Staff Meeting Bulletin Hospitals of the » » » University of Minnesota

Anemias of Pregnancy

Volume XVII | Friday, April 5, 1946 | Number 18

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INDEX

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William A. O'Brien, M.D.

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS
April 6 - April 12,1946
No. 108 Medical Visitors Welcome

Saturday, April 6

7:45 - 8:50 Orthopedics Conference; Wallace H. Cole and Staff; Station 21, U. H.

9:00 - 9:50 Surgery-Roentgenology Conference; O. H. Wangensteen, L. G. Rigler, and Staff; Todd Amphitheater, U. H.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-515 U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

Sunday, April 7

11:00 - 1:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

Monday, April 8

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; Interns Quarters, U. H.

12:15 - 1:15 Pediatrics Seminar; Irvine McQuarrie and Staff; 6th Floor Eustis.

12:15 - 1:15 Obstetrics and Gynecology Journal Club; M-435, U. H.

12:30 - 1:20 Physiology Seminar; Particulate Components of Cytoplasm; Dr. Cyrus Barnum; 214 M. H.

12:30 - 1:20 Pathology Seminar; Phlorhizin Glucosuria; Dr. Moses Barron; 104 I. A.

4:00 - School of Public Health Seminar; Chlorine Dioxide Water Disinfection; George O. Pierce; 6th Floor Student Health Service Bldg., Women's Lounge.

8:00 - Clinical Research Club; Speakers, Dr. Lyle French, Dr. Wendell Hall, Dr. Elizabeth Troxil; Eustis Amphitheater.

Tuesday, April 9

9:00 - 9:50 Roentgenology-Pediatrics Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.

12:30 - 1:20 Pathology Conference; Autopsies; Pathology Staff; 102 I. A.

2:00 - 3:00 Dermatology and Syphilology; H. E. Michelson and Staff; Veterans' Hospital, Bldg. III.

3:15 - 4:15 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

4:00 - 4:50 Surgery - Physiology Conference; Drs. Wangensteen and Armstrong; Eustis Arpitheater.

5:00 - 5:50 Roentgenology Diagnosis Conference; Drs. Oscar Lipschultz and Donald Peterson; M-515 U. H.

Wednesday, April 10

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-515 U. H.

9:00 - 10:30 Pediatrics Staff Rounds; W-205 U. H.

9:00 - 10:50 Neuropsychiatry Seminar; Staff; Station 60 Lounge, U. H.

11:00 - 11:50 Pathology-Medicine-Surgery Conference; Hemachromotosis; E. T. Bell, C. J. Watson, O. H. Wangensteen and Staff; Todd Arphitheater, U. H.

12:30 - 1:20 Physiology Chemistry Journal Club; Staff; 116 M. H.

4:00 - 6:00 Medicine and Pediatrics Infectious Disease Rounds; W-205 U. H.

Thursday, April 11

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; Todd Amphitheater, U. H.

12:30 - 1:20 Physiological Chemistry; Cyrus P. Barnum; 116 M. H.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling Hansen and Staff; E-534, U. H.

4:30 - Bacteriology Seminar; 214 M. H.

5:00 - 5:50 Roentgenology Seminar; Some Unusual Cases; Dr. Samuel Levi; M-515 U. H.

Friday, April 12

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Arphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221 U. H.

10:30 - 12:20 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Otolaryngology Department; U. H.

11:50 - 1:15 University of Minnesota Hospitals General Staff Meeting; Precordial Electrocardiogram; George N. Aagaard; New Powell Hall Addition Arpitheater.

1:00 - 2:00 Dermatologic Allergy; Dr. Stepan Epstein; W-312 U. H.

2:00 - 3:20 Dermatology and Syphilology; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312 U. H.

1:30 - 2:20 Roentgenology-Neurosurgery Conference; H. O. Peterson, W. T. Peyton, and Staff; Todd Arphitheater, U. H.

II. ANEMIAS OF PREGNANCY

Roy G. Holly

The anemias of pregnancy have been extensively studied with varied and conflicting reports. With the advent of modern hematological techniques many fundamental studies have been carried out. However, considerable confusion still exists with respect to diagnosis and therapy. From an analysis of most reports one could conclude that anemia in pregnancy was either hydremia, an iron deficiency, or an anemia effectively treated with liver. Our own studies indicate that many cases of anemia in pregnancy are not that simple. The importance of mixed anemia, as well as the possible etiological role of protein and the hormones, has not been fully appreciated in the past.

During the past year studies have been carried out on the anemias of pregancy with the object of evaluating the various factors which might play a part in the production of anemia. These studies are, as yet, incomplete and definite conclusions cannot be drawn. However, many of the results are suggestive enough to warrant presentation.

The patients for this study were selected from the Out-Patient Obstetrical Clinic of the University Hospital, from the Obstetrical Clinic of Booth Memorial Hospital, and from the private practice of the staff. The patients were selected only because of an existing anemia. When first seen the patients were routinely admitted to the hospital for the initial study. A careful history was taken with special reference to diet and previous anemia and a complete physical examination was done. During a four to five day hospitalization the following studies were obtained.

1. Hemoglobin
2. Erythrocyte count
3. Hematocrit
4. Reticulocyte Percentage
5. M. C. D.
6. Erythrocyte Protoporphyrin
7. Sternal Biopsy
8. Blood morphology
9. Erythrocyte fragility
10. Feces urobilinogen
11. Fractional serum protein
12. Serum bilirubin
13. Vitamin C
14. Gastric Analysis
15. Blood Volume

Follow-up examinations were made at intervals throughout the pregnancy and puerperium. An attempt was made to follow each patient closely, particularly when therapy was given. If possible the patient was kept in the hospital for therapy.

Only a brief summary of the techniques employed will be given. Reference to reports where complete details of procedure may be obtained will be cited. For each procedure an effort was made to obtain uniform and accurate results. Bloods were drawn routinely in the morning between nine and ten o'clock to minimize the known hourly fluctuations. One technician carried out many of the technical procedures, this being particularly important in the erythrocyte count where even with excellent technique wide variations are possible. One set of pipettes, standardized against U. S. Bureau of Standard pipettes, was used throughout the study.

The hemoglobin, erythrocyte count and hematocrit were determined on venous blood drawn without stasis. Heparin was used as the anticoagulant. The hemoglobin was determined by the oxyhemoglobin method with final determination in the Evelyn photoelectric colorimeter. The hematocrit was measured in a Wintrobe tube. One cc. of blood was centrifuged for one-half hour at 3,000 r.p.m., and then re-centrifuged until a constant reading was obtained. The reticulocyte percentage was determined from 1,000 cells. The slide was prepared using the brilliant cresyl blue supravital staining method. Routinely the Haden-Hausser halometer was used for measuring the mean cell diameter, but in cases of special interest, a Price-Jones curve was constructed.

The erythrocyte protoporphyrin was determined by the method used in Watson's laboratory (1) with serial extractions

being carried out on the erythrocytes using ethyl acetate-acetic acid, 10% HCl, ethyl ether and 5% HCl. The final determination was made in the Evelyn photoelectric colorimeter.

Erythrocyte fragility was measured quantitatively as suggested by Hunter (2) with the degree of hemolysis being determined in the Evelyn colorimeter. The feces urobilinogen excretion was measured from a four-day stool by the procedure suggested by Watson (3).

Bone Marrow study and peripheral blood morphology were done by the department of Hematology, earlier by Dr. R. Reiff and more recently by Dr. Dorothy Sundberg.

It was apparent at the beginning of the investigation that by our techniques all the patients examined had elevated mean corpuscular volumes. It was clear from morphological study that this did not represent an alteration in the peripheral blood pattern. Accordingly, it was decided to run a series of determinations on non-pregnant females using the techniques as described above. Fifty-one student and graduate nurses volunteered for the study. In addition to the determination of hemoglobin, erythrocyte count and hematocrit, a brief history was obtained concerning menstruation and previous anemia. The results are shown in figure 1.

Figure 1

Average Hemoglobin, Erythrocyte Count and Hematrocit on 51 Nurses

Average hemoglobin (gm %)	12.8	Range 10.5 - 14.5
Average erythrocyte count (million per cubic mm.)	4.2	Range 3.7 - 4.9
Average hematocrit (%)	41.7	Range 36.0 - 46.0
Average M. C. V. (cubic micra)	98.2	Range 92.0 -100.0
No. with anemia history	19.	
Average hemoglobin (gm %)	12.6	
No. with no anemia history	32.	
Average hemoglobin (gm %)	13.0	

It is evident that decreased values for hemoglobin and erythrocyte count are present, at least among University Hospital nurses. Wintrobe (4) cites 14 gm. hemoglobin, 4.8 million erythrocytes, and 42% hematocrit as the average values for healthy white females. From these values the average M. C. V. would range from 82 to 92 cubic micra.

