

## ON HOOKWORM ANEMIA

(APLASTIC ANEMIA IN HOOKWORM DISEASE)

By EUGENE STRANSKY, M.D., AND FLORENCIO N. QUINTOS, M.D.

**H**OOKWORM anemia has been known since the construction of the Gotthard tunnel in Switzerland in the years 1876-80. Perroncito<sup>1</sup> observed that many Italian workers developed a severe and at times fatal anemia, with hookworm infestation. In the following decades hookworm anemia was called miner's anemia because of its occurrence in deep humid mines. Boycott<sup>2</sup> described cases of hookworm anemia in a coal mine in Cornwall, England, in 1901. Later hookworm anemia was observed in other European countries, in America, and in tropical countries, where suitable conditions for hookworm infestation exist.

The etiology of hookworm anemia is well discussed in the papers of Rhoads, Castle, Payne, and Lawson,<sup>3</sup> Payne and Payne,<sup>4</sup> and Andrews.<sup>5</sup> The anemia is due largely to iron deficiency. Napier, Das Gupta, and Mayinuda<sup>6</sup> in British India indicated that, in the absence of dietary deficiency, even a heavy infestation did not produce anemia. Peña-Chavarria and Rotter,<sup>7</sup> in Costa Rica, observed severe anemia in the districts where meat was too expensive for the poor people, while in the districts where meat was plentiful even for the poor, severe anemia did not occur. Brown and Otto<sup>8</sup> found that in the majority of cases in childhood the infested children were "perhaps on the threshold of anemia" and might simply show reticulocytosis.

Hare<sup>9</sup> in India states: "Poverty and ankylostoma are very faithful bedfellows, for poverty implies primitive living conditions which are just ideal for the spread of the parasites. It is possible that the chronic loss of blood caused by ankylostomiasis may just turn the scale against a marrow, which is fighting hard to make bricks with insufficient straw." Johnston and Adams<sup>10</sup> reported 6 cases of severe anemia due to hookworm infestation in pregnancy. It is probable that in these cases the increased demand for iron in pregnancy, together with the constant loss of iron due to the blood-sucking worm, disturbed the equilibrium maintained between blood formation and destruction before pregnancy despite the hookworm infestation. McKenzie<sup>11</sup> emphasized the frequency of vitamin B<sub>1</sub> deficiency in hookworm disease. Hoff and Shaby<sup>12</sup> reported on polyneuritis in hookworm disease. The well-known fact that children, suffering for a long time from hookworm disease, show retardation of physical and mental development, is in favor of the supposition that hookworm infestation may lead to deficiency of resorption of different food constituents.

Ankylostomiasis is widespread in the Philippines. Therefore knowledge of the end results of hookworm infestation and their prevention is of great interest, especially as regards the public health.

From the Department of Pediatrics, College of Medicine, University of the Philippines, and the Philippine General Hospital, Manila, Philippine Islands.

Our cases were observed in the medical and pediatric wards of the Philippine General Hospital in Manila. Most of the cases came from the provinces surrounding Manila.

We observed three types or stages of blood changes in hookworm disease. In the first type the bone marrow is able to maintain the equilibrium between blood loss and production, and there is no manifest anemia. We call this the stage of "compensated anemia." In the second type the production is unable to counterbalance the blood loss, and a hypochromic anemia results. In the third type the bone marrow is exhausted, and aplastic anemia develops.

*The First Type, or "Compensated Anemia."*—We observed a few cases hospitalized for reasons other than anemia, which were discovered to be infested with hookworms on routine examination of the stools. The findings in the peripheral blood were eosinophilia and reticulocytosis without anemia. The bone marrow findings were characterized by increased erythropoietic activity and likewise eosinophilia. Despite a continuous loss of blood, an increased production in the bone marrow was sufficient to maintain the equilibrium between blood formation and blood loss. Of course it would be of great interest to know the exact data of infestation and its duration. It is well known that this early stage of hookworm disease may not develop into real anemia if food and living conditions are adequate. Lowe and Lancaster<sup>13</sup> in Australia recorded 386 cases of hookworm infestation without finding one in which anemia was present.

