Thalassemia Intermedia, with Iron Overload, Cardiac Failure, Diabetes Mellitus, Hypopituitarism and Porphyrinuria*

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A patient of Sicilian ancestry who had thalassemia intermedia was seen intermittently from the time he was six to forty-one years of age. He had inherited at least one allele for the "high hemoglobin F, normal hemoglobin A_2" type of β-thalassemia. Splenectomy had been carried out during his childhood; he was also given iron medication orally and deliberately ate iron-rich foods. Although he had had only 6 units of blood by transfusion, by the age of forty-one severe iron overload had developed, with the clinical picture of hemochromatosis, including skin pigmentation, liver disease, cardiac failure and multiple endocrine deficiencies. Desferrioxamine was used to demonstrate the degree of iron load and in an attempt to reduce it. The anemia was further complicated by folic acid deficiency and improved with folic acid therapy. Porphyrinuria and urinary excretion of dipyrroles were additional features, probably due to the severe degree of ineffective erythropoiesis. The pathologic mechanisms underlying these various complications are discussed. The danger of administering iron orally to such patients is emphasized.

THALASSEMIA intermedia is a useful phrase to describe a clinical form of intermediate severity. It may represent homozygous thalassemia in mild form or be a particularly severe expression of the heterozygous state. It is an appropriate diagnosis for the patient described herein. As indicated in the title, the complications in this patient included cardiac failure, diabetes mellitus and hypopituitarism, as well as hepatic dysfunction all presumed to be secondary to iron overload.

Iron overload in thalassemia was first recognized by Whipple and Bradford [*1*] and indeed Cooley's anemia has been referred to as "hemochromatosis in the child" [*2*]. Such complications have become increasingly common in severe thalassemia major in childhood since survival is prolonged by blood transfusion and antibiotic therapy, and intractable cardiac failure is now a familiar terminal event [*3–5*]. Endocrine complications are less well documented. It is of particular interest that the patient here described received very few blood transfusions and his iron overload therefore must have been acquired by intestinal absorption. Marked porphyrinuria was an additional feature in this case, and the urine also consistently contained another brown pigment, probably a dipyrrole.

CASE REPORT

A forty-one year old man of Sicilian ancestry was admitted to the Buffalo Veterans Administration Hospital in December 1964 with the chief complaints of increasing shortness of breath and swelling of the legs for two months.

His first hospital admission was in 1930 at the age of six years, when he entered a pediatric hospital because of "adenoids and large tonsils." It was recorded that birth and development up to the age of one year had been normal. Thereafter, he had been "chroni-

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TABLE I
HEMATOLOGIC DATA

Date	Age (yr.)	Red Blood Cells × 10^6 (per cu. mm.)	Hemoglobin (gm./100 ml.)	Hematocrit (%)	Platelets × 10^3 (per cu. mm.)	Reticulocytes (%)
1930	6	4.59	7.6	...	164	...
1931	7	4.23	10.9	...	112	2.0
1931	7*	5.15	12.1	...	266	1.2
1932	8	4.03	8.9	...	620	...
1933	9	3.50	10.9	...	547	...
1940	17	4.25	12.9	...	...	...
1945	22	3.22	9.4	31	...	5.2
1950	27	4.10	10.7	39	...	...
1960	37	4.10	9.3	...	383	...
1964†	41	...	6.0	20	620	4.0
1965‡	41	3.70	10.0	33	...	3.7

* After splenectomy.
† December.
‡ July.

cally run down" and was unable to keep up with other boys at play. Dark-colored morning urine had been noted. He was described as listless and icteric, appeared to be poorly nourished, and the spleen was enlarged to the level of the umbilicus. Laboratory data are reported in Table I. Although the records are incomplete, marked anisocytosis and poikilocytosis of the erythrocytes were reported and fragility studies showed increased osmotic resistance. Normoblasts comprised 10 per cent of the total nucleated cell count. The urine was negative for bile and urobilinogen. On discharge, ferric ammonium citrate (12 cc. of 10 per cent solution, three times a day) and copper sulfate were prescribed and he continued to take the iron mixture for an unknown, but possibly prolonged period.

