

## TREATMENT OF THE ANEMIA ASSOCIATED WITH HOOKWORM DISEASE \*

### Preliminary Report

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"Ponce, Puerto Rico, Nov. 24, 1899.

Chief Surgeon, San Juan:

Have this day proven the cause of many pernicious progressive anemias of this Island to be due to *Ankylostomum duodenale*.

(Signed) ASHFORD." <sup>(1)</sup>

Truly a historical document, this telegram, sent by Capt. Ashford to the military authorities at San Juan, marked a turning point in the medical history of Puerto Rico. As a result of his discovery, the cause of the most prevalent anemia throughout the Island had been determined. It became evident that gastrointestinal disturbances, edema, marked pallor and weakness did not stand for separate disease conditions, but were part of one clinical entity; that this symptomatology so frequently encountered among the laboring classes had a definite cause and was not dependent upon predisposing accidents of environment, upon concomitant disease, mere poverty or bad hygiene<sup>(2)</sup>.

In 1902 Dr. Stiles<sup>(3)</sup>, working with Ashford's specimens of hookworm from Puerto Rico, and with others found subsequently in the United States, announced that, zoologically, the parasite belonged to a new species of *Uncinaria americana*, later renamed by him *Necator americanus*. The mode of infestation, symptomatology, morbid anatomy and treatment of this parasite of the New World was similar to that of the Old World species, *Ankylostoma duodenale*.

The Puerto Rico Anemia Commission<sup>(4)</sup>, created in 1904 for the purpose of beginning an active campaign against the

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disease, marked the first era of the work against hookworm on this Island, and the first demonstration of its endemic presence in American soil. The names of Drs. W. W. King and Pedro Gutiérrez Igaravidez, who, with Dr. Bailey K. Ashford, composed the first Anemia Commission, have found a permanent place in the medical history of Puerto Rico. The observations of Rhoads and Castle<sup>(5)</sup> on the etiology and treatment of the anemia associated with hookworm infestation, suggest that dietary deficiency and gastric secretory changes are of major etiological significance. The more recent work of Dr. Ramón M. Suárez<sup>(6)</sup> deserves special mention in connection with the hematological investigations in this disease. In his series of cases Dr. Suárez studied the clinical aspects of the disease, and for the first time, to our knowledge, electro-cardiographic tracings on patients with the anemia of hookworm disease were made. These authors emphasized the use of large doses of iron in the treatment of the anemia associated with hookworm infestation.

Most, if not all, of the symptoms of hookworm disease are the result of the anemia which may range from very slight grades in the cases with mild infestations, to the most severe, in which the hemoglobin is reduced to 15 or 20 per cent or even lower, and the red cells as low as 754,000 per c. mm. <sup>(7)</sup>. The hemoglobin is usually reduced more than the red cell count, thus giving the low color index so characteristic of secondary anemia. The type of anemia associated with hookworm disease is similar to that resulting from chronic blood loss, and marked changes in the size and hemoglobin content of the red corpuscles may be encountered. The cells are smaller than normal and their hemoglobin content may be greatly reduced. The constant drain on the hemoglobin supply of the body is strikingly compensated by the administration of iron in these types of anemia<sup>(8)</sup>.

The cause of the anemia is still a matter of controversy, some investigators claiming that it is produced by a hemolytic toxin<sup>(9)</sup> elaborated by the parasite, whereas others suggest that it may be due to a long continued blood loss from the ulcerated mucous membrane of the small bowel<sup>(10)</sup>. Analogy suggests also that this anemia is due to the latter cause, since the blood picture resembles that observed in posthemorrhagic anemia.



During the course of a recent investigation on the effect of large doses of iron on the anemia of hookworm disease, we have had occasion to study the effect of other therapeutic agents on the anemia, and to observe the comparative response of the blood to these agents.

