Pathogenesis of Anaemia in Hookworm Disease (*)

Parasite carriers. - Relationship between the activity of the helminth and iron deficiency in the genesis of the disease.

by

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(With plates LX – LXI)

The present paper is the result of investigations tending to elucidate the interrelationship existing in ankylostomiasis between hookworm carriers, nutrition and iron metabolism.

To begin with, I must say that the iron metabolism is here faced from the strict viewpoint of the iron quantity, either ingested along with food, or medically administered in the form of inorganic iron.

The exact determination of the pathogenesis of any disease, we deem it evident, ought to comprehend all its fundamental constituent aspects. Nevertheless, the various explanations put forward in order to make clear the innermost process originating the anaemia of hookworm disease, appear to be entirely unfit for a clear interpretation of the fact which we seek here to prove with documentary evidence.

The fact in question, verified since the first investigations on this disease, is connected with a curious possibility of a complete absence of symptoms, in spite of the most intense infestations. All doctrines on this matter restrict themselves to accounting for the anaemia, i.e. nothing else than to show the interrelationship between helminth and infested organism, without taking into consideration the existence of carriers.

The existence of these carriers evidently indicates a factor foreign to the helminth in the production of the anaemia, which factor is of such great a consequence that it induces the complete disappearance of the pathogenic rôle of the worm, rendering it practically inoffensive for the human organism.

As will be seen later on, we think the main disturbance met with in this anaemia is in the iron metabolism, and we believe in such a way to be able to account clearly and perhaps completely for the

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predominating pathologic picture. The observations of this paper prove with documentary evidence one of the fundamental facts on which our opinion, regarding this matter, is based.

We will begin by collecting the verifications of various authors in different regions of the globe, which will show both the great dissemination of carriers and the importance ascribed to this fact from hygienic and prophylactic viewpoints. Then, we shall deal with the various interpretations put forward by these investigators, which interpretations almost always converge to bring into prominence the rôle of nutrition. Nutrition is taken into consideration by these authors in a general way, assuming that food deficiency is a predisposing or adjuvant cause for any disease. In the last part of this paper, we present clinical cases in which the modifications produced by a continued iron administration make clear the varying relationship between the parasite, the existence of carriers and the rôle of nutrition in the genesis of this anaemia. Thus, the relationship between the facts we are here dealing with, up to now entirely isolated in the pathology of ankylostomiasis, without any connexion with the theories until then accepted in its pathogenesis, in this paper is naturally decurrent, being quite a intelligible consequence of the innermost cause of this disease.

I.—CARRIERS OF PARASITES IN ANKYLOSTOMIASIS.

One of the first verifications of this fact was made in Germany, in the first years of this century. In coal-mines, with their optimum conditions of environment, the development of larvae proceeds on a large scale. The contagion being easy on account of the miners' lack of clothing, the percentage of infested individuals is there very great, nevertheless, only 5% of them present clinical symptoms of the disease. Some time afterwards, Schüffner and his school in the island of Sumatra confirmed this finding. More recently, other authors presented numerous confirmations of this verification, as we shall see later on from the studies made in Brazil by Smillie (1), of the Rockefeller's Commission. From the chapter «Influence of nutrition on hookworm disease» we quote the following extracts: —

"We have already shown that there is considerable variation in individual resistance to hookworm disease. In general, young adults are more resistant than people of 45 or more, and much more resistant than young children. 100 hookworms will produce more severe symptoms and cause more rapid fall in
in the hemoglobin in a child of 6 years than in a child of 12 years.

The breaking down of resistance against hookworm infection in any individual is due to numerous associated causes, one of the most important of which is poor and insufficient food.

From comparative studies between well fed and ill fed individuals he arrives at very clear results. This author verified that the same number of worms produces a different fall in the haemoglobin ratio, in conformity with the age of the patients. Thus, in well fed individuals between 15 and 39 years of age, an infestation with 500 helminths produces a haemoglobin fall to nearly 64%, whereas the observation of three individuals with an average age of 32 years showed a haemoglobin ratio of 33%, or practically half of that observed in the well fed individuals.

The results presented by individuals with alimentary deficiency are also very conclusive. The author verified this facts in Cearenses (inhabitants of Ceará) fleeing from the drought of the North-East of the country, in frank organic exhaustion due to starvation. Comparing them with the original colonists, he says:

"The quality and quantity of food eaten by original colonists could not by any stretch of the imagination be called a full and balanced ration; it was always very limited, very poor in quality, and very poorly prepared. Nevertheless, it gave them sufficient calories to enable them to spend long, laborious hours in field work. The table shows that this group, despite their highly unsatisfactory full diet, had a very much higher average hemoglobin than the Cearenses, who had suffered from both hookworm disease and starvation. These few causes, though inconclusive, tend to prove what seems an obvious fact, that as ample food build up resistance against ravages of hookworm disease, starvation markedly increases the effects produced by the worms upon the body. Unfortunately, the individual who is heavily infected with hookworm disease is so weakened that he cannot do a full day's work. He is thus unable to earn the food which he urgently needs to combat the ill effects of the disease."

Mhaskar and Kendrick(2), in a paper made in India, write:

"There is no correlation between the hemoglobin average and the number of hookworm harboured; the presence of anemia is not necessary a sign of heavy infection."
As a demonstration they present the following Table:

<table>
<thead>
<tr>
<th>Hookworms removed</th>
<th>Cases examined</th>
<th>Average haemoglobin percentage per case, before treatment</th>
<th>Haemoglobin percentage</th>
<th>Cases examined</th>
<th>Average number of hookworms per case</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>1-10</td>
<td>11-15</td>
<td>1</td>
<td>511.0</td>
</tr>
<tr>
<td>1-5</td>
<td>6</td>
<td>80.0</td>
<td>11-15</td>
<td>1</td>
<td>131.0</td>
</tr>
<tr>
<td>6-10</td>
<td>7</td>
<td>72.5</td>
<td>21-25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-15</td>
<td>8</td>
<td>70.6</td>
<td>26-30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-20</td>
<td>7</td>
<td>78.6</td>
<td>31-35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-25</td>
<td>4</td>
<td>62.5</td>
<td>36-40</td>
<td>2</td>
<td>52.5</td>
</tr>
<tr>
<td>26-50</td>
<td>13</td>
<td>64.2</td>
<td>41-45</td>
<td>2</td>
<td>198.5</td>
</tr>
<tr>
<td>51-75</td>
<td>6</td>
<td>78.3</td>
<td>46-50</td>
<td>4</td>
<td>18.2</td>
</tr>
<tr>
<td>76-100</td>
<td>5</td>
<td>67.0</td>
<td>51-55</td>
<td>3</td>
<td>177.3</td>
</tr>
<tr>
<td>101-125</td>
<td>4</td>
<td>60.0</td>
<td>56-60</td>
<td>3</td>
<td>123.3</td>
</tr>
<tr>
<td>126-150</td>
<td>2</td>
<td>61-65</td>
<td>61-70</td>
<td>2</td>
<td>39.5</td>
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<tr>
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<td>75.0</td>
<td>66-70</td>
<td>9</td>
<td>99.3</td>
</tr>
<tr>
<td>176-200</td>
<td></td>
<td>70.0</td>
<td>71-75</td>
<td>10</td>
<td>78.6</td>
</tr>
<tr>
<td>201-250</td>
<td>4</td>
<td>73.7</td>
<td>76-80</td>
<td>11</td>
<td>100.1</td>
</tr>
<tr>
<td>251-300</td>
<td></td>
<td>86-90</td>
<td>81-85</td>
<td>4</td>
<td>100.0</td>
</tr>
<tr>
<td>301-350</td>
<td></td>
<td></td>
<td>86-90</td>
<td>4</td>
<td>100.0</td>
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<tr>
<td>351-400</td>
<td>3</td>
<td>68.3</td>
<td>91-100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>401-500</td>
<td>1</td>
<td>55.0</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>501-600</td>
<td>1</td>
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<tr>
<td>601-700</td>
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</tr>
<tr>
<td>701-800</td>
<td>1</td>
<td>75.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

74                      69.8                                      74                      92.9

Chandler (3) reports:

"In a study of 100 individuals in the Alipore Central Jail, Calcutta (British India), sixty-seven of whom were infected with hookworm, but only six of whom had more than 1,000 eggs per gr. of faeces, no differences in haemoglobin percentage between the infected and uninfected individuals can be found."

Smillie and Augustin (4), in Alabama (U. S. A.), give utterance to their opinion upon the relationship between infestation and disease as follows:

"Formerly every case of hookworm infestation has been considered hookworm disease, and the public health plan of organization has been to treat every child until he is entirely free from parasites."
Recent studies have shown, however, that the important factor in hookworm disease control is not the incidence but the intensity of infestation from the point of view either of an individual or of a community. The great proportion of persons with hookworm infestation of slight degree suffers no measurable harm, and should be considered not cases of disease but carriers. Practical experience has shown that hookworm carriers should not, in fact, cannot be controlled by treatment, but can best be controlled, and eventually eliminated, by sanitation. Treatment should be used only to reduce the intensity of the infestation in actual cases of hookworm disease to an economic cure, i.e., to a carrier state.

Hookworm treatment should be employed as a weapon to combat and control true hookworm disease. It should not necessarily be pushed until all persons treated reach the point of microscopic cure.

This method or any other method of treatment will not reduce the incidence of infestation for any considerable period of time. Hookworms will not disappear from Southern states until the habits and sanitary customs of the rural people are completely changed.

Gordon (5), in West-Africa, observed the relationship between the number of worms and haemoglobin ratio in blood, shown in the following Table (see pag. 445).

Discussing the results, he writes:—

Thus it appears that roughly two thirds of heaviest infections and two thirds of the negative cases fell into the higher hemoglobin group.

From these facts it seems clear that there is no correlation between intensity of infection in the individual and the hemoglobin reading.

This author, in order to account for this fact, believes in a racial factor, when he says:—

This tolerance, so far as ankylostomiasis is concerned, would appear to be shared by some, at any rate, of the Indian races.

or further:—

careful investigation should be made whether ankylostomiasis has any definite pathogenic effect on the race, and if
Showing the ten heaviest Ancylostome, Ascaris, and Trichuris infections observed amongst West African natives, and the haemoglobin reading for each case.

<table>
<thead>
<tr>
<th>Case</th>
<th>Ancylostome</th>
<th></th>
<th>Ascaris</th>
<th></th>
<th>Trichuris</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Haemoglobin</td>
<td>Number of</td>
<td>Computed</td>
<td>Number of</td>
<td>Haemoglobin</td>
<td>Number of</td>
</tr>
<tr>
<td></td>
<td>per cent</td>
<td>ova per gm. of faeces</td>
<td>number of</td>
<td>ova per gm. of faeces</td>
<td>per cent</td>
<td>ova per gm. of faeces</td>
</tr>
<tr>
<td>44</td>
<td>70</td>
<td>23,100</td>
<td>962</td>
<td>38</td>
<td>80</td>
<td>42,630</td>
</tr>
<tr>
<td>71</td>
<td>80</td>
<td>21,100</td>
<td>879</td>
<td>74</td>
<td>75</td>
<td>19,500</td>
</tr>
<tr>
<td>33</td>
<td>80</td>
<td>15,600</td>
<td>650</td>
<td>66</td>
<td>75</td>
<td>17,733</td>
</tr>
<tr>
<td>35</td>
<td>85</td>
<td>13,700</td>
<td>570</td>
<td>30</td>
<td>85</td>
<td>17,400</td>
</tr>
<tr>
<td>60</td>
<td>90</td>
<td>13,600</td>
<td>567</td>
<td>115</td>
<td>80</td>
<td>10,300</td>
</tr>
<tr>
<td>76</td>
<td>85</td>
<td>13,400</td>
<td>558</td>
<td>117</td>
<td>80</td>
<td>9,430</td>
</tr>
<tr>
<td>38</td>
<td>80</td>
<td>13,200</td>
<td>550</td>
<td>57</td>
<td>85</td>
<td>9,130</td>
</tr>
<tr>
<td>47</td>
<td>70</td>
<td>13,100</td>
<td>546</td>
<td>72</td>
<td>75</td>
<td>8,700</td>
</tr>
<tr>
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<td>90</td>
<td>12,660</td>
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<td>116</td>
<td>80</td>
<td>4,260</td>
</tr>
<tr>
<td>55</td>
<td>70</td>
<td>11,200</td>
<td>466</td>
<td>65</td>
<td>85</td>
<td>4,160</td>
</tr>
</tbody>
</table>
pathogenic effects are noted, what what degree of infection they are associated.