The patient was next seen in 1931 because of anorexia, nausea, vomiting, abdominal distention and jaundice. The icterus index was 75 and he was anemic. The diagnosis of "an atypical type of congenital hemolytic anemia" was made and splenectomy was performed. He received 6 units of blood by transfusion during surgery. This was his first and only blood transfusion until the age of forty-one. The spleen was described as "a chronic splenic tumor in some respects resembling the picture of so-called Banti spleen, differing from that in a smaller amount of fibrosis of stroma." After splenectomy the red blood cell and platelet counts increased and normoblasts rose to 47 per cent of the total nucleated cells.

The patient was first seen by one of us (S.V.) in 1932 and the diagnosis of Cooley's anemia was made. In 1933 he was "feeling pretty well" and attending school regularly, but experiencing periodic attacks about one week in duration during which marked apathy occurred, associated with yellow coloring of the skin.

In 1940 at the age of seventeen, the patient was in his third year of high school and participating actively in sports. In a photograph taken about that time his features were normal, with no suggestion of the mongoloid facies, prognathism or malocclusion which are seen in childhood Cooley's anemia. It was noted that at times there was faint scleral icterus and that the liver was palpable. Pubic hair was scanty, with a female distribution. Oral administration of iron had definitely been discontinued by this time, but it was uncertain whether the patient had been taking iron consistently over the previous ten years. However, he continued to eat large quantities of iron-rich foods, such as liver and spinach.

In September 1944 the patient was inducted into the U.S. Army. On physical examination at induction the splenectomy scar was the only abnormality reported. The liver was not palpable. During the fourteen weeks of basic training he had sharp pain in the lower part of the abdomen associated with exercise, particularly long hikes. Because of this complaint and a "cold" he was admitted to an Army hospital in January 1945. He was slightly jaundiced and again no hepatomegaly was noted. Blood examination on admission revealed anemia (Table I) with anisocytosis, poikilocytosis, polychromasia and target cells in the blood film and increased osmotic resistance of the erythrocytes. The icterus index was 19 and the serum bilirubin was 1.8 mg. per 100 ml. Roentgenograms of the skull were reported as showing slight thickening of the diploe with thinning of the inner and outer tables. The long bones were roentgenologically normal. Because of the diagnosis of Cooley's anemia, he received an honorable discharge from the service.

The patient was next seen in 1950. The blood film showed target cells, with many orthochromatic

