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TYPES AND MECHANISMS OF ANEMIA IN SCHISTOSOMIASIS MANSONI

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SUMMARY

Anemia in schistosomiasis, found in poor and undernourished people, is macrocytic and hypochromic. Under better living conditions, it is normocytic and hypochromic. Vitamin B_{12} deficiency in serum was not found in the latter group.

Sideropenia is a regular feature of schistosomotic anemia. At least in part it might be attributed to the association of ankylostomiasis and the chronic bleeding of the esophageal varices.

Hemolysis is an associated anemia co-factor. It is not totally compensated by hyperactivity of bone-marrow, since this is inhibited by "hypersplenism" which manifests itself by a slow and decreased erythrocytic and hemoglobin production rate and, in one third of the cases, by leucopenia and/or platelet deficiency. The hyperactivity of the spleen is shown by the diminished erythrocytic and hemoglobin production rates in the bone-marrow and by splenic erythrocytic sequestration. Hemodilution due to the high plasma volumes is an associated cause of anemia.

INTRODUCTION

Anemia in schistosomiasis is a feature of the advanced forms of the disease, with hepatic and splenic involvement. It has been studied in several areas of the world where the disease is endemic.

In the Phillipines, PESIGNAN & BAZON [20], in Japonic schistosomiasis, described a macrocytic hypochromic type of anemia. In Venezuela, WUANI & VILLALOBOS CAPRILES [27], found a moderate normocytic normochromic type of anemia, with increase in blood and plasma volumes. In Egypt several studies have been made by ATA [1], MOUSSA & EL-GAREM [13] and KHATTAB et al.[10].

PESSÔA [17] established a clinico-epidemiological classification based on the evolutive stages of the infection. Anemia becomes more severe in the more advanced stages. This notion is clearly derived from the studies of PESSÔA & COUTINHO [16], who, in 210 cases, classified the anemia according to the clinical stage. The anemia was found to be macrocytic and hypochromic. This study was done in Aracaju, State of Sergipe, Northeastern Brazil, where the living conditions are very poor and the food intake consists mainly of vegetables and carbohydrates. In the study of PESSÔA & COUTINHO [18] no relation was found between age, sex or race and the degree of anemia. The patients were separated in two groups, with and without ankylostomiasis. The anemia was of the macrocytic hypochromic type, even in the presence of concomitant ankylostomiasis.

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In an area in South Brazil, Santos, where only scattered foci are registered, the presence and type of anemia have also been investigated by COUTINHO & TSUZUKI [3], in 1956, using 21 schistosomotic patients living in fairly good conditions, with adequate food intake. A comparison was made with 30 other patients in the same clinical stage, grade II, of the Aracaju study, i.e., of the Northeastern area. The patients were infants and young men, with average ages of 13.3 and 12.8 years, respectively.

A statistically significant difference, between the two groups of patients, is evidenced. The Northeastern group shows a macrocytic anemia, while the Santos group, at the same clinical stage, has erythrocytometric indexes close to normal. The worm has not produced, by itself, a definite anemic state. Anemia in schistosomiasis is, at least up to stage II, apparently more linked to the nutritional status than to the direct pathogenic action of the worm. In stages III and IV the influence of the worm is evident through the consequences of the lesions due to the deposited eggs in the portal vein system. Such eggs lead to hepatic fibrosis, portal hypertension, congestive splenomegaly, and gastrointestinal hemorrhages.

The pathogenic role of the worm is clarified by the studies of PESSÔA, SILVA & COSTA [19]. Among people living in the same quarter of the same city (João Pessoa), and submitted to five stool examinations, with negative intradermal test for schistosomiasis and considered as presumably not infected by *S. mansoni*, only about one third of the cases showed macrocytic anemia. In people of the same area and infected by the worm, anemia was present in a larger proportion of cases, about three-fourths. The worm was apparently able to enhance the macrocytic anemia already present in the poorly nourished people. In clinical stage III this role of the worm is evidenced. Presumably in stage IV the same occurs.

