ANAEMIA OF PREGNANCY

A REPORT ON THE HAEMATOLOGICAL STUDY OF 48 CASES OF PREGNANCY, WITH REVIEW OF THE LITERATURE

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INTRODUCTION

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Studies of anaemia occurring during pregnancy have been of two main types. The first type, from which information of great value has been collected, is the mass survey of large series of cases. Studies of such a nature have the disadvantage that the less common varieties of pregnancy anaemia are pooled amongst the more common, a feature which is largely responsible for the perpetuation of traditional rather than factual ideas on the subject of these less common forms. The second type of study, of which the present is an example, consists of a more intensive and detailed investigation of individual cases with the main purpose of interpreting pathogenesis in terms of deviation from that which is physiological.

Anaemia and pregnancy are common associations. It is important to distinguish between anaemia which is apparently due to pregnancy and anaemia which is associated coincidentally with pregnancy. In the present enquiry, the phrase "anaemia during pregnancy" generically

denotes that a case is pregnant and anaemic at the same time. "Anaemia of pregnancy" and "pregnancy anaemia" are used synonymously to indicate that the anaemia is conditioned directly by pregnancy; it is perhaps too strong to refer to such anaemia as being due to pregnancy. "Anaemia complicated by pregnancy" indicates that pregnancy occurs coincidentally with some disorder of the blood which ordinarily occurs quite apart from and is quite unrelated to pregnancy.

The present investigation has sought to establish normal standards for the less commonly noted physical features of red cell fragility and red cell size during normal pregnancy, and to investigate these features in mild and severe grades of anaemia during pregnancy, followed through to the puerperium. At the same time, full haematological investigations were carried out and the results of various types of treatment followed. The type of response to treatment was used as an important aid to the diagnosis of the type of anaemia.

That the investigation of the red cell fragility in pregnancy might afford information of value was suggested by Dr. J.M. Vaughan on the evidence of a single case under

her own observation some time previously in which the fragility was increased. The observations of Cassells (1938) also suggested that with an accurate technique for fragility estimation the red cells during pregnancy could be shown to behave differently from other forms of anaemia as regards their fragility. As no controlled work had been published on the subject, it was necessary to establish standards of red cell fragility for pregnancy uncomplicated by anaemia, and to compare these standards with the findings in pregnancy complicated by anaemia.

On the assumption that red cell fragility is at least in part related to red cell thickness (Haden, 1934, Dacie and Vaughan, 1938), estimations of mean cell volume and mean cell diameter were an essential part of the investigation. Red cell counts, haemoglobin estimations, reticulocyte counts, white cell counts, and estimation of plasma bilirubin were part of the routine investigation.

METHODS

METHODS

RED CELL COUNTS

On occasions when fragility and mean corpuscular diameter were estimated, red cell counts were made from capillary and heparinised venous blood within half an hour of the taking of the blood. The average of four counts was taken, two capillary and two venous. If one of the four differed more than 200,000 from the other three, it was discarded. If more than one differed more than 200,000 the counts were repeated. The same counting chamber was used throughout the investigation.

On occasions apart from those on which fragility and mean corpuscular volume were estimated, two counts on capillary blood were done.

WHITE CELL COUNTS

A single count was made from either capillary or venous blood.

HAEMOGLOBIN

Haemoglobin was measured by Haldane's standard whereby 100 per cent haemoglobin is equivalent to 18.5 per cent oxygen capacity. On the assumption that one gramme of haemoglobin combines with 1.34 cc oxygen, 100 per cent haemoglobin corresponds to 13.8 grammes per cent haemoglobin. The average of two readings was taken, one of them being from heparinised venous blood if available.

MEAN CORPUSCULAR VOLUME

This was estimated by the Wintrobe haematocrit (Wintrobe, 1930). Heparinised venous blood was centrifuged at 3000 revolutions per minute for 30 minutes. The average of two readings of volume of packed red cells was taken.

RETICULOCYTES

Reticulocytes were counted by mixing a small drop of heparinised venous blood or capillary blood on a paraffin slide with a slightly larger drop of a mixture of one part saturated alcoholic solution of brilliant cresyl blue and five parts of one per cent sodium citrate in normal saline, and incubating the mixture in a damp chamber for about 15 minutes at 37 degrees Centigrade. After incubation, smears of the mixture of blood and stain were made on slides and counterstained with Jenner's stain for two minutes. The stain was washed off with distilled water and the slides allowed to dry in air. They must not be blotted. It is important to follow this technique accurately to get correct results. The number of reticulocytes per thousand red cells was counted and the number expressed as a percentage.

PLASMA BILIRUBIN

The plasma bilirubin of heparinised blood was estimated by the method of Haslewood and King (1937). A single estimation was made on each case tested.

MEAN RED CELL DIAMETER

The mean red cell diameter was estimated by the method of Price-Jones (1933). A thin blood film is dried in air

without heat, fixed and stained for one to two minutes with Jenner stain, and superstained with a 1% watery solution of eosin for 5 minutes. The eosin intensifies the image of the red cells. A microscope is arranged horizontally in a dark room, with the eye piece supplied with a prism. A strong source of light projects the images of objects in focus on the microscope stage on to a piece of paper placed flat on the bench on which the microscope is placed. A micrometer scale divided into 1/100 millimetres is put in place on the microscope stage, and using the oil immersion lens, the length of the microscope tube and the distance of the piece of paper from the prism is adjusted so that the micro-millimetre scale is sharply focussed on the paper. A paper scale is superposed on the image ofthe micromillimetre scale and the distance of the paper from the prism adjusted until one 1/100 mm division of the micro scale corresponds to 10 mm of the paper scale. This gives a magnification of 1000, so that one millimetre on the paper represents one mu on the microscope stage. Having adjusted the distances in this manner, the blood smear is put in the place of the micro scale and the images of the red cells brought in to sharp focus on the paper. A thin portion of smear is selected, and 500 cells are outlined on the paper, using a sharp pencil; the drawing of the outlines should be restricted to the centre of the field. Cells must be drawn without selection. The cells that have been traced are then measured with a glass millimetre scale, in two diameters for each cell, the longest and the shortest; the average of these two diameters is taken as the cell diameter. The diameter values are then regarded as a collection of variables and treated statistically, the arithmetic mean, standard deviation and co-efficient of variation being calculated. The arithmetic mean is the mean red cell diameter, and the standard deviation and coefficient of variation are a measure of the scatter about the mean,

namely, anisocytosis. This will be discussed more fully in a later section, but it may be mentioned here that there is a slight difference of opinion as to whether the standard deviation or the coefficient of variation is the better indication of anisocytosis; Price-Jones (1933) holds that the latter is, whilst Mogensen (1938) favours the former. For this reason all the tables of the present investigation include both. As the tracing, measurement and calculation necessary for one Price-Jones red cell distribution curve takes about 4 hours, not all the cases in the present series were estimated.

RED CELL FRAGILITY

Red cell fragility was determined by the method described by Dacie and Vaughan (1938) which is a modification of the method of Creed (1938). By this method, the factors of temperature and oxygen saturation are standardised, as it is known that lowering of the temperature of a haemolytic solution increases the fragility (Jacobs and Parpart, 1931, Ponder, 1934), and that the greater the carbon dioxide tension the less fragile the red cell (Whitby and Hynes, 1935, Creed, 1938, and Dacie and Vaughan, 1938). The effect of the degree of anaemia on red cell fragility will be discussed later.

A better description than the original one of Dacie and Vaughan cannot be given. A stock solution of 20% sodium chloride is prepared, using desiccated salt. This is diluted with distilled water so as to obtain a series of saline dilutions varying from 0.10 to 0.72 per cent in concentration, at 0.02 intervals. These are kept in tightly stoppered bottles in a refrigerator. For the actual test, small Wassermann tubes of as nearly as possible the same internal diameter are placed in a rack, and 1 cc of each of the saline solutions added to each, the range of concentrations

being varied according to the degree of haemolysis expected. For routine purposes, 15 concentrations were set out in the Wassermann tubes, ranging from 0.2 to 0.48 per cent saline concentration. The pipette used for abstracting the salt solutions from their respective stock bottles must be washed between each abstraction, and dried. Into each of 4 additional Wassermann tubes, 2 cc of distilled water is delivered. A series of racks can be made up as occasion demands, and can be kept ready for use as long as all the tubes are corked and the racks kept in the refrigerator to prevent evapouration. The refrigerator is kept at 3 degrees Centigrade.

Blood is withdrawn from a vein using a dry syringe, and transferred immediately into a dry tube containing heparin sufficient to prevent coagulation. The blood may be tested up to 4 hours after withdrawal. Before use, the blood is mixed by gentle inversion, and about 3 cc is placed in a cylindrical glass separating funnel of about 175 cc capacity. This is rotated, without a stopper, horizontally, so that the blood spreads out in a thin film on the sides of the funnel. This operation oxygenates the blood to a standard degree of saturation. Using a standard dropping pipette which measures 22 drops to the cc, one drop of aerated blood is added to each of the saline concentrations and mixed by inversion; two drops of blood are put into each Wassermann tube containing the distilled water. The tubes are corked and placed in the refrigerator for half an hour. At the end of this period, they are removed and centrifuged for 5 minutes at about 2000 revolutions per minute. Standards for quantitative estimation of the degree of haemolysis are made from the completely haemolysed blood in the tubes which contained distilled blood, by adding 0.1, 0.2, 0.3, etc cc of the completely haemolysed dilution

to 0.9, 0.8, 0.7, etc cc of distilled water; in this way nine Wassermann tubes are set up representing 10 to 90 per cent haemolysis at 10 per cent intervals. The percentage of haemolysis in the supernatant fluid of the various red cell-saline mixtures is estimated by direct matching with the prepared standards. Readings above 85 per cent haemolysis cannot be made with accuracy.

The tabulated percentages of haemolysis are then plotted graphically (Fig. 1) with percentage haemolysis as ordinates and percentage saline concentration as abscissae. From the point at which the graph cuts the line of 50 per cent haemolysis, a vertical is dropped, and the reading of saline concentration along the base-line at which the vertical crosses the base-line is the median corpuscular fragility (MCF). A "shift of the curve to the right" indicates an increase in fragility, a "shift to the left", decrease. The shaded area indicates the range of normal.

That the degree of anaemia has an effect on the red cell fragility has been shown by Dacie and Vaughan. In a given amount of anaemic blood there is more plasma and therefore more electrolyte than in the same amount of normal blood. Therefore the addition of a drop of anaemic blood to a saline concentration increases the electrolytic strength of that particular concentration more than does a similarly sized drop of normal blood. The extra electrolyte from the anaemic blood gives an apparent decrease of red cell fragility. This difficulty can be partially overcome, as suggested by Dacie and Vaughan, by "correcting for anaemia".

The operation of correcting for anaemia is carried out as follows: The anaemic blood is gently centrifuged, and an amount of plasma, calculated from the volume of packed red cells in the haematocrit, is removed by pipette so as to make the volume of packed red cells in the remainder equal to 40 per cent, 40 per cent being selected as an arbitrary normal. The blood from which the plasma has been taken is carefully shaken up and the fragility test repeated with it. The resultant curve and MCF reading is known as the reading "corrected for anaemia". To make the matter quite clear, the following is a hypothetical example:

In a given blood, the volume of packed red cells (VPC) by the haematocrit is 25 per cent. It is required to remove from a gently centrifuged sample of the blood, say about 5 cc, enough plasma, so that, if a haematocrit reading were taken on the remainder, the VPC would be 40 per cent. Suppose the original volume of blood to be 5.6 cc; in this amount of blood the volume of red cells is 25 per cent of 5.6 cc, namely, 1.4cc. In the modified sample, this 1.4 cc is to be 40 per cent of the total volume of blood, which is the case when the total volume is 1.4 x 100÷40 cc, i.e. 3.5 cc. Therefore the amount of plasma to be removed is 5.6 minus 3.5 cc, namely, 2.1 cc. The remaining volume of blood is carefully shaken up and the fragility tested in the usual way.

The corrected reading cannot be calculated from the uncorrected reading, but must be worked out for each case by the usual routine test. The correction is partial only.

Strict adherence to the standard technique is of extreme importance in so delicate a test. A possible error

specially to be controlled is alteration in the sodium chloride concentrations with the passage of time. The sodium chloride concentrations used in this investigation were originally corrected by titration against silver nitrate, and throughout the course of the investigation were not removed from the refrigerator. All test racks were set up in the refrigerator from the same stock solutions. The same stock solutions were used for every fragility test carried out. As a further measure of control, a fragility test was done at the outset of the investigation on the author's blood, and repeated at the end of the investigation five months later; at the time of the repeat examination, the blood was tested using another set of sodium chloride concentrations freshly made up and found correct by titration against silver nitrate. As shown in Fig. 1, the three tests

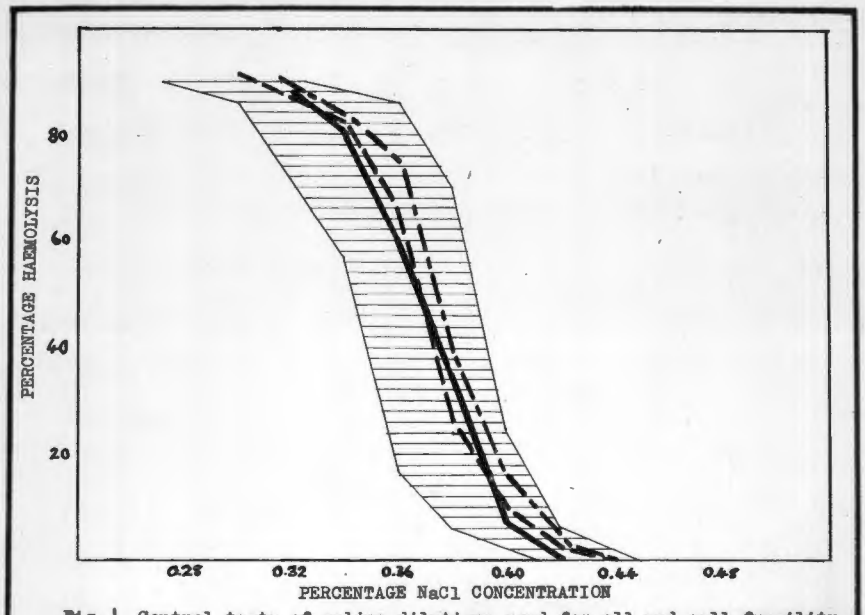

Fig. 1 Control tests of saline dilutions used for all red cell fragility estimations in the present investigations. Author's (G.A.E) blood used in each of the three control tests.

Curve at commencement of investigation (14.9.38). M.C.F. 0.368

Curve at conclusion of investigation (9.2.39). M.C.F. 0.368

Curve at conclusion of investigation (9.2.39), using a set of saline dilutions newly made up and known by titration to be accurate. M.C.F. 0.378

Fig. 1.

coincided almost exactly, there being a difference of 0.005 between the three median corpuscular fragilities. During the investigation, duplicate tests were occasionally done on the same samples of blood, the tally being comparable in accuracy with the tally in the figure.

All the tests in this investigation were carried out by the author, with the exception of those in the groups of post-haemorrhagic anaemia, idiopathic hypochromic anaemia, pernicious anaemia, acholuric jaundice, and "miscellaneous" illustrated in Fig. 3. These latter tests were carried out by Dr. D.A.K. Cassells, using the same salt solutions, and therefore comparable with the results of the author; they have been borrowed from his publication (Cassells, 1938) and with his permission.

CLINICAL MATERIAL AND RESULTS

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CLINICAL MATERIAL

The cases examined in this investigation were selected from the Antenatal Clinic and Obstetric Wards of the London County Council Hospital, Hammersmith. They were, with few exceptions, in poor circumstances, the diet being mainly carbohydrate. Many were visited in their homes which were of semi-slum standard. They were together more or less representative of the average pregnant woman attending the hospital practice.

The total number of cases included in the investigation was 48. No case was included if there were any signs of toxaemia of pregnancy, pyelitis, heart disease, or any other organic disease. 20 of the 48 cases were selected as normal controls, the arbitrary "normal" decided upon at the outset of the investigation being that the case should have a haemoglobin of 80 per cent Haldane or over, and should be free of all symptoms which could not be explained by a normal pregnancy. It was recognised and later confirmed, that this arbitrary standard of normality might have to be modified at a later date.

The form of examination applied to each case consisted

of a full haematological investigation when the case was first seen, as outlined in the section on "methods", that is, red cell count, haemoglobin, mean corpuscular volume, reticulocyte percentage, plasma bilirubin, mean red cell diameter and median corpuscular fragility. In a number of cases the complete haematological investigation was repeated during pregnancy and again on one or more occasions postpartum. The above procedure was the main theme of the investigation. In addition, many cases had numerous additional haemoglobin, red cell and reticulocyte estimations, with a view to following the untreated or treated course of the case; this was a secondary theme of the investigation, graphic records of which will be shown. Full clinical history and examination was included in every case.

The prime object of the investigation was to determine whether any change occurred in the fragility of the red cells during normal pregnancy or in certain cases of pregnancy anaemia. Complete haematological investigation of each case was necessary, including determination of the type of anaemia present if any, in order to correlate alterations in fragility if found, with the other haematological features of the case.

RESULTS

NORMAL CONTROL CASES

The results of complete haematological investigations

in the 20 normal controls are summarised in Table 1 (Fig. 2).

HAEMOGLOBIN PERCENTAGE

The haemoglobin percentage ranged between 80 and 100 per cent, the majority of the readings being nearer 80 than 100. These will later be seen to fall in the accepted normal limits for pregnancy. In so small a series of cases no discussion of the haemoglobin level at various stages of pregnancy ~~are~~ is justified.

RED CELL COUNTS

The red cell counts ranged between 4.10 and 5.80 million per cu.mm. These too are within normal limits for pregnancy, but cannot be commented on further in this short series.

COLOUR INDEX

The colour index fell between 0.8 and 1.0, with one reading of 0.69. Inhowfar a colour index of 0.8 can be regarded as being compatible with a normal blood picture will be considered after the facts of the colour index in the anaemic series and the mean cell diameter in the normal and the anaemic series have been presented.

TABLE I

HAEMATOLOGICAL STUDY OF 20 NORMAL PREGNANCIES

CASE	RBC	HB%	CI	MCV	VPC	MCD	MCT	MCF	V	sig	STAGE
1	4.30	80	0.9	83	36			0.367			35
	4.11	79	1.0	85	35			0.350			3 dys PP
2	4.66	90	1.0	82	38	7.6	1.8	0.393	8.8	0.667	30
12	4.96	100	1.0	80	40	7.0	2.1	0.355	6.6	0.466	38
	4.83	84	0.9	85	41			0.348			7 wks PP
16	4.50	84	0.9	87	39	7.2	2.2	0.368	7.1	0.512	37
	4.58	90	1.0	90	41			0.349			4 dys PP
19	4.80	80	0.8	73	35	7.1	1.9	0.393	7.6	0.533	38
14	5.40	82	0.8	76	41	7.2	1.9	0.350	8.9	0.637	39
	4.97	90	0.9	88	44			0.358			8 wks PP
23	4.08	82	1.0	78	32	7.3	1.9	0.394	8.9	0.653	24
	3.90	76	0.9	87	34			0.384			32
25	4.88	96	1.0	82	40	6.7	2.3	0.372	7.5	0.503	22
	4.09	80	1.0	88	36			0.380			30
35	4.36	88	1.0	87	38			0.349			10
36	5.80	80	0.7	62	36	6.8	1.7	0.388	7.5	0.510	38
38	4.36	80	1.0	78	34	7.0	2.0	0.358	7.6	0.523	38
	4.71	88	0.8	91	43			0.356			12 wks PP
39	4.68	82	0.9	83	39			0.348			20
44	4.75	86	0.9	79	38	7.2	1.9	0.390	7.7	0.554	39
45	5.30	88	0.9	88	47	6.7	2.5	0.374	7.9	0.524	37
46	4.60	82	0.9	83	38			0.360			29
48	5.10	84	0.8	77	40	7.3	1.8	0.366	8.5	0.626	39
51	4.23	80	0.9	85	36	6.9	2.2	0.358	6.9	0.482	28
52	4.91	82	0.8	76	37	7.7	1.6	0.348	9.2	0.708	39
	4.24	80	0.9	85	36			0.366			7 dys PP
55	4.27	82	0.9	83	36			0.378			30
57	4.10	80	1.0	88	36			0.380			30

For definition of abbreviations see footnote

Fig. 2.

Interpretation of abbreviations. RBC - red cell count in millions per cu,mm. HB% - haemoglobin percentage (Haldane). CI - colour index. MCV - mean corpuscular volume. VPC - volume of packed red cells. MCD - mean red cell diameter. MCT - mean red cell thickness. MCF - median corpuscular fragility. V - variability per cent. Sig - standard deviation. Stage - antepartum or postpartum period.

MEAN CORPUSCULAR VOLUME

The mean corpuscular volume fell between the limits of 73 and 88 cu.mu, with one exception of 62 cu.mu (a case with colour index of 0.69 and certain other unusual features to be discussed). 73 and 88 cu.mu are within the accepted normal limits for pregnancy.

MEAN RED CELL DIAMETER

The mean red cell diameter ranged between 6.7 and 7.7 mu. The accepted normal for males and non-pregnant females is 6.686 and 7.718 mu (Price-Jones, 1933)

The standard deviation varied between 0.466 and 0.708 mu, the normal limits of Price-Jones (1933) and Mogensen (1938) being 0.430 to 0.535. The variability per cent ranged between 6.6 and 9.2 per cent, the upper limit of normal range being 7.3 per cent. For comparison with the anaemic series, the readings of standard deviation and variability per cent are recorded in Fig. 9 and Fig. 10. The significance of this wider than normal range, expressing as it does an abnormal degree of anisocytosis, will be discussed in a later section.

MEDIAN CORPUSCULAR FRAGILITY

The results of the red cell fragility tests are tabulated in Table 1 (Fig. 2), and charted graphically in

Figs. 3 and 4. It is seen that the conformation of the composite curve of fragility for the 20 cases (Fig. 4) and the range of sodium chloride concentration within which the median corpuscular fragility lies (Fig. 3), is for practical purposes within the normal indicated in this and subsequent graphs by the shaded area.

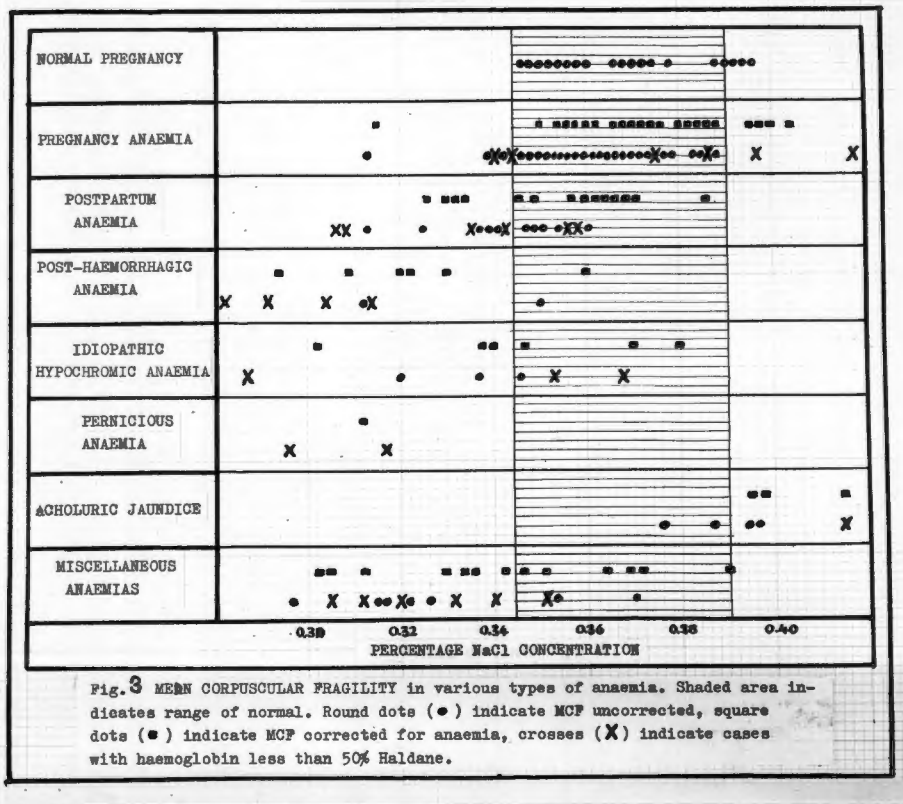


Fig. 3 MEAN CORPUSCULAR FRAGILITY in various types of anaemia. Shaded area indicates range of normal. Round dots (●) indicate MCF uncorrected, square dots (■) indicate MCF corrected for anaemia, crosses (X) indicate cases with haemoglobin less than 50% Haldane.

Fig. 3.

(In acholuric jaundice, the MCF is usually increased to a concentration of sodium chloride per cent higher than the highest (i.e. 0.420) included in Fig. 3. In a series of

37 cases examined by Vaughan (1937), the MCF ranged between 0.420 and0.700 grammes sodium chloride per cent, the majority of the readings falling below 0.550.)

The slight "shift to the right" occurs in too few of the normal cases and

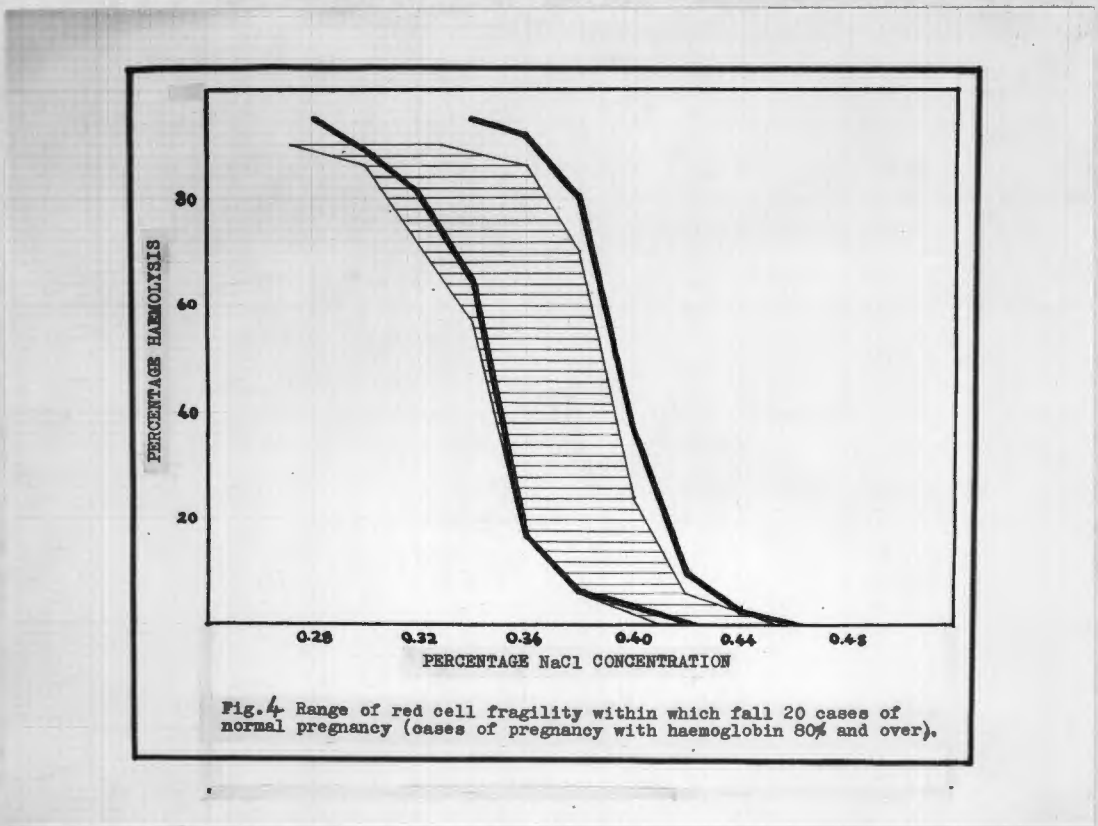


Fig. 4 Range of red cell fragility within which fall 20 cases of normal pregnancy (cases of pregnancy with haemoglobin 80% and over).

Fig. 4.

is too slight to be significant. In Fig. 3 the MCF of the normal cases is charted in a manner which enables it to be compared at a glance with the MCF in various blood disorders.

Differences in antepartum and postpartum fragility are tabulated in Table 2, Fig. 5, for 6 normal cases. The results

are too variable to show any significant alteration in any

TABLE II.

COMPARISON OF ANTEPARTUM AND POSTPARTUM MCF IN NORMAL PREGNANCY

CASE	ANTEPARTUM			POSTPARTUM			AP - PP DIFFERENCE
	STAGE	MCF	VPC	STAGE	MCF	VPC	
1	35 wks	0.367	36%	3 dys	0.350	35%	— 0.017
12	39½ wks	0.355	40%	7 wks	0.348	41%	— 0.007
14	39½ wks	0.350	42%	8 wks	0.358	44%	+ 0.008
16	38 wks	0.368	39%	4 dys	0.349	41%	— 0.019
38	38 wks	0.358	34%	9 wks	0.356	43%	— 0.002
52	39 wks	0.348	37%	8 dys	0.366	36%	+ 0.018

Fig. 5.

particular direction; the only comment at this stage is that four of the six show a postpartum decrease, a very common finding, as will be shown, in anaemia of pregnancy.

RETICULOCYTE PERCENTAGE

The reticulocyte percentage in pregnancy, including the findings in this series, will be discussed in a special section.

PLASMA BILIRUBIN

will be discussed in a special section.

CASES OF ANAEMIA

The results of complete haematological investigations in the 28 anaemic cases are summarised in Table 111 (Fig.6). Red cell counts, haemoglobin percentages and reticulocyte counts carried out exclusive of the occasions on which red cell fragility tests were done, are not included in the table.

HAEMOGLOBIN PERCENTAGE

The haemoglobin percentage of the 28 cases at the time of the first complete haematological investigation ranged from 32 to 76 per cent. The distribution of the percentages is charted in Fig. 7.

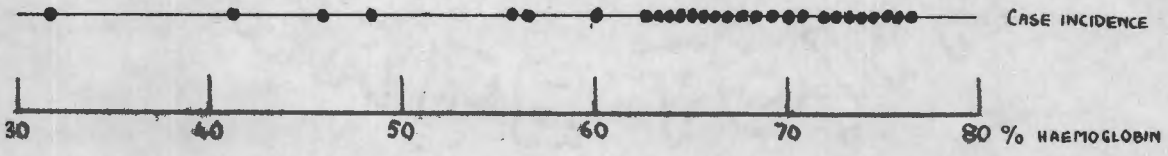


Fig. 7

Haemoglobin percentage distribution chart for 28 cases of pregnancy anaemia.

RED CELL COUNTS

The red cell counts ranged from 3.27 to 5.00 million

TABLE III

HAEMATOLOGICAL STUDY OF 28 CASES OF ANAEMIA OF PREGNANCY

CASE	RBC	HB%	CI	MCV	VPC	MCD	MCT	MCF	v	sig	STAGE
3	3.80	46	0.6	68	26			0.342 0.358c			30
	4.60	78	0.9	84	39			0.369			36
	4.95	86	0.9	81	40			0.336			8 dys PP
4	5.00	48	0.5	62	31	6.3	2.0	0.376 0.385c	9.1	0.575	32
	5.00	52	0.5	62	31	6.5	1.9	0.360 0.369c	14.7	0.959	34
	5.76	68	0.6	64	37			0.367			36
	4.76	70	1.0	78	37			0.346			5 dys PP
7	3.27	32	0.5	66	22	6.3	2.1	0.397 0.404c	9.1	0.575	39
	3.56	42	0.6	70	25			0.392 0.397c			2 dys PP
	4.70	62	0.7	70	33	6.9	1.9	0.397 0.402c	13.2	0.911	9 dys PP
	5.75	90	0.8	73	42			0.373			8 wks PP
10	4.37	76	0.9	74	32			0.358			39
11	4.24	64	0.8	75	32	7.0	1.9	0.369 0.376c	7.3	0.509	37
	4.25	62	0.7	73	31			0.336			9 wks PP
13	4.80	66	0.7	76	37			0.356 0.362c			37
	5.40	82	0.8	76	41	7.2	1.9	0.350	8.9	0.637	39
	4.97	90	0.9	88	44			0.358			8 wks PP
* 15	4.10	74	0.9	83	34			0.325			28

THE LETTER C AFTER MCF READINGS INDICATES A READING CORRECTED FOR ANAEMIA.

(CONTINUED OVERLEAF)

FIG. 6

TABLE III (CONTINUED)

CASE	RBC	HB%	CI	MCV	VPC	MCD	MCT	MCF	v	sig	STAGE
17	4.50	74	0.8	78	35			0.375 0.380c			34
	5.60	88	0.8	80	45			0.371 0.378c			38
18	4.31	56	0.7	73	32			0.378 0.384c			34
20	3.50	42	0.6	74	26	6.0	2.6	0.420	13.3	0.798	34
	4.80	82	0.9	83	40	6.5	2.5	0.376	12.6	0.818	7 dys PP
22	3.28	66	1.0	98	32	7.2	2.4	0.370 0.373c	8.4	0.603	36
	4.88	90	0.9	87	43			0.376			14 wks PP
24	3.80	70	0.9	82	31	6.8	2.3	0.370 0.380c	7.7	0.522	33
	4.68	82	0.9	81	38			0.368			3 wks PP
*26	4.05	68	0.9	81	33	7.2	2.0	0.356 0.370c	7.4	0.530	36
27	4.40	70	0.8	74	33			0.348			33
28	4.28	72	0.9	77	33			0.355			22
29	4.83	68	0.7	64	31			0.343			30
	5.10	84	0.8	77	40	7.3	1.9	0.366	8.5	0.625	39
30	4.27	66	0.8	77	33			0.388 0.397c			38
31	4.64	56	0.6	58	27	6.5	1.7	0.372 0.387c	10.7	0.700	25
	5.15	74	1.1	71	37			0.373 0.378c			6 wks PP
32	4.27	74	0.9	76	33			0.342 0.350c			38
33	3.55	66	1.0	83	30			0.365 0.371c			28

CASE	RBC	HB%	CI	MCV	VPC	MCD	MCT	MCF	v	sig	STAGE
34	4.33	68	0.8	72	31			0.370 0.377c			36
37	3.56	65	0.9	88	32	7.2	2.1	0.346 0.358c	6.8	0.495	34
40	3.80	75	0.9	84	32	7.1	2.1	0.360 0.368c	9.1	0.650	34
41	4.10	75	0.9	84	34	7.1	2.1	0.364	8.5	0.601	36
	5.03	86	0.9	79	40			0.367			4 mos PP
42	3.88	65	0.8	80	31	7.4	1.9	0.360 0.370c	8.6	0.635	34
47	3.80	60	0.8	74	28	6.9	2.0	0.386 0.397c	7.6	0.522	34
50	4.40	76	0.8	77	34			0.384			39
	4.93	89	0.9	87	43			0.365			5 wks PP
56	3.81	68	0.9	88	34			0.344 0.356c			34

For definition of abbreviations see footnote, Fig. 2

* The following additional findings should be included in the Table :-

15	4.50	84	0.9	87	39			0.368			38
26	5.00	86	0.9	84	42			0.367			10 wks PP

FIG. 6

per cu.mm. No special comment will be made on these figures for haemoglobin percentage and red cell counts, as they are in themselves too few to be of statistical value.

