Isolated Malabsorption of Vitamin B$_{12}$ Causing Megaloblastic Anemia and Hyperpigmentation in a Nigerian

Report of Case

By E. J. WATSON-WILLIAMS AND A. F. FLEMING

Vitamin B$_{12}$ DEFICIENCY is relatively unusual in Negroes.$^{1,2}$ In particular, it is uncommon in Africa, although cases have been reported from East Africa$^3$ and in South African Bantus.$^4,5$ At University College Hospital, Ibadan, Nigeria, only two patients have been found to have this deficiency, although full hematological facilities, including bioassay of vitamin B$_{12}$, have been available since 1958. Because of the great rarity, the manner in which these patients presented themselves is of interest. One patient had pernicious anemia, as demonstrated by the Schilling test.$^6$ This patient displayed no unusual feature apart from hyperpigmentation of palmar skin, as has been described in Indians with vitamin B$_{12}$ deficiency.$^7$ The other patient is described here in detail, as his case had many unusual features.

CASE REPORT

The patient is a man aged about 45 years of the Nupe tribe. He lives in Lafiagi, a town near the middle Niger, in Northern Nigeria, about 100 miles north and east of Ibadan. He is a Koranic teacher. He has one wife, one son aged about ten years, and one living brother. On April 6, 1961, he came to U.C.H., Ibadan, complaining of dyspnoea on exertion for the past 3 months. He had had to give up his farm work. About 15 months previously, his illness began with diarrhea with blood and mucus. He had noticed loss of weight and loss of appetite since that time. Food tasted bad, and peppers, which are used in large quantities in cooking in Nigeria, tasted too hot. His tongue had become smooth and the palms of his hands dark (Fig. 1). He still had up to four motions a day, which was more than before he had started feeling ill. He had not noticed any change in sensation.

On examination there was pallor of the mucous membranes, and the tongue was raw and smooth along the edges. There was a hemic murmur over the mitral area. The skin of the whole body was darker than usual, but the most outstanding observation was black pigmentation over the whole of both palms (Fig. 1). The knuckles were also hyperpigmented. The liver and spleen were not palpable. There were no abnormalities detected in the central nervous system.

Investigations

The results of the principal hematologic investigations were as follows: Hemoglobin (Hb) 5.9 Gm./100 ml.; packed cell volume (P.C.V.) 19 per cent; red cell count 1.86 million/cu.

From the Subdepartment of Hematology, University of Ibadan, Nigeria.

Expenses of radioisotopic and microbiologic studies were defrayed by a grant to E. J. Watson-Williams from the West African Council for Medical Research and a research contract (No. 278/R1/RB) to A. F. Fleming from the International Atomic Energy Agency.

First submitted Jan. 19, 1966; accepted for publication March 26, 1966.

E. J. WATSON-WILLIAMS, M.B., B.CHIR., M.R.C.P: Senior Lecturer, Manchester University Department of Clinical Hematology, Manchester, England. A. F. FLEMING, M.B., B.CLIN.: Senior Registrar, Sub-Department of Hematology, University College Hospital, Ibadan, Nigeria.

Blood, Vol. 28, No. 5 (November), 1966
ISOLATED MALABSORPTION OF VITAMIN B₁₂ IN A NIGERIAN

mm.; mean corpuscular volume (M.C.V.) 102 cu. μ; mean corpuscular hemoglobin (M.C.H.) 31 μg.; platelets 32,000/cu. mm.; white cell count 3500/cu. mm. The red cells showed great anisocytosis, polychromasia and poikilocytosis. Bone marrow aspirate (iliac crest) showed grossly megaloblastic erythropoiesis; large quantities of intracellular iron were seen. Serum vitamin B₁₂ 50 μg./ml. (Lactobacillus leichmannii) and 54 μg./ml. (Euglena gracilis). His hemoglobin electrophoretic type was AA.

Before further investigations were performed, and before the results of serum vitamin B₁₂ assay were known, it was decided to see the effect of a single intramuscular dose of cyanocobalamin, 100 μg. There was a reticulocyte response, reaching a maximum of 23.5 per cent on the seventh day, followed by a rise of the P.C.V. A further intramuscular injection of cyanocobalamin, 100 μg., on the twelfth day was not followed by any reticulocyte response. On the sixteenth day from the first dose the P.C.V. was 28 per cent, the red cells showed slight hypochronmia, and the bone marrow showed normoblastic erythropoiesis, with occasional giant metamyelocytes. Intramuscular folic acid. 15 mg./day for 5 days, and ferrous sulphate 60 mg. t.d.s. by mouth, were given. There was a second small reticulocyte response, reaching a maximum of 4.6 per cent on the fourth day. The P.C.V. continued to rise steadily. He was given a single injection of cyanocobalamin, 1000 μg., and 100 μg. weekly until he was discharged on June 19, 1961, when the P.C.V. was 45 per cent. Since then he has been maintained on 100 μg. every three weeks. The patient felt much improved from the time of the first dose of cyanocobalamin. The diarrhea improved rapidly, and the tongue and pigmentation of his palms returned to normal 10 months after starting treatment (Fig. 2).

