5-1-1937

Anemia in pregnancy

Harold B. Graves
University of Nebraska Medical Center

A N E M I A I N P R E G N A N C Y

by

Harold B. Graves

***

Presented to the Faculty of the University of Nebraska,
College of Medicine, 1937.

Table of Contents.

Table of Contents.

Tables.

Graphs.

ANEMIA IN PREGNANCY

Introduction

"Ten years ago the term, 'Anemia of pregnancy', carried very little meaning." This quotation taken from Eastman, 1935 (30) expresses the truth in a rather startling fashion. In William's text, 1930 (94) we find, "in the later months of pregnancy the amount of hemoglobin and of red corpuscles is normal, or even slightly increased." Kehrer (46) in the exhaustive German system of Halban-Seitz, published in 1925, states, "during normal pregnancy the red cells and hemoglobin range in the upper limits of normal and in the last months increase still further." Feldman, 1920 (93) felt that, "women suffering from anemia often improve during pregnancy." De Lee (26) in his 1934 edition dismisses the subject with a short paragraph in small print at the end of the chapter on, "The Pathology of Pregnancy, Labor, and the Puerperium." He states, "Pregnancy, generally held to be a normal function, produces pathological anemia in 50-65 per cent of cases. It is a simple secondary anemia with low hemoglobin, low specific gravity, and red count."

These quotations from recent editions of outstanding texts give the reader the textbook idea of this subject. Nasse (62) in 1836 was the first to record a reduction in

the red blood cells in the pregnant woman and spoke of the "anaemisierenden" influence of pregnancy. In 1842 Channing (16) reported ten cases of severe anemia, all termenating fatally, in which he eliminated postpartum hemorrhage, puerperal infection and other obvious causes. His cases were probably of that group known as pernicious anemia of pregnancy. These works were almost the only ones relative to the subject before the 1870's and 1880's when methods of estimating reduction in red blood cells and hemoglobin were discovered. These discoveries led to more interest in anemias, and a number of men did a few experiments on pregnant women. As is characteristic of all early works in any field, much contradicition arose. This early work can be dismissed by saying that some found a decrease, others slight or no decrease, and still others an actual increase. And so the field remained in utter confusion with an occasional case of pernicious anemia in pregnancy reported, and little else, until shortly after 1926 when Murphy and Minot (60) reported their epioc making work on liver therapy. These discoveries stimulated new thought and research on anemias in general, and the anemias of pregnancy came under new fire. With this we find the number of articles and authors jumping by leaps and bounds. I hope to give to most of these authors, due recognition in the body of my thesis.

With this short history allow me to define the length

and breadth of this paper. "There seems to be no form of anemia, however grave, in which pregnancy has not been recorded." (96) Strauss, 1935 (88) has given the following classification of anemias.

I. Anemia due to excessive requirement for blood resulting from blood loss or excessive blood destruction.
   A. Blood loss - hemoptsis, epistaxis, hemorrhoids, placenta previae etc.
   B. Excessive destruction due to action of
      1. Chemical agents - lead etc.
      2. Infections - malaria, strepcoccus etc.
      3. Congenital or Acquired red blood cells defects as hemolytic jaundice and sickle cell anemia.

II. Anemia due to inadequate blood formation resulting from bone marrow injury, lack of blood building materials, severe damage to vital organs or bone marrow disturbances of unknown etiology.
   A. Bone marrow injury - physical, chemical and mechanical.
   B. Lack of blood building materials - hypochromic due to iron deficiency, and macrocytic due to deficiency of material effective in Addisonian anemia, and the anemia due to deficient Vitamin C as in scurvy.

As any of these may occur in pregnancy, I shall choose

only those of group II B, specifically those due to iron deficiency and the macrocytic type. The macrocytic type is rare and consequently will form a minor portion. This leaves the iron deficiency anemia to form the major portion.

Normal Values for Normal Women

Allow me to refresh your memory on the normal standards for non-pregnant women. In those standards for hemoglobin, we find a great deal of confusion due to different standards used by different authors. I will attempt to give the data in grams of hemoglobin per 100 cc of blood whenever possible. Dieckmann and Wegner, 1935 (27) from an analysis of the literature (278 cases) found the hemoglobin 13.9 gms., R.B.C., 4,780,000, and hematocrit, 41.1%, all average values. Wintrobe, 1933 (95) from an analysis of the literature (369 cases) found the hemoglobin, 13.9 gms., R.B.C., 4,850,000, and hematocrit, 41.8%, all average values. He recommended the normal to be, hemoglobin 12-16 gms., average 14 gms; R.B.C., 4.2-5.4 million, average 4,800,000; hematocrit, 37-47%, average 42%. These values are presented in more detail in Table I.

Normal Values for Pregnant Women

Let us now look at those values found on pregnant women. Those articles presenting range values sufficient for graphing are shown in Graph I and accompanying Table III and the others presented in Table II. For comparision the figures of

Table I

The Blood of Normal Women*

Locallity	No. Subjects	R.B.C.	Hgb.	Vol. pack. R.B.C.
U. S. East.....	73	4.78	14.0	41.5
U. S. Mid-West.....	15	4.89	14.3	43.1
U. S. West.....	2	4.70	14.1	41.5
U. S. South.....	11	4.85	14.1	43.0
U. S. Mid-West (Haden).....	30	4.38	13.4	—
U. S. Mid-West (Haden).....	12	4.26	13.3	39.0
U. S. West (Osgood).....	100	4.80	13.7	42.4
U. S. South (Wintrobe).....	50	4.93	13.8	41.5
Various Parts of the World...	210	4.78	13.9	41.0
Denmark (Gram & Norgard).....	10	4.65	13.0	40.5
Denmark (Bie & Moller).....	10	4.70	13.3	38.7
England, London (Price-Jones)	100	5.01	13.9	—
Williamson #.....	49	4.65	13.0	40.6
Average *.....	369	4.85	13.9	41.8
Average #.....	278	4.78	13.91	41.1

From Dieckman & Wegner (27)
* From Wintrobe 1933 (95)

Values Recommended by Wintrobe (95)

	Normal	Range	Proportion outside Lit. 101 by Author	
R.B.C. in millions.....	4.8	4.2-5.4	6.8	0.1
Hemoglobin in grams/100cc.....	14	12-16	2.0	1.2
cc/100cc Vol. Pack. Red Cells..	42	37-47	4.4	1.7

Table II

The Blood of Pregnant Women*

Author	Hb. Gms. No.	Hb. Gms. Norm	Hb. Gms. Preg Ave Min	R.B.C. Norm	R.B.C. Preg Ave Min	Hematocrit Norm	Hematocrit Preg Ave Min
Bernhard 1892.....	—	12.6	12.6	4.56	4.55	—	—
Thompson 1904.....	—	—	65% Gower	—	4.30	—	—
Harvey 1931.....	100	—	13.8	—	3.58	—	39.8
Kerwin & Collins 1926.	242	—	13.1	—	—	—	—
Lyon 1929.....	200	—	12.9	—	3.51	—	—
Moore 1929.....	100	—	10.8	—	4.14	—	—
Jerlov 1929.....	1143	—	10.48	—	—	—	—
Galloway 1929.....	382	—	11.1	—	3.87	—	—
Bland, First, & Goldstein 1930.....	300	—	11.2	—	3.50	—	—
Dietrich 1911.....	19	12	incr.	4.50	incr.	—	—
Skajaa 1929.....	120	—	—	—	—	43-47.5 44.4	27.5-44.5 36.4
Plass & Bogert 1924...	78	—	—	—	—	39.5	31.6
Gram 1920 Autenriegth.	—	11.6	10-11	—	—	36-45	—
Venous blood	62	—	—	—	—	40	36
Kuhnel 1926.....	15	15.8	12.7	—	—	39.5-44.5	—
Venous blood	—	—	—	4.75	3.85	41.5	35
Davidson#.....	819	—	10.78	—	—	—	—
Mackay#.....	109	—	11.52	—	—	—	—
Boycott#.....	222	13.8	12.11	—	—	—	—
Balfour & Drury#.....	311	—	11.96	—	—	—	—
Rowe.....	77	—	10.2	—	—	—	—
Richter, Meyers, & Bennet.....	61	—	10.4	—	—	—	—
Adair, Diekman, & Grant 1936.....	7412±	—	11.56	—	3.77	—	37.31
Diekman & Wegner.....	115±	—	13.0	—	4.16	—	38.32

*Modified from Diekman & Wegner (28)
#From Boycott (15)

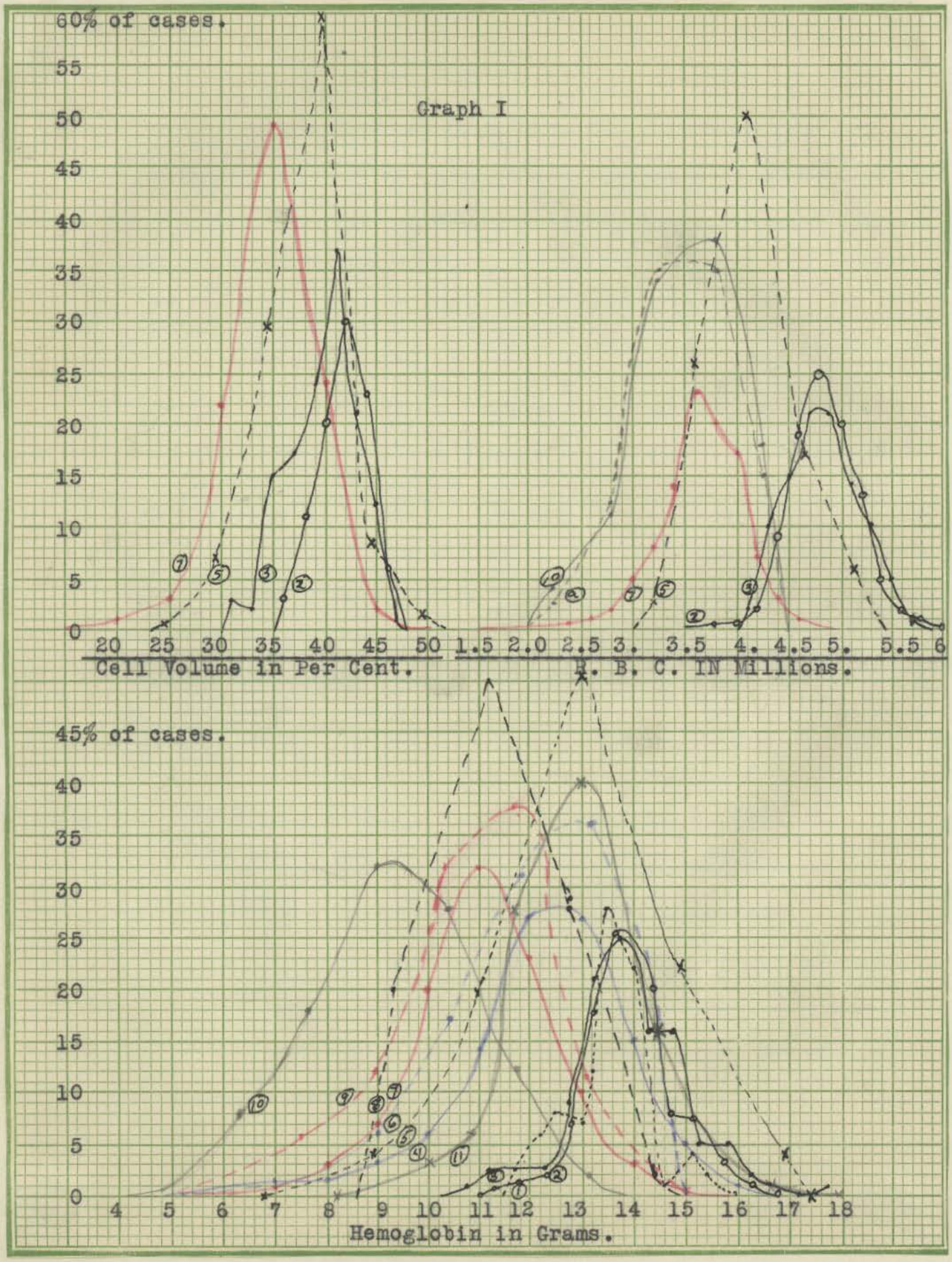

60% of cases.
55
50
45
40
35
30
25
20
15
10
5
0
Graph I
20 25 30 35 40 45 50
Cell Volume in Per Cent.
1.5 2.0 2.5 3. 3.5 4. 4.5 5. 5.5 6
R. B. C. IN Millions.
45% of cases.
40
35
30
25
20
15
10
5
0
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Hemoglobin in Grams.

