Tropical Macrocytic Anemia in Puerto Rico*

REPORT OF TWO CASES

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In 1932 a study of tropical anemias as they occur in Puerto Rico was undertaken at this Institution by the writer. Since then, several cases of macrocytic anemia have been occasionally encountered in which the accompanying symptomatology did not entirely fit into either the clinical pattern of the sprue syndrome as it is most frequently observed on this Island, or into that of clinical pernicious or Addisonian anemia of the temperate zones. The interesting work on tropical macrocytic anemia by Wills[1, 2, 3] and her collaborators in India, and more recently that of Hamilton Fairley and co-workers on nutritional macrocytic anemia in Macedonia,[4] suggested to us at the time that those cases with a macrocytic anemia that did not seem to be sprue or Addison's anemia, could well be diagnosed tropical macrocytic anemia or, as was recently suggested by Hamilton Fairley, nutritional macrocytic anemia.

The work of Hernández Morales† includes important data on the incidence of tropical macrocytic anemia in Puerto Rico. In a study comprising one hundred and four girls, 27% presented a macrocytic-hyperchromic anemia, and in 28% a macrocytic-hypochromic anemia was found. Such types of anemia, however mild in their intensity, encountered in a group of apparently healthy girls, appear to be correlated with a deficient dietary as it was determined by bio-chemical studies made of their diet.‡

REPORT OF CASES

Case No. 1. A. C. (U.H. 1286). A 60-year-old widowed mulatto woman, who was admitted to the Out-Patient Department of the University Hospital, April 25, 1933. She complained of intense weakness, dyspnea on exertion, palpitations, marked anorexia and headache, accompanied by frequent dizzy spells and, recently, by swelling of the feet and ankles. This symptomatology ensued quite insidiously since October, 1932, but has slowly and progressively become worse. For about one year previously she had not felt well, and during the past three months she

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has been bedridden because of weakness. The tongue has been occasionally sore and red, but this has not been a persistent or annoying feature. No diarrhea has occurred; in fact, she has frequently been constipated, there being one solid, yellow bowel movement every two or three days. No noticeable fever or chills have occurred, nor has there been any appreciable loss in weight. Some flatulence and epigastric fullness after ingestion of food has been present. Fried foods, rice, beans or potatoes do not agree with her. Five years ago similar symptoms appeared, at which time liver extract (amount unknown) was taken by mouth, followed by prompt return of strength and vigor. However, several (?) vials of Lilly's extract recently given *per os* have not offered relief of present condition. Moderate numbness and coldness of extremities have been present also. Her previous health has been good.

Physical examination revealed a fairly well nourished and developed elderly female, appearing chronically ill and obviously anemic, and complaining of marked weakness and prostration. She was hardly able to walk, and any effort, however slight, increased the dyspnea. There were no evidences of dehydration or of recent weight loss. Other important clinical findings were marked pallor of the skin and mucous membranes, left side enlargement of the heart with a mitral systolic murmur, blood pressure 138/76; tachycardia, congestion of lungs and slight temperature (101.4°F.). The tongue was pale but there were no signs of glossitis.

As the type and nature of the anemia was not known to us at the time of her first visit to the Out-Patient Department, iron ammonium citrate was prescribed and the patient was recommended for admission to the hospital. The blood values at this time gave the following results: Red blood cells, 710,000 per cu. mm.; hemoglobin, 2.9 grams, or 20% (Newcomer); volume of packed red cells, 7.63 cc. per 100 cc. of blood; mean cell volume, 107 cubic micra; mean cell hemoglobin, 40 micromicrograms; mean cell hemoglobin concentration, 38 per cent; leukocytes, 2,900. A differential white count was not made at this time. Upon examination of the stained smear, no nucleated red cells were found; marked aniscocytosis and poikilocytosis as well as macrocytosis of the red cells were observed.

In spite of the similarity of this blood picture to that often encountered in sprue and Addison's anemia, it was felt at the time that the case was not one of sprue. However, with a macrocytic-hyperchromic anemia, parenteral liver therapy was indicated. Aplastic anemia was considered as a probable diagnosis, but no marrow studies were available to confirm this possibility. The course of the condition is considered proof against this contention.