Other investigations were performed at this time and one year later (July 1962). There was free acid (15. mEq./L.) in the patient’s resting gastric juice. Following carbachol, 0.25 mg. intramuscularly, 1 μg./1 μc. Co³⁸ vitamin B₁₂ was given by mouth. Eighty per cent of the oral dose was recovered in the feces. The absorption of vitamin B₁₂ was not improved by guanamycin (4 tablets stat., and 2 tablets t.d.s. for 2 days), when 73 per cent of an oral dose was recovered from the feces. A year later, there was still no appreciable absorption of vitamin B₁₂, and absorption was not increased by 100 ml. of normal gastric juice, an extract of fresh pig’s ileal mucosa, or 6 capsules of hog’s stomach; 90 per cent of an oral dose 1 μg./1 μc. Co³⁸ B₁₂ was recovered from the feces in each experiment. No radio-
activity was detected over his liver. The patient’s gastric juice was found to promote vitamin B₁₂ absorption in a patient known to have pernicious anemia, as did the same preparation of hog’s stomach.

On the patient’s first admission, folic acid clearance was found to be rapid, the serum level falling to zero 25 minutes after an intravenous dose of 0.015 mg./Kg. Folic acid absorption was above average (serum concentration 174 mg./ml. 2 hours after an oral dose 0.04 mg./Kg. body weight). Fat excretion was normal (3.5 Gm./day, average of 3 days); total protein 7.2 Gm./100 ml.; albumen 2.24 Gm./100 ml.; alkaline phosphatase 10 King-Armstrong units/ml.; blood urea 43 mg./100 ml. Small bowel barium enema and barium meal with follow-through demonstrated no diverticulae, but there was a persistent narrow segment in the distal ileum. At laparotomy (Professor W. W. Davey), no abnormality of the gastro-intestinal tract could be seen and no explanation was found to explain the radiographic abnormality. Unfortunately, a biopsy specimen of the ileum was not taken. The contents of the small bowel were cultured, but only two organisms were grown, a Staphylococcus and a Diphtheroid bacillus, neither of which were dependent on vitamin B₁₂ for growth. (The patient had not received diaminopyrimidine or any other antibiotics at this time.)

Later Investigation

The patient remained well, receiving injections of cyanocobalamin, 100 µg, every 3 weeks. He was readmitted to hospital on November 26, 1964, for reassessment. After an oral dose of Co⁺⁺ vitamin B₁₂, 1 µg./1 µc., only 1 per cent was recovered in the urine. He was constipated, and the radioactivity could be detected over the area of the cecum and ascending colon. Following a “dulcolax” suppository, the patient had a large bowel action. Some of the feces was not collected, but that which was collected accounted for 56 per cent of the oral dose. No radioactivity could be detected over the liver. In a normal subject 22 per cent and 24 per cent was present in urine and feces, respectively, with radioactivity detectable over the liver. Further investigations at this time were as follows: P.C.V. 45 per cent; serum folic acid activity (Lactobacillus casei) 7.0 µg./ml.; alkaline phosphatase 13.0 King-Armstrong units/100 ml.; serum calcium 8.5 mg./100 ml.; serum inorganic phosphate 4.4 mg./100 ml.; microscopy of feces showed no evidence of tapeworm or other parasites.
Family Studies

The parents of the patient are not alive. His only brother is well and has no symptoms of anemia. His only son, aged 10 years, was found to be a healthy, well-developed boy with no abnormalities on examination. His serum vitamin B12 concentration was 950 μg./ml. (Lact. leichmannii).

Discussion

That the patient’s anemia, hyperpigmentation of skin and glossitis were due to vitamin B12 deficiency has been demonstrated by the grossly megaloblastic erythropoiesis and the low serum vitamin B12 concentration. The therapeutic response to a single dose of 100 μg. cyanocobalamin supports this view, but is not conclusive. When the remission was still incomplete, there was some evidence of an iron deficiency unmasked by the treatment, although the iron in the marrow had been plentiful before treatment. The small reticulocyte response following oral iron and intramuscular folic acid might suggest deficiency of the latter, but folic acid absorption was normal. There was almost no absorption of vitamin B12 from the gastrointestinal tract.