There is evidence, however, that the average hemoglobin among healthy females is not as high as reported by Wintrobe. Moore (5) cites 13.1 gm. hemoglobin and 4.29 million erythrocytes as the average normals in his experience. Arens (6) found 13.1 gm. as the average hemoglobin among 200 students entering high school and college in Duluth. She also cites Donelson who found 13.1 gm. as the average hemoglobin in a survey of seven midwest state colleges.

Nineteen of the nurses studied gave a history of previous anemia and only one in the group was taking iron at the time of the study. The average hemoglobin was 12.6 gm.% in this group of nineteen. For the thirty-two nurses with no previous knowledge of anemia the average hemoglobin was 13.0 gm.%.

No correlation was found to exist between the hemoblogin value and the amount, duration, or frequency of menstruation. Only three of the group admitted profuse menstrual bleeding and their hemoglobins were 13.9, 13.9, and 12.2 gms. respective-

ly. Whether their menstrual blood loss was really profuse or not may be open to question.

Of importance to the present investigation was the finding that by our technique the range for the average corpuscular volume (M. C. V.) was from 92 to 100 cubic micra. The reason for this difference from the usually accepted figure lies with the erythrocyte count since the hematocrit value agrees very closely with previously reported values. The reason for the reduced erythrocyte count is not clear. It is important to note that this was a constant finding. Accordingly, values of less than 92 cubic micra have been taken to represent microcytosis and values above 100 cubic micra have been taken to represent macrocytosis.

There are two physiologic changes which occur during pregnancy that bear directly on the problem of anemia. One of these is the known increase in blood volume during pregnancy. If the degree of this increase were roughly equal in all pregnancies and were the increase evenly distributed between the plasma and cell fractions, it would make little difference in interpretation of results of the study of anemias. Previously reported studies of the blood volume increase in pregnancy have shown that it varies from individual to individual with the plasma volume increasing out of proportion to the total cell volume.

Miller, Keith, and Rowntree (7) in 1915 reported an increase of blood volume in pregnancy to 9.56% of body weight as compared with 8.8% in the non-pregnant female. Dieckmann and Wegner (8) in 1934 reported a 25% increase in total blood volume, the greatest increase being noted in the plasma volume. In 1938 Thomson (9) reported his observations which are probably the most complete to date. An average plasma volume increase of 65% and a total blood volume increase of 45% was noted in the 9th lunar month of pregnancy. At term the plasma volume had decreased to 50% and the total blood volume to 32.4% above the non-pregnant normal.

It has been amply demonstrated that blood volume does increase in pregnancy, that the plasma volume increases out of proportion to other blood constituents, and that the maximum increase occurs about the 36th week of pregnancy. However, it is important to remember that the increase in blood volume varies widely from individual to individual. With the object of knowing the blood volume change in each individual under study, 42 determinations have been done on 21 patients. For determining the blood volume, Gibson's method (10) using the Evelyn photoelectric colorimeter as adapted to a macro-technique by Dr. Wendell Hall, was used. The total blood volume was calculated from the plasma volume and the hematocrit. The results are seen in figures 2 and 3 and again demonstrate the increase in blood volume during the first two trimesters, following which there is a gradual decrease toward term. The scatter graphs demonstrate the wide variation from patient to patient.

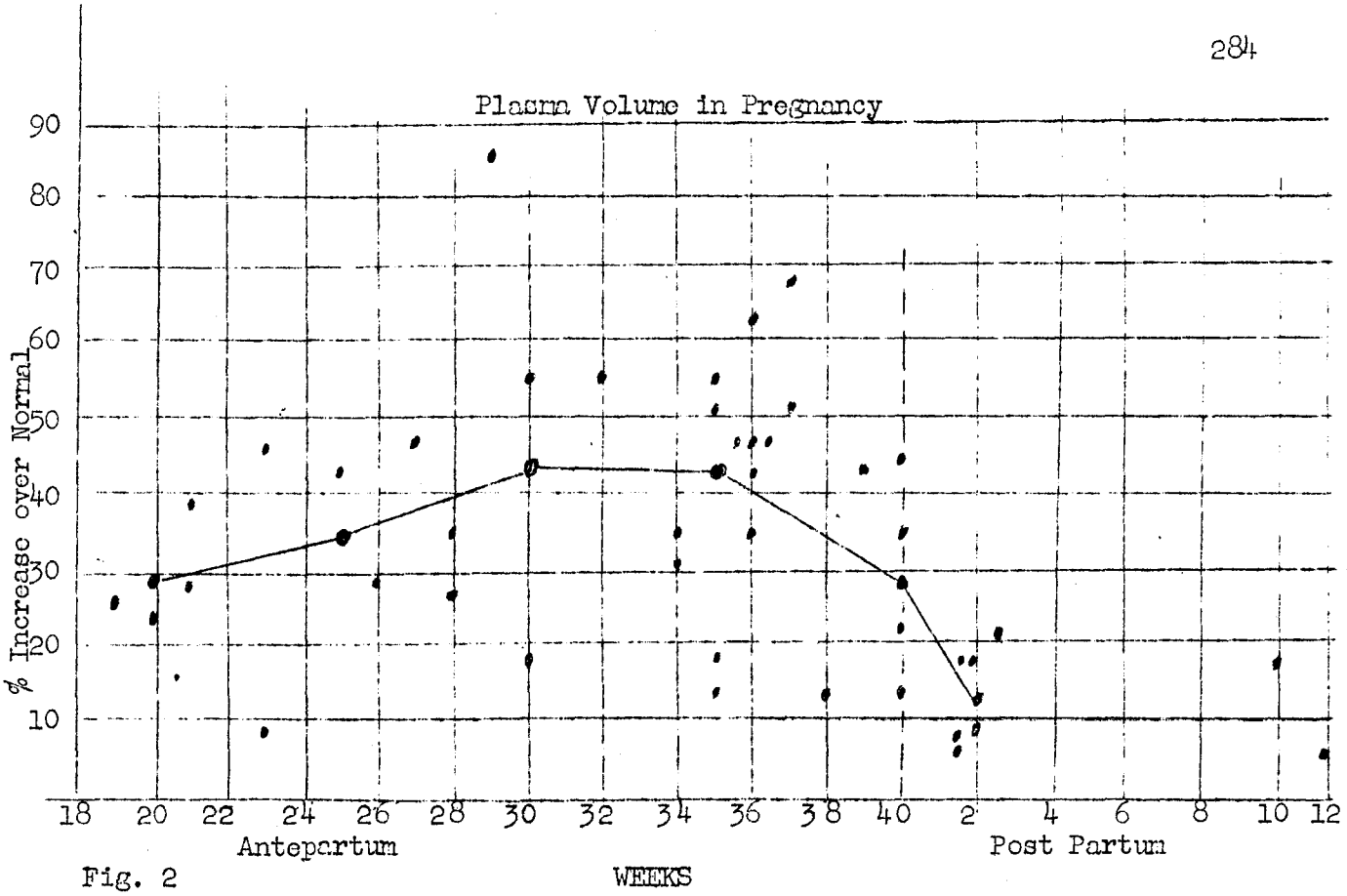

Plasma Volume in Pregnancy
% Increase over Normal
90
80
70
60
50
40
30
20
10
18 20 22 24 26 28 30 32 34 36 38 40 2 4 6 8 10 12
Antepartum
Post Partum
WEEKS