We studied 33 cases of severe anemia in hookworm disease, 24 of which were males and 9 females. Although the number is very small, the difference in the sex distribution is striking. There were 18 adults, of whom 13 were males and 5 females. There were 15 children, of whom 11 were males and 4 females. The youngest patient was a female of 4 years, the oldest a male of 60 years. Of these 33 cases, 25 belonged in the second stage and 8 in the aplastic anemia stage.

*The Second Type.*—This is characterized by anemia, microcytosis, hypochromia, eosinophilia, and reticulocytosis in the peripheral blood; and eosinophilia and marked erythropoietic activity of the bone marrow. There is more marked erythropoietic activity than in the first type. According to a recent paper of Fenton<sup>14</sup> in West Virginia, hookworm anemia is hypochromic and microcytic, with a red cell count of 1.0 to 3.5 millions per cu. mm. In advanced cases the red cell count may drop to below 1 million. There is usually an eosinophilia of 5 to 15 per cent, although in more advanced cases eosinophilia may no longer be present. In some cases there may be a hypoplastic tendency of the bone marrow, but the condition is still reversible and the patient recovers.

We present the following cases to illustrate the second type.

*Case 1.* A 36 year old male laborer came with symptoms of weakness, chest oppression, headache, and pallor. The disease started 2½ years before admission with bloody diarrhea, tenesmus, and weakness.

Laboratory findings:

- (1) Feces examination revealed hookworm eggs + + +, trichuris eggs + +.
- (2) Blood:
 

Hemoglobin	.....	6.0 and 6.7 Gm.
Red cell count	.....	2.7 and 3.6 millions

White cell count.....	9,000 and 12,400
Reticulocytes.....	9.3%
Platelets.....	300,000
Differential count.....	P—37%, B—3%, E—36%
	L—20%, Mo—4%*

## (3) Bone marrow:

Total count—262,000; Blast cells—4%, Prom—13.2%, Myel—22.0%, Y—19.2%, B—13.2%, Mature forms—3.2%, L—3.2%, E—21.2% in all stages of development, Mitotic cells—0.4%, ratio of nucleated red cells to white cells = 1.1:1.0

After administration of reduced iron and anthelmintic treatment, the patient improved so much that after a stay of 26 days in the hospital, the anemia was relieved, and he was sent home recovered.

This case demonstrates a moderately severe anemia with marked eosinophilia in the peripheral blood and a high cell count with eosinophilia in the bone marrow. The evidences for a good erythropoietic activity of the bone marrow are the high percentage of reticulocytes in the peripheral blood and the very high ratio of nucleated red cells to white cells in the bone marrow. This is the clinical pattern of most of the cases of the second type.

*Case 2.* A 10 year old boy was admitted with symptoms of rapid, shallow respiration, abdominal pain with nausea and vomiting of blackish, sour, mucoid material. The disease started 10 months before admission with pallor, easy fatigability, and vertigo. The child was poorly nourished and poorly developed. The heart was markedly enlarged. There was a loud systolic murmur over the precordium. The skin was very pale with a subicteric tinge. There were no hemorrhages.

## Laboratory findings:

## (1) Feces were positive for ankylostoma ova.

## (2) Blood:

Hemoglobin.....	2.2 Gm.
Red cell count.....	0.68 million
White cell count.....	10,700 and 15,200
Differential count.....	P—78%, B—4.4%, L—15.2%, Mo—
	2%, E—0
Reticulocytes.....	9.8%
Nucleated red cells.....	3.2 per 100 white cells
Icterus index.....	10 units
Bilirubin (serum).....	0.5 mg. per 100 cc.

