PROPHYLAXIS OF HOOKWORM ANEMIA-DEFICIENCY DISEASE

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IN VIEW of present knowledge of hookworm anemia, it has become evident that, qualitatively and in conjunction with helminthic infestation, deficient nutrition is of importance in the genesis of this disease. The possibility of curing the anemia, even though the intestinal parasitism remains, has provided us with the opportunity of observing which symptoms and clinical signs result from a hemoglobin deficiency and which are caused directly by the presence of the helminths. Contrary to what might be expected, with the exception of intestinal hemorrhages and eosinophilia, all other pathologic changes disappeared as the blood became normal. So great is the importance of these symptoms and signs that yield with the treatment by iron, and so insignificant are those that remain, that we should, in this case, consider the anemia not as a syndrome connected with the signs, but as the disease itself. The specificity of the treatment of anemia by iron and the astonishing nature of the cure are the usual characteristics of conditions of deficiency.

Up to the present time, prophylaxis of hookworm anemia has been considered as the prophylaxis of a disease which is strictly parasitic in origin. The methods are difficult and costly, amounting almost to radical changes in the firmly established habits of a population (use of shoes) or sanitary engineering measures amounting almost to sudden civilization of backward zones (construction of privies, etc.). These classic methods of prophylaxis, consisting in avoiding the infestation of man by *Ancylostoma*, have been of no practical effect with respect to the incidence of the anemia.

If we consider the prophylaxis from the point of view of the second agent in the etiologic complex of hookworm anemia, i.e., qualitative nutritional deficiency, a different plan of prophylactic campaign can be outlined. The application of iron in prophylaxis is not sufficient to eliminate completely the disease from a community, and in addition, it requires periodic application. On the other hand, this method is one of the easiest to apply, when it is duly supported by the proper public health laws.

Following these principles, Cruz and de Mello[1] attempted to create the bases for a prophylaxis of hookworm anemia considered as a deficiency disease (similar to the prophylaxis of endemic goiter). This consisted in adding an iron salt, hematologically active, to the foods habitually eaten by the lower social classes. The difficulties encountered were considerable, as compared with the prophylaxis of endemic goiter. In the latter, 0.005 Gm. of potassium iodide are sufficient, whereas in hookworm anemia we had to use a much higher dose of usable iron salt. Various trials were made, not only for choice of food, but also of the iron salt with highest therapeutic value and stability. The authors concluded that the mixtures of ferrous sulfate with manioc flour and of ammoniacal ferric citrate with bean gravy were

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sufficient not only to cure, but later to prevent the fall of blood values during long periods of time, in individuals who were heavily infested. Various cases were described,[1] a summary of which may be seen in table 1.

With the various experimental mixtures used, it was attempted to fulfill the following requirements: taste, stability, appearance, hematologic efficiency, and low cost. Only two were found to be satisfactory: ferrous sulfate mixed with manioc flour and ferric ammonium citrate, brown, added to bean gravy. The salts

TABLE 1

Name	*Age*	*Weight*	*No. of worms eliminated*	*No. of worms per kilo body weight*	*Intensity of infestation**	*Hemoglobin level maintained (Gm. 100 ml. blood)*	*Days maintained*	*Iron salt used*	*Daily dose*	*Equivalent in metallic iron*	*Food to which added*
	yrs.	*kilos*							*Gm.*	*Gm.*	
Pedro.....	8	23	500	22	VI	10.00	40	Ferrous sulfate	0.50	0.185	Manioc flour
Pedro.....	8	23	500	22	VI	9.50	85	" "	0.25	0.092	" "
Argentina..	20	45	717	16	VI	10.25	82	" "	0.50	0.185	" "
Argentina..	20	45	717	16	VI	10.25	91	" "	0.25	0.092	" "
Carlos.....	45	50	758	15	VI	9.00	80	" "	0.50	0.185	" "
Edno.....	13	26	350	13	V	11.00	82	" "	0.50	0.185	" "
Edno.....	13	26	350	13	V	11.50	91	" "	0.10	0.037	" "
Jose V.....	16	38	499	13	V	11.25	112	" "	0.50	0.185	" "
Jose V.....	16	38	499	13	V	11.00	45	" "	0.25	0.092	" "
J. Magalhães.....	9	28	300	11	IV	10.25	90	Ammoniacal ferric citrate	1.00	0.210	Bean gravy
Valdir.....	12	30	280	9	IV	9.50	87	Ferrous sulfate	0.50	0.185	Manioc flour
Mario.....	18	46	230	5	IV	10.00	65	" "	0.50	0.185	" "
Mario.....	18	46	230	5	IV	10.00	128	" "	0.25	0.092	" "
Delvair....	9	26	130	5	IV	10.50	87	" "	0.50	0.185	" "
Maria.....	19	45	180	4	III	11.00	80	" "	0.50	0.185	" "
Maria.....	19	45	180	4	III	11.75	90	" "	0.10	0.037	" "