Fig. 2

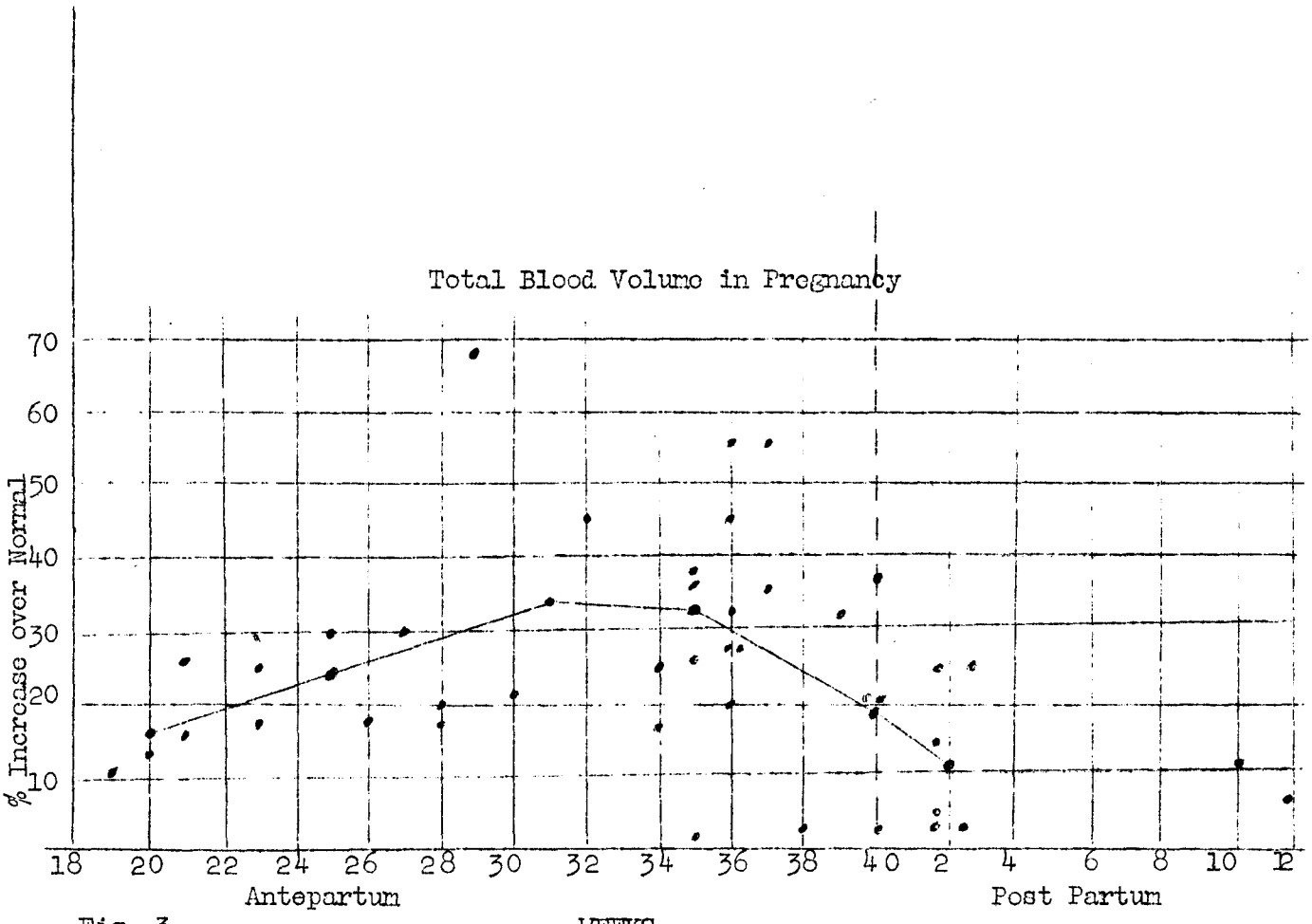

Total Blood Volume in Pregnancy
% Increase over Normal
70
60
50
40
30
20
10
18 20 22 24 26 28 30 32 34 36 38 40 2 4 6 8 10 12
Antepartum
Post Partum
WEEKS

Fig. 3

The effect of the blood volume changes on the peripheral blood may be expressed as the reciprocal of the curve for blood volume change. It has been repeatedly demonstrated that there is a gradual fall in the hemoglobin, erythrocyte count, and hematocrit up to the point of maximum blood volume increase, followed by gradual rise from this time to term (11, 12). Following delivery there is a rapid rise toward the non-pregnant normal. Recognizing that hemodilution does occur, many authors include the so-called "Physiological anemia of pregnancy" in their classifications. It is highly improbable that hemodilution alone can cause an anemia of pregnancy if the criteria for diagnosis of anemia are set at less than 10 gm. % hemoglobin, 3.5 million erythrocytes, or 36% hematocrit. It is important to know the change in blood volume in each patient under study. The accompanying graph (Figure 4) shows the average values for hemoglobin, erythrocyte count, and hematocrit in the various stages of gestation. The lowest line represents the minimum normal hemoglobin values for pregnancy.

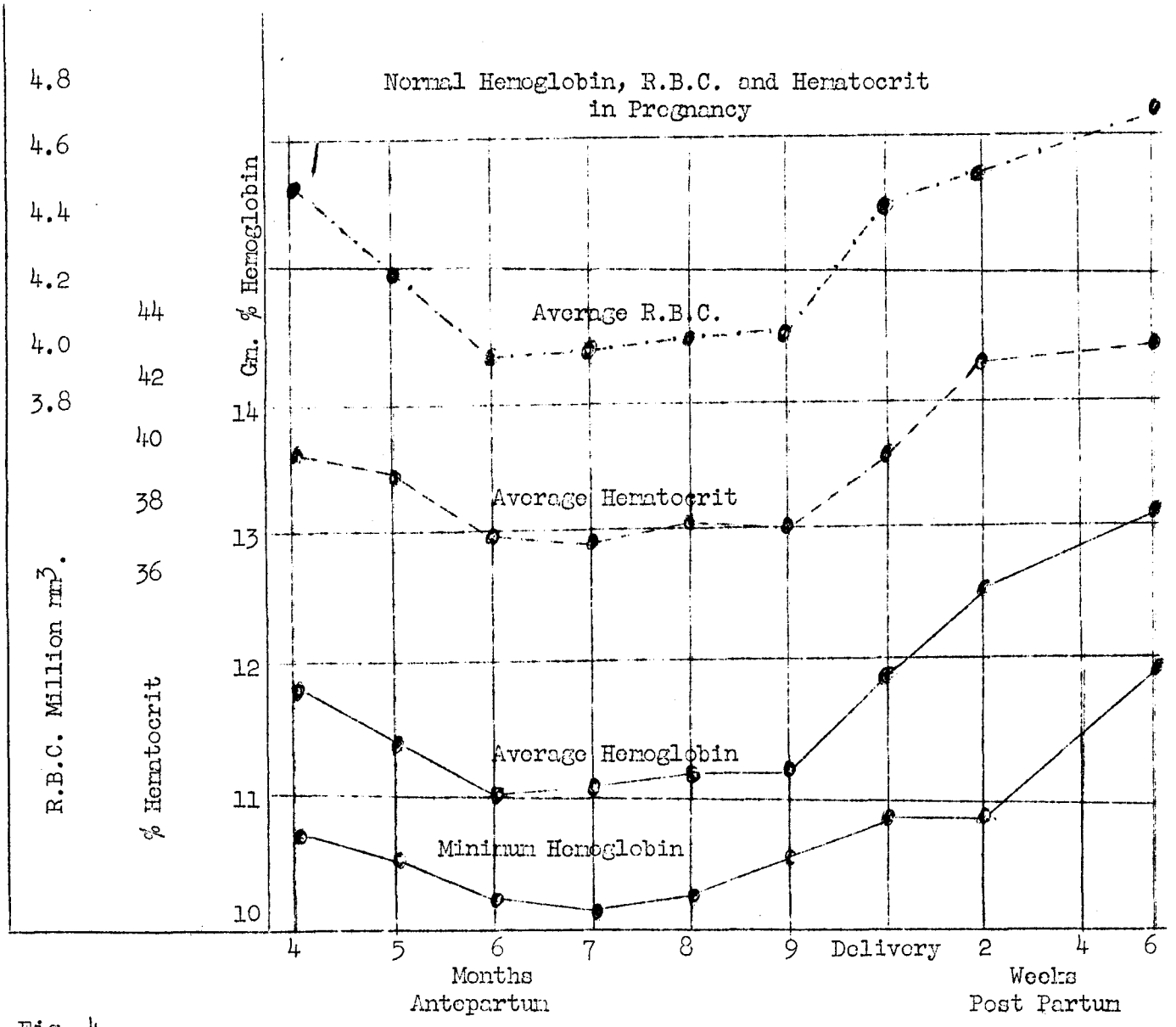


Fig. 4

A second physiologic change associated with pregnancy is the depression of gastric function as manifested by decreased acid secretion. This has been amply demonstrated by Kehrer (13), Nakai (14), Arzt (15 & 16), Strauss and Castle (17), Gottlieb (18), and LaBate (19). The relation of diminished gastric acidity to the anemias of pregnancy is debatable. Metier and Minot (20), by demonstrating that iron is more effectively absorbed from the gastrointestinal tract at a low pH, led many to conclude that impaired absorption was a probable cause of iron deficiency in pregnancy. There is sufficient evidence to the contrary to warrant the statement that diminished acid secretion exerts no more than a conditioning influence on iron absorption (18, 19).

In the course of the present investigation a total of 60 gastric analyses have been performed on 33 pregnant patients. Seven of these patients were normal pregnant controls. In all 33 patients there was reduced acid secretion. Arbitrarily the results of these analyses have been placed into four categories as shown in figure 5. Thirty degrees free HCl has been taken as the lower limit of normal gastric acidity.

Figure 5

Group A ..... Histamine Fast Achlorhydria
Group B ..... Acid only after Histamine
Group C ..... Hypo-acidity
Group D ..... Normal Acidity

The analysis in each case was made in the morning. After removing the entire fasting gastric content, 0.5 mgm. of histamine hydrochloride was given. Four samples were then removed at 15 minute intervals. Titration was carried out with 0.1 N NaOH.