## (3) Bone marrow:

Total cell count—34,000 cells per cmm. Blast cells—2.8%, Prom—8.0%, Myel—17.0%, Y—26.8%, B—15.0%, Mature forms—15.5%, L—7.0%, Mo—0.7%, E—6.5%, Mitotic cells—0.7%, ratio of nucleated red cells to white cells = 0.6:1.0

On account of the very serious condition and the severe anemia, a blood transfusion of 200 cc. was administered. After the blood transfusion the child improved considerably. Nine days after the blood transfusion the blood showed:

Hemoglobin.....	67 Gm.
Red cell count.....	1.8 million
White cell count.....	5,700

## \*Abbreviations:

P—polymorphonuclears	L—lymphocytes
B—band forms	Mo—monocytes
Y—young forms	Prom—promyelocytes
E—eosinophils	Myel—myelocytes

Note: Bone marrow materials were obtained by sternal puncture.

Platelet count.....	93,000
Reticulocytes.....	2.9%
Icterus index.....	8 units

After the blood transfusion 4 Gm. of reduced iron was administered daily. The heart murmur soon disappeared. During the third week of his stay in the hospital the boy was up and about. After five weeks he was sent home entirely recovered.

This case showed a tendency to hypoplastic reaction of the bone marrow as shown by the rather low white cell count, the thrombocytopenia, the low cell count in the bone marrow, and the erythropoietic activity which is not so high as compared with the previous case. However, the condition was still reversible and the patient recovered entirely.

The youngest case (a 4 year old girl) and a 33 year old male had a similar hematological picture, but both recovered.

*Case 3.* This was a 12 year old boy in whom there was a simultaneous infection with schistosomiasis chronic amebiasis, ascariasis, and trichuriasis, besides the ankylostomiasis.

Blood findings:

Hemoglobin.....	11 Gm. and 12 Gm.
Red cell count.....	3.0 and 3.6 millions
White cell count.....	26,000 and 36,000

In the differential count there were 63.2 and 76.0% eosinophils

Bone marrow findings:

Normal count, normal erythropoietic activity with a ratio of nucleated red cells to white cells of 0.3:1.0.

As far as we could ascertain, the anemia was not influenced by the other parasitic infections. In schistosomiasis without hookworm infestation, there is usually no severe anemia, even in the stage of parasitic cirrhosis. Stransky, Jongco, and Pascual<sup>15</sup> examined the blood of 443 apparently normal Filipino children, 70 per cent of whom were infested with ascaris and trichuris. There was no case of anemia among them.

*The Third, or Irreversible Type (Aplastic Anemia).*—This is characterized clinically by severe anemia, dizziness, easy fatigability, and hemorrhagic diathesis. The erythropoietic activity of the bone marrow is almost nil. There is so-called panmyelophthisis with low cell count; relative lymphocytosis; and lack of erythropoietic, granulocytopoietic, and thrombocytopoietic activity of the bone marrow. The clinical symptoms of panmyelophthisis may develop prior to the definite hematological changes. In this stage anthelmintic and antianemic treatments are of no avail. Blood transfusions and iron are ineffective in improving the irreversible process.

While there is an extensive literature in hookworm anemia, aplastic anemia as a possible outcome of hookworm infestation has only rarely been mentioned. Heilig and Wisweswar<sup>16-18</sup> observed several cases of severe anemia in India but without recording one of aplastic anemia. Cruz<sup>19</sup> in Brazil examined the bone marrow of 24 individuals suffering from hookworm anemia. Red bone marrow was observed in 23 cases, and in only 1 case was yellow bone marrow encountered. Diwany<sup>20</sup> in

Egypt found red bone marrow in his 9 cases of hookworm anemia in children. Schretzenmayer<sup>21</sup> in China reported on aplastic anemia in hookworm disease without discussing its development. The observation of fatal anemia in dogs infested with *Ankylostoma caninum* (Foster and Landsberg<sup>22</sup>) cannot be compared with the anemia of man as the consequence of massive infestation in dogs is an acute anemia, while human hookworm anemia is chronic.