Table III Distribution in Pregnancy

Volume of Packed Red Blood Cells in Per cent (Hematocrit)

Author & Subjects	Rep.	Cases	Range Per cent							Ave.
Osgood(66) normal	③	132	30-34	34-36	36-38	38-40	40-42	42-44	44-48	41
			4	11.5	13	18.5	28.5	16.1	10.5	
Wintrobe normal(95)	②	303	35-37	37-39	39-41	41-43	43-45	45-47	47-49	41.8
			2.9	12	20	32	23.3	6.6	1	
Adair et al preg.(1)	⑦	7696	15-20	20-25	25-30	30-35	35-40	40-45	45-50	37.31
			1	1	3	22	49	24	1.5	
Dieckmann & Wegner preg.(28)	⑤	117	22-27	27-32	32-37	37-42	42-47	47-52		38.32
			1	7.3	30	60	8.2	1		
R. B. C. in Millions per cu. mm										
Osgood(66) normal	③	132	4.0-4.4	4.4-4.8	4.8-5.0	5.0-5.4	5.4-5.8			4.80
			12.3	36.9	21.5	24.6	6			
Wintrobe normal(95)	②	402	3.7-4.3	4.3-4.7	4.7-5.1	5.1-5.5	5.5-5.9			4.85
			4	28	45	18	3			
Bland et al preg.(12)	⑩	1000	2.5	2.5-3.0	3.0-3.5	3.5-4.0	4.0-4.5			—
			4	11	34	38	18			
Bland et al preg.(14)	⑭	200	2.5	2.5-3.0	3.0-3.5	3.5-4.0	4.0-4.5			—
			2.5	12.5	35	35	15			
Adair et al preg. (1)	⑦	4345	2.6-3.0	3.0-3.4	3.4-3.8	3.8-4.2	4.2-4.4			3.77
			8	22	43	24	4			
Dieckmann & Wegner preg.(28)	⑤	111	3.0-3.4	3.4-3.9	3.9-4.4	4.4-4.9	4.9-5.4			4.16
			3.6	26.4	48.2	17.2	5.5			
Hemoglobin in Grams										
Price - Jones (71) normal	①	100	12.4-12.7	12.7-13.3	13.3-14	14-15.2	15.2			13.5
			14	19	50	5	1			
Wintrobe normal (95)	②	403	11-12	12-13	13-13.5	13.5-14	14-15	15-17		13.9
			2.5	10.5	17.5	25	34	13		
Osgood(66) normal	③	124	11-12	12-13	13-13.5	13.5-14	14-15	15-17		13.5
			5.6	11.4	10.9	25	32.2	12.8		
Davidson parous(22)	⑥	603	8.3	9.7	11	11-12.4	12.4			11.2
			10	16	33	31	36			
Dieckmann & Wegner preg.(28)	⑤	115	5.9-9.9	9.9-11.9	11.9-13.9	13.9-15.9	15.9			13.0
			4.3	18.2	51.3	21.7	4.3			
Adair et al (1) gyn. pts.	⑦	2399	5 6	7 8	9 10	11 12	13 14	15 16		12.5
			1 1	2 1.5	3 6	14 27	27 15	5 1		
Davidson preg.(22)	⑨	819	8.3	9.7	11	11-12.4	12.4			10.8
			5.5	17.5	49.5	38	12.5			
Adair et al preg.(1)	⑦	7835	5 6	7 8	9 10	11 12	13 14	15 16		11.56
			1 1	2 3	7 20	32 23	10 3	1 1		
Bland et al preg. (12)	⑩	1000	8.3	8.3-9.7	9.7-11	11-12.4	12.4-13.8			—
			26	32	28	12	2			
Toland (90) preg.	⑪	670	8.2-10.4	10.4-11.3	11.3-12	12-13.8	13.8-18			—
			3	6	28	45	17			
Adamson (2) & Smith preg.	⑧	116	8.6-10.4	10.4-12.1	12.1-13.8	13.8-15.6				—
			20	50	28	2				

several normal series are presented. At first Graph I is a confusion of curves from which nothing is apparent. But if we look more closely we find that curves 1, 2, and 3, representing normal women, are very nearly the same and surprisingly in agreement. These are chosen because they are representative and easy for graphing. Those I wish to discuss first are hemglobin values at the bottom. The two blue curves, 4 and 6, are taken upon gynecology patients, (where hemorrhage and sepsis are notoriously common) and be referred to later. This leaves curves 5, 7, 8, 9 and 10 taken on large series of pregnant women; 5, by Dieckmann and Wegner (28) 115 patients; 7, by Adair et al (1) 835 patients; 8, by Davidson (22) 819 patients; 9, by Adamson & Smith (16) 116 patients; 10, by Bland et al (12) 1,000 patients. These are in surprising disagreement, possibly due to different methods of estimating hemoglobin and to different values at which per cent of patients are recorded, but present the subject rather well. The thing I should like to point out is, <u>all</u> of these curves are below those of normal women. The same can be said of cell volume (upper left) and R.B.C. (upper right), although the series are smaller and fewer, and agreement better. Certainly this lowering of all values conventionally used to represent anemia is suggestive and confirmatory of Nasse's (62) idea of the "anaimisierenden" influence of pregnancy.

This phenomena has also been observed in other animals. Van Donk et al, 1934 (92) observed a mild progressive anemia in rats with rapid recovery postpartum. Mitchel & Miller, 1931 (57) also observed this in rats. Spiegelberg & Gescheidler (80) observed this in dogs.

Before discussing evidence suggesting an etiology, let us pause to say something of the course of these various determinations throughout pregnancy. The evidence available is presented in brief in Graph II and accompanying Table IV. The evidence is more or less contradictory, but shows a gradual progressive drop in hemoglobin, cell volume, and R.B.C. of a slight degree. In the records of individual cases, it soon becomes apparent that the extent of change varies markedly in different patients, and at different times. Numerous authors have observed normal changes in normal people greater than the changes shown here. Also several authors have observed even greater changes (Adair et al (1) 2, 3, and even 6 grams in 4-6 weeks) during pregnancy which could not be transformed into any logical curve, suggesting a labile condition in pregnancy. Furthermore, differences in simultaneous determinations on venipuncture and finger-prick blood in edematous patients (frequent in pregnancy) are greater than the differences observed. These are only a few of the more serious objections to taking these curves too seriously.

Let us now plunge into even more uncertain ground in an

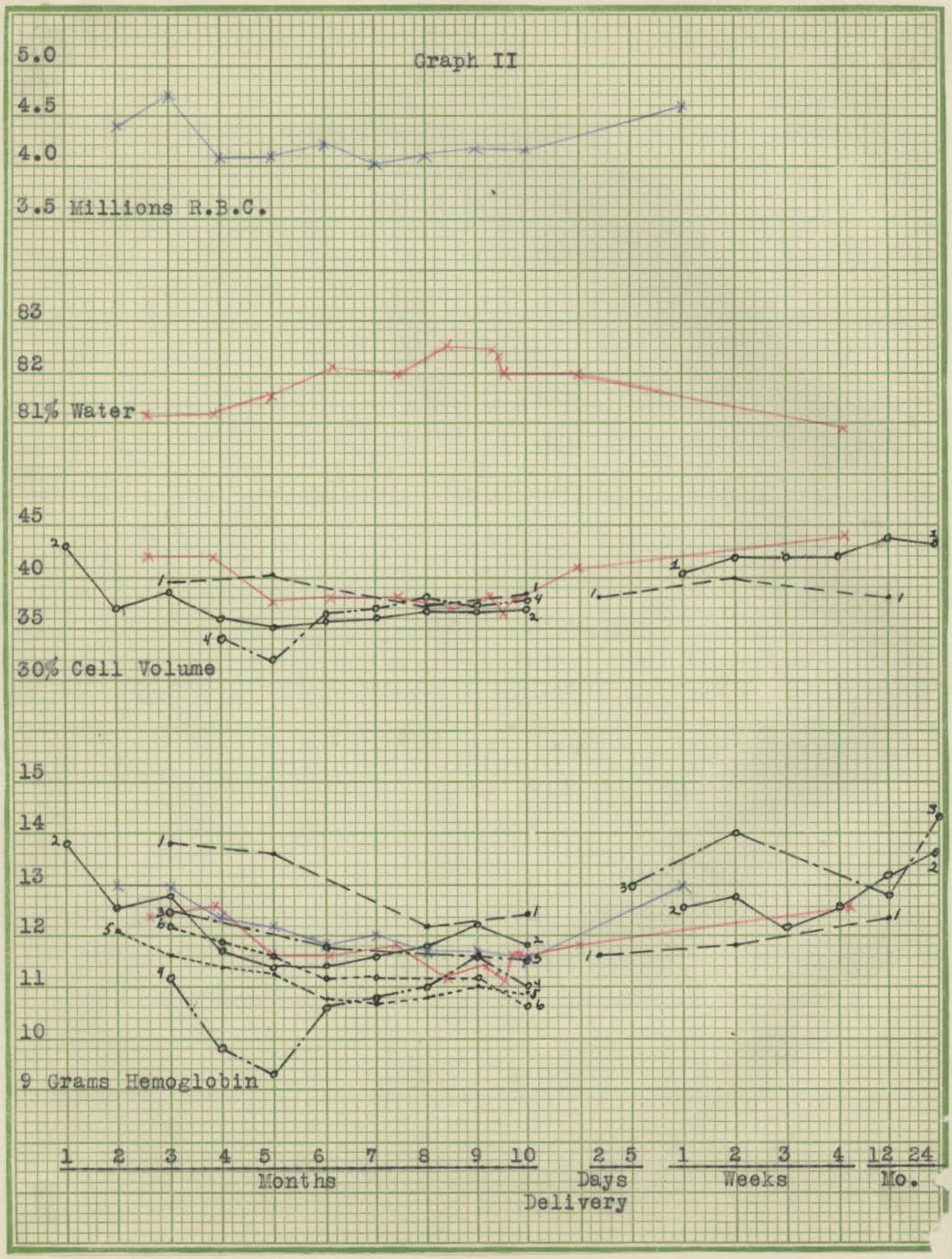

Graph II
5.0
4.5
4.0
3.5 Millions R.B.C.
83
82
81% Water
45
40
35
30% Cell Volume
15
14
13
12
11
10
9 Grams Hemoglobin
1 2 3 4 5 6 7 8 9 10
Months
2 5
Days
1 2 3 4
Weeks
12 24
Mo.
Delivery