Figure 6 shows the results of correlation between anemia type and gastric acidity. The two macrocytic anemias were not pernicious anemia of pregnancy. In the group listed as normocytic normochromic were placed cases not diagnosed as to etiology and two cases of spheroidocytosis to be discussed later. No apparent relation exists between the type of anemia and gastric acidity, since there is a similar distribution of the degree of acid secretion in all types of anemia and in the normal cases.

Figure 6
Correlation of Gastric Function with Anemia

Diagnosis	A	B	C	D
Macrocytic	1	1	0	0
Iron deficiency	1	4	4	0
Normocytic normochromic	2	5	2	0
Hemolytic	0	2	0	0
Hypoplastic (refractory)	1	2	1	0
Normal	0	4	3	0
	5	18	10	0

Figure 7 shows the results in 14 patients who were studied both prenatally and postpartum. This again demonstrates diminished acid secretion during pregnancy with a return toward normal after delivery.

Figure 7
Antepartum and Postpartum Gastric Analyses on 14 Patients

	A	B	C	D
Antepartum	2	8	4	0
Postpartum	0	5	9	0

More studies on the problem of gastric function in pregnancy are warranted. Very little is known concerning the etiology of this phenomonon.

Iron Metabolism in Pregnancy

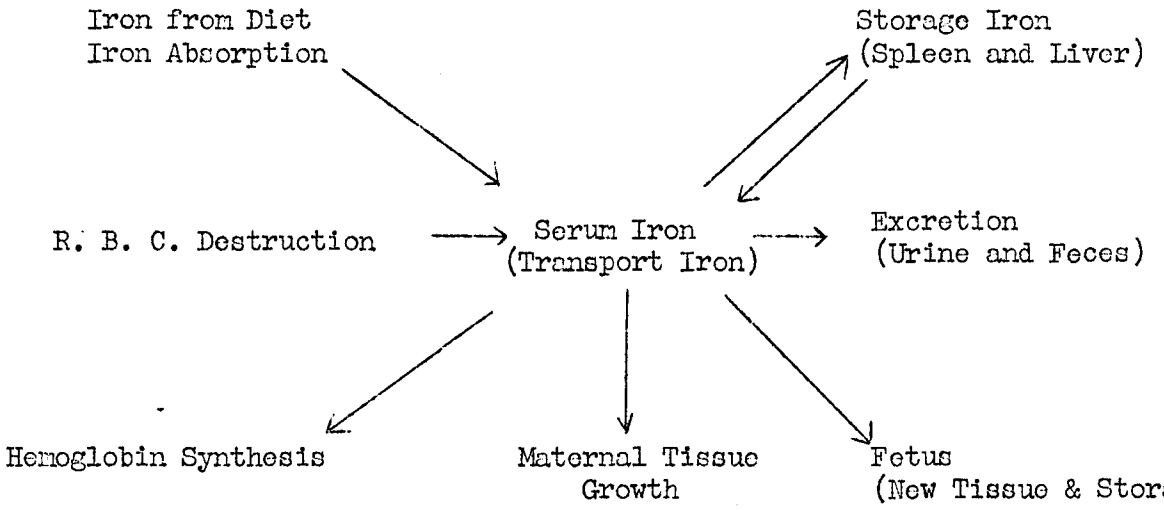
Iron metabolism is a complex process in which many factors are not, as yet, fully understood. In pregnancy, with added factors of new tissue growth and fetal demand, the metabolism is probably even more complicated.

Figure 8 is a schematic representation of some of the factors involved in iron metabolism in pregnancy.

Serum iron is now generally conceded to represent transport iron (21). Only a few studies on the pregnant woman have been reported and for the most part these have been done on women with normal pregnancies. Dahl (22) reported 58% of 43 women to have serum iron values of less

Figure 8

Iron Metabolism in Pregnancy



than 70 gamma percent in the last month of pregnancy. (Normal 70-130) Forty-eight percent of the same group had less than 70 gamma percent serum iron in the puerperium. From these studies he concluded that serum iron is reduced in pregnancy and that there is a slow tendency for values to rise in the puerperium. Other workers have reported values within normal limits for pregnancy (22). Albers found elevated values in pregnancy (22). Moore (23) reported one case of pernicious anemia of pregnancy with the expected high serum iron value which fell to normal after liver therapy. Callender (24) reported four similar observations. From these conflicting reports no definite conclusions can be drawn concerning serum iron in pregnancy.

Little is known about iron storage in pregnancy. Coons (25) reported positive iron balance in 9 pregnant women, lower values being present in the last month of pregnancy. Bethell reported a normal iron balance in one normally pregnant woman studied throughout the last trimester (26). Iron retention does not necessarily mean that the iron is utilizable for hemoglobin synthesis. A direct approach to the question of the availability of iron for hemoglobin synthesis is possible by study of the erythrocyte protoporphyrin.

The protoporphyrin is apparently synthesized in the bone marrow for the maturing erythrocyte and perhaps elsewhere in the body. In the absence of sufficient iron for hemoglobin synthesis, the amount of erythrocyte protoporphyrin in the circulating erythrocytes is increased. Watson has established the normal value as less than 30 gamma percent (27). In iron deficiency states, markedly elevated values are present. Cartwright and associates (28) in cases of chronic anemia associated with infection have demonstrated elevated protoporphyrin values. These cases did not respond to iron therapy and they postulated that the iron was diverted to other tissues. An analogous situation might exist in pregnancy.

Unfortunately, protoporphyrins were not determined on many of the cases seen early in the investigation. Recently all cases under study have had the erythrocyte protoporphyrin determined. A few suggestive results have been obtained which will be reported at the present time.

In five pregnancies with apparently normal erythropoiesis as indicated by peripheral blood study, the erythrocyte protoporphyrin was determined. The results are shown in fugure 9.

Figure 9
Eruthrocyte Protoporphyrin in Normal Pregnancy

	Age	Gest. Week	Hgb. Gm.%	R. B. C. Millions	H'crit %	Retic. %	Protoporphyrin %
1. L.T.	21	35	13.3	4.28	42	0.2	19.4
2. H.G.	20	25	11.1	4.16	38.5	1.7	50
3. M.J.	19	15	11.4	4.09	39	0.6	31
4. L.B.	21	37	13.0	4.2	41.5		30
5. G.K.	16	25	13.7	4.24	42	0.4	22
		26.5	12.9	4.25	40	1.2	60
		32	12.5	3.95	38.5	0.8	30
		36	14.1	4.56	43		39

There was, apparently, a mild iron deficiency in case 2. The value of 60 gamma percent in case 5 can be explained only as a technical error since the other values on the same patient are much lower. On the basis of these few determinations it is suggested that iron is readily available for hemoglobin synthesis in the normal pregnancy.

Figure 10 is a chart of erythrocyte protoporphyrin determinations on anemia cases under study. It is becoming well established that the protoporphyrin is a valuable aid in anemia diagnosis. Further studies are in progress at the present time.

It is of interest to note that in the three cases of hyperemesis gravidarum, elevated protoporphyrin values were obtained. It remains to be seen whether this finding will hold true for all cases of hyperemesis. Two of the cases had apparent anemia. The third case had normal peripheral blood findings. However, on the last determination, the hematocrit had fallen below the accepted normal standard. Further observations in this case will be necessary to determine whether the elevated protoporphyrin is pathognomonic of an impending anemia. The explanation of the elevated erythrocyte protoporphyrin in hyperemesis gravidarum is not clear. In many respects these cases resemble the chronic anemia associated with infection as reported by Cartwright (28). Case 2 showed no effect on the hemoglobin or protoporphyrin after one month of iron therapy. Case 1 showed only a partial effect from the iron but subsequently responded more completely to liver. The only conclusion that can be drawn from these observations is that there is incomplete utilization of erythrocyte protoporphyrin associated with hyperemesis gravidarum. Further studies are contemplated.