* See table 3.

listed in table 2 were also tried, but did not fulfill the requirements and their use was not continued.

With regard to the infestation index listed in table 1, we should keep in mind that, according to present knowledge, the contribution of the helminths to the formation of anemia appears to be exclusively through their blood-sucking activities. The hemorrhages caused by this action have a distinctive significance in the physiology of the blood. The organism reacts in various ways according to the hematic constituents lost in a hemorrhage. It seems to possess an unlimited quantity of protein for reconstitution of the red blood cell strome, of globin, and of amino radicals present in the chemical structure of heme. This is not the case with

relation to the basic metal for the respiratory function. This metal is a vital raw material for reconstitution of respiratory pigment, and the organism is entirely dependent on the reserves supplied to it by nutrition to maintain a normal hemo-

TABLE 2.

Iron Compound	*Food to which added*	*Color of mixture*	*Taste*	*Hematologic activity in therapeutic dose*
Iron carbonate	Kitchen salt	brown	o	−
" "	Flour	brown	o	−
" "	Sugar	brown	o	−
Iron glycerophosphate	Kitchen salt	yellowish	+	+
" "	Kitchen salt	o	+	+
" "	Sugar	yellowish	+	+
Iron proto-oxalate	Kitchen salt	yellowish	o	+
" "	Flour	yellowish	o	+
" "	Sugar	yellowish	+	+
Iron pyrophosphate	Kitchen salt	white	o	+
" "	Flour	o	+	+
" "	Sugar	o	+	+
Ammoniacal iron sulfate	Kitchen salt	dark yellow	+++	++
" " "	Flour	o	+++	++
" " "	Sugar	darkish	+++	++
" " "	Sugar	darkish	++	++
Iron phosphate	Kitchen salt	dark green	+	++
" "	Flour	grey	+	++
" "	Sugar	greenish grey	+	++
Iron albuminate	Kitchen salt	brown	o	−
" "	Flour	brown	o	−
" "	Sugar	brown	o	−
Ammoniacal ferric citrate	Kitchen salt	yellow	+++	++
" " "	Flour	o	+++	++
Tartrate of iron and potassium	Kitchen salt	light brown	++	−
" " " " "	Kitchen salt	light brown	++	−
" " " " "	Flour	brown	o	−
" " " " "	Sugar	dark brown	o	−
Iron benzoate	Kitchen salt	dark brown	+++	−
" "	Flour	dark brown	+++	−
" "	Sugar	dark brown	+++	−
Iron lactate	Kitchen salt	greenish	+++	+
" "	Flour	o	++	+
" "	Sugar	brown	++	+
Ferrous sulfate	Kitchen salt	yellow	++	++++
" "	Flour	o	o	++++
" "	Sugar	yellow	++	−

globin metabolism. Accordingly, when the helminths withdraw blood from the body, they withdraw essentially the iron metal. Therefore, each helminth represents a unit of consumption in the iron balance in the body. This unit will increase in importance in proportion to the decrease of iron in the circulation of the host. It is known that in mammals the total amount of blood is approximately 10 per

cent of the body weight. Hence, the damage caused by a worm will be less important in an adult of 60 kilos than in a child of 20 kilos. This means that the intensity of infestation can be expressed only by a relationship between the number of worms living on the intestine and the mass of circulating blood, or roughly the body weight of the host. Based on these data, we suggest that the intensity of infestation from *Ancylostoma* be figured according to table 3.