The patient was admitted to our service in the University Hospital on May 2, 1933. The weight was 114 lbs., height, 62¾ inches, respiration 40, pulse 120, temperature 101.4°F. The blood values on admission were about the same as those observed when she was first seen at the Out-Patient Department. Examination of stomach contents revealed hypoacidity with free hydrochloric acid. A total serum protein of 4.53 mgs. per cent, with preservation of normal albumen-globulin ratio was obtained. The non-protein nitrogen of the blood was normal. The icterus index was slightly increased, 8.6 units. Examination of the urine was negative. No parasites were detected in the feces. The blood Kahn was negative, also. Determination of the basal metabolic rate gave —6%.

Course in hospital: The patient was given a soft diet, later followed by full

hospital diet. No special sprue diet was required. The daily fluid intake was limited to 1,000 cc. Four cc. of parental liver extract prepared from Lilly's 343 (amount derived from 18 grams of liver), were administered daily during the patient's sojourn in the hospital. A maximum retiulocyte rise of 11.6% was obtained on the tenth day of liver therapy, which was followed by a gradual and steady rise in the blood values on discharge. The red cell count and hemoglobin were then 4,020,000 and 11.7 gms. or 80%, and the mean corpuscular volume had come down to 90 cubic microns under liver therapy. The temperature gradually returned to normal, the cardiac murmur disappeared and the area of cardiac dullness decreased. At no time during hospitalization had the patient diarrhea, and laxatives or enemas were often required to effect a bowel movement. After remaining seventy-seven days in the hospital, the patient was discharged markedly improved on July 18, 1933. The weight was 116 lbs.—only slightly more than on admission, but it must be recalled that at this time there was considerable tissue edema. No objective evidence of edema was present on discharge.

Follow-up: During the first six months after discharge, the patient was treated by several physicians besides the writer at the Out-Patient Clinic. This may account for the irregularity in the blood studies performed during this period. Clinical improvement continued until October 20, 1933, when she stated that she was going to have a relapse and complained of headache, weakness and anorexia. Some diarrhea had occurred whenever greasy foods were taken. After a series of liver injections she again felt fairly strong and well by January, 1934. The weight was then 128 lbs. However, in spite of liver therapy (5 to 8 cc. intramuscular injections twice or thrice weekly), considerable anemia was still present: R.B.C., 2.45 millions; hemoglobin, 10.2 gms. (70.5 per cent) and a mean cell volume of 120 cubic microns. Therapy was continued, and during the first four months of 1934, she felt fairly strong and active. She was discharged April 3, the blood having reached the highest levels for hemoglobin (18.5 grams or 127%), and the red cells rising to 3.71 millions. However, by September of 1934, a second relapse occurred. Again she responded to liver therapy, better clinically than hematologically (R.B.C. 2.93; hemoglobin, 8.2 grams, or 56%). All during 1935 the patient received maintenance doses (from 10 to 16 cc. weekly) of liver extract and was able to remain fairly active and to be able to withstand an attack of upper respiratory infection. No blood studies were made during 1935. In January 1936 she was again discharged, much improved, weighing 136 lbs. A third relapse was in progress by June of this year (R.B.C., 2.95; hemoglobin 10 gms., 68%), requiring continuous liver therapy throughout the remainder of 1936 and most of 1937. By October of this year, a substantial rise in blood values had been attained: R.B.C., 4.00 millions (highest since discharge), hemoglobin, 14.4 gms. or 98%, and she felt stronger. However, occasional sore tongue with flatulence and slight diarrhea were present. Liver therapy was continued during 1938. An attack of grippe brought forth another relapse with a fall in blood values in June 1938 (R.B.C., 3.43; hemoglobin, 10.4 gms., 70%). When last seen in February 1939, the patient was feeling fairly well and strong. The weight was 123 lbs. No blood studies are available on this date. Liver therapy is being administered at present.