In the iron deficiency anemia an elevated erythrocyte protoporphyrin value is consistently present. With iron therapy the hemoglobin returns toward normal and the protoporphyrin value falls. This is in agreement with observations on the non-pregnant individual (27). Cases 4, 5, and 6 were typical cases of iron deficiency anemia. Case 7 was first observed after two months of iron therapy. She was taken off iron therapy and 5 weeks later the protoporphyrin value had risen significantly. This patient undoubtedly had depleted iron stores. Associated with increased fetal demand for iron there was insufficient iron for hemoglobin synthesis. In the five weeks, however, the effect had not manifested itself on the peripheral blood. Case 8 is of interest in that it represents delayed hemoglobin synthesis in the presence of active erythropoiesis. The patient was first seen shortly before delivery and a diagnosis of iron deficiency anemia was made. The protoporphyrin value was 121 gamma percent. Following delivery, iron was withheld for two weeks to see if more iron was available for hemoglobin formation after removal of fetal demand. The postpartum value was identical with the value before delivery. Iron therapy was instituted and the values up to five weeks postpartum are shown. The erythrocyte count and hematocrit returned to normal very rapidly but hemoglobin syn-

Figure 10

Patient	Diagnosis	Age	Gest. Week	Hgb. Gm. %	R. B. C. Millions	H'crit %	Retic. %	Protoporphyrin %	Therapy
1.	Hyperemesis Gravidarum	23	32	7.9	2.9	29	2.1	122	
			34	8.0	3.29	26.5	1.8	92*	----------Iron
			36	8.1	3.22	29	1.8	86	
			P.P.	11.3	3.56	37.5	0.4	57	
2.	Hyperemesis Gravidarum	19	32	9.4	3.44	31	1.4	52.7*	----------Iron
			36	9.2	3.21	31	1.0	52	
3.	Hyperemesis Gravidarum	26	9	12.2	3.65	36	0.4	58	
			15	12.5	3.78	38		125	
			21	11.5	3.5	34.5		64	
	Erythrocyte Protoporphyrin in Hyperemesis Gravidarum								
4.	Iron Deficiency	42	37	8.8	3.47	30	5.7	140	
								*----------	Iron
			P.P.	12.8	3.88	38	7.5	40	
5.	Iron Deficiency	36	37	9.9	3.66	33.5	1.8	93	
								*----------	Iron
			39	9.4	4.19	35	1.1	68	
			P.P.	11.0	4.11	41	1.8		
6.	Iron Deficiency	28	P.P.	7.1	3.62	27	1.5	129	
								*----------	Iron
			6 wks.P.P.	11.3	3.82	40	0.4	70	
7.	Iron Deficiency	26	30	10.7	3.54	36		*-------Iron (2 no) 40	
								*-----Discontinued	
			35	11.0		36		66	

Patient	Diagnosis	Age	Gest. Week	Hgb. Gm. %	R. B. C. Millions	H'crit %	Retic. %	Protoporphyrin %	Therapy
8. [illegible]	Iron Deficiency	21	39	10.0	3.61	34	0.8	121	
			9 days P.P.	10.0	3.79	34.5	1.1	121	
								*	----------Iron
			4 wks. P.P.	12.3	4.58	41.5	0.4	147	
			5 wks. P.P.	12.3	4.65	43	0.7	107	
9. [illegible]	Hypoplastic	21	18	10.2	3.15	33	0.6	49	
								*	----------Iron
			22	10.3	3.21	32	1.0	26	
10. [illegible]	Hypoplastic	23	26	9.0	3.18	31	1.2	32	
								*	----------Iron
			29	9.5	3.33	32	2.7	27.5	
11. [illegible]	Hypoplastic(?)	16	20	10.5	3.37	33	1.8	29	
12. [illegible]	Hemolytic	21	24 (Abortion)	7.2	2.07	22	11.1	50	
			4 days	8.0	2.15	25	7	101	
			2 weeks	9.4			2.5	43.5	
			4 weeks	11.2	3.81	36	0.8	77	
			2 months	13.5	4.39	43		48	

Erythrocyte Protoporphyrin in Iron Deficiency Anemia

Erythrocyte Protoporphyrin in the Anemias of Pregnancy

thesis lagged behind. This is indicated by the low cell indices and the erythrocyte protoporphyrin which was still elevated. A further check on this patient will undoubtedly reveal a higher hemoglobin with further fall in the protoporphyrin.

Cases 9, 10, 11, and 12 will be discussed in detail later. In these cases the erythrocyte protoporphyrin was a valuable aid in diagnosis, indicating an absence of iron deficiency. In case 9 there was a mild iron deficiency which was promptly corrected with iron therapy. Case 10 was refractory, as anticipated, to iron therapy.

Iron excretion is probably normal during pregnancy. Coons (25) reported normal excretion values in her study of iron balance. There is no evidence that erythrocyte destruction is increased during a normal pregnancy. Serum bilirubin determinations and excretion of feces urobilinogen were normal in all cases in this study in the absence of hemolytic anemia.

The fetus creates a real demand on the maternal iron reserve. It is improbable that, in the presence of adequate diet and sufficient iron stores, this demand could produce a deficiency of iron for hemoglobin synthesis. On the other hand, it is probable that where the fetal demand exceeds the maternal supply, the fetus takes its supply at the expense of the mother. The total fetal demand has been variously estimated between 340 and 450 mgm. of iron (29, 30). Cord blood serum iron study emphasizes the large demand by the fetus for iron. Dahl (22) reported the average cord blood serum iron value as 213 gamma percent. There is a rough correlation between the maternal serum iron value and the cord blood serum iron value. In the group where the maternal value was below 70 gamma percent, the cord blood value averaged 176 gamma percent. In the group where the maternal values were normal, the cord blood values averaged 234 gamma percent. In 13 premature infants, the average cord blood serum iron was 107 gamma percent. This would indicate that the greatest demand by the fetus for iron is in the last month or two of pregnancy. It is known that this is the period of intrauterine life when the greatest iron storage occurs in the fetus.

Absorption of iron from the gastrointestinal tract, as previously indicated, is probably little affected during pregnancy. On the other hand, diet is the only exogenous supply of iron and its role in the production of anemia is obvious. Fifteen milligrams has been established as the average daily maternal requirement for iron during pregnancy (31).

Several studies have served to emphasize the relation of diet to iron deficiency anemia. Fullerton (29) found 50% of 819 pregnant women among the poor class to have a hemoglobin of less than 80% (100% = 13.8 gm). In an iron treated group he found an 8% increase in hemoglobin values over the control group (32). Many others have reported similar observations. Bethell (26) has experimentally produced hypochromic anemia in pregnant rats on iron deficient diets. Napier (33) studying the anemia of pregnancy in India, reported the large majority of his cases to be iron deficiency anemia and recognized the dietary factor as of etiological importance.

Aside from the economic factor, gastrointestinal disturbances so commonly associated with the early months of pregnancy, play an important part in faulty iron intake. This will be stressed in reporting one of the cases.

Other factors, though not directly related to iron equilibrium, require mention. One of these is infection, and this is most commonly a urinary tract infection or puerperal infection. Acute blood loss associated with delivery or abnormal obstetrical bleeding is a second. A third factor and one which plays a large part in the etiology of iron deficiency anemia of pregnancy is depletion of iron stores before the onset of pregnancy. This may have been associated with excessive menstrual blood flow. In the face of increased demand for iron by the fetus, a full blown iron deficiency anemia can develop.

It is clear that our knowledge of iron metabolism in pregnancy is incomplete but it appears that in the absence of blood loss or infection, pregnancy will not produce an iron deficiency anemia unless conditioned by factors of diet or low iron reserve.

Iron Deficiency Anemia in Pregnancy

Iron deficiency anemia is the most common anemia of pregnancy. In its simplest form it is characterized by erythrocytes which are hypochromic but which may be normocytic or microcytic. The bone marrow shows normoblastic erythropoiesis (34). The erythrocyte protoporphyrin is elevated. With iron therapy a gradual increase of hemoglobin follows the reticulocyte response. It is important, however, to keep in mind that iron deficiency may complicate or be complicated by other anemia producing factors with a resulting confused blood pattern. The following are examples of iron deficiency anemias.

(1) . Age 28 Para 5-0-0-5 U.H.
Delivery 1-7-46

The patient was admitted in labor, having received no prenatal care. Diet was adequate by history. No abnormal bleeding noted during pregnancy. Her menses had been regular with a fairly profuse 4 day flow. Previous hemoglobins not known. Physical examination revealed only marked pallor and a smooth tongue. Delivery uncomplicated with a 100 cc. estimated blood loss. The hematological data is presented in figure 11.

Figure 11
Iron Deficiency Anemia

	HGB Gm%	RBC Mill.	H'crit %	Retic. %	MCV λ^3 u	MCH m.m.Gm.	MCC %	MCD micra	Protoporphyrin %
1-14-46	6.6	3.52	30	2.6	85.2	18.7	22	6.7	129
1-21-46	7.8	3.71	30	4.2	80.0	21.0	26		
2-19-46	11.3	3.82	40	0.4	104.7	29.6	28	7.2	70

Ferrous Gluconate gr. V t.i.d. begun on 1-17-46

Gastric analysis revealed 4° free HCl in the fasting specimen with 72° free HCl after histamine. Other studies were within normal limits. A maximum reticulocyte response of 4.2% was noted. At the last examination minimal iron deficiency was still apparent as shown by the elevated protoporphyrin and reduced indices. Normal values should be present when this patient is re-examined in April.

(2) Age 42 Para 6-0-1-6 U. H.
Delivery 10-6-45

Patient admitted for study of mild toxemia in 37th week of pregnancy. Diet was adequate by history. No abnormal bleeding had been noted during pregnancy. Menses had not been considered profuse. Examination revealed a palpable liver and spleen. Liver function studies were normal. Diagnosis of abdominal viscoroptosis made by the medical consultant. The hematological data is presented in figure 12.