In order to determine approximately the number of helminths per kilo of body weight, based on egg counts, the following formula is used: $\frac{N}{18P}$, in which N represents the number of eggs per gram of feces and P the weight of the individual expressed in kilograms. Usually the infestation occurs with an equal number of male and female helminths, and as the females of the Necator are responsible for eliminating 36 eggs per gram of stools, we should divide the egg count by half of 36, which explains the factor 18 in the denominator of the formula. Therefore, for

TABLE 3

Intensity of infestation—Groups	*Helminths per kilo of body weight*
I	0
II	0- 0.9
III	1- 4.9
IV	5- 9.9
V	10-14.9
VI	over 15

example: in a child, 31 kilo body weight, with 5,000 eggs per gram of feces we have $\frac{5000}{560} = 8.9$ helminths per kilo of body weight, a case belonging to group IV of our classification.

Following these studies on the administration of iron in the prophylaxis of hookworm anemia considered as a deficiency disease, it would doubtless be very important to determine the minimum dose of salt to be used, in order to maintain the blood values at a normal level. For this purpose, we submitted a patient, with a high index of infestation, to several doses of ferrous sulfate added to the food.

CASE REPORT

C. G., 22 years old, raidroad worker, white, Brazilian, resident of Magé. Weight, 45 kilos. Admitted to the hospital on January 11, 1946. Discharged April 4, 1947.

Patient complains of extreme weakness, is easily tired, has dyspnea and palpitation after making the slightest physical effort. Can not say for certain when illness commenced; the symptoms appeared and progressed in unnoticeable manner. Says he had no venereal or rheumatic past. Although living in malaria zone, informs never had malaria. Drinks alcohol in moderation.

General examination: Asthenic, badly nourished individual. Skin yellowed; visible mucosas highly discolored, almost white. Lesions of chronic scabies spread over trunk, abdomen, base of thighs, and hands. In the malar region on both sides and as far as the edges of the nose, symmetrical, irregular zones of dark coloring and a little shiny can be noted. On malleoli slight edema, less than one month old. No decrease or changes in appetite. Teeth are in poor condition. Tongue is white, broadened, and marks of teeth can be seen on tip.

Digestive system: Epigastric region is sensitive to touch, but does not present spontaneous pain. No constipation; in last two months, attacks of diarrhea have been frequent. Liver and spleen not increased in volume.

Circulatory system: Pulse light, soft, and rhythmic, with 84 pulse beats per minute. Blood pressure is 110/75. Lack of thrill in neck vessels. Ictus weak, located in fifth intercostal space, one centimeter inside the hemi-clavicular line. Systolic murmur (++) soft, audible at point and at base. Not spread by any focus. Diminishes in intensity at beginning of inspiration, and, on the other hand, increases when the individual lies down or when the auscultation point is pressed with stethoscope. In the pre-systole, the auricular sound is heard in the mesocardiac region. A2 and P2 are equal and normal.

Respiratory system and other systems, normal.

Sequence in hospital: The stay of the patient in the hospital was not apyrexial due to two factors not connected with the Ancylostomiasis: (1) a secondary infection in some lesions of the scabies mentioned; (2) a dental abscess, both occurring when health conditions were very poor. With the use of iron, the symptoms and signs caused by the anemia diminished immediately. At the end of the first week, the

TABLE 4.—*Hematologic Tests*

	Date												
	1946										1947		
	1:18	1:25	2:4	2:15	2:25	4:19	5:21	8:12	9:26	11:19	1:3	2:6	4:12
	Days of observation												
	0	7	16	27	37	91	123	204	248	301	345	378	444
Red blood cells (10^6/ml.)	1.2	1.9	2.6	3.7	3.7	4.9	5.1	4.5	4.8	4.6	4.3	3.8	5.0
Hemoglobin (Gm./100 ml. blood)	1.5	4.4	6.2	8.8	8.2	11.2	12.0	9.6	11.2	9.0	10.2	8.6	11.6
Hematocrit (%)	7	14	21	29	30	35	38	34	36	33	32	29	38
Mean corpuscular volume (cubic micra)	58	73	80	78	80	71	75	76	75	72	75	76	76
Mean corpuscular hemoglobin (micro-micrograms)	12	23	24	24	22	23	23	21	23	20	24	23	23
Mean corpuscular hemoglobin concentration (%)	21	31	29	30	27	32	32	28	31	27	32	30	31