Fülleborn (6), in the province of Corrientes (Argentina), investigated the relationship between the number of eggs of Necator in the faeces and the haemoglobin ratio. The result arrived at by this author is summarized in the ensuing Table:—

Result of examination of 493 persons, with Sahl's apparatus and scale.

<table>
<thead>
<tr>
<th>Haemoglobin accordingly to Sahl's scale</th>
<th>Percentage among the examined</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than 80</td>
<td>21.7%</td>
</tr>
<tr>
<td>Between 80 and 71</td>
<td>43.6%</td>
</tr>
<tr>
<td>,, 70 ,, 61</td>
<td>26.8%</td>
</tr>
<tr>
<td>,, 60 ,, 51</td>
<td>4.7%</td>
</tr>
<tr>
<td>,, 50 ,, 41</td>
<td>1.4%</td>
</tr>
<tr>
<td>,, 40 ,, 31</td>
<td>0.6%</td>
</tr>
<tr>
<td>,, 30 ,, 21</td>
<td>0.4%</td>
</tr>
<tr>
<td>,, 20 ,, 11</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

Healthy (perhaps slightly affected by the helminthes) 63.3%  
Ascertained as affected .................................. 6.1%  
Severely ill ............................................. 1.8%

This Table shows that, in spite of the high index of infestation in the province of Corrientes (98%), only 8% are obviously damaged by the parasites.

This author observed that when there is a decrease of haemoglobin, it is in proportion to the number of eggs in the faeces; above 5,000 eggs per gram of faeces the decrease of this pigment is already remarkable; yet, in the majority of cases this decrease of haemoglobin does not take place, even in individuals with 10,000 to 20,000 eggs per gram (800 to 1,600 parasites). Accounting for it, he writes:

The fact already expounded, that in the province of Corrientes young people from 10 to 20 years of age with an infestation up to 240 uncinariae (from 2,000 to 3,000 eggs per gram of faeces) present no decrease of haemoglobin, is a very remarkable finding because in other parts of the world a decrease of haemoglobin was verified in much lesser infestations. It is perhaps due to an abundant mixture with Indian blood, which however does not go beyond a mere conjecture. The good food and
plentiful meat diet which the people of Corrientes consume are
doubtless more important factors in the prevention of the pro-
duction of demonstrable clinical symptoms owing to the large quan-
tity of uncineriae ».

And he concludes:

«From the hygienic viewpoint the number of infected in-
dividuals is less important that that of patients suffering from the
pathogenic action of uncineriae because, as is known, not every
carryer of uncineriae is afflicted with uncineriasis. Consequently,
regions can exist with a high percentage of carriers, but that the
worms on that account do not determine modifications which
would influence the general sanitary state of such districts ».

One of the instances which make fairly clear that ankylostomiasis
is a regional disease is the verification of severe endemic in zones rela-
tively not very distant from those where there is no anaemia, in spite
of a high index of intense infestations. A little to the South of Cor-
rrientes, province of Santa Fé, there exists a well defined region where
the poor state of cattle-breeding and very bad life conditions of the
inhabitants fairly show how local environment is disfavourable. In re-
gard to this region R. Quiroga states (32):

«The first information of this disease at an endemic state
goes back to the year 1897, when an intense focus has been proved
to exist in Cayastá which focus was efficiously combated by the
Council General of Hygiene banishing the alarming features which
the disease was acquiring, but which could not be completely
extirpated, owing mainly to the obstinacy of the disease itself,
to the telluric and climatic conditions, to the indolence of the
inhabitants and to economic factors ».

In regard to the usual dietary regimen, he informs:

«The alimentation of the people is scanty, based on fruits
and cereals such as: pumpkin, corn on the cob, water melon,
melon, etc.

«They seldom eat beef, but fish being very abundant,
especially sabalo, a kind of herring, fish constitutes their favourite
dish ».

From all data here recorded, we may conclude that the existence
of parasite carriers, to a much greater extent than one may suppose,
is completely verified, and that this factor must be faced as depending upon food.

II.—THE ROLE OF NUTRITION IN HOOKWORM DISEASE AND IN THE GENESIS OF ANAEMIAS.

Among nematodes, parasites of man, those which cause the greatest damage to health are undoubtedly *Necator* and *Ankylostoma* owing to the severe anaemia they are able to occasion in certain cases. This specific morbidic nature was accounted for by a secretation of an anemiant toxin, peculiar to these helminthes. Nevertheless, as already stated as the outset of this paper, whatever may be the mode of action of this worm, exists a factor foreign to it and of capital consequence in the pathogenesis of this disease. And this foreign factor is of such a consequence that, the same being present, the parasitism of these animals disappears, as they continue to live in human intestine but in a parasitic inoffensive state, just the same as generally occurs with the other nematodes.

Various factors have already been indicated as having a direct or indirect action upon the anemiant mechanism of the hookworm disease, such as a hereditary constitution, race, climate, deficient hygienic conditions, excessive work, and nutrition.

Some of the factors mentioned exert their influence upon the possibilities of infestation, such as: lack of footwear (deficient hygienic conditions), age (in certain regions the individuals use footwear only after a certain age), the greater thickness of skin in negroes, climatic conditions preventing the dedevelopment of the egg, etc. We, however, will consider only the influence of foreign factors in individuals already infested to a degree sufficient to induce anaemia.

The most elementary observation, in regions where the infestation is ravaging, shows that in some of them anaemia is a symptom existing in individuals of any age (we observed cases from 11 months to 58 years of age), of any race, consequently without any correlation with the corresponding factors. In other regions we also observed the same as far as the distribution of parasite carriers is concerned as these parasites are found in individuals under any of the conditions mentioned above. There is consequently a regional factor which determines anaemia in infested individuals. This factor, the consequence of which is not sufficiently emphasized in the great majority of labours regarding ankylostomiasis, is nutrition.

Among the authors who studied the regions inhabited by parasite carriers, we did not find a detailed description of the dietary system
in practice by the people residing there. Fülleborn alone remarks the abundance of meat. This can be accounted for by the un consequential significance ascribed to nutrition in the genesis of ankylostomotic anaemia, owing to the want of experimental demonstration of its action.

We had the opportunity of a conversation with Dr. C. Romaña, residing in Santa Fé, a province bounded on that of Corrientes, regarding the usual alimentation in that zone. This colleague making his references to the habitual nutrition in that region, informs:

"Meat is the food which is most ingested. Contrary to the majority of Brazilian regions, this food is of an extraordinary low price, and consequently accessible to every social class. This food constitutes at least 50% of the two, and not rarely three, daily meals.

The early use of meat diet among the inhabitants of this region is amazing; children, not yet weaned from the breast, suckle pieces of meat, ingesting the juice or even small fragments. The facility of supply of this food and its low cost are easily understood, since we are dealing with a cattle breeding region.

In general, meat is prepared by passing it quickly through fire, so that only its surface is roasted, its central part remaining more or less raw and bleeding. The diet is completed by cooked maize, sweet potatoes, oranges, milk and mate-tea.

The individual, a genuine creole, having fed almost exclusively on meat, now owing to civilization tends evermore to mixed diet, so that at present meat constitutes almost about the half of the alimentary substances.

A consequential fact is met with in the features of the cattle of Corrientes. This cattle is of an inferior stock, not comparable to that bred in the South of the country, where the breed is purified to the highest degree.

Notwithstanding, a difference in the quality of meat coming from the cattle of Corrientes is to be seen in a very marked manner. This meat is much more tasteful and, apparently, much more substantial. This property is well known to the managers of factories of preserves, who prefer to import the inferior cattle of these regions of the North of the Republic for the manufacturing of meat extract not merely for economic reasons, but also on account of the better quality of the extract obtained.

The difference in the quality of meat is due, most likely, to the difference of pasture of the herds. In the South, the nourish-
ment of the cattle consists mainly of lucern, but in the North, where lucern is practically uncultivable, the cattle feed on the common vegetation of the fields. Apart from that, the soil presents different features in Corrientes and in the South of the country. All these data show the importance which the verification of iron percentage in meat from the various herds of Argentine cattle may have. Although the enormous quantity of meat ingested by the inhabitants of Corrientes should contain a more sufficient quantity of iron than is required to maintain in normal boundaries the reserves of this metal in the human organism infested by ankylostoma, a larger richness of this element in the nutritive substances of these regions would be a verification of actual interest both in practice and in theory.

Though made in a different region (South of the province of Buenos Aires), there is an old observation by Darwin (1838), in his journey around the globe; in that work this naturalist draws attention to the alimentary regimen of these regions. It is a primitive system of feeding, i.e., an alimentation of the primordial time of colonization, and which at present is not observed any more. Nevertheless, this fact is of interest for the comprehension of the alimentation of Corrientes and for its development during a century.

Herewith we copy the description of this author in order to show to what degree the easy and cheap acquisition of a certain aliment can exercise its influence on the dietary regimen.

Darwin refers (29) to this fact as follows:

"We were here able to buy some biscuit. I had now been several days without tasting anything besides meat; I did not at all dislike this new regimen; but I felt as if it would only have agreed with me with hard exercise. I have heard that patients in England, when desired to confine themselves exclusively to an animal diet, even with the hope of life before their eyes, have hardly been able to endure it. Yet, the Gauchos in the Pampas, for months together, touch nothing but beef. But they eat, I observe, a very large proportion of fat, which is of a less animalized nature; and they particularly dislike dry meat, such as that of agouli. Dr. Richardson also has remarked, that when people have fed for a long time solely upon lean animal food, the desire for fats becomes so insatiable that they can consume a large quantity of
unmixed and even oily fat without nausea; this appears to me a curious physiological fact. It is, perhaps, from their meat regimen that the Gauchos, like other carnivorous animals, can abstain long from food. I was told that at Tandeel (Tandil) some troops voluntarily pursued a party of Indians for three days, without eating or drinking.

Following we are giving the main data found in the literature of that question, showing the correlation between nutrition and anaemia, and we will lay stress on the various interpretations of the authors. In several works, the importance of the development of larvae in the infested organism is remarked; thus, a diet poor in A and B vitamins render the rat susceptible to the infestation with *Ankylostoma caninum*; experimental infestations in young dogs are much more intense when they are fed deficiently. As far as our viewpoint is concerned, these facts are here of no interest, as in speaking about nutrition we do so inasmuch as it regards the already infested individual. We also must make our reservations as regards the mode of alimentation of severe hookworm patients. It is well known that these patients manifest an obvious decrease of appetite, at times even anorexia, accompanied by alimentary perversion (in the majority of cases indicated by ingestion of earth, cloth, lime of the walls, small pieces of wood, etc. . .). When there is an intense anaemia, there always exists ingestion of food quantitatively deficient accompanied in some cases by perverted appetite which increases in proportion to the progression of anaemia. We sought among the authors for data regarding the diet of the individuals of a certain region, i. e. the alimentation, so to say, characteristic of that region, but not the particular alimentation of severe cases of this disease. Suarez (7) describes the diet of the population of Porto Rico as one of the important factors in the mechanism of anaemia: —

«The Porto Rican peasant breakfasts on coffee and a small loaf of pale white bread. His lunch consists of a large quantity of polished rice and kidney beans, with scanty vegetables. His dinner is a stew of rice, chick-peas, pumpkin and perhaps one or two tropical vegetables such as yautia. Once or twice a week he has the great good fortune to eat some salted codfish. This diet has been taken without variation since childhood. Many of these individuals have never hat meat, eggs or milk.»

Porto Rico is one of the regions where ankylostomiasis easily de-
velops and where average infestation is always accompanied by marked anaemia.

Rhoads and Castle (8) close a previous note with the following considerations:

"Since in studying these cases of hookworm anaemia deficient diets were found to be the rule and gastric acidity, a frequent finding, as is the case in hypochromic anaemias not associated with hookworm, it is suggested that dietary deficiency and gastrointestinal changes are of major etiological significance."

The observations of these authors have also been made in Porto Rico where, as was seen, the diet is deficient.