COLOUR INDEX

The colour index ranged from 0.5 to 1.0. The distribution was as follows:

0.5 . . . . . 2 cases
0.6 . . . . . 3 cases
0.7 . . . . . 3 cases
0.8 . . . . . 8 cases
0.9 ... . . . .10 cases
1.0 ... . 2 cases.

The significance of the colour index reading will be discussed when the facts of the mean red cell diameter have been presented. The range of normal for colour index is 0.91 to 1.07 (Price-Jones, 1933).

MEAN CORPUSCULAR VOLUME

The mean corpuscular volume ranged between 58 and 98 cu.mu. The distribution in the 28 cases is indicated in the chart, Fig. 8. For comparative purposes, the figures for the series of 20 normal cases is also charted.

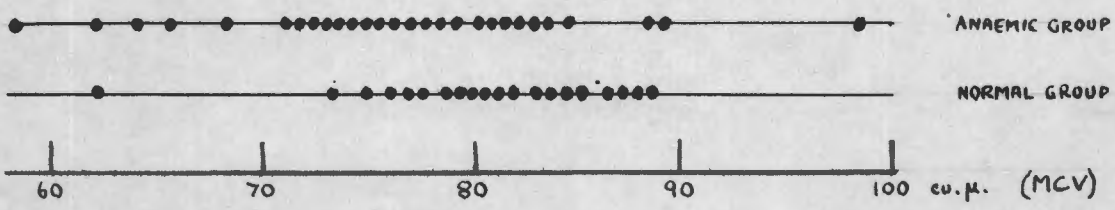


Fig. 8.

It is seen that about 10 of the readings from the anaemic cases are below accepted normal levels, and one (98 cu.mu) just above the upper level of normal for the non-pregnant state. The upper limit of normal for pregnancy is 100 cu.mu.

MEAN RED CELL DIAMETER

The mean red cell diameter ranged from 6.0 mu to 7.4 mu. 6 out of 18 were below 6.76 mu, the lower limit or normal. Reference to Table 111 Fig. 6, shows that the smallest diameter is found with the lowest colour index, and the mean cell diameter tends to increase along with the colour index as treatment becomes effective.

The standard deviation in the series varied from 0.495 to 0.959. The distribution of the readings is charted in Fig. 9 along with the normal series findings for comparative use.

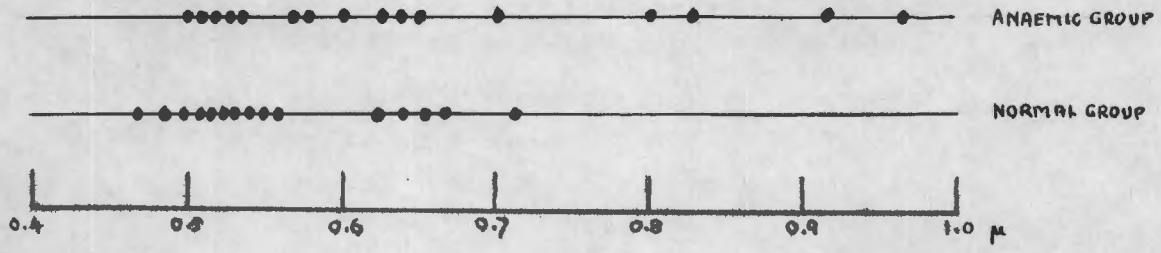


Fig. 9.

Distribution of standard deviation readings in cases of anaemia and of normal pregnancy.

The coefficient of variation (variability) varied from 6.8 to 14.7 per cent. The distribution of the readings is charted in Fig. 10 along with the normal series findings for comparison.

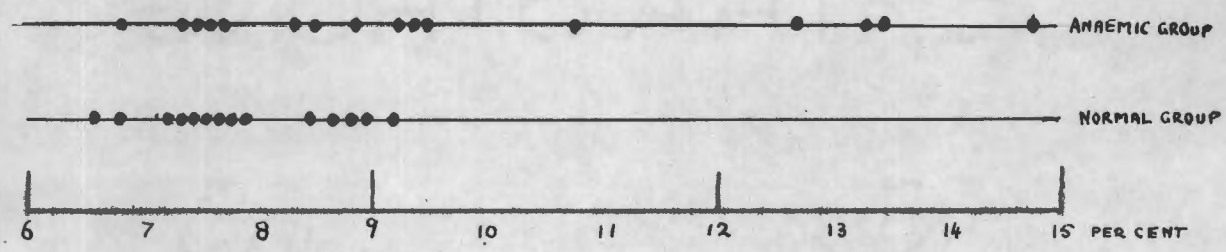


Fig. 10

Distribution of coefficient of variation in cases of anaemia and of normal pregnancy.

It is to be noted at this stage that the standard deviation and variability per cent are within normal limits in some of the "anaemic" group. This will be discussed when normal standards have been presented.

Discussion of the findings so far will be reserved until the normal standards have been presented. Suffice to draw attention now to the fact that in the normal group there were examples with fairly gross degrees of anisocytosis, and in the anaemic group, cases with a normal degree of anisocytosis, as expressed by the standard deviation and the coefficient of variation. To what extent these and other facts indicate that the cases have in some instances been erroneously grouped into "normal" and "anaemic" groups will be fully discussed.

MEDIAN CORPUSCULAR FRAGILITY

The range of red cell fragility in the 28 cases of anaemia of pregnancy is recorded graphically in the composite curve, Fig. 11. In this chart it is possible to compare the range of fragility for the pregnancy cases with the range for 16 cases of postpartum anaemia. In Fig. 3, the range of MCF in pregnancy anaemia, both the corrected and the uncorrected readings, can be compared with the corrected and uncorrected readings for anaemias of various sorts.

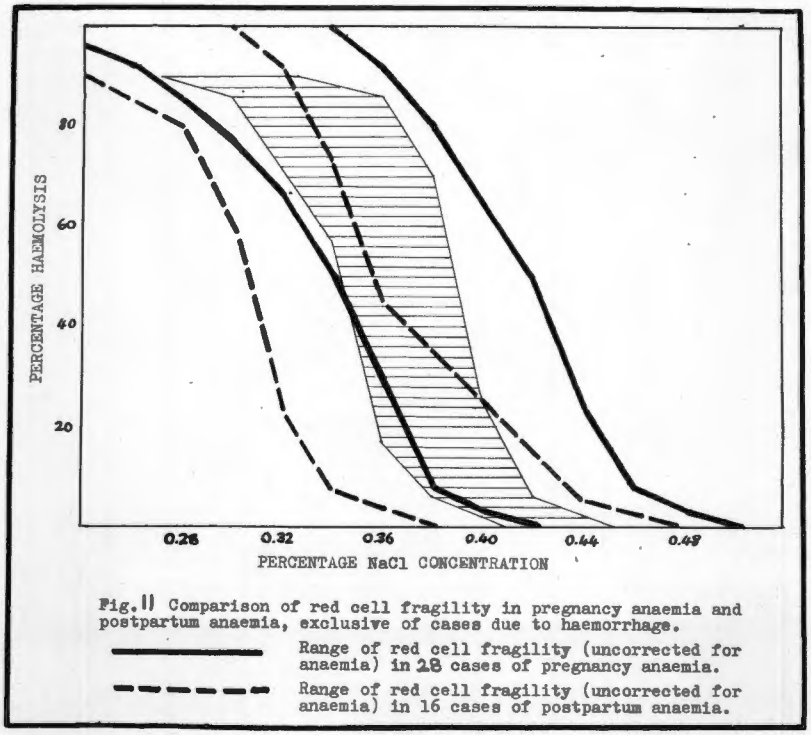


Fig.11 Comparison of red cell fragility in pregnancy anaemia and postpartum anaemia, exclusive of cases due to haemorrhage.

Range of red cell fragility (uncorrected for anaemia) in 28 cases of pregnancy anaemia.

Range of red cell fragility (uncorrected for anaemia) in 16 cases of postpartum anaemia.

Fig. 11.

From these two figures, it is apparent that the red cell fragility in the case of pregnancy anaemia differs from that in most other types of anaemia. In spite of a grade of anaemia which is in most conditions associated with an increased resistance of the red cells (excluding acholuric jaundice), the fragility curve in pregnancy anaemia of even severe grade does not "shift to the left", and in many instances actually shifts to the right.

The problem has been approached from another aspect

in this investigation. In 12 of the anaemic group, tabulated in table IV (Fig. 12), the red cell fragility was estimated both antepartum and postpartum. The red cell fragility curves

TABLE IV

COMPARISON OF ANTEPARTUM AND POSTPARTUM MCF IN PREGNANCY ANAEMIA

CASE	ANTEPARTUM			POSTPARTUM			AP - PP DIFFERENCE
	STAGE	MCF	VPC	STAGE	MCF	VPC	
3	30 wks	0.358c 0.342	26%	8 dys	0.336	40%	— 0.022
	36 wks	0.369	39%	8 dys	0.336	40%	— 0.033
4	32 wks	0.385c 0.376	31%	5 dys	0.346	37%	— 0.039
	34 wks	0.369c 0.360	31%	5 dys	0.346	37%	— 0.023
	36 wks	0.367	37%	5 dys	0.346	37%	— 0.021
7	39 wks	0.404c 0.397	22%	3 dys	0.397c 0.392	25%	— 0.007 — 0.005
	39 wks	0.402c 0.397	22%	9 dys	0.402c 0.397	33%	+ 0.002 — 0.000
	39 wks	0.404c 0.397	22%	8 wks	0.373	42%	— 0.031
11	37 wks	0.369c 0.376c	32%	8 wks	0.336	31%	— 0.033
13	37 wks	0.362c 0.356	37%	8 wks	0.358	44%	— 0.004
	39 wks	0.350	41%	8 wks	0.358	44%	+ 0.008
20	34 wks	0.420	26%	7 dys	0.376	40%	— 0.044
22	36 wks	0.373c 0.370	32%	14 wks	0.376	43%	+ 0.003
24	33 wks	0.380c 0.370	31%	3 wks	0.368	38%	— 0.012
26	35 wks	0.370c 0.356	33%	10 wks	0.367	42%	— 0.003
31	25 wks	0.387c 0.372	27%	6 wks	0.378c	37%	— 0.009
41	36 wks	0.364	34%	18 wks	0.367	40%	+ 0.003
50	39 wks	0.384	34%	5 wks	0.365	43%	— 0.019

Fig. 12.

of the 12 individual cases of table IV are reproduced in Figs. 13 to 24. Each figure indicates the antepartum and

postpartum fragilities in one case. The volume of packed red cells is stated in order to give ~~a true idea~~ an indication of the grade of anaemia at the time of each reading; corrected and uncorrected readings are given, and as far as possible, comparisons are made with the volume of packed red cells of comparable percentage, corrected or uncorrected. Numbers, for example 0.033, in the following description indicate concentration of sodium chloride in grammes per cent. The stage of pregnancy is expressed in weeks antepartum, for example, 35 weeks antepartum means 5 weeks off full term.

The results may be classified into two groups, those in which there is after parturition a significant alteration (more than 0.010 grammes NaCl concentration per cent) in the MCF and a "shift to the left" of the fragility curve, and those in which there is very little if any alteration.

In the first group are included 7 cases.

Case 3 (Fig. 13) shows a decrease in MCF of 0.033 by the 8th day postpartum, and a tendency for the curve to shift to the right as pregnancy advances from the 30th to the 36th week.

Case 4 (Fig. 14) shows a decrease in MCF of 0.021 by the 5th day postpartum; the curve tends to shift to the left between the 32nd and 34th weeks (between which periods a blood transfusion was given) and then to remain stationary for another two weeks before the shift to the left postpartum.

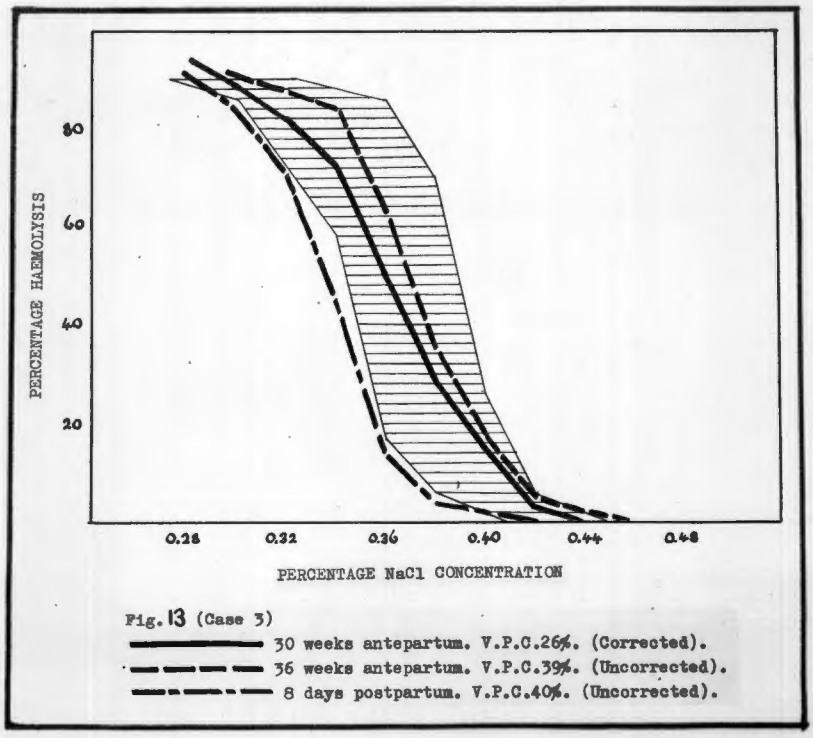


Fig. 13 (Case 3)

30 weeks antepartum. V.P.C.26%. (Corrected).
36 weeks antepartum. V.P.C.39%. (Uncorrected).
8 days postpartum. V.P.C.40%. (Uncorrected).

FIG. 13

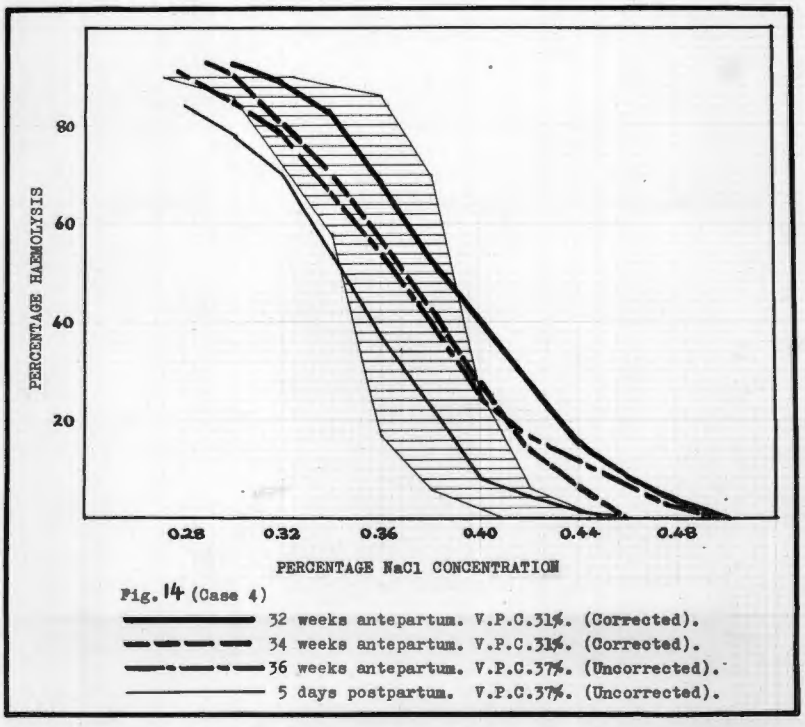


Fig. 14 (Case 4)

32 weeks antepartum. V.P.C.31%. (Corrected).
34 weeks antepartum. V.P.C.31%. (Corrected).
36 weeks antepartum. V.P.C.37%. (Uncorrected).
5 days postpartum. V.P.C.37%. (Uncorrected).

FIG. 14

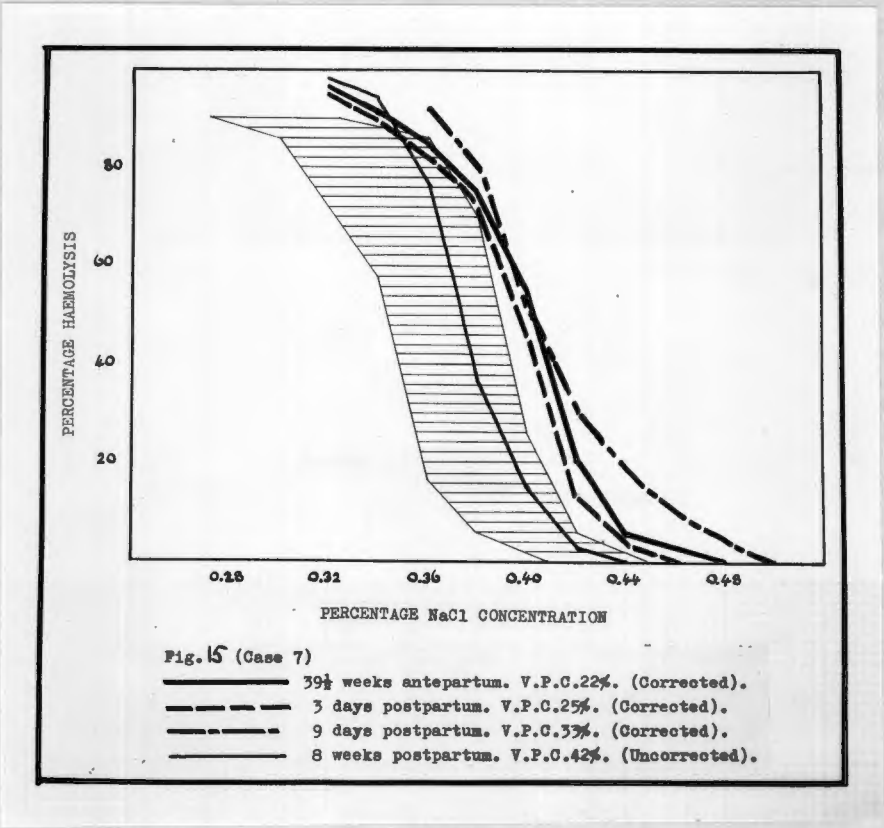


Fig. 15.

Case 7 (Fig. 15) shows a decrease in MCF of 0.031 which took place some time between the 9th day postpartum and the 8th week. Up to the 9th day, there was no shift of the curve, the maximum change in MCF in this period being 0.007.

Case 11 (Fig. 16) shows a decrease in MCF of 0.033 by the 8th week; intermediate fragility tests were not done after delivery. This case received no treatment for her anaemia either antepartum or postpartum. The antepartum and postpartum VPC was the same (32 and 31 per cent respectively). With a similar grade of anaemia as judged by the VPC, the difference in the position and the slope of the antepartum and postpartum curves is obvious.

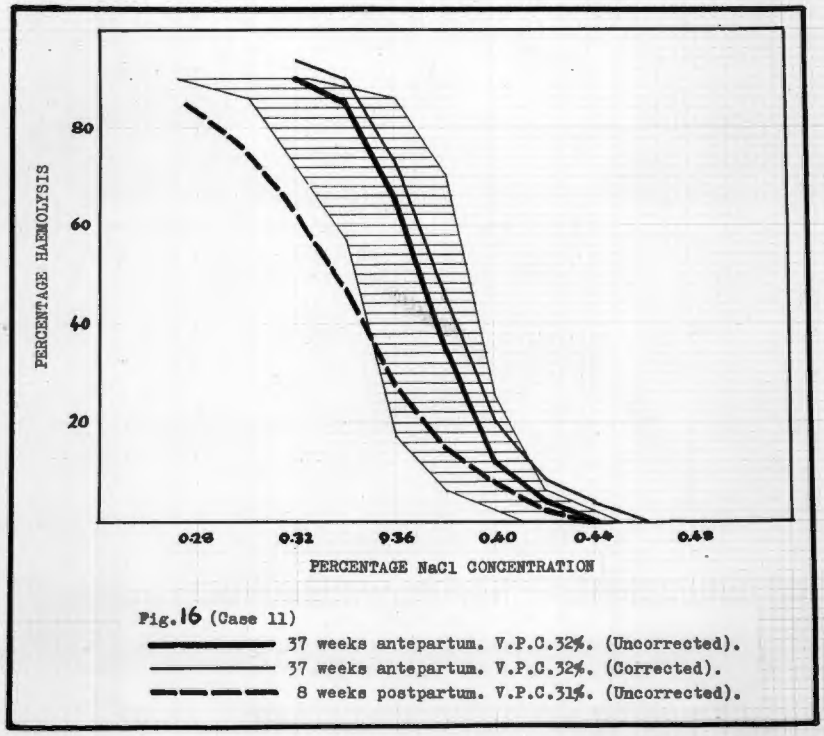


Fig.16 (Case 11)
37 weeks antepartum. V.P.C.32%. (Uncorrected).
37 weeks antepartum. V.P.C.32%. (Corrected).
8 weeks postpartum. V.P.C.31%. (Uncorrected).

FIG. 16

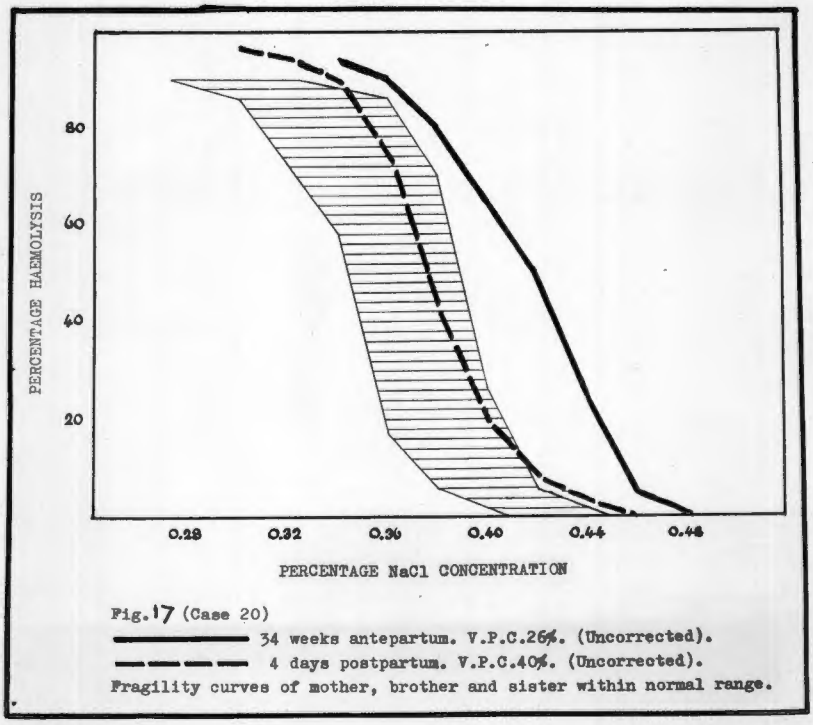


Fig.17 (Case 20)
34 weeks antepartum. V.P.C.26%. (Uncorrected).
4 days postpartum. V.P.C.40%. (Uncorrected).
Fragility curves of mother, brother and sister within normal range.

FIG. 17

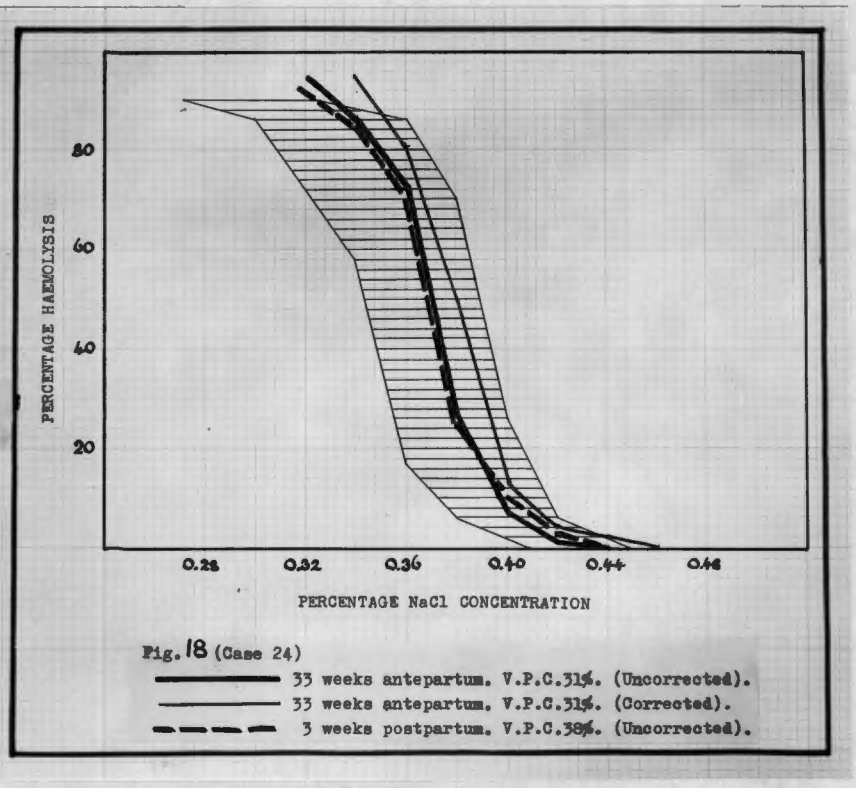


Fig. 18 (Case 24)

33 weeks antepartum. V.P.C.31%. (Uncorrected).

33 weeks antepartum. V.P.C.31%. (Corrected).

3 weeks postpartum. V.P.C.38%. (Uncorrected).

FIG. 18

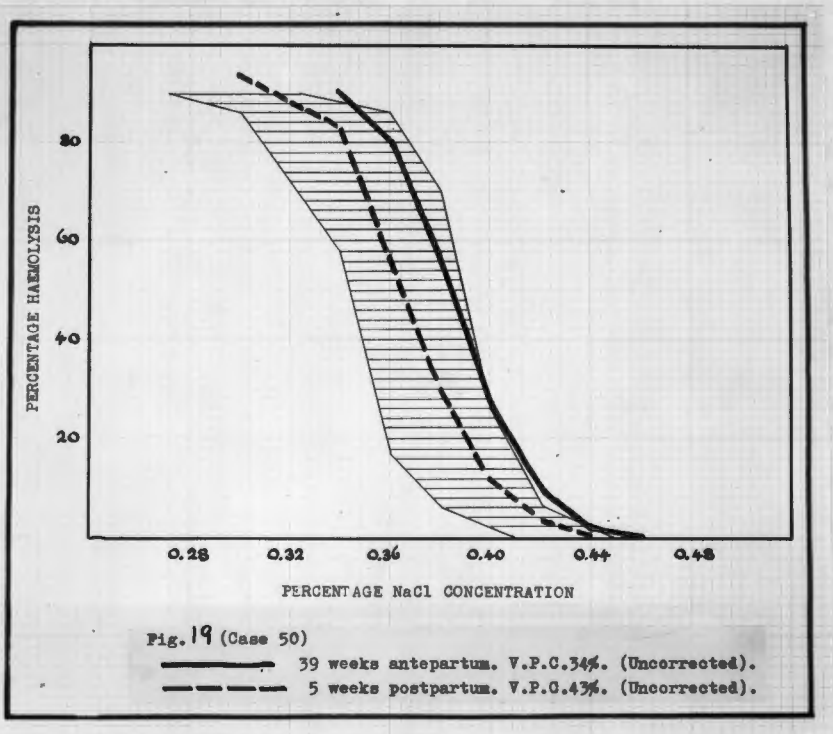


Fig. 19 (Case 50)

39 weeks antepartum. V.P.C.34%. (Uncorrected).

5 weeks postpartum. V.P.C.43%. (Uncorrected).

FIG. 19

Case 20 (Fig. 17) shows a decrease in MCF of 0.044, by the 7th day, the largest alteration in the series of cases. The antepartum reading was not corrected; had there been a corrected reading, the alteration would have been greater, as the antepartum VPC was only 26 per cent.

Case 24 (Fig. 18) shows no significant change in MCF by the 3rd week postpartum, but comparing the corrected antepartum reading with the postpartum reading the decrease in MCF is 0.012.

Case 50 (Fig. 19) shows a decrease in MCF of 0.019 by the 5th week postpartum, there being no intermediate tests. No correction was made in the antepartum reading; had there been a corrected antepartum reading, when the VPC was 34 per cent, the difference would have been greater.

In the second group, in which there is very little if any change in the postpartum fragility, there were 5 cases.

Case 13 (Fig. 20) shows an insignificant decrease in MCF of 0.004 between 37 weeks antepartum and 8 weeks postpartum, and an increase of 0.008 between 39½ weeks and 8 weeks postpartum. The two antepartum readings showed a slight shift to the left, the MCF difference being 0.006.

Case 22 (Fig. 21) shows an increase in MCF of 0.003 by the 14th week postpartum, there being no intermediate reading.

Case 26 (Fig. 22) shows a decrease on the corrected antepartum reading of 0.003 by the 10th week postpartum.

Case 31 (Fig. 23) shows a decrease of 0.009 on the corrected antepartum and postpartum readings, the postpartum reading being at 6 weeks.

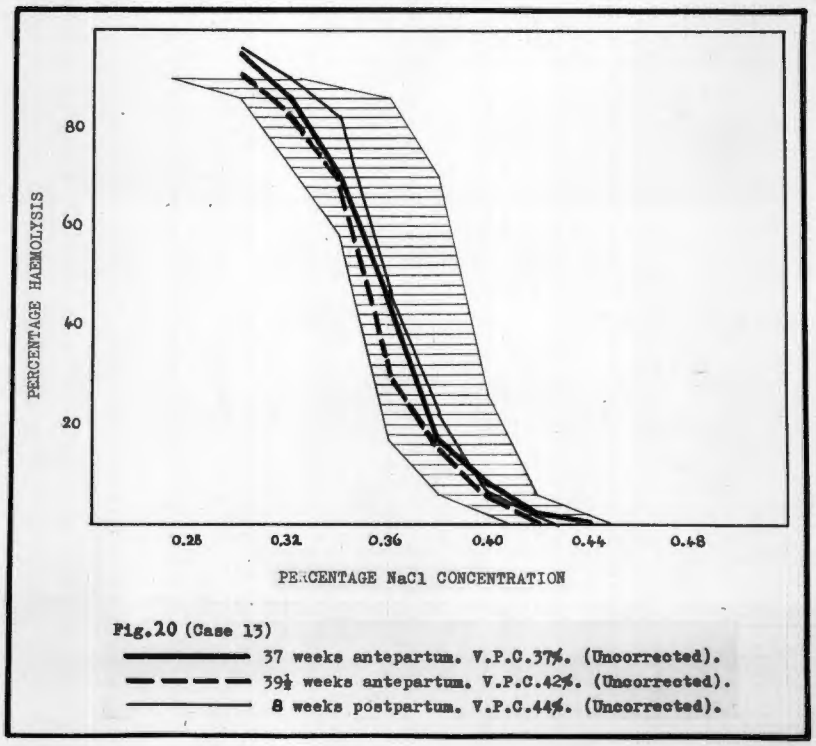


Fig.20 (Case 13)

37 weeks antepartum. V.P.C.37%. (Uncorrected).

39½ weeks antepartum. V.P.C.42%. (Uncorrected).

8 weeks postpartum. V.P.C.44%. (Uncorrected).

FIG. 20

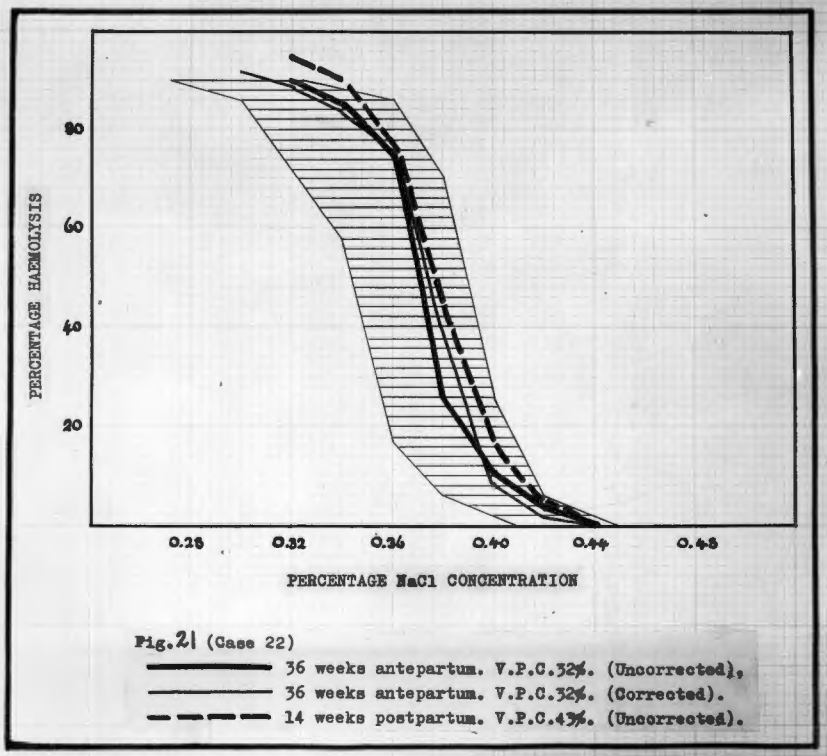


Fig.21 (Case 22)

36 weeks antepartum. V.P.C.32%. (Uncorrected).

36 weeks antepartum. V.P.C.32%. (Corrected).

14 weeks postpartum. V.P.C.43%. (Uncorrected).

FIG. 21

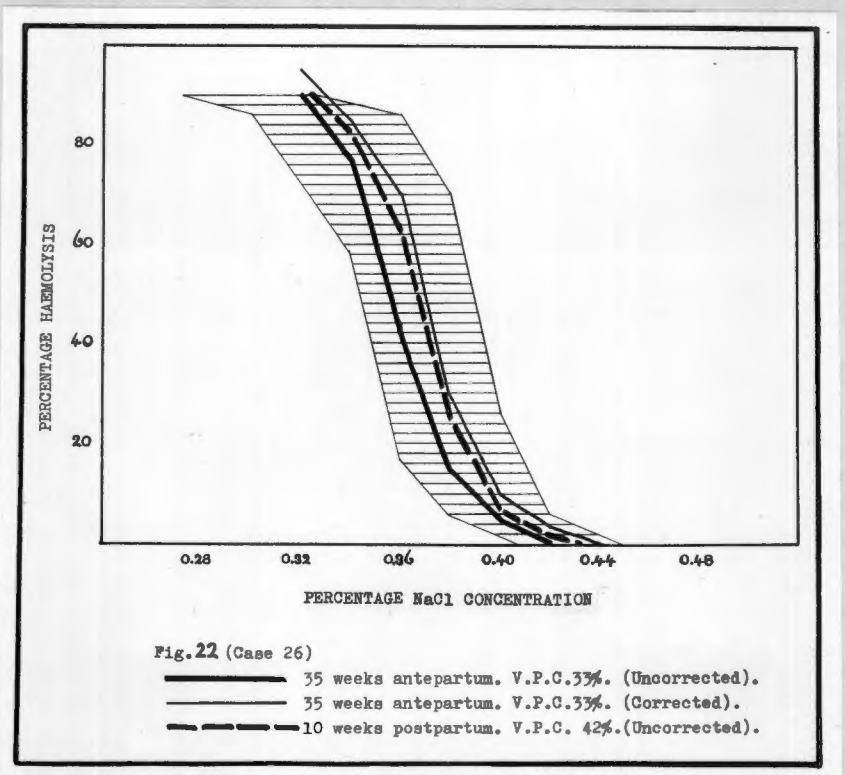


Fig. 22 (Case 26)

35 weeks antepartum. V.P.C.33%. (Uncorrected).
35 weeks antepartum. V.P.C.33%. (Corrected).
10 weeks postpartum. V.P.C. 42%.(Uncorrected).