Our data were collected from patients in stages III and IV. In 1951, studying the cases of MEIRA's work [12], we already observed a macrocytic anemia in 11 out of 16 severely ill schistosomotic hepato-splenomegalic patients. In those stages, besides the above mentioned role of undernutrition, two other factors were considered: (1) hemodilution and (2) the specific role of the spleen itself.

1. There was an increase in blood plasma, producing hemodilution. The erythrocytic mass was not reduced in absolute numbers, according to data determined by FIORILLO, JAMRA, ESTON & PAGANO [7], who measured separately the plasma volume with Evans blue (T-1824), and the erythrocytic mass with radioactive phosphorus, P^{32}.

2. The pathogenic role of the spleen was due, either to sequestration of erythrocytic mass (congestive splenomegaly), or by acting at distance over the hemopoietic bone-marrow, through the mechanism called "hypersplenism". In an appraisal made by us (JAMRA [8]), we were not able to verify a proportionality ratio between the degree of leucopenia and the size of the spleen and/or the level of the portal venous system pressure measured by splenic puncture, in 12 adult patients of clinical stages III and IV.

In stages III and IV anemia is present in every case. Leucopenia is not regularly present. There are some cases with severe leucopenia, without a corresponding anemia.

Table I, reproduced from the work of MEIRA [12], indicates the distribution of leucopenia in a group of 58 cases of the hepato-splenomegalic form of schistosomiasis.

TABLE I

Leucocytes $10^3/mm^3$	Frequency
2.1 — 3.6	12
3.6 — 5.1	8
5.1 — 6.6	16
6.6 — 8.1	14
8.1 — 9.6	5
9.6 — 11.1	2
11.1 — 12.6	1
Mean: 5.9	Total: 58

DIAS [5], in 22 patients, found the following variations in the leucocyte numbers per mm³:

more than	5,000 —	3 cases
between	4 to 5,000 —	3 cases
up to	4,000 —	16 cases

Platelets are frequently diminished in the hepato-splenomegalic form of schistosomiasis. MEIRA [12] found platelet deficiency (under 100.00 platelets per mm³) in 8 out of 33 patients, i.e., about 25%. DIAS [5], in hepato-splenomegalic schistosomiasis, stages III and IV, registered platelet deficiency in 11 out of 22 cases, i.e., in 50%.

CARVALHO [2] mentioned platelet deficiency in 22 out of 41 cases. JAMRA [8], in a survey of 41 cases, pointed out that in certain evolutive phases of schistosomiasis platelet deficiency was observed.

TABLE II

	DIAS [5]	CARVALHO [2]
Pancytopenia	10 (45.0%)	21 (51.2%)
Leucopenia	2 (9.0%)	6 (14.5%)
Anemia	2 (9.0%)	— —
Thrombocytopenia .	— —	1 (2.4%)
Leucopenia and anemia	4 (18.0%)	7 (17.0%)
Leucopenia and thrombocytopenia	1 (4.5%)	6 (14.5%)
Without cytopenia .	3 (13.5%)	— —
Total	22	41

The association of anemia, platelet deficiency and leucopenia had the following frequency distribution in 22 cases of DIAS [5] and 31 cases of CARVALHO [2] (Table II).

Such pancytopenia is to be attributed to a state of "hypersplenism". Considering "hypersplenism" as the blood condition in which anemia, leucopenia and/or thrombocytopenia are found isolated (partial cytopenias) or together (pancytopenia), and are removed by splenectomy, such condition is present in the hepato-splenomegalic form of schistosomiasis. To be able to define a hypersplenic state, it is necessary to have a clinico-hematological follow-up study sufficiently long to permit the demonstration of the eventual inhibitory role of the spleen, producing well stablished cytopenias and the long-lasting, if not permanent, removal of such cytopenias with splenectomy.

The large and hyperactive spleen has a sequestrational capacity which increases its inhibitory activity, according to arguments in favour of both mechanisms, recently reviewed and critically discussed by CROSBY [4]. Splenectomy is regularly followed by a rise of the erythrocytes, leucocytes and platelet levels. A follow-up study for a period of years, by DIAS [5] and JAMRA [8], in a few patients, suggests that such raised levels are maintained without relapses.