We already transcribed Smillie’s opinion on the influence of nutrition upon the production of anaemia. This author accounts for the deficiency in a general way, when he referring to infested but well fed individuals states:

"Nevertheless, it gave them sufficient calories to enable them to spend long, laborious hours in field work."

Nutrition is alleged to be a pathogenic factor in the regions where ankylostomiasis is ravaging (disease but not infestation), as well as it is alleged that, if abundant, it prevents the individual from being attacked by anaemia. In the same manner Fülleborn (6) makes reference to nutrition by stating that thanks to diet exceptionally rich in meat the individuals inhabiting the region of Corrientes, though intensely infested, remain without morbid disorders.

In our opinion one of the best modern works on the pathogenesis of ankylostomotic anaemia is that of the Dutch author Langen (9), published in May 1933, wherein a keen review of the theories is made and a primary rôle is given to food among the causes originating anaemia.

Following we quote various extracts from the last part of this work entitled: The significance of alimentation in the clinical picture:

"Defective alimentation, not hunger with rest but insufficient food with working, is especially able to induce anaemia. This statement of Krehl, given in his treatise, is of value in many respects, as seen in preceding chapters, for the understanding of anaemia and other clinical manifestations in ankylostomiasis.

"...emphasizing that, as far as normal blood destruction is concerned, a more consequential rôle is due to food than to spleen."
It is also clear that our alimentation is doubtless the most important outer factor because, day by day, it exerts its influence upon our organism, and even upon generations and generations. Apart from this, alimentation is in my opinion the most variable factor in human life among the various peoples of the earth and contrarily to what is frequently believed, it has a more important significance than the climatic factors, with exception of the case where alimentation is indirectly much influenced or even controlled by the latter.

Snyders informs that on the Oriental Coast (Dutch Indies) alimentary conditions exert a great influence. The more severe anaemia, in case of equal infestations, is met with exactly where the alimentary conditions are worse.

In Java, where ankylostomiasis is very much disseminated, the main features of popular food are: preponderance of carbohydrates, percentage of albumins a little lower that that found in Europe, with predominance of vegetal albumins, whilst fats and lipids are present in scanty quantity mainly coming from the vegetal kingdom. In the poorer social classes these features are still more pronounced and among them ankylostomiasis appears in a severer form.

As far as we know, this author was the only one who sought to ascertain which are the substances met with a deficiency state in this alimentation, the lack of which substances occasions a disturbing action upon blood or haematopoietic organs. As we shall see in the following, Langen alleged a disturbance in the correlation between cholesterol and lecithin as being able to produce anaemia and, consequently, the disease:

An important fact, as already seen, is that the concentration of these substances (cholesterol and lecithin) in the organism is partially dependent on food. A sufficient quantity of these two lipids existing in food, the quotient (lipolytic coefficient of Mayer and Schaeffer) easily remains in equilibrium. But if there is in the alimentation a small quantity of the two (they are generally parallel), then there is an inclination to the predominance of cholesterol, because phosphatides (lecithin) are much easier to be attacked and partake much more in the intermediate metabolic processes than cholesterol. In inanition and in hungry animals a rise of the coefficient as well as an increase in the percentage of water in the tissues and organs are observed.
As regards the accounting for anaemia in ankylostomiasis, we believe we are able to conclude that alimentation may interpret many a thing which, up to now, always represented a point of disagreement among several investigators.

We consequently have ascertained the existence of parasite carriers in this disease in a much larger number than could be supposed, and also that this factor must be faced as being dependent upon food.

Food may produce of itself severe dyscrasias of blood only in children (Nutritional anaemia of infants), and even in adults (Tropical nutritional anaemia) and in some cases of the same anaemic type as that verified in ankylostomiasis (according to Rhoads and Castle quoted above). We also have seen that food, when rich in iron, prevents the appearance of the anaemic picture, the existence of parasitic carriers being in this manner accounted for in this anaemia.

We shall next review the most important correlations between alimentary conditions and blood image in several others anaemiae and in the normal process of blood formation.

Already in 1890, the importance of the rôle of nutrition in blood formation was known, as we shall see from the following extracts from a paper by von Hoesslin (10):

Almost all investigations now admit that the quality of nutrition exerts a forceful action upon blood conditions. The authors believe that nutrition being permanently insufficient, especially in albumins, the haemoglobin percentage and the number of blood cells diminish in an appreciable manner, although they return to normal again when nutrition is improved. The authors suppose that the influence of the quality of food upon blood conditions is of so great an importance that, without fear of falling into error, we may ascribe to food deficiency all anaemiae in which a decrease of more than a half is observed in haemoglobin and red cells readings, provided there is an absence of any other cause. Perhaps, it will be of interest to compare these ideas with the clinical and experimental facts by an examination of their exactitude. In fact, many more cases of anaemia are met with in ill fed individuals. To conclude from this fact that poor alimentation is of itself the cause of this anaemia is as erroneous as to consider poor alimentation as a cause of pulmonary tuberculosis only owing to the fact of meeting with tuberculous individuals in a greater number among people living in conditions of insufficient aliment-
ation. If an insufficient nutrition were the only cause of anaemia, it would be unavoidable that in all cases of more permanent deficient conditions a decrease of haemoglobin ratio should appear, which decrease should be in proportion to the insufficiency of food and to the time of its duration. Now the facts disagree with this conclusion. Several investigators have found in a series of extremely emaciated persons a normal or almost normal average of blood readings.

Alimentation is here considered in a great way; yet the necessity of seeking after the elementary substance acting upon the haematopoietic organs appears in the following extract:

«The sole component of food, in respect of which a permanent action upon the richness of blood in haemoglobin was verified, is iron.»

And concluding:

«Investigations made up to now by no means allow us to infer a direct influence of the quantity of food and any influence of albumin percentage upon haemoglobin formation; the total blood quantity alone decreases in case of poor alimentation, the same also occurring to the muscular bulk and organic mass of the whole body.»

From the modern viewpoint, the results of this author must be taken as being very incomplete, as he only considers the quantity of food. In fact, a quantitatively normal alimentation or even an overalimentation exerts very little influence upon blood crasis, if the food is not complete also qualitatively. To exemplify with ankylostomiasis, we believed that the nutritive value as regards this anaemia consists in the larger iron percentage of food and in the quantity of this ingested food. Thus, dry beans contain 0.072 gr. of iron per kilogram of comestible substance, whereas meat contains 0.030 gr.; nevertheless, the weight of meat usually consumed daily being much larger than the weight of beans, we understand that the latter food is much less important than the former.

From the viewpoint of iron metabolism, one daily kilogram of meat is equivalent to a alimentation composed by 1 k. of beet-root, 1 k. of cauliflower, 1 k. of bananas and two litres of milk, i. e. an absurd dietary regimen, so large is the quantity of food.

The nocive action of diet in blood formation depends with the
deficient substance or substances in food. The fundamental works on this matter which definitively show the interrelationship between various food components and haemoglobin formation, are due exclusively to the North-American scientists Whipple and Robbins (11, 12, 13, 14).

The experiments were made on dogs rendered anaemic by three, four or more blood-lettings, which place the haemoglobin at a ratio of about 50%. The authors verified that regeneration strictly depends on food, and they used the method of verifying the differences of the quantities of produced haemoglobin causing the ratio to return to the previous 50% through suitable blood-letttings. In the following we will give a list of various foods and the verified haemoglobin quantities:

<table>
<thead>
<tr>
<th>Diet (grs. per day)</th>
<th>Haemoglobin produced in the space of a fortnight (in grs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood strawberry</td>
<td>250 — bread 350</td>
</tr>
<tr>
<td>Fish liver</td>
<td>150 — bread 350</td>
</tr>
<tr>
<td>Bread</td>
<td>350</td>
</tr>
<tr>
<td>Bread</td>
<td>450</td>
</tr>
<tr>
<td>Milk</td>
<td>450 — bread 450</td>
</tr>
<tr>
<td>Codfish</td>
<td>100 — bread 300</td>
</tr>
<tr>
<td>Cream</td>
<td>100 — bread 500</td>
</tr>
<tr>
<td>Butter</td>
<td>100 — bread 350</td>
</tr>
<tr>
<td>Fresh fish</td>
<td>250 — bread 300</td>
</tr>
<tr>
<td>Spinach</td>
<td>250 — bread 400</td>
</tr>
<tr>
<td>Cheese</td>
<td>100 — bread 450</td>
</tr>
<tr>
<td>Muscle of pork</td>
<td>300 — bread 300</td>
</tr>
<tr>
<td>Vegetables</td>
<td>200 — bread 300</td>
</tr>
<tr>
<td>Muscle of beef</td>
<td>200 — bread 400</td>
</tr>
<tr>
<td>Raisins</td>
<td>300 — bread 350</td>
</tr>
<tr>
<td>Brains</td>
<td>300 — bread 300</td>
</tr>
<tr>
<td>Ox spleen</td>
<td>200 — bread 250</td>
</tr>
<tr>
<td>Powdered bone marrow</td>
<td>30 — bread 600</td>
</tr>
<tr>
<td>Heart muscle</td>
<td>200 — bread 300</td>
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<tr>
<td>Hog’s sweetbread</td>
<td>250 — bread 350</td>
</tr>
<tr>
<td>Apples</td>
<td>250 — bread 350</td>
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<tr>
<td>Plums</td>
<td>250 — bread 350</td>
</tr>
<tr>
<td>Apricots</td>
<td>200 — bread 300</td>
</tr>
<tr>
<td>Peaches</td>
<td>200 — bread 300</td>
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<tr>
<td>Ox liver</td>
<td>300 — bread 300</td>
</tr>
<tr>
<td>Pig’s kidney</td>
<td>200 — bread 350</td>
</tr>
<tr>
<td>Chicken liver</td>
<td>200 — bread 250</td>
</tr>
<tr>
<td>Chicken gizzard</td>
<td>300 — bread 200</td>
</tr>
<tr>
<td>Ox kidney</td>
<td>250 — bread 250</td>
</tr>
<tr>
<td>Ox liver</td>
<td>400</td>
</tr>
</tbody>
</table>
Out of the inorganic elements, the authors experimented iron, but only in little doses. Iron citrate 0.25, bread 500, salmon 50, produced in 1 week, i.e. in half the time given above, 20 grs. of haemoglobin which must be placed to the account of iron, as the same quantity of bread and salmon produced 1.2 gr. of haemoglobin. This labour being a fundamental work for modern interpretation of some types of anaemia, we will transcribe some considerations, not concerning directly the questions here dealt with, but which will bring a general better understanding of the matter. According to the interpretation of the author, the experiments show a primordial importance of the liver and kidneys in the metabolism of pigment and especially in the metabolism of haemoglobin:

« We believe the liver is concerned with pigment conservation and that the liver may be a most important organ in the fabrication of the amino acid groups, which presumably are the parent substances of the haemoglobin which appears in its finished form within the red corpuscles of the red marrow.

It would seem that the kidney was concerned in the conservation of the haemoglobin and that some of the building stones suitable for haemoglobin construction were stored here. »

And as far as the action of iron is concerned, he states:

« These experiments appear to separate sharply the iron effect of liver effect. »

Finally, Whipple presents a conception of anaemias based upon these verifications, i.e. focalizing the importance of the lack of some substances in the appearance of the anaemic syndrome.

« Anaemia Problems. We are convinced that a wrong assumption has seriously hampered the study of certain human anemias. Attention has been focused upon hypothetical toxins which were supposed to destroy red cells in vivo and thus bring about the anemia. Because it can be demonstrated that a few types of anemia were due to toxic or parasitic destruction of red cells (septicemia, drugs, malaria), it was assumed that all other forms of anemia must be due to some hemolytic toxin produced in the intestinal tract, kidneys, tumor growths, etc.

It is almost impossible for physicians to give up these hypothetical toxins which they have treasured for many years,
about which volumes have been written. Yet let us attempt to put them aside for a moment and look at a large group of interesting anemias as due to the lack of something. We may consider the anemias associated with tumors or nephritis or malnutrition and intestinal disturbances. It may be permissible to assume that in the anemia of cancer cachexia we are dealing with a default of hemoglobin building material which perhaps is absorbed by the more vigorous and rapidly growing tumor cells. Or again, with intestinal stricture or general malnutrition, we may find a severe anemia due to lack of materials unabsorbed from the intestinal tract. Again, we may look at the anemia of nephritis as due to faulty conservation of hemoglobin building material. The normal kidneys plays a part in the conservation of pigment material and we may assume that the diseased kidneys fail in this function as in other excretory ones.