FIG. 22

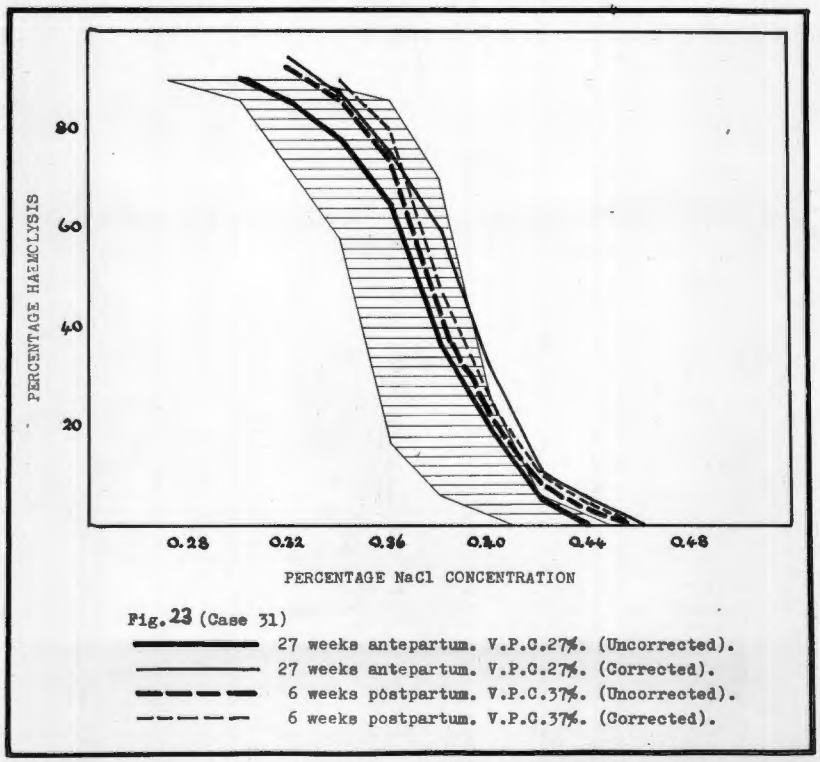


Fig. 23 (Case 31)

27 weeks antepartum. V.P.C.27%. (Uncorrected).
27 weeks antepartum. V.P.C.27%. (Corrected).
6 weeks postpartum. V.P.C.37%. (Uncorrected).
6 weeks postpartum. V.P.C.37%. (Corrected).

FIG. 23

Case 41 (Fig. 24) shows an increase in MCF of 0.003 by the 18th week postpartum, there being no intermediate readings. The antepartum reading was not corrected; as the VPC was only 34 per cent, the corrected reading would have fallen to the right of the postpartum reading.

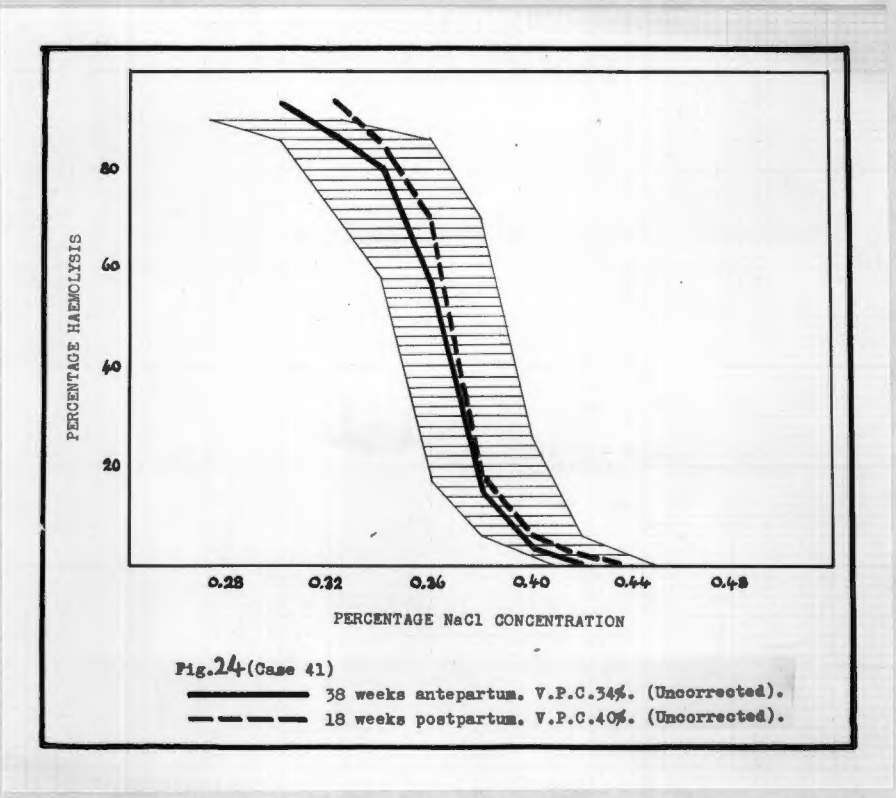


Fig. 24.

In no case in which antepartum and postpartum readings were done was there any significant increase in the MCF or shift of the fragility curve to the right in the postpartum period.

FROM THESE OBSERVATIONS it is clear that in the majority of cases of pregnancy anaemia there is after

parturition a distinct shift to the left of the fragility curve and a decrease in MCF as compared to the antepartum reading. The earliest that this change was demonstrated was the 5th day after delivery (Case 4, fig. 14); it was shown to be delayed at least 9 days in one case (Case 7, fig. 15). The data are insufficient to say when the change takes place as a rule. In less than half the cases, there was no significant alteration in the MCF after parturition, that is, the change was less than the arbitrarily selected figure of 0.010 grammes sodium chloride concentration per cent. In no case was there a significant increase in MCF postpartum, the greatest being 0.008. In the matter of red cell fragility, therefore, anaemia in pregnancy behaves differently from other types of anaemia, exclusive of acholuric jaundice.

Observations on the red cell fragility on several occasions in one case as pregnancy advanced were too few to allow of any conclusions. The cases, six in all (apart from two normal cases), are tabulated in table V (Fig. 25). In four (cases 3, 15, 17 and 29) there was an increase of 0.011, 0.043, 0.002 and 0.021 respectively; in two (cases 4 and 13) there was a decrease of 0.016 and 0.012 respectively. The fragility curve for case 29 is reproduced in Fig. 26. The curves for cases 3,15,17,4 and 13 have already been presented.

TABLE V

CASES IN WHICH MORE THAN ONE ANTEPARTUM MCF WAS TESTED

(Cases 23 and 25 NORMAL, the remainder ANAEMIC)

CASE	ANTEPARTUM (a)			ANTEPARTUM (b)			AP - RP DIFFERENCE
	STAGE	MCF	VPC	STAGE	MCF	VPC	
23	24 wks	0.394	32%	32 wks	0.384	34%	— 0.010
25	22 wks	0.372	40%	30 wks	0.380	36%	+ 0.008
3	30 wks	0.358c 0.342	26%	36 wks	0.369	39%	+ 0.011
4	32 wks	0.376 0.385c	31%	34 wks	0.360 0.369c	37%	— 0.016
	32 wks	0.376 0.385c	31%	36 wks	0.367	37%	— 0.009 — 0.018
	34 wks	0.360 0.369c	37%	36 wks	0.367	37%	+ 0.007
13	37 wks	0.356 0.362c	37%	39½ wks	0.350	42%	— 0.006 — 0.012
15	28 wks	0.325	34%	38 wks	0.368	39%	+ 0.043
17	34 wks	0.375 0.380c	35%	38 wks	0.378	45%	+ 0.002
29	30 wks	0.343	31%	38 wks	0.366	40%	+ 0.021

FIG. 25

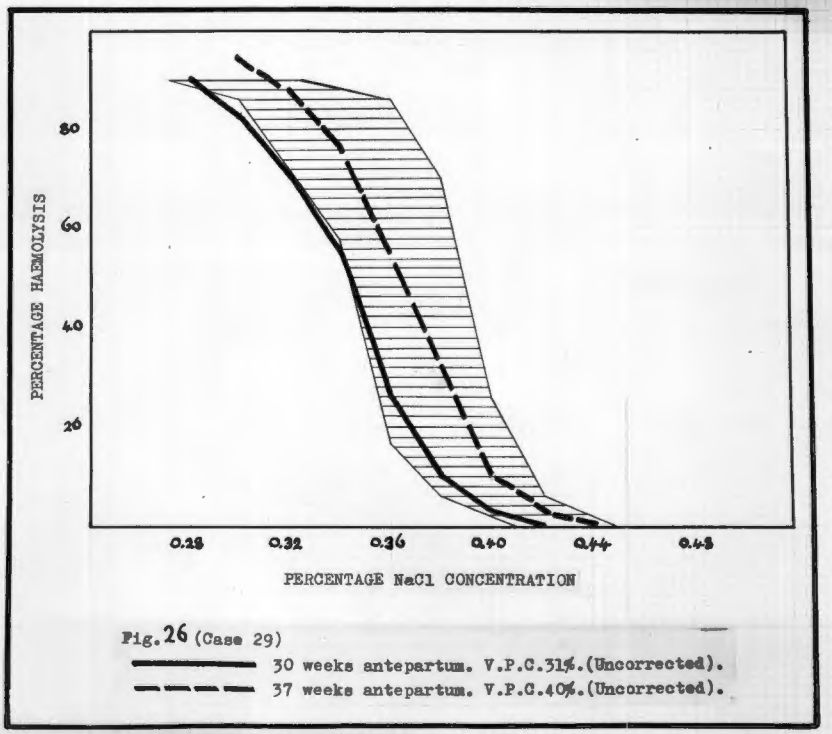


Fig. 26 (Case 29)

30 weeks antepartum. V.P.C.31%.(Uncorrected).

37 weeks antepartum. V.P.C.40%.(Uncorrected).

FIG. 26

Observations on the red cell fragility on more than one occasion during the postpartum period in an individual case were only made on one case (Case 7), the figures being tabulated in table Vl Fig. 27. There was an insignificant change of 0.002 up to the 9th day, and then a decrease of 0.031 by the 8th week. More observations on this aspect are required.

TABLE VI

CASE IN WHICH MORE THAN ONE POSTPARTUM MCF WAS TESTED

CASE	POSTPARTUM (a)			POSTPARTUM (b)			PP - PP DIFFERENCE
	STAGE	MCF	VPC	STAGE	MCF	VPC	
7	2 dys	0.404c 0.397	25%	9 dys	0.402c 0.397	33%	— 0.002
	2 dys	0.404c 0.397	25%	8 wks	0.373	42%	— 0.031
	9 dys	0.402c 0.397	33%	8 wks	0.373	42%	— 0.029 — 0.024

Fig. 27.

THE CORRELATION between the MCF and certain other haematological findings of the cases is to be considered.

The red cell fragility has been shown to be directly proportionate to the red cell thickness, that is, the thicker the cell, the more fragile (Haden, 1934, Dacie and Vaughan, 1938, Cassells, 1938, et al). Dacie and Vaughan consider that the relationship is better demonstrated by plotting

the MCF, not against the mean cell thickness (MCT) but against the ratio of the mean cell thickness to the mean cell diameter. This has been done in the present series of cases in Fig. 28, in which the figures for both the normal and the anaemic series

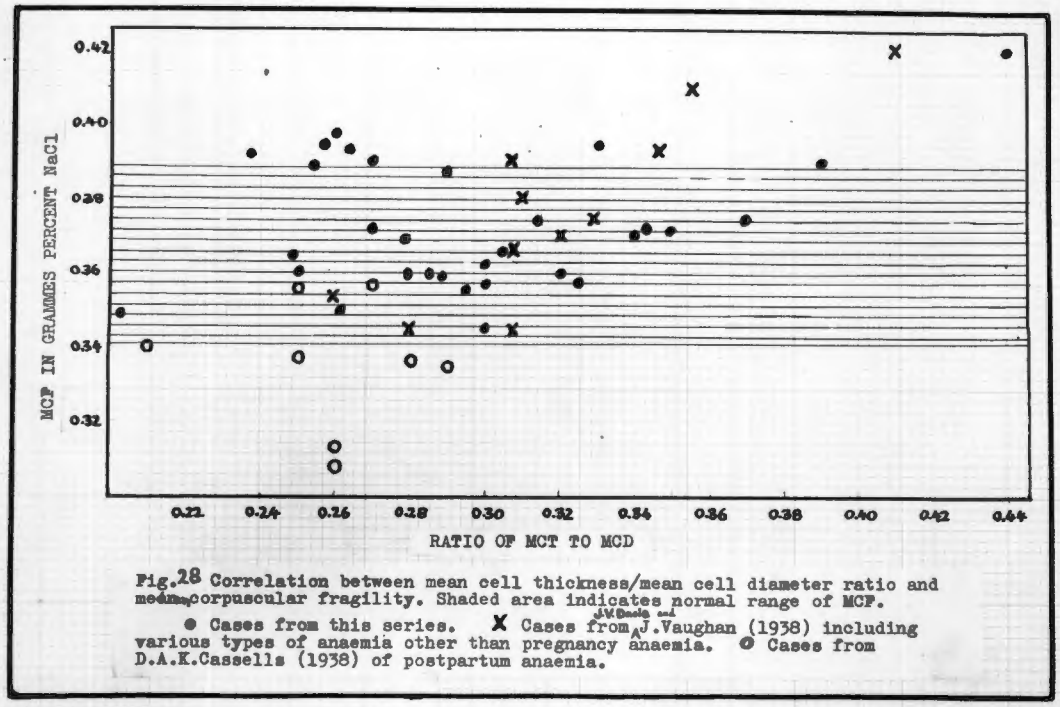


Fig.28 Correlation between mean cell thickness/mean cell diameter ratio and median corpuscular fragility. Shaded area indicates normal range of MCF.
● Cases from this series. X Cases from J.W.Dacie and J.Vaughan (1938) including various types of anaemia other than pregnancy anaemia. ⊙ Cases from D.A.K.Cassells (1938) of postpartum anaemia.

Fig. 28.

are included. On the same chart are included, for comparative purposes, figures for various types of anaemia selected from Dacie and Vaughan (1938) and for cases of postpartum anaemia from Cassells (1938). The shaded area indicates the normal range of fragility. It is seen that there is a fair degree of correlation in normal and anaemic pregnancy between the

MCF and the MCT/MCD ratio.

In the normal and anaemic series of the present investigation it can be demonstrated that there is no correlation

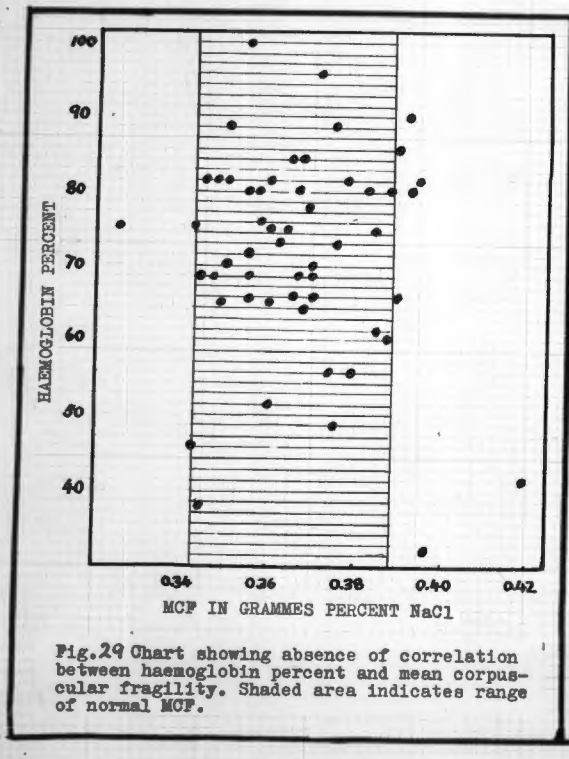


Fig.29 Chart showing absence of correlation between haemoglobin percent and mean corpuscular fragility. Shaded area indicates range of normal MCF.

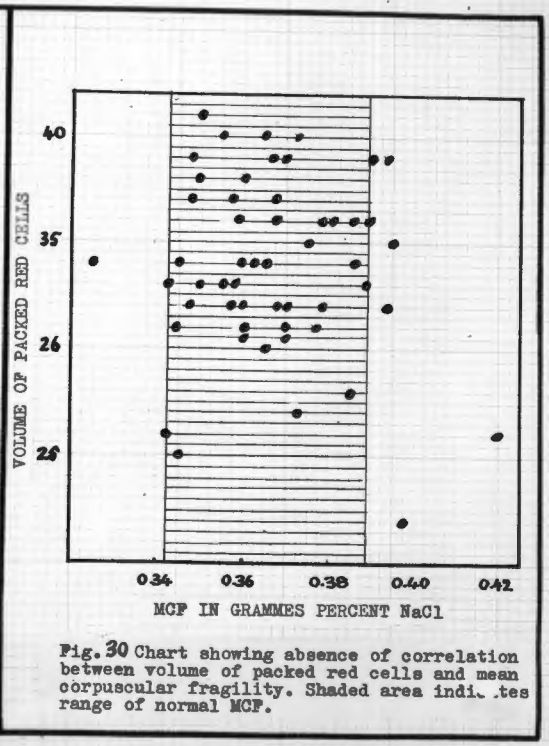


Fig.30 Chart showing absence of correlation between volume of packed red cells and mean corpuscular fragility. Shaded area indi..tes range of normal MCF.

Fig. 29.

Fig. 30.

between MCF and haemoglobin percentage (Fig. 29), MCF and VPC (Fig. 30), or colour index and MCF (Fig. 31). The arrows in Fig. 31 indicate the different readings on different occasions in one case; there can be seen to be no relationship between the changing colour index and the changing MCF.

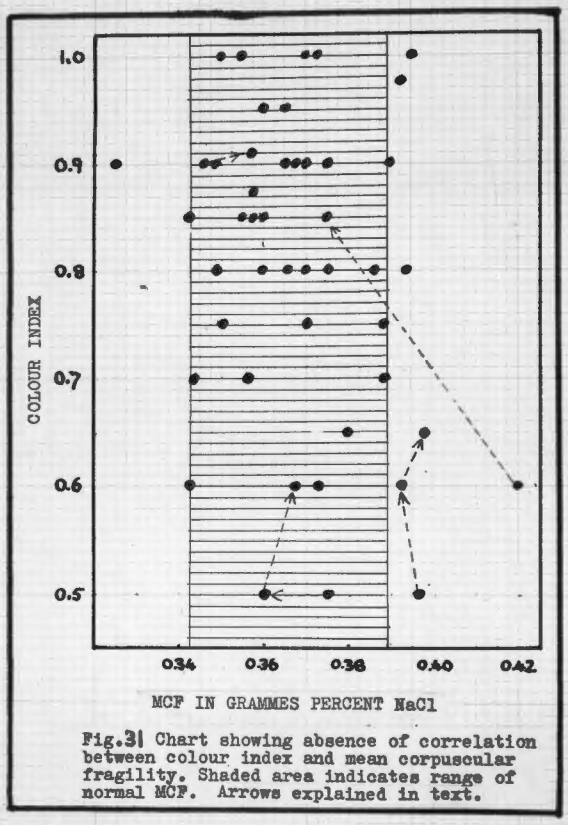


Fig.31 Chart showing absence of correlation between colour index and mean corpuscular fragility. Shaded area indicates range of normal MCF. Arrows explained in text.

Fig. 31.

The possibility that dilution of the blood by the hydraemia of pregnancy may be responsible for the behaviour of the fragility in pregnancy anaemia and ~~possibly~~ in normal pregnancy will have to be considered when more facts concerning the alteration in blood volume and blood chemistry during pregnancy have been presented.

RETICULOCYTE PERCENTAGE

The reticulocytes in pregnancy anaemia will be

discussed in a special section.

PLASMA BILIRUBIN

The plasma bilirubin will be discussed in a special section.

TREATMENT AND FOLLOW UP OBSERVATIONS

In this investigation, there are too few cases for the results of treatment to be of any statistical significance. The observations are however of value for the purposes of this investigation in that they aid in the classification of the various cases into accepted types of anaemia of pregnancy. They also illustrate what is of some importance in pregnancy anaemia, that an appreciable number of cases, regarded individually, do not conform to the rules of average behaviour laid down for the anaemias of pregnancy.

Graphs have been constructed of the haematological course in 17 of the anaemic cases (Figs. 32 to 45). These cases will be considered for convenience under four headings, namely, cases that received no treatment, cases that received iron treatment, cases that received blood transfusions, and cases that received liver by injection. The cases on which too few haematological studies were done for the construction of graphs will be considered separately.

CASES RECEIVING NO TREATMENT

Case 31 (Fig. 33), a 30 year old 4-para. Refused all treatment during pregnancy "because it made her sick". The steady decline in haemoglobin to a level of 32 per cent at full term and the normal level of the reticulocytes are to be noted. This decline, together with the microcytosis (MCV 58 cu.mu, MCD 6.5 mu), anisocytosis (variability of 10.7 per cent), are in keeping with a pure iron deficiency anaemia. There were no difficulties at parturition, in

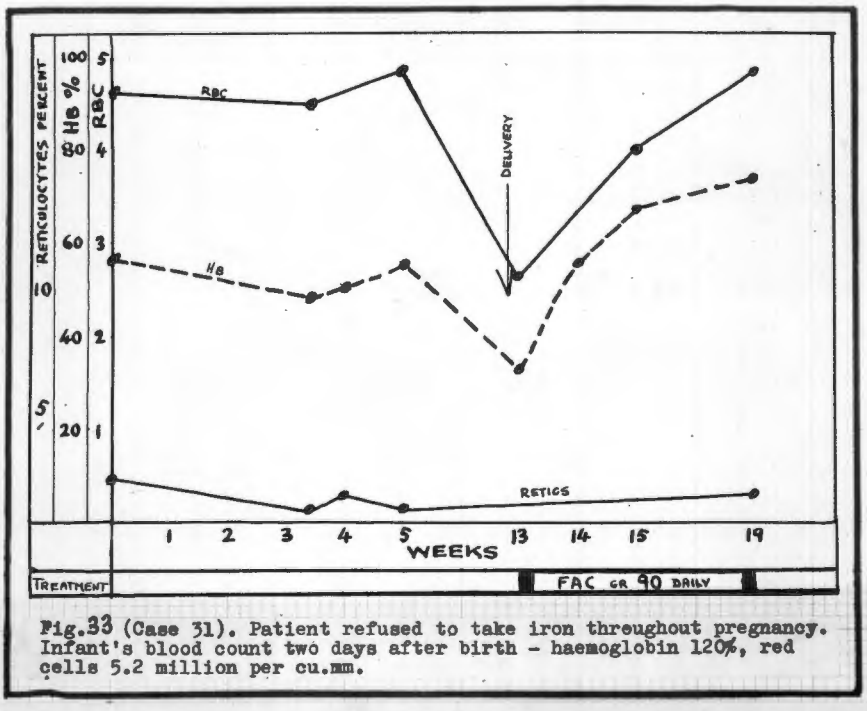


Fig.33 (Case 31). Patient refused to take iron throughout pregnancy. Infant's blood count two days after birth - haemoglobin 120%, red cells 5.2 million per cu.mm.

Fig. 33.

spite of the bloodless state. The postpartum improvement was rapid, iron being administered. The improvement must not necessarily be ascribed to the iron, as spontaneous improvement after parturition, even to normal figures, may occur as in Case 22 (Fig. 21). Observation of the

reticulocyte count immediately after the start of iron treatment after parturition was not done.

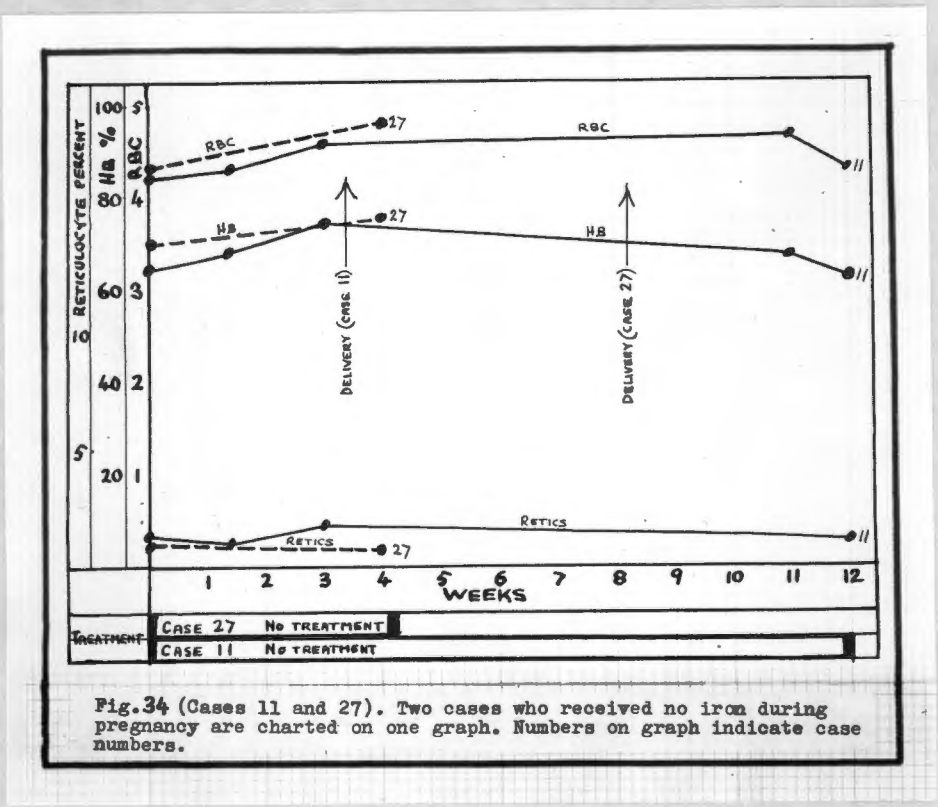


Fig.34 (Cases 11 and 27). Two cases who received no iron during pregnancy are charted on one graph. Numbers on graph indicate case numbers.

Fig. 34.

Cases 11, a 25 year old 3-para, and 27, a 22 year old 2-para (Fig. 34), showed no drop in haemoglobin as pregnancy advanced from the 37th and 32nd weeks respectively. The original haemoglobin levels were in the anaemic range, namely 64 and 70 per cent respectively; reticulocytes normal. The absence of reduction in haemoglobin is not in accordance with the usual behaviour in normal or anaemic pregnancy. It must however be noted that in case 11, the haemoglobin at 8 weeks postpartum had fallen to 64 per cent; whether this is due to her taking no iron will be considered later.

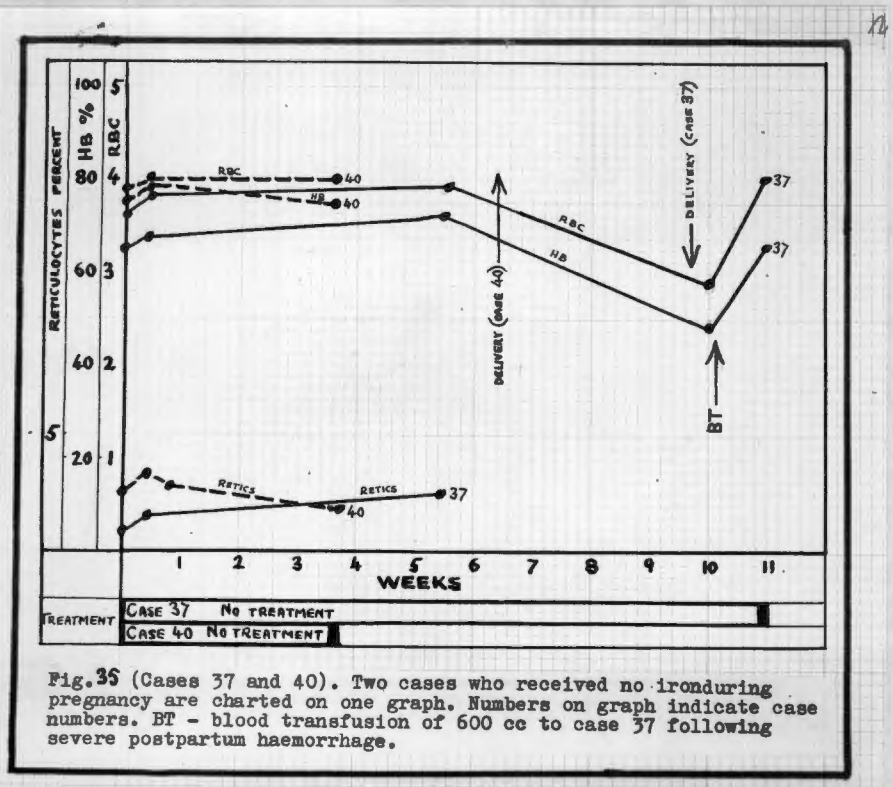


Fig.35 (Cases 37 and 40). Two cases who received no ironduring pregnancy are charted on one graph. Numbers on graph indicate case numbers. BT - blood transfusion of 600 cc to case 37 following severe postpartum haemorrhage.

Fig. 35.

Cases 37, an 18 year old primip, and 40, a 22 year old primip (Fig. 35) showed no change in haemoglobin over the last 4 weeks of pregnancy in case 40, and a drop in case 37. Reticulocytes in both were within normal range.

CASES RECEIVING IRON TREATMENT

Exclusive of three cases who were given blood transfusions as the main treatment, but who were given iron as well, subsequent to the transfusion, the effect of iron can be studied in nine cases graphically.

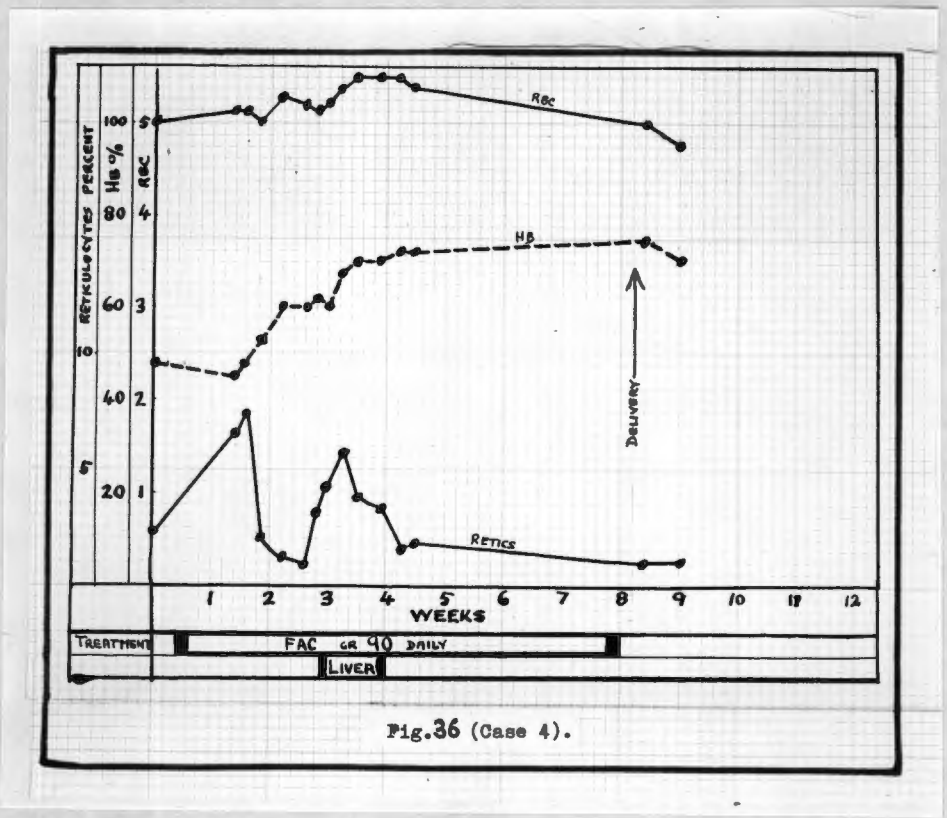


Fig.36 (Case 4).

Fig. 36.

Case 4 (Fig. 36), a 33 year old 6-para, is typical of a case that responds to iron treatment. Following a reticulocyte increase to 7.5 per cent, the haemoglobin rose from 44 to 75 per cent in 4 weeks. A second reticulocyte increase could not have been due to the liver given, as it occurred before the first liver injection. The liver treatment in this case consisted of 5 cc of Campolon daily for three days and then alternate days for 3 doses. The haematological characters (MCV 62 cu.mu, MCD 6.3 mu) low colour index and the response to iron treatment classify this case as one of pure iron deficiency anaemia. During the response to iron, at the second week, the Price-Jones red cell distribution curve showed changes characteristic of a responding blood in an increased MCD (6.5 mu) and an

increase in variability (14.7 per cent, as opposed to 9.1 originally) (Fig. 64).

Case 13 (Fig. 37), a 27 year old 2-para. Following the administration of iron, the haemoglobin rose from 64 to 80 per cent in three weeks. Reticulocyte increase was not observed as the patient was an Out Patient; but at the second week the type of anisocytosis shown in case 4 was apparent, suggesting a response to therapy. This is probably an iron deficiency anaemia of relatively mild degree.