The spleen has a definite pathogenic role towards the anemia and the other cytopenias of hepato-splenomegalic schistosomiasis. The role of the other pathogenic factors, such as undernutrition and hemodilution, should be kept in mind.

3. The role of undernutrition and chronic famine is well demonstrated when the averages of erythrocytes and hemoglobin are compared through the analysis of groups with nutritional correction alone, and before and after nutritional correction plus stibiumtherapy. In an appraisal made by us (JAMRA [8]), two groups were collected in two medical clinics. In one, the medical care was only directed to correct the nutritional deficiency, while in the other stibiumtherapy was used in addition to nutritional deficiency correction (Fig. 1).

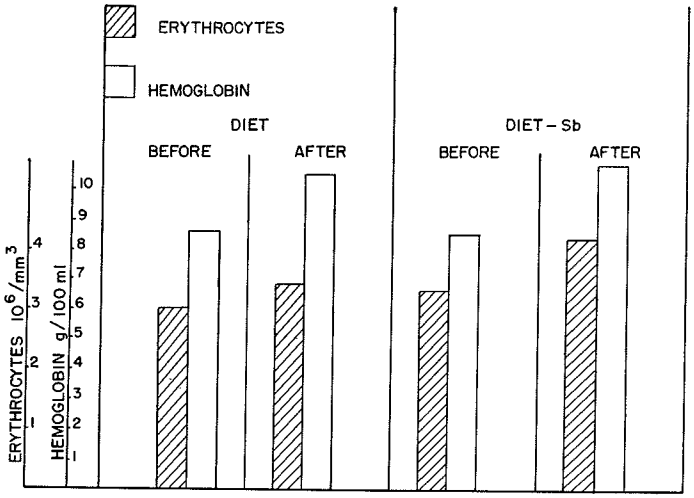

FIG. 1 – INFLUENCE OF THE DIET (AVERAGE OF 22 CASES) AND OF THE DIET ASSOCIATED TO ANTIMONIUM (AVERAGE OF 19 CASES) IN CORRECTING SCHISTOSOMOTIC ANEMIA. DATA FROM JAMRA (1957)

In Fig. 1 the effect of a corrective diet is well evidenced. The worm therapy does not lead to a significant difference of response. Both groups, the one treated with corrective diet and the other with diet and "repodral", do not differ in reference to the erythrocytes and hemoglobin levels, before and after treatment. So, the role of the worm, by itself and deposited eggs, is not direct. The worm acts through the liver lesion and consequent splenomegaly. Figure 2 represents a scheme of the pathogenesis of schistosomotic anemia.

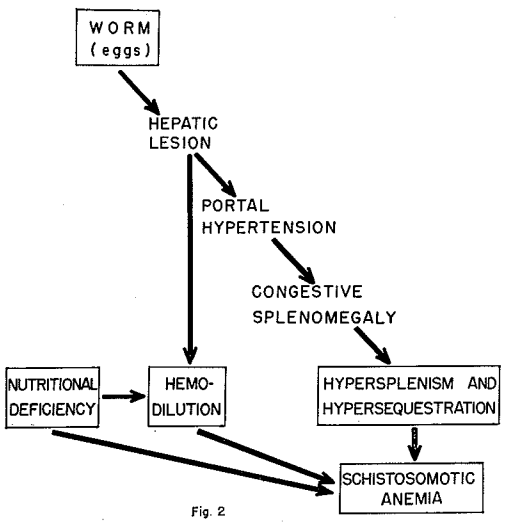

Fig. 2

An adequate diet or the same diet plus stibiumtherapy (JAMRA [8]) did not modify the leucocyte levels.

In reference to blood platelets no definite modifications were seen. In only 5 patients, followed over a suitable period of time, 4 showed higher platelet levels with medical care.