We have observed 8 cases of aplastic anemia in hookworm disease. There were 7 males and 1 female. During the same time of observation we observed 5 so-called primary idiopathic aplastic anemias. There were 4 females and 1 male. This probably demonstrates that there is no particular sex susceptibility for aplastic anemia, and the preponderance of males here only follows the predominant number of males in the whole series as mentioned above.

We shall now discuss the cases of aplastic anemia.

*Case 4.* The first case of aplastic anemia is a 20 year old male who was admitted with a history of 2 months' weakness and pallor. With these symptoms he noticed simultaneously slight bleeding of the gums. One month later he was hardly able to walk and had palpitations and occasional fever. Two weeks before admission he felt numbness of both legs.

Conspicuous findings on admission were marked pallor, bleeding from the gums, and enlarged heart with functional murmurs.

Laboratory findings:

(1) Blood:

Hemoglobin.....	3 Gm.
Red cell count.....	0.9 million; rose to 1.1 millions after transfusion, then down to 0.7 million
White cell count.....	6,000 and 2,600
Differential count.....	L—56% to 89%, E—7 and 1%
Reticulocytes.....	2.0% and 0.8%
Platelet count.....	64,000 and 26,000

(2) Bone marrow was extremely poor in cells. The total counts were: 29,000, 4,200, and 5,300. L—60 to 85%. Ratio of nucleated red cells to white cells was 0.1 : 1.0  
Very rare megakaryocytes seen

Improvement was only temporary after transfusion. The patient left the hospital against advice in very serious condition.

This case was characteristic of chronic aplastic anemia. There were hypochromia, anemia, leukopenia with granulocytopenia, and relative lymphocytosis, thrombocytopenia, and reticulocytopenia in the peripheral blood. There were low cell count, relative lymphocytosis, poor erythropoietic activity, and megakaryocytopenia in the bone marrow. Blood transfusions, large doses of reduced iron, anthelmintic, and dietary treatments did not improve the condition, and the patient was taken home against advice after 5 months in the hospital.

*Case 5.* This second case is similar to case 4. A 15 year old male was admitted with bleeding of the gums and petechial hemorrhages in the skin.

(1) Blood findings were:

Hemoglobin.....	4 Gm.
Red cell count.....	1.2 million

White cell count.....	4,100
Platelet count.....	21,600
Reticulocytes.....	1, 2%
Differential count.....	P—3.6%, B—3.2%, L—84.4%, Mo—4.0%, Plasma cells—0.4%, E—0.4%, no nucleated red cells, no anisocytosis

## (2) Bone marrow:

Total cell count—4,450, L—86.4%, ratio of nucleated red cells to white cells = 0.05 to 1.00

Megakaryocytes were not found

The patient stayed in the hospital for 3 months. During this period he received 8 blood transfusions. The red cell counts ranged from 0.68 to 1.39 millions, the white cell counts from 1,800 to 4,800, the lymphocytes from 67% to 89%. Eosinophils were absent. Two days before the patient left, in very serious condition, there developed ulcerations in the tonsils. The hemorrhagic symptoms persisted. The beneficial effects of blood transfusions became less and less and the patient continued to become worse until his discharge against advice in dying condition.

The first two cases discussed were typical of the aplastic anemia following hookworm disease. The diagnosis can be made easily from the clinical picture with the characteristic peripheral blood and bone marrow findings.

The next two cases illustrate a clinical picture in which, while the outcome was the same as aplastic anemia, the hematological picture at first was not definitely that of panmyelophthisis.

*Case 6* is a 10 year old male, admitted with epistaxis, hematemesis, and epigastric pain, which developed 4 hours before admission. For a year the boy had suffered from repeated attacks of epistaxis, hemorrhages from the gums, subcutaneous ecchymosis, and pallor. On admission the child had rapid, weak pulse, cold extremities, and ecchymoses in the skin and subcutaneous tissue of both legs.