Table IV

Course Throughout Pregnancy

Author	Deter.	Months 1	2	3	4	5	6	7	8	9
		Grams or Millions or Per cent								
Adamson & Smith 116 pts.(2)	No.	—	—	5	11	17	20	53	124	204
	Hb.	—	—	13.0	12.6	12.4	11.6	12.0	11.6	11.6
	No.	—	—	5	11	17	20	53	124	204
	R.B.C.	—	—	4.7	4.2	4.2	4.3	4.0	4.1	4.2
Feldman et al 20 pts.(34) 8 for 180 days	No.	—	2	10	15	15	19	24	41	35
	Hb.	—	12.4	12.7	11.5	11.6	11.8	11.1	11.2	11.6
	No.	—	1	9	14	15	19	24	39	33
	C.V.	—	4.2	4.2	3.7	3.8	3.8	3.5	3.8	3.9
	No.	—	2	10	15	15	15	23	39	34
	Water	—	81.2	81.2	81.6	12.1	82	82.5	82.4	82.1
Dieckmann & Wegner (27) 183 pts.	No.	—	—	—	—	—	—	—	—	—
	Hb.	—	—	13.8	—	13.6	—	12.1	—	12.5
Kuhnel* 342 pts.	Hb.	13.9	12.5	12.8	11.7	11.4	11.6	11.8	12.3	11.8
Galloway 382 pts. (36)	Hb.	—	—	12.4	—	—	11.8	—	—	11.5
Kerwin & Collins 242 pts. (47)	Hb.	—	—	12.4	—	—	11.8	—	—	11.5
Gram* 62 pts.	Hb.	—	—	11.0	9.8	9.3	10.5	10.8	11.6	10.9
Strauss & Castle 200 pts.(83)	Hb.	—	—	12.1	11.6	11.2	10.7	10.8	11.0	10.9
Jerlov* 1,143 pts.	Hb.	—	—	12.3	11.8	11.6	11.0	11.0	10.9	10.7

*Adair et al 1936(1)

attempt to explain this apparent lowering of values during the normal pregnant state. The explanation must be a physiological one because many normal pregnancies are observed to show these changes without symptoms or signs of ill health or anemia and are apparently in the "pink of condition". Mitchel & Miller, 1931 (57) observed a slight progressive anemia till three days postpartum in 92% of 145 pregnancies in rats with spontaneous recovery postpartum. They could not affect this anemia by adding iron, copper manganese and Vitamin B complex to their diet. Van Donk et al, 1934 (92) also observed the same thing in rats adding copper, iron, manganese, iodine, arsenic, yeast, dried beef liver, egg yolk and cod liver oil to their diet without affect. These certainly suggest a "physiological anemia", and, whereas conclusions from different species are not entirely justified, the comparison is suggestive.

Harvey, 1931 (41) studied 100 pregnancies finding 13.8 grams average hemoglobin, 3,580,000 red cells, and 38.7% cell volume in labor but found 14 grams, 3.660,000 red cells, and 39.3% cell volume five to seven days postpartum. 53% of his patients had hemoglobin below 13.9 grams in labor, only 47%, five to seven days postpartum; 47% cell volume below 39% in labor, and only 39%, postpartum; 28% showed gains of .5 grams or more hemoglobin, and 33%, 200,000 red cells postpartum. Patients with marked edema showed gains of 1.2 grams hemoglogin

and 437,000 red cells postpartum. All of the above are average values. All patients showing loss postpartum, had fever or loss of blood at delivery of over 300 cc. In other words, all patients in whom the labor and postpartum could be considered normal (no fever or loss over 300 cc of blood) showed a gain in hemoglobin, red cells, and cell volume. These results indicated an etiology to pregnancy and disappearing rather quickly postpartum. He suggested the answer lay in hydremia with blood volume increases in pregnancy and dehydration with blood volume decreases postpartum.

Adamson & Smith, 1932 (2) observed 200 pregnancies finding some degree of anemia in practically every case as judged by a single determination; cause hydremia.

Davis & Shelley (23) studied 45 normal pregnancies in which 40 showed a slight fall in the last three months and five a reduction in the fifth to sixth months. They considered these changes insignificant.

Galloway (36) made 364 determinations on 228 patients, pre and postpartum, in which he showed a definite decrease in a large per cent. He concluded that the majority of women show a reduction in red cells and hemoglobin during pregnancy which disappears within two weeks postpartum.

Green Armytage (40) feels that hydremia is the cause, and the condition not serious.

Adair et al, 1936 (1) after examining 7,412 pregnancies

stated, "There is no doubt that there is a significant difference between non-pregnant and pregnant patients and that pregnancy, in a corresponding stratum of patients, lowers the hemoglobin at least relatively." 63.2% were anemic according to non-pregnant standards, only 11.6% by pregnant statistical standards. They placed the statistical normal minimum at 10.16 grams hemoglobin; 33.11% cell volume; and 3,360,000 R.B.C. They felt that these changes were not affected by treatment. They observed changes of 2, 3, and even 6 grams hemoglobin in periods of four to six weeks in individual patients.

Polowe, 1932 (70) from a study of specific gravity (75 patients, 172 observations) felt that below 1.050 showed anemia (average normal 1.053 from literature) and on this basis 66% in first trimester, 70% in second, and 83% in third; 69% in first six months, 19% throughout, 100% in eighth month, 85% in puerperium showedanemia. From his observations he felt values from 1.040-1.050 could be considered physiological indicating a normal hydremia.

Feldman et al (34) found an increase in water content from about 81.2% to 82.5% (greatest at 220-250 days) which returned to normal in 30-60 days postpartum. He also observed a slight decrease in total protein suggesting dilution or hydremia.

Adamson & Smith, 1932 (2) did blood volumes on eight patients, red cell counts, hemoglobin, and cell volume at three

stated, "There is no doubt that there is a significant difference between non-pregnant and pregnant patients and that pregnancy, in a corresponding stratum of patients, lowers the hemoglobin at least relatively." 63.2% were anemic according to non-pregnant standards, only 11.6% by pregnant statistical standards. They placed the statistical normal minimum at 10.16 grams hemoglobin; 33.11% cell volume; and 3,360,000 R.B.C. They felt that these changes were not affected by treatment. They observed changes of 2, 3, and even 6 grams hemoglobin in periods of four to six weeks in individual patients.

Polowe, 1932 (70) from a study of specific gravity (75 patients, 172 observations) felt that below 1.050 showed anemia (average normal 1.053 from literature) and on this basis 66% in first trimester, 70% in second, and 83% in third; 69% in first six months, 19% throughout, 100% in eighth month, 85% in puerperium showedanemia. From his observations he felt values from 1.040-1.050 could be considered physiological indicating a normal hydremia.

Feldman et al (34) found an increase in water content from about 81.2% to 82.5% (greatest at 220-250 days) which returned to normal in 30-60 days postpartum. He also observed a slight decrease in total protein suggesting dilution or hydremia.

Adamson & Smith, 1932 (2) did blood volumes on eight patients, red cell counts, hemoglobin, and cell volume at three

weeks prepartum and ten days postpartum. All showed a decrease in plasma volume of 500-800 cc while the blood loss at delivery is about 300 cc showing a plasma volume loss of 200-500 cc greater. Coincident there was a rise in hemoglobin, red cells, and cell volume suggesting dehydration postpartum. Their blood smears were normal.

Oberst & Plass, 1936 (65) studied ten non-pregnant, 10 pregnant and 10 parturient women finding a significant increase in water concentration of whole blood during gestation, returning to near normal near delivery, and going sub-normal at delivery. One week postpartum, figures were normal. They felt that the hemoglobin content of the cells (grams per kilogram) was increased in the latter months of pregnancy, increasing further during labor (approximately 7% then) and decreasing slightly postpartum. "With water concentration of the cells rising slightly during gestation, it may be assumed that the corresponding increase in hemoglobin represents actual new production." They felt that the changes at delivery could be resolved to dehydration. They say in conclusion, "The slight anemia of normally pregnant women recognized by clinical methods is only apparent and can be explained by physical dilution of the blood associated with an increase in blood volume and by the further dilution of finger-prick blood with the fluid from edematous subcutaneous tissues."

Pastore, 1936 (67) found a dehydration of 0.3% of the body

weight in the first three days postpartum, and that, cell volume increased on the third day postpartum if the blood loss at delivery was less than 0.3% of the body weight. He feels that thesefigures are constant enough to calculate the cell volume on the third postpartum day at the time of delivery.

Richter et al (72) examined 99 patients finding 51 showing reduction in red cells and hemoglobin, with color indexes of .9-1.0. Blood volume determinations were made on 14 of these, 8 treated and 6 not. Of the 8 treated there was a reduction of 1,871 cc (1,327 cc plasma) in blood volume and an increase of 3.2% in mean cell volume. Of the six untreated there was an average drop of 1,809 cc (1,361 cc plasma) of blood volume and an increase of 51.% in mean cell volume.

Suwa (89) studied 146 pregnant women finding no change up to the fourth month; diminution in R.B.C. and hemoglobin in mid-pregnancy, greatest in primipara in the ninth month and multipara in the tenth month, further slight decrease in the first and second stages of labor, greatest one to three days postpartum, with gradual return to normal.

Rowe (74) examined 77 patients finding the average hemoglobin prepartum, 66% (Dare) and postpartum, 73%; average R.B.C. 4,140,000 antepartum and 4,380,000 post partum; average color index antepartum 0.80 and postpartum 0.83. He felt these changes could be explained on the basis of a 10%

increase in blood volume during gestation and dehydration at delivery. In some cases the hemoglobin showed a greater drop than the R.B.C. and had not returned to normal in eight weeks postpartum; hence some showed some other factor then hydremia.

Dieckmann & Wegner, 1935 (27) "In a careful review of the literature, we have not been able to find any data which absolutely demonstrates an increase, but we have found a marked lack of uniformity in the reports".

From De Lee (25) "The total quantity of blood is augmented, especially in the last month, a true plethora existing (Kaboth & Zuntz), a fact proved by Miller by means of the 'vital red' method, the volume being between 6 and 9% of the body weight (Bohnin, 7-7.3%), the gain being from 400-500 grams.

Kerher (46) reviewed the literature to 1923, finding that there was during the second half, and especially the last two months, a marked increase in blood volume; non-pregnant 5-6.3% of the body weight, 7-8.3% in pregnancy.

Spiegelberg & Bescheidler (80) found blood volume increase in dogs from normal of 7.87%, to 10.5% in the last half of pregnancy.

Miller et al (56) found the normal blood volume to be 80-91 cc per kgm., average 87 cc; in pregnancy - 67-115 cc per kgm., average 96 cc.

Changes must be 5% to show change as this is observed normally. "Previously reported values for blood and plasma volume

in pregnancy are at variance with each other, due to the methods used and the method of calculating. The volumes are reported either in cc per kgm. or in per cent of the body weight, either of which is unreliable because of the constantly changing weight in pregnancy." "Statistical analysis indicates that the changes are of no significance." From their studies on the same women throughout pregnancy they found the blood and plasma volume begin to increase in the first trimester and by the thirteenth week the gain is 16%, and 18% respectively. At term the blood and plasma volume are 23% and 25% above normal respectively. They termed this, "oligocythemia hypervolemia". At eight weeks postpartum there was a decrease of 16% (discrepancy to gain in weight retained after pregnancy). Values from the literature are shown in Table V. (27)

I believe we are now justified in saying that there is a normal increase in blood volume ranging from 18-25% (approximate) progressing till labor, when blood volume returns to normal in the first three days or more postpartum. Also that this is largely an increase in the water content of the blood, and results in a commensurate lowering of hemoglobin, R.B.C., and cell volume. The color index should remain very nearly 1.0.

As for explanations for this phenomena, Polowe, 1932 (70) suggests (on basis of specific gravity) that it is to allow transudation of fluid into the amniotic sac and thus forming the amniotic fluid.