*Pernicious anemia* is the stronghold of those who believe in toxic red-cell destruction as the essential etiologic factor. A few years ago we ventured the heretical belief that in this much-studied disease there was a lack of a stroma-producing substance so that the pernicious anemia may prove to be a deficiency disease. It is difficult to reconcile the prompt remission in pernicious anemia due to liver feeding with a causative agent in the form of an intestinal toxin.

The anemia associated with bothriocephalus infections, which is often called pernicious anemia, has long been cited as the real proof of the toxic etiology of pernicious anemia. Yet when we examine the actual fabric of proof it is indeed a tenuous structure. This evidence has been recently reviewed carefully by Meulengracht and the interested reader is referred to his paper. He reviews all the known facts and admits that no direct evidence can be furnished for any demonstrable toxic substances in the bothriocephalus anemias, yet he concludes that pernicious anemia is due to an obscure *intestinal intoxication*. One can take each of his admirable deductions and use it with force to support the theory that pernicious anemia is due to lack of something.

We believe it will be profitable to reexamine all of these anemias and search for a possible deficiency factor rather than for the elusive toxin. We believe it is not open to debate but may be accepted as established that simple anemias due to loss of blood can best be treated by means of diet therapy. Pernicious anemia has been shown to be amenable to diet therapy. Why not
examine many other obscure anemias and marrow diseases for a possible deficiency factor? At least some interesting data will accumulate and may lead to a better understanding of a puzzling but important disease complex.

This last question of the author has been answered by numerous investigators in the ensuing years and recently Witts (15) compiled a complete review on the causes and innermost processes of various anaemia. From this paper we quote the following passages:

«In this second lecture I propose to discuss the anaemias resulting from disturbances of nutrition and disorders of the alimentary tract. They form a group which impresses both by its size and its unity. It is my opinion that all are of nutritional origin. The normal human diet contains substances which are necessary for the maturation of normoblast into erythrocyte, such as vitamin C, thyroxin, iron, and traces of other minerals. Animal experiments suggest that food substances are also necessary for the development of the megaloblasts from the reticulo-endothelium of the marrow, and that their absence leads to aplasia. Anaemia arises whether these substances are not supplied with the diet or whether they are not absorbed in digestion. The anaemia is due to the diminished blood formation or anæmopoiesis, and according to the level at which haemopoiesis is arrested, the marrow may be normoblastic, megaloblastic, or aplastic.»

After Whipple’s ideas, various anaemias have their explanation in the deficiency of haematopoietic principles, and Witts (15) describes the nutritional anaemia of children as being produced by iron deficiency; the scurvy anaemia through deficiency of C vitamin; tropical nutritional anaemia as being the result of a manifold deficiency; the pernicious anaemia through deficiency of liver haematopoietic principle or principles; the anaemia met with in disturbances of gastric secretion, in intestinal diseases such as: stenose, ulcers and parasites (he only quotes anaemia from Botrioccephalus), fatty diarrhea, diseases of the cocum, chylous diarrhea, pancreaticogenic diarrhea, gastroecolic fistula, as well as in resection of intestine, as being isolated or manifold deficiencies all arising from defective digestion of haematopoietic principles; the anaemia of pellagra through deficiency of B vitamin and, finally, the anaemia of thyreoid diseases due to deficiency of thyroxin.

The ankylostomotic anaemia, however, was not considered in this
paper and, in fact, the most modern ideas on this helminthiasis still continued to turn around the two classical doctrines — the toxic and haemorrhagic theories.

III. — PATHOGENESIS OF ANKYLOSTOMOTIC ANAEMIA

It is really surprising that facts, so closely analogous to those observed in ankylostomiasis, already verified in 1890 and ascertained and accounted for by Whipple in 1928, did not lead the investigators of this matter to the search of a similar mechanism for the uncinariotic anemia, so as to point out the deficient haematopoietic factor of food in the hookworm disease.

In our opinion, in this case we have a striking instance of the paralysing rôle, on the progress of knowledge, of an erroneous, premature idea, lacking a firm experimental support, but, owing to its apparent accomodation to the explanation of certain facts, it obtained a large increment among tropicalists and succeeded in being the doctrine mostly agreed upon in these last times, even among specialists in the matter. Our intention is to make reference to an alleged existence of toxins which, being secreted by the helminthes, would act upon bone marrow paralysing it or changing it greatly. Authorities like Langen, Fülleborn, Morawitz, Itami, Flu, and even Whipple (16) (toxins produced by the intestinal flora) prior to his investigations of 1928, introduced this doctrine into all treatises on Tropical Medicine; being a pathogenic theory, it contaminated all notions concerning this verminosis.

This notion was so strongly enjoined upon the minds that the Japanese author Kobayashi (17) in 1929, though he verified the almost total uselessness of the elimination of the helminthes upon the anaemia and the surprising action of iron in this disease, (which facts would obviously lead any investigator without preconceived ideas to the notion of a deficiency of a haematopoietic principle), makes references to the cause of anaemia in this helminthiasis, in quotations like the following: —

"...which, most likely, has its reason in the decreased incitation of hematopoiesis on account of the parasital toxins, wherefrom a slight weakening of the regenerative capacity of blood is derived.

The resistance of the red cells is almost the same as it was before the vermilifugal treatments. Consequently, I suppose that the influence of the toxins continues during this time."
One of the many hypotheses in support of this theory was that the toxin remained active in the organism, even after the elimination of the helminthes secreting this toxin. A great number of necessary hypotheses is a sure sign of the impeding failure of a theory.

One of the most perfect criticisms of the toxic theory was lately produced by one of its earlier partisans (Langen), one of those who were closely engaged, especially, in the pathogenesis of this disease.

"The haemorrhagic theory is of value to a certain degree, because nobody denies a certain loss of blood by the intestine, but the theories based upon the existence of toxins are all, still, pure hypotheses; up to the present, no one has yet succeeded in verifying this substance said to be the cause of ankylostomotic anaemia.

Still, for good reasons, we believe that the substances extracted from ankylostoma and producing anaemia in animals have nothing to do, at any rate directly, with the anaemia observed in ankylostomiasis.

Up to the present, in no other blood disease has the verification of a similar substance been achieved. The idea of toxin comes from bacteriology and, without any further examination, this idea was transferred to haematology.

Summarizing the question of the toxic theory as a cause of ankylostomotic anaemia, we may state that this theory is supported exclusively by clinical arguments; still, up to the present, no proof, thoroughly experimental, has been produced as yet."

Kobayashi's results caused impression upon us, as he first showed the little influence of the expulsion of helminthic parasites on the blood image. The cure of anaemia, independent of the expulsion of the worms, induced us to interpret the facts already observed in this disease as resulting from the deficiency of this repairing substance in the organism.

Having met with several facts which may be accounted for in this manner and which until then were obscure and a point of discrepancy among the authors, we announced in a preceding note (18), by way of hypothesis, a causal relationship between an alimentary haematopoietic factor in deficiency and ankylostomotic anaemia. Through facts which now became more numerous, more important and more demonstrative, we were even induced to believe that there was not a
deficiency of factors, but of one sole factor, at least of one primordial factor, which we believed to be iron.*

In the same month of the publication of our note, the paper of Rhoads and Castle (8) appeared, in which paper the authors state that the facts observed by them suggested that the most important factors in the etiology of the disease were in the gastro-intestinal disturbances and in a deficiency of food. They include ankylostomotic anaemia in anaemia arising from deficiency, when they write: —

«Since it was demonstrated that the intramuscular injection of red blood cells into these patients produced increased blood formation, it is logical to assume that the effect of blood loss produced by the hookworm may be significant as a loss of potential haematopoietic factors leading to defective blood formation».

Ottenberg (19) on the basis of the aforesaid paper, states: —

«That continued anaemiae due to simple blood loss is essentially an iron deficiency is now well recognized».

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* Dr. C. Perissé (Folha Medica, 1933, 14, 473), making reference to one of our works, states that we, apart from confirming Kobayashi’s experiments (which, by the way, is expressed in our note), repeated those of Rhoads and Castle. The minutiae of the recorded data, referring to these quoted works, can only be interpreted as a hint because we have not quoted these latter authors.

In the case in question, we think it prudent to elucidate completely this matter, mainly to the conclusion drawn by Ottenberg from the work of Rhoads and Castle.

He alone who did not read the original paper in question may be ignorant of the fact that it was presented in May, 1932, in the «Proceedings of the twenty-fourth annual meeting of the American Society of clinical investigation held in Atlantic City» and issued only in July of the same year, in the «Journal of Clinical investigation».

The publication, consequently, was made in the same month of our first note, the latter, by the way, being published in a weekly review at the very beginning of the first week of that month (July, 2nd.). For the effects of priority, it seems to us to be evident that only the date of the publication may be of value, as on the contrary one never can be sure of the priority in any work whatever. As as instance we will mention the upright custom observed with regards to this matter in questions of zoology.

The question we really consider of our direct responsibility is not any therapeutical innovation, but the pathogenic interpretation of ankylostomotic anaemia which we affirm to be of deficiency origin (iron deficiency). The only author who categorically states that ankylostomotic anaemia is essentially due to a marial deficiency is Ottenberg (1933), on the basis of Rhoad’s work quoted above. In case of confirmation of this fact, we have no doubt in stating that, as far as we know, we were the first to state it in a direct manner, moreover because Rhoad’s work does not refer expressly to a marial deficiency but solely that the results suggested to him that the anaemia of uacinarasias belongs to the group of deficiency anaemiae.
Nevertheless, it seems to us that, as regards ankylostomotic anae-
mia in which another and very different viewpoint was always taken
into consideration, a deficiency, a straightforward and simple deficiency,
should have a larger documentary evidence based upon more varied
facts, in order to enable one to state that in this disease a continual
blood loss induces an essential deficiency of iron.

From our works, or from those of Rhoads and Castle, we may,
by no means, generalize either that every anemia due to mere blood
loss is essentially an iron deficiency, or that ankylostomotic anaemia
arises solely from a mere, though continual, loss of blood.

We have seen above the prudence of the ideas of Rhoads and
Castle, who make no direct reference to iron deficiency, but to potential
haematopoietic factors (factors and not one factor).

Thus, we also announced, by way of mere hypothesis, that an-
kylostomotic anaemia until then considered as being the result of a direct
biological action of intestinal parasitic helminthes (toxins, haemolysins,
blood destruction, or bone marrow destruction, haemorrhages, etc....),
should be faced as a simple deficiency of a certain substance.

We, then, sought for observations necessary to show whether this
hypothesis can be verified scientifically or not. Our conclusion was
that the following studies are necessary in order to verify which actions
may be directly imputed to the worm, and which to a martial de-

1) — Histopathology of bone marrow.

As is known, in anaemias induced experimentally by iron
deficiency, bone marrow appears intensely hyperplastic with
predominance of orthochromatic erythroblasts among the cells
of the red series.

In anaemias induced by toxins or originated through destruc-
tion of bone marrow, this organ presents degenerative, haemor-
rhagic or even necrotic zones with a scarce number of cells.

2) — Verification of blood modifications, after elimination of the
helminth, without any other treatment.

3) — Verification of blood modifications, after iron administration,
without elimination of the helminthes.

4) — Verification of the correlative influence of both factors (iron
and helminth).

Is an intense infestation possible without anaemia?
Is anaemia possible, in spite of a slight infestation or even
no infestation at all?
5) — Verification whether experimental anaemia due to iron deficiency resembles that observed in ankylostomiasis.

6) — Verification whether the action of administered iron is not a mere medicamental action, i.e. an action which is antagonistic to that of the helminth.

Therefore, the dosage of iron in the main organs of its metabolism (spleen and liver), becomes imperative.

Our contribution to this matter is constituted by these six fundamental points, less those which have already been investigated. The first was published by us in a preceding work (20); the second and third will take their part in studies in course of conclusion, the fourth is taken into consideration in the present note, whereas to the fifth and sixth we find sufficient data already published by others.

The findings of the fifth and sixth points were presented by the authors who dealt with them, in order to give documentary evidence for doctrines entirely different, without any reference to the notion of deficiency. Therefore we intend collecting them, together with the facts which we have verified, in a covering paper, after the publication of our observations.