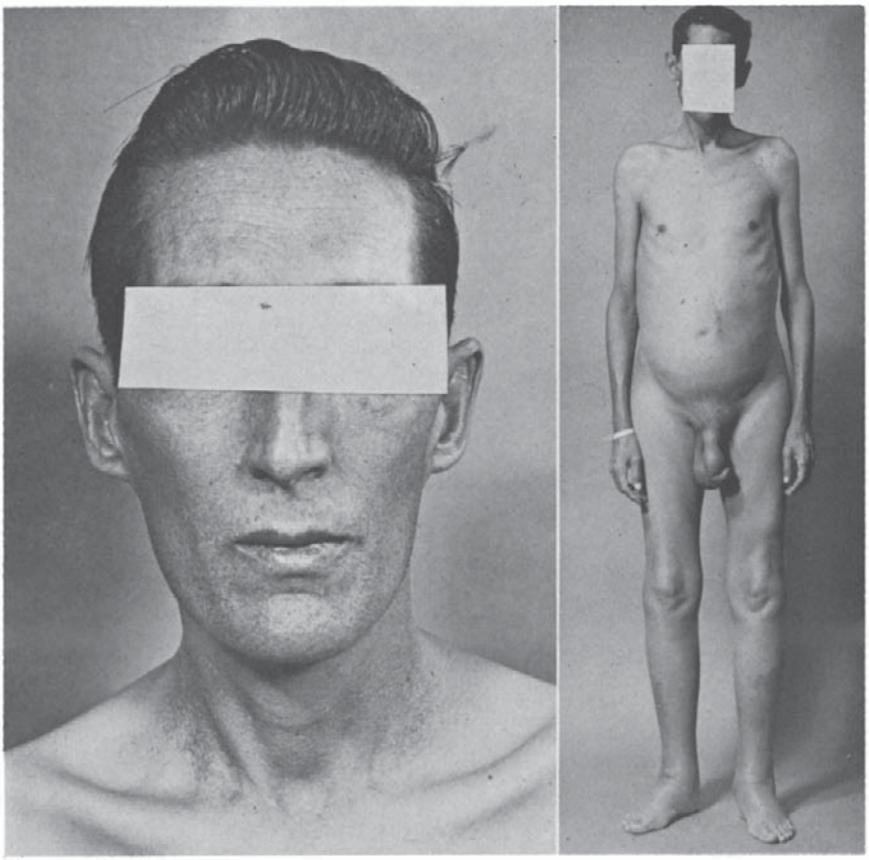

FIG. 1. Patient J.G., showing diffuse and mottled facial pigmentation and youthful appearance.

FIG. 2. Patient J.G. on admission to hospital in December 1964, with cardiac failure and severe edema. Sparse body hair and splenectomy scar can also be seen.

normoblasts and increased numbers of platelets with many giant forms. Aspiration of the bone marrow revealed a very cellular marrow with a tremendous increase in erythropoiesis. The myeloid:erythroid ratio was 0.2.

In 1960, while living in California, he was seen at a hospital because of discomfort in the lower right quadrant of the abdomen. His skin was reported to be slate gray in color, there was scleral icterus, and the liver edge was firm and palpable at the iliac crest. He was found to be anemic and the blood film showed macrocytes, microcytes, target cells and many nucleated red cells. The serum bilirubin was 2.5 mg. per 100 ml. with 2.3 mg. indirect reacting. The serum total protein was 7.3 gm. per 100 ml., albumin 3.1 and globulin 4.2 gm. per 100 ml. The serum alkaline phosphatase was 22 King-Armstrong units, prothrombin time was 20 per cent of normal, and the thymol turbidity was 7.6 units. Serum iron was 299 μg. per 100 ml. and the total iron-binding capacity was 595 μg. per 100 ml. The tentative diagnosis of thalassemia intermedia with secondary hemochromatosis was made and liver biopsy was advised, but refused.

Since that time the patient noticed gradually increasing darkening of the skin and, for one year, loss of libido and thinning of the axillary and pubic hair. Swelling of the legs started two months before admission and increased rapidly. For the month before admission he experienced nocturia, increased sweating and dyspnea on exertion, and orthopnea developed. He complained of vague discomfort in the lower part of the abdomen, particularly at night, and periodic "spasms" of the calf muscles and hands which were relieved by massage. There was no history of alcoholism.

On examination, the patient was a thin, ill-looking man with remarkably intense brown-gray color of the skin, particularly of the exposed areas. The distribution of the pigmentation was somewhat irregular with a mottled appearance (Fig. 1) and his features were lean and aquiline. He looked younger than his chronologic age. Facial and body hair were very sparse, with female distribution of pubic hair (Fig.

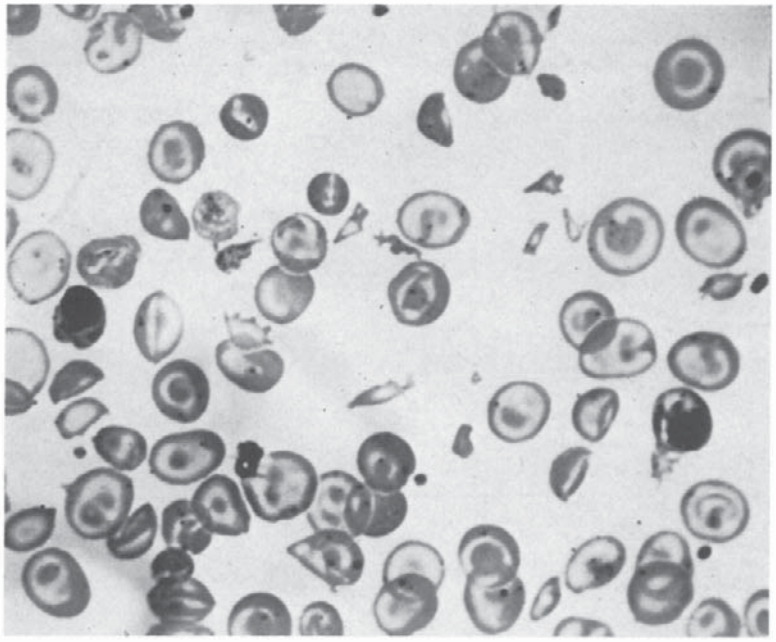

FIG. 3. Blood film with very marked anisocytosis and poikilocytosis, hypochromia and target cells, inclusion bodies (Howell-Jolly bodies and iron granules), cellular fragments and normoblasts. Wright's stain, original magnification × 1,350.