Adamson & Smith, 1932 (2) state that the plasma is concerned mainly with katabolism (that is, building of tissues), since it carries food products, and that the cellular elements (namely red cells) are concerned with anabolism (carrying oxygen and carbondioxide). Since the pregnant woman is most concerned with building new tissues; she should have more plasma and less red cells.

Diekmann & Wegner (21) found foetal blood to have an oxygen capacity of 32% prenatal and 23% postnatal. Blood from the umbilical vein (arterial blood) is 63% saturated, while normal arterial blood is 95% saturated and venous 71% saturated. From their oxygen studies they say, "Sufficient oxygen could be brought to the placenta, either by increasing the blood flow per minute, which would allow less time for gaseous diffusion, increasing the concentration of hemoglobin in the cell, or by increasing the number of red cells. The latter would result in an increase in the viscosity of the blood and require more work by the heart. However, if both cells and plasma are increased proportionately, there would be no increase in viscosity, and gaseous exchange would be normal. The blood and plasma do increase, but the increase in plasma is greater thus reducing the viscosity, and, as a result, the periferal resistance may be dimished, thereby increasing cardiac output. The result is that more time is permitted for proper foetal respiration.....The changes in blood volume, cell volume and hemo-

Table V

Blood Volume in Pregnancy*

Authors	Method	Blood Volume in Per cent			No.
		Non-Pregnant	Preg. at term	Puerp.	
Plesch.....	CO.	4.7-6.1	—	—	-
Zuntz.....	CO.	—	8.4	6.9	6
Schoenholz.....	CO.	6.3	6.7	6.5	40
Schoenholz.....	Trypan Red	—	9.0	—	9
Fries.....	Anti-toxin	7.9	7.4	8.7	10
Mahnert.....	Refrac-tometric	6.3	8.0	—	10
Gueissa & Wanner..	Refrac-tometric	—	12-15% incr.	—	12
Kaboth.....	Congo Red	6.2	6.8	—	20
Neubauer.....	Congo Red	6.8	7.4	6.2	8
Koch & Jakabovits.	Congo Red	5.7	5.4	—	24
Bohnen & Boormann.	Congo Red	6.4	7.6	—	20
Bottcher.....	Trypan Red	8.4	9.7	—	10
Hnatek.....	Trypan Blue	7.8	9.4	8.6	-
Rowntree & Brown..	Vital Red	80.2-91.3 ave. 84.2cc/kg	—	—	-
Rowntree & Brown.	Congo Red	Pl. 47.8p56 ave. 50.5cc/kg	—	—	-
Miller, Keith & Rowntree.....	Vital Red	—	9.6 67-115, 91cc Pl. 38.1-72.7 ave. 54.5cc/kg	— 85.7	13

*From Dieckmann & Wegner

globin are a part of the mechanism by which the body is able to take care of its own increase in tissues and the metabolism of the foetus with the expenditure of the least amount of work."

These changes have been termed, "physiological anemia", but this is a missnomer and best dropped.

Hypochromic Anemia in Pregnancy

Definition. The most common anemia in pregnancy is a microcytic, hypochromic anemia of slight to severe degree, low color index, insidious in onset, slowly progressive, usually asymptomatic, associated with pregnancy, frequently improving postpartum, and due to an iron deficiency.

It has been referred to under a number of different names such as, nutritional anemia of pregnancy, chlorotic type of pregnancy, (43); physiological anemia of pregnancy, secondary anemia, (93); achlorhydric anemia of pregnancy (23); but hypochromic anemia probably is the better term as it classifies it on a more accurate basis.

Incidence. This anemia is extremely wide spread and has been reported in all European countries, America, India and the far east, (93). Race and color seem to play no part in this anemia.

Age. The age incidence is that of the child bearing period but may be prolonged to old age as the hypochromic anemia of Witt's. The incidence seems to increase with the advancing years.

Sex. The sex distribution is that of the female entirely and a direct relation to pregnancy is usually found. The patient dates her illness from some previous pregnancy or is pregnant at the time. If, as is intimated above, this anemia

is identical with that described by Witt, a few cases have been recorded in males.

Parity. It is difficult to differentiate between age and multiparity in small series of patients, and no series large enough has been reported, but some men feel that multiparity as well as age increases the incidence and severity in direct relationship (47). The incidence increases markedly as pregnancy nears term (63).

Social Status. In numerous comparative studies between clinic and private patients, a higher incidence of anemia has been pointed out in the clinic patients, (14), (1), (35). The factor of importance here is probably not social status but dietary differences.

Seasonal incidence. Davis & Walker (28) studied 189 pregnancies finding and incidence of 43-56% in the summer, and 90-95% in February and March. These are the only authors to point out a seasonal variation.

In Table VI the various per cents reported by different authors are shown. From this we see the percentage varies markedly between different authors; 3% by Schultz (77) to 95% by Davis & Walker (24). If we look more closely, we see, especially in the larger series, that the variation is more or less dependent upon the level of hemoglobin accepted by the author as minimal. In past pages it has been shown that hydremia is a frequent occurence in pregnancy and that it may

Table VI

Incidence of Anemia in Pregnancy

Author	No.	Definition of Anemia	Per Cent Anemia
Davis & Walker (24)	189	<70%* Hb. & 3.5 m R.B.C. (summer & <75%* Hb. & 4. m & smear evid. fall)	43%
		<70%* Hb. & 3.5 m R.B.C. (Feb. & <75%* Hb. & 4. m & smear evid. Mar.)	56%
			90%
			95%
First & Goldstein (35)	1000	<3.6 m R.B.C.	47.4%
		<70%# Hb.	58.6%
First & Goldstein (35)	100 priv.	<3.5 m R.B.C.	26%
		<70%# Hb.	62%
	179 ward	<3.5 m R.B.C.	52%
		<70%# Hb.	80%
Moore (58,59)	300	Sufficient to require R/	50%
		Non-pregnant standards	63.2%
Adair et al (1)	7412	<10.16 gm Hb.; 3.36 m R.B.C.; & 33.11% C.V.	11.6%
		<10 gm Hb. private patients	7%
		<10 gm Hb. clinic patients	12%
Toland (90)	670	<8.6 gm Hb.	.6%
		<10.1 gm Hb.	9.4%
		<10.9 gm Hb.	36%
Davis & Shelley (23)	51	<9.66 gm Hb.	12%
Galloway (36)	222	<11.25 gm Hb.	65%
Kerwin & Collins (47)	115	<10 gm Hb.	—
Kilduffe (49)	12	<13.78 gm Hb.; 4. m R.B.C.; 1st tri.	—
	72	<13.78 gm Hb.; 4. m R.B.C.; 2nd tri.	91%
	216	<13.78 gm Hb. ; 4.m R.B.C.; 3rd tri.	87%
Polowe (70)	75	<1.040 specific gravity	16%
Rickter et al (72)	99	0.6-0.8 color index	11%
		<10.35 gm Hb.	78%
Jerlov (44)	1143	<9.66 gm Hb.	25.9%
Boycott (15)	222	<11.04 gm Hb.	22%
		<9.66 gm Hb.	11%
Davidson (22)	819	<11.04 gm Hb.	49.5%
		< 9.66 gm Hb.	17.5%
		< 8.28 gm Hb.	5.5%
Mackay (53)	109	9.66-11.58 gm Hb.	56%
		< 9.66 gm Hb.	4.5%
Balfour & Drury (8)	311	<11.04 gm Hb.	14.5%
		<9.66 gm Hb.	7.4%
Lyon (50)	177	<12.14 gm Hb.	32%
Esch (31)	700	<10.35-11.04 gm Hb.	15%
		<10.19 gm Hb.	8%
Adamson & Smith (2)	200	10.35-11.98 gm Hb.	50%
		8.56-10.19 gm Hb.	20%
McGeorge (54)	100	<10.35 gm Hb.	16%
		<8.28 gm Hb.	2%
Schultz (77)	567	Not given	3%
Bethell (10)	66	<3.7 m R.B.C.; & 11.3 gm Hb.	70%

*Hayden & Hansen
#Dare

result in lowering the hemoglobin to as low as 10 gms. For this reason articles, not presenting figures on the number of cases below this fugure must be discarded.

Adair et al (1) in the United States (7,412 cases), found 7% of private patients and 12% of clinic patients below 10 gms; Toland (90) in the United States (670 patients), found 9.4% below 10.1 gms; Davis & Shelley (23) in England (51 patients), found 12% below 9.66 gms; Jerlove (44) in Denmark (1,143 patients), found 25.9% below 9.66 gms; Boycott (15) in England (222 patients), found 11% below 9.66 gms; Davidson (22) in England (819 patients), found 17.5% below 9.66 gms; Mackay (53) in England (109 patients), found 4.5% below 9.66 gms; Balfour & Drury (8) in England (311 patients), found 7.4 below 9.66 gms; Esch (31) in Germany (700 patients), found 8% below 10.19 gms; Adamson & Smith (2) in Canada (200 patients), found 20% below 10.19 gms; McGeorge (54) in New Zealand (100 patients), found 16% below 10.35 gms. From these we can feel that 5-30% covers the incidence and more than likely, it is 10-20% over most of the world. Rickter et al (72) in the United States (99 cases), found 78% below 10.35 gms; and Schultz (77) in Germany (567 patients), found only 3% but these figures are out of line with those of most authors. Mackay's (53) figures were taken on girls in a home where the diet was probably more nearly adequate than in the other series.

Rickter et al (72) on the basis of color index of 0.6-0.8 found 11% anemic and Polowe (70) (75 patients), on the basis of specific gravity below 1.040 found 16% anemic; both in the United States.

Etiology. Plass, 1936 (69) has grouped the various etiological information into the following outline which I will follow.

I. Factors favoring the development of hypochromic anemia in pregnancy.
   1. Inadequate diet.
      a. Low normally.
      b. Due to nausea and vomiting.
   2. Defective utilization.
      a. Tendency to hypo or anacidity.
      b. "Gastric factor" deficiency.
   3. Foetal demand.
      a. Foetus receives adequate at the expense of mother.
      b. Foetus requirement.
   4. Foetal iron storage, greatest in last trimester, 3 mg. per day as to 2/3 mg.
   5. Maternal demands for new tissues, 1/2 mg. per day.
   6. Total requirements are about 1 mg. per day throughtout pregnancy.

II. Compensatory factors operating to preserve iron equilibrium.

1. Natural reserves-hypothesis that there is a storage began at puberty (chlorosis).

2. Economical iron metabolism greater than normal.

III. Factors serving to confuse the picture.

1. True hydremia.

2. Increase in volume.

IV. Other pertinent data.

1. Increased rate of formation of R.B.C. and hemoglobin content.

2. Increase in R.B.C. and hemoglobin toward end of pregnancy inspite of increased drain (slightly above normal level, much due to concentration).

V. New data bearing on the problem - parturitional blood concentration as shown by hematocrit figures.

Those factors involved in III, IV and V have been discussed previously in this paper under normal pregnancy and will be omitted here.

I. Factors favoring the development of hypochromic anemia in pregnancy. 1. Inadequate diet. a. Strauss and Castle (82) 1932, felt that anemia was more marked in women with poor diets. Beard & Meyers (9) felt that iron deficient diet was partially responsible for the anemia observed in 138

pregnancies in 87 rats. Adair et al (1) after studying 7,412 cases felt that the difference of incidence of anemia in private patients and clinic patients was due to differences in diet and hygiene. Davis & Shelley (23) emphasized dietary deficiency as an etiological factor as do Gray & Wintrobe (39). Strauss & Castle (84) in a study of 30 patients with hypochromic anemia (less than 7 gms.) found 22 had had poor diets over a period of years. Many other authors have pointed out the high percentage of dietary deficiencies among these anemia patients. The foods most emphasized as lacking are meats, fruits and vegetables.