Case No. 2. S. P., a 48-year-old, married, mulatto female, was admited to the Out-Patient Department of San Alberto Hospital, Bayamón, P.R., July 25, 1938.

She complained of progressive weakness, pallor, shortness of breath on exertion, headache, accompanied by marked anorexia of several months' duration. The tongue had never been sore and no redness or aphthae have appeared. Lately, coldness of lower extremities has been a frequent, annoying symptom, accompanied by tingling and formication in toes. No diarrhea has occurred, ever, and the patient has frequently been constipated. As a rule, stools were described as of normal color and appearance. However, the patient does admit that occasionally grayish or clay-colored, though formed, movements have occurred. There has been no apparent intolerance to fatty or farinaceous foods. Some loss of weight has occurred, amount unknown to patient. No similar symptomatology had previously occurred, and liver extract was never administered until two months ago when nine intramuscular injections (Lederle's, 2 cc.) were given with no apparent relief of symptomatology. Hospitalization was advised, but the patient refused.

Physical examination showed a well-developed, fairly well nourished, middle-aged woman, appearing chronically ill. There was a waxy appearance with a dirty yellow tint of the skin, and areas of increased brownish pigmentation in the exterior surfaces of both forearms and at the nape of the neck posteriorly were observed. These areas of hyperpigmentation did not resemble pellagrine lesions. The mucosa of the tongue was pale, but not inflamed or atrophied. There were no evidences of edema anywhere, and the remainder of physical examination was negative. The patient's weight was 121 pounds; the height, 5 ft. 3 inches, the temperature and pulse, normal. Blood studies showed marked anemia of the macrocytic-hypochromic type, with the following values: R.B.C., 1.99 millions; hemoglobin, 4.4 gms. or 30 per cent; volume of packed red cells, 20.7 cc. per 100 cc. of blood; mean cell volume, 104 cubic microns; mean cell hemoglobin, 22 micromicrograms; mean cell hemoglobin concentration, 21 per cent; leucocytes, 3,200 per cu.mm.; examination of smear showed anisocytosis, poikilocytosis, achromia of the red cells, normoblasts, few giant staff leukocytes and several macropolycytes. No studies for determination of gastric acidity or of blood chemistry were made in this case, nor was it possible to determine the reticulocyte response following treatment. Campolon (2 cc. intramuscularly) was given three times weekly, an amount which has been found to produce sufficient hematological response in sprue. One month under this therapy did not produce appreciable clinical improvement and the blood findings had not significantly improved (R.B.C., 2.3 millions; hemoglobin, 5.0 gms., 34%). The patient's weight was about the same as previously. Vegex (marmite) was then prescribed, 16 cc. daily after meals, to be taken with fruit juice. One gram of iron sulphate daily to be taken in 0.25 gm. doses was also prescribed with the purpose of combatting the iron deficiency present as shown by the low mean cell hemoglobin (21 micromicrograms) and cell concentration (21 per cent). The improvement that followed was marked and rapid, both clinically and hematologically. There occurred a steady return of strength and vigor, the appetite improved by the second week and the marked pallor of the skin and mucous membrane gradually disappeared; however, the patches of hyperpigmentation had not faded when the patient was last seen on October 19, 1938. The highest blood values were observed two months after starting treatment with Vegex and when a total of approximately 700 cc. had been taken: R.B.C., 3.82 millions; hemoglobin, 12.0 gms. or 82.6 per cent; mean cell volume, 97 cubic micra; mean cell hemoglobin, 31 micromicrograms; mean