2). There was scleral icterus, and slit-lamp examination revealed bilateral early subcapsular cataracts. The patient was very breathless. The pulse rate was 120 per minute and the blood pressure 120/70 mm. Hg. The heart was enlarged, a left ventricular heave was palpated, and a gallop rhythm and a grade 2/6 ejection systolic murmur were heard at the left sternal border. The jugular venous pressure was raised, and there were signs of a right-sided pleural effusion. The liver was very large, extending to below the umbilicus in the midline, and an enlarged Riedel's lobe extended to the right iliac crest. There was a left paramedian scar from previous splenectomy. The testes were small and soft. There was slight ascites and severe pitting edema of the legs extending into the penis and scrotum (Fig. 2).

The hemoglobin was 6 gm. per 100 ml., hematocrit 20 per cent and reticulocyte count 4 per cent. Of the nucleated cells, 71 per cent were normoblasts, and the corrected white cell count was 13,000 per cu. mm., with a normal differential except for 3 per cent eosinophils. The direct total eosinophil count was 782 per cu. mm. The blood film showed marked anisocytosis and poikilocytosis with hypochromia and occasional target cells (Fig. 3), and staining for iron [6] revealed many siderocytes and sideroblasts. Staining for fetal hemoglobin [7] demonstrated uneven distribution with variation in the intensity of staining from cell to cell. (Fig. 4).

Further hematologic data are summarized in Table II. Bone marrow aspiration showed erythroid hyperplasia with megaloblastic changes, principally giant band neutrophils. The Diagnex® blue test and direct examination of fasting gastric juice were negative for free hydrochloric acid without stimulation. Serum folic acid was low; the vitamin B_{12} level was normal (Table II). Hemoglobin electrophoresis did not reveal any abnormal hemoglobins. Hemoglobin F was greatly increased [6] and hemoglobin A_2 was normal (Table III). The plasma hemoglobin was 57 mg. per 100 ml.

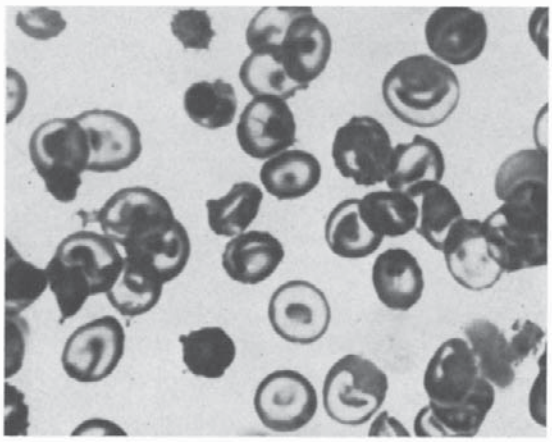

FIG. 4. Blood film stained by the Kleihauer and Betke method [7] for fetal hemoglobin showing that it is irregularly distributed from cell to cell and is present in normoblasts. Original magnification × 1,350.

TABLE II
SPECIAL BLOOD STUDIES

Test	Results
Serum iron (μg./100 ml.)	135
Serum total iron-binding capacity (μg./100 ml.)	150
Plasma hemoglobin (mg./100 ml.)	57
Plasma haptoglobin (mg./100 ml.)	15.6
Serum folic acid (mμg./ml.)	
On admission (12/64)	4.9 (normal range 7–27*)
After lapse of therapy (10/65)	2.0 (normal range 3–27†)
Serum vitamin B_{12} (μμg./ml.)	
12/64	284 (normal range 200–350*)
10/64	987 (normal range 150–1,500†)
Serum bilirubin (mg./100 ml.)	7.8 (6.1 indirect)
Serum total protein (gm./100 ml.)	6.8 (albumin 3.1, globulins 3.7)
Prothrombin time (sec.)	21.5 (control 12.5)
SGOT(units)	85
SGPT (units)	41
LDH (units)	>2,000

* Bio-Analytical Laboratories, Inc., Albany, New York.
† Courtesy of Dr. K. B. Taylor, Stanford University School of Medicine.