Vaugham (93) points to heritage as co-operating against the patients when he states, "There is still a mistaken idea that meat is bad for pregnant women, and many well-to-do women take a diet throughout pregnancy on their doctor's orders which is deficient in essential factors."

b. In pregnancy we find still other factors tending to lower the iron in the diet. Nausea is very common and frequently results in anorexia or fickle appetite, and vomiting all of which tend to limit the food intake.

2. Defective utilization. a. Mettier & Minot (55) showed that the efficiency of iron utilization or absorbtion was dependent upon the acidity of the stomach in direct relationship.

Evy and his co-workers (32) performed gastrectomy on

dogs, finding no anemia developed, but when pregnancy occured, in every case a hypochromic anemia developed which was cured by cod liver oil by mouth and iron subcutaneously. They conclude, "We believe that the achlorhydria is a predisposing factor for the development of anemia in that it reduces the factor of safety of digrestion."

In this connection it is interesting to note that Kehrer (93) as early as 1905 (before the Rehfus tube) found a decrease in hydrochloric acid in pregnancy.

Arzt (6,7) studied the acid content of the stomach in 50 cases with shredded wheat and 300 cc of water, finding a decreased amount of acid in all, greatest in the first three months, less marked later; 29 showed achlorhydria in the first three months. Strauss (81) emphasized the importance of the achlorhydria in three cases of severe hypochromic anemia with normal diets. Strauss & Castle (84) found 75% of 24 normal pregnancies secreted little or no acid and improved postpartum. Davis & Shelley (23) studied 51 pregnancies, all showed a progressive lowering of HCl, worse in the last trimester (two with achlorhydria - not histamine) and all showed good acid secretion postpartum. Six of their cases showed hypochromic anemia and the gastric analysis in these showed two hypochlorhydria, three achlorhydria, and one normal acid. The one normal acid had a very poor diet and was delivered of twins. They believed the

achlorhydria to be the most important single factor in etiology of hypochromic anemia in pregnancy. Strauss (84,87) in a study of 30 patients with hypochromic anemia (less than 7 gms) and no concomitant disease or hemorrhage, found 17 had an anacidity with histamine. Even postpartum 10 had little or no acid after alcohol test meal and diminished after histamine, two had normal acid postpartum. From his dietary studies of these 30 patients, he found that all had a poor diet or hypoacidity or both. Green Armytage (40), Kickham & Titus (48), Sharp (78), and others have emphasized hypochlorhydria and achlorhydria as the etiological factor in this anemia.

b. "Gastric factor" also known as "intrinsic factor of Castle" tends toward production of a macrocytic type of anemia and will be referred to under that subject.

3. a. Numerous studies have failed to show any differences between the infants of anemic mothers and those of normal mothers at birth. Apparently the infant will obtain the iron necessary for a normal blood picture at birth regardless of the condition of the maternal blood. This will be referred to later.

b. As all studies of new borns indicate, the blood is higher in hemoglobin and hemoglobin carrying elements than that of the adult. This is lost a few days after birth and is evidenced by the icteric tint to the skin of many newborns.

Plass (69) gives us these figures, hematocrit 52% (adult 40%), and hemoglobin 16.50 gms. (adult 13.75 gms) which are fairly representative.

4. Foetal iron storage. Coons (17) from a study of 23 iron balances on women at different stages of pregnancy found the intake to be 9.69-19.49 mgs. per day and retentions of 0.88-6.97 (one-2.21 mgs.). It was high early in pregnancy for the development of maternal tissues, and late for foetal demands (somewhat lower). From the study of the literature on analysis of human foetuses a special committee (19) found the average daily requirement for foetus to be 0.4 mg. during the first two-thirds of pregnancy and 4.7 mg. during the last one-third, average foetal iron content 375 mg. (17)

Plass (69) uses the figures 3 mgs. per day in the last trimester and two-thirds mgs. per day in the first and second trimesters.

Bethell (10) gives the foetal iron content as 350-450 mgs. He made an iron balance on one normal patient for 63 days antepartum and 12 days postpartum finding the intake to be 2.20 mgs. and the output 2.15 mgs. per day showing no significant retention.

Coons and co-workers (18) in a later work found a positive daily balance of 3.16 mgs. on a daily intake of 14.72 mgs., foetal requirement of 8 mgs. per day at term, (during last trimester 4.7 mg per day) all average values.

5. Maternal tissues require about one-half mgs. per day and total requirement about 1 mg. per day throughout pregnancy (69).

This has been credited by many to be the equivalent of chronic mild hemorrhage.

II. Compensatory factors operating to preserve iron equilibrium. 1. Natural reserves. It has been long felt that there are iron reserves in the body. This is evidenced by the rapid recovery following acute hemorrhage when the iron reserves are present, and the slow recovery from chronic hemorrhage when these reserves are depleted. It has been suggested that the laying down of these reserves occurs at or about puberty, especially in the female for future pregnancies. It has been suggested that chlorosis results from the too rapid laying down of these reserves and resultant privation of the organism for iron. These are merely theories and as far as I know lack experimental foundation.

2. Coons (18) from iron studies felt that iron metabolism was more economical in the pregnant female with a resultant saving of available iron.

Other etiological factors that have been suggested are syphilis, infection, poor health, poor hygiene, and many other types of infection but no one has been able to demonstrate the importance of these. Toxins of various kinds have been suggested but these theories are true "Arm chair" phylosophies with no foundation. Strauss and Castle (85) have torn down these factors rather nicely when they said, "The

first that a toxic hemolysin is produced by the foetus or placenta is unsound, since there is no evidence that such a factor exists or that there is increased hemolysis under the conditions of normal pregnancy. The second that toxic inhibition of the bone marrow occurs, lacks, in the first place, evidence of the existing toxin; second, evidence that inhibition of the leukocytes such as is found in other types of toxic action on the bone marrow; and third, evidence that the hemoglobin returns to normal during the third month after delivery when the toxic factor should no longer be present."

Conclusion. In conclusion allow me to say that the bulk of evidence supports Strauss and Castle and co-workers (81, 82, 83, 84, 85, 88), and others in the contention that the factors of major importance are: 1. Iron deficient diet, 2. Achlorhydria or hypochlorhydria, and 3. Foetal demands. Or as Strauss (81) says, "It is believed that the added demand of pregnancy for hemoglobin, resulted in an iron deficiency condition by gastric achylia."

Lately Bethell (10) has made some observations (66 cases) under well controlled conditions which tend to discredit these findings. He feels that the low level of hydremia is 11.3 gms. of hemoglobin and 3,700,000 red cells and on this basis 70% were anemic. His patients were maintained in an institution for most of the last trimester of pregnancy and consequently received a better than average diet. He did an iron balance

on one patient for 63 days prepartum and 12 days postpartum maintaining a balance on 7.1 mgs. daily intake and the output figures over the entire period practically equalled those of the intake showing no significant retention. He also states that the average foetus contains 350-450 mgs. of iron and that this amount is equal to the amount saved by the amenorrhea for ten periods plus one medium sized transfusion. These figures minimize the importance of foetal demands. The patient on whom the iron balance was done, showed an achlorhydria to the alcohol test meal on two occasions (present with histamine), but the blood picture was a high normal for pregnancy tending to discredit the importance of achlorhydria. He desires to divide this anemia into two about equal groups; 1. hypochromic microcytic, low color index. 2. normocytic, normochromic, normal color index. 1. is an iron deficiency and he believes he can show definite response to iron therapy. 2. is not an iron deficiency and does not respond to iron. He feels that this is a protein deficiency and responds well to protein of "high biologic value" as in milk. The cells tend to become spherical ("sphero-cytosis") in this type. These observations are supported by some work done on rats not yet published.

In a small control group of normal non-pregnant women (nurses) he (10) found an almost identical proportion showing the cellular characteristic of these two groups. This led

him to say, "The explanation of occurence of hypochromic anemia in pregnancy is not to be found in the circumstances incident to gestation, but should be sought in the status of the hematopoietic mechanism prior to conception".

Dameshek (21) says, "In conclusion, I cannot refrain from mentioning the constitutional or hereditary tendency which is particularly noticable in diseases of the blood forming organs"; which is along the same lines of thought. These articles suggest new fields of endeavor and may prove to be forerunners of a profound concept of anemia.

Morbid Anatomy and Physiology. I have been unable to find any studies on the pathology involved. These women rarely die of the anemia and no one has made biopsy studies of the bone marrow although this has been suggested numerous times. Maybe in the future we may learn some startling facts to this effect.

Symptoms and Signs. Strauss and co-workers (81, 84, 87, 88) have made the outstanding studies in this anemia and have given us the most complete list of symptoms. From their studies (84) of 36 cases of anemia below 7 gms. hemoglobin and 2,500,000 red cells without obvious cause, they found the chief presenting symptom to be pallor. This with a lack of the sense of well-being and excessive fatiguability are about the only symptoms present early and when mild are frequently laid at the door of the "woman's condition". They appear in

mid-pregnancy or later and gradually, progressively, slowly become worse frequently never becoming severe enough to be brought to the doctor's attention. They frequently disappear postpartum or may be lost in the other complaints relative to the pureperium. They may persist for years as mild chronic ill-health and lead to a diagnosis of hypocondriac or psyco-neurotic personality. If the anemia progresses to a more severe condition, all of the symptoms relative to anemia appear. Dyspnea and prostration, even edema appear. Splenomegaly in almost 10% of the severe cases is observed. Palpitation is frequent in all stages. Brittle, spoon-shaped nails, atrophy of the lingual papillae, and glossitis are present in cases where the anemia was present for sometime before pregnancy. The temperature is almost never elevated unless infection is present. The pulse is likely to be somewhat rapid and hemic murmurs are frequently heard in severe cases. The only physical finding frequently is pallor of a mild degree. The anemia is frequently found on a routine blood examination.

Laboratory findings. The laboratory findings are normal except for the blood findings which will be discussed under diagnosis. Albuminuria is rarely present (93).

Diagnosis and Differential Diagnosis. There are no clinical symptoms which are specific of this anemia but vague complaints of weakness and easy fatiguability associated with

pallor in a pregnant woman should arouse suspicion and a blood count be done. The diagnosis rests entirely upon the blood findings for which there is no obvious cause. Such causes of secondary anemia as hemmorrhage, malaris, "rheumatism", parasites etc. should be considered and ruled out (73). Other factors to be considered are hydremia and the wide range of values found normally in pregnant women; these have been referred to before.

Plass (69) says, "it is unwise to diagnose hypochromic anemia of pregnancy unless repeated determinations show the red count to be below 3,500,000 and the hemoglobin below 10.8 gms." Numerous definitions have been given by various authors for the lower limit of normal in pregnancy and these are fairly well shown in Table VI under definition. Plass (69) is the only one given here as it is fairly representative and was determined after a study of the literature.

Roberts (73) states that the hemoglobin must be below 10.8 gms. and the red cells have pale or clear centers and be of small size. Strauss (88) states that the disease is easily recognized from the periferal blood. The color index is low, moderate anisocytosis and poikilocytosis, small red cells with low hemoglobin content, and diminished mean corpuscular volume. Strauss and Castle (84) from 30 cases found marked reduction in hemoglobin, less in red cells, small pale erythrocytes, moderate variation in size and shape, no true

microcytes, macrocytes, tailed or oval forms. Leucocytes and platelets have been reported as normal in most cases (84, 88, 73). Mussey et al (61) felt that a large per cent showed toxic changes in the leucocytes. Sharp (78) from a study of the literature says that the findings were identical with those of idiopathic hypochromic anemia. Boycott (15) felt that the color indexes of 0.9 or above were normal and below 0.9 showed anemia. He found the normal mean diameter as determined by the Price-Jones method was 7.202μ ± 0.172μ and the normal variability 6.326 ± 0.331%, while those for this anemia tended to be lower. Rickter et al (72) felt that the color index should be below 0.8 for a diagnosis. Polowe (70) felt that specific gravity below 1.040 showed anemia.