The observations reported in the present study were obtained from five carefully selected cases of advanced hookworm disease. The patients were all males between the ages of 20 and 30 years. One of them came from the northern coastal plain and the others from the mountain districts of Puerto Rico. More than one thousand worms were recovered from each individual, after anthelmintic treatment. All but one of the patients were hospitalized for a minimum period of 50 days during which blood studies were carried out three times a week. Other clinical studies, such as determination of basal metabolic rate, measurement of heart diameters, blood chemistry, gastric analysis and other hematological tests were also done, but will not be discussed in this paper. During hospitalization four of the five patients received an iron-deficient diet. For ten days after admission no drugs were administered with the view of studying the extent and type of anemia during a period of standardization. After this period the drug therapy used in each case was instituted, and the same dose administered daily until the patients were discharged from the hospital. This procedure enabled us to observe the effect of the different therapeutic agents on the anemia before the removal of the worms harbored by each patient. On the fortieth day after admission the patients received anthelmintic treatment (2.5 cc. carbon tetrachloride) and the worms recovered from the feces were recorded. Hematological studies were continued during a period of ten days after the administration of the anthelmintic for the purpose of observing any change in the blood values after removal of the worm burden.

*Therapeutic agents used:*

Cases Nos. 1 and 2 received 6 gms. of iron ammonium citrate daily.

Case No. 3 received 45 cc. of liver extract with iron by mouth, daily; this represented approximately 350 gms. of raw liver and 3 gms. of iron ammonium citrate.



Case No. 4 received 6 gms. daily of a well known commercial preparation containing a gastro-hepatic concentrate and 2.0 gms. of ferric ammonium citrate.

Case No. 5 received full hospital diet alone.

After the discharge of patients from hospital an attempt was made to perform weekly hematological studies for a minimum period of two months on each patient with the object of observing the effect of environment, home diet and new infestations on the blood picture and well-being of the patient.

#### *Results:*

The duration of the illnesses of the five patients under study varied from two months to several years. None of them had received anthelmintic treatment previous to hospitalization. The most prominent symptoms were those referable to the anemia such as pallor, weakness, and inability to work. One individual presented marked edema of the legs and gave a history of epigastric pain with anorexia. The former symptom became so disturbing during hospitalization that opiates were required on several occasions for its relief. None of the patients showed evidence of emaciation on admission to the hospital and all gained weight during the course of the experiment. A slight afternoon temperature was present in all patients during hospitalization.

The anemia encountered on admission and during period of standardization was of the microcytic hypochromic type, or one in which the mean cell volume, as well as the hemoglobin content of the cells, was greatly reduced\*. Marked variation in the size and shape of the red cells was encountered and these appeared poorly stained and achromic. No nucleated red cells were observed at any time during this study.

The red cell count\*\* on admission and during period of standardization ranged between 1.5 million to 3.5 millions and the hemoglobin from 4.2 gms. to 5.3 gms. (29 to 36.4%). (Newcomer-Klett hemoglobinometer was employed, 14.5 gms. of hemoglobin per 100 cc. of blood = 100%).

\* Wintrobe's hematocrit was employed to determine the volume of packed red cells per 100 cc. of blood.

\*\* Blood counts were made with pipettes and counting chamber certified by the United States Bureau of Standards.



During the period of observation before the anthelmintic was given, the response of the blood was quite similar in all cases irrespective of the therapeutic agent administered. There occurred a gradual and persistent rise in both the red cell count and hemoglobin percentage until a certain level was attained, after which no further significant increase in these values was observed. The highest figures during this period varied from 3.5 to 4.3 millions, and from 10.6 gms. (72.9%) to 12.2 gms. (83.4%) in all cases. The highest red blood cell count and hemoglobin values were observed in one of the two patients who received 6 gms. of iron ammonium citrate daily, and the lowest values were observed in the patient on the full hospital diet. The peak of the red blood cell count and hemoglobin was attained about two weeks sooner in those patients who received iron alone, than in the others who did not. In no case did the blood reach normal limits before administration of the anthelmintic. However, there was definite clinical improvement in all cases, more marked in those who received iron (6 gms. daily).