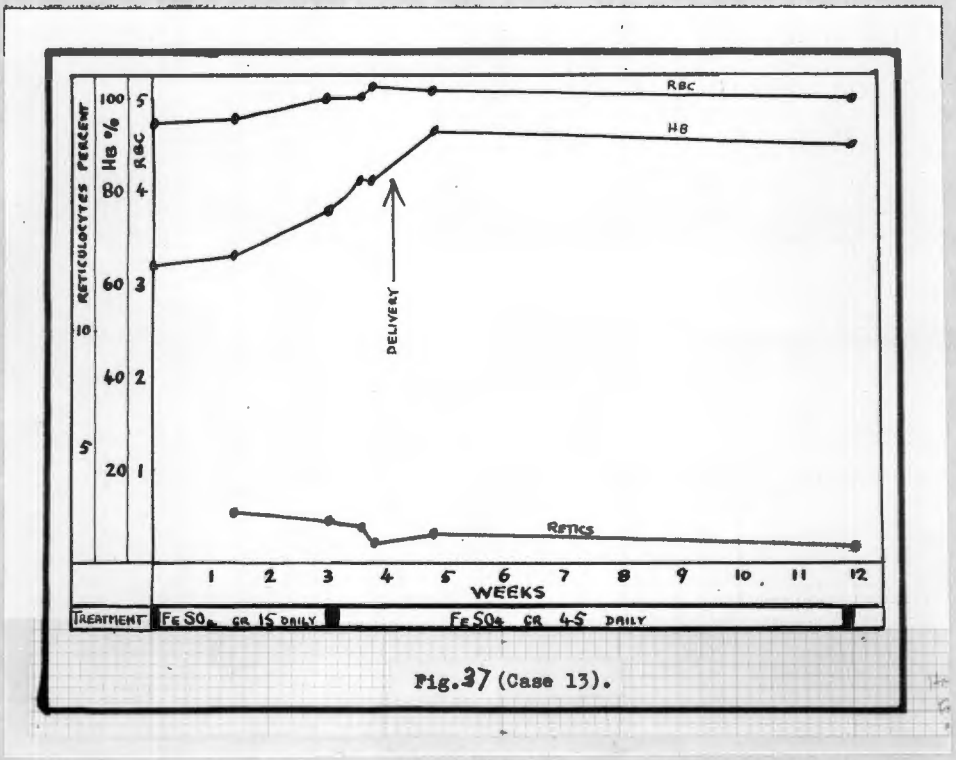


Fig.37 (Case 13).

Fig. 37

Case 15 (Fig. 38), a 33 year old 2-para, is, from the chart, possibly another mild iron deficiency anaemia. The fluctuations in haemoglobin could be ascribed reasonably to the irregularity with which she took iron, as charted.

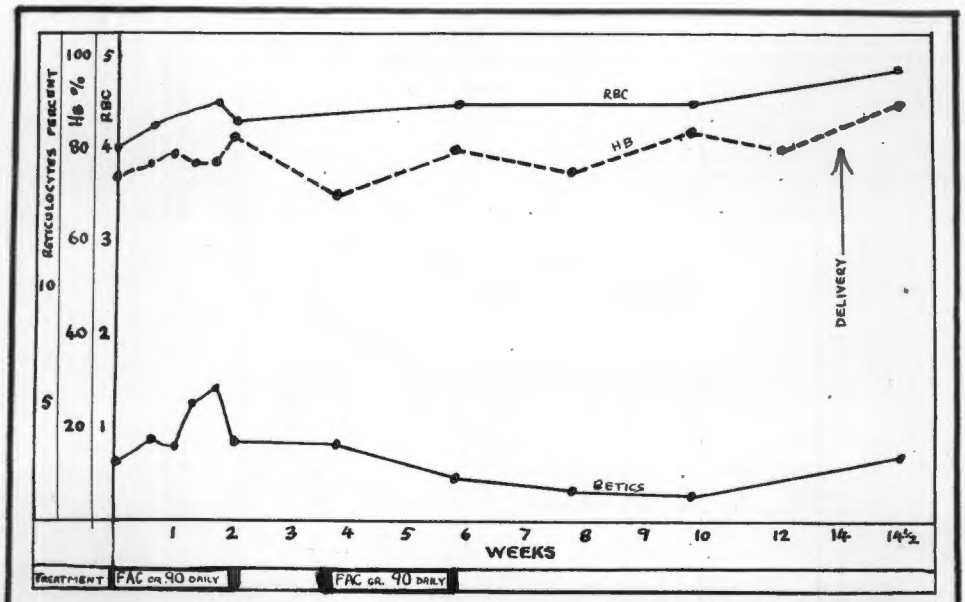


Fig.38 (Case 15).

FIG. 38

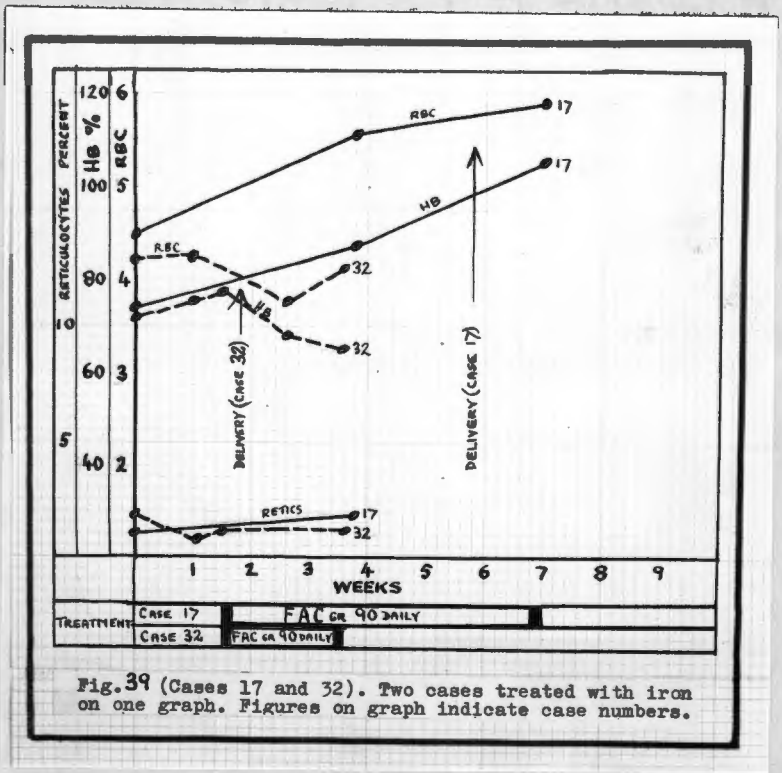


Fig.39 (Cases 17 and 32). Two cases treated with iron on one graph. Figures on graph indicate case numbers.

FIG. 39

Cases 17, a 28 year old primip, and 32, a 31 year old 2-para (Fig. 39). Case 17 apparently responded to iron, whilst case 32, who received her first iron postpartum, had not yet improved after 2 weeks.

Cases 18, a 25 year old primip, and 26, a 22 year old primip (Fig. 40). In both, the haemoglobin rose following iron administration. Reticulocytes could not be counted at the critical period as the cases were Out Patients. It is of importance to compare this degree of rise with the rise in case 27 (Fig. 34) who received no treatment. The rise is of equal degree. A slight rise such as occurred in these two cases, unless there is recorded a reticulocyte increase (as in case 15, Fig. 38) cannot be regarded as being due to the iron or other form of treatment given.

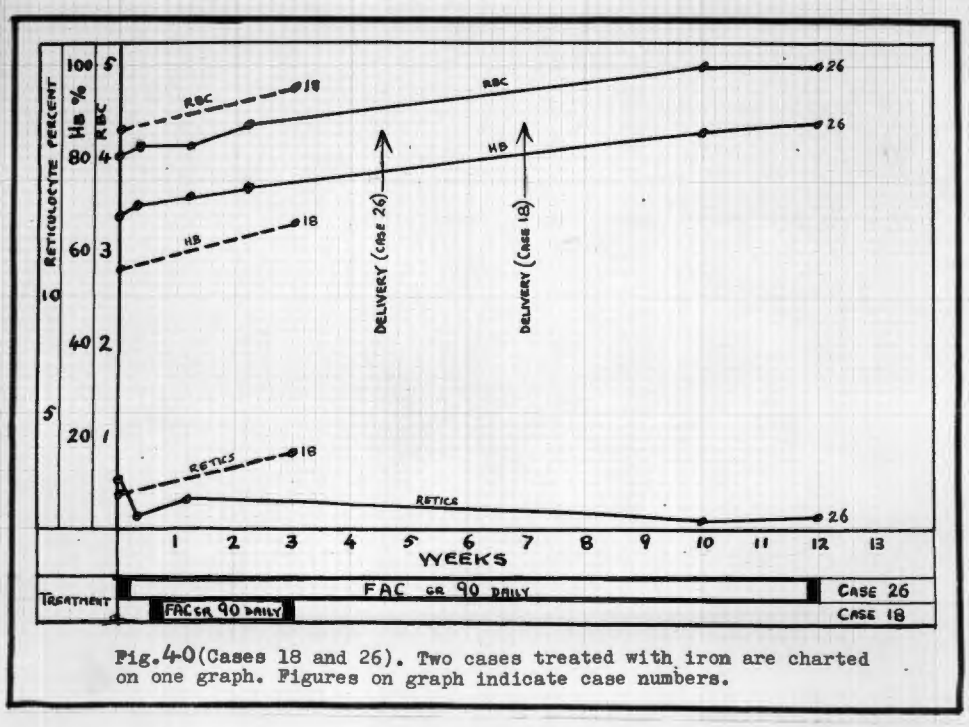


Fig.40(Cases 18 and 26). Two cases treated with iron are charted on one graph. Figures on graph indicate case numbers.

Fig. 40.

Case 29 (Fig. 41), a 40 year old 3-para, cannot be regarded as a response to iron without a recorded reticulocyte increase. Actually, when admitted to hospital, it was found that she was suffering from bleeding haemorrhoids, which ceased bleeding at rest. It was of interest too that the MCF in this case was originally towards the left, namely, 0.343 grammes per cent sodium chloride concentration, as occurs in post-haemorrhagic anaemia rather than pregnancy anaemia. (See Fig. 26)

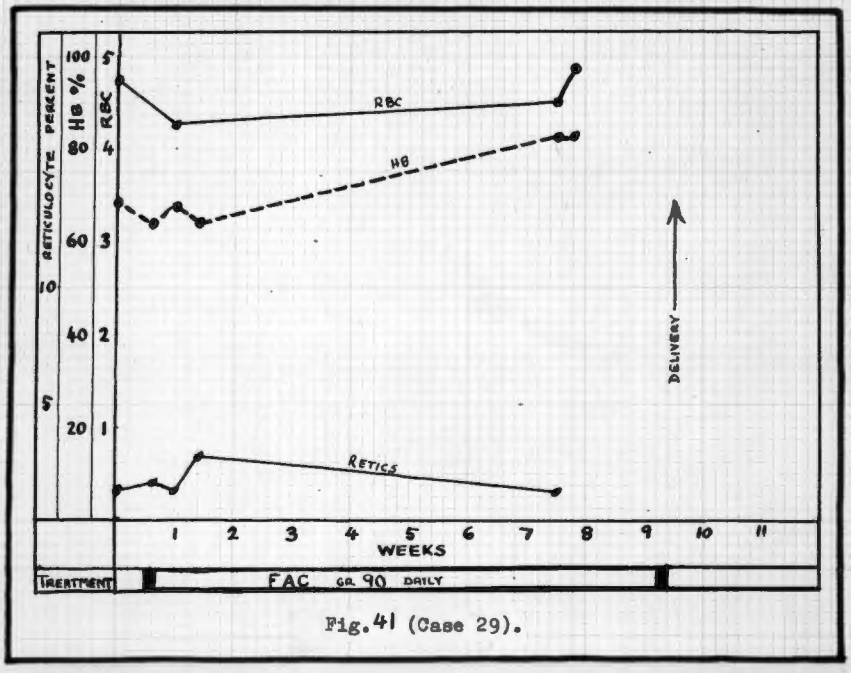


Fig.41 (Case 29).

Fig. 41.

Case 22 (Fig. 42), a primip of 16 years, gave no response to iron, either in reticulocytes or in haemoglobin. This was not unexpected as the anaemia was not of the iron deficiency type morphologically. Colour index 1.0, MCV 98 cu.mu. Liver treatment consisted of 5 cc of hepastab daily for 5 days; it is possible that there was an increase of

reticulocytes following the liver, although the increase came sooner than usually occurs (see chart); no response on the part of the red cells or haemoglobin occurred. After delivery, all treatment was stopped, and there was a spontaneous return to a normal blood count within 4 weeks. The patient was put on to full hospital diet for the period of observation from the 8th to the 14 week on the chart, including meat and eggs.

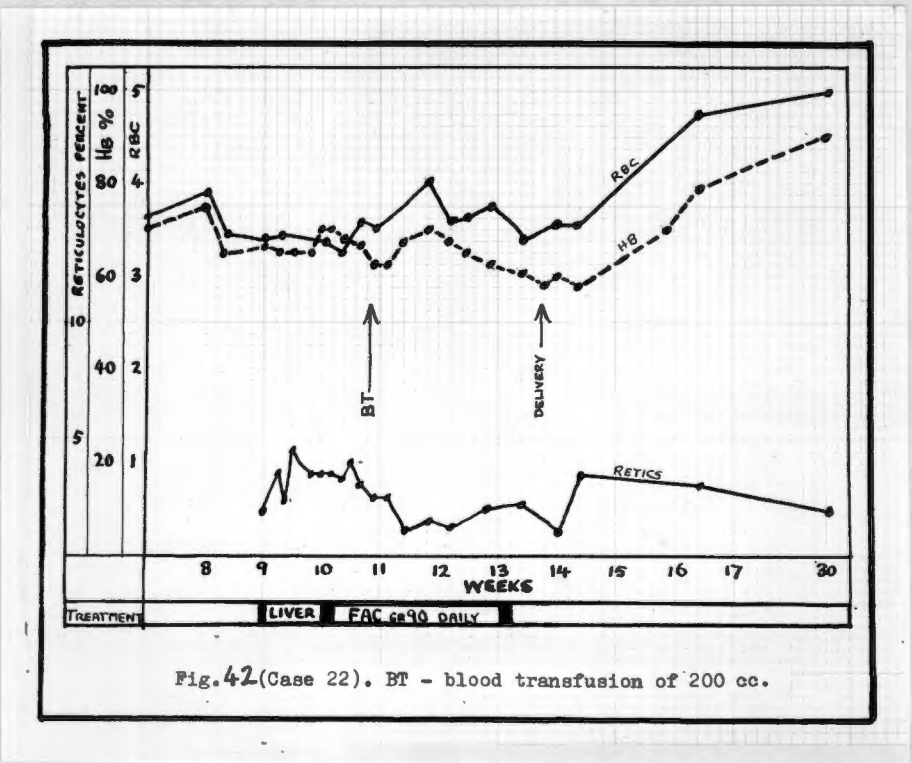


Fig.42(Case 22). BT - blood transfusion of 200 cc.

Fig. 42.

CASES RECEIVING LIVER TREATMENT

Liver was given under conditions controlled by reticulocyte counts in only two cases.

Case 4 (Fig. 36), a 33 year old 6-para, received Campolon 5 cc daily for 3 days, and then 5 cc alternate days for 3 doses without any effect. The case was one of pure iron deficiency anaemia.

Case 22 (Fig. 42), a 16 year old primip, has been described above. It is of interest that the case is the nearest to a macrocytic anaemia of the series, and did not respond with any definiteness to liver. It is also of interest that the blood returned spontaneously to normal after delivery. Was this due to the return of intrinsic factor into the gastric juice?

CASES TREATED BY BLOOD TRANSFUSION

Continuous drip blood transfusions were given to three cases with severe grades of anaemia.

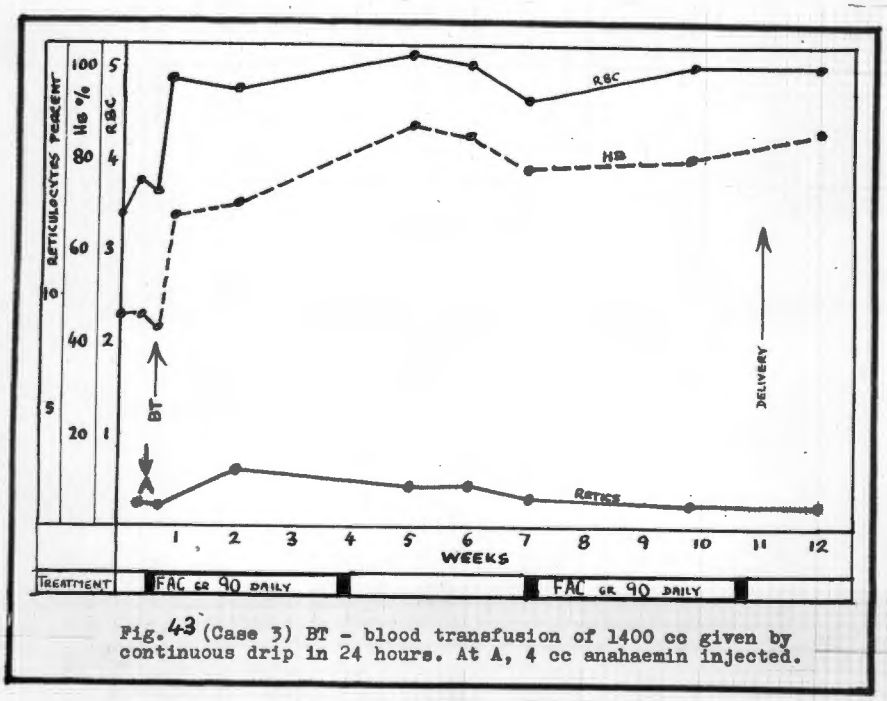


Fig. 43 (Case 3) BT - blood transfusion of 1400 cc given by continuous drip in 24 hours. At A, 4 cc anahaemin injected.

Fig. 43.

Case 3 (Fig. 43), a 23 year old primip, had the haematological features of a severe iron deficiency anaemia (MCV 68, colour index 0.6). Transfusion advised on account of the severity of the anaemia. 1400 cc were given by continuous drip. The satisfactory response is shown. Iron was given in two courses as shown. The second course possibly prevented what appeared to be a downward trend in haemoglobin percentage.

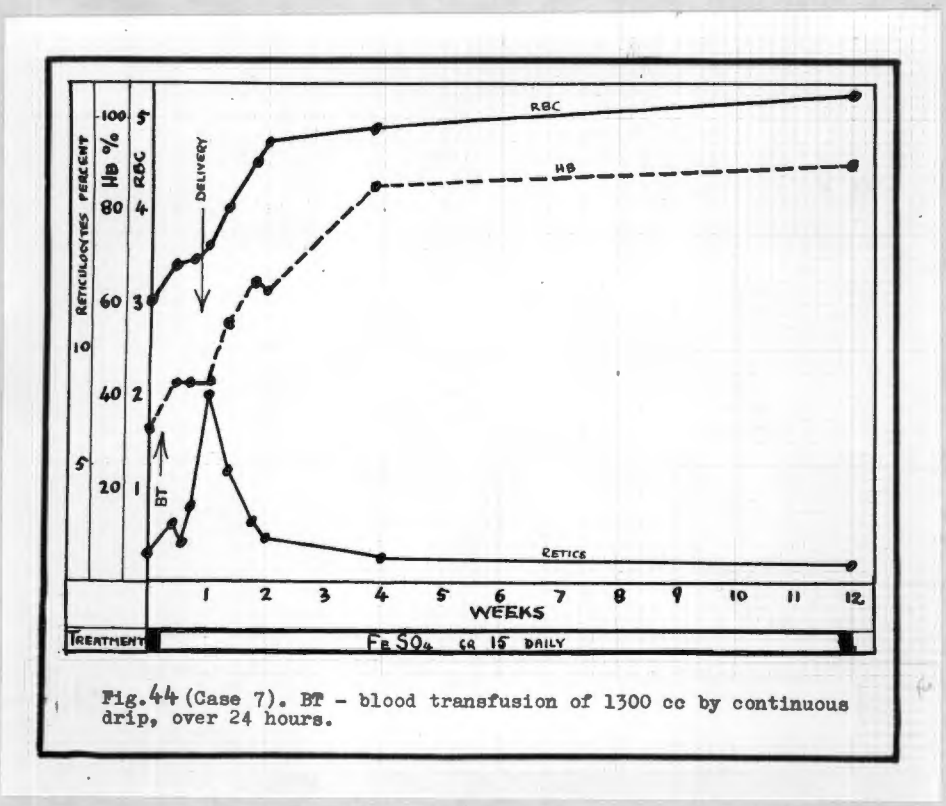


Fig.44 (Case 7). BT - blood transfusion of 1300 cc by continuous drip, over 24 hours.

Fig. 44.

Case 7 (Fig. 44), a 23 year old primip, also had the features of a severe iron deficiency anaemia (MCV 66 cumu, colour index 0.5). As she was near full term, transfusion was advised and 1300 cc given by continuous drip; iron was started at the same time. Delivery occurred 6 days after the transfusion. The response is shown on the chart. The

increase of reticulocytes to 8 per cent might have been due to iron or the transfusion. More probably the iron. The return of the blood to normal figures within 4 weeks was very satisfactory.

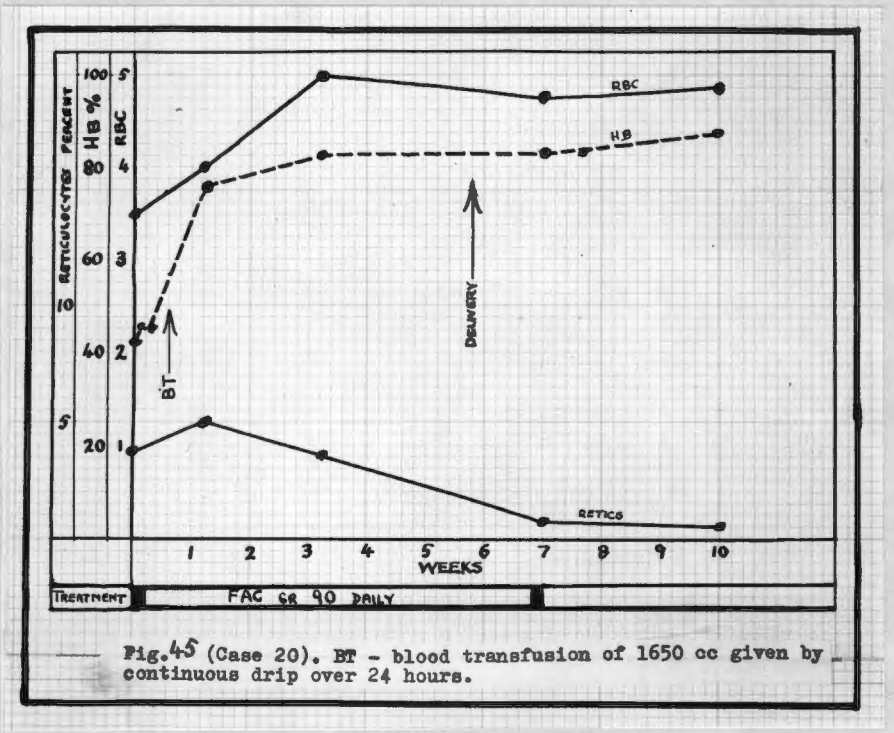


Fig.45 (Case 20). BT - blood transfusion of 1650 cc given by continuous drip over 24 hours.

Fig. 45.

Case 20 (Fig. 45), a 22 year old primip, had a severe grade of anaemia, not typical of pure iron deficiency (MCV 74, colour index 0.6, with haemoglobin 46 per cent). Continuous drip transfusion of 1650 cc given on account of the severity of the anaemia. Iron started at the same time. The response is shown on the chart. It is possible that the reticulocytes of 5 per cent 6 days after the transfusion and the start of iron treatment was due to the iron, as in case 7. The type of anaemia was in doubt; in addition to its not having the characteristic features of pure iron deficiency anaemia

than 74 cu.μ
(including a lower MCV for a haemoglobin of 46 per cent), it was the case in the series with the highest MCF (0.420 uncorrected for anaemia); its features will be discussed more fully later.

The administration of two or three pints of blood by the continuous drip technique is a safe and useful measure in cases of severe pregnancy anaemia. Where a rapid response is desired, for example, when the patient is near full term, this form of treatment is of great value. In all severe anaemias of pregnancy that do not conform to a type which can haematologically be recognised as a type that will respond to other forms of treatment, continuous drip blood transfusion must be considered as a form of treatment. Case 20 (Fig. 45) is an example of this type, as pointed out in the case description.

The value of transfusion in cases of severe anaemia of pregnancy has been recognised for many years. Without going into the question of accuracy of diagnosis, the safety of the procedure is evidenced by its general use. Amongst a few of the observers who have found it valuable and at times life saving are Rowland (1924), Larabee (1925), Allan (1928), Peterson et al (1930), Whitby (1932), Wilkinson (1932), Witts (1932), Adair et al (1936), Lull (1937) and Barnum and Woodward (1938). None of these authors have used the continuous drip transfusion technique, the value of which is

in the present author's opinion, considerable.

Whilst advocating the use of transfusion in certain cases, sight must not be lost of the fact that even very severe cases of anaemia may go through a normal delivery and have an uncomplicated puerperium (case 31, Fig. 33).

ADDITIONAL OBSERVATIONS

Observations not included in the preceding charts but which have some bearing on the use of iron during pregnancy are tabulated in Table V11 (Fig. 46).

TABLE V11 (Fig. 46)

Cases taking no iron before or subsequent to the first recorded haemoglobin estimation.

CASE	AGE	PARITY	STAGE	HB %	REMARKS
10	21	2	39	76	
24	24	2	33	70	Hb at 3 wks postpartum 82%
30	22	1	38	66	Normal delivery 2 weeks later
34	34	7	36	68	
41	41	14	38	75	Hb at 4 mos postpartum 86%
50	30	4	39	76	Hb at 5 wks postpartum 89%
42	25	1	34	65	
47	23	1	34	60	
56	28	1	34	68	

In the three cases in which a postpartum reading was taken, the fact that no iron was taken did not seem to predispose to the development of a postpartum anaemia; it must however be noted that the initial haemoglobin levels were not much below the "normal" of 80 per cent. Case 11 (Fig. 16) on the other hand had a definite postpartum anaemia, having taken no iron during pregnancy.

One case (No. 33) not recorded on the charts had an initial haemoglobin of 66 per cent, was a 3-para of 21 at the 28th week of pregnancy, was put on iron, and at one week postpartum had a haemoglobin of 84 per cent.

For purposes of comparison, the cases of the normal series who received no iron during pregnancy are tabulated in Table Vlll, (Fig. 47).

In the 6 remaining normal cases not included in Table Vlll 2 might not or might have taken iron during pregnancy (cases 2 and 57), and 4 (cases 14, 16, 48 and 52) definitely had taken iron. Of these, case 14 had Hb 90% at 8 weeks having been 82% at 39 weeks antepartum, case 16 had Hb 90% at 4 dys postpartum having been 80 per cent at 37 weeks antepartum, case 52 had no change in haemoglobin percentage at 7 days postpartum, and in case 41 there was no postpartum haemoglobin estimation. Amongst the "normals"

TABLE Vlll. (Fig. 47)

Cases of normal series who took no iron before or after the first estimation of haemoglobin.

CASE	AGE	PARITY	STAGE	HB %	REMARKS.
1	26	3	35	80	Hb 3 dys postpartum 78%
12	25	2	38	100	Hb 7 wks postpartum 84%
19	40	4	38	80	
23	19	1	24	82	Hb at 32 wks 76%
25	25	2	22	96	Hb at 30 wks 80%, at 33 wks 84%
35	25	4	10	88	
36	22	2	33	100	Hb at 37 wks 86%, at 38 wks 80% with rbc's 5.8
38	28	3	38	80	Hb 3 mos postpartum 88%
39	24	1	20	82	
44	18	1	39	86	
45	34	2	37	88	
46	28	2	29	82	Hb at 17 wks had been 100%
51	25	3	28	80	
55	37	3	30	82	

therefore, the taking of iron during pregnancy may tend to raise the postpartum haemoglobin; or at least prevent a postpartum fall (seen in cases 1 and 12, Table Vlll).

SUMMARY OF FINDINGS AND CONCLUSIONS

SELECTION OF CASES.

Cases were arbitrarily selected as "normal" or "anaemic" according as the haemoglobin was above or below 80 per cent Haldane. No cases were included in either the normal of the anaemia group if there was any evidence that the pregnancy was complicated by toxaemia, nephritis, heart disease, or any other organic disorder apart from anaemia.

HAEMATOLOGICAL FINDINGS IN NORMAL GROUP (20 CASES).

Haemoglobin 80 to 100 per cent Haldane.

Red cells 4.10 to 5.8 million per cu.mm.

Colour index 0.8 to 1.0, with one reading of 0.69.

M.C.V. 73 to 88 cu.mu, with one reading of 62 cu.mu.

M.C.D. 6.7 to 7.7 mu, in 14 cases tested. Standard deviation 0.466 to 0.708 mu (normal 0.43 to 0.535). Variability 6.6 to 9.2 per cent (normal - under 7.3 per cent).

M.C.F. 0.348 to 0.394 grammes NaCl per cent (within normal limit) with tendency to "shift to the left" after parturition.

Reticulocytes and bilirubin to be presented later.

These findings are within normal limits, with the exception of (a) colour index, which should not be below 0.90

normally, (b) an M.C.V. below normal in one case (62 cu.mu), (c) anisocytosis greater than normal in several cases, gauged by the standard deviation and variability per cent. These abnormal features will be discussed fully later.

HAEMATOLOGICAL FINDINGS IN ANAEMIC GROUP (28 CASES).

Haemoglobin 32 to 76 per cent Haldane, with majority between 60 and 76 per cent (Fig. 7).

Red cells 3.27 to 5.00 million per cu.mm.

Colour index 0.5 to 1.0. 12 cases had colour index 0.9 to 1.0.

M.C.V. 58 to 98 cu.mu, with majority below 80 (Fig. 8).

M.C.D. 6.0 to 7.4 mu, with 6 out of 18 below 6.76 mu.

Standard deviation 0.495 to 0.959 (Fig. 9).

Variability 6.8 to 14.7 per cent (Fig. 10).

M.C.F. There is a failure, even in cases of severe anaemia, for the M.C.F. and the fragility curve to "shift to the left", as happens in most anaemias except acholuric jaundice, and a tendency to shift to the left after parturition. In some cases the fragility is increased beyond normal limits, returning to normal after parturition. There is a rough correlation between M.C.F. and M.C.T/M.C.D. ratio, but none between M.C.F. and colour index, haemoglobin per cent or volume of packed red cells.

The M.C.F. may be an aid in differentiating between anaemia of pregnancy and other types of anaemia; e.g. Case 29, in which anaemia was partly at least due to small repeated haemorrhage.

These findings will be discussed, especially (a) colour index, which in several cases is normal, (b) the occurrence of cases in this group with normal standard deviation and variability per cent, and therefore anisocytosis of normal degree, and (c) the peculiar behaviour of the red cell fragility in pregnancy anaemia.

FOLLOW-UP RECORDS.

The existence of a simple iron deficiency anaemia of pregnancy, diagnosable on haematological characters and on the characteristic response to iron treatment, is confirmed (Case 4, Fig. 36).

Spontaneous improvement in the haemoglobin percentage during or after pregnancy must not be confused with improvement due to treatment. Improvement due to treatment can be differentiated by the characteristic reticulocyte crisis which precedes the rise of haemoglobin percentage, and the gross increase in anisocytosis as the blood responds.

There is a general tendency for the haemoglobin percentage to fall as pregnancy advances, whether the case

be originally normal (Cases 23, 25, 36 and 46, Table VIII, Fig. 47) or anaemic (Cases 37, Fig. 35, and 31, Fig. 33), and a tendency for it to rise after delivery. There are, however, examples of a rise of haemmoglobin as pregnancy advances, independent of treatment (Cases 11 and 27, Fig. 34). These spontaneous variations must always be borne in mind.

In mild cases of anaemia of iron deficiency type, failure to give iron during pregnancy does not necessarily result in postpartum anaemia (Cases 24, 41 and 50, Table VII, Fig. 46). In severer grades of anaemia (Case 11, Fig. 16) failure to give iron may predispose to postpartum anaemia. The general results in the "no treatment" and "iron treatment" groups favour the use of iron in all doubtful cases.

The effect of giving or not giving iron in "normal" cases cannot be studied on results in so few cases.

The severest anaemias need not have complicated deliveries.

The existence of types of anaemia during pregnancy which are not of the iron deficiency type, nor of the pernicious type (described later), is demonstrated. These cases cannot be classified on the present evidence. Examples are (a) Case 22 (Figs. 21 and 42), with a high

normal M.C.V., failure to respond to iron or liver during pregnancy and spontaneous return to normal after delivery, without treatment of any sort, and (b) Case 20 (Fig. 17 and 45) with M.C.V. just below normal in spite of a severe grade of anaemia, a definitely raised M.C.F. which returned to normal after delivery, with a normal reticulocyte count. Cases such as these, with one or more features that do not conform to the recognisable types of anaemia of pregnancy, are for the time being, better regarded as "unclassifiable" rather than as cases with definite names. The terms "hypoplastic", "haemolytic", etc. applied to exceptional cases of this type are inaccurate and misleading. The group of "unclassified" anaemia of pregnancy will be discussed fully.

The safety and value of large volume blood transfusions is demonstrated (Cases, 3, 7 and 20, Figs. 43, 44 and 45). Transfusions are useful in any type of severe anaemia near term, and in all cases that do not or look as if they will not respond to iron or other known treatment.

No conclusions regarding the value of liver can be arrived at from the cases in this series, as there were no examples of macrocytic anaemia. Not unexpectedly, liver was ineffective in the cases of iron deficiency anaemia, and also in one case of the "unclassified" type (Case 22).

Discussion of the findings of this investigation is dependent on a knowledge of the normal haematological values for pregnancy. It is therefore necessary to proceed to the description of the normal haematological standards during pregnancy.

NORMAL HAEMATOLOGICAL STANDARDS IN PREGNANCY

NORMAL HAEMATOLOGICAL STANDARDS DURING PREGNANCY.

The accepted normal haematological standards for women do not apply to women in the pregnant state owing to the profound physiological alterations in the circulation which occur during pregnancy. Before considering what can be accepted as the normal range of haemoglobin and red cell levels during pregnancy it is necessary to discuss the physiological alteration in blood volume which is mainly responsible for the fall in haemoglobin and red cells that occurs.

BLOOD VOLUME DURING PREGNANCY.

Nearly sixty years ago, Willcocks (1881) suggested that in normal pregnancy the red cells and haemoglobin fell proportionately as pregnancy advanced, and that this proportionate fall might be due to a physiological hydraemia. In contrast, he described the chlorotic type of anaemia of pregnancy characterised by a greater fall in haemoglobin than in red cells. Willcocks' suggestion of so long ago has since been shown to be remarkably true by modern laboratory methods.

Keith, Rowntree and Geraghty (1915), pioneers in the technique of blood volume estimations, demonstrated that at

term the average total blood volume was 6176 cc, and at ten days postpartum, 5076 cc; allowing for 300 cc reduction due to blood loss, it was considered that the balance of 800 cc was accounted for by a physiological increase in blood volume during pregnancy.

Dieckmann and Wegner (1934a) published the first satisfactory report on blood volume in pregnancy. In 13 patients they estimated the blood volume by the congo red technique on three occasions antepartum and one or more occasions postpartum. The antepartum readings were made at approximately the 15th, 25th and 40th week respectively.