Gastric findings are of no importance for a diagnosis. The diagnosis rests upon the finding of a hemoglobin of 10-10.8 gms. or below, a somewhat proportionately smaller lowering of the red count, a color index of below 0.9, decrease cell volume, and evidence of hypochromia in the smears, in the absences of demonstrable etiological agents. If these points are kept in mind, the diagnosis need not be missed.

Pernicious anemia of pregnancy may be confused with this but this disease is a macrocytic anemia, with high cell volume and color index, relatively greater lowering of the red count and responses to liver and similar principals. It

is a very severe acute anemia often producing fever and splenomegaly and progressing rapidly to recovery or death postpartum. It is rare in this part of the world and will be duscussed more in detail later.

Course and Prognosis. During pregnancy the course, without treatment, is slowly progressive being most marked after the sixth month (61, 1, 90, 20, 43, 44, 63, 72). Nalle (5) observed a slight improvement in the eighth and ninth months. During the puerperium there is a slightly further decrease for about three days and then frequently slow improvement occurs, (1, 15, 20, 24, 35, 42, 43, 50, 61, 72, 90) and others. Many of these authors agree that the anemia is likely to persist for many weeks postpartum unless treated. Many of the above authors and others have observed improvement with adequate iron therapy but few have ever succeeded in raising the blood to normal figures until postpartum. They are agreed that adequate iron therapy produces a rapid return to normal and complete recovery postpartum. Failures have been recorded when the pregnancy was complicated by some factor such as, pyelitis, chronic infection, focal infection, and poor general health.

The prognosis for life is ordinarily good but depends upon the severity of the anemia. In temperate climates the incidences of severe anemia is ordinarily so small that it is of little importance. Adair et al (1) over a period of

three years eight months (906 anemic patients) observed that only two deaths occured in which the chronic anemia was a possible factor.

Davis and Walker (24) in 189 pregnancies felt that the anemic group, untreated, showd more premature deliveries, greater number of toxemias, higher foetal mortality, higher morbidity and longer labor than the corresponding group of treated cases. Adair et al (1) stated that properly treated cases are less likely to have toxemia, tolerate labor better, have more resistance to infection and recover more rapidly. Nalle (63) makes the following statement, "an anemia of such severity as to interfere decidedly with the well-being of the patient during pregnancy; to impair her endurance during labor; to lower her resistance to disease and infection of pregnancy and the pueperium; to predispose her to the toxemias of pregnancy; and to make miscarriage and premature births more frequent." Machay (53) has suggested that anemia predisposes to infection. The above thoughts give the reader an idea of some of the theories advanced by different authors.

These are true theories as no series of sufficient size to be at all conclusive, has been analysed.

<u>Treatment.</u> Adair et al (1) pointed out the changes in hemoglobin 2, 3, and even 6 gms. were not unusual in pregnancy. Other authors have observed these changes, and consequently one must be very careful in interpreting information as to

results of therapy. I shall not enter into the arguement of the value of therapy but shall say only that the majority of observations and the opinions of those who have done the most work is that iron therapy in adequate amounts produces definite results. The question of the most suitable preparation is immediately raised. Witts (97) from a study of various iron preparations, Table VII, said, "The most active preparation of iron is not necessarily the most suitable for prescription, and the choice of a preparation for medical use is governed by a number of additional factors such as, price, palatability, tolerability, durability, and ease of prescription. The soluable simple salts of iron are all irritating to the stomach. The ferrous salts tend to oxidize in solution, though this may be inhibited by avoiding over-dilution and making up the mixture with glucose and/or acid, if they are given in solid form they may cause vomiting whilst tablets become hard and insoluable unless carefully and freshly prepared. The solution of ferric chloride is intensely irritating, and I have found it quite impossible to use in effective doses till I learnt the device of adding it to milk immediately before taking. The massive amounts of iron which must be injested when reduced colloidal ferric iron, or the scale preparation are used may cause indigestion, diarrhea, cramps, and constipation and even intestinal obstruction. There is also evidence that large amounts of unabsorbed iron in the intestine may interfere with

Table VII*

Average Effective Dose of Common Preparations of Iron and Per Cent of Iron Administered Utilized for Hemoglobin Formation.

Preparation	Daily dose in gms. or cc.	Iron Content	Utilization (per cent)
Metallic			
Ferrum Redactum	1.5-6.0	1200-5000	0.5-2.0
Ferrous			
Ferrous Chloride	0.25-0.5	100-200	12.5-25
Ferrous Sulphate	0.6	180	14
Ferrous Lactate	1.5	300	8
Pil. Ferri Carb. (Blauds pills)	3.0-4.0	300-400	6-8
Ferric			
Liq. Ferri Perchlor.	8.0	400	6
Ferric Citrate	2.0	400	6
Idozan (Ferric Hydroxide)	30-45	1500-2250	1.1-1.7
Sol. Ferric Oxide	35	1000	2.5
Complex Ferric			
Iron et Ammonium citrate	4.0-8.0	800-1600	1.5-3.0
Injection			
Injection Iron B.P.	5.0-10.0	16-32	100

*Modified from Witts (97)

the absorbtion ofother minerals and vitamins. The ideal preparation of iron still awaits discovery, but the following are some useful and cheap prescriptions:

Ferrous Chloride 3 grs.
Syrup 15 Min.
Chloroform water to 1 drachm
e lacte tds pc

Pil ferri carb. 15 grs.
tds pc to be crushed before taking

Iron and ammon citrate 30 grs.
Glycerin 15 Min.
Td pc "

From Table VII we see that the most effective preparation is injection iron but it has been shown that this is dangerous and the margin of safety very narrow. The next most effective are the ferrous salts but these are said to be irriatating to the stomach in effective doses. Thomas Fitz-Hugh Jr. (91), Kickham & Titus (48), Corrigan & Strauss (20), Adair et al (1) and others have found ferrous sulphate a very effective and cheap drug with few gastric symptoms. I should like to call attention to this one in addition.

Other things that have been used are: bone marrow extract 2 gr. tid, powdered foetal liver teaspoon in grape juice (no effect) (61), Vitamin D (1), Cupperin A, 3 gms., liver extract Lilly 200-400 gms (43), arsenic (47,44) and aqeous liver extract and glycerated iron 1½ oz. (84.4 gms. liver, 104.24 mgs. iron, and 1.4 mgs. copper) (72). Transfusions have been recommended by various authors as a means of rapid recovery in severely anemic patients or in those where rapid recovery is advantageous.

Due to accidents in early work in transfusions. This useful tool suffered considerable criticism and a superstition has grown up that it is more likely to cause trouble in pregnancy inspite of adequate matching. Adair et al (1) state that it is a useful weapon in combating anemia, that it is specific for relief of anemia and it carries no additional hazard in pregnancy if typing is carefully carried out. I believe that is the general opinion of those men who have had the most experience with it.

Diet has been recommended by some as thebest method of control and prevention. All authors are agreed that the diet should be well balanced and plentyfully supplied with vegetable, particular green, and animal protein. Many authors feel that an adequate diet will prevent the occurence of this anemia, and that adequate doses of iron throughout pregnancy will prevent this anemia. Good hygiene, exercise, fresh air, and similar measures to promote general health are advantageous. Focal infection or other infection should be handled by appropriate measures for their early removal.

Pernicious Anemia of Pregnancy

Definition. "The pernicious anemia of pregnancy," as defined by Allen (3,4) " is an acute haemolytic anemia, which occurs in women under 35 years of age, is due to pregnancy, progresses steadily without remissions to death or recovery and is curable by blood transfusions."

Incidence. Allen (3) has taken the following figures from the literature. In the British Isles it occurs once in about every 2,000-10,000 pregnancies; 3% of Osler's cases of pernicious anemia began in pregnancy; Hoskins considers the condition common in northern India; McSweeney gives 1.69% in Calcutta; Balfour in Bombay more commonly. He believes it is not uncommon in North Carolina from his own studies. In 500 cases reported in the literature, 75% were under 30 years and 25% were primiparas.

Witts (96) from a study of the literature gives us these figures. Beckman 6 in 66,000 births in Vienna, none in 4,000 labors in Queen Charlotte's Maternity Hospital, one case in 10 years at Guy's Hospital.

Etiology. Pepper (68) says, "Unquestionably the evidence favors the view that the anemia is a hemolytic anemia, but no evidence to permit us to designate the

hemolytic factor at work".

Smith & Kinlaw (79) and Rowland (75) and others believe in view of the evidence of Strauss (82) and others on gastric analyses, that the etiology is the same as that in Addisonian pernicious anemia: that is, deficiency of extrinsic or intrinsic factors or poor absorbtion during prègnancy.

Symptoms and Diagnosis. Rowland (75) describes the disease as follows, "An insidious onset of anemia in the latter weeks of pregnancy, often not recognized till in the puerperium, usually antepartum symptoms of weakness, breathlessness on exertion, palpitation, dizziness, edema of the feet, and occasionally an associated definite toxemia of pregnancy with albuminuria and hypertension. Labor may come on prematurely, is characteristically short, and relatively painless. Still births may occur, but a living child does not share in the anemia and developes normally. Labor aggravates the anemia, and the patient may go into collapse at once if the anemia is marked. Typically there is a rapid progression in the anemia for the first week or two. Or it may be slow requiring two months before recognition.

Smith and Kinlaw (79) Studied 22 cases finding the following. Wasserman negative in 18, not done in 4;

no hook-worm; fever in all, 100 F or over in 19, 104-105 the highest; albuminuria of 1-3 in 18; 21 below 3,000,000, 16 below 2,000,000, 4 below 1,000,000; color index of 1 in 13; 16 showed definite anisocytosis and poikilocytosis; nucleated red cells (263 per 100 W.B.C.) only once; W.B.C. 8,000 or below in 15, 8,000-20,000 in the rest; 5 gave histories of recurrance (2 with observed recurrance) always in pregnancy, age 16-38 years average 26 years, 3 died.

Allan (4) gives us the following findings; appearance of severe anemia, lemon tint in ½, puffiness of face and feet common, weakness, vertigo, dyspnea, palpitation, poor vision, and especially sore mouth, diarrhea and vomiting, fever, retinal hemorrhages, enlargement of the spleen in 8-16%, pain and paraesthesias common, no cord lesions (probably due to short duration), blood pressure low or high, ½ showed albuminuria and urobilinogenuria and occasional casts and bile, hypoacxidity or anacidity not invariable, nucleated red cells, normoblasts in major, bile pigment of blood increased, increased fragility, leukopenia to leukocytosis, rapid death in a week or a recovery after months, insidious in onset, recovery unknown before labor, moretality 40% in literature, Gallup and O'Hare 50%, Larrabee 75%, and Delmen 87%, McSwenney 35%,

Balfour 42%, autopsy findings same as in chronic pernicious anemia.

Witts (96) calls attention to frequent (one-third) tendency to causeless hemorrhage from the nose, mouth, mucous membranes, and under the skin, liver enlargement occasionally. He describes the blood findings as meglocytic anemia, signs of rapid regeneration, polychromasia, punctate basophilia and nucleated reds. They reach a climax with remission after labor with recovery partial or complete. Fragility increase during pregnancy but returns to normal postpartum, W.B.C. normal or poly-leukocytosis, myelocytes from a few to a leukemic picture, platelets diminished or absent returns to normal, blood loss at labor below normal.