Gastric analysis showed a histamine fast achlorhydria on two occasions. Serum bilirubin was normal, erythrocyte fragility was slightly decreased. Feces urobilinogen excretion was 102 mgm. per day. The reticulocytosis suggested a mild hemolytic anemia but other studies were normal. A diagnosis of iron deficiency anemia was made and the patient was discharged on iron therapy.

In order to recheck the erythrocyte protoporphyrin, the patient was recalled this past month. The liver and spleen were still palpable. The blood picture was normal with the exception of the reticulocytosis. The protoporphyrin fall was the expected response to iron therapy. Serum bilirubin was now abnormal. One minute value was 0.3 mgm.%

Figure 12
Iron Deficiency Anemia

	Hgb. Gm.%	R.B.C. Millions	H'crit %	Retic. %	M.C.V. u³	M.C.H. m.m.gm.	M.C.C. %	M.C.D. micra	Proto-porphyrin %
9-14-45	8.8	3.47	30	5.7	86.4	25.3	29.3	6.7	140
9-20-45	9.4	3.82	30	4.7	78.5	24.6	31.3		
10-8-45	10.0	3.79	34	2.6	89.5	26.4	29.4		
10-15-45	9.4	3.47	30	2.8	86.5	27.1	31.4	6.6	
11-27-45	13.2	4.4	40.5		92.1	30.0	32.6		
3-12-46	12.8	3.88	38	7.5	97.9	32.9	33.7		40

Ferrous Gluconate gr. 5 t.i.d. started on 10-15-45 and continued until December 1945.

with the total value equal to 2.6 mgm.%. The patient has been requested to return for further investigation. This could represent a hemolytic anemia or liver cirrhosis.

(3) Age 19 Para 1-0-0-1 U.H.
Delivery 8-12-45

Admitted to the hospital in the 23rd week of pregnancy for anemia study. There was a previous history of anemia which had been treated with iron (1943). Diet was inadequate. Menses were not considered to be profuse. Petit mal seizures had been present since early childhood. Examination revealed only marked skin pallor. The hematological data is presented in figure 13.

Bone marrow study on this patient showed erythroid hyperplasia. The myeloid-erythroid layer was 14. Gastric analysis revealed no free acid in the fasting sample, 56° after histamine. Other studies were normal. Iron therapy produced a maximum reticulocyte response of 4%. A diagnosis of normocytic hypochromic anemia was made. Iron therapy was discontinued on this patient with still evident iron deficiency so that other forms of therapy might be evaluated. These proved ineffectual. The postpartum value indicates slight iron deficiency is still present. The patient's diet had been wholly inadequate for many years, and must be considered as a primary etiological factor in this anemia.

Figure 13
Dietary Iron Deficiency Anemia

	Hgb. Gm.%	R.B.C. Millions	H'crit %	Retic. %	M.C.V. u³	M.C.H. m.m.gm.	M.C.C. %	M.C.D. micra
4-14-45	7.9	3.4	31.5	1.4	92.7	23.2	25.1	7.2
4-20-45	Ferrous Gluconate gr. 5 t.i.d. until May 16, 1945							
4-25-45	8.5	3.69	32.0	2.0	86.7	23.0	26.5	
5-15-45	10.3	4.28	36.0	1.8	84.1	24.1	28.6	
8-31-45	11.0	3.93	39.0	1.0	99.2	28.0	28.6	

(4) Age 22 Para 1-0-0-1 U.H.
Delivery 8-24-45

Admitted to the hospital with an acute febrile illness in the 34th week of pregnancy. Hemoglobin of 9.5 gm. % had been recorded earlier in the pregnancy. History of anemia with pregnancy in 1942. Menses were considered profuse. Diet was adequate by history. Physical examination was negative. Etiology of the febrile reaction was not determined. The patient responded to penicillin therapy promptly and was discharged in one week.

The hematological data is presented in figure 14.

Figure 14
Iron Deficiency Anemia with Infection

	Hgb. Gm%	R.B.C. Millions	H'crit %	Retic. %	M.C.V. u^3	M.C.H. m.m.gm.	M.C.C. %	M.C.D. micra
7-24-45	8.6	3.41	28.5	2.2	83.8	25.2	30.2	6.7
7-27-45	Ferrous Gluconate gr. 5 t.i.d.							
8-8-45	10.0	3.28	33.0	3.6	100.2	30.5	30.3	
9-24-45	10.7	3.79	35.0	1.4	92.4	28.2	30.6	
11-5-45	11.1	3.65	36.0	0.3	98.5	30.4	30.8	

Gastric analysis showed no free HCl in the fasting specimen; there was 40° free acid after histamine. Other data is non-contributory. The patient undoubtedly had a long standing iron deficiency anemia from profuse menstrual bleeding. Associated with pregnancy and the acute febrile illness the anemia was accentuated. Unfortunately, in this and the last case protoporphyrin determinations were not made.

(5) Age 23 Para 2-0-0-2 U.H.
Delivery 4-16-45

Admitted to the hospital for the second time in the 27th week of pregnancy with severe hyperemesis gravidarum. There had been continuous vomiting for 4 months. Diet was inadequate before pregnancy, principally in protein containing foods. History of anemia and hyperemesis with pregnancy in 1943. Menstrual blood loss was considered slight. Examination was negative. The hematological data is presented in figure 15.

Figure 15
Iron Deficiency Anemia Associated with Spheroidocytosis

	Hgb. Gm.%	R.B.C. Millions	H'crit %	Retic. %	M.C.V. u^3	M.C.H. m.m.gm.	M.C.C. %	M.C.D. micra	Protoporphyrin %
1-22-45	9.7	2.94	31	2.0	105.4	32.9	31.3	7.0	
3-1-45	7.0	2.94	26	1.3	88.4	24.0	27.0	6.25	122
3-7-45	Ferrous Gluconate gr. 5 t.i.d. continued until 4-5-45								92
4-5-45	8.5	3.12	35	1.6	112.1	27.2	24.0	7.0	86
3-25-45	Armour's Liver Extract 40 units I.M.								
4-16-45	9.2	3.07	31	3.3	100.9	30.0	29.7		
4-30-45	11.0	4.06	38	1.2	93.6	27.1	28.9		
3-6-46	11.3	3.56	37.5	0.4	105.3	31.7	30.1		57

This case has been most instructive. Other studies at the time of admission were as follows. There was a histamine fast achlorhydria. The bone marrow showed marked erythroid hyperplasia with a myeloid-erythroid layer of 26. The Vitamin C and serum bilirubin were normal. Feces urobilinogen excretion was 28 E.U. per day on the first determination and 47 E.U. per day on a subsequent check. Total serum protein was 5.2 gm.% with an A/B ratio of 3.9/1.3. Erythrocyte fragility was slightly increased on two determinations. A diagnosis of normochromic macrocytic anemia was made although the M.C.D. was normal.

Vomiting persisted and the patient remained in the hospital. One month later a severe anemia was manifest. The anemia was now hypochromic and microcytic but the M.C.V. was only slightly reduced. Blood morphology showed many hypochromic microcytes but many of the cells stained deeply and resembled spherocytes. The only positive finding to suggest a hemolytic anemia was the slightly increased cell fragility. Iron deficiency was apparent from the low cell indices and the elevated erythro-

cyte protoporphyrin. Ferrous gluconate gr. 5 t.i.d. was begun and continued for one month. A maximum reticulocyte response of 4.5% was noted followed by slight but incomplete improvement of the blood values. The original macrocytic normochromic anemia was again present. Forty units of intramuscular liver were given and was followed by a reticulocyte response of 6%.

The patient had now been in the hospital for several months. The vomiting had ceased and she went home for the week prior to delivery. At home the patient's husband forced her to eat liver every day and on return to the hospital another reticulocyte response was evident. Delivery was uncomplicated. The postpartum values suggest a normocytic slightly hypochromic anemia.

The behavior of the erythrocyte protoporphyrin in this case has been referred to previously. At the time iron therapy was instituted the protoporphyrin was 92 gamma percent and after one month of iron therapy the value was the same, this being in the absence of active erythropoiesis as indicated by the slight rise in erythrocytes. When rechecked recently one year following delivery a slightly elevated value was obtained.

Final interpretation of this case awaits further investigation. One other case similar to the one reported is under observation at the present time. We have applied the term "spheroidocytosis" to this blood picture. The mean corpuscular diameter is normal but the mean corpuscular volume is increased. The anemia is associated with a low serum protein. If there is an associated iron deficiency the M.C.D. will be reduced but the mean cell volume is larger than one would anticipate from the cell diameter. Morphologically the cells resemble spherocytes. The bone marrow shows only erythroid hyperplasia. Pernicious anemia is ruled out by the absence of megaloblastic change. It is thought at the present time that spheroidocytosis, if such an entity exists, is related to protein metabolism.