The urine contained no protein or sugar, and no cells or casts were seen in the spun sediment. It was almost invariably a rich deep brown. The fasting blood sugar was 106 mg. per 100 ml., blood urea nitrogen 25 mg. per 100 ml. and creatinine 1.5 mg. per 100 ml. Serum sodium concentration varied from 126 to 135 mEq. per L. and potassium from 4.3 to 6.0 mEq. per L. Serum bilirubin was increased to 7.8 mg. per 100 ml. with 6.1 mg. indirect reacting, and urinary urobilinogen was increased. Total serum protein was 6.8 gm. per 100 ml. with a reversal of the albumin:globulin ratio (3.1:3.7). The one-stage prothrombin time was 21.5 seconds (control 12.5 seconds). Alkaline phosphatase, serum glutamic oxalic (SGOT) and glutamic pyruvic transaminase (SGPT) levels were slightly elevated. The lactic dehydrogenase was increased to >2,000 units.

A roentgenogram of the chest on admission confirmed the presence of cardiac enlargement and a small right pleural effusion. Roentgenograms of the upper gastrointestinal tract gave no evidence of esophageal or gastric varices. The stomach and second portion of the duodenum were displaced to the left and the hepatic flexure was displaced medially and inferiorly by the large liver. The colon was normal in appearance on roentgenogram. The skull was normal roentgenologically but there was some demineralization of the femurs and of the bones of the hands.

A punch biopsy specimen of the skin showed excess melanin deposited in the basal layer of the epithelium but no stainable iron. Although it was desired to carry out an aspiration biopsy of the liver, this was not done because of the prolonged prothrombin time, which was not significantly altered by vitamin K therapy. However, on a subsequent admission primarily for dental extractions, a gastric biopsy specimen was obtained and the report was as follows:

TABLE III
HEMOGLOBIN STUDIES IN PATIENT AND RELATIVES

Subject and Sex	Hemoglobin A_2 (%)	Hemoglobin F (%)	Diagnosis
J.G. (propositus), M	1.1*	44.0	Thalassemia intermedia
R.G. (sister), F	Normal†	1.7	Normal
S.A. (maternal aunt), F	Normal†	1.9	Normal
L.S. (maternal aunt), F	Normal†	9.3	Thalassemia minor

* Determined by starch block electrophoresis.
† Estimated by paper electrophoresis.

"section shows a segment of gastric mucosa, the glandular epithelium being diffusely and markedly infiltrated by golden brown pigment, which on special stain is identified as iron."

SPECIAL STUDIES AND COURSE

Family Investigation. The patient's parents were born in Sicily and died in Buffalo, New York, where the patient was born. He was not aware of any history of anemia, jaundice or other symptoms suggesting thalassemia in his parents or in any other member of the family. Few living members were accessible for testing, but two maternal aunts and the patient's only sibling, an unmarried sister, were seen (Table III). No abnormality was detected in their blood films, and the hemoglobin electrophoresis patterns were normal, with no increase in the A_2 fraction. One aunt showed 9.3 per cent hemoglobin F by the alkali denaturation method [6], suggesting that she is a heterozygous carrier of a gene for the "high-F, normal-A_2" type of β-thalassemia.

Treatment and Hospital Course. The initial diagnosis was thalassemia major or intermedia, complicated by iron overload and associated cardiac failure and hepatic disease. An additional complication was secondary megaloblastic anemia, thought to be due to relative folic acid deficiency, as confirmed by the subsequent report of low serum levels of folic acid. At first treatment was directed towards reversal of the cardiac failure by administration of digitalis and mercurial and thiazide diuretics. There was little improvement until a marked diuresis followed blood transfusion (3 units of packed red cells) and continued during treatment with hydrochlorothiazide and triampterene. The patient's initial weight was 143 pounds and it fell after diuresis to 105 pounds, remaining at about this level over the subsequent months.

The changes in hematologic findings are

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