Differential diagnosis. Smith & Kinlaw (79) have given the following to be considered; Addisonian pernicious anemia, toxemia, puerperal sepsis, nephritis, and endocarditis. In all of these the differential diagnosis is very difficult and many times impossible except by the response to treatment. The diagnosis of any of these in the face of severe anemia is unwise until proper therapy has failed to give relief.

In this paper we are interested in differentiating it from hypochromic anemia which is easy. Hypo-

chromic anemia is less severe, more slow in onset, not associated with signs of toxemia or infection, improves postpartum and is a hypochromis microcytic anemia with low color index and cell volume. The smears alone will differentiate without difficulty.

Treatment. The treatment is the same as for true Addisonian pernicious anemia but frequently there is an associated iron deficiency and iron will frequently speed recovery or make it more complete. Transfusions have been emphasized (5) as a specific measure and are certainly advised where the patient's life is in immediate danger. They can be repeated and usually result in a cure in one, two, or three times. (5).

Effect of Anemia on the Child.

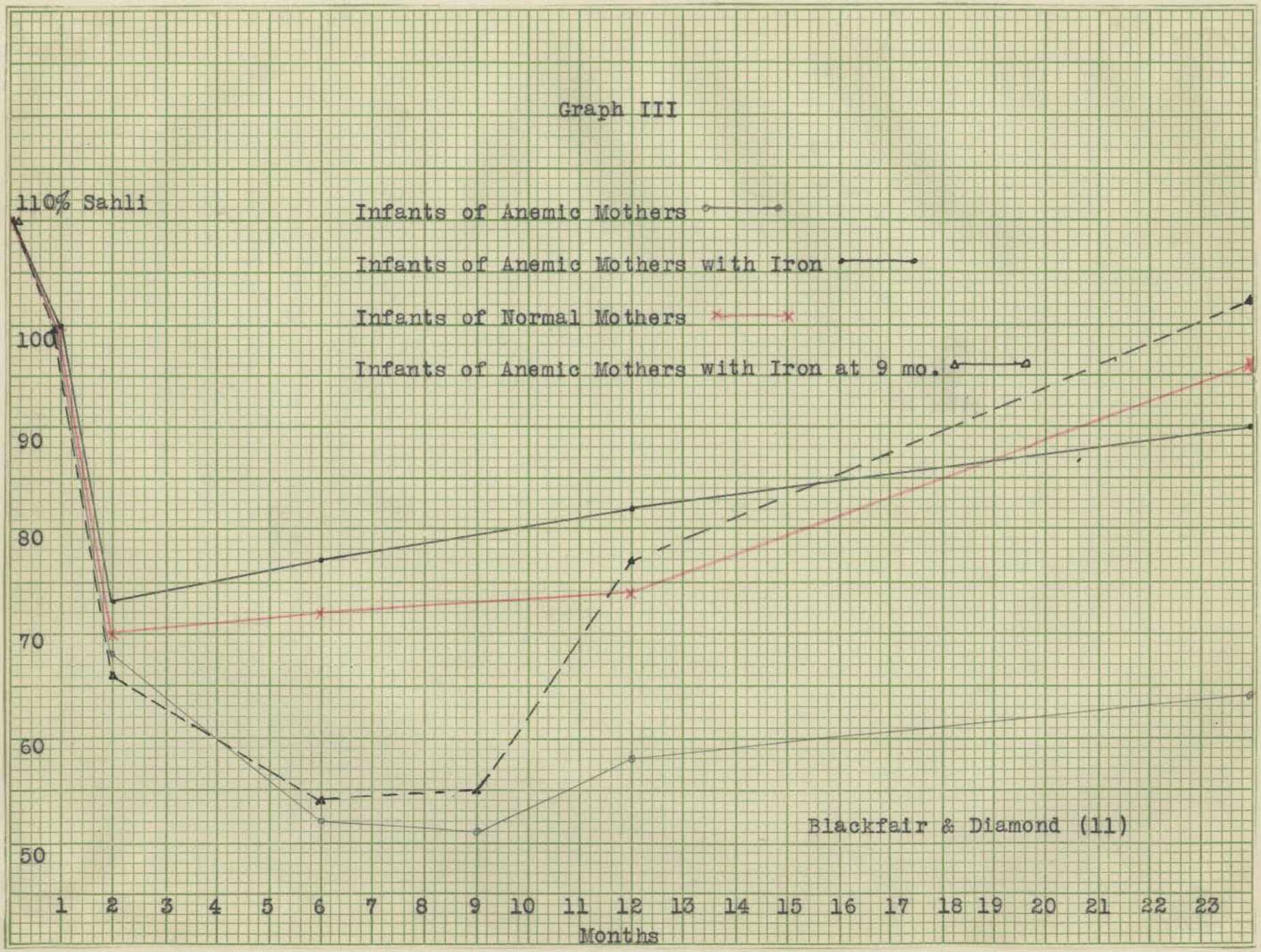
Numerous studies on infants at birth have failed to show any difference between those of anemic mothers and those of non-anemic mothers regardless of the severity of the maternal anemia. (1,11,51,52,53,84,86, 87,88, and others).

Mackay (51) in a special study of nutritional anemia in infancy in 1931 suggested that many of the cases occured in children of mothers who could be reasonable suspected of having had an anemia during pregnancy. In 1935 (52) he again noticed this relationship and felt that it was more than a casual one and in 1935 (53) felt that anemia in the mother predisposed to anemia in the infant.

Strauss (86) in 1933 studied 15 infants of mothers below 7.0 gms hemoglobin in the last trimester and 12 of mothers over 10.9 gms hemoglobin in the last trimester; within 48 hours of birth finding 18.1 gms. in the offspring of the anemic mothers and 19.2 gms. in those of the non-anemic which was regarded as insignificant because of the error of means being greater than the difference. The smears were normal. Six of each group were examined at one year (diet, care, infection, etc. being approximately equal in the two groups) finding all of those of normal mothers

to have 9.98 gms. or more, average 10,4 gms; of anemic mothers all were below 9.05 gms., average 7.18 gms; a difference of 3 times the probable error. Five other children (not examined at birth) of anemic mothers were below 8.74 gms., average 7.18 gms. at one year. The histology on the anemic showed small cells poorly stained, anisocytosis and poikilocytosis moderate to severe; R.B.C. were 4,440,000-5,810,000 average 5,040,000; hence they showed an iron difficiency anemia. Three cases of hypochromic anemia in the pregnant mother were treated with an R/ of 6 gms. of iron ammonium citrate daily in the last three months; average hemoglobin at birth was 10.30 gms.; the infants were normal at birth and at one year. The above six anemic infants were given 1 gm. of iron ammonium citrate daily (no other changes in the care) which resulted in a prompt response and the blood uas usually normal in one month. The microscopic appearance was slower in returning to normal.

Blackfair & Diamond (11) in 1936 from their studies shown in Graph III feel that anemia in the mother definitely predisposes to anemia of an iron deficiency type in the first year of life. This is probably due to deficient storage of iron in the last few months of pregnancy by the foetus and is readily curable by iron therapy.


Graph III
110% Sahli
100
90
80
70
60
50
Infants of Anemic Mothers
Infants of Anemic Mothers with Iron
Infants of Normal Mothers
Infants of Anemic Mothers with Iron at 9 mo.
Blackfair & Diamond (11)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
Months

Conclusions

1. That normal pregnancy is attended by a blood volume increase, a true plethora, due to water retention (hydremia), varying considerably in different patients and amounting to about a 25% increase.

2. That hydremia accounts for hemoglobin values down to 11 gms. and probably to 10 gms. and explains the lowered values found in normal pregnancy.

3. That 10-20% of all pregnancies in this country shows an anemia due to an iron deficiency, the exact mechanism of which is not too well understood.

4. That this anemia is curable by adequate iron therapy.

5. That this anemia is preventable by diet and in some cases additional iron therapy.

6. That there is a macrocytic anemia in pregnancy resembling Addisonian pernicious anemia and probably on the same etiological basis but of a temporary nature which is likely to become severe with a high mortality but is uncommon in this part of the world, and is curable by substances active in true pernicious anemia and by transfusions.

7. That anemia in the pregnant woman is no different from anemia in the non-pregnant.

8. That anemia during pregnancy predisposes to an iron deficiency anemia in the first year of life which is preventable by iron therapy in pregnancy or during the first year and is readily curable by iron therapy.

Literature Cited.

1. Adair, F. L.; Dieckmann, W. J.; and Grant, K.; Anemia in Pregnancy; Am. J. Obst. & Gynec., 32:560, 1936.

2. Adamson, J. D.; and Smith, F. H.; The Blood in Pregnancy; Canad. M. A. J.; 26:669, 1932.

3. Allan, W.; Hemolytic Anemia in Pregnancy; Surg. Gynec. & Obst.; 47:669, 1932.

4. Allan, W.; Hemolytic Anemia; Tr: a. Am. Physicians; 43: 103, 1928.

5. Allan, W.; Specific Action of Blood Transfusions in Hemolytic Anemia; South. M. J.; 22:624, 1929.

6. Arzt, F.; On the Gastric Juice During Pregnancy; Am. J. Obst. & Gynec.; 12:879, 1926.

7. Arzt, F.; On the Grastic Juice During Pregnancy; Am. J. Obst. & Gynec.; 20:382, 1930.

8. Balfour, M. and Drury, J.; Motherhood in Special Areas of Durham and Tyneside, London, 1935, p. 25.

9. Beard, H. H.; and Meyer, V. C.; Nutritional Anemia in Rat; Anemia in Pregnancy; Am. J. Phys.; 106:449, 1933.

10. Bethell, F. H.; The Blood Changes in Normal Pregnancy; J. A. M. A.; 107:564, 1936.

11. Blackfair, K. D. and Diamond, L. K.; Secondary Anemia in Infancy and Childhood; Int. Clin.; 1:119, 1936.

12. Bland, P. B., Goldstein, L., and First, A.; Physiological Anemia of Pregnancy, 1000 Patients; Surg. Gynec. & Obst.; 50:954, 1930.

13. Bland, P. B, and Goldstein, L.; Anemia in Pregnancy with Recovery, 50 Cases; J. A. M. A.; 93:582, 1929.

14. Bland, P. B., and Goldstein, L., and First, A.; Secondary Anemias in Pregnancy and the Puerperium, a Study of 300 Cases; Am. J. M. Sc.; 179:48, 1930.

15. Boycott, J. A.; Anemia in Pregnancy; Lancet, 1:1165, 1936.

16. Channing, W.; Notes on Anemia, Principally in its Connections with the Puerperal State and with Functional

Diseases of the Uterus with Cases; New Eng. Quart. J. Med. & Surg.1:157, 1842.

17. Coons, C.; Iron Retention by Women During Pregnancy; J. Biol. Chem., 97:215, 1932.

18. Coons, C.; Metabolism Studies in Pregnancy; Okla. Agri. Exp. Station, Bull. No. 223, 1935.

19. Growth and Development of the Child, Part III Nutrition; White House Conference Report, New York; p. 225, 1932.

20. Corrigan, J. C. and Strauss, M. B.; Prevention of Hypochromic Anemia in Pregnancy; J. A. M. A., 106:1088, 1936.

21. Dameshek, W.; Progress in Hematology 1929-1933; New Eng. J. Med., 210:531, 1934.

22. Davidson, L. S. P.; Fullerton, H. W.;and Campell, Q. M.; Nutritional Iron-deficiency Anemia with Special Reference to Prevalence, Age, and Sex Distribution; Brit. Med. J., ii:195, 1935.

