MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

24 September 1964

THE HYPOCHROMIC MICROCYTIC ANEMIC STATES

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[redacted]

This 34-year old [redacted] female was referred to the hematology clinic, having previously been seen, with a 6-month history of recurrent and progressive low back pain and progressive weakness. She had noted ease of fatigue for some years but had been able to carry on her usual life as housewife. She was referred to us because of evidence of osteoporosis on bone films as well as evidence of an apparent anemia. The referring diagnosis was multiple myeloma. The remainder of the history at this time was quite unremarkable. Past history was of interest in that the patient had had two children without difficulty and had had an anemia at the time of each delivery (some 16 and 14 years before). She had been treated with iron at that time but was unfamiliar with the results of such therapy. Past history was also of interest in that she had had a hysterectomy six years ago.

Family history revealed that her mother and one sister also had an anemia. The type was unknown by the patient.

Physical examination revealed a well developed, slightly obese white female, with normal vital signs. The only significant finding was that of a spleen easily palpable 2 cm beneath the left costal margin. There was no bony tenderness, no lymphadenopathy and no abnormal findings.

Laboratory examination revealed a hemoglobin of 9.6 grams with a hematocrit of 33 vols.%. The white count was 10,900 with a normal differential. An occasional nucleated red cell was seen in the peripheral blood. The platelets were 425,000. The blood smear demonstrated hypochromia, microcytosis, marked aniso- and poikilocytosis, occasional basophilic stippling of the red cells, a considerable targeting and a reticulocytosis of 5.2%. The serum iron was 224 micrograms% and the total was 268 micrograms%. Bone marrow aspiration demonstrated erythroplastic hyperplasia of the neuroblastic type with evident increased iron stores. Fetal hemoglobin was 3.5% and A_2 hemoglobin was 5.6%.

Comment: The presence of osteoporosis and anemia here clinically suggested multiple myeloma and the past history of a hysterectomy raised the question of osteoporosis secondary to it. A final historical review revealed that the patient's grandmother was from Albania and that the historical heritage was quite in keeping with the Mediterranean localization of this rather characteristic thalassemia minor.

[redacted]

This 38-year old [redacted] male [redacted] of Irish-German descent was admitted to the [redacted] for the first time on [redacted], 1961, with weakness and fatigue and a history of recurrent thrombophlebitis. His history apparently dated back to [redacted] 1960 at which time his constitutional symptoms led him to consult his family physician who made a diagnosis of an anemia. He was treated with a broad variety of hematinics as well as transfusion. He was referred to another hematologic center where splenomegaly was identified, and in [redacted] of 1961 a splenectomy was performed for a hemolytic anemia. Within three weeks of splenectomy the patient developed thrombophlebitis affecting the deep veins of his extremities and sustained at least two episodes of pulmonary embolism with evidence of infarction, and was then referred to the [redacted] for lack of funds.

Positive physical findings on admission were obesity; pallor of the conjunctivae; thrombophlebitis affecting the superficial veins of both upper extremities; deep phlebitis affecting both lower extremities, with edema and a positive Homan's sign; rales at the left lung base; and a well-healed splenectomy scar. No definite hepatomegaly or lymphadenopathy was present.

Hematologic studies were as follows: RBC 3,850,000; hematocrit 25%; hemoglobin 6.7 gms.; reticulocyte count 1.8%; WBC 24,000 with normal differential; platelet count 485,000. Peripheral smear revealed hypochromia, microcytosis, target cells, anisocytosis, poikilocytosis. RBC's of the peripheral smear contained numerous round deposits, staining positive for iron. A bone marrow revealed normoblastic hyperplasia and iron stores were increased. Serum iron was 340 micrograms with total iron binding capacity of 361 micrograms %. Hemoglobin electrophoresis was AA type, starch block electrophoresis showed no fetal hemoglobin and 1.5% A-2 hemoglobin. RBC fragility was normal. Coombs test, Ham's test, Donath Landsteiner Tests were negative. Streptococcus MG and cold agglutinins were absent. Stool guaiacs were negative for occult blood. LE cell agglutinations were negative, urine was negative for hemosiderin cells. Complete GI X-ray surveys were negative for any findings. Long bones, skull, spine, and pelvis X-rays showed no defects. Radioisotope studies were as follows: Fe-59 incorporation in red cells was 55% with organ counting showing an increased deposition of iron in the liver; Cr-51 RBC survival T $\frac{1}{2}$ (normal 27-32 days), a tryptophane loading test was normal.