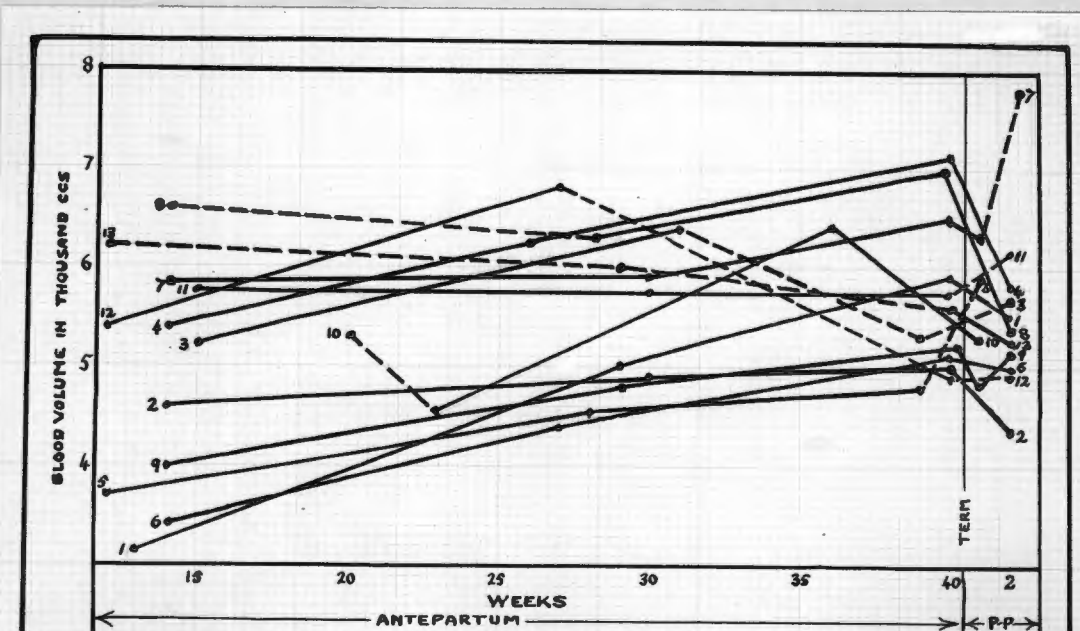


Fig.48 BLOOD VOLUME READINGS through pregnancy and in first two weeks of puerperium. From W.J.Dieckmann and C.K.Wegner, Arch.Int.Med.53,1934,71. Continuous lines indicate readings which conform to the "rule" of an increase during pregnancy with a fall at term. Interrupted lines indicate exceptions to the "rule". Figures on chart indicate Dieckmann's case numbers.

Fig. 48.

The antepartum readings were made on the first two or three days after parturition. Previous investigators had not followed up individual cases in this way. Their findings in the cases so studied are summarised in the reproduction of their chart (Fig. 48). In 10 cases, they estimated the blood volume immediately before term and on several occasions up to 8 weeks postpartum; the findings in these 10 cases are summarised in their chart (Fig. 49). This work of Dieckmann and Wegner has since been extensively quoted, but the quotation has usually been of the average figures for the whole group; these average figures are that there is an increase in blood and plasma volume commencing during the first trimester to a gain of 16 and 18 per cent respectively by the 13th week and a gain of 23 and 25 per cent respectively at term, with a drop of 16 per cent at 8 weeks postpartum for both plasma and blood volume. The discrepancy between the total average rise of 23 and 25 per cent and the fall of 16 per cent is not adequately explained, but it must be remembered that the figures are average for a relatively small number of cases. It is important to note the detailed findings in the individual cases of the two series; it will be seen that there are many exceptions to the rule deduced from the average results for the groups. It will be observed that in three cases (Fig. 48, Cases 8, 11 and 13) the antepartum increase in blood volume is insignificant or absent, and that in five cases of the first series

(Fig. 48, Cases 3, 5, 7, 11 and 12) there was no postpartum fall for the observed period of two or three days; in Case 12, the maximal rise was at the 27th week and at term, the volume was actually less than in early pregnancy. In their second group of 10 cases followed further into the puerperium, one case (Case 3, Fig. 49) had a greater volume 8 weeks postpartum than at full term.

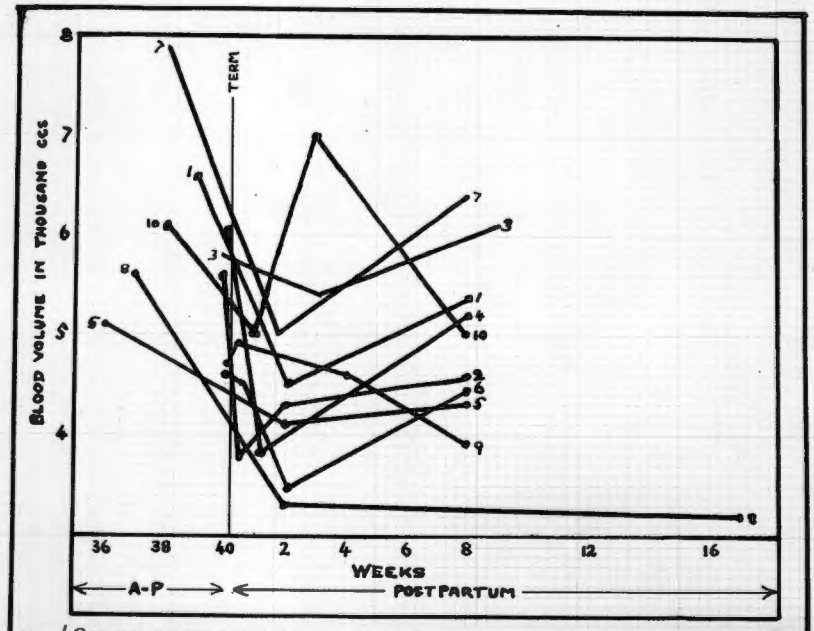


Fig.49 BLOOD VOLUME READINGS near full term and followed for at least 8 weeks of puerperium. From W.J.Dieckmann and C.K.Wegner, Arch.Int.Med.53,1934,71. Figures indicate Dieckmann's case numbers.

Fig. 49.

It must be realized from Dieckmann and Wegner's work that the exceptions to the general rule are sufficiently frequent and of sufficient magnitude to be significant. It is wrong to assume in a particular case that there must be

an increased blood volume during pregnancy; this has to be borne in mind when considering what is a normal and what is an anaemic blood picture during pregnancy.

Richter, Meyer and Bennett (1934) estimated the blood volume in 14 pregnant women on one occasion in each antepartum, and one occasion postpartum (8 days). In 6 normal pregnant women the postpartum drop in volume averaged 1900 cc (from 6000 to 4100 cc); and in 8 anaemic pregnant women the drop averaged 1800 cc (from 6100 to 4300 cc). The work indicates a definite postpartum drop in blood volume, and presumably therefore an increase during pregnancy.

Thomson, Hirsfheimer, Gibson and Evans (1938), using an improved technical method described by Gibson and Evans (1937) and by Thomson and Cohen (1936), estimated the blood volume through pregnancy and up to 6 weeks postpartum in 14 women; in all, 56 estimations were made, 40 antepartum and 16 postpartum. Their conclusions, illustrated graphically in Fig. 50, were that the volume increases up to the 9th lunar month when the average is 45 per cent over normal, falling to a level of 30 per cent over normal at term; two weeks postpartum the level has reached average normal figures. Again, these figures are average, represented by the thick continuous line in the graph; there is a wide range in which individual figures fall, this being represented by

the shaded area. There is no way of telling whether a particular case has a volume near the upper range or the lower range of normal except by direct measurement of volume, a conclusion which tallies with that of Dieckmann and Wegner.

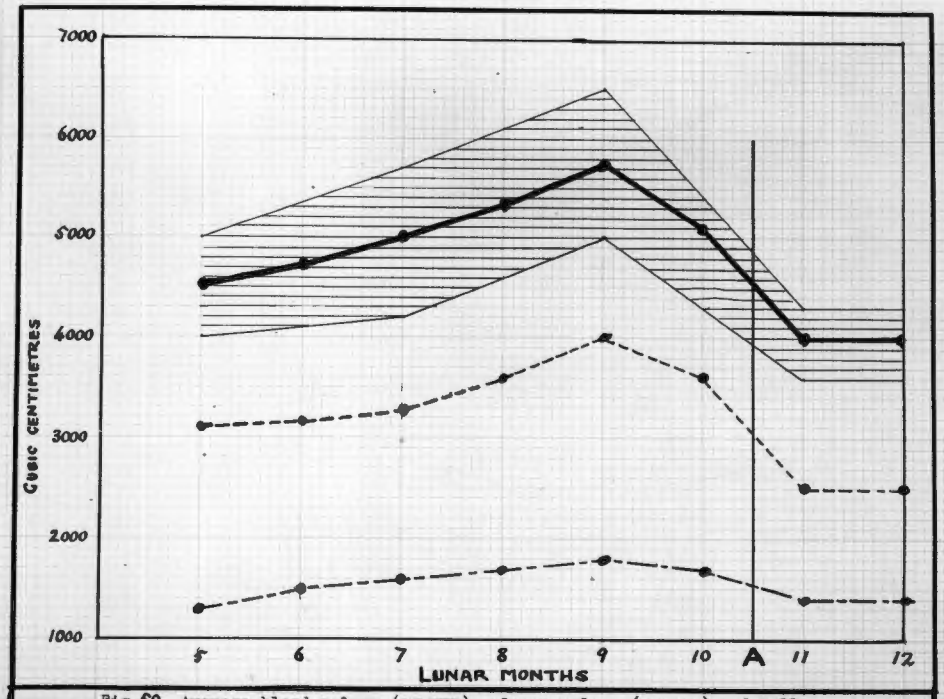


Fig.50 Average blood volume (———), plasma volume (– – –) and cell volume (—·—·—) in 14 normal pregnant women. Readings taken at monthly intervals antepartum and postpartum. Delivery occurred at "A". The shaded area represents the range within which the individual blood volume readings fell. From K.J.Thomson, A.Hirsheimer, J.G.H.Gibson and W.A.Evans (1938).

Fig. 50.

Burwell (1936, 1938) confirmed the findings of an average tendency for an increase of blood volume during pregnancy, and Thomson and Cohen (1939) re-affirmed their findings of the earlier publication of Thomson et al (1938).

A more indirect method of studying the problem is that of the estimation of water content of the blood. Van Donk, Feldman, and Steenbock (1934) studied water content of the blood in pregnant rats, their findings being summarised in their graph (Fig. 51). Their conclusions were that the 5 per cent increase of blood water, maximal near term, was not sufficient to account for the reduction in haemoglobin percentage and red cells on a pure dilution basis. Feldman, van Donk, Steenbock and Schneiders (1936) confirmed the rise of blood water in human pregnancy, maximal about the 220th day, and came to similar conclusions regarding the dilution

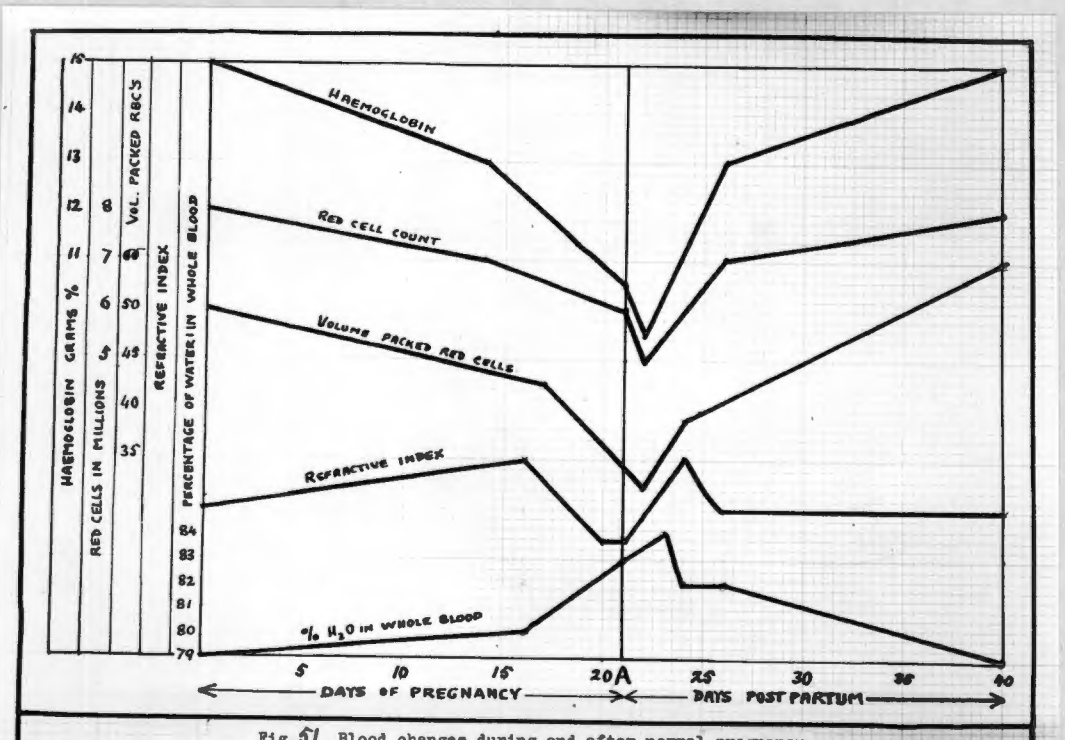


Fig. 51 Blood changes during and after normal pregnancy in the rat. At "A" full term delivery occurred. From E.C.van Donk, H.Feldman and H.Steenbock (1934).

Fig. 51.

theory of the drop in haemoglobin and red cells. Oberst and Plass (1936) on the other hand, working on the same subject, came to the conclusion that the increase in water content of the blood was sufficient to account for the drop on a dilution basis; their complicated mathematical calculations render their conclusions invulnerable to the mind untrained in higher mathematics.

THE CONCLUSIONS regarding the blood volume during pregnancy are that there is an average tendency to increase during pregnancy, the increase amounting to about 25 per cent over normal. The volume tends to diminish about a month before term probably and has returned to normal within a month postpartum. The range of individual observations from which the average figures of various observers are calculated is wide, being from a minimum of no increase at all in an appreciable number of cases to a maximum of at least 40 per cent above normal. These latter observations must be appreciated in considering the blood diluting effect of pregnancy.

HAEMOGLOBIN DURING PREGNANCY.

The haemoglobin during pregnancy has to be considered under the two headings of haemoglobin percentage and total circulating haemoglobin. As the majority of observations,

and the observations of more practical value, are expressed in haemoglobin percentage, this aspect will be considered first.

HAEMOGLOBIN PERCENTAGE

The facts concerning the behaviour of the haemoglobin percentage during pregnancy have been recorded by numerous observers. In the majority of these investigations, which have their conclusions based upon calculation of averages for large or small numbers of cases, no attempt is made to define accurately what can be accepted as normal and what as abnormal. With few exceptions, however, this type of investigation indicates that during pregnancy there is a fall of haemoglobin percentage as pregnancy advances with return to pre-pregnancy levels after parturition; the demonstration of this fact does at least signify that in normal pregnancy the haemoglobin percentage will be lower than the normal for non-pregnant women.

Dieckmann and Wegner (1934b) showed that the haemoglobin percentage through pregnancy and up to 2 weeks postpartum in a group of 14 cases, and from full-term up to 8 weeks postpartum in a group of 9 cases, fell on the average to a maximum of 15 per cent below the original level by the 26th to the 32nd week; at 2 weeks postpartum the average was 17

per cent below normal and at 8 weeks still 14 per cent under normal. They concluded that a haemoglobin percentage of under 10 grammes per cent (72 per cent Haldane) constituted a true anaemia. Individual cases showed gross deviations from these average figures, and in two the level actually rose as pregnancy advanced, from 13.8 to 16.3 and 11.3 to 12.4 grammes per cent respectively; in seven of the series the postpartum level was actually lower than the last antepartum reading.

This series of Dieckmann and Wegner is valuable in that it is the only published series which allows of comparison between haemoglobin percentage and blood volume as pregnancy advances. If the blood volume figures tabulated on Page 81 of their original article are compared with the haemoglobin percentages on Page 202, there is a tendency, but a tendency with many exceptions, for the haemoglobin percentage to be inversely proportional to the blood volume. The exceptions to the general tendency cannot be correlated with the colour index of the cases; the general tendency is not therefore upset by the haemoglobin falling out of proportion to the red cell count. The demonstration of this tendency favours blood dilution as partly responsible at least for the fall of haemoglobin percentage during pregnancy.

Richter, Meyer and Bennett (1934) have also presented facts indicating an inverse relationship between the haemo-

globin percentage and the blood volume, but as they present average values only their findings are of less significance. Their results are tabulated in Table 1X, Fig. 52.

TABLE 1X. Fig. 52.

GROUP	STAGE	HB%	RBC	VPC%	BV
A	Antepartum	61	3.60	36	6000 cc
	8 dys postpartum	69	4.05	39	4100 cc
B	Antepartum	60	3.76	37	6100 cc
	8 dys postpartum	78	4.34	42	4300 cc
C		75	4.33	43	4500 cc

Group A consists of 6 normal non-treated pregnant women, group B of 8 pregnant women treated with iron and liver, and group C, 6 non-pregnant healthy women. The antepartum period is not specified in each case. This investigation of Richter et al definitely shows the inverse ratio between haemoglobin percentage and blood volume. The same article also shows the fall of haemoglobin percentage with pregnancy in examination of 61 cases.

Fig. 53 indicates the trend of the haemoglobin percentage during pregnancy, and in some cases, into the puerperium, as observed by several workers. Kühnel (1927)

constructed curve A from the study of 15 women through pregnancy, Strauss and Castle (1932b) from haemoglobin estimations on 200 pregnant women constructed curve B (amplified in Fig. 55), Galloway (1929) made his observations on 382 private patients, and Boycott (1936) on 152 cases considered to be normal pregnancy; curve D1 of Boycott indicates the range of lowest contributing to the average curve. The amplified curve of Strauss and Castle (Fig. 55) also shows the range over which isolated readings may occur, and for any one month there may be a 30 per cent difference in haemoglobin percentage of different cases tested;

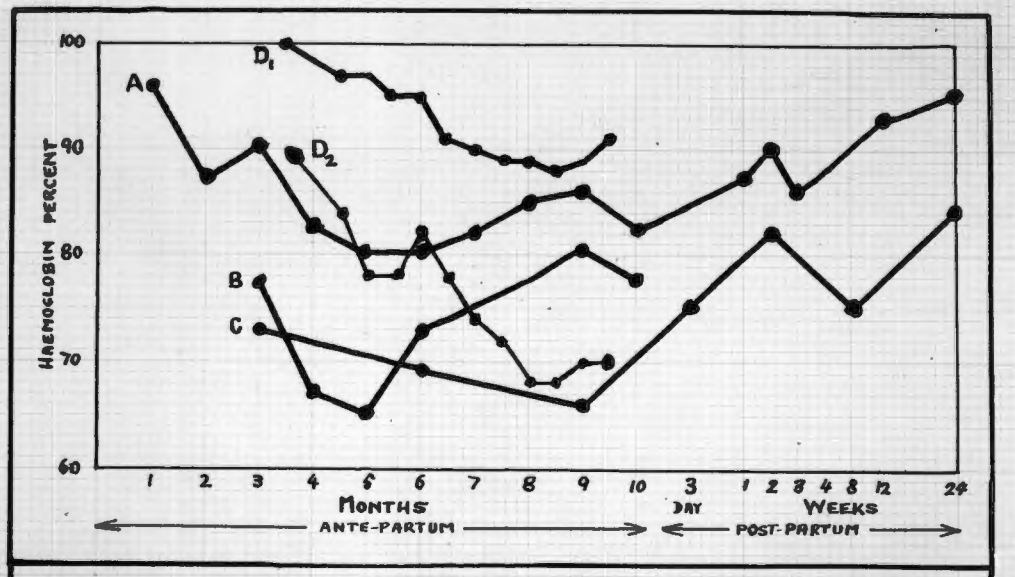


Fig. 53 Haemoglobin levels during pregnancy and puerperium as observed by various observers. Curve A from Kühnel (1927), curve B from Strauss and Castle (1932b), curve C from Galloway (1929), curve D1 from Boycott (1936); and curve D2 also from Boycott (1936) but being constructed from the lowest, as opposed to average, haemoglobin readings for each stage of pregnancy.

Fig. 53.

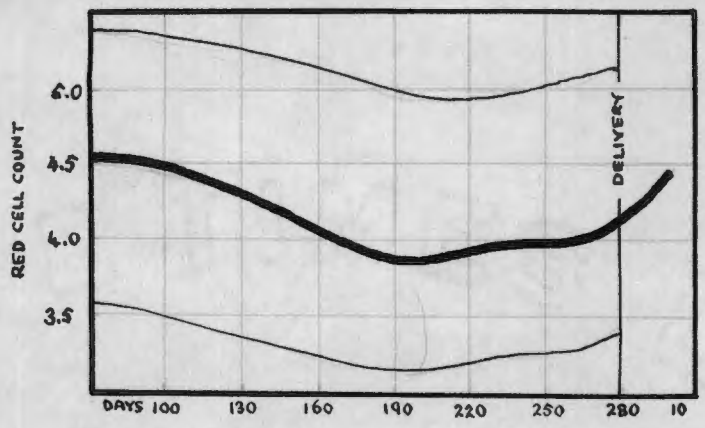


FIG. 54 RED CELL COUNT IN PREGNANCY

CURVE OF AVERAGE READINGS FOR 200 CASES

RANGE OF INDIVIDUAL CASE READINGS

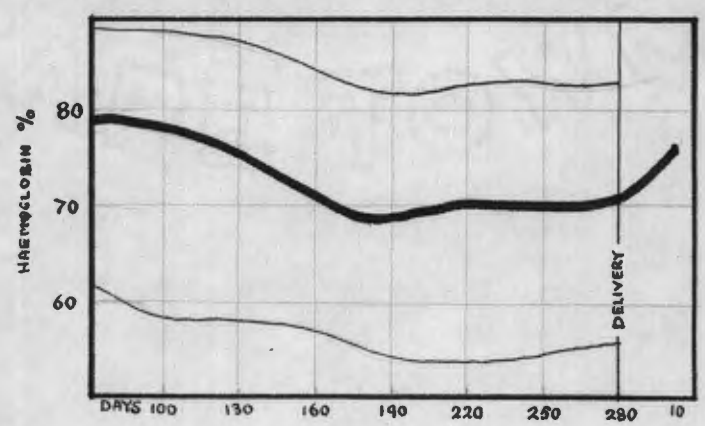


FIG. 55 HAEMOGLOBIN IN PREGNANCY

CURVE OF AVERAGE READINGS FOR 200 CASES

RANGE OF INDIVIDUAL CASE READINGS

FROM STRAUSS AND CASTLE (1932 B)

Fig. 54 is a curve of similar type constructed from the red cell counts in the same 200 women, showing the same trend as the haemoglobin, and in which it is seen that in any one month there may be a difference of 2.0 million red cells between the highest and the lowest reading observed.

Davidson, Fullerton and Campbell (1935) have demonstrated the trend of haemoglobin percentage by another method which envolves the examination of a very large number of cases to be of any significance, in this case, 1534 observations of haemoglobin. The average haemoglobin percentage in different age groups is shown to be 5 per cent lower in pregnancy than apart from pregnancy. See Fig. 56.

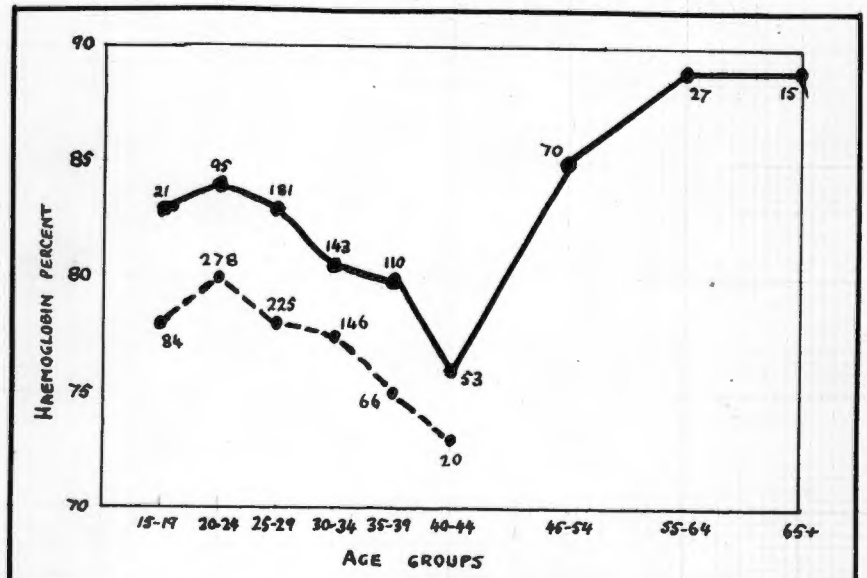


Fig. 56 Haemoglobin levels in 715 non-pregnant poor class women (upper curve ——), and 819 pregnant poor class women (lower curve — — —). Figures along each chart line indicate number of women examined at each stage. From L.S.P.Davidson, H.W.Fullerton and R.M.Campbell (1935).

Fig. 56.

Fullerton (1936b) examined 1166 women at various stages of pregnancy and puerperium and constructed the chart shown

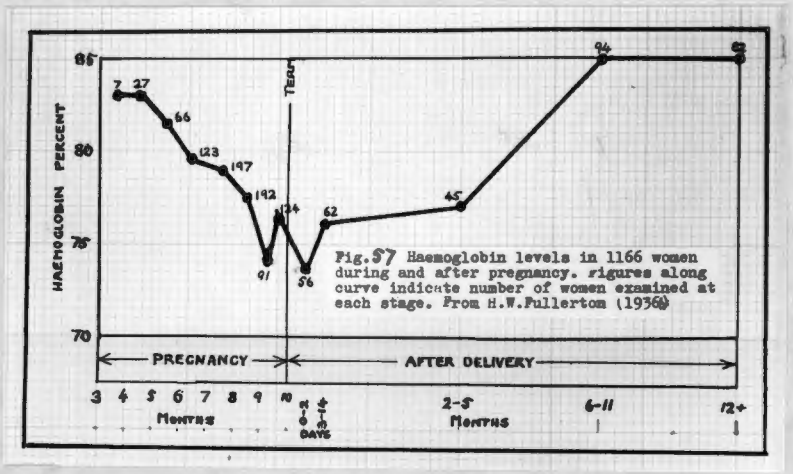


Fig. 57 Haemoglobin levels in 1166 women during and after pregnancy. Figures along curve indicate number of women examined at each stage. From H.W.Fullerton (1936b)

Fig. 57.

in Fig. 57, and also the chart of Fig. 58, both of which confirm the findings of previous observers.

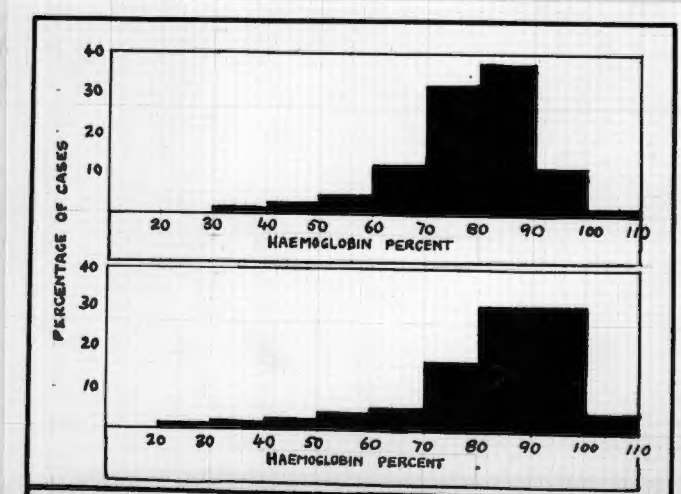


Fig. 58 Distribution of haemoglobin levels in 819 pregnant women (upper chart) and 603 non-pregnant women (lower chart) From H.W.Fullerton (1936b).

Fig. 58

Numerous other observers have obtained similar results. Goodall and Gottlieb (1936) and later Gottlieb and Stean (1939) examined 200 cases and found that the average haemoglobin in the first, second and third trimesters to be 80, 75 and 65 per cent respecitvely. Bland, Goldstein and First (1930) examining 1000 cases confirmed the fall in pregnancy and in 92 of 100 cases followed up to 6 months into the puerperium found that the haemoglobin had returned to normal by 6 months. Davies and Shelley (1934) with 51 cases and McGeorge (1935) with 100 cases confirmed the drop of haemoglobin in pregnancy; McGeorge described cases in New Zealand, and it is significant that there, the lowest haemoglobin average percent never fell below 87 per cent; only a few individual observations fell below 70 per cent.

Van Donk, Feldman and Steenbock (1934) found that in normal pregnant rats the haemoglobin fell from the normal 15.0 grammes per cent to 10.5 grammes. See Fig. 51.

THE CONCLUSIONS from these observations are that there is a fall in haemoglobin per cent as pregnancy advances, whatever the original level of haemoglobin, maximal towards the end of the second and the beginning of the third trimester, and showing a tendency to rise slightly up to full term. The maximum fall averages about 10 per cent haemoglobin, but there is a wide variation in degree of fall in different

pregnancies, a fall of 20% being possible. Sometimes the haemoglobin per cent actually rises.

Results which differ from these conclusions have been recorded occasionally. Adair, Dieckmann and Grant (1936) divided a group of 235 cases Table X (Fig. 59) into various sub-groups of those receiving no treatment, those given ferrous carbonate, those given citrated iron and liver, and those transfused. Their conclusions, which seem justified on the facts presented in Fig. 59, were that the normal trend of haemoglobin percentage in pregnancy was not necessarily downwards, and that in the treatment and the no-treatment

TABLE X

COMPARISON OF TREATED AND UNTREATED CASES OF PREGNANCY ANAEMIA

From F.L.Adair, W.J.Dieckmann and K.Grant, Am.Jnl.O.& Gyn.32.1936.560.

CHANGE IN HB in GRAMS PER CENT.	NORMAL PREGNANCY Dieckmann and Wegner cases (q.v).				PREGNANCY ANAEMIA CASES (ADAIR) - TOTAL OF 235											
					UNTREATED				TREATED							
									Fe.Carb.		Fe.Am.Ci		Liver,Fe Vit.B		Transfus.	
	A				B				C		D		E		F	
	A - P		P - P		A - P		P - P								AP	PP
	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	+
0.1 to 0.4		1		1	8	1		1	2		1					
0.5 to 0.9	1		2		15			1	3	1	3		1			
1.0 to 1.9	1	1	4	1	21	2	8	3	14	3	11	2	6		1	1
2.0 to 2.9	1	2	3		15		7		12		8		2		1	1
3.0 to 3.9		2		1	3		4		8		5		3		5	1
4.0 to 4.9		1			2		5		4		2		1		1	2
5.0 to 5.9		2	1		1		2								1	4
NO CHANGE	2		1		6		0		13		3		4		0	0
TOTAL CASES	14		14		74		31		60		35		17		9	9

Pregnancy anaemia cases in this table were cases with Hb of under 9 grammes % on two occasions at least.

Fig. 59.

series, the trends were not much different. Watson (1938) using Sahli standards, examined 40 cases through pregnancy and on the average found a steady rise of haemoglobin percentage from 68 per cent at the 4th month to 77 per cent at full term; only one of 40 showed a fall. These results are entirely contrary to the results reported from all other sources. In another report on 500 cases he did, however, demonstrate that the tendency is for the haemoglobin percentage to be lower than normal during pregnancy, rising

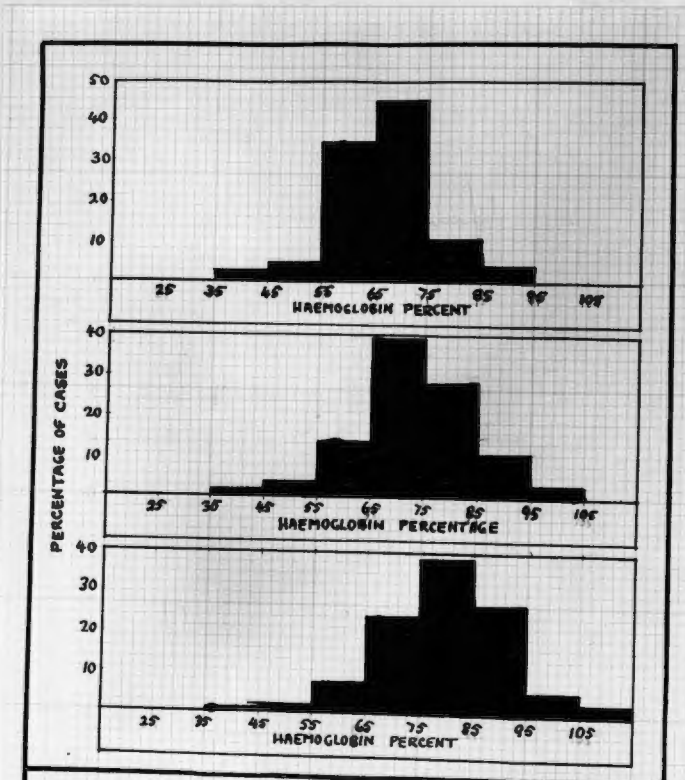


Fig. 60 Percentage incidence of haemoglobin levels in 500 cases. Upper chart shows incidence antepartum, middle chart 3 days postpartum, and lower chart 10 days postpartum. The tendency for the haemoglobin to rise after delivery is clearly shown. From H.G.Watson (1938).

Fig. 60.

by the third day postpartum to normal by the 10th day post-partum; these results of his are charted in Fig. 60, the chart being constructed from his published figures.

What then is to be regarded as the normal haemoglobin percentage value for pregnancy? Owing to the factor of blood dilution, the degree of which varies from case to case and at different stages of the same case, it is not possible to lay down a standard which will apply to all cases. Adair, Dieckmann and Grant (1936) in a large scale statistical survey calculated the lowest normal to be 10.16 grammes per cent (74 per cent Haldane, 60 per cent Sahli). Dieckmann and Wegner (1934b) gave 10.0 grammes per cent as the lowest normal acceptable (72 per cent Haldane, 58 per cent Sahli). Boycott (1936) is less dogmatic and regards 70 per cent Haldane as a usual normal lower limit, but considers that figures even lower can sometimes be normal; his very thoughtful article will be referred to again. Bethell (1936) calculated on a basis of 25 per cent increase in blood volume that the lowest normal limit was 70 per cent Sahli; the figure of 25 per cent increase in blood volume has been shown to be an average figure, with many higher and many lower readings contributing to the average. Labate (1940) considers 80 per cent Haldane the lowest limit of normal.

TO SUMMARISE the conclusions regarding the haemoglobin percentage in normal pregnancy, it may be stated that (a) the haemoglobin percentage in normal pregnancy is lower than the haemoglobin percentage in non-pregnant women, (b) the lowest acceptable normal figure is 70 per cent Haldane, although many observers consider this too low, and (c) the lowest limit of normal must vary from case to case owing to the variable degree of blood dilution due to hydraemia of pregnancy.

TOTAL CIRCULATING HAEMOGLOBIN

Although the haemoglobin percentage falls during pregnancy, the total circulating haemoglobin increases. The increase is insufficient to maintain a normal haemoglobin percentage in the presence of a relatively greater increase in blood volume. Dieckmann and Wegner (1934b) gave the average increase as 13 per cent.