Bone marrow cellularity is described uniformly by several authors (MEIRA [12], DIAS [5], RODRIGUES DA SILVA [24] and CARVALHO [2]). MEIRA [12], in 23 cases, verified a normocellular sternal bone-marrow count with relative predominance of the erythroblastic cells and decreased granulocytopoietic cells. Hemoglobin elaboration and erythroblast maturation were preserved, the hyperplasia of the erythroblasts being of the polychromatophilic stage.

In the granulocytopoietic system, an increase of the promyelocytes and myeloblasts was seen, indicating an inhibited delayed maturation rate of these cell series. Megacaryocytic cells were in active platelet elaboration, no signs of inhibitory platelet production being noticeable. Reticulum, plasmatic and lymphoid cells were described as not significantly deviated from the normal pattern.

DIAS [5], performed the cytological study of sternal bone-marrow in 17 cases, verifying

normal cellularity in every case with erythroblastic hyperplasia, inhibition of the granulocytic series at the metamyelocyte stage and, in the red series, preservation of the maturation rate, with predominance of the polychromatophilic stages. Plasmatic and lymphoid cells were not specially altered, neither were the megakaryocytic cells.

CARVALHO [2] found in a study of 38 cases of the hepato-splenomegalic form of schistosomiasis, 27 (71%) with hypercellularity of the bone-marrow and 11 (29%) with normoplasia. The red series was hyperplastic in 30. Every case showed blockade of the granulocytopoietic series, with active maturation of the red cell series in 26 cases (68%). Megakariocytes were decreased in 31 cases (81%). Reticulum and plasma cells were within normal ranges.

In summary, with reference to bone-marrow cells, as a rule, there is hyperplasia of the erythroblastic series, blockage of the neutrophilic and eosinophilic series, increase of the eosinophilic cells, normal or subnormal numbers of megakariocytes, and no deviations of the mononuclear cells from the normal ranges.

With the purpose of extending investigations on schistosomotic anemia, data were collected on the serum B_{12} vitamin content, the rate of production and destruction of erythrocytes (erythrokinetics) and also on some iron metabolism factors.

Vitamin B_{12}

Serum determination were done in 9 patients, by the microbiologic method [21] using *L. leishmanii* growth with turbidimetric readings. Patients (Table III) were on clinical stages III and IV, living in the State of São Paulo, South Brazil, in environmental and nutritional conditions supposed to be adequate. The following data were obtained (Table IV).

TABLE III

Conditions and morbid associations in schistosomotic patients used in the present study

Case number	Age	Sex	Disease duration since the first symptoms (years)	Other parasitic infections	Hemorrhages (hematemesis due to esophageal varices)
1	39	m.	1	ankylost.	no
2	29	f.	4	no	yes
3	16	f.	2	no	no
4	24	f.	2	no	yes
5	23	f.	½	ankylost.	no
6	19	m.	1	ankylost.	no
7	28	f.	8 months	no	yes
8	39	m.	2	ankylost.	no
9	26	m.	16	no	no
10	38	f.	2	no	no
11	24	f.	2	no	no
12	24	f.	1 ½	no	no
13	48	f.	8 months	ankylost. trichoc.	yes
14	23	f.	15	no	no
15	18	f.	3	ankylost.	no
16	30	m.	6 months	ankylost. trichoc.	yes
17	40	m.	1	no	no
18	22	f.	5	ankylost. trichoc.	yes
19	37	m.	2	ankylost.	yes
20	30	m.	18	ankylost.	no
21	40	f.	1	ankylost. trichoc.	yes
22	31	f.	3	ankylost. trichoc.	yes

The serum vitamin B_{12} content was, in every case, above 200 micromicrograms/ml. At least in the special group of patients observed no deficiency of vitamin B_{12} was demonstrated. The patients exhibited slight reduction of the hemoglobin levels, without definite anemia (Table IV). Serum vitamin B_{12} determinations should be repeated in other types of patients, in other conditions of living and nutrition.