malleolar edema no longer existed. Urine examinations, made immediately after the patient was admitted to the hospital, and subsequent examinations, showed nothing to indicate that renal function was affected. Appetite was always good. The attacks of diarrhea disappeared. Forty days following beginning of treatment, the patient had gained 6 kilos weight. Color of skin and of mucosas practically normal, for our environment, at end of February, that is, 45 days after admittance. Tongue had regained tonus. Physical resistance permitted the practice of active exercise without reappearance of dyspnea and palpitations. Heart beat remained about 70 per minute. Blood pressure not changed, systole continuing between 105 and 115 and diastole at 75 mm. Hg. Beginning the middle of March, systolic murmur no longer heard; only first sound found to be extended at point. Auricular sound heard only when the heart, because of the requirements of physical effort, became hyperactive. No opportunity to make radiologic study of this case.

We accompanied clinical course of the anemia with frequent electrocardiograms. We will analyze only two, spaced about three months apart. The others are transitional between these two, or repeat the second, which represents, so to speak, the final modification observed.

In figure 1 (January 16, 1946) and figure 2 (April 9, 1946), the second (fig. 2) shows the following modifications when compared with the first:

1. Slight rotation of electric axis of the QRS to the left.
2. Increased voltage on wave-length T in D1 and in precordial positions left of the ictus;
3. Positivity of wave-length T in V_3.

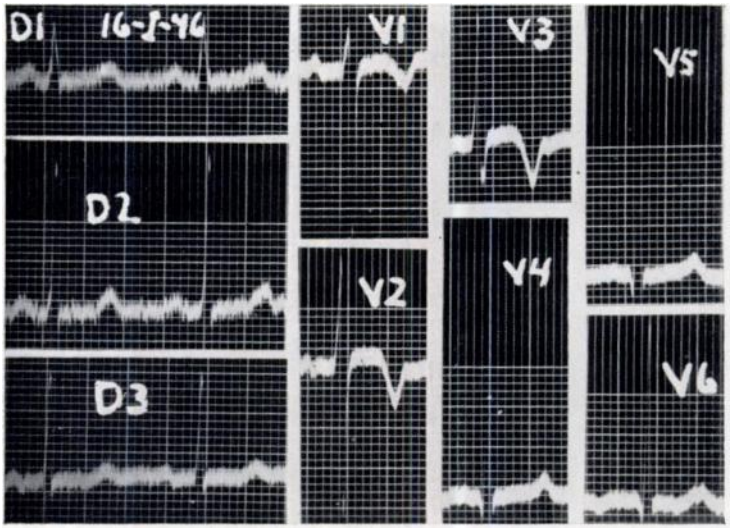

FIG. 1

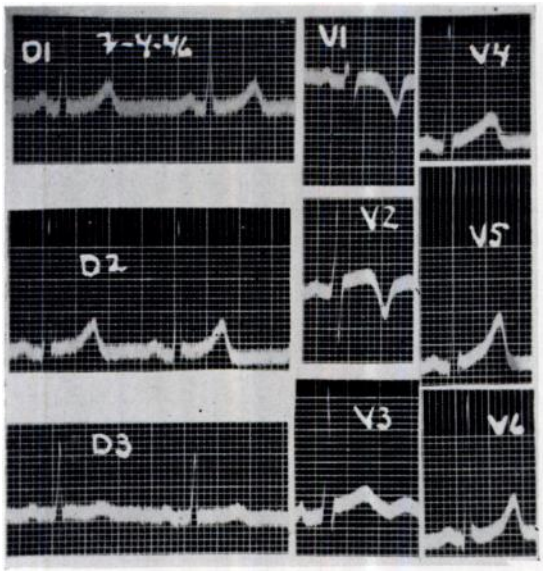

FIG. 2

The electrocardiographic changes may partly be due to changes in the position of the heart. Increase of wave-length T in precordial positions left of the ictus in

D1 is probably due to changes of the process of repolarization of ventricular myocardium, caused by better nutritive conditions of muscular fibers.