Most known causes of impaired absorption have been excluded. The patient does not have addisonian pernicious anemia, as administration of intrinsic factor from two sources did not improve absorption. Furthermore, the patient’s gastric juice contained free acid and promoted vitamin B12 absorption in a patient known to have pernicious anemia. The deficiency was not due to utilization of the vitamin by intestinal micro-organisms or parasites, as these could not be demonstrated by culture or microscopy, and absorption was not increased by the administration of antibiotics. The intestinal tract was anatomically normal at laparotomy. The patient did not have steatorrhea. The serum calcium was marginally low and is the only evidence suggesting other malfunction of the small intestine. It seems likely in such a patient that a specific factor or factors needed for the absorption of vitamin B12 by the ileum could be deficient, but absorption was not improved by an extract of fresh hog’s ileal mucosa.

The mechanisms of vitamin B12 absorption at the terminal ileum is poorly understood, but there appears to be a factor or factors specifically involved. There has been demonstrated in rats a so-called “releasing factor,” releasing the vitamin from its complex with intrinsic factor.10,11 Fluoroacetate blocks the absorption of cyanocobalamin by rats but not the absorption of coenzyme B12, suggesting that factors in the intestinal wall convert the vitamin to the coenzyme during absorption, and that this is a necessary step in absorption.12,13

Deficiencies of such factors have been postulated by Herbert, who described five patients with apparently isolated vitamin B12 malabsorption,14 and in patients with familial malabsorption.15 Movitt et al.16 described two patients with megaloblastic anemia due to malabsorption of vitamin B12 whose absorption was somewhat improved by the addition of human intestinal juice. Similar results have been reported17 in a partially gastrectomised patient, but this man had other absorption defects as well. There are reports of transient selective malabsorption of vitamin B12 in an adult,18 and in a nutritionally deficient subject,19 by Schloesser and Schilling.19 Similarly, malabsorption of vitamin...
B₁₂, corrected by intrinsic factor, which reverted to normal after three weeks treatment with folic acid, was recorded in a 23-year-old male with vitamin B₁₂ deficiency due to anticonvulsant drugs.²⁰

The age of our patient and the absence of proteinuria make the diagnosis of hereditary disease unlikely. The condition does not appear to be transitory, as malabsorption is unchanged after four years. The illness seems to have started with diarrhea, with blood and mucus, which suggests that an infective incident caused the disease.

The relationship between megaloblastic anemias and disturbed pigment metabolism are not understood. Melanin production could be reduced by the interruption of the hydroxylation of phenylalanine by folic acid antagonists.²¹ Amethopterin acts by inhibiting folic acid reductase, which also reduces the pteridine cofactor of the hydroxylation reaction.²² These observations may be relevant to the hypopigmentation observed in kwashiorkor, in which there is frequently folic acid deficiency and also interference with the hydroxylation of phenylalanine.²³ There is evidence that the flagellate *Crithidia fasciculata* is able to convert folic acid 2-C¹⁴ to unconjugated pteridines, and hence to the hydroxylation cofactor, biopterin,²⁴ but in man a similar conversion of H³-folic acid could not be demonstrated.²⁵

In patients with pernicious anemia, serum biopterin remains normal,²⁶ but in the most severe folic acid deficiency, serum biopterin may be considerably raised.²⁷ From what is known at present, it is not possible to explain hyperpigmentation observed with vitamin B₁₂ deficiency.

**Summary**

A Nigerian patient is described with megaloblastic anemia due to vitamin B₁₂ deficiency. The deficiency resulted from malabsorption of the vitamin, but no other abnormal functioning of the gastrointestinal tract could be demonstrated. The patient did not have Addisonian pernicious anemia. He had remarkable hyperpigmentation of the skin, especially of the palms of the hands. What is known of possible connections between megaloblastic anemias and melanin metabolism cannot explain this hyperpigmentation.

**Sommaio in Interlingua**

Es describite un patiente nigerian con anemia megaloblastic causate per carentia de vitamina B₁₂. Le carentia resultava ab malabsorption, sed nulle altre anormalitate functional del vias gastrointestinal esseva demonstrabile. Le patiente non habeva anemia perniciose de Addison. Ille manifestava un remarkabile hyperpigmentation del pelle, particularmente in le palmas manual. Lo que es cognoscite de un possibile connexion inter le anemias megaloblastic e le metabolismo de melanina non suffice a explicar iste hyperpigmentation.

**References**


Isolated Malabsorption of Vitamin B12 Causing Megaloblastic Anemia and Hyperpigmentation in a Nigerian: Report of Case

E. J. WATSON-WILLIAMS and A. F. FLEMING

Updated information and services can be found at:
http://www.bloodjournal.org/content/28/5/770.full.html

Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml