MEDICAL GRAND ROUNDS
PARKLAND MEMORIAL HOSPITAL
OCTOBER 17, 1957
[Megaloblastic and Macrocytic Anemia]

Case 1 [redacted]

This 69 year old white male was admitted [redacted]-56 with complaints of weakness, orthostatic dizziness and anorexia of two to three years duration but more marked for the nine days prior to admission. A history of chronic alcoholism with dietary neglect antedated this admission for 20 years.

Physical examination revealed a scaling rash over the upper body, hepatomegaly (6 cms below RCM in MCL), spleen not palpable and intact neurological examination. Upper G.I. series showed a deformed duodenal bulb but no active ulcer crater. Barium enema was not remarkable. Liver function studies were not deranged. Stools were consistently negative for occult blood. A liver biopsy was interpreted as displaying Laennec's cirrhosis.

Hematological data: Hgb. 5.2 gms., RBC 1.89, Hct. 19.19 with MCV 101.5 and MCHC 27.1. A bone marrow was interpreted as showing erythroid hyperplasia with a mixed megaloblastic-normoblastic state. The patient was started on folic acid 5 mgms. tid and the Hgb. subsequently showed: 11/12-Hgb. 6.5 with retic. of 9.1%, 11-14 hgb. 7.3 with retic. of 9.7% and 11-16 hgb. 9.3 gms. with retic. of 8%

Diagnosis: Megaloblastic anemia of cirrhosis

Case 2. [redacted]

A 35 year old white male was admitted [redacted]-57 with a history of ingestion of 4 ounces of Cheracol cough syrup daily for two years. The dietary history consisted almost entirely of Cheracol for this period of time. However, for the two weeks prior to admission his appetite had returned and he was eating a relatively normal diet. On entry to the hospital he had generalized dependent edema, puffiness of the hands and face and mental confusion.

Past history revealed a subtotal gastrectomy and appendectomy in 1948. The patient had polio myelitis in 1952 with little residual neurological findings. The pertinent physical findings, aside from the edema, included generalized hypoactive deep tendon reflexes, poor position sense and diminished vibratory sense.

Initial work revealed a hemaglobin of 3.6 grams, RBC of 1.01 and a Hct. of 12.5, MCV 123.7, MCHC 29. The platelet count was 60,000 direct. Eight nucleated red blood cells per 100 RBC's were seen in the blood smear. Retic. count was 42%. The WBC and differential counts were normal. The bone marrow showed erythroid hyperplasia with an intermediate megaloblastic state. Two plus iron was present in the marrow. A Schilling test showed 30% excretion of Vit. B12. Stools were con-

sistently negative for occult blood. [redacted].

On admission the patient was given 6 units of whole blood. Liver function studies included BSP, cephalin flocculation and A/G ratio were not remarkable except for an albumin that rose from 2.4 to 4 gms. while on the hospital diet.

Diagnosis: Nutritional macrocytic anemia

Case 3. [redacted]

This 27 year old white female was seen in O.B. clinic when 6 months pregnant with her seventh gestation. The chief complaints consisted of weakness, breathlessness and ankle edema.

Initial work revealed serum iron of 40 micrograms, total serum iron binding capacity of 350 micrograms and a saturation of 11.4%. Hemogram showed 6 gms. of Hgb, RBC of 3.02 and a Hct. of 22.6 with an MCV of 75 and MCHC of 26.6. From [redacted]-56 to [redacted]-56 the patient was given 1800 mgms. of I.V. iron and by [redacted]-56 the Hgb. remained at 7.5 gms. A bone marrow aspirate at this time showed maturation arrest of the myeloid and erythroid series with an M:E ratio of 1.6:1 and a mixed megaloblastic state. On [redacted]-56 the patient was started on folic acid 5 mgms. tid and by [redacted]-56 the Hgb. was 9.9 and on [redacted]-56 was 13.4. Other hematological data in [redacted] July revealed a WBC of 4,400 with 77 segs, 22 lymphs and 1 band. A repeat bone marrow in August showed complete conversion to the normoblastic series.

Diagnosis: Megaloblastic anemia of pregnancy

Case 4. [redacted]

This 62 year old white male was first seen in hematology clinic in latter part of 1951 with complaints of weakness, anorexia and weight loss. He was found to have a macrocytic anemia with a megaloblastic bone marrow, hepato-splenomegaly, dark brownish pigmentation of face and extremities, more marked on the extensor surfaces and a BSP test of 14% retention. An upper G. I. series was not remarkable and a barium enema showed a few sigmoid diverticula apparently asymptomatic.

The patient was placed on B12 and folic acid and was said to have shown a good response in his anemia but no repeat bone marrow examination was done. There was a history of heavy alcoholic intake in the mid 1930's but none since. The patient was then lost to follow-up until the latter part of 1952 when he was admitted for the first time to evaluate the hepatosplenomegaly. During this admission he had a normal glucose tolerance test, free HCl on gastric analysis. A liver and skin biopsy

were performed and said to be compatible with hemochromatosis. Several phlebotomies were performed in the next year as treatment for his hemochromatosis and these were stopped when the patient failed to return and was not seen again until [redacted]-54 and admitted because of 6-8 months of progressive weakness and dyspnea.

Findings at this time revealed hemogram Hgb. 2.6, RBC 600,000, Hct. 9.4, MCV 156, MCHC 27.7, platelets 16,000, WBC 1,800 with normal differential. The bone marrow showed erythroid hyperplasia of megaloblastic type. The direct Coombs test was negative. A urine urobilinogen was 4+. The serum bilirubin was 2.5. Liver function studies were not deranged on this admission. Free Hcl was present in the gastric juice and a glucose tolerance test was again normal. Upper G. I. series showed an active ulcer crater with deformity of duodenal bulb. The patient was given 3 units of packed cells and 60 micrograms B12 on [redacted]-54 and B12 was continued daily through [redacted]-54. However, because the patient failed to show a reticulocytosis and the severe thrombocytopenia and leucopenia persisted a repeat marrow was done and the megaloblastic state remained. On [redacted]-54 folic acid 5 mgms. bid was started. The hematological response was as follows:

Date	Hemaglobin	Retic.	WBC	Platelets
[redacted]-54	8.0	0.4	2,400	54,000
[redacted]-54	8.4	2.4	9,000	236,000
[redacted]-54		5.7		
[redacted]-54		4.4		
[redacted]-54	11.0	2.5	7,800	214,000
[redacted]-54	14.0			

During the 1954 admission attention was called to typical liver palms and the patient had a tender, beefy red tongue that appeared normal at the time of the first clinic visit on [redacted]-54 following his discharge. Unfortunately, the patient was again lost to follow-up for most of 1955. In April of 1956 the serum showed 100% saturation.

Diagnosis: Hemochromatosis with megaloblastic anemia

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Megaloblastic States

Deficiency in Vit. B12

*1. Addisonian Pernicious Anemia
2. Sprue (certain cases)
*3. Total gastrectomy
4. Partial gastrectomy plus gastritis
5. Diphyllobothruim latum infestation
*6. Blind loop, intestinal stricture, etc.
7. Pancreatic insufficiency?
8. Regional ileitis?
9. Juvenile pernicious anemia
10. Dietary deficiency (no animal protein in diet)
*11. Malignant disease in bone marrow?

Deficiency in Folic Acid

* 1. Nutritional macrocytic anemia (including alcoholism and cirrhosis)
*2. Sprue (certain cases)
*3. P. A. of pregnancy
*4. Megaloblastic anemia of infancy
*5. Adult scurvy (certain cases)
6. Folic acid antagonist?
*7. Hemochromatosis
*8. Malignant disease in bone marrow?

Anticonvulsant therapy

* Types seen in this hospital

Megaloblastic States at Parkland Memorial Hospital
October, 1956 through September, 1957

Type	Number of Cases
Addisonian Pernicious Anemia	6
Malnutrition (cirrhosis) with megaloblastic anemia	10
Megaloblastic anemia of pregnancy	4
Undifferentiated carcinoma with megaloblastic anemia	2
Total number of megaloblastic marrows	22

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Megaloblasts in bone marrow:

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Objective Diagnostic Tests:

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4. Sauberlich, H. E. and Baumann, C. A.: A Factor Required for the Growth of Leuconostoc Citrovorum, J. Biol. Chem. 176:165, 1948
Considered as satisfactory bio-assays for folic acid and citrovorium factor from biologic material, especially the urine. Urinary excretion, with and without loading, used as an index of deficiency and normal state.
Normal urinary excretion per day:
Folic acid average 4 ug. (1.6 - 5.9)
Citrovorium factor average 0.4 ug.

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Folic Acid Metabolism:

6. Welch, A. D. and Heinle, R. W.: Hemopoietic Agents in Macrocytic Anemias, Pharmacol. Rev. 3:345, 1951
A good review of B12 and FA up to 1951

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Extensive bibliography on the role of folic acid in one-carbon transfer systems. This began with the identification of the structural formula of folic acid and its active form citrovorum factor. Emphasis on how little is known of the precise action of Vitamin B12. Likely this will improve with the identification of the structural formula of B12 by Hogkin et al (Nature 178: 64, 1956

8. Mueller, J. F. and Will, J. J.: Interrelationship of Folic Acid, Vit. B12 and Ascorbic Acid in Patients with Megaloblastic Anemia, Symposium on Nutritional Aspects of Blood Formation, The Natl. Vitamin Fdn., Inc. New York, No. 10, pp 30-44, Jan. 1955
Diagrams of possible metabolic interrelationship herein borrowed. Also a good discussion of response of macrocytic anemia to various substances, including Vit. C, uracil and thymine.

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MEDICAL GRAND ROUNDS
OCTOBER 17, 1957

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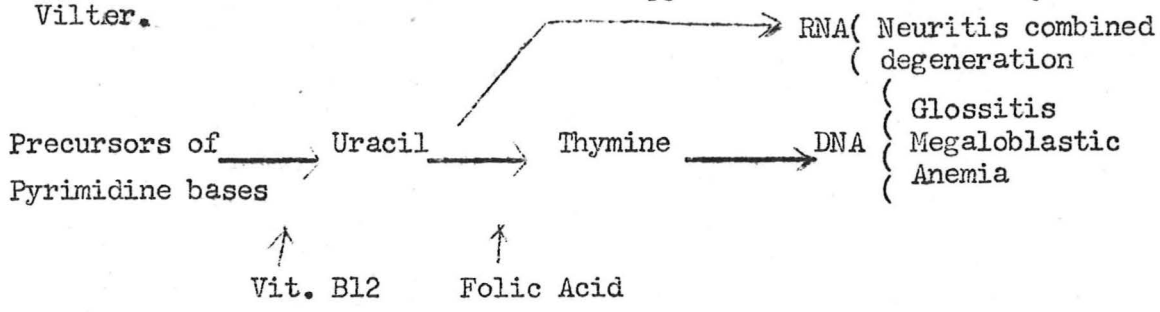
Discusses position of folic acid and B12 in metabolism of nucleic acids according to concept of Jukes supported in discussions by Vilter.



In this scheme B12 is essential for nuclear (DNA) and cytoplasmic (RNA) nucleic acids. Since RNA is plentiful in CNS, deficiency of B12 causes degeneration here. The scheme explains the lack of effectiveness of B12 in pure folic acid deficiency since it acts posterior to it metabolically. It also explains the influence of FA in PA improving the anemia by mass action while aggravating the B12 deficiency of the CNS, RNA synthesis and aggra vating the CNS lesion.

Clinical States Associated with Folic Acid Deficiency:

11. Darby, W. J.: Folic Acid and Citrovorum Factor in Human Nutrition, Current Research on Vitamins in Trophology, The Natl. Vitamin Fdn., Inc., New York, No. 7, pp 85-99, 1953
A general review of clinical aspects; some historical data.

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12. Jandl, J. H.: The Anemia of Liver Disease: Observations on Its Mechanism, J. Clin. Invest. 34:390, 1955
A general discussion of the anemia of liver disease emphasizing the macrocytic state and a decreased life-span of the RBC as measured by the Ashby method (isotransfusion). This confirmed observations made by Chaplin and Mollison. A hemolytic component with insufficient compensation by the bone marrow was considered as the main cause. An extracorpuscular hemolytic process was indicated since transfused cells were involved. Spontaneous improvement with reticulocytosis on hospital diet was noted. Folic acid deficiency was incriminated in a few instances.

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Using primarily the Price-Jones curve and the mean RBC diameter, the macrocytosis of liver disease was analyzed in detail. The cell diameter was increased while the thickness was decreased thus explaining the resistance to hypotonic saline solutions. Altered erythroid maturation was considered likely. Niacin was suggestively incriminated. The response to therapy was not clearcut as in P.A.

17. Wills, Lucy: Pernicious Anemia, Nutritional Macrocytic Anemia and Tropical Sprue, Blood 3:36, 1948
A general review of the problems in these macrocytic states with emphasis on deficiency of "liver principle" (B12) in PA, folic acid in sprue and unknown factors in nutritional macrocytic anemia. This discussion implies the background for the so-called Will's factor, considered to be folic acid by some and possibly a special factor by others.

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Good response to folic acid in these cases. Similar observations have been made in India and elsewhere. These results tend to refute the view held by Wills.

Sprue:

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20. Israels, M.C.G. and Sharp, J.: Idiopathic Steatorrhea (Non-Tropical Sprue) with Megaloblastic Anemia, Lancet 1:752, 1950
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Emphasizes combined use of Vitamin C and FA in management

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24. Bronte-Stewart, B.: Anemia of Adult Scurvy, Quart. J. Med. 22:309,1953

25. Brown, A.: Megaloblastic Anemia Associated with Adult Scurvy: Report of a case Which Responded to Synthetic Ascorbic Acid Alone, Brit. J. Haemat. 1:345, 1955
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VILTER SCHEME