THE RED BLOOD CELLS DURING PREGNANCY

There is general agreement that a fall in the red cell count comparable to the fall in haemoglobin percentage occurs during pregnancy. As in the case of the haemoglobin, there is a considerable difference between the highest and the lowest possible readings at a particular month of pregnancy if any large group of pregnant women is examined. Strauss

and Castle (1932b) examined 200 pregnant women at different stages and found that the average red cell count fell from 4.50 million per cu. mm. at 10 weeks to 4.00 million at 27 weeks, rose very slightly to full term, and within 10 days of delivery was near normal. They also demonstrated that the difference in any one month between the highest and the lowest readings in the cases examined was 2.00 million. Their results are charted in Fig. 54, which shows the average trend and the range of individual readings at the different periods of observation. As in the case of haemoglobin, individual variation from the average is sufficiently frequent and of sufficient magnitude to be significant when considering an individual case.

There is some difference of opinion as to what the lowest limit of normal for the red cell count in pregnancy is. Labate (1939) demands 4.00 million, which is an unreasonably high figure as it is the same as the lower limit of normal for non-pregnant women. Adair et al (1936) from a statistical analysis of several thousand observations concluded that 3.36 million was the lowest limit of normal.

It is generally accepted that the fall of red cells and the fall of haemoglobin should be proportionate to be normal. A greater fall of haemoglobin than red cells

constitutes a true anaemia. This aspect will be considered fully under the subject of colour index.

COLOUR INDEX DURING PREGNANCY

Strauss and Castle (1932b) found that the average colour index in their series of 200 cases was 0.87 at the 14th week and 0.87 at the 35th week; individual readings are not given. Bland, Goldstein and First (1930) gave an average of 0.94 for 50 cases. Dieckmann and Wegner (1934b) in their study of 24 cases through pregnancy and puerperium, found the colour index usually near unity, but gave individual examples of 1.33 and 1.44 in apparently otherwise normal blood counts; their lowest was 0.84. Fullerton (1936) stresses that a colour index below the normal range indicates that there is more than simple hydraemia, probably an iron deficiency anaemia. Boycott (1936) has made the most detailed study of the subject, and his work requires fuller mention. He divided a group of 26 cases of pregnancy, all with haemoglobin under 80 per cent, into two groups of thirteen cases each. The first group consisted of cases with a colour index of 0.91 to 1.07 (the Price-Jones normal range), and the second, with colour index below 0.90, the lowest being 0.60. In the first group, the lowest haemoglobin percentage was 67; Price-Jones curves were constructed from four of these cases (Table XI, Fig. 62, Cases 1 to 4) and the mean

red cell diameter, standard deviation and coefficient of variation were all normal; Boycott concluded that in this group there was no haematological abnormality in the way of true anaemia, in spite ofthe low haemoglobin in some. In the second group, with colour index from 0.60 to 0.89, the haemoglobin in only four was never below 70 per cent, indicating that the group included most of the lower haemoglobin cases; the lowest was 48 per cent. Price-Jones curves were constructed in all the cases of this group; the mean red cell diameter was found to be below the normal mean of 7.2 mu in every case; coefficient of variation tended to be increased over normal, but this was an inconstant finding. The tendency to microcytosis and anisocytosis indicates that there is more than mere hydration responsible for the low haemoglobin in this group. Boycott therefore stresses the size and shape of the red cells as an index of normality or abnormality of the blood in cases of pregnancy with haemoglobin percentage below the accepted normal range. The only other work on this aspect of the blood in pregnancy is that of the present investigation which has already been presented, and is to be discussed.

THE HAEMATOCRIT DURING PREGNANCY

The volume of packed red cells in the normal non-pregnant woman averages 41.1 per cent (Wintrobe, 1930,

Osgood and Haskins, 1927), or 39.5 per cent according to Plass and Bogert (1924). During pregnancy there is a reduction in the volume of packed red cells. Plass and Bogert (1924) gave figures of 35.6 per cent in the first trimester, 31.5 per cent in the second trimester, and 34.7 per cent 3 weeks postpartum. Skajaa (1929) gave an average of 36.4 per cent for 120 women at full term, and 43 per cent at 2 weeks postpartum. Dieckmann and Wegner (1934c) averaged 38.1 per cent at the 36th to the 40th week, and 41.1 per cent at a week postpartum. Labate (1940) in 40 cases of pregnancy apparently normal found a range of 32 to 45 per cent, with an average of 38.9 per cent. Thomson et al (1938) gave an average of 38 per cent at 16 weeks, falling gradually to 32 per cent at 32 weeks or 36 weeks, rising to 38 per cent at 2 weeks postpartum. Van Donk et al (1934) noted a fall from the normal 50 per cent to 35 per cent at term in the case of pregnant rats. The minimum of these readings is about 32 per cent.

The mean corpuscular volume for healthy non-pregnant women lies between 80 and 94 cu.mu. (Wintrobe, 1932). In pregnancy, Labate (1940) reports an average of 89.6 cu.mu. in a series of 40 cases with range of 74 to 109 cu.mu. Dieckmann and Wegner (1934c) gave a usual range of 77 to 100 cu.mu. but found occasional higher readings, up to maximum of 120 cu.mu. They found that the chief increase

came between the 26th and 35th weeks. Bethell (1936) examined 66 apparently healthy pregnant women in the last 13 weeks of pregnancy and found the mean corpuscular volume tending to increase, the highest reading being 108 cu.mu. His results are charted in Fig. 72. Watson (1938) in 40 cases found the average at 4 months to be 75 cu.mu. at 9 months 88 cu.mu. falling to 78 cu.mu. at 3 months postpartum.

CONCLUSIONS from these observations are that (a) the volume of packed red cells is reduced during pregnancy, the maximum degree of decrease being to 32 per cent in normal pregnancy, and (b) the mean corpuscular volume tends to increase in normal pregnancy up to a maximum of possibly over 100 cu.mu.

MEAN RED CELL DIAMETER DURING PREGNANCY

Apart from the work of Boycott (1936) no references to the diameter of the red cell in normal pregnancy can be found. Neither Price-Jones (1933) nor Mogensen (1938) in their special works on the subject of red cell diameters mention the case of pregnancy.

Boycott's work has already been referred to in the discussion on colour index in pregnancy. His series was a selected one in that he set out to investigate the size

and shape of the red cells in pregnancy in those cases with haemoglobin below 80 per cent; in four cases with colour index within the normal range he showed that the cell diameter and the degree of anisocytosis was within normal limits and concluded that in these cases, in spite of a lower haemoglobin than "normal", there was no true anaemia. In the 13 cases with colour index below normal, he showed the cell diameters to be smaller than normal and the degree of anisocytosis to be greater than normal. His investigation was incompletely controlled and his conclusions therefore possibly not justified, in that he included no cases with haemoglobin percentage within the range of accepted normal. It is obviously important to decide this matter of the association of a low colour index with a greater than normal degree of anisocytosis.

In the present investigation, cases within a range of 32 to 100 haemoglobin per cent have been included. Some of these are obviously normal haematologically, some are obviously abnormal, and some are doubtful.

In the fourteen cases of the "normal" series of 20 on which red cell distribution curves were constructed, the mean red cell diameter fell within the Price-Jones normal range of 6.686 to 7.718 mu. The question of the normality of the cells therefore centres around the degree of anisocytosis as measured by standard deviation and

variability per cent. The upper limit of normal variability per cent on the Price-Jones standard is 7.3 per cent; Mogensen considers that 7.5 per cent is normal. Taking Mogensen's higher figure, it is seen that only 6 of the 15 cases have a variability of 7.5 per cent and under; the figures for the remainder are tabulated in Table IV, Fig. 12. Five have actually a reading of over 8 per cent, which must be regarded as definitely abnormal. A haemoglobin over 80% may therefore be associated with a degree of anisocytosis greater than normal.

In order to see whether there is any correlation between the variability and colour index, as suggested by Boycott, and possible between the variability and the haemoglobin per cent, a chart has been constructed (Fig. 61), including both the normal and the anaemic groups of my series, and the series reported by Boycott. For the purpose of reference to details, Boycott's protocol is reproduced in Table XI, Fig. 62. His Cases 1 to 4 are those with a normal colour index but with haemoglobin in three below normal. Examination of the chart Fig. 61, gives the following information: (a) of the normal cases in my series, 6 fall to the left of 7.5 per cent variability, and 5 actually are above 8 per cent, (b) of the 5 "normal" cases with variability over 8 per cent, three had been

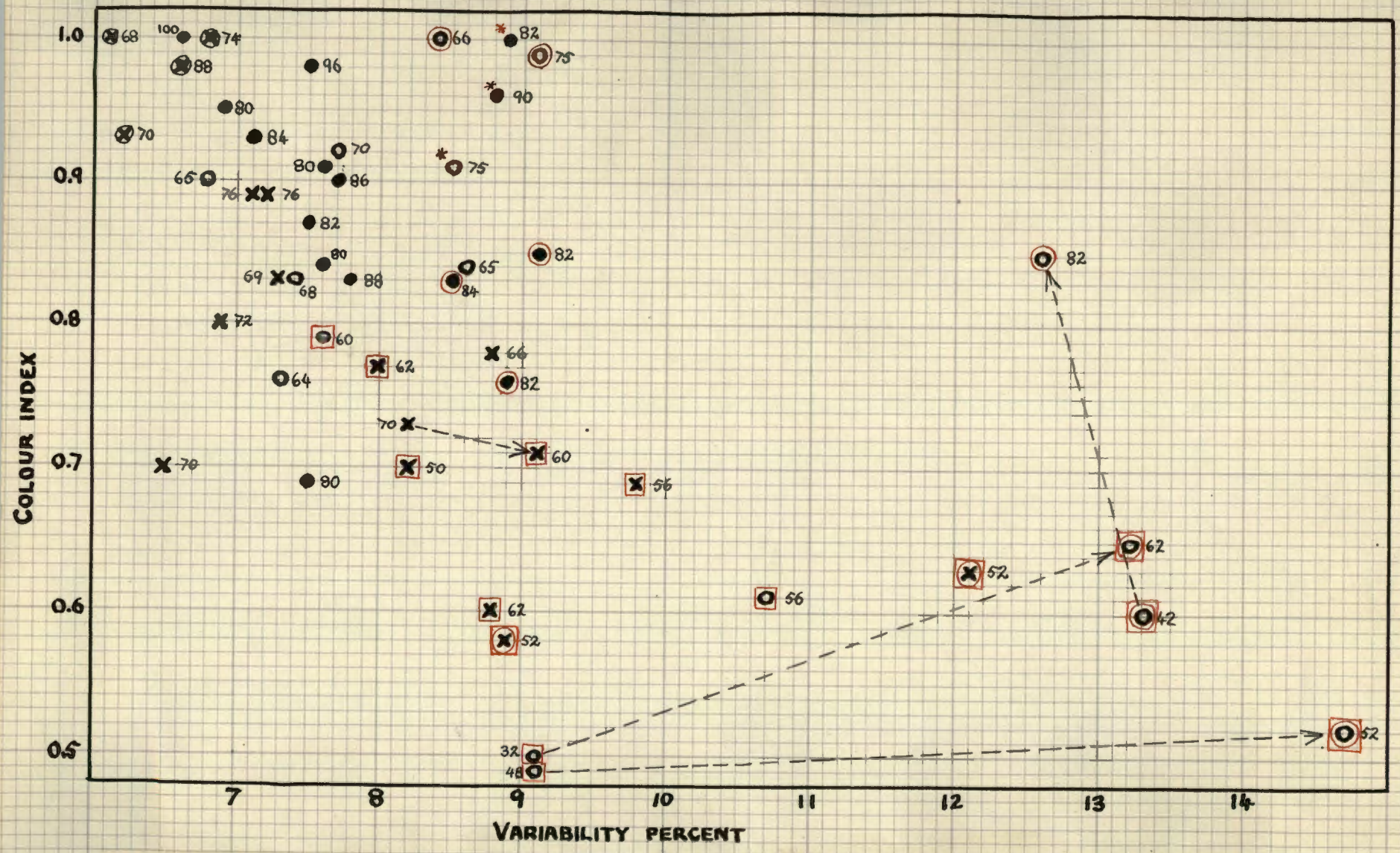


Fig.61 Chart of correlation between colour index and variability per cent.

✕ — Cases of Boycott (1936). ⊗ — Boycott's cases 1 to 4 referred to in text
● — Cases of present investigation, normal group. O—Anaemic group
Red circle (◯) indicates iron being taken recently. Red square (□) indicates haemoglobin under 62 per cent. Figures (84) indicate haemoglobin per cent. Arrows indicate consecutive readings on the same case.

TABLE XI

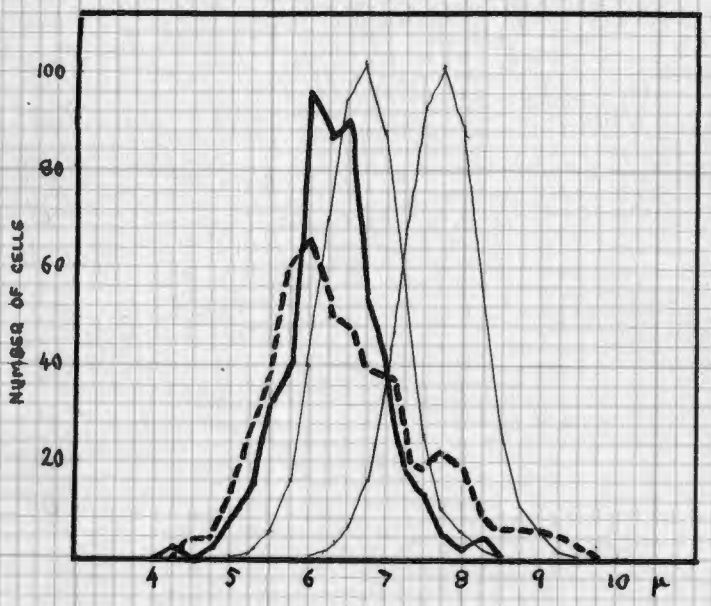
MEAN RED CELL DIAMETER AND VARIABILITY PERCENT IN 17 CASES.
Cases 1 to 4 with colour index 0.91 to 1.07 (i.e. normal range).
Cases 5 to 17 with colour index under 0.90.
From J.A.Boycott, Lancet, 1.1936.1165.

CASE	STAGE	HB%	CI	MCD mu	v	REMARKS
1	37 wks	70	0.93	7.134	6.2	Hb 30 wks 72%, 33 wks 67%.
2	30 wks	74	1.00	7.187	6.8	Hb 13 wks 89%, 17 wks 84%, 36 wks 76%(CI 0.94).
3	34 wks	68	1.05	7.578	6.1	Hb 32 wks 79%, 38 wks 76%(CI 0.9
4	39 wks	88	0.98	7.389	6.6	Hb 25 wks 103%, 29 wks 88%, 31 wks 86%, 32 wks 78%.
5	23 wks	70	0.73	6.868	8.2	Hb.19 wks 78%, 27 wks 68%, 30wks 68% (CI 0.72), 33 wks 62% (CI 0.73).
	39 wks	60	0.71	6.323	9.1	
6	31 wks	69	0.83	6.735	7.3	Hb 29 wks 74%, 36 wks 68%, 38 wks 68%.
7	32 wks	52	0.58	6.388	8.9	Hb 30wks 53%, 36 wks 48% (CI 0.54), 37 wks 58% (CI 0.6) Pil.Blaud.gr 30 t.i.d. from 34 to 37 wks.
8	35 wks	76	0.89	6.776	7.1	Hb 18 wks 85%, 28 wks 80%, 33 wks 70%, 36 wks 70% (CI 0.9)
9	25 wks	78		7.145	7.2	Hb 32 wks 76% (CI 0.85)
	38 wks	72	0.80	7.195	6.9	
10	16 wks	90		7.223	6.5	
	28 wks	80		6.881	6.8	Hb at 35 wks 72% (CI 0.74)
	34 wks	70	0.70	6.613	6.5	
11	38 wks	66	0.78	6.627	8.8	Hb 24 wks 62%
12	29 wks	68	0.60	6.464	8.0	Hb 35 wks 58%
	39 wks	62	0.60	6.489	8.9	
13	33 wks	50	0.70	6.274	8.2	Hb 18 wks 66%
14	34 wks	62	0.77	6.770	8.0	Hb 19 wks 70%, 31 wks 66% (CI 0.84), 38 wks 64%(CI 0.8)
15	36 wks	76	0.89	6.786	7.2	Hb 18 wks 100%, 27 wks 84%, 32 wks 78%.
16	39 wks	56	0.69	6.759	9.8	Hb 26 wks 50%, 37 wks 52% (CI 0.67).
17	37 wks	52	0.63	6.723	12.1	Hb 24 wks 56%, 26 wks 52% (CI 0.6), 30 wks 52% (0.63), 39 wks 56% (CI 0.67). Pil Blaudi gr 30 t.i.d.

Normal MCD 7.202 mu (±0.172 mu) (Price Jones)
Normal variability 6.326% (±0.331%) (Price Jones).
Normal colour index range 0.91 to 1.07 (Price Jones).

Fig 62

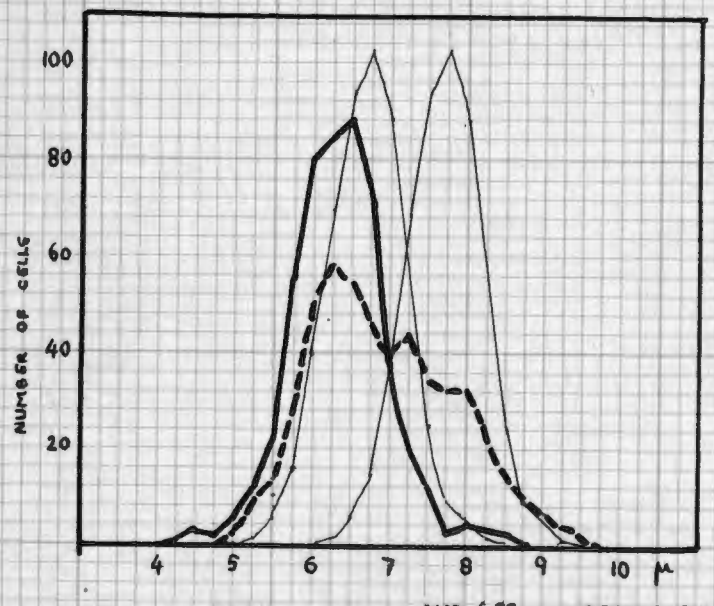
on iron recently; the increase in anisocytosis during the response to iron might account for the high variability; two of the cases had definitely not had iron or other treatment, and the high variability was apparently natural (these two are indicated by red asterisks), (c) one of the normal series, with a haemoglobin of 80 per cent and a colour index of only 0.69, has a normal variability (7.5 per cent) which is contrary to Boycott's findings, (d) four of the anaemic cases with haemoglobins of 64, 60, 68, and 65 per cent respectively, untreated with iron, had variability of 7.6 per cent and under, and colour indices of 0.76, 0.79, 0.83, and 0.90 respectively, (e) all the cases which had been given iron recently, both "normal" and anaemic, had variability above 8 per cent, and (f) there is a rough correlation between the colour index and the variability, particularly in the more anaemic cases, and more notable in Boycott's shorter series than in mine; it is to be noted that this correlation is common to any type of low colour index anaemia, especially the iron deficiency type, and that there can clearly be no accurate correlation in any series of cases including both low and high colour index anaemias, (g) the effect of treatment on the variability is well illustrated in two cases with initial haemoglobins of 32 and 48 per cent, initial variability of 9.1 per cent each, and initial colour indices of 0.50 and 0.49 respectively, and after treatment, haemoglobins of 62 and 52 per cent, variability of 13.3 and 14.7 respectively. The colour



BEFORE TREATMENT. MCD 6.31μ. σ=0.575. v=9.12%
Hb 48%. VPC 31%.

AFTER 2 WEEKS IRON. MCD 6.51μ. σ=0.959. v=14.7%
Hb 52%. VPC 31%

FIG. 64 (CASE 4)



BEFORE TREATMENT. MCD 6.33μ, σ= 0.575. v= 9.08%
Hb 32%. VPC. 22%.

AFTER TRANSFUSION AND 2 WEEKS IRON. MCD 6.92μ. σ= 0.911. v=13.16%
Hb 62%. VPC 33%.

FIG. 65 (CASE 7)

indices changed very slightly, the final readings of colour index being 0.65 and 0.52 respectively. See Figs. 64 and 65.

The variability in the anaemic group in my series is over normal in the majority, but mention has been made (paragraph d above) of four with normal variability. One case (No. 37, Table 111, Fig. 6.) in particular is of interest, with a colour index of 0.9, haemoglobin of 65 per cent, and variability of 6.8 per cent. Is this a case of blood dilution due to hydraemia of pregnancy, and not a true anaemia in spite of the low haemoglobin? The mean cell diameter in the anaemic group shows a reading below normal frequently.

THE CONCLUSIONS from inspection of the chart, Fig. 61, are:

(1) Variability is increased over normal in a fair proportion of apparently normal pregnant women with a haemoglobin of over 80 per cent. The grosser degrees of increase in such cases are accountable for by the patients recently having taken iron. The lesser grades of increase appear to be a natural phenomenon in pregnancy.

(2) Variability is increased to a greater extent in cases with haemoglobin under 80 per cent, but in a small proportion of such cases, with haemoglobin even under 70 per

cent Haldane, variability is normal.

(3) All cases, "normal" or "anaemic", which had been given iron recently, had increased variability, sometimes very grossly increased.

(4) There is a rough correlation between colour index and variability in the cases examined. The correlation is upset in cases recently given iron.

(5) In considering the normality or abnormality of the blood picture in pregnancy, consideration must not only be given to haemoglobin value, but also to colour index, mean cell diameter, variability and standard deviation. It is possible that a haemoglobin of 70 per cent, or even lower, may be physiological, if associated with a normal colour index, normal mean cell diameter and normal variability; the cause of such a physiological picture would be an unusual degree of increased blood volume during pregnancy. Conversely, a haemoglobin of over 80 per cent may be present in true anaemia. The matter can be settled only by estimation of blood volume in such cases.

MEDIAN CORPUSCULAR FRAGILITY

No references to work on the red cell fragility in normal pregnancy can be given apart from the present

investigation. The technique of Dacie and Vaughan (1938) allows the fragility to be estimated with great accuracy, and it has been shown (Figs 3 and 11) that in normal pregnancy the median corpuscular fragility falls within the normal limits for non-pregnant women or for men. These limits have been defined by Dacie and Vaughan as result of the investigation of 50 normal individuals of both sexes. The median corpuscular fragility, that is, the percentage sodium chloride concentration that produces 50 per cent haemolysis, lies between 0.347 and 0.387 grammes sodium chloride percent; haemolysis commences at between 0.40 and 0.44, and is complete at between 0.10 and 0.22 grammes sodium chloride per cent.

The bearing of red cell fragility on the development of anaemia during pregnancy will be discussed fully in a later section.

CONCLUSIONS REGARDING THE BLOOD PICTURE IN NORMAL PREGNANCY

In view of the diverse opinions that have been expressed on the standards required for a normal blood picture in pregnancy, it is as well to conclude this section on normal standards with a brief summary of what can be considered, in the author's opinion, as normal values.

It is possible for a haemoglobin as low as 65 per cent Haldane and a red cell count as low as 3.20 million to be physiological during pregnancy provided certain other conditions are satisfied. These other conditions are (a) the colour index must be near unity, (b) the mean cell diameter must be within normal limits, (c) the standard deviation and variability, expressing the degree of anisocytosis, must be normal, and (d) the mean corpuscular volume must be within the normal limits for pregnancy. The cause of the reduction of red cells and haemoglobin percentage in such a case may be the physiological hydraemia of pregnancy which is well known to vary greatly in its degree. A possible example of this type in this series is Case 37, with haemoglobin 65 per cent, red cells 3.56 million, colour index 0.9, mean cell diameter 7.2 mu, standard deviation 0.495 mu, variability 6.8 per cent, mean corpuscular volume 88 cu.mu. and no symptoms of anaemia. An additional condition could be that no reticulocytosis occurs following the administration of iron.

Conversely, if one of the above conditions is not satisfied in a case with haemoglobin percentage within the range which the most critical observer would consider normal, the physiological normality of the blood picture must be doubted. An example of such a Case is No. 36,

with haemoglobin percentage of 80, mean cell diameter of 6.8 mu, standard deviation 0.509, variability of 7.5 per cent, but colour index of 0.69 and mean corpuscular volume of 62 cu.mu.

If a more practicable method of estimating blood volume is found, it should form part of the routine examination of every case of suspected anaemia of pregnancy.

RETICULOCYTE PERCENTAGE IN PREGNANCY

In 20 cases of normal pregnancy, at stages varying from 28 to 39 weeks, the reticulocyte counts estimated on one occasion in each case were 0.8, 2.2, 1.3, 1.2, 2.2, 0.8, 1.0, 1.2, 0.8, 0.6, 2.6, 1.8, 1.3, 1.8, 1.8, 0.2, 0.7, 1.1 and 2.0 per cent. All the readings are within normal limits with the exception of three which are above the accepted upper limit of normal of 2.0 per cent. The most that can be said about the reticulocyte level in these normal pregnancies is that it tends towards the upper limit of normal. There was no tendency for the higher readings to occur in later pregnancy than the lower readings.

In the cases of pregnancy anaemia in this series, there does not appear to be any natural tendency for the reticulocyte count to be abnormal in any direction, even in the most severely anaemic cases. Attention will be drawn to certain exceptions to this general statement. In cases 11 and 27 (Fig. 34), 31 (Fig. 33), 37 and 40 (Fig. 35), in which no treatment was given for the anaemia during the period of observation and which therefore represent the natural trend of the reticulocyte count, the charts show that on the several occasions on which the reticulocytes were counted, they were, with few exceptions, well within normal limits; in case 40 they were on two occasions 3 per cent for no discernable extrinsic reason. In Case 22 (Fig. 42) the

reticulocyte count was 3 to 4 per cent before the institution of any treatment; after treatment the count fluctuated above and below normal, which might have been a partial response to treatment, in which case a rise in haemoglobin and red cells might have been expected, or which might have been the natural tendency irrespective of treatment. The case was exceptional in other respects, having the largest mean corpuscular volume of the series (98 cu.mu.), failing to respond to both liver and iron treatment, and making a spontaneous return to normal figures after delivery; it is to be noted that the mean corpuscular fragility (0.370 grammes NaCl per cent) was well within normal limits. In Case 20 (Fig. 45) one reticulocyte count of 3.5 per cent could not be accounted for by any therapeutic response; unfortunately more counts should have been done, as in this case the red cell fragility was the highest of the series (mean corpuscular fragility of 0.420 grammes NaCl per cent). In the anaemic group not charted, reticulocyte counts taken outside the time period of any possible response to treatment were of the order 1.2, 1.5, 2.4, 1.1, 1.4, 1.2, 0.9, 0.6, 2.4, 2.1 and 1.1 per cent, readings which are of the same level as in normal pregnancy.

In contrast to the natural tendency, the reticulocytes in response to treatment were found to increase, as would be expected. Reticulocyte increases in response to iron

treatment are shown in Cases 3 (Fig. 43), 4 (Fig. 36), 15 (Fig. 38) and 29 (Fig. 41); in case 4 iron was given on two separate occasions, a reticulocyte response occurring each time followed by a rise in haemoglobin. Reticulocyte increases probably due to blood transfusion are illustrated in Cases 7 (Fig. 44) and 20 (Fig. 45), although the response could have been due to the iron which was given at the same time. In Cases 13 (Fig. 37), 17 and 32 (Fig. 39) 18 and 26 (Fig. 40) reticulocyte counts could not be done during the first week of treatment as the cases were out-patients.

An important correlation, or rather absence of correlation, is that of the reticulocyte count with the mean corpuscular fragility. With the exception of Case 20, in which the mean corpuscular fragility was the highest of the series (Fig. 17) and in which one reticulocyte count was above normal but very slightly so (3 per cent), cases with naturally higher counts, for example Case 22 (Fig. 42), did not have any tendency to increased fragility (Fig. 21). On the evidence of the reticulocyte count in pregnancy anaemia in this series, a haemolytic factor in the etiology is not favoured. It must be remembered that in this series all the described types of pregnancy anaemia are not included.

The literature on the subject of the reticulocyte count in pregnancy is not extensive. Statements such as

the following, without the support of any published facts, are common: "the reticulocytes are depressed early and increased late in pregnancy" (Mussey, Watkins and Kilroe, 1932), "there is a slight increase in the latter part of pregnancy in the case of rats" (Van Donk, Feldman and Steenbock, 1934), "the reticulocyte count in the pernicious type of pregnancy anaemia is often slightly increased" (Stevenson, 1938), "the reticulocytes in iron deficiency anaemia of pregnancy tend to be raised" (Larabee, 1925), "there is an increased percentage of reticulocytes in the iron deficiency type of anaemia, and a percentage below the normal range in the protein deficiency type of anaemia" to be described later (Bethell, 1936), "in a survey of 275 cases of pregnancy examined without selection, the reticulocytes were increased, depending on the degree of anaemia" (Gottlieb and Strean, 1939). None of these statements are supported by facts.

Boycott (1936) publishes some figures on the subject, in a series of 26 cases, and on his facts is justified in his conclusions that reticulocytes are never increased in cases of pregnancy with colour index between 0.91 and 1.07 (the normal range, which Boycott considers to be an important indication of the physiological normality of the blood in pregnancy), nor in cases with colour index below 0.9

except as a manifestation of response to iron. Labate (1940) in a series of 19 women examined at the 38th, 39th and 40th weeks of pregnancy, found the "average" reticulocyte counts at these weeks to be 1.8, 1.28 and 0.66 per cent respectively; the average haemoglobin and red cell counts at these stages of his cases was 64% and 3.47 million, 66% and 3.45 million, and 68% and 3.70 million, respectively. He observed too that postpartum, the average reticulocyte count on alternate days for 10 days remained within the range 0.53 to 1.31 per cent. Strauss and Castle (1933) in their series of iron deficiency and macrocytic anaemias of pregnancy found no increase of reticulocytes during the control period of observation without treatment.

Isolated examples of pregnancy and postpartum anaemia cases with reticulocyte counts included are constantly being quoted and re-quoted. Minot (1921) records a case with reticuloeytes persistently above 16 per cent, an increased red cell fragility, and jaundice; Minot himself would probably now agree that this was a case of pregnancy occuring in acholuric jaundice. Larabee (1925) quotes figures of 4, 11 and 2.5 per cent reticulocytes in three cases of his series of 16; these figures were from three cases of postpartum anaemia, allegedly macrocytic. Evans (1929) records one case a week postpartum with normal fragility, haemoglobin 14%, red cells 1.0 million and 40% of reticulocytes; van den

Bergh 1.0 mg per cent. The patient had "severe epistaxis for several hours 6 days before this blood count," WHICH MIGHT HAVE ACCOUNTED FOR THE RETICULOCYTE CRISIS. 10 days later haemoglobin was 30%, red cells 2.5 million, reticulocytes 20%, and in another 2 weeks, haemoglobin 30%, red cells 2.7 million, reticulocytes 2%. The cases of these three authors are specially mentioned here, as they are constantly being quoted in publications, usually wrongly; and, since the article by Witts (1932) on haemolytic anaemia of pregnancy, as cases of acute haemolytic anaemia of pregnancy, chiefly on the evidence of the high reticulocyte counts. On the incomplete investigation, according to modern standards, of these cases, the assumption is quite unjustified. Peterson, Field and Morgan (1930) record two cases fully, one of which was macrocytic with 10 per cent of reticulocytes before treatment on a single occasion; the case will be discussed under the heading of macrocytic anaemia of pregnancy, but at this stage it should be memtioned that this case too is even to-day being quoted as a case of "haemolytic anaemia of pregnancy". Numerous cases of anaemia of pregnancy are quoted by various authors with reticulocytes within normal limits. Ritter and Crocker (1939) for instance mention 1 to 2 per cent as the upper limit of reticulocytes in a case of "severe macrocytic anaemia of pregnancy" before liver treatment was started; following liver, the count rose to 8 per cent. Goodall and Gottlieb (1936) gave the average reticulocyte count in first, second and third trimesters as 2.0,

3.0 and 5.0 per cent, when haemoglobins were 80, 75 and 65 per cent respectively. No other authors quote such high figures.

The conclusions regarding the reticulocyte count in pregnancy, if based upon the figures of my series of cases and published figures of most authors quoted above, are that in normal pregnancy the reticulocyte count is within normal limits; that in the majority of cases of anaemia of pregnancy there is no natural tendency for the reticulocyte count to rise even if the anaemia is severe; but that isolated cases are recorded in which the reticulocyte count is raised apart from the response to specific treatment. In the face of published figures, opinions published without the support of figures which differ from the above conclusions, cannot be accepted. The matter requires further controlled investigation.

Discussion of these conclusions will be reserved for a later section when the pathogenesis of anaemia of pregnancy is considered.

VAN DEN BERGH REACTION

The plasma bilirubin in milligrammes per cent was estimated in 10 normal pregnancies and 20 cases of anaemia of various grades, bythe method of Haslewood and King (1937). The readings in both the normal and the anaemic groups fell within the normal range as laid down by Vaughan and Haslewood (1938). The distribution of the readings is diagramatically represented in Fig. 63, where it is seen that the distribution is approximately the same for the normal and the anaemic group, in other words, there is no tendency for the plasma bilirubin to increase even in the severe grades of anaemia of pregnancy of this series. The single high reading of 0.8 mg per cent was found the day after a continuous drip blood transfusion which could have been followed by sufficient haemolysis to account for the higher reading.

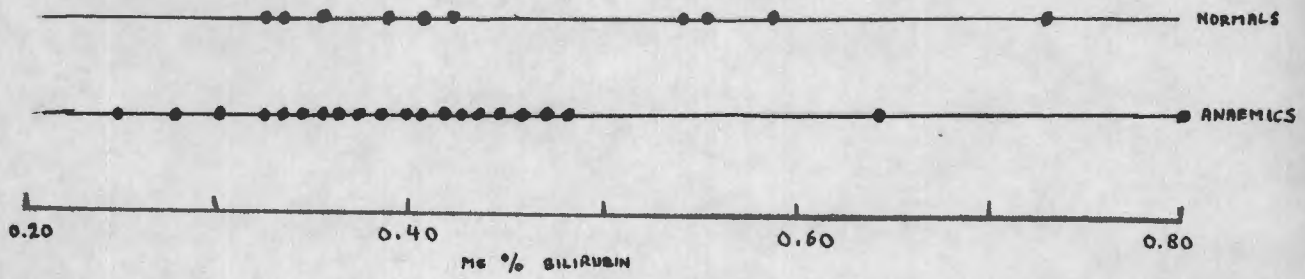


Fig. 63

Indicates the distribution of plasma bilirubin readings in the normal and anaemic groups of pregnant women.

The readings included cases in which the red cell fragility was increased slightly. There was no correlation between the mean corpuscular fragility and the level of plasma bilirubin. Nor was there correlation between the level of plasma bilirubin and the reticulocyte count. These features are of some significance in excluding any haemolytic factor in the anaemic cases of this series.

The literature on the subject of the plasma bilirubin in pregnancy is scanty. No long series of cases the investigation of which includes estimations of plasma bilirubin in normal pregnancy and in anaemia of pregnancy can be referred to. In cases of anaemia of pregnancy, Stevenson (1938) states that in the "pernicious" type it is "only slightly increased", whatever that may mean; Witts (1932), quoting other authors' observations, states that it is increased in "acute haemolytic anaemia of pregnancy", the existence of which as a clinical entity is doubtful. Isolated cases are recorded, in most of which the level is within normal limits; Evans (1929) for instance gives figures of 0.7 and 1.0 mg per cent in two cases of postpartum anaemia not due to haemorrhage. It may be of significance that in the few cases in which a raised level is recorded, the investigations have been so incomplete that the cases cannot be regarded as uncomplicated cases of anaemia of pregnancy.

The conclusions then regarding the plasma bilirubin in pregnancy are that in normal pregnancy it is not raised above normal, in cases of anaemia of pregnancy included in this series it is not raised above normal, and that in other types of anaemia of pregnancy not included in this series but to be discussed later there is no conclusive evidence that it is ever raised.

CLASSIFICATION OF ANAEMIA OF PREGNANCY

CLASSIFICATION OF ANAEMIA OCCURRING DURING PREGNANCY

Anaemias occurring during pregnancy may be classified into two main groups, those actually induced by pregnancy, and those complicated by pregnancy. This principle of classification must be constantly remembered during the consideration of the following grouping of types of case. At the conclusion of the discussion of these various types, a slightly modified classification will be presented which excludes one or two "traditional" varieties which have never been actually proved to exist as clinical entities, but which are included in the provisional classification out of deference to tradition.

1. PHYSIOLOGIC ANAEMIA OF PREGNANCY
2. DEFICIENCY ANAEMIA OF PREGNANCY

   A. Iron deficiency anaemia
   B. Macrocytic or pernicious anaemia of pregnancy
   C. Mixed iron deficiency and pernicious anaemia of pregnancy.

3. MISCELLANEOUS GROUP OF ANAEMIAS OF PREGNANCY

This group includes a variety of conditions, some unproven, some disproven but still quoted as clinical entities.

A. Acute haemolytic anaemia of pregnancy

B. Hypoplastic anaemia of pregnancy

C. Protein deficiency anaemia of pregnancy (Bethell)

D. Vitamin B deficiency anaemia of pregnancy (Elsom)

E. Unclassified group of anaemia of pregnancy.

4. ANAEMIA COMPLICATED BY PREGNANCY

Any type of anaemia may be complicated by pregnancy. As long as this principle is remembered, it is not necessary here to give a general classification of the anaemias. Conditions which will receive attention are Addisonian pernicious anaemia, idiopathic hypochromic anaemia, anaemia due to haemorrhage, especially haemorrhage from the gastro-intestinal tract, and aleukaemic anaemia.

I. PHYSIOLOGIC ANAEMIA OF PREGNANCY

Evidence has already been led which indicates that during normal pregnancy the haemoglobin percentage and the red cell count fall as pregnancy advances, and return to normal promptly after delivery. This has been called the physiologic anaemia of pregnancy. The main cause of this is now generally accepted to be the increase in blood volume which occurs in pregnancy and to which full reference has been made. The

degree of increase of blood volume varies in wide limits for different cases, probably accounting for the varying degrees of physiologic anaemia observed in normal pregnancy. Earlier theories of "syncytial haemolysins" (Hofbauer, 1908) or other sorts of haemolysins, or of "toxic" inhibition of the bone marrow, have no facts to support them. That the foetal demands for haemopoietic material are greatest at the stage of the greatest degree of physiologic anaemia may be co-incidental, or may be another factor in lowering the haemoglobin percentage and the red cells in normal pregnancy.

Certain haematological standards to be satisfied before a case can warrant consideration as a possible case of physiologic anaemia have been laid down (Page 101). If these conditions are satisfied, it is unlikely that an erroneous diagnosis will be made. The importance of the colour index cannot be stressed too much.

The condition of physiologic anaemia of pregnancy is harmless. It is necessary to ensure that an adequate diet is taken. Haemopoietic substances such as iron are unnecessary but do not harm and should be given if there is any suspicion of their lack.

When associated with a true anaemia, such as the iron deficiency type, the physiologic hydraemia probably accounts for the peculiar watery appearance of the patient.

2A. IRON DEFICIENCY ANAEMIA OF PREGNANCY

There is no doubt that the term iron deficiency anaemia of pregnancy is descriptive of a definite clinical entity. Whether the anaemia is primarily due to pregnancy or whether it is a pre-existing condition aggravated by pregnancy has to be discussed. Every case has to be decided on its own merits, the two considerations being, is the anaemia of the iron deficiency type, and if so, is it due to or merely aggravated by pregnancy?

A voluminous literature, too large to be reviewed completely, has arisen about the subject. Much of the investigation has been badly controlled or not controlled at all, and in the present discussion only publications of value will be included. Investigations of value have been of two types, the mass survey type and the detailed study of individual cases.

HAEMATOLOGICAL CHARACTERS

The haematological characters of the anaemia are similar to any type of iron deficiency anaemia. Strauss and Castle (1932b) described 30 cases in which the colour index lay between 0.47 and 0.71, there was moderate anisocytosis, mean corpuscular volume was below normal, reticulocytes and

plasma bilirubin normal. Case 4 of this series, charted in Fig. 36, is a typical example, with red blood cell count 5.00 million, haemoglobin 48 per cent, colour index 0.48, mean corpuscular volume 62 cu.mu, mean cell diameter 6.3 mu, variability 9.12 per cent, reticulocytes 2.0 per cent. In the milder cases, with haemoglobin 60 to 70 per cent, the blood picture is less characteristic and other means of diagnosis must be relied on, for example, the response to treatment. It must be mentioned that there has been some difference of opinion on the reticulocyte count in this type of anaemia, Bethell (1936) saying that it tends to be raised. The majority state that the count is normal.

RESPONSE TO IRON TREATMENT

Response to iron treatment is an important diagnostic aid, especially in the milder cases. The matter can be considered under four headings, (1) the dosage of iron required, (2) the reticulocyte crisis resulting from the iron, (3) the increase in anisocytosis as the case responds, and (4) the rise in haemoglobin percentage. As many of these conditions as possible should be studied in each case before ascribing success to the treatment.

DOSAGE OF IRON

The dose must be adequate. Ammoniated citrate of

iron, grains 90 daily (Strauss and Castle, 1932b, and many others), ferrous sulphate gr 9 to 15 daily (Fullerton, 1936a, Corrigan and Strauss, 1936, Gottlieb and Streatn, 1939, Labate, 1939, and others), or Blaud's pill gr 45 daily (Boycott, 1936) are considered adequate. The ferrous sulphate is less inclined to produce gastro-intestinal upsets. The additional use of dilute hydrochloric acid to aid absorption is only necessary if the iron alone fails to produce improvement.

RETICULOCYTE CRISIS

The rise in the reticulocyte count is the earliest and most reliable sign that the case is responding to iron, and in doubtful cases of iron deficiency anaemia, should be looked for between the 4th and 10th days of treatment. Cases 4 (Fig. 36) and 7 (Fig. 44) are examples of small but definite crises. Strauss and Castle (1932b) show charts which show similar rises, which do not often exceed 10 per cent. It is surprising that a test so simple technically should be used so infrequently as a diagnostic aid.

INCREASE IN ANISOCYTOSIS

The increase in anisocytosis as the case responds may be of some diagnostic value. It was observed in many cases of the present series, and is graphically demonstrated in the

Price-Jones curves of Cases 4 and 7, Figs. 64 and 65 respectively. It is seen within a week or two of the start of treatment. It is not of course specific for iron treatment, and does not require a Price-Jones curve to be apparent, as a moderately experienced observer can see it at a glance.

RISE IN HAEMOGLOBIN PERCENTAGE

The test of the rise in haemoglobin percentage may be unsatisfactory as a guide to the effectiveness of the iron treatment for two reasons. It has already been shown that in individual cases the haemoglobin percentage may rise spontaneously, independent of any treatment, and secondly, it is sometimes undesirable to have to wait the two or three weeks necessary for the haemoglobin to show any appreciable rise after treatment. A typical response to iron is shown in the chart of Case 4 (Fig. 36). Strauss and Castle (1933) in their excellent description of 30 cases of iron deficiency cases in pregnancy include several similar types of chart.

The method of mass investigations on large series of cases, if well controlled, also demonstrates the response to iron in cases of anaemia of pregnancy, but in terms of haemoglobin percentage only. Provided the number of cases in a series is large enough, the influence of exceptional

individual cases is lost in the general average results. Some of this type of investigation can be quoted. Corrigan and Strauss (1936) observed 200 women through pregnancy, leaving 100 untreated, and treating 100 with adequate iron. They found that the average haemoglobin at 3 to 7 months antepartum in the treated group was 73 per cent and in the untreated group 75 per cent; at one week postpartum the average haemoglobin for the treated group was 85 per cent and for the untreated group 75 per cent. In none of the treated group, but in 24 of the untreated group, was the postpartum haemoglobin below 70 per cent. Their conclusions were that adequate iron dosage (ferrous sulphate, gr 9 daily) prevents postpartum anaemia. Fullerton (1936b) compared the course of haemoglobin percentage level in groups of pregnant women with and without iron (ferrous sulphate gr 9 daily). Their findings are recorded graphically in Fig. 66,

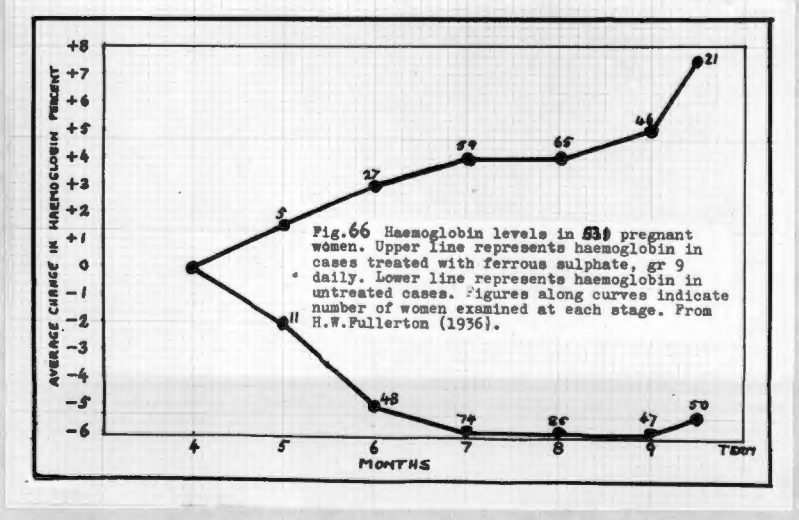


Fig.66 Haemoglobin levels in 531 pregnant women. Upper line represents haemoglobin in cases treated with ferrous sulphate, gr 9 daily. Lower line represents haemoglobin in untreated cases. Figures along curves indicate number of women examined at each stage. From H.W.Fullerton (1936).

Fig. 66.

where it is seen that the average rise of haemoglobin from the 4th month to term is 8 per cent, whilst the average fall for the same period in the untreated group is 5 per cent, making a final difference of 13 per cent haemoglobin at term between the two groups. Gottlieb and Strean (1939) divided 525 pregnant women into groups of 275 and 250. The group of 275 was untreated, and the haemoglobin readings at the first, second and third trimesters was 80, 75, and 65 per cent respectively. The group of 250 was subdivided into subgroups of 50, 50, 50 and 100, each group being given a different form of iron. The average initial haemoglobin was 58 per cent, and in 4 to 6 weeks the haemoglobin was normal. They favoured ammoniated citrate of iron as the most rapid in its effect, but ferrous sulphate as the least likely to produce gastro-intestinal upsets. It is to be noted however, that their two main groups are not comparable, owing to the difference in initial haemoglobin percentage levels. Labate (1939) treated 325 pregnant women with ferrous sulphate gr 15 daily, starting at an unspecified period of pregnancy, and found the average haemoglobin readings before treatment to be 9.45 grammes per cent rising to 11.17 grammes per cent, also at a period of pregnancy not specified; further treatment with iron, liver, protein, failed to raise the haemoglobin percentage higher, so that he concluded that the physiological anaemia limit had been reached. His work

was uncontrolled and far from convincing. Adair et al (1936) studied a group of 235 pregnant women, with results rather contrary to the usual. Their findings are tabulated in Table X, (Fig. 59). From these results, they concluded that in their series at least, there was no difference in the course of the haemoglobin percentage as pregnancy advanced in the treated and untreated groups. This was due, not to a failure of the haemoglobin percentage to rise, but to the fact that in both groups, treated and untreated, it rose with equal frequency and in equal degree; 65 out of their 74 untreated cases imporved spontaneously. These results are definite; the facts must be accepted, but the details of individual cases investigated are not produced in detail, and cannot therefore be criticised or agreed with. Bethell (1936) used the absence of response to iron to distinguish between his iron deficiency anaemias and "protein deficiency" anaemias of pregnancy (See Fig. 73). From the facts produced, it seems quite likely that the failure to respond to iron was due to the fact that the alleged protein deficient anaemias were really normal.

Other investigations consulted in this matter of response to iron treatment have been unsatisfactory in that the work has been completely uncontrolled or the procedures

adopted unsound. Galloway (1929) stated that 16 of 74 cases treated with iron failed to respond; he failed to report the dose of iron administered, which at that time was probably inadequate. Richter, Meyer and Bennett (1934) concluded that an aqueous extract of liver with glycerated iron caused a rise of haemoglobin percentage in a series of 99 women divided into control and test groups; their results hardly justify their conclusions. Davis and Walker (1934) in a series of 89 pregnant women with controls used 6 different preparations of iron and found that whatever preparation was used, the treated series had higher haemoglobin readings than the control series; unfortunately it is known that several of the patent preparations they used contain fractional doses of iron, quite inadequate. Jerlov (1929) reported improvement on iron in 108 cases out of a total of 120 treated; he had no controls at all. This group of investigations has been referred to as examples of uncritical work not justifying the conclusions arrived at.

Whilst much useful work of the mass survey type has been done on the subject of the effect of iron in the treatment of anaemias of pregnancy, most of the advance in the knowledge of the iron deficiency anaemias of pregnancy has been due to the more intensive detailed study of individual cases.

THE CONCLUSIONS in general so far based upon close study of individual cases and upon results of mass surveys, and in spite of a certain amount of differemce of opinion to which reference has been made, are that an iron deficiency anaemia may occur during pregnancy, of severe degree sometimes, which responds to iron treatment, and which is a common condition.

Having established this fact, it is necessary to consider certain aspects relating to the etiology of iron deficiency anaemia of pregnancy. These will be considered under four headings: (1) Is iron deficiency anaemia of pregnancy an anaemia arising de novo during pregnancy or is it an aggravation of a pre-existing anaemia? (2) The hydrochloric acid of the stomach during pregnancy. (3) The influence of social conditions and diet. (4) Iron metabolism.

PRE-EXISTING ANAEMIA OR NOT?

For obvious reasons, it is a very difficult matter to prove whether a pregnant woman was anaemic before she became pregnant. No large series has been found in the literature in which cases have been followed haematologically before the pregnancy in which anaemia occurred. Numerous references can be quoted which vaguely are of opinion that there is or

is not anaemia present before. Bethell (1936) for instance states on quite inadequate evidence that "pre-existing iron depletion is a possible factor"; Richter et al (1934) similarly consider that pre-existing anaemia is present; Boycott (1936) in a detailed study of 26 cases did not consider there had been anaemia before the pregnancies. These and other opinions are based on inadequate facts.

Three methods of investigation are possible, (a) the study of a large series of women before pregnancy as well as during; this is almost impracticable, especially if the cases are to be studied for a sufficient length of time beforehand, (b) the follow-up of cases through the puerperium to see whether they return to normal standards of haemoglobin spontaneously, and (c) animal experimentation.

No reference can be made to any series of pregnant women in whom blood studies were made before the pregnancy. The matter cannot therefore be further considered.

The follow-up of cases of anaemia into the postpartum period is a very indirect method of investigation, as what happens after a pregnancy is not necessarily a true reflection of what happened before. Again, reference has to be made to two types of investigation - the mass survey, and the study of the individual case.

The mass survey investigations in general show that where the haemoglobin percentage is below normal during pregnancy, it usually spontaneously returns to normal after delivery. Bland, Goldstein and First (1930b) in their study of 1000 cases found that 58.6 per cent had a haemoglobin below 70 per cent in the third trimester; of the 100 cases followed into the postpartum period for a period up to 6 months, 92 had returned to normal within 2 to 6 months. They discounted the idea of pre-existing anaemia. Watson (1938) followed 40 cases into the postpartum period and came to the conclusion that if the postpartum level of haemoglobin per cent is a guide to the pre-pregnancy level, then pre-existing anaemia is not a factor in cases of pregnancy anaemia. Fullerton (1936b) on the other hand by a complicated system of reasoning concluded that "such anaemias (hypochromic) probably antedate the pregnancy and apparently are rendered more severe by the hydraemia of pregnancy"; he does not go into the question of blood pictures in individual cases, so that his conclusions lose much of their force.

Detailed study of smaller groups of cases are of more value, but are very few. Strauss (1930) reported two cases of severe hypochromic anaemia seen first 2 weeks after delivery which responded at once to iron; from enquiry, he considered that they were not anaemic before the pregnancy.

Strauss and Castle (1932b) gave as their opinion that "the existence of anaemia prior to the beginning of pregnancy apparently need not condition anaemia of greater degree during pregnancy", and they gave details of two cases, both of whom had moderate anaemia before pregnancy and who were on adequate diets; one case continued to eat poorly through pregnancy and became severely anaemic, and the other ate well during pregnancy and became no more anaemic, in fact, the haemoglobin rose as pregnancy advanced. 3 months post-partum the first case had a haemoglobin of 40 per cent, the second, of 60 per cent. These observations of Strauss and Castle are of fundamental importance and will be referred to again.

Experimental evidence indicates that pregnancy anaemia can, under certain conditions, arise de novo during a particular pregnancy. Ivy, Morgan and Farrell (1931) demonstrated that in the case of gastrectomised dogs, pregnancy uniformly induced a hypochromic anaemia when the dogs were on a diet which maintained their strength, health and blood picture when not pregnant. In one dog, 3 successive pregnancies were associated with the development of anaemia, with spontaneous return to normal between pregnancies. It was also noted that if the dogs were put on inadequate diets

in the periods when not pregnant, they developed an identical type of anaemia. Dragstedt, Bradley and Mead (1931) kept four gastrectomised dogs anaemic by bleeding and demonstrated that they made haemoglobin less efficiently than normal dogs; they showed that liver (1933) was more effective than iron in aiding haemopoiesis; the significance of their findings in the present discussion is the fact that the dogs had to be bled to be kept anaemic; the anaemia in dogs was not a natural consequence of the gastrectomy. Maison and Ivy (1935) showed that in gastrectomised pigs, a hypochromic anaemia developed regularly after three months. The significance of these experimental observations is to show that the haemopoietic system of different species is affected differently by the same operation; hence it is not possible to draw dogmatic conclusions with regard to what might happen in the human being. With this reservation, it may be of significance to the human that dogs "prepared" in a certain way regularly develope anaemia during pregnancy, not having been anaemic before. It suggests that in the case of the anaemia of pregnancy in the human it is possible for it to arise de novo due to an inherent defect present but harmless apart from pregnancy; such defect may develope during pregnancy, not having been present before; and such defect, in association with extrinsic factors concerned for example, with diet, may be responsible for the anaemia of pregnancy.

THE CONCLUSIONS on the subject of pre-existing anaemia may be summarised as:

If the return to a normal haemoglobin percentage within a few weeks of delivery in cases showing moderate or severe degrees of anaemia during pregnancy can be taken to indicate that the haemoglobin percentage was normal before pregnancy, then the anaemia of pregnancy is not usually associated with pre-existing anaemia.

Pre-existing anaemia, when present, is not necessarily aggravated by pregnancy, provided an adequate diet is taken during pregnancy; but may become aggravated if an inadequate diet is taken.

The development of anaemia in pregnancy is conditioned, not by the presence or absence of a pre-existing anaemia, but by certain factors, present or not before pregnancy, known or unknown; and by the adequacy or inadequacy of the diet. Of the known factors, diet and the gastric hydrochloric acid are important, both of which are to be discussed.

GASTRIC HYDROCHLORIC ACID DURING PREGNANCY

Diminution in the hydrochloric acid during pregnancy

has been demonstrated by most authorities who have investigated the matter. Arzt (1930) investigated 50 cases and found that 60 per cent had no free hydrochloric in the first trimester, and 100 per cent had a decreased amount; the lower levels were found in the earlier months. Histamine stimulation was not used, so that his results are not strictly comparable with the more modern investigations. Strauss and Castle (1932a) performed fractional test meals on 24 apparently normal pregnant women at monthly intervals during pregnancy and at 2 weeks postpartum. Histamine was given "where necessary." They found that in 75 per cent of 24 patients, less than normal amounts of hydrochloric acid were secreted through at least half of pregnancy, and that 80 per cent secreted three times as much at 2 weeks postpartum as at the sixth month of pregnancy.

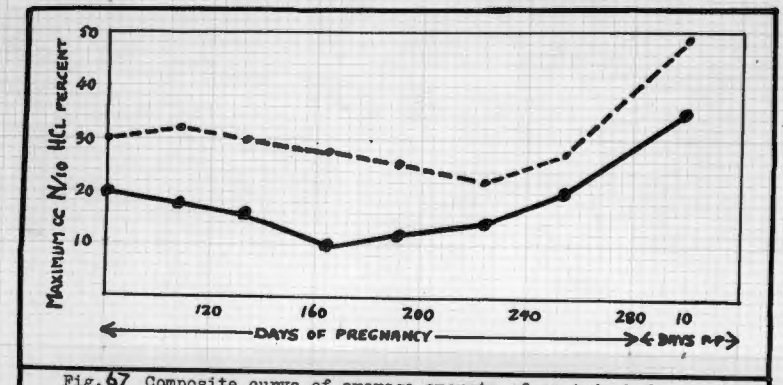


Fig. 67 Composite curve of average amounts of gastric hydrochloric acid in 21 pregnant women. No cases of complete achlorhydria are included. Interrupted line indicates total acidity. From M.B.Strauss and W.B.Castle (1932).

Fig. 67.

Excluding three cases with complete achlorhydria to histamine, they constructed a composite curve of 21 cases, showing the average maximum amount of decinormal hydrochloric acid in the gastric juice at each month. Their curve is reproduced in Fig. 67. It is seen that the maximum fall is at the 5th to the 6th month. Davies and Shelley (1934), including histamine stimulation in every test, carried out test meals on 51 pregnant women in the first and third trimesters and 2 months postpartum. Their findings showed that the hydrochloric acid falls off in the last trimester and rises postpartum. The lowest acid curves were found in the most anaemic cases, an observation which Strauss and Castle also noted. Their findings are graphically recorded in Fig. 68.

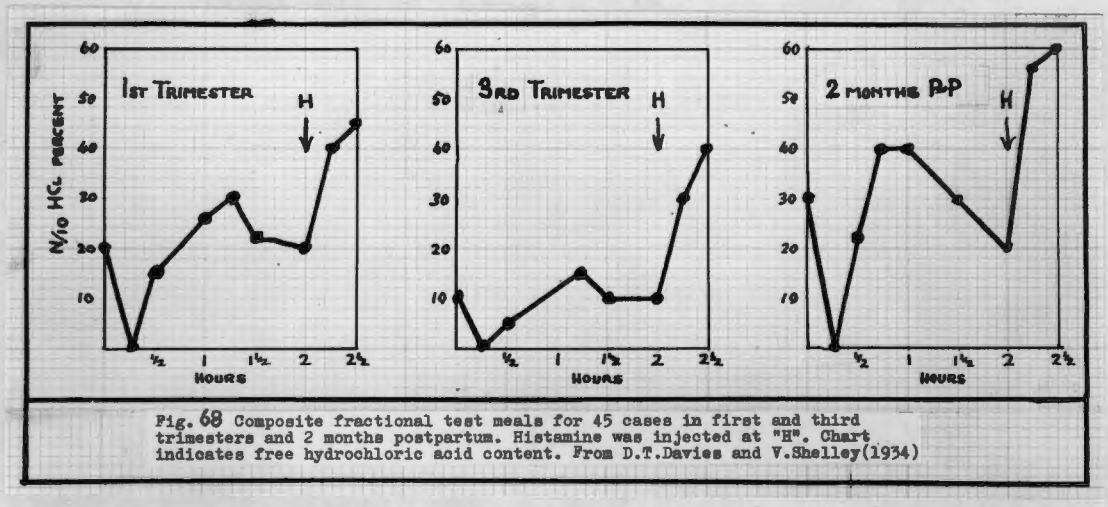


Fig. 68 Composite fractional test meals for 45 cases in first and third trimesters and 2 months postpartum. Histamine was injected at "H". Chart indicates free hydrochloric acid content. From D.T.Davies and V.Shelley(1934)

Fig. 68.

Goodall and Gottlieb (1936) examined 115 women on one occasion

each; in all, 60 test meals were done antepartum, at various stages, and 55 postpartum. They examined the fasting contents and the content at one hour. Histamine was not used in any cases. They found normal hydrochloric acid in 51 per cent at the first trimester, 0 per cent in the second trimester, 0.5 per cent in the third trimester, and 85 per cent at one week postpartum. Low hydrochloric acid was found in 40 per cent in the first trimester, 13 per cent in the second trimester, 3.5 per cent in the third trimester, and 12 per cent at one week postpartum. Achlorhydria was found in 9 per cent in the first trimester, 87 per cent in the second trimester, 96 per cent in the third trimester, and 3 per cent at one week postpartum. It is a pity that they did not record the effect of histamine. Watson (1938) agrees that the acid is reduced in pregnancy, but did not find any relation between the degree of reduction and the degree of anaemia. Bethell (1936) did not find any relation between the degree of anaemia and the level of acid, but did find the acid reduced in the 15 cases examined. Numerous isolated cases have been reported showing the reduction in hydrochloric acid during pregnancy. In the present investigation, a fractional test meal was done in only one case (Case 4, Fig. 36) and achlorhydria to histamine was present.

The significance of the reduction in hydrochloric

acid that occurs during pregnancy has been best investigated by Strauss and Castle (1932b), who showed that ~~in~~ 7 cases with good acidity, and a good diet, had an average drop of 5 per cent haemoglobin at the end of pregnancy; in 6 with poor acidity, and a good diet, the haemoglobin loss was 9 per cent average, and in 5 with poor acidity, and poor diet, the average loss of haemoglobin during pregnancy was 13 per cent. Their original charts must be consulted for the value of their work to be appreciated. No other investigation has been carried out as thoroughly as their's. Other work which disagrees or agrees with it has been carried out without adequate control. The demonstration by Strauss and Castle of the relationship between the acid level and the degree of anaemia that developes during pregnancy was not unexpected in view of the work of Minot and Mettier (1931) and others which showed that the effect of iron in hypochromic anaemia was influenced by changing the acidity of the gastro-duodenal contents. In 10 cases of hypochromic anaemia they concluded that iron is more potent for blood formation when absorbed from acid than from alkaline medium of the stomach and duodenum.

It must be remembered that a normal gastric acidity may be associated with a specific absence of certain

haemopoietic factors; this observation has not been applied to the matter of iron deficiency anaemia, but it has been shown by Castle, Heath and Strauss (1931) that in two cases of pernicious anaemia of Addisonian type but with free hydrochloric acid present in normal amounts, intrinsic factor was absent from the gastric juice. Lastly, it must be remembered that even where the hydrochloric acid is absent to histamine stimulation during pregnancy, it can return to normal after delivery; this has been observed in cases who developed no anaemia in pregnancy, or who developed iron deficiency anaemia, or the rare type of pernicious anaemia of pregnancy.

THE CONCLUSIONS are that there is a temporary reduction in the amount of free hydrochloric acid during pregnancy, which may bear some relationship to the degree of anaemia which developes. The reduced or absent hydrochloric acid appears to be one of the factions which conditions the development of anaemia during pregnancy.

THE INFLUENCE OF DIET AND SOCIAL CONDITIONS

Although it would seem obvious that diet be an important factor conditioning the development of anaemia in pregnancy, the matter is not as simple as it may appear.

Most of the mass survey investigations which on first reading indicate poor diet as being an association of anaemia of pregnancy have been done on populations which are anaemic quite apart from pregnancy. Few of them, if any, are able to prove that the anaemia developing in pregnancy is more than can be accounted for by the hydraemia of pregnancy. Davidson and Fullerton (1933) demonstrated that the diet of 49 families, representative of the general population under investigation, was poor in iron; many hundreds of women of the population, some pregnant and some not, were found to be anaemic, the pregnant women having an average haemoglobin 5 per cent lower than the non-pregnant women for different age groups. Their findings are charted in Fig. 56. The small difference of 5 per cent, if anything, favours hydraemia as the cause of the difference. Fullerton (1936a) taking income level as the standard of dietetic adequacy, showed that amongst 332 pregnant women, 164 with low income levels had average haemoglobin of 73.1 per cent and 168 with higher income levels had average haemoglobin of 79.6 per cent. The control group of 140 non-pregnant women showed 87 with low income level to have an average haemoglobin of 83.2 per cent, and 43 with higher income level an average haemoglobin of 86.3 per cent. The pregnant women with low income had 6 per cent less haemoglobin than the pregnant women with higher income, whilst the difference between the non-pregnant low and higher income groups was only 3 per cent.

This difference may possibly be significant enough to suggest that the poor group of pregnant women became relatively more anaemic than the better off group, hydraemia alone not being responsible for the greater drop in the poor group. Fullerton (1936b) is of opinion that the lowering of haemoglobin in both groups is due to hydraemia only. Reid and Mackintosh (1937a) found the haemoglobin of 1108 pregnant women to be under 70 per cent in 10 per cent of the cases, but that the incidence of the lower haemoglobin levels was greater in the lower income groups. There was no control series of non-pregnant women, so that no conclusions can be drawn from their work. Adair et al (1936) found that a group of hospital class pregnant women was slightly more anaemic than a group of private patients; again, there was no control group of non-pregnant women in each class. Watson (1938) considered diet unimportant, but his figures were obtained from uncontrolled work.

The method of mass survey, therefore, is not very helpful in settling the problem of the relationship of diet to the development of pregnancy anaemia. The studies quoted show that the haemoglobin level is lower in any given population amongst the pregnant women, but the only study that suggests that poor diet induces an anaemia greater than can be explained by hydraemia is that of Fullerton (1936a); and his index of dietetic sufficiency was income level.

It remains once again for detailed study of individual cases to give the necessary information. The work of Castle and Strauss (1932 a and b) has been referred to, in which it was shown that a low protein diet, especially when associated with low gastric hydrochloric acid, resulted in a greater loss of haemoglobin in pregnancy than a good diet, and that an adequate diet given during pregnancy to cases previously anaemic will produce an improvement in the anaemia. Other studies are unconvincing. The work of Bethell (1936) on protein deficiency anaemia has been referred to, and the work of Elsom (1935, 1937) on vitamin B deficiency anaemia of pregnancy to be referred to later, has not been confirmed. In tropical megalocytic anaemia the factor of diet was thought to be important in pregnancy, but has not been proved; the condition as it applies to pregnancy is discussed later.

The only satisfactory detailed study of the problem is that of Strauss and Castle, which does appear to show a relationship between anaemia and low protein diet in pregnancy.

Animal experimentation shows that pregnant animals fed on inadequate diet may become more than physiologically anaemic (Van Donk et al, 1934). There is, however, work of an experimental type which shows the matter to be very complicated. Alt (1938) found that an iron free diet in pregnant rats gave no anaemia of pregnancy until the second

generation pregnancy, although the stores of iron in the liver after the first pregnancy were reduced to subnormal figures. The same iron free diet, given to non-pregnant rats, gave no anaemia after it had been given for long periods, up to 240 days, but the iron stores in the liver became reduced. Pregnancy therefore induced an anaemia which would not have occurred if the animals had not become pregnant, and which was definitely lower than the physiological anaemia of pregnancy.

THE CONCLUSIONS on the matter of diet are that clinical investigation suggests but does not prove that a diet which is adequate to maintain the blood picture at a certain level apart from pregnancy, may be insufficient to maintain that level during pregnancy, due allowance having been made for the effect of the hydraemia of pregnancy. The index of a poor diet is difficult to standardise; it has been variously assessed according to the protein content, income level and iron content.

Experimental investigations afford stronger evidence that favours the development of a true anaemia in pregnancy, greater than can be accounted for by hydraemia, if an inadequate diet is given.

IRON METABOLISM DURING PREGNANCY

The intake of iron during pregnancy was investigated in 49 families by Davidson and Fullerton (1933). They calculated that the average daily intake was 7.71 mg for women. Quoting several authorities (Widdowson and McCance, 1936, Shackleton and McCance, 1936, Elvehjem et al, 1933, 1934) it was considered that about 75 per cent of this was available, and as about 50 per cent is absorbed as a rule (Witts, 1936), the amount that the women absorbed averaged 2.5 mg daily. This is less than half of what is required to maintain a positive balance in the reproductive period. Coons (1935) calculated that in pregnancy an intake of 14.7 mg daily gives a positive balance of 3.16 mg. The ~~survey of the~~ IN A INVESTIGATION population studied by Davidson and Fullerton was later shown to be anaemic, the anaemia being worse in the pregnant women (Fig. 56). Their work demonstrates as facts that in a poor class carbohydrate eating population the iron intake is inadequate, and that such a population is anaemic.

The iron requirements during pregnancy have been reviewed by Fullerton (1936a), who, quoting many references, and especially the work of Coons (1932, 1935), and taking into consideration every possible debit and credit of iron during pregnancy, delivery, the puerperium and lactating period, concluded that during pregnancy the extra demand

for iron is 2 mg per day. The maternal tissues require no more than in the non-pregnant state; the whole extra requirement is for the foetus. The amount of iron in the blood during pregnancy has been investigated by Sacks (1936) who found that it was reduced below the level for non-pregnant women, the figures being 40 and 45 mg per cent respectively. The blood copper varied inversely with the iron.

The foetal demands for iron as measured by the amount of iron storage in the foetal liver at different stages of gestation have been shown to be greatest in the last trimester both in animals (Bunge, 1889) and humans (Hugonenq, 1899). The foetal haemoglobin percentage, which is an additional reflection of the foetal requirements, increases rapidly in the early part of the last trimester; in the rat foetus (Nicholas, 1928) the rise is from 5 grammes to 9 grammes per cent in the early part of the third trimester, and in the rabbit foetus (Zeidberg, 1929) the rise is from 8 to 12 grammes per cent during the whole of the last trimester.

THE CONCLUSIONS are that the increased demand for iron during pregnancy is due to the requirements of the foetus. That there is an increased demand has been proved by metabolic studies of iron balance in pregnant women. The greatest demand has been shown to occur in the last trimester.

The increased demand must be satisfied by a diet of sufficient iron content. The absorption of iron, dietetic or medicinal in form, is decreased by the lowered hydrochloric acid content of the gastric juice, and therefore it may be necessary to supplement the diet with iron by mouth. There is no safe injectable form of iron (Heath, Castle and Strauss, 1932).

GENERAL SUMMARY OF IRON DEFICIENCY ANAEMIA OF PREGNANCY

There is no doubt that iron deficiency anaemia of pregnancy is a clinical entity. Its haematological characters are similar to any other form of iron deficiency anaemia, as is its response to iron treatment. Spontaneous improvement in haemoglobin percentage during pregnancy must be differentiated from improvement due to iron. Means of differentiation are discussed.