Erythrokinetics

According to the data already published by JAMRA et al.[9], obtained in 4 patients and reproduced in Table V, the production rate

TABLE IV

Serum vitamin B_{12} determinations in schistosomotic patients

Patient N.º	Erythroc. millions/ mm³	Hemoglobin g/100	Hemoglobin %	VG	Hematoc. value %	MCV μ^3	MCH $\mu\mu$g	MCHC %	Vit. B_{12} $\mu\mu$g/ml
13	4.2	12.5	78	0.92	42	100	29	29	225
14	4.0	11.2	70	0.87	37	92	28	30	—
15	4.7	13.9	87	0.92	47	100	29	29	340
16	4.2	9.5	59	0.7	33	78	22	29	553
17	5.0	14.7	92	0.92	47	94	29	31	750
18	4.3	11.8	74	0.86	40	93	27	29	394
19	4.0	10.3	64	0.8	36	90	25	28	900
20	4.0	11.8	74	0.92	39	97	29	30	216
21	4.1	12.6	79	0.96	40	95	30	31	450
22	4.0	10.6	66	0.82	40	100	26	26	258
Normal	4.0-5.0	13-16	80-100	0.9-1.1	40-50	90-100	28-32	± 32	200-400

TABLE V

Erythrokinetics

Patient N.º	Iron-plasma μg/100 ml	Iron-plasma turnover (T½-min)	Iron-plasma turnover mg/day/ 100 ml	Iron incorp. in Hb %	Iron incorp. in Hb mg/day/ 100 ml	Erythr. lifes span (days)	Hemogl. produc. rate (g/day/ 100 ml)	Hemogl. destruc. rate (g/day/ 100 ml)	Produc./ Destruc. Index
1	64	21	2.01	90	1.81	57	0.54	0.28	1.93/1
2	49.5	40	0.63	100	0.63	57	0.18	0.28	0.67/1
3	43	24	1.34	83	1.11	28	0.31	0.57	0.54/1
4	19.7	27	0.50	82	0.41	36	0.12	0.43	0.28/1
Normal	70-160	60-100	0.55-0.65	80-90	0.45-0.55	80-130	0.15	0.15	1/1

of erythrocytes is decreased while the destruction is 2 or 3 times the normal.

It is observed that the production rate of hemoglobin does not overpass the destruction rate, with the exception of case 1, observed in a recuperative phase during the 3 weeks period of blood collections for the erythrokinetic study. In the other patients the destructive rate predominated. It should be pointed out that this destructive rate is not high and that the mean survival erythrocyte time is only slightly reduced. This fact leads us to the notion that anemia is not only due to hemolysis but also to a diminished production rate, presumably associated with the hyperactivity of the spleen, since the spleen removal enhances the production rate, according to JAMRA et al.[9].

Such situation is even more evident when the mean times of survival of the erythrocytes are studied. This survival time was measured in 12 schistosomotic patients through the method of erythrocytes tagged with radioactive chromium, Cr^{51}. The values were corrected for the chromium elution following the indications of DOHOHUE et al.[6], 60 days being the value used as the half elution time according to a method already in use in our laboratory (MASPES et al.[11]). The results are indicated in Table VI.

TABLE VI

Erythrocyte survival time (CR^{51})

Patients	Mean erythrocyte survival time (days)	Patients	Mean erythrocyte survival time (days)
1	57	7	53
2	57	8	56
3	28	9	31
4	36	10	53
5	44	11	34
6	57	12	25
Normal	80-130	—	80-130

In 8 patients a correlation was made between the serum bilirubin content (Malloy-Evelyn's method), the osmotic fragility test (Dacie's method) and the reticulocyte level (supravital coloration and enumeration on dry slides) (Table VII).