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OBSERVATIONS

The following are cases of ankylostomiasis, with intense anaemia and intense infestation, turned by means of continued iron administration into parasitic carriers. Though these individuals continue to be intensely infested, there has been a total disappearance of pathological phenomena.

In this question, as regards the value of the result, we judge the observation of a few cases during a long period to be of a greater importance than the observation of numerous cases during a short period; therefore, we selected only five patients but we prolonged our study of them, from five months to one year.

In dealing with cases presenting characteristic clinical features, we judged dispensable a minute and complete examination of them prior to treatment, like that accomplished after the cure of the anaemia.

Out of these five cases, two were straightforward ones of ankylostomiasis, two other presented a positive Wassermann’s reaction, and the last was a mixed case of ankylostomiasis and malignant malaria; this patient during our observation fell dangerously ill of lobar pneumonia.
The results, all similar in these cases, show that ankylostomotic anaemia is corrected by iron salts, even in case of the intercurrence of these other diseases, as well as in case of permanency of the helminth in the intestine, which elements do not prevent, nor even interfere with the reparation, sometimes integral, of blood.

Case n.° 1.

Manoel, 11 years old.

*Examination of the patient* (26-IX-32): He arrived at the hospital in a state of advanced weakness. Visible mucosae entirely discoloured, large oedema of the eyelids and lower limbs (see figs. 1 and 2). Systolic souffle audible on the whole cardiac area. Liver and spleen not enlarged. Geophagy.

*Examination of the faeces*: Presence of numerous eggs of *Necator* and *Ascaris*.

*Examination of blood*: See Table 1, in 26-IX-32.

This patient was kept on a diet poor in iron (rice, macaroni, potatoes and milk), and was treated with reduced iron, at the daily dose of 3 grs. After 11 days of treatment the oedema almost entirely disappeared (see figs. 3, 4), and blood already presented signs of regeneration (see Plate I, of 8-X-32). After 2 months of treatment (28-XI-32) the blood image was fairly well improved, as it showed only a slight anaemia; in spite of this, we noted complete disappearance of the oedema and perversion of appetite (geophagy), as well as of the subjective ill feeling of the patient.

He remained in this state, still improving, for 3 months (2-III-33), despite incomplete diet and permanence of parasites in the intestine, as appears from the following examination of the faeces:

*Examination of the faeces* (2-3-33): Numerous eggs of *Necator* and *Ascaris*.

*Blood test in the faeces* (Weber's reaction): positive.

In fact, this case cannot be considered as a transformation of a patient into a parasite carrier, as the blood readings are not quite normal. Nevertheless, the intense modifications undergone by this patient, mainly the quick disappearance of the oedema and the permanence during 3 months of a blood image slightly below normal in spite of incomplete diet, supply a strong documentary evidence in favour of the pathogenic mechanism of this helminthiasis.
Table 1

| Date      | Ht. mme. | Hb. o/o | Hb. grs. 100 cc. | Hematocrit | Ind. Volume | Ind. Hemogl. | Ind. Satura-
<table>
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<tr>
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<tr>
<td>11 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26-9-32</td>
<td>1.34</td>
<td>13</td>
<td>1.8</td>
<td>7</td>
<td>52</td>
<td>13.4</td>
<td>25</td>
</tr>
<tr>
<td>8-10-32</td>
<td>2.22</td>
<td>34</td>
<td>4.7</td>
<td>-</td>
<td>-</td>
<td>21.2</td>
<td>-</td>
</tr>
<tr>
<td>2 months</td>
<td>28-11-32</td>
<td>3.75</td>
<td>69</td>
<td>30</td>
<td>80</td>
<td>25.2</td>
<td>32</td>
</tr>
<tr>
<td>3 months</td>
<td>2-3-33</td>
<td>4.82</td>
<td>81</td>
<td>37</td>
<td>77</td>
<td>23.2</td>
<td>30</td>
</tr>
</tbody>
</table>

Case n. 2.

Benedita, 10 years old.

Examination of the patient: Very pronouced general weakness. Visible mucosa totally discoloured. Oedema of the eyelids, face and lower limbs. Mesosystolic souffle audible on the whole cardiac area. Spleen and liver not enlarged.

Examination of the faeces: Presence of numerous eggs of Ankylostoma.

Wassermann’s reaction: positive.

Examination of blood: See Table 2, in 25-IX-933

In the first period of treatment the patient was kept on usual diet, but without meat. Ammoniacal ferrous sulphate was administered in a daily dose of 1 gr. In the second period (from 4-XI-33 to 3-1-34) diet was complete. After the treatment of one month and ten days, the blood image changed very materially presenting only a slight difference below normal readings. This image was improved and remained so during 3 months.

In the third period (from 4-I-934 to 3-IV-934) only 0.2 gr. of ammoniacal ferrous sulphate was administered. In the fourth period (4-IV-934 to 5-V-934) 0.05 gr. of the same salt was administered and in the last period (5-V to 12-VI-934), other time 1 gr. daily.

Table 2

| Date      | Ht. mme. | Hb. o/o | Hb. grs. 100 cc. | Hematocrit | Ind. Volume | Ind. Hemogl. | Ind. Satura-
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 days</td>
<td>25-9-33</td>
<td>2.52</td>
<td>20</td>
<td>14</td>
<td>56</td>
<td>10.9</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>4-11-33</td>
<td>4.10</td>
<td>69</td>
<td>31</td>
<td>76</td>
<td>23.2</td>
<td>30.5</td>
</tr>
<tr>
<td>2 months</td>
<td>3-1-34</td>
<td>4.78</td>
<td>78</td>
<td>34</td>
<td>71</td>
<td>22.5</td>
<td>32</td>
</tr>
<tr>
<td>3 months</td>
<td>3-4-34</td>
<td>4.74</td>
<td>77</td>
<td>35</td>
<td>74</td>
<td>22.4</td>
<td>30</td>
</tr>
<tr>
<td>1 month</td>
<td>3-5-34</td>
<td>4.10</td>
<td>65</td>
<td>33</td>
<td>80</td>
<td>21.9</td>
<td>27</td>
</tr>
<tr>
<td>1 month</td>
<td>10 days</td>
<td>12-6-34</td>
<td>4.70</td>
<td>74</td>
<td>36</td>
<td>77</td>
<td>21.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>28.5</td>
</tr>
</tbody>
</table>

| Date      | Ht. mme. | Hb. o/o | Hb. grs. 100 cc. | Hematocrit | Ind. Volume | Ind. Hemogl. | Ind. Satura-
<table>
<thead>
<tr>
<th></th>
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</tr>
</tbody>
</table>
Case n. 3.

Charneca, 55 years old.


Examination of the faeces: Presence of numerous eggs of Necator and Ascaris.

Wassermann's reaction: negative.

Investigation of haematozoa: presence of plasmodium falciparum rings.

Examination of blood: See Table 3, in 16-VI-933.

In the first period of observation (from 16-VI-33 to 11-IX-33) hydrochlorate of quinine and ammoniacal ferrous sulphate were administered in the respective daily doses of 1.5 and 0.4 grs. daily. During this period the patient was attacked by a severe lobar pneumonia.

At the end of this time (nearly 3 months), quinine was suspended as well as the symptomatic treatment of the pneumonia, as the patient recovered from these two diseases. The examination of the faeces, however, still showed the permanence of a considerable number of helminthes.

The administration of ammoniacal ferrous sulphate in the daily dose of 0.4 gr. continued until 20-VII-33, passing after that to the daily dose of 0.8 gr. By the latter doses the blood readings were maintained normal during 5 months and 20 days, after which time our observation could not go on because the patient applied for discharge.

<table>
<thead>
<tr>
<th></th>
<th>Date</th>
<th>Ht. mmc.</th>
<th>Hb. o/o</th>
<th>Hb. grs. 100 cc.</th>
<th>Hematoerit</th>
<th>Ind. Volume</th>
<th>Ind. Hemogl.</th>
<th>Ind. Saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mos.</td>
<td>16-6-33</td>
<td>1.51</td>
<td>16</td>
<td>2.2</td>
<td>9</td>
<td>59</td>
<td>14.4</td>
<td>24.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ammoniacal ferrous sulphate, 0.8 grs daily.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mos.</td>
<td>11-9-33</td>
<td>4.39</td>
<td>67</td>
<td>9.2</td>
<td>31</td>
<td>70</td>
<td>21</td>
<td>20.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Common diet.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 days</td>
<td>2-3-34</td>
<td>5.15</td>
<td>82</td>
<td>11.3</td>
<td>38</td>
<td>74</td>
<td>22</td>
<td>30</td>
</tr>
</tbody>
</table>

Case n. 4.

Oscar, 8 years old.


Examination of the faeces: Numerous eggs of Ankylostoma and rare eggs of Trichocephalus.
Stern’s reaction (syphilis): positive.

Examination of blood: See Table 4, in 31-VIII-933.

Ammociacal ferrous sulphate in the daily dose of 1 gr. was administered, the patient being kept on usual, complete diet. After twenty-one days of treatment, he represented a blood image approaching normal, complete disappearance of oedema and excellent feeling. The blood image continued the same until 28-XII-33 (nearly three months), after which time only 0.2 gr. of ammoniacal ferrous sulphate was administered, i.e. a dose five times less than the initial. In spite of this, the haematologic aspect continued the same until 3-IV-34 (3 months and five days). During the ensuing period (from 4-IV-34 to 4-V-34) only 0.05 gr. of ammoniacal ferrous sulphate was administered. In the last period (5-V-34 to 12-VI-34), other time 1 gr. of the same iron salt was administered.

Table 4

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>21 days</td>
<td>31-8-33</td>
<td>2.53</td>
<td>23</td>
<td>3.2</td>
<td>14</td>
<td>56</td>
<td>12.7</td>
<td>23 Ammoniacal ferrous sulphate 1 gr. daily. Common diet.</td>
</tr>
<tr>
<td></td>
<td>22-8-33</td>
<td>3.96</td>
<td>72</td>
<td>9.9</td>
<td>33</td>
<td>83</td>
<td>25.1</td>
<td>30</td>
</tr>
<tr>
<td>3 months</td>
<td>28-12-33</td>
<td>4.70</td>
<td>79</td>
<td>10.9</td>
<td>35</td>
<td>75</td>
<td>23.2</td>
<td>31 The same 0.2 grs. daily Common diet.</td>
</tr>
<tr>
<td>3 m. 5 days</td>
<td>3-4-34</td>
<td>4.78</td>
<td>77</td>
<td>10.0</td>
<td>30</td>
<td>75</td>
<td>22.2</td>
<td>29.5 The same 0.05 grs. daily. Common diet.</td>
</tr>
<tr>
<td>1 month</td>
<td>3-5-34</td>
<td>4.55</td>
<td>70</td>
<td>9.6</td>
<td>35</td>
<td>77</td>
<td>21.2</td>
<td>27.5 The same 1 gr. daily. Common diet.</td>
</tr>
<tr>
<td>1 month 10 days</td>
<td>12-6-34</td>
<td>4.46</td>
<td>76</td>
<td>10.5</td>
<td>35.5</td>
<td>80</td>
<td>23.6</td>
<td>30</td>
</tr>
</tbody>
</table>

Case n. 5.

Arnaldo, 25 years old.


Examination of the faeces: Presence of very numerous eggs of Ankylostoma.

Wassermann’s reaction: negative.

Examination of blood: See Table 5, of 3-VI-33.

The first period of this observation was made, the patient remaining on usual diet. Ammoniacal ferrous sulphate was administered in
the daily dose of 0.6 gr. This period lasted from 5-VI-33 to 5-IX-33 (3 months), after which time the blood image and the general state of the patient could be considered as being practically normal. The second period lasted from 6-IX-33 to 29-XI-33 (two months and thirteen days), during which time the normal blood image remained the same, despite the permanence of worms. The third period lasted from 30-XI-933 to 3-IV-934 (four months), during which time the same blood image was maintained by the administration of only 0.3 gr. of ammoniacal ferrous sulphate. In the last period (from 4-IV-34 to 14-VII-34), consequently 3 months and 10 days, iron administration was suspended and the patient was kept on a diet rich in this metal (2 underdone beefsteaks and two eggs daily, apart from the habitual diet).