In recent years the relation between protein and anemia has been repeatedly emphasized. Whipple (35) has stressed this relationship and demonstrated the importance of protein for hemoglobin synthesis in Eck-fistula dogs (36). Others have reported similar observations. In 1936 Bethell (30) described cases of anemia of pregnancy in which he noted spherocytes. In pregnant rats on protein deficient diets he produced macrocytic anemias which were corrected by protein feeding (26). Miller and Studdert (37) in describing cases of macrocytic anemia of pregnancy with normoblastic bone marrow mention the presence of cells in peripheral blood smears which resemble spherocytes. It is entirely possible that in hypoproteinemic states, the cellular morphology is disturbed with the production of spherocytes. In the present investigation several patients with normocytic normochromic anemia refractory to iron and liver were treated with high protein feedings, both oral and intravenous, without demonstrable effect on the peripheral blood. Bethell has recently reported 25 cases of macrocytic anemia of pregnancy which were effectively treated with increased dietary protein (11). The exact pathology of spheroidocytosis remains to be worked out.

Hemolytic and Refractory Anemia of Pregnancy

Three other interesting cases have been observed recently which will be presented in detail. They further serve to confuse the concept of anemia in pregnancy.

(6) ___ Age 21 Para 0-0-0-0 U.H.
EDC 7-9-46

Admitted to the hospital in the 20th week of pregnancy for anemia study. Complained of mild weakness. Hemoglobin taken in first month of pregnancy was 13.3 gm.%. History of bleeding and anemia denied. Diet was adequate by history. Physical examination was negative. Hematological data is shown in figure 16.

Figure 16
Refractory Anemia of Pregnancy

	Hgb. Gm.%	R.B.C. Millions	H'crit %	Retic. %	M.C.V. u^3	M.C.H. m.m.gm.	M.C.C. %	M.C.D. micra	Protoporphyrin %
Oct. 1945	13.3								
1-30-46	8.9	2.94	30.2		102.7	30.4	29.6		
2-6-46	10.2	3.15	33.0	0.6	104.7	31.8	30.9	7.24	49
2-18-46	10.5	3.13	31.5	0.6	100.6	33.5	33.3		
3-1-46	10.3	3.44	30.5	1.2	88.7	30.0	33.7		
3-7-46	10.3	3.21	32.0	1.0	99.7	32.1	32.0		26
3-25-46	10.5	3.21	32.0	0.8	99.7	32.7	32.8		

Gastric analysis showed a histamine fast achlorhydria. Bone marrow revealed erythropoiesis to be relatively decreased with marked myeloid hyperplasia. The myeloid-erythroid layer was 11. Peripheral blood morphology was interpreted as normal. All other studies were within normal limits. Blood volume was only slightly increased. A diagnosis of hypoplastic anemia with minimal iron deficiency was made. Iron therapy produced no reticulocytosis but the protoporphyrin value returned to normal. The patient has since been proven refractory to intramuscular liver and folic acid. In a 47 day period no demonstrable change in blood values has been observed.

(7) Age 23 Para 0-0-0-0 U.H.
EDC 5-24-46

Patient admitted to the hospital in the 26th week of pregnancy for anemia study. The patient is colored. Diet was adequate by history. No abnormal bleeding has been noted. Physical examination was negative. Data is presented in figure 17.

Figure 17
Refractory Anemia of Pregnancy

	Hgb. Gm%	R.B.C. Millions	H'crit %	Retic. %	M.C.V. u^3	M.C.H. m.m.gm.	M.C.C. %	M.C.D. micra	Protoporphyrin %
1-30-46	9.9	3.16	32		101.2	31.3	31.0		
2-13-46	9.2	3.16	31	1.2	98.1	29.1	29.7		
2-15-46	9.0	3.18	31		97.5	28.3	29.0	7.2	32
3-6-46	9.5	3.33	32	2.7	96.1	28.5	29.7		27.5
3-11-46	8.6	3.05	30	3.1	98.4	28.2	28.7		
3-25-46	9.5	3.28	30.5	2.6	92.9	28.9	31.1		

Gastric analysis revealed 140 free HCl in the fasting sample. Bone marrow was reported as showing slight erythroid hypoplasia. All other studies were within normal limits. The patient has been proven refractory to iron and folic acid. Intramuscular liver produced a maximum reticulocytosis of 3.1% as noted. Over 55 days no improvement of the blood values has been noted.

The diagnosis of bone marrow hypoplasia associated with pregnancy in the human has not been reported previously. Lamarzi and Wolff in an analysis of 105 patients on whom bone marrows were studied at various intervals during pregnancy do not mention hypoplasia of the bone marrow. Thirty of their patients were anemic and the bone marrow in each of these cases was distinctly hyperplastic. The etiology of the hypoplasia in these cases is not clear. Usual therapeutic agents have produced no or slight effect. Sensitivity to estrogen stimulation is suggested. Hypoplasia and aplasia of the bone marrow of dogs has been experimentally produced with estrogens (38, 39). Other forms of sensitivity

to estrogens in humans is known, and among these is thrombocytopenia.

One other case of anemia in pregnancy associated with a severe toxemia of pregnancy will be presented.

(8) Age 21 Para 0-0-0-0 U.H.
Abortion 11-21-45

The patient was admitted for therapy of a severe toxemia of pregnancy. Blood pressures were recorded over 300 systolic with the diastolic value ranging between 140 and 160. Kidney function was normal. Previous hypertension was not known. Physical examination revealed marked eye-ground changes, one eye being completely obliterated with blood. Duration of the pregnancy was estimated at 24 weeks. On the day following admission the patient spontaneously aborted. The hematological data is presented in figure 18.

Figure 18
Hemolytic Anemia Associated with Severe Toxemia of Pregnancy

	Hgb. Gm.%	R.B.C. Millions	H'crit %	Retic. %	M.C.V. u^3	M.C.H. m.m.gm.	M.C.C. %	M.C.D. micra	Protoporphyrin %
11-20-45	8.5	2.4	26	8.3	108.3	35.4	32.7	7.1	
11-21-45	8.2	2.33	25	11.1	107.3	35.2	32.8		
11-23-45	7.2	2.07	22		106.3	34.3	33.6		50
11-27-45	8.0	2.15	25	7.0	116.2	37.2	32.0		101
12-10-45	9.4	3.04	30	2.4	98.6	30.9	31.3		43.5
1-9-46	11.2	3.81	36	0.8	94.5	29.3	31.1		77
3-13-46	13.5	4.39	43						48

Gastric analysis revealed no free HCl; 60° HCl was present after histamine. Erythrocyte fragility was normal. Serum bilirubin was normal. Feces urobilinogen excretion was 308 E.U. per day. The blood volume was normal. Bone marrow study revealed an erythroid hyperplasia with a shift to the right. The myeloid-erythroid layer was 11.5. The bone marrow findings were interpreted as being consistent with a mild hemolytic anemia.

A diagnosis of mild hemolytic anemia was made on the basis of the reticulocytosis and increased urobilinogen excretion with calculated increased erythrocyte wastage. This diagnosis was confirmed by bone marrow study. The hemolytic element proved to be transitory. Without therapy the hemoglobin and erythrocyte count returned to normal. Subsequent check revealed a normal urobilinogen excretion of 50 mgm. per day. A brief review of the literature reveals no mention of acute hemolytic anemia in association with toxemia of pregnancy.

Conclusions

1. The erythrocyte protoporphyrin is a valuable aid in studying iron metabolism and in diagnosing iron deficiency anemia in pregnancy. It is probable that iron is readily available for hemoglobin synthesis in the normal pregnancy.

2. The erythrocyte protoporphyrin is elevated in hyperemesis gravidarum. The significance of this phenomenon is not known.

3. Refractory anemia with bone marrow hypoplasia has been found in two cases. The suggestion that this might represent estrogen sensitivity has been advanced.

4. Mixed anemia, in which two or more anemia producing factors are present, may be found in pregnancy with a resulting confused blood picture.

5. Spheroidocytosis has been suggested as a name for the anemia of pregnancy in which spherocytes are found in the peripheral blood. The possible relationship of spheroidocytosis to hypoproteinemia is discussed.

References

1. Grinstein, M. and Watson, C. J.
Journal Biological Chemistry, 1943, 147:675.

2. Hunter, F. T.
Journal of Clinical Investigation, 1940, 19:691.

3. Schwartz, S. and Watson, C. J.
American Journal of Clinical Pathology, 1944, 14:598.

4. Wintrobe, M. M.
Textbook of Clinical Hematology, Chapter II.

5. Moore, C. V.
Journal of Clinical Investigation, 1939, 18:543.

6. Arens, M. A.
American Journal of Medical Technology, 1945, 2:249.

7. Miller, J. R., Keith, N. M., and Rowntree, L. G.
Journal of the American Medical Association, 1915, 65:779.

8. Dieckmann, W. J. and Wegner, C.
Archives of Internal Medicine, 1934, 53:71.

9. Thomson, K. J., Hirshcimer, A., Gibson, J. G., and Evans, W. A.
American Journal of Obstetrics and Gynecology, 1938, 36:48.