## Laboratory findings:

(1) Feces examination: ascaris + + +, ankylostoma eggs + +, trichuris eggs + +

## (2) Blood:

Hemoglobin.....	6.7 Gm.
Red cell count.....	1.5 million
White cell count.....	6,250
Differential count.....	P—43.5%, B—5.5%, L—47.5%, Mo—2.5%, plasma cell—1.0%, no nucleated red cells
Platelet count.....	78,500
Reticulocytes.....	1.5%

## (3) Bone marrow:

Total cell count—78,500

Differential count: Basophils—0.4%, Blast cells—2.4%, Prom—11.2%, Myel—16.4%, L—24%, Mo—1.2%, E—10.4%, mitotic cells—0.8%, ratio of nucleated red cells to white cells = 0.3:1.0

Normal megakaryocytes in number and structure.

The first impression of this particular case was that of a blood dyscrasia, like purpura, primary or secondary. Although the thrombocyte count was low, coagulation and bleeding time were normal, and the tourniquet test negative. The severe anemia and the normal megakaryocytes in the bone marrow pointed against primary thrombocytopenic purpura. In spite of repeated blood transfusions there was no marked improvement of the anemia.

The blood findings chronologically were:

Date	Hemoglobin (Grams)	Red cell count (Millions)	White cell count	Ratio nucleated red cell:white cell
8-24-40	6.3	1.5	6,200	
8-27-40	5.6	1.5	7,400	
8-29-40	5.6	1.8	4,800	0.01 : 1.3
8-31-40	5.6	1.35	6,000	
9-5-40	5.6	1.6	6,200	
9-19-40	5.6	1.8	5,500	
9-24-40	5.6	1.8	6,000	
9-27-40	4.9	1.57	5,700	
10-2-40	5.2	1.6	3,000	0.005 : 1.3
10-4-40	5.2	1.56	6,300	

The differential count and the reticulocyte percentage did not change markedly. After the first blood transfusion the eosinophils rose to 13% in the peripheral blood and the bone marrow examination showed a count of 217,000 cells with 22% eosinophils, and a 1:1 ratio of nucleated red cells to white cells.

The child stayed in the hospital for 7 weeks. Reduced iron and ammonium citrate were administered in large amounts; oil of chenopodium was given as anthelmintic treatment. The weight increased from 19.8 Kg. to 22.9 Kg. The hemorrhages disappeared. In spite of the increased erythropoietic activity of the bone marrow, and the gain in weight during the short period of remission, the red cell count and hemoglobin level did not improve. Two weeks after discharge the child was brought back with severe hemorrhages from the nose and gums, and petechial bleedings in the skin. He was pulseless, semi-conscious, and apparently exsanguinated. Blood transfusion was recommended, but the parents refused and he was taken home, where he died a few hours later.

This case is an example of severe anemia with symptoms of early hemorrhagic diathesis. From the hematological picture alone, the diagnosis of aplastic anemia could not be definitely made during the stay of the patient in the hospital for 7 weeks. However, the outcome was fatal and, in 2 weeks after discharge, there was probably a rapid breakdown of the bone marrow. It was unfortunate that no examinations were made during the second admission when the patient was in extremis, as the parents refused further examination and treatment.

*Case 7* is a fatal case of ankylostomiasis with autopsy report, in a 15 year old male. He was admitted with gum hemorrhages, epistaxis, petechial hemorrhages of the skin, bleeding from the right ear, and extreme pallor. Bleeding from the gums started 2 months previously, and epistaxis, 20 days before admission. A few days later skin bleedings developed, weakness and pallor set in.

(1) Blood findings:

Hemoglobin	5.2 Gm.
Red cell count	1.5 millions
White cell count	2,900
Platelet count	14,100
Reticulocytes	0.9%
Differential count	P—29%, B—2%, L—66%, Mo—2%, E—2%, no nucleated red cells

(2) Bone marrow: total cell count—105,000, with E—3.2%.