We started the therapy with iron, administering ferrous sulfate, 1.0 gram daily mixed with manioc flour, a food widely used in certain regions of Brazil. The blood values increased rapidly from 2.0 grams to 7.0 grams of hemoglobin per 100 cc. of blood. We decreased the dose to 0.5 Gm. daily, always added to the same food. At the end of two months, the hemoglobin value was practically normal (11.0 grams per 100 cc. of blood). We then tried to determine the minimum dose necessary to maintain a relatively normal hemoglobin level. The administration of 0.1 Gm. daily was insufficient to maintain this level, and hemoglobin decreased from 11.0 Gm. to 8.0 Gm. at the end of 110 days. Experiments with 0.2 Gm. of ferrous sulfate, however, proved to be a sufficient dose to avoid the decrease, and enough

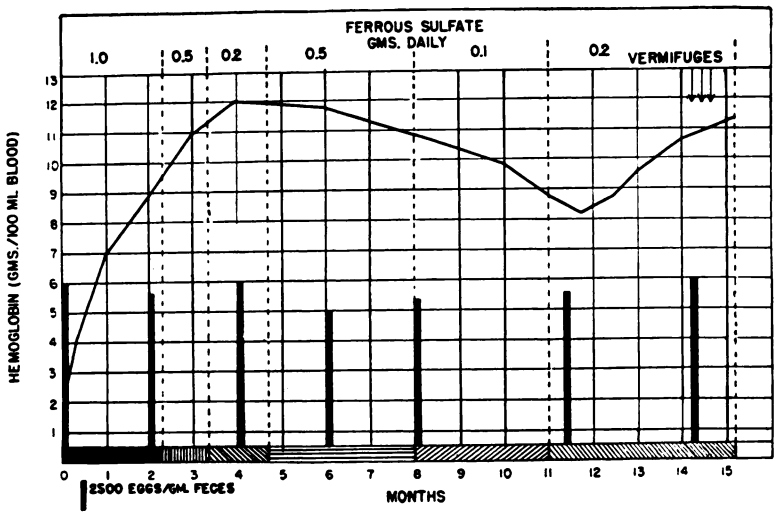

FIG. 3

to keep the blood levels normal for 100 days. A graphic presentation of this observation is given in figure 3.

Attention should be called to the extreme clinical changes which occurred in this patient after iron was administered. When he was hospitalized, the patient was entirely apathetic, without strength to move, remaining in bed for a considerable portion of the day. As the blood values became normal, his functional activity was restored. In the final period of treatment, he remained semi-hospitalized, and worked in our laboratory. In carrying out his work, he walked daily about two kilometers from the hospital to the place of work. He became quite active, as can be seen by the fact that several times a day he went to the animal house, about 200 meters away, going up a steep incline and climbing three flights of stairs on returning to the laboratory. He no longer felt the symptoms of which he complained when he was hospitalized. He became, from all points of view, a perfectly normal individual.

Eggs of Necator were counted periodically, for control of the biologic activity of the helminth and the persistence of the degree of infestation.

At the end of the trial period, five vermifuges (carbon tetrachloride 1.8 ml. + Chenopodium oil 0.6 ml.) were administered at weekly intervals. Helminths to the number of 1051 were eliminated, representing one of the most heavily infested cases we have observed (infestation index = 24 helminths per kilo of body weight). The fact should be kept in mind that the number of helminths eliminated represents a minimum, since it is easy to understand that not only do some escape at time of counting, but also others disappeared by natural death during the period of hospitalization.

Summary

1. In individuals severely infested with *Ancylostoma* or *Necator*, it is possible to maintain the normality of blood value by the administration of a sufficient dose of an iron salt.

2. The minimum dose necessary to maintain normality of the blood in an individual weighing 45 kilograms, with 1051 helminths, was 0.2 Gm. daily of ferrous sulfate, administered in mixture with manioc flour.

3. The patient observed became clinically normal two weeks after the beginning of blood regeneration up to the end of the trial period one year later. In this period, with the various doses of iron tried, hemoglobin varied from 8.0 to 11.0 per 100 ml. of blood.

ACKNOWLEDGMENT

We owe thanks to the kindness of our colleague, Dr. Genard Nobrega, for the case report and electrocardiographic study of the patient.

REFERENCE

[1] Cruz, W. O. and Pimenta de Mello, R.: Prophylaxis of hookworm anemia-deficiency syndrome. Mem. Inst. Osw. Cruz *42:* 401–448, 1946.