<table>
<thead>
<tr>
<th>Date</th>
<th>Ht. mmc.</th>
<th>Hb. o/o</th>
<th>Hb. grs. 100 cc.</th>
<th>Hema-</th>
<th>Ind. Volume</th>
<th>Ind. Hemogtl.</th>
<th>Ind. Saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>3-6-33</td>
<td>3.40</td>
<td>30</td>
<td>4.1</td>
<td>17</td>
<td>50</td>
<td>12.2</td>
</tr>
<tr>
<td>2 months</td>
<td>5-9-33</td>
<td>4.88</td>
<td>83</td>
<td>11.4</td>
<td>38</td>
<td>78</td>
<td>23.4</td>
</tr>
<tr>
<td>13 days</td>
<td>29-11-33</td>
<td>4.85</td>
<td>88</td>
<td>12.1</td>
<td>36.5</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>4 months</td>
<td>3-4-34</td>
<td>4.84</td>
<td>94</td>
<td>13</td>
<td>38</td>
<td>79</td>
<td>26.5</td>
</tr>
<tr>
<td>3 months</td>
<td>14-7-34</td>
<td>4.95</td>
<td>94</td>
<td>13</td>
<td>41</td>
<td>83</td>
<td>26.2</td>
</tr>
</tbody>
</table>

RADIONEOLOGIC AND ELECTROCARDIOGRAPHIC EXAMINATION

(Dr. E. Chagas' contribution)

Case 1. — Manoel.

*Telecardiograph at three meters* (Thorax). — Considerable enlargement of the cardiac area. Dilatation of all heart chambers. Longitudinal diameter 14.5. Transverse diameter 13. Globate heart. Widened vascular pedicle of the basis. Lungs of normal anatomoradiologic appearance (1-X-932) (Fig. 5). Considerable decrease of the cardiac area. Longitudinal diameter 11.0. Transverse diameter 10.5. Normal vascular pedicle of basis. Lungs of normal anatomoradiologic appearance (24-X-932). Very moderate enlargement of the cardiac area. Longitudinal diameter 11.0. Transverse diameter 10.0. Slight deviation to the right of the vena cava superior. Lungs of normal anatomoradiologic appearance (1 XI-933) (Fig. 7).

*Electrocardiogram*. 27-IX-932: — Total tachycardia. Very low volt-
age of wave T in the three derivations. Electric preponderance of the left ventricle (Fig. 6).

28-IV-933: — Electric preponderance of the left ventricle. Wave T normal (even increased). Total respiratory arrhythmia (Fig. 8).

Conclusion: — The former examinations revealed a considerable dilatation of the heart accompanied by functional deficiency brought into evidence by the electrocardiogram. The later examinations show the existence of a vagosympathetic dystonia with good function of the heart.

Case 2. — Benedicta.

Teleradiograph at three meters (Thorax): — Globate heart with sensitive increase of all diameters (longitudinal 12.0 and transverse 10.5). The left border of the heart (the outlines corresponding to the ventricle) is extraordinarily accentuated. The lungs have their normal anatomoradiologic appearance.


Conclusion: — Dilatation of the heart. The meaning of the deformation of line S-T in children is obscure.

Case 3. — Charneca.

Teleradiographs at three meters (Thorax): — The first, of (30-VIII-933), shows a considerable lengthening of the aorta which is also opacified and slightly widened. The heart has a flattened form with increase of the transverse diameter (13.5). The left costo-phrenic sinus is veiled, but there is no sign of liquid effusion. The second, of 12-III-934, shows the same signs with regard to the aorta, but the heart has no more the flattened form and its diameters are normal (longitudinal 14.5 and transverse 12.5). The lungs have their normal anatomoradiologic appearance in this second examination.

Electrocardiograms: — The first, of 30-VIII-933, shows a concordant and homotopic, tachycardic auriculo-ventricular rhythm with normal conduction and slight electric preponderance of the left ventricle. The second, of 12-III-934, is quite comparable to the first; tachycardia, though persisting, is of diminished intensity.

Conclusion: — The case in question is one of sclerosis of the aorta (Lues). The modifications of the transverse diameter at the first examination present nothing significative of any myocardial process as,
at this moment, the diafragm considerably forced the heart upward. The
electrocardiographic signs are in accordance with the aortic process.

Case 4.—Oscar.

_Teleradiograph at three meters (Thorax):_ — Very moderate en-
largement of all diameters of the heart. Longitudinal diameter 9.5 and
transverse 8.8. The lungs have their normal anatomicradiologic ap-
pearance.

_Electrocardiogram: _—Concordant and homotopic auriculo-ventric-
ular rhythm. P-R-II-0.16. R-T-II-0.32. R-S-II-0.06.

_Conclusion: _—Slight total enlargement of the heart (Dilatation?).

Case 5.—Arnaldo.

_Teleradiograph at four meters (Thorax): _—The first, 5-IV-933,
shows a lengthened aorta which is neither opacified nor widened. The
heart presents its left outlines (the part corresponding to the left ventricle)
slightly accentuated (enlargement of the left ventricle). The longitudinal
diameter is slightly increased (13.5). The lungs have their normal ana-
tomradiologic appearance. The later, 12-III-934, has the same appear-
ance as the former.

_Electrocardiograms: _—The first, 24-IV-933, shows a concordant
and homotopic tachycardic auriculo-ventricular rhythm. Conduction is
normal and there is a little deformation of the space S-T-I, II, III. The
later has the same appearance as the former.

_Conclusion: _—Sclerosis of the aorta and possible initial sclerosis
of the myocardium. The radiologic and electrocardiographic signs of
the heart point to a chronic cardio-aortic process.

In Plate VI we summarized the observations of the four latter
cases, observations carried out during the periods of maintenance of
cure by iron, i. e. in periods when the patients may be considered car-
rriers of Necators. This Plate must be interpreted in a very superficial
manner as the data, presented as being normal, are so in a very general
way; they comprise the lowest normal figures in woman and the highest
normal figures in man. The data presented as being characteristic of
ankylostomiasis are those met with by us or by several other authors
in cases of greater severity of the disease.

The methods employed in the examination described in Plate
VI are the following:
Numbering of red blood cells and of leukocytes was made by means of a common counting pipette and camera of Neubauer. Haemoglobin was dosed by means of Sahl’s apparatus, this pigment being transformed into haematin hydrochlorate by means of decinormal hydrochloric acid. The haematokrit employed was the microhaematokrit of Van-Allen, and we followed the technique recommended by this author. The indices were calculated in accordance with Wintrobe’s publications. Numbering of platelets was obtained by verifying the numeric proportion to the red blood cells in slides. With regard to the specific count of leukocytes, we observed in every patient 400 of these cells. Coagulation time was taken by placing blood on a watch glass and by verifying clot formation every thirty seconds; hemorrhage time was observed according to Dücke’s technique, and viscosity by means of the viscosimeter of Hess. As to globular resistance we employed a particular process which we shall describe in detail in another paper. For the verification of the percentage of reticuocytes we used the vital staining with brilliant cresyl blue, and afterwards we stained with May-Grünwald’s. The dosage of proteins was carried out by means of Reiss’ technique with refractometer Abbe-Zeiss and the dosage of lecithin according to a mixed method (extraction by means of Bloor’s technique and dosage of phosphorus according to the technique of Fiske and Subbarow. Lecithin was calculated through the values in phosphorous rating). The number of eggs in the faeces was verified by Stoll’s process.

INTERPRETATION

Case 1.—Martial medication with large doses, in 11 days, produced a remarkable improvement of general condition, mainly of oedemas (see Figs. 3, 4); in 2 months and 11 days a clinical cure was induced, which was maintained for more than three months. The examination of the faeces showed that, during observation, the number of parasites did not decrease.

Case 2.—Administration of ammoniacal ferrous sulphate, in the daily dose of 1 gr., produced clinical cure in 1 month and 10 days, which condition was maintained for more than 2 months. A dose five times less (0.2 gr. daily) still maintained the blood readings for more than 3 months. Administration of a dose four times less than the latter (0.05 gr. daily), though preventing the sudden decrease of haematic indices, did not succeed in maintaining them during 1 month. The administration of 1 gr., during one month more, increased the blood readings to the previous condition. The count of eggs in the faeces, made on
<table>
<thead>
<tr>
<th>Ratio</th>
<th>Red Blood Cells</th>
<th>Hemoglobin</th>
<th>Erythrocytes</th>
<th>White Blood Cells</th>
<th>Neutrophils</th>
<th>Monocytes</th>
<th>Lymphocytes</th>
<th>Nucleated RBC (%)</th>
</tr>
</thead>
</table>

Table 4

<table>
<thead>
<tr>
<th>Location</th>
<th>Diameter (μm)</th>
<th>Length (μm)</th>
<th>Width (μm)</th>
<th>Height (μm)</th>
<th>Volume (μm³)</th>
<th>Area (μm²)</th>
<th>Surface Area (μm²)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulus</td>
<td>8.5</td>
<td>12.5</td>
<td>6.5</td>
<td>4.5</td>
<td>7.5</td>
<td>5.0</td>
<td>1.2</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Sedimentation Rate [s]: 0.8, 1.2, 1.4, 1.6

RBC: Red Blood Cells
WBC: White Blood Cells
N: Neutrophils
M: Monocytes
L: Lymphocytes
21-II-934, 4-V-934 and 13-VI-934, did not present great variations, disclosing the number of 35,000 eggs per gram of faeces.

Case 3.—Administration of 0.8 gr. of ammoniacal ferrous sulphate, during the intercurrency of two other morbid entities (malaria and pneumonia), succeeded in increasing the blood readings and in producing a clinical cure of the ankylostomiasis in 3 months, this condition being maintained for more than 5 months and 20 days. Examination of the faeces always showed a large quantity of ankylostoma eggs; the count, made on 3-II-934, revealed 25,000 eggs per gram of faeces.

Case 4.—Administration of 1 gr. of ammoniacal ferrous sulphate produced the cure of the blood in 21 days and maintained it for more than 3 months. A dose five times less (0.2 gr. daily) also maintained the same condition for more than 3 months; yet, the dose of 0.05 gr. daily did not succeed in maintaining the haematic readings during a month, although it prevented their pronounced decrease. After a new administration of 1 gr. daily of the same salt, the condition of the blood appeared as before the previous period. The count of eggs (3-II-934, 4-V-934 and 13-VI-934) presented a slightly variable number of about 26,000 eggs per gram of faeces.

Case 5.—Administration of 0.6 gr. of ammoniacal ferrous sulphate produced clinical cure of the disease in 3 months and maintained it for more than 2 months and 13 days. Half the dose (0.3 gr. daily) maintained normal the haematologic aspect for more than 4 months, after which martial medication was suspended and patient was kept on a diet rich in iron (two underdone beefsteaks and two eggs per diem, beside habitual food); maintainance of normal condition of the blood and of good general condition was observed for more than 3 months and 10 days. This patient continues under observation. The count of ankylostoma eggs in the faeces (3-II, 5-II, 4-V, 19-V and 13-IV-934) presented an average number of 40,000 eggs per gram of faeces.

In conclusion, we were able to verify that administration of ammoniacal ferrous sulphate, in the daily dose of 0.6 gr., is already efficient in adults; in the dose of 0.3 gr. it maintains the haematic condition in adults despite intense helminthic infestation; in the dose of 0.2 gr. it maintains normal the haematic condition in children; in the daily dose of 0.05 gr. it is not efficient to maintain normal this condition in children. Substitution of martial medication by a diet rich in iron is quite possible after normalization of the blood, in order to maintain normal this condition, even in adults.

The interpretation of Plate VI, where all findings of the four last cases are summarized, shows various important modifications pro-
duced in blood by the assimilated iron, despite the permanence of activity of the parasitic helminth.

The first verification concerns the quality of the red blood cell produced after iron administration. The rates showing the volume, the haemoglobin quantity and the concentration of this substance in one red blood cell prove that this blood cell is formed with normal features (perhaps slightly diminished in volume). The number of these red cells per mmc. and the haemoglobin percentage are always very near or even within the normal boundaries. The number of platelets is slightly diminished, but without any really remarkable decrease, i.e. a pathologic one. The coagulation time, the hemorrhage time and the blood viscosity are always within normal boundaries and, in rare cases, approaching normal. The resistance of the red blood cells to hypotonic solutions of natrium chloride, which resistance is always increased in ankylostomiasis, in these individuals presented quite normal readings.