Within a week after the administration of an anthelmintic the red cell count rapidly rose to normal limits ranging between 5 and 6 millions in all cases; the hemoglobin, however, did not follow the same rapid rise and remained around 11.4 gms. (78.4%) in three of the five cases. In the remaining two individuals who had received 6 gms. of iron daily, the hemoglobin rapidly rose to normal values ranging from 15.3 gms. (106%), to 16.3 gms. (112%).

Two of the five patients in this group have been studied for eight weeks after discharge. No medication was used during this period, but both had received iron (6 gms. daily) during hospitalization. Three weeks after discharge both presented evidence of a light infestation of worms. The results obtained in the study of the blood of these patients have been strikingly opposite. In one individual the red cell count continued to rise after discharge to 5.8 million cells per c. mm. and the hemoglobin increased to 17.0 gms. (116%), while the other suffered a loss of one million cells and 2.4 gms. hemoglobin (15%) in the same period of time.

#### *Summary and Conclusions:*

1. Observations in the present study of a small number of cases suggest that iron administered in large daily doses (6



gms.) is the treatment of choice in the anemia associated with hookworm disease as compared to liver extract with iron by mouth, to a widely-known commercial preparation used in the treatment of secondary anemia, and to a well-balanced full hospital diet.

2. The administration of each of the therapeutic agents used during a period of thirty days without removal of the worms resulted in a rise of the red cell count and hemoglobin percentage to a practically constant subnormal level. This level was reached more quickly by those patients receiving iron alone. After this rise there was no further significant increase previous to removal of the worms.

3. Administration of an anthelmintic was followed in all cases by a rapid (5 to 7 days) increase in the red cell count to normal values. In the two patients who received iron alone a rapid increase in hemoglobin parallel to the increased red cell count was observed.

4. It is inferred from these studies that an intensive iron therapy and a well-balanced and nutritious diet aided by an effective anthelmintic seem to provide the optimum conditions of a rapid recovery from the chronic anemia encountered in hookworm disease.

#### ACKNOWLEDGMENT

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#### Note:

Since the preparation of this work the following papers have appeared which have not been referred to in the present work:

1. Observations on the Etiology and Treatment of Anemia Associated with Hookworm Infection in Puerto Rico, by C. P. Rhoads, W. B. Castle, G. C. Payne and H. A. Lawson. *Medicine*, Vol. 13, No. 3, September, 1934.

2. Hookworm Anemia: Etiology and Treatment with Special Reference to Iron, by C. P. Rhoads, W. B. Castle, G. C. Payne and H. A. Lawson. *American Journal of Hygiene*, Vol. 20, No. 2, September, 1934.

3. The Nature and Cause of Hookworm Anemia, by A. O. Foster and J. W. Landsberg. *American Journal of Hygiene*, Vol. 20, No. 2, September, 1934.

#### BIBLIOGRAPHY

1. ASHFORD, B. K. and GUTIÉRREZ IGARAVÍDEZ, P.: Uncinariasis in Porto Rico.— A Medical and Economic Problem. Senate Document No. 808, 61st Congress, 3rd Session, 1911.
2. Idem.



3. Idem.
4. Idem.
5. RHOADS, C. P. and CASTLE, W. B.: Observations on the Etiology and Treatment of the Anemia of Hookworm Disease in Porto Rico. *Journal of Clinical Investigation*, Vol. 2, page 809. 1932.
6. SUÁREZ, R. M.: Clinical Aspects of Uncinariasis. *The Puerto Rico Journal of Public Health and Tropical Medicine*. Vol. 8, No. 3, March, 1933.
7. ASHFORD, B. K. and GUTIÉRREZ IGARAVÍDEZ, P.: Uncinariasis in Porto Rico. 1911.
8. MUSSER, J. H. and WINTROBE, M. M.: Diseases of the Blood. *Tice's Practice of Medicine*. Vol. 6.
9. ASHFORD, B. K. in Archibald and Byam. "The Practice of Medicine in the Tropics", 1929.
10. HUART, A. J.: On the Causes of Anemia in Ankylostomiasis. *Acta Leidensi, Scholae Medicinae Tropicae*, Vol. 4, page 48, 1929.