A presumptive diagnosis of potential pyridoxine responsive anemia was made. The patient was begun on oral pyridoxine and a reticulocytosis to 12.6% was achieved by the 8th day of therapy. Subsequently a rise in hemoglobin and hematocrit occurred, carrying his hemoglobin from 7 grams to a peak of 12 grams. The iron deposits in the marrow remained increased in spite of pyridoxine therapy. The serum irons also remained consistently high with almost complete saturation of the total iron binding capacity. Radioisotopic studies done following pyridoxine therapy, however, revealed a normal incorporation of Fe-59 in the red cells and a normal Cr-51 survival time. The peripheral blood smear after pyridoxine therapy showed no significant change. On four separate occasions

the patient has been withdrawn from pyridoxine with a resultant fall in hemoglobin to levels of 6 to 7 grams. Reinstitution of pyridoxine resulted in a reticulocyte response and a rise in red cell values. At no time did his hemoglobin rise above 12 grams on pyridoxine alone. In an attempt to reduplicate the Gardner study, added testosterone and crude liver extracts were also employed which transiently did increase his hemoglobin well beyond the 12 gram level. Reduplication with these agents has not been carried out as yet.

His clinical course has somewhat limited therapeutic manipulation since it has been punctuated by a series of episodes of thrombophlebitis secondary to his high platelet count, a result of his splenectomy. He is, however, at the present time asymptomatic and is still being studied on an out-patient basis.

Of interest is that this patient has a brother who has a very similar anemia of lesser degree and who has been well maintained in a normal hemoglobin range on pyridoxine.
Comment: This is a rather classic clinical presentation on a pyridoxine responsive anemia, often diagnosed as a mild hemolytic anemia and often associated with significant postsplenectomy thrombocytosis and the resultant problems secondary to such platelet increases.

[redacted]

This 79-year old [redacted] male was in good health until approximately 6 years ago when he had a cerebrovascular accident. Since that time his ambulatory activity was quite limited and he was unable to leave his house. He, however, apparently had eaten a good diet in spite of this and was apparently stable until approximately 2 months prior to his admission, at which time fatigue and a marked decrease in exercise tolerance were noted by the family. He was seen by his family physician who noted a hemoglobin of 7.5 grams and a white count of 3,500. Retrospectively the patient's wife was aware that he had been anemic ever since his cerebrovascular accident. There was no toxic exposure.

Physical examination revealed a thin white male with essentially normal vital signs. The pertinent positive physical findings included some rales at both bases and a liver edge that was palpable 3 cm beneath the right costal margin and a spleen tip easily palpable at the left costal margin.

Laboratory study revealed an initial hemoglobin of 6.1 grams, a hematocrit of 18.5. His white count was 2,650 with 42 segs, 14 bands, 42 small lymphocytes, 2 monocytes. His platelets were 137,500 and retics 1.7%. Peripheral smear demonstrated marked aniso- and poikilocytosis, some very minimal polychromatophilia and significant evidence of occasional stippled red cell and an occasional nucleated red cell. Hypochromia and some microcytosis was apparent. Bone marrow aspiration demonstrated a moderate erythrocytic hyperplasia with marked evidence of increased iron stains with a great number of sideroblasts present. The patient was given 2 units of whole blood and antibiotics in order to manage xray evidence of an infiltrate in the right lower lobe. His response was not complete, but his family was anxious to take him home and for discharge. We elected to begin him on a trial of pyridoxine at home in order to evaluate his hematologic response. Six days following his discharge the patient was again brought to the emergency room, having had a shaking chill and apparently rapidly slipping into coma at home. Physical examination revealed a comatose patient who was breathing very deeply. His lungs were clear to percussion and auscultation in the emergency room but by the time the patient reached the ward he was

noted to have pulmonary edema. The remainder of the physical examination was essentially as before except that the patient was in deep coma and there were absent deep tendon reflexes. The patient was treated supportively with IPPB, antibiotics, vasopressors and a tracheostomy, but expired some 12 hours after admission. The major autopsy finding was a bronchopneumonia.

Impression: This patient demonstrated the morphologic evidence of an iron-loading anemia or of a sideroachrestic anemia of Heilmeyer. At autopsy massive iron infiltration in the liver was apparent. (No fibrosis was present.)

[redacted]

First [redacted] admission for this 39-yearold [redacted] male laundry worker who entered on [redacted]/64 with a 2 week history of a constant periumbilical dull non-colicky pain and difficulty swallowing. He had experienced mild constipation for 4 weeks PTA. The patient had been employed during the months of [redacted] and [redacted] in a lead factory in which he handled lead dust. He was required to wear a mask but stated that after work he would have to clean the lead dust from his nose. He was checked twice while there with an ear lobe retic count and was told it was "normal". Toward the end of [redacted] he developed severe bitemporal headache and had to quit work; the headache went away and he returned to laundry work, but was forced to seek medical aid when the abdominal pain occurred. The "difficulty in swallowing" appeared to be anorexia - he had to force the food down but had no regurgitation and the food "stuck" in his mouth. No past history of anemia, melena, hematemesis, ulcer symptoms. Physical exam revealed BP 120/80, P 80, R 16, T 98°. The only positive physical f nding was a lead line at the gingival margins and extremely poor teeth and oral hygiene. No evidence of neuropathy or encephalopathy.

The dx of lead poisoning was made on the basis of history, hypochromic microcytic anemia with basophilic stippling, and urine lead of .363 mgm/li. His abdominal symptoms cleared spontaneously before treatment with ca versonate. He was given a 5-day course of 2 gms ca versonate per day and discharged to the Best 0 Life Lead company physician for followup.

Lab: Hgb 9.0; Hcrt 29; WBC 9000; platelets 457,500; retics 7.8 ⟶ 6.9 ⟶ 2.8
Urine: Strongly plus copropoenphyrin - qualitative
Urobilinogen 2+
Trace albuminuria - 1 of 5 urinalyses
Stool guaiac neg.
BUN 24 ⟶ 18
Creatinine 1.4
Bilirubin 0.4/1.4 ⟶ 0.8
Urine lead: #1 - Before Rx - .363 mgm/li
#2 - After 1 day Rx - .42 mgm/li
#3 - After 2 days Rx - .75 mgm/li
#4 - After 4 days Rx - 3.45 mgm/li
Coproporphyrin 103 micrograms/l.
Porphobilinogen 10.0 micrograms/l.

Comment: This is a classic case of lead intoxication.

	Serum Iron (µgm%)	Total Iron Binding Capacity (µgm%)	% of Saturation	Plasma Iron Turnover mgm/day/gm Hb	Iron Stores	Free Erythrocyte Protoporphyrin
Normal Values	60-140	270-350	25-33%	0.061		32 µgm/100 ml RBC's
Iron Deficiency Anemia	D	I	D> 10%	N or I	D	High
Thalassemia	I	N	I	I	I	Normal
Pyridoxine Response Anemia	I	N	I	I	I	D
Sideroachrestic Acquired	N-I	D	D	N clearance	I	Slt D
Anemia of Heilmeyer Hereditary	I	N	D	N	I	Low
Congenital Atransferrinemic Anemia	Almost Absent	Almost Absent	-----	Very Rapid Plasma Clearance 5 minutes	I esp. liver	
Hypocupremic Syndrome	D	I	D	Normal	N	Normal
Lead Intoxication	N	N	N	N	N-I	N
Anemia of Chronic Infection, Uremia, etc.	D	D	D > 10%	N	I	I Slt

I = Increased
D = Decreased
N = Normal

TABLE I

FACTORS AFFECTING RELIABILITY OF SERUM IRON OR BINDING CAPACITY DETERMINATIONS

1. Hemolysis - frank hemolysis where serum Hb exceeds 25 mgm%.
2. Lipemia - generally can be avoided by obtaining fasting specimen. If lipemia present, the determination can be performed by cold centrifugation of the serum in plastic tubes followed by needle point puncture of tube to yield outflow of clear serum below the fat layer.
3. Ferritinemia - secondary to massive liver necrosis.
4. Parenteral iron therapy - which may circulate for days or weeks; especially the iron complexes such as saccharates.

TABLE II

Drug	#	RESPONSE TO IRON THERAPY Hemoglobin (gm%) Initial	Final	Increase	Days Rx	Increase Per Day gm%
Proferrin IV	14	4.9	10.9	6.0	18	0.33
Imferon IM	14	5.0	10.4	5.4	20	0.27
Ferrous Gluconate 220 mgm/day	14	4.9	10.2	5.3	23	0.23

from J. Pritchard

TABLE III

IRON ABSORPTION TEST

A rise in serum iron occurs 2-4 hours after the ingestion of an oral dose of iron:

Procedure:

1.) Fasting serum iron
2.) Four tablets of oral iron (ferrous gluconate) are given fasting.
3.) Repeat serum iron at 3 hours.

Positive Test:

Rise in serum iron over 60 µgm% presumptive positive (normal) and over 100 µgm% is considered normal.

Decreased Values:

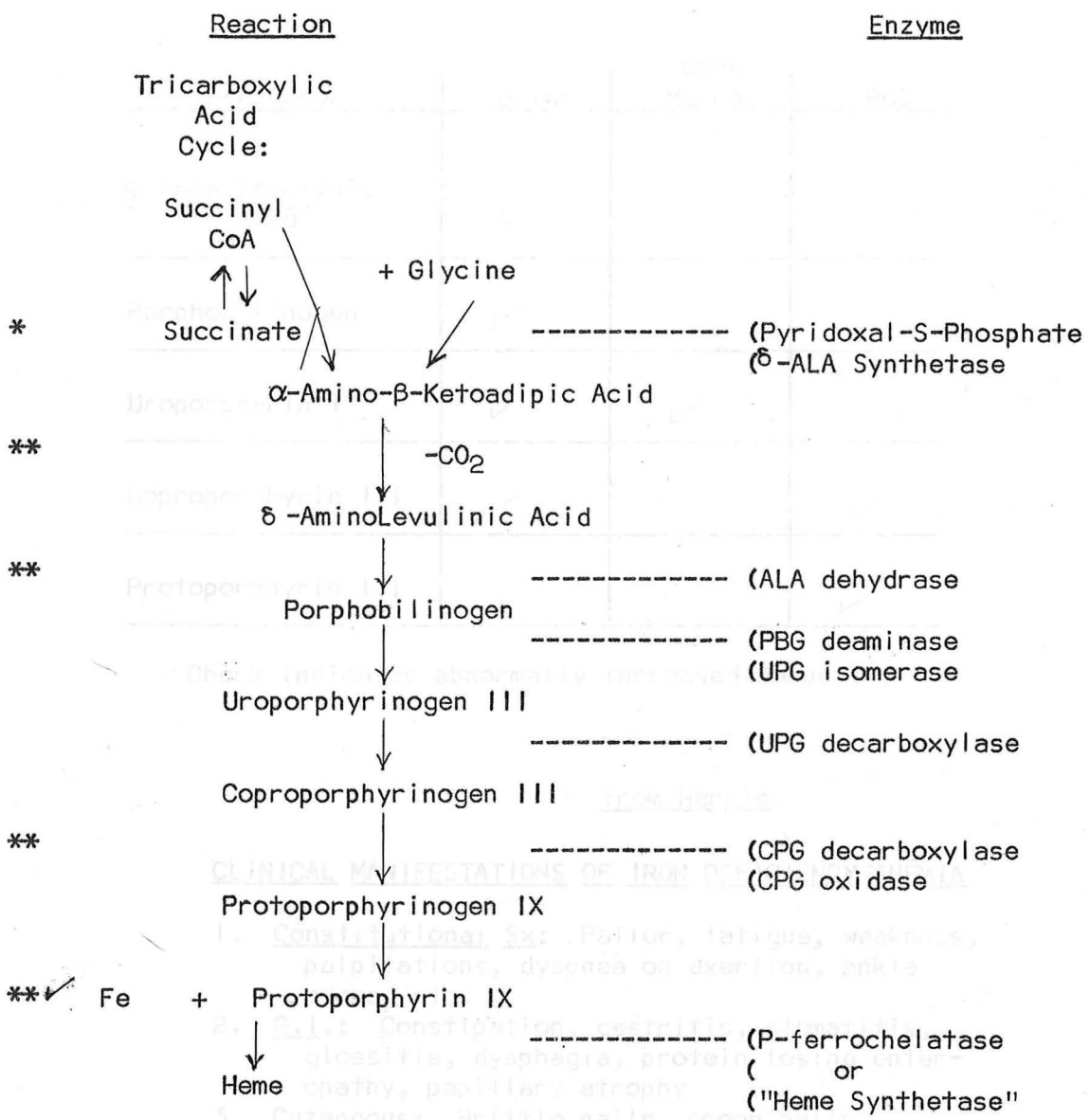
1.) Malabsorption of Fe
2.) Abnormal intestinal motility
3.) Anemia associated with Chronic Infection and/or Uremia

Factors Affecting Results:

Multiple including rate of absorption, rate of plasma iron clearance, etc.

TABLE IV

PATHWAY OF HEME SYNTHESIS



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* B6 Responsive Site
** Sites of Lead Interference
✓ Site of Copper Effect

from Remington, etc.

EFFECT OF LEAD POISONING ON PRESENCE OF HEME PRECURSORS

Precursor	Urine	Bone Marrow	RBC
δ-AminoLevulinic Acid	✓		
Porphobilinogen	✓		
Uroporphyrin I	✓	✓	
Coproporphyrin III	✓		✓
Protoporphyrin III			✓

Check indicates abnormally increased amount.

from Harris.

CLINICAL MANIFESTATIONS OF IRON DEFICIENCY ANEMIA

1. Constitutional Sx: Pallor, fatigue, weakness, palpitations, dyspnea on exertion, ankle edema, etc.
2. G.I.: Constipation, gastritis, stomatitis, glossitis, dysphagia, protein losing enteropathy, papillary atrophy
3. Cutaneous: Brittle nails, spoon nails, cheilosis
4. Osseous: "Hair-on-end" skull changes
5. R.-E.: Splenomegaly
6. Gyn.: Disturbed menses
7. CNS: Papilledema, "pseudo-brain tumor", peripheral neuropathy
8. Diboba: edematous, depigmentation syndrome
9. Plummer-Vinson Syndrome: dysphagia and post cricoid esophageal stricture, etc.
10. Absent cytochrome oxidase

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