TABLE I—TROPICAL MACROCYTIC ANEMIA
TABLA I—ANEMIA MACROCITICA TROPICAL

Case No. 1
Caso 1

Blood studies
Estudio hematológico

Date *Fecha*	R.B.C. millions per cu. mm. *Hematies; millones por mm. c.*	Hemoglobin Grams *Gm.*	Hemoglobin Per cent *Hemoglobina %*	Volume packed R.B.C. cc. *Hematies apilados, volumen*	M.C.V. cu. microns *M.V. Glob. micras cúbicas*	M.C.H. yy *M. Hem. Glob. micro-micro-gramos*	M.C.H.C. Per cent *M.H. de concentr. %*	Leucocytes per cu. mm. *Leucocitos por mm. c.*	Differential leukocyte count—200 cells *Recuento diferencial (200 células)* Juvenile neutrophils *Neutrófilos jóvenes*	Segmented neutrophils *Neutrófilos segmentados*	Eosinophils *Eosinófilos*	Basophils *Basófilos*	Lympho-cytes *Linfo-citos*	Mono-cytes *Mono-citos*	Platelets per cu. mm. *Plaquetas por mm. c.*	Remarks *Anotaciones*
4.25.33	0.71	2.9	20	7.63	107	40	38	2,900								
5.25.33	1.81	8.5	58	23.9	132	47	35	3,200							120,000	Anisocytosis. No nucleated reds. Poikilocytosis. *Anisocitosis. Hematies no nucleados. Poiquilocitosis*
6.27.33	3.54	10.0	68	31.6	90	28	31	4,850	3.0	25.0	10.0	0	50.0	12.0		
7.14.33	4.02	11.7	80						5.5	24.5	2.0	0	47.0	21.0		
1. 4.34	2.45	10.2	70.5	29.43	120	41	34	4,200								
2. 1.34	2.92	12.4	85.5	35.97	123	42	34	2,700	4.0	35.0	0	5.0	55.0	0		One lymphoblast seen. Anisocytosis. *Observóse un linfoblasto. Anisocitosis.*
3. 1.34	2.93	13.5	95.8	35.97	124	46	37	3,700								
4. 3.34	3.71	18.5	127.0	37.90	102	50	48	5,800	0	42.0	1.0	0	56.0	1.0	180,000	
12.21.34	2.93	8.2	56.0					5,700								
6.30.36	2.95	10.0	68.0					4,950		32.0	2.0	0	64.0	2.0		
3. 2.37	3.30	11.3	77.0					4,300		47.0	0	0	51.0	2.0		
10. 4.37	4.00	14.4	98.0					6,900								
5. 6.38	3.43	10.4	70.0					6,000		57.0	2.0	0	38.0	3.0		
Case No. 2 *Caso 2*																
7.25.38	1.99	4.4	30.0	20.7	104	22	21	3,200	5.0	49.0	0	0	44.0	2.0	120,000	Anisocytosis; poikilocytosis; achromia; few normoblasts; giant staff cells; macropolycytes *Anisocitosis; poiquilocitosis; acromia; algunos normoblastos; células gigantes, tipo cayado; macropolicitos.*
8.26.38	2.30	5.0	34.0	23.5	102	21	21	3,800								
9.27.38	2.92	11.0	75.0	34.8	120	37	31	6,000	7.0	51.0	6	0	33.0	3.0	174,000	Slight anisocytosis and poikilocytosis. No nucleated red cells. *Ligera anisocitosis y poiquilocitosis; ausencia de hematies nucleados.*
10.19.38	3.82	12.0	82.6	37.0	97	31	32	6,700	4.5	66.0	1.0	0	25.5	2.5	200,000	Slight anisocytosis and poikilocytosis. No nucleated red cells. *Ligera anisocitosis y poiquilocitosis; ausencia de hematies nucleados.*

cell hemoglobin concentration, 32 per cent. Although slight macrocytosis of the red cells was still present, the iron deficiency had apparently been relieved. The patient has not returned to the clinic. A gain of nine pounds occurred during treatment.

In table 1 are shown the blood findings encountered in these two individuals.