The other cells were almost normal. Ratio of nucleated red cells to white cells = 0.19:1.00

The patient stayed in the ward for 2 weeks. Unfortunately, a suitable donor could not be obtained, as the cross-matching always revealed hemolysis. The patient became weakened, and paler from day to day. Subsequent examinations revealed a further drop in the red and white cell counts. The hemorrhagic tendency became worse, and retinal bleedings set in. The patient rather suddenly died, probably from heart failure.

The autopsy findings were: anemia, severe, generalized; tigroid heart with dilatation; petechial hemorrhages in the epicardium; hemorrhage and edema of the lungs, endocardium, and cerebellum; yellow bone marrow with reddish (hemorrhagic) areas; purpura of the skin; ankylostomiasis, severe.

In this case the anemia was not extreme at first, with a count above 1 million; the bone marrow count was 105,000, which is about normal, and the differential count was not much altered; but the erythropoietic activity of the bone marrow was low, the ratio of nucleated red cells to white cells was 0.19:1.0 compared to 0.3:1.0; 0.6:1.0; and 1.1:1.0 in those that recovered in the second type. The hemorrhagic symptoms, leukopenia, with relative lymphocytosis, thrombocytopenia, low reticulocyte count, and absence of nucleated red cells in spite of the anemia, shown by the peripheral blood, were in favor of aplastic anemia even in the beginning of the observation, despite the somewhat normal bone marrow findings. Repeated bone marrow punctures in the follow-up would probably have shown more definite aplastic reaction.

The last two cases were similar in that the anemia was not very severe at first, the bone marrow findings were not definitely those of aplastic anemia, and the leukocyte and differential counts were not much altered. Therefore a definite diagnosis of aplastic anemia could not be made at first, typical aplastic anemia later developing. In both cases, hemorrhagic tendency was observed early in the course of the disease. This symptom, when observed in hookworm infestation, may be a danger signal as it was observed in all those cases that died, even before the other findings of aplasia were evident; and it was not observed among the cases of hookworm anemia that recovered. Quintos in an unpublished paper (1943) called attention to this early danger signal in hookworm anemia, and although the number of cases observed is small, it is an interesting point for further study.

The next consideration is: Are these cases of aplastic anemia simply coincidental with hookworm anemia? It is indeed difficult to give a definite answer. During the same period of time we observed 5 cases of so-called idiopathic aplastic anemia, compared to the 8 cases associated with hookworm anemia. The incidence of an aplastic bone marrow response in hookworm anemia is therefore high compared to that without hookworm disease; a definite causal relationship may therefore be present.

The pathogenesis is still a more difficult problem. Our experience is that hookworm anemia is rare in young children. Our youngest case was 4 years old, the next was 7 years old, and all the others were at least 10 years old. On the other hand, it is probable that infestation takes place early, and after anemia has developed, it takes some time more for aplastic anemia to manifest itself. We did not see a case of aplastic anemia below the age of 10 years. We believe therefore that it takes several years before aplastic anemia develops. While the pathogenesis is obscure, we are of the opinion that there is an exhaustion of the bone marrow following continuous blood loss in the presence of various factors, including dietary deficiency. It is known that aplastic anemia does not develop in chronic hemolytic anemia where



there is an abnormal load on the bone marrow to produce red blood cells to counterbalance hemolysis during the whole life of the individual or until therapy is instituted. Therefore it is presumed that some other factor besides the blood loss must play a part in the development of aplastic anemia in hookworm disease.

## SUMMARY

We have discussed three types or stages of blood changes in hookworm disease. Attention is directed to a severe irreversible aplastic anemia which occurs not infrequently in hookworm disease. The pathogenesis is obscure, but we believe that it is due to bone marrow exhaustion following continuous blood loss in the presence of various factors, including dietary deficiency.

The symptomatology, hematologic and bone marrow findings are described.

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