor in the abnormal red blood cell values. Table 1 summarizes the findings of the family before and after the therapy with iron.

Summary and Conclusions

1. The fifth known case of Cooley’s anemia in a Chinese child is reported. Death occurred following a febrile illness which was thought to be mumps encephalitis.
Autopsy findings were consistent with this diagnosis and with Cooley’s anemia.  
2. The remainder of the family showed the characteristic blood findings of 
Cooley’s trait.

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