DISCUSSION

The cases reported present several interesting features. Both were elderly, colored women who were suffering from symptoms referable to a marked anemia, and very little else. While it may be questioned by some that the symptomatology and blood picture are compatible with the diagnosis of incomplete sprue, we do not believe that the clinical picture of these cases was that of the sprue syndrome as it is frequently encountered in Puerto Rico. Although the incidence of sprue among colored people in Puerto Rico is low, the fact that these individuals were colored could be interpreted as mere coincidence and should not be considered a characteristic of tropical macrocytic anemia. In regard to the blood picture, there is a general agreement among different investigators that the blood picture in tropical macrocytic anemia resembles quite closely that in sprue and in pernicious or Addisonian anemia. Such was found to hold true in the present work, and even some of the abnormalities of the leukocytes recently described by the writer[5] in sprue were observed in the second case reported here. Macrocytic tropical anemia has been usually encountered elsewhere in association with pregnancy. This association did not occur in the cases studied by us.

The relatively poor response to liver therapy following discharge from the hospital in the first case might in part be explained by the low economic status of the patient and lack of balanced dietary. An inquiry into the dietary history revealed that the basic articles of food were rice, beans and native tubers; meats, dairy products and fresh vegetables were rarely eaten. The advanced age of the patient should be taken into consideration, also. It would appear that the liver extract administered in the Out-Patient Department was just enough to compensate for the lack of an adequate diet, and maintain the patient up and about, at a low threshold of health and activity, yet insufficient to build up her blood to normal levels. This state of affairs is not infrequently seen in the treatment of sprue cases in our clinic. It does seem too much to expect from this form of therapy, or from the aim of a hospital which cannot in other ways contribute to further the welfare of the indigent sick. In the second case the economic factor may not

appear significant, as the patient had been able to provide an adequate diet previous to her illness, and was able to take a nutritious diet as soon as her appetite returned. However, it seems to us that this is important in explaining the rapid and persistent improvement observed, but only after Vegex and iron were instituted. It is an interesting observation that a macrocytic-hypochromic anemia developed in this patient instead of a macrocytic-hyperchromic of the first case. Such observation is not infrequent in sprue in Puerto Rico and suggests that an iron deficiency, probably of dietary origin, is at fault. In this connection, the similar findings of Hamilton Fairley (*loc. cit.*) in eleven cases of nutritional macrocytic anemia and in which the mean corpuscular hemoglobin concentration was less than 30%, also points to an iron deficiency as a complicating factor in tropical macrocytic anemia.

In regard to the quite different effect of liver therapy in these cases a crude liver extract was employed in the first (1 cc. derived from 4.5 grams of liver prepared according to Castle's method), and Campolon was employed in the second case without appreciable hematologic or clinical results. However, this extract has been found to be effective in sprue by the writer and by others. But it was not until autolyzed yeast extract containing vitamins B_1 and B_2 (G), that a prompt and sustained improvement was attained. However, the failure of one case to respond to Campolon should not be considered sufficient evidence against the effectiveness of this or other commercial liver extracts in tropical macrocytic anemia. Possibly, the dosage given was not enough.

In a general way, the observations in the second case resemble those obtained by Wills[6] in tropical macrocytic anemia and experimental nutritional macrocytic anemia of monkeys. In the opinion of this investigator, these conditions seem to be due to a dietary deficiency involving some factor as yet unidentified, but other than Castle's extrinsic factor. This factor is not present in purified liver extracts, but is present in crude liver extracts or in autolyzed yeast extract (Vegex, marmite) and is believed to be part of the vitamin-B complex. Therefore, in treating tropical macrocytic anemia, the cruder liver extracts and autolyzed yeast extract constitute the treatment of choice.

SUMMARY

The case records of two colored women aged 60 and 48, respectively, and suffering from tropical macrocytic anemia are reported. A table containing hematologic data before and during the course of treatment is included.

CONCLUSIONS

It is believed that tropical macrocytic anemia is a syndrome that can be distinguished from classical sprue and pernicious anemia. The blood picture bears a close resemblance to that of sprue and pernicious anemia. This condition appears to be brought about by a deficiency in the diet of some factor at present unidentified, but other than Castle's extrinsic factor. The parenteral use of adequate amounts of crude liver extracts or of autolyzed yeast extract by mouth, in addition to a well-balanced diet, appears to be the treatment of choice. When an iron deficiency is present, iron sulphate is also recommended.

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