We reported above the importance ascribed by Langen to a disturbance in the metabolism of lipoids and fats, in the genesis of anaemia. As was seen, this author remarks that these substances in the organism strictly depend on food. The deficiency of one of these substances in food is always accompanied by a deficiency of the other. Still, as lecithin is quickly transformed in the metabolic processes whilst cholesterol remains stable, the poverty of these substances in comestibles always induces a simple deficiency of lecithin. Langen observes that in blood of hookworm patients the lipocytic coefficient is always increased owing to lecithin deficiency.

O. Oliveira (27), quoting a work of J. Villela, publishes the following results:

| Table 7 |
|------------------|------------------|------------------|------------------|------------------|
|                | Number of cases | Hb o/o | Total lipoidic extract (o/o in 100 cc. of total blood) | Fatty acids | Cholesterol | Lipocytic coeff. |
| Normal individuals | 8 | 80 | 0.392 | 0.281 | 0.111 | 0.39 |
| Hookworm patients | 9 | — | 0.290 | 0.174 | 0.120 | 0.69 |

Just as Langen observes, J. Villela’s work shows that blood cholesterol is almost normal in ankylostomiasis, whilst fatty acids (such as lecithin) diminish, which modifies the lipocytic constant from 0.39 to 0.69.
We will remark that the lipocytic coefficient of Mayer and Schaef-
fer is given by the formula \( \frac{\text{cholesterol}}{\text{lecithin}} \) or by the formula \( \frac{\text{cholesterol}}{\text{free fatty acids}} \); thus,
as cholesterin does not vary in blood of the hookworm patient, lecithin
or fatty acids may be dosed in order to bring about the aforesaid
coefficient.

Dr. G. G. Villela, to whom we are very much indebted, dosed
the lecithin in the plasma of our patients. According to the data presented
by numerous authors, the normal values of lecithin in plasma are from
175 to 330 mgrs. per 100 cem. The result of our cases varied from 220 to
350 mgrs. In these cases we deemed dispensable the dosage of cholesterin
because this substance, as stated above, does not undergo quantitative
changes in this anaemia, it being sufficient to verify the lecithin in
order to be able to infer that, despite the permanence of worms, the
lipocytic coefficient returns to normal, thus showing that this change
is dependent upon the anaemia.

The same verification was made with regards to the percentage
of proteins in serum. In only one patient (Case 3) we made an examina-
tion before the treatment. From 6.4 grs. per thousand he presented
an increase up to 7.3 grs. during the period of maintenance. In the
other three patients we observed during the period of maintenance normal
figures which observation denotes a probable increase of the total proteins.
We believe that before treatment these patients presented a decrease of
proteins in serum and this we did, based on the work of G. Villela and
C. Teixeira (28), who always observed a decrease in cases of oedema,
which symptom was always present in our patients.

Later on, in a more suitable place we shall comment this result
thanks to which it becomes fairly evident that a decrease of proteins
in the serum of hookworm patients also arises from iron deficiency,
and is not a primary cause in the genesis of this anaemia.

The roentgenologic examination of the heart and the electro-
cardiograms were made and interpreted by Dr. E. Chagas, to whom
we are very much indebted. Excluding the changes originated by syphilis,
only in Case 2 a dilatation of heart was still observed; in the other
three cases a complete or almost complete (Case 4) regression of the
changes of this organ was verified.

These are the results we must impute to a direct or indirect action
(through formation of haemoglobin) of the administered iron.

As regards leukocytes, in three cases we observed figures per
cmm. within normal limits, whilst in one case (Case 2) we remarked
a frank leukocytosis. The specific blood count revealed a normal rate both of monocytes and basophiles, but an increase, at times a very considerable one, in the percentage of eosinophiles was remarked accompanied by a great decrease in the percentage of neutrophiles and mainly of lymphocytes. This appearance, by the way, is met with in severe cases of the disease. This fact brings into evidence a direct action peculiar to the helminth.

We will give here an answer to a possible erroneous interpretation of our ideas expounded in other papers, i.e. as if this eosinophilia were caused by a local or general action of toxic origin (we did not state it in an absolute manner); when we deny the existence of this substance, or state the failure of the toxic theory, our intention is only to say that there is no toxin which produces anaemia. Therefore, we only state the inexistence of poisons which would act upon the red blood cells, or in general upon the elements of the red series. The existence of toxins or of specific substances of the worm foreign to the human organism (as the allergic phenomena seem to indicate) which act upon the white series producing a larger formation of eosinophiles is not a fact which points out and, still less, proves a toxic theory of anaemia. We will also mention here that an eosinophilia has not any known relationship with anaemia; it is observed in the most divergent cases of macro-parasitism in which cases there is no disturbance in the elements of the red series.

In all five cases, after the iron treatment, even when blood regeneration was still incomplete (haemoglobin 60%) we never observed either any disorder of health (and therefore in some cases we consider as the beginning of cure maintaining when patients present this haemoglobin ratio), or even digestive disturbances, or nervous disorders due to nervous origin, already pointed out in order helminthiasis (ascaridiasis, tricocephalasis). Along with the treatment the following symptoms disappeared little by little: head-ache, dizziness, pulsating sensation in the head, general weakness, indisposition to work, oedema, anorexia and — a curious fact — even geophagy. A rather interesting fact is that anorexia is the effect of anaemia and not an adjuvant cause; this proves that the infestation by the helminthes and the gastro-intestinal disturbances conveyed by them have no action upon the appetite, but the latter also depends upon the low haemoglobin rate.

We had our doubts about the innocuousness of iron administration for so long a time. As known, this medicament in small doses produces constipation, and in large doses (reduced iron, daily 3 grs.), on the contrary, produced diarrhea. Only in the beginning of the administration
of large doses of reduced iron we observed diarrhea and intestinal colics, some times violent. The same, however, did not occur with ammoniacal ferrous sulphate, which at the daily dosage of 1 gr. produced none of the aforesaid enteric disturbances. We also observed no harmful effect arising from its continued employment. As during 10 months of observation we did not observe any anomaly arising from iron, we believe that this substance, in all likelihood, may be administered continually for an indefinite time.

DISCUSSION

Since our first observations we know that rest and the habitual diet of the hospital where we are engaged have not any paralysing influence either upon the progress of anaemia or upon the vitality of the parasite helminth. Consequently, all changes of the haematic image as well as those of the general condition must be directly or indirectly caused by assimilation of iron, administered to the patient.

As is easily seen, — and our results afford confirmation and documentary evidence —, the greater part of the clinical symptoms of ankylostomiasis are decurrent from anaemia not merely because they appear in other anaemia from differing causes but they also depend directly upon the haemoglobin ratio, as they progressively disappear along with the cure of the blood dyscrasia.

In our cases, after normalization of blood, the most varying examinations were made, giving results approaching normal or even normal. In these patients the pathogenic action of ankylostoma and the subjective ill-feeling had entirely disappeared; the patients presented the best disposition to work and, in case of children to play, just as occurs in infestations by inoffensive intestinal macroparasites.

In this way we succeeded in producing experimentally carriers of ankylostoma, and thus in elucidating the preponderant rôle of food in the genesis of anaemia. In fact, in analysing the dietary regimen indicated by the authors here quoted, we see that in regions where severe anaemia are observed, where the disease actually exists, the regimen is constituted by foodstuffs poor in iron, and on the other hand in regions where intense infestations exist but without the anaemic syndrome, the ingested food contains a large quantity of this metal.

That nutrition has a great influence not only on this helminthiasis but also, in a general way, on the whole blood metabolism is a fact which is verified by several authors. The most evident result of these
five cases is that the nutritive substance which acts on blood in ankylostomiasis is iron.

We did not try to modify, with diet rich in iron, the blood image in initial ankylostomiasis. The negative result of such an experiment is clearly understood, as the iron quantity contained in these diets is, by no means, able to exert its influence upon blood. In our opinion, in ankylostomiasis the organism is in a state of martial deficiency, i.e. of very diminished or even exhausted iron reserves. The quantity of these reserves is of a proportional value incomparably greater than the iron contained in food: hence the necessity of massive iron administration and not of milligrams contained even in the richest diets. The contrary is observed after the recovery of the reserve; then, the necessary doses of iron progressively diminish and even a diet rich in iron prevents the disparity of the metabolic equilibrium.

The cases presented show this in a clear way, a circumstance which satisfactorily accounts for the existence of carriers, as in the regions where this fact is verified diet, as already stated above, is always abundant and rich in iron. The influence of the richness of food in iron upon the appearance of anaemia is fairly obvious, as will be seen further on in the case of anaemia of bovines, quite analogous to the case of ankylostomiasis in nature and to the cases here presented.

Apart from these facts drawn from studies upon ankylostomiasis itself or upon other human anaemia, we find some flagrant analogies in diseases of other animals, and we shall here transcribe those which are more closely related with the matter, particular to this note.

As to the factors which involve the distribution of these diseases, a curious finding observed in nutritional anaemia of cattle encounters analogy in the facts described above. Aston (21) in New Zealand, Orr (22) and Gunn (23) in the South of Scotland, Dickinson (24) in Tasmania, Neal and Becker (25) in Florida, proved that a certain anaemia observed in sheep and oxen is the consequence of the deficiency of alimentary iron in the pasturages upon which they graze, which deficiency is due to the poverty in this metal of the soil of certain pastures. The animals living there and feeding on grass with scarce quantity of iron present an anaemia, the features of which are similar to those observed in ankylostomiasis.

We, thus, find in this disease of cattle a striking instance of an anaemia consecutive to the deficiency of a haematopoietic factor in habitual aliments.

In ankylostomiasis, which in our opinion essentially obeys the same pathogenic determinism, we observe, just as in this disease of
bovides, a geographical distribution by zones. In infested regions, without anaemia, there is always an alimentation rich in iron, just as there always exists a soil rich in iron in the regions where cattle live in healthy conditions. On the contrary, ankylostomotic anaemia is observed only in regions where foods presents deficiency of this metal, just as occurs with the anaemia of those herbivora.

The demonstration of innocuousness of the infestation by Necator renders perfectly similar the facts described above with regard to the distribution of ankylostomotic anaemia and of nutritional anaemia of cattle. The facts presented in this work, consequently, show that the helminthes, the supposed direct responsible for the severe organic disturbances, may live in human organism in a state of mere inoffensive commensalism and they, moreover, can be reduced to such a state by iron administration to the infested and sick man, all clinical symptoms disappearing progressively.

Essential considerations, especially concerning the innermost mechanism of the genesis of anaemia and the decurrent consequences thereof.

The importance not only of the facts here reported but also of several other facts verified in ankylostomiasis gave rise to our idea about a mechanism of the genesis of anaemia in this helminthiasis, mechanism differing from those accepted until then. We who indicated (18) martial deficiency as the fundamental cause of anaemia, now believe that the main occasional factor of this deficiency is to be found in a dietary deficiency. Firstly, we must answer and document two essential questions which arise immediately:

1.) — Is a deficient nutrition able, of itself alone, to induce anaemia in man with features identical of those observed in ankylostomotic anaemia?

2.) — Alimentary deficiency being the preponderant factor in the genesis of ankylostomic anaemia, which is the interference of the helminthic infestation?

We have already quoted in infants anaemia caused by a mere deficient ingestion of iron (Nutritional anaemia of lactants). Rhoads and Castle (8) find in adults microtyc, hypochromic anaemia, just as that observed in ankylostomiasis, of straightforward nutritional origin. Witts (15) indicates amongst anaemia induced by dietary deficiency, apart from the anaemia of lactants, the scorbutic anaemia and the tropical nutritional anaemia. These anaemia observed in adults, however, require a detailed study for the exclusion of any other cause. But even in ankylostomiasis,
in certain cases of it, the severe anaemia associated with slight infestations seem to indicate the possibility of a simple dietary cause, as in those cases the helminthic action seems to be practically of no effect.