23. Davis, D. T., and Shelley, U.; Hypochromic Anemia and its Relation to Pregnancy; Lancet, 2:1094, 1934.

24. Davis, M. and Walker, E. W.; Anemia of Pregnancy; New Eng. J. Med., 210:1315, 1934.

25. De Lee, J. B.; Principals and Practice of Obstetrics, ed. 5, Phil., W. B. Sanders Co., 1928, p. 105.

26. De Lee, J. B.; Principals and Practice of Obstetrics, ed. 6, Phil., W. B. Sanders Co., 1934, p. 413.

27. Dieckmann, W. J. and Wegner, C.; The Blood of Normal Pregnancy, I Blood and Plasma Volumes; Arch. Int. Med., 53:71, 1934.

28. Dieckmann, W. J. and Wegner, C.; The Blood of Normal Pregnancy, II Hemoglobin, Hematocrit, and Erythrocyte Determinations and Total Amount of Variation of Each; Arch. Int. Med., 53:188, 1934.

29. Dieckmann, W. J. and Wegner, C.; The Blood of Normal Pregnancy, III Hemoglobin and Cell Volume Coeffieients, Erythrocyte Volume, Hemoglobin Content and Concentration; Color, Volume and Saturation Indexes; Arch. Int. Med. 53:345, 1934.

30. Eastman, N. J.; Anemias of Pregnancy; Inter. Clin. 2:257, 1935.

31. Esch, P.; Chlorosis During Gestation Period and its Relation to Pregnancy Anemia Resembling Pernicious Anemia; Zentrabl. f. Gynak., 50:857, 1926.

32. Evy, A. C., and Morgan, J. E., and Farrel, J. I.; Effects of Total Gastrectomy; Experimental Achylia Gastrica in Dogs with Occurence of Spontaneous Anemia and Anemia in Pregnancy; Surg. Gynec. & Obst., 53:611, 1931.

33. Feldman, H.; The Principals of Antenatal and Postnatal Child Physiology, London, Longman Green & Co. 1920.

34. Feldman, H., Van Donk, E. C., Steinback, H., and Schneiders; Hydremia as a Factor in the Anemia of Pregnancy; Am. J. of Physio., 115:69, 1936.

35. First, A. and Glodstein, L.; Anemia in Pregnancy; Inter. Clin., 2:257, 1935.

36. Galloway, C. E.; Anemia in Pregnancy; Am. J. Obst. & Gynec., 17:84, 1929.

37. Galloway, C. E.; Anemia in Pregnancy; J. A. M. A., 93: 1695, 1929.

38. Goodall and Gottlieb; The Association of Pregnancy, Hypochromic Anemia, and Achlorhydria; Canad. M. A. J., 35:50, 1936.

39. Gray, L. A. and Wintrobe, M. M.; Chronic Hypochromic Anemia in Women; Am. J. Obst. & Gynec., 31:3, 1936.

40. Green Armytage, V. B.; Influence of Food on Childbearing; Lancet, 1:1253, 1935.

41. Harvey, H. E.; A Study of the Hemoglobin, Cell Volume per cent, and Red Cell Count, Intrapartum and Postpartum, with Observations on Relation to Morbidity; Am. J. Obst. & Gynec., 21:476, 1931.

42. Henderson, J. Observations on the Maternal Blood at Term and During the Puerperium; J. Obst. & Gynec. Brit. Emp., 1:168, 1902.

43. Irving, F. R.; Anemia of Pregnance; 60 Cases of Hypo-Chromic Type; Am. J. Obst. & Gynec., 29:850,1935.

44. Jerlov, E.; The Lack of Hemoglobin During Pregnancy and a Suggestion on the Prophylaxis of Anemia; Act. Obst. et Gynec. Scand., 8:356, 1929.

45. Kehrer, 1905. from (93)

46. Kehrer, E.; Halban and Zeitz, Biologie und Pathologie des Weibes, Berlin, Urban & Schazewberg, 1925, vol. 6, p. 783.

47. Kerwin, W. and Collins, L. L.; Haemoglobin Estimates in Pregnancy, Am. J. Med. Sci., 172:548, 1926.

48. Kickham, C. J. and Titus, R. S.; The Anemias of Pregnance; New Eng. J. Med., 213:586, 1935.

49. Kilduffe, R. A.; The Anemias of Pregnancy; J. Med. Soc. New Jersey, 28:341, 1931.

50. Lyon, E. C.; Anemia in Late Pregnancy; J. A. M. A., 92:11, 1929.

51. Mackay, H. M. M.; Medical Research Council Special Report 157 on Nutritional Anemia in Infancy, London, 1931.

52. Mackay, H. M. M.; The Normal Hemoglobin Level During the First Year of Life; Revised Figures; Arch. Dis. Child., 8:221, 1933.

53. Mackay, H. M. M.; Hemoglobin Level Among London Mothers of Hospital Class, and its Probable Bearing on Infection; Lancet, 1:1431, 1935.

54. McGeorge, M.; Anemia in Obstetrical Practice in New Zealand; J. Obst. & Gynec. Brit. Emp.,42:1027, 1935.

55. Mettier and Minot; The Effect of Iron on Blood Formation as Influenced by Changing the Acidity of the Gastric Contents in Certain Cases of Anemia; J. Clin. Invest., 7:510, 1929.

56. Miller, J. R., Keith, N. M., and Rowntree, L. G. Plasma and Blood Volume in Pregnancy; J. A. M. A., 65:779, 1915.

57. Mitchel, H. S. and Miller, L.; Effect of Age, Pregnancy, and Lactation on the Hemoglobin of the Albino Rat; Am. J. Physio., 98:311, 1931.

58. Moore, J. H.; Anemia in Pregnancy; Am. J. Obst. & Gynec., 18:424, 1929.

59. Moore, J. H.; Anemia in Pregnancy, Final Report of 300 Cases Observed; Am. J. Obst. & Gynec., 20:254, 1930.

60. Minot, G. R.; and Murphy, W. P.; Treatment of Pernicious Anemia by a Special Diet; J. A. M. A., 87:470, 1926.

61. Mussey, R. D., Watkins, C. H., and Kehoe, J. C.; Secondary Anemia During Pregnancy; Am. J. Obst. & Gynec., 24:179, 1932.

62. Nasse. from (12).

63. Nalle, B. C.; Anemia of Pregnancy; South. M. J., 23:490, 1930.

64. Neale, A. V. and Hawksley, J. C.; Nutritional Anemia in Mother and Child; Arch. Dis. Child., 8:227, 1933.

65. Oberst, F. W. and Plass, E. D.; Water Concentration of Blood During Pregnancy, Labor, and Puerperium; Am. J. Obst. & Gynec., 31:61, 1936.

66. Osgood, E. E.; Normal Haematological Standards; Arch. Int. Med., 56:849, 1935.

67. Pastore, J. B.; The Cell Volume Following Delivery and its Relation to Blood Loss and Postpartum Infection; Am. J. Obst. & Gynec., 32:859, 1936.

68. Pepper, O. H. P.; Review of Our Knowledge; M. Clin. North Am., 12:925, 1929.

69. Plass, E.D.; Some Observations of the Anemia of Pregnancy; South. M. M., 29:417, 1936.

70. Polowe, D.; Specific Gravity of Blood in Pregnancy and in Puerperium; Study of 75 Patients; Am. J. Obst. & Gynec., 23:843, 1932.

71. Price-Jones, C.; The Concentration of Hemoglobin in Normal Human Blood; J. Path. & Bact., 34:779, 1931.

72. Rickter, O., Meyer, A. E., and Bennett, J. P.; Relation of Anemia of Pregnancy to Hydremia and its Treatment with Aqueous Equine Liver Extract and Glycerated Iron; Am. J. Obst. & Gynec., 28:543, 1934.

73. Roberts, S. R.; Circulation in Pregnancy; South. M. J., 25:1122, 1932.

74. Rowe, A. W.; The Metabolism in Pregnancy, VII The Blood Morphology; Am. J. Phys., 96:112, 1931.

75. Rowland, V. C.; Anemia of Pregnancy; Ann. Int. Med., 1:129, 1927.

76. Rowland, V. C.; Relation to Anemia in General; J. A. M. A., 100:537, 1933.

77. Schultz; Ueber Schwangerschaftsanamien; Munch med Woch 80:679, 1933.

78. Sharp, J. C.; The Diagnosis and Treatment of Anemia, VII The Anemias of Pregnancy; Nebr. S. M. J.; 21:427, 1936.

79. Smith, C. T. and Kinlaw, W. B.; Clinical Consideration of an Anemia of Pregnancy and the Puerperium; Ann. Int. Med., 4:939, 1931.

80. Spieglberg, O. and Gescheilder, R.; Untersuchungen uber die Blutmenze trachtiger Hunde; Arch. f. Gynak, 4:112, 1872.

81. Strauss, M. B.; Chloratic Anemia of Pregnancy., 3 Cases; Am. J. Med Sci., 180:818, 1930.

82. Strauss, M. B. and Castle, W. B.; Anemia in Pregnancy, Gastric Secretion in Pregnancy and Puerperium; Am. J. Med. Sci., 184:655, 1932.

83. Strauss, M. B. and Castle, W. B.; Anemia in Pregnancy, Relationship of Dietary Deficiencies and Gastric Secretion to Blood Formation During Pregnancy; Am. J. Med. Sci., 184:663, 1932.

84. Strauss, M. B. and Castle, W. B.; Anemia in Pregnancy; Etiological Relationship of Gastric Secretory Defects and Dietary Deficiency to Hypochromic and Macrocytic (Pernicious) Anemias of Pregnancy and Treatment of these Conditions; Am. J. Med. Sci., 185:539, 1933.

85. Strauss, M. B. and Castle, W. B.; Etiology and Treatment; Lancet 1:1198, 1932.

86. Strauss, M. B.; Anemia of Infancy from Maternal Iron

Deficiency (in Women with Hypochromic Anemia); J. Clin. Invest., 12:345, 1933.

87. Strauss, M. B.; Etiology and Treatment of Anemia in Pregnancy; J. A. M. A., 102:281, 1934.

88. Strauss, M. B.; Anemia in Pregnancy; Intern. Clin. 4:56, 1935.

89. Suwa, Y.; Hematologic Investigation of Anemia in Pregnancy, Part I Changes in Blood Picture in Cases of Normal Pregnancy, Labor and Puerperium; Jap. J. Obst. and Gynec., 13:73, 1930, Abst. by J.P. Greenhill, Am. J. Ob. and Gyn.; 23:459, 1932.

90. Toland, O. J.; Incidence and Treatment of Secondary Anemias in Outpatient Maternity Patients; Am. J. Obst. and Gynec., 31:640, 1936.

91. Thomas, Fitz Hugh Jr.; Discussion of Toland (90); Am. J. Obst. and Gynec., 31:644, 1936.

92. Van Donk, E. C., Feldman, H., and Steinbock, H.; Analysis of Anemia of Pregnancy in Rat; Am. J. Phys., 107:616, 1934.

93. Vaugham, J. M.; The Anemias; Oxford Uni. Press., London; Humphrey Milford 1936, p. 64-71.

94. Williams, J. W.; Obstetrics, New York, D. Appleton & Co., ed. 6, 1930, p. 207.

95. Wintrobe, M. M.; Blood of Normal Men and Women, Erythrocyte Counts, Hemoglobin and Volume of Packed Red Cells of 229 Individuals; Bull. Johns Hopkins Hosp., 53:118, 1933.

96. Witts, J. J.; Pathology and Treatment of Hemolytic Anemia (Gaulstonian Lecture); Lancet, 1:653, 1932.

97. Witts, J. J.; Therapeutic Action of Iron; Lancet 1:3, 1936.