TABLE VII

Patient N.º	Mean erythrocyte survival time (days)	Bilirubin mg/100 ml direct	Bilirubin mg/100 ml total	Osmotic fragility test	Reticulocytes %
5	44	0.1	0.8	normal	1.8
6	57	0.2	0.8	normal	2.4
7	53	0.2	0.8	normal	0.6
8	56	0.2	0.8	normal	2.0
9	31	0.2	2.6	normal	4.3
10	53	0.2	0.7	normal	2.0
11	34	0.2	1.6	normal	7.0
12	25	0.5	3.7	normal	3.0
Normal	80-130	0.2	1.0	—	0.5-1.0

Cases 9 and 11, observed after porto-caval anastomosis, showed lower survival time and higher indirect bilirubin and reticulocyte indexes than the others. They were observed in post-operative conditions, post porto-caval anastomosis, with the spleen still present, and with hemolytic components still active (JAMRA et al.[9]). Such hyperbilirubinemia post porto-caval anastomosis has been the subject of a thesis by CAETANO DA SILVA [25, 26]. Case 12 (Table VII), illustrates the rare situation of an association of a severe crisis of hemolytic anemia with the hepato-splenomegalic syndrome of schistosomiasis. This patient became free of the clinical symptoms of hemolysis after splenectomy.

Indirect evidence of hemolysis was also searched by determination of the serum haptoglobin content. Haptoglobin was measured by two methods: that of NYMAN [14, 15] and that of OWEN et al.[16] (Table VIII).

TABLE VIII

Serum haptoglobin in schistosomotic anemia

Patient N.º	Electrophoretic method of NYMAN [15,16] (mg/100 ml)	Colorimetric method of OWEN et al.[17] (mg/100 ml)
13	20-40	14
15	0-20	8
16	20-40	23
17	20-40	37
18	—	14
19	—	24
20	20-40	26
21	0-20	13
22	0-20	21
Normal	60-150	60-150

A low haptoglobin content was found. Such low concentrations have been described and considered as a special feature of hemolytic states. In schistosomiasis a greater than normal haptoglobin consumption would occur as a result of greater offer of destroyed hemoglobin.

As a rule, schistosomotic anemia is associated with a hemolytic state and with a low erythrocyte production rate, according to the data available up to the moment.

Iron

On the other side, there would be iron deficiency as seen in Table IX, which presents iron metabolic indexes, obtained in 9 patients. Serum iron was determined by the method of RAMSAY [22] and the total and free siderophilin by the method of the same author [23].

The low iron content of the serum is due to other causes. Besides schistosomiasis, an associated ankylostomiasis contributes to this deficiency (patients 16, 18, 19, 20, 21 and 22). Gastro-intestinal tract hemorrhages were present in 5 of the above mentioned cases and in case 13. Case 17 was free of ankylostomiasis and hemorrhages. In this case the serum iron content was normal.

In 6 out of 9 patients the serum iron was low. Siderophilin saturation was diminished. Free siderophilin was high in 8. The percentage of sideroblasts and the hemosiderin granules content in sternal bone-marrow were also diminished.

TABLE IX

Iron metabolic indexes

Patient N.º	Serum iron μ g/100 ml	Total siderophilin — binding capac. of iron μ g/100 ml	Free siderophilin — binding capac. of iron μ g/100 ml	Satur. siderophilin %	Sternal bone-marrow	
					Sideroblasts %	Hemosiderin
13	81	220	139	37	8	++
14	64	494	430	13	9	—
16	57	512	455	11	2	—
17	128	476	348	26	6	++
18	71	441	370	16	0	±
19	47	503	456	9	2	—
20	64	490	430	13	0	—
21	92	372	280	24	10	++
22	71	512	441	14	0	—
Normal	80-130	180-320	300-360	60	3-20	+

For adequate interpretation of the data obtained, a table was elaborated indicating the presence or not of hemorrhages, due either to ankylostomiasis or to esophageal varices and the presumed duration of the disease (Table III).

CONCLUSIONS

The majority of our patients suffered a twofold parasitic infection: schistosomiasis and ankylostomiasis. On the other hand, there was portal hypertension, esophageal varices, which bled, either through frank hemorrhage (hematemesis) or in a subclinical way.