10. Gibson, W. A. and Evelyn, K. A.
Journal of Clinical Investigation, 1938, 17:153.

11. Bethell, F.
Annals of Internal Medicine, 1939, 13:91.

12. Dieckmann, W. J. and Wegner, C.
Archives of Internal Medicine, 53:188, 1934.

13. Kehrer, W.
(1905) Cited by Arzt in American Journal of Obstetrics and Gynecology, 1926, 12:879.

14. Nakai, T.
Tokio Journal of Biochemistry, 1925, 5:465 (Cited by Arzt).

15. Arzt, F.
American Journal of Obstetrics and Gynecology, 1926, 12:879.

16. Arzt, F.
American Journal of Obstetrics and Gynecology, 1930, 20:382.

17. Strauss, M. B. and Castle, W. B.
American Journal of Medical Science, 1932, 184:655.

18. Gottlieb, R.
The Canadian Medical Association Journal, 1936, 35:50.

19. LaBate, J. S.
American Journal of Obstetrics and Gynecology, 1939, 38:650.

20. Mettier, S. R. and Minot, G. R.
American Journal of Medical Science, 1931, 181:25.

21. Moore, C. V.
Journal of Clinical Investigation, 1937, 16:613.

22. Dahl, S.
Monatsschriff für geburts hilfe und Gynäkologie, 1945, 119:281.

23. Moore, C. V.
Journal of Clinical Investigation, 1937, 16:627.

24. Callender, S. T.
Quarterly Journal of Medicine, 1944, 19:75.

25. Coons, C. M.
Journal of Biological Chemistry, 1932, 97:215.

26. Kyer, J. L. and Bethell, F.
Proceedings of American Society of Biological Chemistry, March 1936.

27. Watson, C. J.
Journal of Clinical Investigation, 1944, 23:69.

28. Cartwright, G. E., Lauritsen, M. A., Humphreys, S., Jones, P. J., Merrill, I. M., and Wintrobe, M. M.
Science, 1946, 103:72.

29. Fullerton, H.
British Medical Journal, 1936, 2:523.

30. Bethell, F.
Journal of the American Medical Association, 1936, 107:564.

31. Lund, C. J.
Journal of the American Medical Association, 1945, 128:344.

32. Fullerton, H.
British Medical Journal, 1936, 2:577.

33. Napier, L. E.
Indian Medical Research Memoirs, 1941, No. 33.

34. Wolff, J. and Lamarzi, L. R.
Journal of the American Medical Association, 1945, 128:482.

35. Whipple, G. H., Robscheit-Robbins, F. S., and Hawkins, W. B.
Journal of Experimental Medicine, 1945, 81:171.

36. Miller, L. L., Robscheit-Robbins, F. S., and Whipple, G. H.
Journal of Experimental Medicine, 1945, 81:405.

37. Miller, H. G. and Studdert, T. C.
Lancet, 1942, 2:332.

38. Tyslowitz, R.
Endocrinology, 1941, 29:817.

39. Castrodate, D.
Endocrinology, 1941, 29:363.

III. GOSSIP

The Staff for the Continuation Course in "Psychotherapy in General Practice" at the Center for Continuation Study, April 1 to 13 includes Eleanor Barnes, Information Secretary, New York City Committee on Mental Hygiene; Walter Bauer, Associate Professor of Medicine, Harvard Medical School; Douglas D. Bond, Professor of Psychiatry, Western Reserve University School of Medicine; Donald W. Hastings, Professor of Psychiatry, University of Minnesota Medical School; M. Ralph Kaufman, Psychiatrist, The Mount Sinai Hospital, New York; John W. Murray, Psychiatrist, Boston, Massachusetts; Thomas A. C. Rennie, Associate Professor of Psychiatry, Cornell University Medical College; John Romano, Professor of Psychiatry, University of Cincinnati College of Medicine; Cecil J. Watson, Professor of Medicine, University of Minnesota Medical School; and Katharine M. Wickman, Psychiatric Social Worker, Pediatric-Psychiatric Clinic Babies Hospital, Columbia-Presbyterian Medical Center, Instructor, New York School of Social Work (Columbia University). Paul C. Benton, Gibbon; Randall S. Derifield, Crookston; George F. Engstrom, Belgrade; Thomas E. Eyres, Pequot; Leonard H. Fredericks, Bismarck; Gordon Erskine, Grand Rapids; Merrian G. Fredricks, Duluth; Rolv S. Hegge, Austin; Herman Juergens, Belle Plaine; Eugene Rinkey, St. Paul; John H. Bond, Fargo; Arthur C. Fortney, Fargo; Olaf Heiberg, Worthington; Royal V. Sherman, Red Wing; Ralph Smiley, Mason Rapids; John L. Batty, Hibbing; Holden Brink, Palo Alto, Calif.; Marshall Byerly, Lexington, N. C.; Robert D. Mooney, St.Paul; Arthur Peterson, Greely, Colo.; Edward D. Anderson, Minneapolis; John W. Johnson, Minneapolis; O. L. Norman Nelson, Minneapolis; John Rukavina, Duluth; Theodore W. Stransky, Owatonna; and J. A. Lazarte, D. L. Groom, J. M. McMahan, J. P. Robson, and P. F. H. Pugh of the Mayo Foundation are the student physicians. Henry W. Brosin, Professor of Psychiatry, University of Chicago, and Harold G. Wolff, Associate Professor of Medicine and Associate Professor of Psychiatry, Cornell University Medical College will be here next week. Daily schedule includes a lecture, group discussion, seminar, and study of patients. Doctor Rennie sums up the situation in the Bulletin of the New York Academy of Medicine in January, 1946, "The old-time family doctor was uniquely successful in treating his patients because with no knowledge of psychiatry he knew them as people, their families, their backgrounds, their communities, and their day-by-day problems. With the increasing specialization of medicine, and the growing preoccupation with particular areas of the human body, the person having the disease came more and more to be neglected. The specialty of psychiatry has brought into modern medicine a renewed emphasis on the importance of knowing a human being and it has developed specific techniques and procedures of scientific validity for the understanding of the person. With knowledge of these principles the physician will be in a better position to practice what Dr. David Barr felicitously calls 'comprehensive medicine'. Could such an orientation be guaranteed to every young graduate there would be less unnecessary surgery performed, more patients would be provided support and understanding throughout their illness and numbers of human beings could be spared the process of running fruitlessly from one doctor to another in search of help which they do not find. The practitioner is in the major position to help troubled and emotionally sick human beings. To this end it is of the first importance to attempt to elicit from every doctor his interest, sympathy, curiosity and his desire to help sick people in the fullest sense. Until the practitioner's attitude toward psychotherapy can be brought to one of constructive optimism, little can be expected from him as a therapist. He must begin with the conviction that medicine deals not primarily with disease entities or organ pathology but with human beings reacting to various kinds of noxious stimuli. These may be chemical bacteriological, physical traumtic or emotional unrest. Whatever the precipitating factor the end result is the same; a sick human being. There is no such thing as differentiating between organic or functional; it is always both.

Pre-eminently the practitioner still has to learn to recognize emotions in their many varieties and their effect upon the living being. His greatest effectiveness lies in the taking of a complete and proper history which gives due emphasis to the individual's emotional make-up and responses. He must learn how to establish an effective rapport or working relationship with his patient and he will succeed in this in direct proportion to the degree of genuine interest he shows. This is facilitated by his sensitive and kindly inquiry into the patient's personal life, his respect for the facts he obtains thereby, his genuine unfeigned desire to be helpful, his unspoken interest evidenced by his undivided attention, by his capacity for silence, by his facial expression--his smile, his gesture, and by his more willingness to take the time to listen. He must learn to recognize that everything the patient says and does is of importance, that the patient's reactions during the physical examination may be as important as the patient's utterances in revealing sensitiveness and prevailing attitudes and emotions. Equally important, he must learn to observe and evaluate his own reactions toward the patient. Only thereby can he avoid those common pitfalls: that he will tell the patient there is nothing wrong with him, or that his troubles are 'imaginary'. Or he may immediately resort to sedatives for relief when they are clearly not indicated. He may put too much attention on the physical examination thereby heightening the patient's anxiety and implanting the wrong impression that things are seriously at variance from the normal. He may waste time in protracting his laboratory studies to no avail, or more important, he may let his own emotional responses color his evaluation and management. Unless he understands his own emotional life, he may err in the direction of too much sympathy, paternalism, and protectiveness, or the converse: indifference to the problem, abrupt dismissal of the patient, peremptoriness, show of annoyance, disdain, anger, scolding, or thinly disguised punitive behavior. Perhaps such self-analysis is asking too much of the practitioner. He may be little inclined to study or analyze his own emotional responses toward his patient. Although he would be a better psychotherapist if he did, it may be enough to ask that he learn to control his own emotional reactions to his patient. If his attitude is primarily disdain and annoyance toward neurotic patients, he should not try to treat them."