Nevertheless, not every case of deficient nutrition is invariably accompanied by anaemia. It is also known that it is difficult to anaemiate by this process any adult mammal. The same does not occur with fowls, as Cook and Harmon (26) proved in hens. This animal has not the property of reserving iron, and when egg-laying a great decrease of haemoglobin ratio is observed in it. These facts suggest that in more differentiated animals there is a better equilibrium in iron metabolism, owing to the possibility of storing up this metal in the organs (mainly in spleen) and of utilizing it in case of any disturbance in the metabolism of this substance. In fowls only the material intended for eggs induces iron deficiency and consecutive anaemia; as to cattle, a long stay in regions poor in iron is necessary in order to observe the same effect, whilst in man the abundant splenic reserves of this metal are even able to prevent in many cases the appearance of this syndrome.

Thus we are enabled to answer the first question affirmatively, but we must add that anaemia of a straightforward nutritional cause is not observed frequently.

Nevertheless, when in human organism the action of an accessory factor is added to a nutritional iron deficiency, in such cases severe anaemia are always brought about. Various are the factors which are able to interfere in iron metabolism: some by rendering assimilation difficult or even by checking it (action of alpha-dipyridil, when mingled with food, disturbances of hydrochloric secretion of the stomach, lesions of the small intestine, physico-chemical disturbances of the juxtagastric region), others by eliminating from the economy large quantities of this metal (haemorrhages, exaggerated secretion of organic fluids rich in iron, haemoglobinuria), and others disturbing the intermediary metabolism so as to induce a deficient utilization of the iron which is stored up in the organism (copper deficiency, and most likely certain endocrinious disturbances).

On the strength of the aforesaid, we believe that in ankylostomiasis none of the factors may be considered as the main cause of iron deficiency, which we consider to exist. The main cause lies in the deficiency of iron ingested by the patients along with food. Nevertheless, in examining the biological activities of ankylostoma and nector, we shall find some points of contact between these activities and iron metabolism in the organism, and then we shall easily understand its true and limited action in the genesis of anaemia.
Thus, apart from the action common to all intestinal macro-parasites, on the wall of the small intestine lesions occur which are peculiar to this helminth, and these most likely induce a disturbance in the assimilation of food together with slight haemorrhages. This bad assimilation conveys a lesser benefit from the iron contained in nutritive substances; the slight hemorrhages occurring during a long time also drain out from the organism the iron contained in haemoglobin.

In tropical and subtropical regions, where the climate greatly favours the development of these helminthes, or even in cold zones when the conditions of temperature and humidity allow this development, this accessory factor acquires importance in the genesis of the disease. We then shall understand that, in the majority of cases, in organisms predisposed by defective food to nutritional deficiency, with an iron metabolism at the extreme limit compatible with normal, any harmful cause able to repercuss on this metabolism (in tropical regions ankylostomotic infestation is one of the main) produces the appearance of the anaemic syndrome in these individuals.

In the great majority, if not in the totally of severe cases, even before the beginning of the disease we find a deficient dietary regimen which contains insignificant quantities of iron. This fact verified by several authors and mainly by Langen, we have always observed in all cases which have come to our direct knowledge. On the other hand, we have seen that the attention of the authors turn to food rich in iron, when they seek for the verification of the causes which determine the resistance, met with in parasite carriers, to the anaemic process.

It is necessary to state that we have not the intention wholly to eliminate or deny the action of ankylostoma, which would evidently be inconsistent; our only intention is to delimit exactly its true action, which leads us to state that this helminth has a secondary rôle in the genesis of anaemia as compared to iron deficiency in food.

Such is our opinion because, out of these two factors generally associated, one (iron deficiency in food) is the primordial one as it is indispensable and sufficient to induce the anaemic syndrome, whilst the other (helminthic infestation) is secondary as, in the great majority of cases, it is not sufficient and in some cases quite dispensable.

Our experiments here reported finally show in a sure manner the preponderant influence of food, and in this latter the exclusive influence of its iron contents, when we verify that, even in incomplete diet, iron administration cures the disease; moreover, after recomposition of the organic reserves of this metal, a diet rich in this element is sufficient to maintain the state of health.
An important proviso becomes here imperative. When we state that food is a more consequential factor than the helminthic infestation, we mean to refer to the great majority of cases of ankylostomiasis (chronic cases). Evidently, in the disturbances caused by the penetration or immigration of larvae into the organism, or in acute cases of the cases of the disease which present a massive infestation (mainly in children), in these exceptional cases then the disease assumes a particular form which has nothing to do with the classical aspect of chronicity of this helminthiasis. In these rare cases alone a direct and exclusive action may be ascribed to ankylostoma.

Things so standing, how can it be understood why Ankylostoma and Necator for a long time were alleged to be the exclusive and direct cause of all cases of the disease.

A short historical recapitulation will come in our aid in order to elucidate this question. The disease, now called ankylostomiasis, has primordially had the denomination of Intertropical Hypoanaemia. This disease, most likely known since the times of the Egyptians, had its etiology cleared up only in 1838, when Dubini, in Italy, discovered in the faeces of several individuals eggs of a parasite helminth, denominating it Uncinaria duodenale. As the elimination of this parasite cured the anaemia, uncinaria was alleged to be the exclusive and direct agent of the disease. However, in these cases of cure there was not used, at any rate, the isolated administration of vermicidal remedies. After having verified that iron was one of the constituents of the haemoglobin molecule, in every anaemia this metal was recommended as a remedy. Its excellent results in chlorosis induced the physicians to employ it on a large scale, and therefore they, of course, always have used it in ankylostomiasis.

If Dubini and, later on, the authors who confirmed his work (Perroncito and Wucherer) had sought for eggs of this helminth in a zone of parasite carriers, the sound condition of the individuals examined would certainly have shaken their conviction concerning the etiology of the tropical hypoanaemia. Or, if these authors had sought the elimination of the worms avoiding any administration of iron salts, by no means would they have been able to assure, as they did, that the exclusive cause of the anaemia was in this helminthic parasitism.

Up to now, the cure of the ankylostomotic anaemia was obtained by a factor which was thought to be of secondary value in the therapeutical process of this helminthiasis. Iron, like arsenic, was considered a good stimulant of the haematopoietic organs or of metabolic changes, in a general way. The idea that the helminth was the primordial
factor in the genesis of anaemia induced the employment of vermicides at the beginning of the treatment and all regenerative phenomena were ascribed to the elimination of the worms. This doctrine, however, does not agree with the numerous and important facts verified in this disease, facts which indicate, like those presented here, that the fundamental cause of the anaemia depends upon a factor foreign to the activities of the parasite helminth. An iron deficiency in the organism always involves an anaemia with features identical with those observed in ankylostomiasis, whilst even an intense infestation without a simultaneous martial deficiency produces no organic disturbance.

Thanks to these data, it will be much easier to acknowledge in ankylostomiasis a deficiency disease than a disease directly produced by toxins or haemorrhages, as was considered up to the present. Tropical hypohaemia is a more appropriate name for it than ankylostomiasis or whatever other denomination pointing to the preponderant rôle of the worm.

Finally, in summarizing we will state that the iron deficiency in the organism, — the causal factor of the disease —, is mainly induced by food deficiency, as is here documented by us. The parasite helminthies are met with as an adjuvant factor interfering in iron metabolism through some of their biological activities.

The clear understanding of the importance of this manner of viewing the genesis of the disease is afforded by the great modifications which it determines in the prophylactic and therapeutical methods of this anaemia.

We have already indicated the exceptional importance of these facts in the prophylaxis (18) and therapeutics (30) of this disease. As regards the method of treatment, we recommend iron administration prior to the employment of vermicides, and this modification is of vital consequence in severe cases of anaemia.

Once more, we will here insist on the substitution of the classical prophylactic methods by the continued employment of iron in ankylostomotic regions. In man, the removal from an infested zone, is evidently not able to cure the disease, as it occurs with the above quoted anaemia of cattle. These herbivora are under a more restrictive dependency upon the environment, and a larger amount of alimentary iron is already sufficient for the cure of the blood. In man, the same does not occur, and in order to normalize the iron reserves large quantities of this metal must be administered; but, as we have demonstrated in this paper, after normalization of blood readings, the iron quantity necessary for maintenance is incomparably less. Thus,
a therapeutical administration of iron (large doses) must be followed by an administration of maintenance (small doses), which method renders easy and practical the employment of this substance in prophylaxis.

It may be that these notions concerning the innermost cause of ankylostomotic anaemia, i. e. considering nutrition as the more consequent factor than the helminthic parasitism, encounter difficulty in meeting with acceptance amongst the investigators, or may even be considered exaggerated. Nevertheless, as these notions gather and account for numerous controversial facts shedding light on the question and thus enabling new attainments and also because we consider them useful enough for the correct interpretation of the etiopathogenesis of the Intertropical Hypoanaemia, we do not hesitate a single moment in bringing them forward here.

SUMMARY

We epitomized the principal data which document the existence of parasite carriers in ankylostomiasis, the rôle of nutrion in this disease and in anaemia in general, and also the various ideas concerning the pathogenesis of this verminosis.

We presented five cases of ankylostomiasis associated by severe anaemia (Hb. from 13 to 30 %), cured and so preserved by means of daily iron administration for a long time (3 to 10 months), despite the persistence of very intense infestations (25 to 40 thousand eggs of ankylostoma per gr. of faeces). During the period of maintenance, different examinations were made which always presented normal readings or approaching normal. The only exception was the verification of intense eosinophilia in peripheral blood.

Thus then are determined which disturbances may be corrected by iron and which derive from a direct action of the parasite worm.

Finally, the secondary action of the helminth is discussed with regard to the preponderant influence of food, laying stress on the essential importance of the richness of diet in iron.

CONCLUSIONS

1) — It is a fact sufficiently documented that in certain regions of the globe there are individuals intensively infested by *Ankylostoma duodenale* and *Necator americanus* without any disturbance of blood or of the general health.

2) — The factor which prevents anaemia is met with in the food habitual in these regions.
3) — Even in an individual with 40 thousand eggs of ankylostoma per gr. of faeces we succeeded in raising up the haemoglobin percentage from 30 to 90%, and in preserving it during 10 months. For this purpose, we employed an iron salt in doses progressively decreasing until we replaced it by a diet rich in this metal.

4) — This last attainment shows that in the aforesaid diet the active nutritive substance is iron.

A diet rich in iron, when the organic reserves of this metal are not exhausted, maintains the condition of health, in spite of intense intestinal parasitism by helminthes. On the contrary, it is known that a diet poor in iron may in certain conditions produce of itself in man an anaemia exactly alike to that observed in ankylostomiasis.

5) — We must consider as depending upon anaemia not merely the symptoms ascribed so far to same (cardiac and circulatory disturbances, dyspnœa, anorexia, abundance of urine elimination, pallor of skin and mucosae, fever, headache, indisposition to work, dizziness, oedema, general weakness and even geophagy), but also the chemical disturbances of plasma (decrease of proteins, fatty acids and lecithin).

6) — The results presented show that the primordial factor in the genesis of the Intertropical Hypoæmia, afterwards denominated Ankylostomiasis, lies in a dietary deficiency which produces an iron deficiency in the organism, thus conveying an anaemia which in its turn, determines the main symptoms of the disease.

7) — Although the helminth is imputed as the single etiologic agent of ankylostomiasis, the direct action of the parasite, in the genesis of anaemia, is of very slight effects, always fairly less consequential than those due to the preponderant action of alimentary deficiency.

EXPLANATION OF PLATES LX—LXI

PLATE LX

Figs. 1 and 2 — Case 1. Manoel, 11 years old. Large oedema of the face and lower limbs. Ascites.

Figs. 3 and 4 — The same patient 11 days after iron treatment, without elimination of parasite helminthes. Figs. 1 and 3 are not
be perfectly compared, as the photographs were made at a slightly different distance, nevertheless, the disappearance, almost complete, of the oedema may be clearly seen.

PLATE LXI

Fig. 5 — Radiograph made before treatment. A considerable enlargement of the cardiac area is seen, with dilatation of all heart chambers. Longitudinal diameter 14.5. Transverse diameter 13.

Fig. 6 — Electrocardiogram made before treatment. Total tachycardia. Very low voltage of wave T. Electric preponderance of the left ventricle of heart.

Fig. 7 — Radiograph made after 23 days of martial medication, without elimination of helminthes from intestine. Considerable decrease of the cardiac area. Longitudinal diameter 11. Transverse diameter 10.5.

Fig. 8 — Electrocardiogram made after martial treatment. Electric preponderance of the left ventricle of heart. Wave T normal (even enlarged). Total respiratory arrhythmia.