Due to these circumstances, the schistosomotic anemia has some special features in the clinical stages III and IV: macrocytic or normocytic; sideropenic and hypochromic; with an hemolytic component; and with an insufficient bone-marrow, uncapable of satisfying the needs of the erythrocytic regeneration. The sideropenia as well as the hemolysis lead to the erythroblastic hyperplasia of hemopoietic bone-marrow. Meanwhile, there is no complete compensation. Thus, anemia results from the inhability of the bone-marrow to compensate the hemolysis of medium or slight intensity, in the presence of an associated sideropenia. Hemolysis by itself, perhaps, could be compensated only by the erythroblastic bone-marrow hyperplasia. With the simultaneous association of sideropenia there is, however, no complete compensation of hemolysis, thus leading to anemia.

The bone-marrow is hypercellular. In the series of cases studied in this paper, data were obtained which indicate that erythroblastic hyperplasia (Table X) is not sufficient to compensate the mechanism which leads to anemia.

Mild anemia was present in 4 out of 10 patients, partially compensated, and none of the cases shows less than 9.0 g of hemoglobin per 100 ml blood. The 10 cases used for this study, in reasonable living and nutritional conditions, show that schistosomiasis is a parasitosis which may lead to anemia. In adequate nutritional conditions there is partial compensation of the mechanisms of hemolysis and of iron losses due to gastrointestinal hemorrhages.

The hyperactivity of the spleen is seen in the leucopenia and platelet deficiency observed in 3 out 10 patients and is expressed

TABLE X

Correlation between bone-marrow cellularity and the blood picture

Patient N.º	Erythrocytes mm³ × 10⁶	Hemoglobin g/100 ml	Hematocrit %	MCV u³	MCH μ ug	Leucocytes mm³ × 10³	Platelets mm³ × 10³	Bone-marrow			Granulopoiesis/ erythropoiesis ratio
								Granulocy-topoietic %	Erythrocy-topoietic %	Magaka-ryocytes %	
13	4.2	12.5	42	100	29	4.2	172	49.2	41.4	0.4	1:1
14	4.0	11.2	37	92	28	3.5	—	57.4	29.6	0.0	1.9:1
15	4.7	13.9	47	100	29	2.6	22	43.8	41.0	0.0	1:1
16	4.2	9.5	33	78	22	4.0	210	27.2	58.6	0.2	0.5:1
17	5.0	14.7	47	94	31	12.0	259	52.4	30.2	0.0	1.7:1
18	4.3	11.8	40	93	27	5.0	259	41.2	35.8	0.2	1.1:1
19	4.0	10.3	36	90	25	5.0	160	51.8	36.8	0.0	1.4:1
20	4.0	11.8	39	97	29	7.7	220	53.4	34.4	0.4	1.6:1
21	4.1	12.6	40	97	30	15.0	28	38.6	53.6	0.0	0.7:1
22	4.0	10.6	40	100	26	32	3.8	27.2	62.0	0.0	0.4:1

in the anemia which is also associated to a diminished hemoglobin production rate, even when observed in patients in good nutritional conditions.

RESUMO

A anemia esquistossomótica encontrada em pessoas subalimentadas é macrocítica e hipocrômica. Nos que vivem em melhores condições, ela é normocítica e hipocrômica. Neste último grupo, não se observou deficiência de vitamina B_{12} no sôro.

A sideropenia constitui aspecto constante da anemia esquistossomótica e deve ser atribuída à associação com ancilostomose e ao sangramento crônico das varises esofageanas.

A hemólise é um cofator associado da anemia. A vida média, um tanto curta, das hemácias se relaciona com o ligeiro grau de hemólise. Esta não é compensada por hiperatividade da medula óssea, pois há inibição devida ao hiperesplenismo, manifestando-se por uma produção lenta e diminuída de eritrócitos e hemoglobina e, em um têrço dos casos, por leucopenia e plaquetopenia. A hiperatividade do baço se evidencia pelo ritmo reduzido de produção de hemácias e hemoglobina, na medula, e pelo sequestro maior ou menor de hemácias no baço.

Outra causa da anemia é e a hemodiluição.

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