The anaemia may be (a) an aggravation of a pre-existing anaemia by the hydraemia of pregnancy, (b) an anaemia developing de novo conditioned by factors such as reduced hydrochloric acid, these factors appearing during pregnancy and disappearing after parturition; or by factors such as diet, adequate to keep blood normal apart from pregnancy, but inadequate with the increased requirements of pregnancy, and (c) due to the demands of the foetus, especially during

the last trimester. These possibilities have been discussed in full.

The effect of this form of anaemia on the maternal and infantile health is to be discussed in a special section.

2B MACROCYTIC OR PERNICIOUS ANAEMIA OF PREGNANCY

It is surprising that whereas the haematological characters of Addisonian pernicious anaemia have been well recognised for many years, the term "pernicious" and more recently the term "macrocytic" have both been badly misused in relation to the anaemias of pregnancy. The majority of authors on the subject appear to consider the word "pernicious" to be synonymous with "severe", and the word "macrocytic" to be applicable to any blood picture which contains a macrocyte or two! Furthermore the term "haemolytic anaemia of pregnancy" is frequently used synonymously with "pernicious anaemia of pregnancy", entirely erroneously of course.

In view of the confusion of nomenclature, it is necessary to have some uniform definition of this group of anaemias of pregnancy. That of Vaughan (1936) affords the most reasonable working basis upon which to build up a clinical entity. It can be defined as "a megalocytic, hyperchromic anaemia occurring during pregnancy or the puerperium, not necessarily associated with achlorhydria, due to a temporary deficiency of P-A factor". A corollary to this definition should be that the blood should respond to liver, and that the response should include a

reticulocyte crisis to exclude as far as possible the response being coincidental; also, that other causes of macrocytic anaemia must be excluded.

The number of cases in the literature, apart from tropical megalocytic anaemia associated with pregnancy, which conforms to this definition is astonishingly small. For every dozen cases which various authors, even to-day, are pleased to call "pernicious anaemia of pregnancy", there is perhaps one which conforms to the definition. Even in cases which conform more or less to the definition, opinions differ on such important points as the spontaneous recovery after parturition or the possibility of relapse in future pregnancies.

As there were no cases in my present series of this type of anaemia, the discussion must depend entirely on a study of the literature.

The most convincing and the largest series of cases reported are the eight of Strauss and Castle (1933). In this series, the colour index was from 1.0 to 1.25, mean corpuscular volume 105 to 130 cu.mu, there were in stained films microcytes, macrocytes and tailed forms, and morphologically the blood picture was "similar to true

pernicious anaemia". There was complete achlorhydria to histamine in two, and one of these two had normal gastric hydrochloric acid two years later; in four the gastric hydrochloric acid was low. Subsequent treatment, after parturition, was not necessary to prevent relapse. Strauss and Castle's observations on the effect of treatment are important enough to warrant detailed description. It was possible to observe four of the cases for a control period varying from 8 to 23 days, without treatment, during which period the blood state, including a normal reticulocyte count, remained unchanged. It is reasonable to assume that a similar control in the other four cases would have given similar results. Various types of treatment were prescribed, more than one type, at different times of course, in one case in some instances. The reticulocyte percentage was taken as the crucial test of efficacy of any one form of treatment. Their findings were (a) in the cases of this type in which iron was given either before or after other forms of effective or ineffective treatment, a prompt reticulocyte response following the iron administration with a rise of haemoglobin in some cases, indicating an associated iron deficiency; (b) liver extract gave a prompt response whether given before or after iron therapy, indicating lack of P-A factor either intrinsic or extrinsic or both; (c) decinormal hydrochloric acid with beefsteak gave no response until after parturition when a reticulocyte response occurred on

the 10th day postpartum followed by a rise in haemoglobin, suggesting an inhibition of intrinsic factor during pregnancy (an increase in the reticulocyte percentage in the puerperium is not a physiological finding); (d) human normal gastric juice with beefsteak given subsequent to the response (c) gave a still better reticulocyte response and increase in haemoglobin and red cells, suggesting that the intrinsic factor had only partially returned in experiment (c); (e) autolysed yeast product (marmite) gave a very poor response during pregnancy until given with normal human gastric juice, suggesting that there was a partial deficiency in intrinsic factor as well as a lack of extrinsic factor; and (f) autolysed yeast product given alone in one case after parturition gave a maximal reticulocyte and haemoglobin response, suggesting that at that period there was only a lack of extrinsic factor. Fig. 69 represents the course of one of their cases. To summarise their conclusions, in the macrocytic anaemia of pregnancy there may be an associated iron deficiency; the lack of P-A factor may be due to lack of intrinsic or of extrinsic factor, or both; and the inhibition of intrinsic factor is temporary, returning after parturition. No details are available to indicate how long after parturition the normal conditions of haematopoiesis are re-established. It was noted that main dietary lack in these cases was protein, which is interesting in relation to

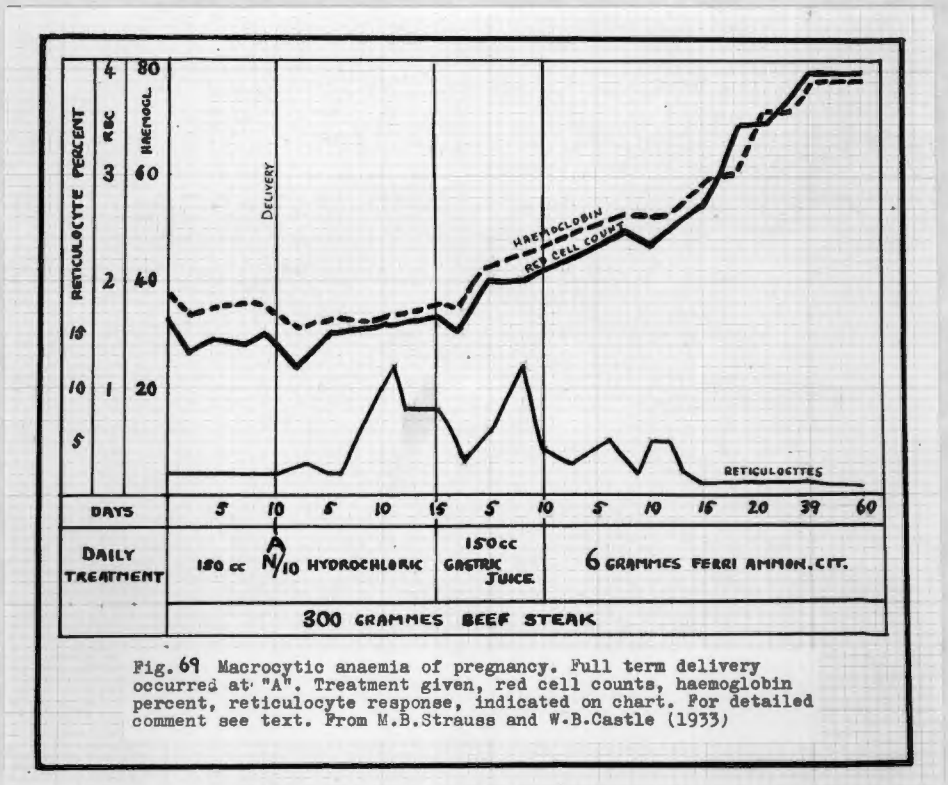


Fig. 69 Macrocytic anaemia of pregnancy. Full term delivery occurred at "A". Treatment given, red cell counts, haemoglobin percent, reticulocyte response, indicated on chart. For detailed comment see text. From M.B.Strauss and W.B.Castle (1933)

Fig. 69.

the observations of Bethell (1936) discussed later. The association of iron and P-A factor deficiency in the same person is not confined to pregnancy, as the same condition is described by Beebe and Lewis (1931) in several cases of otherwise typical Addisonian pernicious anaemia.

No other series of cases has been so well worked out as the 8 cases of Strauss and Castle. Larabee (1925) is still quoted extensively by modern authors for his 8 cases

of "pernicious anaemia of pregnancy"; 7 of the cases were studied for the first time from 3 weeks to 2 years postpartum. The only standard of macrocytosis is the colour index, which ranged from 1.1 to 1.53; there were no measurements of cell diameter or volume. Out of the 8 cases described, two might be considered to conform to the modern definition (exclusive of the effect of liver which was then unknown), namely, case XI with two subsequent normal pregnancies and a normal blood count 10 years later without treatment, and Case XII with a normal blood count 6 years later. The remaining six cases were, on the evidence, more likely to have been pregnancy associated with pernicious anaemia, or other blood conditions with macrocytic blood picture, such as acute leukaemia. It should here be mentioned that many authors, including Larabee, ascribe anaemias to a pregnancy which might have occurred as long as two years before the date of first haematological study, which hardly fits in with the "temporary" inhibition of intrinsic factor.

Of the numerous isolated cases reported in the literature as pernicious anaemia of pregnancy in the last decade or two, the following can be selected as possibly conforming to the definition. Most of these cases have been very incompletely investigated, corpuscular volume and mean cell diameter readings rarely being included, reticulocyte

responses not recorded, and follow-up periods being all too short. The cases are selected on the basis of a high colour index anaemia occurring during pregnancy, a response to liver treatment, the presence or absence of hydrochloric acid in the gastric contents, other causes of macrocytic anaemia being more or less excluded. Rowland (1924) described two cases of "pernicious or haemolytic anaemia of pregnancy", only the second of which can be included in the macrocytic group the first case will be referred to later. Peterson, Field and Morgan (1930) presented three cases of "pernicious anaemia of pregnancy" treated with liver; two of the three were seen for the first time 6 and 7 weeks postpartum respectively, and although showing "no macrocytosis" were given liver followed by a reticulocyte response which appeared to justify their claim that the response was due to the liver; this is a thoughtful article, and suggests that the pernicious anaemia of pregnancy has a less marked macrocytosis than true pernicious anaemia. Wilkinson (1932) attempts to distinguish between true pernicious anaemia with associated pregnancy, and pernicious anaemia of pregnancy. He gives an extensive review of the literature but this review is of little value, as he ingenuously accepts the diagnosis of the various authors without any criticism, and his conclusions regarding the size of the red cell in this type of pregnancy anaemia, the effect of various treatments, maternal and foetal morbidity and

mortality, and chances of recurrence in future pregnancies are of no value. He records two cases of his own of alleged macrocytic anaemia of pregnancy with high colour index and improvement after liver; both are incompletely investigated but may have been what he claims them to be. He also records three cases of true pernicious anaemia complicated by pregnancy, one of which was called pernicious anaemia of pregnancy until there was a spontaneous haematological relapse 19 months later, requiring liver treatment and indicating it as true pernicious anaemia. Whitby (1932) describes two cases (Cases 1 and 4 of his series) which can be accepted. The findings in Case 4, a girl of 19, are reproduced in graphic form in Fig. 70. to show the

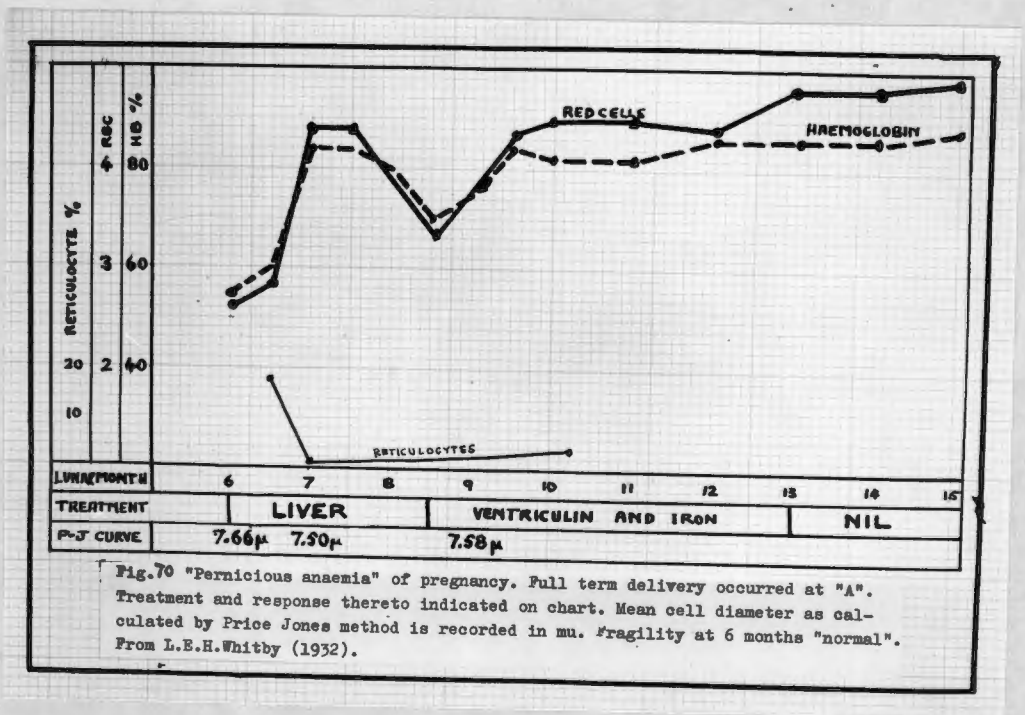


Fig.70 "Pernicious anaemia" of pregnancy. Full term delivery occurred at "A". Treatment and response thereto indicated on chart. Mean cell diameter as calculated by Price Jones method is recorded in mu. Fragility at 6 months "normal". From L.E.H.Whitby (1932).

Fig. 70.

improvement, including reticulocyte response, following liver. The mean cell diameter in this case, at the height of the anaemia, was 7.66 mu, suggesting again that the diameter in even the severest of pernicious anaemias of pregnancy is less than in true pernicious anaemia. Rowland (1933) recorded 26 cases of severe pregnancy anaemia, 6 of which he claimed as of the pernicious type. He gives figures for only one of the cases; this one case had a colour index of 1.3 to 1.4, and recovery during pregnancy was probably due to the liver received. Studdiford (1934) briefly reports a poorly investigated single case which can be accepted as a macrocytic anaemia in a woman of 27, and responding to liver treatment; no reticulocyte readings are recorded. Atkin (1938) describes two postpartum cases, the second of which, aged 40, could have been true pernicious anaemia. The first case was of interest in that it was macrocytic when first seen on the fifth day postpartum, with haemoglobin 38%, colour index 1.15, and reticulocytes 16 per cent; liver and iron were given at once, and on the 10th day postpartum haemoglobin was 44%, colour index 0.98, reticulocytes 38 per cent. In two months the blood count was normal, but the follow-up was too short thereafter. In the light of the observations of Strauss and Castle (1933), the first reticulocyte response may have been the result of the return of intrinsic factor following parturition,

and the second response, the result of liver and iron. Ritter and Crocker (1939) record a case which can probably be accepted as a case of pernicious anaemia of pregnancy.

Observations on the gastric hydrochloric acid in the cases in which the test was done showed in some a complete achlorhydria and in others a reduced content. This finding ~~will later be~~ has been shown to be a physiological occurrence in normal pregnancy.

The cases that have so far been selected from the literature, a mere handful, are all that can be found in the American and British publications which possibly fulfil the requirements of the definition of pernicious anaemia of pregnancy.

It is next necessary to draw attention to the numerous cases reported as pernicious anaemia of pregnancy and handed down from author to author as such without any attempt at criticising the diagnosis. The observations of Channing (1842) on 8 cases of severe anaemia of pregnancy ending fatally, of Beckmann (1921) on 6 cases occurring in 60,000 pregnancies in Vienna, of Esch (1921) on 23 cases collected in 20 years, are quoted and re-quoted as examples of pernicious anaemia of pregnancy without any justification

whatsoever on the meagre facts available. No further mention will be made of these observations, nor of many other constantly quoted reports before the days of modern haematology. There are, however, a number of reports which can and should be referred to, published within the last 20 years. Hampson and Shackle (1924) presented a case referred to as a case of macrocytic anaemia of pregnancy, with a mean cell diameter of 8.23 mu. Death occurred ten days after first observations. The interest lies in the fact that in the same article, the authors describe a case with an exactly comparable blood picture which also died and on which there was a postmortem held, the findings being acute leukaemia. Smith (1925) with his report on 8 cases of high colour index is regularly quoted; the cases are so incompletely and probably so inaccurately investigated that they are valueless; haemoglobin, for instance, was "estimated by the method of Tallqvist's scale, and 10 per cent subtracted". Allan (1928) similarly can be excluded. Hoskin and Ceirog-Cadle (1927) describe a case of "severe anaemia of pregnancy simulating pernicious anaemia" in which the 6 recorded blood counts have a colour index of 0.8 to 0.9; there was no follow-up, and the case might well have been an aleukaemic leukaemia. Evans (1929) has two cases, both postpartum, which are quoted as cases responding to liver; colour index was 0.6 and 0.7 respectively, and the postpartum recovery, ascribed to liver, could well have been spontaneous as in one of my cases

(Case 22, Fig. 42); no reticulocyte counts were recorded after the institution of liver treatment. Kersley and Mitchell (1934) have one case of "megalocytic anaemia of pregnancy" diagnosed as such on a colour index of 1.1 and the appearance of the smear; the case failed to respond to liver and died a few hours after parturition ; investigations were very incomplete. The case of Lull (1937) cannot be accepted as pernicious, although called so. Barnum and Woodward (1938), describing a case of "severe hyperchromic macrocytic anaemia of pregnancy" state that the colour index was 1.0 and "macrocytes were observed"; haemoglobin was 23%. Blood transfusion, liver, and yeast produced no response, but recovery occurred after delivery. As has been shown (Figs. 64 and 65), the observation of some macrocytes does not necessarily indicate a macrocytic anaemia. In these two cases, the increase in number of macrocytes was the result of iron treatment. Stevenson (1938) in a very misleading article describes one hundred cases of anaemia of pregnancy and puerperium, 30 of which, collected in Edinburgh over six years between 1928 and 1934, were alleged to be of the "pernicious type". Her article has been frequently quoted as evidence that the macrocytic type of pregnancy anaemia is more common in certain localities than in others, for example, more common in Edinburgh than in London. There is very little justification for her conclusions on the facts

published. Stevenson's own summary ofthe blood findings in the 30 cases is: colour index above unity in 17, at unity in 7, and below unity in 7; Price-Jones curves show a shift to the right in only 6 cases "in spite of the presence of macrocytes", and a broadened base in all cases, (See Fig. 71); response to liver shows "an earlier reticulocyte response and higher than in true pernicious anaemia,

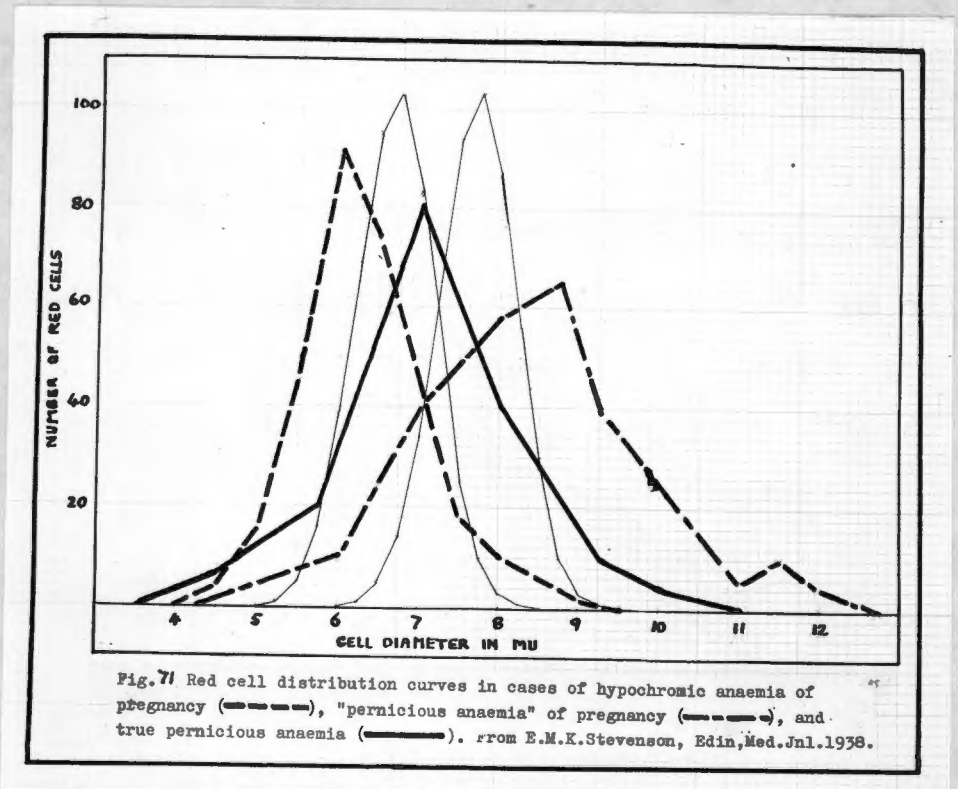


Fig. 71 Red cell distribution curves in cases of hypochromic anaemia of pregnancy (– – –), "pernicious anaemia" of pregnancy (– – – –), and true pernicious anaemia (————). From E.M.K.Stevenson, Edin.Med.Jnl.1938.

Fig. 71.

there may be a striking output of nucleated red cells before the crisis, the blood is normal in 4 weeks, but

some fairly early cases reacted slowly to treatment although usually early cases responded quickly and late cases responded slowly; treatment was stopped after 4 to 16 weeks and patients are known to be well up to 5 years later." No facts are given to substantiate the vague character of this report. One case was thought to be "probably a case of true pernicious anaemia". The bad impression caused by this article is increased by studying a microphotographic plate of several blood smears of the "pernicious" type of pregnancy anaemia; a reproduction of a film of true pernicious anaemia is fortunately included for comparison; there is no justification for calling any of the blood pictures from the pregnancy series macrocytic. The question of definition also arises in the statement of Labate (1940) that 62% of 811 pregnant women had a macrocytic blood picture, and did not respond to liver (or iron); curiously, he gives no range of what he considers normal, and the probability is that all his macrocytic cases are normal; his estimate of cell size is by haematocrit.

The preceding review of the literature on the subject of pernicious anaemia of pregnancy is far from complete. It is sufficiently extensive, however, to indicate that the term pernicious anaemia of pregnancy is even to-day too loosely used. If we accept Vaughan's definition, then it can be stated that this type of pregnancy anaemia is very rare.

Very few figures are available to indicate its incidence. Boycott (1936) noted no case in 222 pregnant women examined haematologically, and Reid and Mackintosh (1937) no cases in 1108 pregnancies. The majority of surveys of long series of pregnancy cases concentrate on average haemoglobins, red cell counts and mean corpuscular volumes and therefore any macrocytic cases are lost in the average figures.

There remain three syndromes to describe which do not conform to the Vaughan definition in every respect, but which have the one common feature that they are macrocytic. One of these, tropical macrocytic anaemia, is a well recognised entity, and the other two, Bethell's protein deficiency macrocytic anaemia of pregnancy, and Elsom's vitamin B deficiency macrocytic anaemia of pregnancy, still require confirmation as clinical entities.

Tropical megalocytic anaemia as described by Wills (1931, 1933) Wills and Mehta (1930), Wills and Talpade (1930), Wills and Evans (1938), Balfour (1927), and MacSwiney (1927), may occur coincidentally with pregnancy, and in some parts of India complicates 3 per cent of deliveries. It is undoubtedly macrocytic. Associated with pregnancy, it is a serious condition, having a maternal mortality of 40 per cent

and a foetal mortality of 63 per cent. It has been produced by Wills in monkeys be feeding them on a diet deficient in protein and vitamin B. In a dietetic survey in Bombay, where tropical megalocytic anaemia is common, the average daily intake of protein in the hospital class was 8 grammes only. This is less significant than it sounds, as the meat eating Mohammedon women also contract the condition. The condition is cured by the administration of the less pure extracts of liver (anahaemin, for instance, is ineffective) and by autolysed yeast products such as marmite. Occurring with pregnancy, it is not an anaemia of pregnancy, but an anaemia coincidental with pregnancy.

Bethell (1936) has described an anaemia of pregnancy characterised by a colour index near unity, a high normal or increased mean corpuscular volume (up to 108 cu.mu) in his series of 6 cases out of a total of 66 pregnant women examined, and a percentage of reticulocytes below the normal range. The cases fail to respond to iron, but do respond to high protein diet. Fig. 73, graphically illustrates the failure to respond to iron in five of the cases. Fig. 72 contrasts the mean corpuscular volumes in the pregnant and the non-pregnant control group. Bethell also found that there was an inverse ratio between the serum albumin fraction and the mean corpuscular volume (in 6 cases with a

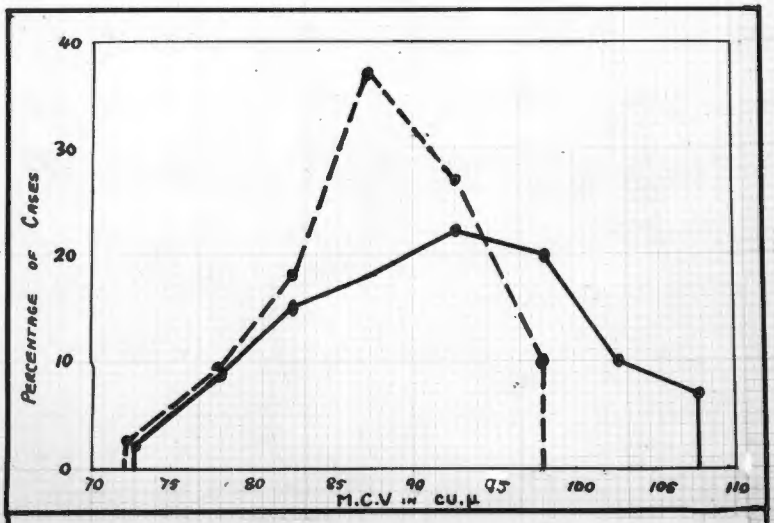


Fig. 72 Mean corpuscular volume in pregnancy. Interrupted line indicates M.C.V. incidence in 50 non-pregnant women ; continuous line indicates M.C.V incidence in 66 pregnant women. The tendency to increased M.C.V. during pregnancy is shown. From F.H.Bethell (1936).

FIG. 72

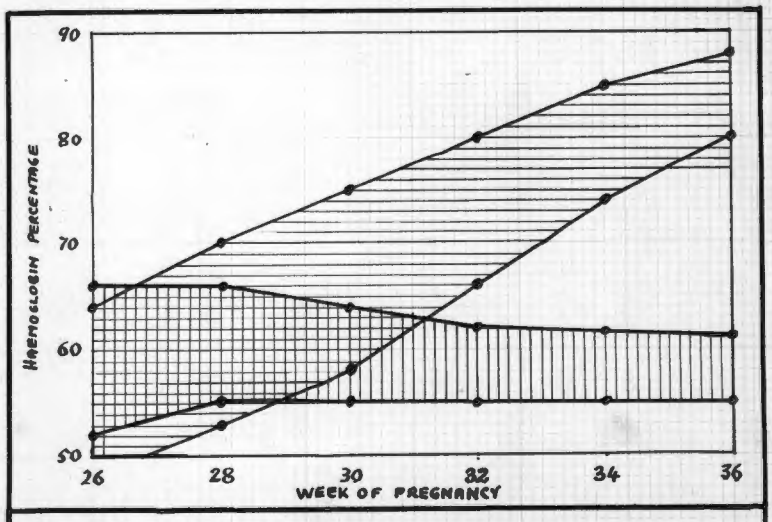


Fig. 73 Response to treatment in pregnancy anaemia. The horizontal shaded area represents the range of haemoglobin during pregnancy in 14 cases of iron deficiency anaemia treated with iron. The vertically shaded area represents the range of haemoglobin during pregnancy in 5 cases of "macrocytic" or "protein deficiency" anaemia treated with iron. For details see text. From F.H.Bethell (1936).

FIG. 73

mean corpuscular volume of 100 to 108 cu.mu. the serum albumin fell between 2.3 and 3.2 grammes per cent, whilst in 23 cases with a mean corpuscular volume of 76 to 96 cu.mu. the serum albumin fell between 3.25 and 4.5 grammes per cent). The syndrome is therefore called "macrocytic protein deficiency anaemia of pregnancy". Bethell presents his case lucidly, but the work has not been confirmed. The only case in my series with a raised mean corpuscular volume (Case 22, mean corpuscular volume 98 cu.mu.) failed to respond to liver or iron during pregnancy, nor to full hospital diet; furthermore, the reticulocyte count tended to be raised. Spontaneous return to a normal blood count occurred after parturition.

Elsom (1935, 1937) claims to have produced a macrocytic anaemia in pregnant women with a diet deficient in vitamin B. The investigation was carried out in the United States on European women. A group of 8 cases of early normal pregnancy were put on a vitamin B deficient diet, and a group of 3 on a full diet as control. The control group remained normal throughout pregnancy and the puerperium. The test group, about the eighth month of pregnancy, developed clinical symptoms of vitamin B deficiency and the blood picture changed from the initial average values of 3.93 million red cells, 12.8 grammes haemoglobin per cent

and mean corpuscular volume of 100 cu.mu, to 3.23 million red cells, 12.0 grammes per cent haemoglobin and mean corpuscular volume of 121 cu.mu, with reticulocytes up to 3.5 per cent. All returned to normal, clinically and haematologically, as soon as brewer's yeast was administered; after the institution of brewer's yeast treatment, the reticulocytes "rose in some" to 5.4 per cent and then fell to normal level. The figures of red cell count, haemoglobin and mean corpuscular volume quoted, and the detailed figures in the original case protocols, barely justify Elsom's dogmatic conclusions, and the work has not been confirmed, but is interesting in relation to tropical megalocytic anaemia and its cure by marmite.

THE CONCLUSIONS regarding pernicious or macrocytic anaemia of pregnancy can be summarised as follows:

(a) It is necessary to establish that the anaemia is macrocytic, responds to the administration of P-A factor, is not Addisonian pernicious anaemia or other recognised type of macrocytic anaemia, and does not require treatment once the blood has returned to normal figures after parturition. The follow-up must be for an adequate period. The macrocytosis may be of less grade than occurs in true pernicious anaemia. Hydrochloric acid may or may not be present in the gastric contents.

(b) There may be lack of either intrinsic factor, or extrinsic factor, or both, according to the work of Strauss and Castle (1933). The lack of intrinsic factor is temporary during pregnancy. There is some doubt as to how long it is after parturition that the secretion of intrinsic factor returns to normal; the return may be immediate or delayed.

The gastric hydrochloric acid may be absent to histamine stimulation, or may be present in quantities less than normal.

(c) It may be possible to include under the heading macrocytic anaemia of pregnancy the type of case described by Elsom (1935, 1937) due to vitamin B deficiency, and the type described by Bethell (1936) due to protein deficiency, if these workers' observations are confirmed. It is in the writer's opinion doubtful whether the work will be confirmed.

(d) Macrocytic anaemias associated coincidentally with pregnancy, and possibly aggravated by it, must always be excluded. In this connection, it must be remembered that true macrocytosis occurs in many blood disorders besides pernicious anaemia and tropical megalocytic anaemia; aleukaemic leukaemia particularly must be considered.

The study of this rare and interesting type of pregnancy anaemia will be greatly simplified if the rules laid down in these conclusions are adhered to.

2c MIXED IRON DEFICIENCY AND PERNICIOUS ANAEMIA OF PREGNANCY

Strauss and Castle (1933) have been able to demonstrate that in pregnancy there may be an iron deficiency as well as a temporary deficiency of P-A factor. This double deficiency has been referred to in the discussion on macrocytic anaemia of pregnancy, where it was pointed out that a similar double deficiency may occur in true Addisonian pernicious anaemia.

As long as the condition is recognised, it is readily treated with iron and P-A factor.

3 MISCELLANEOUS GROUP OF ANAEMIAS OF PREGNANCY

The types of anaemia of pregnancy previously discussed, namely, the physiologic anaemia of pregnancy, iron deficiency anaemia of pregnancy, macrocytic or pernicious anaemia of pregnancy and mixed iron deficiency and pernicious anaemia or pregnancy, have all been proved as distinct clinical entities. There is a miscellaneous group of anaemias

occurring during and claimed to be due to pregnancy, the existence of which as clinical entities is doubtful in greater or less degree. In this group, the protein deficiency anaemia of Bethell and the vitamin B deficiency anaemia of Elson have been discussed under the heading of macrocytic anaemias of pregnancy. There remain acute haemolytic anaemia, hypoplastic anaemia, and an unclassified group of heterogenous character.

ACUTE HAEMOLYTIC ANAEMIA OF PREGNANCY

More confusion has arisen around the subject of acute haemolytic anaemia of pregnancy than around any other form of pregnancy anaemia. The term is frequently still used synonymously with pernicious anaemia of pregnancy. Allan (1928) speaks of the "pernicious anaemia of pregnancy is an acute haemolytic anaemia" dogmatically. With more modern concepts of haemolysis it might be expected that such statements would no longer be used, but as recently as 1938, Stevenson, in presenting 30 cases of alleged pernicious anaemia of pregnancy stated and accepts that "some writers (quoting Witts and Wilkinson) refer to the condition as the haemolytic anaemia of pregnancy".

The characteristics of an acute haemolytic anaemia are now fairly well defined as a rapidly advancing anaemia,

with pyrexia, leucocytosis with appearance of premature cells of myelocytic type, increase in nucleated red cells, a persistently raised reticulocyte percentage, and an increased amount of circulating bilirubin. The excretion of faecal and urinary urobilin is increased to many times the normal. The condition may be self-limited, or may terminate fatally; treatment is by blood transfusion and is rapidly effective.

The number of cases in the literature of anaemia in pregnancy that conform to the definition, exclusive of the urobilin excretion which is not a practicable test in ordinary practice, is remarkably small. Witts (1932) reviewed the literature exhaustively, but accepted cases on quite insufficient evidence. The cases here detailed were all accepted by him without question. Peterson, Field and Morgan (1930) describe one case (Case 1 of their series of four) which at 3 weeks before parturition had a red cell count of 0.96 million, haemoglobin 33 per cent, colour index of 1.5, white cell count of 13,000 with a normal differential count, one nucleated red per 100 white cells and 10 per cent of reticulocytes. Van den Bergh not recorded. Whilst the raised reticulocyte count was suggestive, there is enough in the rest of the blood count to throw doubt on the diagnosis of acute haemolytic anaemia. The blood recovered after

parturition, but it was impossible to say whether the recovery was spontaneous or due to liver or to blood transfusion. Evans (1929) describes a case seen on the 7th day postpartum with a blood count of 0.9 red cells, haemoglobin 12 per cent, colour index 0.7, white cells 7000 with 7 per cent of myelocytes, 5 nucleated reds per 200 whites; reticulocytes not counted at that time. 4 days later, red cell count 1.0 million, haemoglobin 14 per cent, white cells 14,000 with a few myelocytes, 28 nucleated reds per 200 whites, reticulocytes 40 per cent, and van den Bergh 1.0 mg per cent. 10 days later, red cells 3.5 million, haemoglobin 30 per cent, white cells 4,000, and reticulocytes 20 per cent. Recovery proceeded, reticulocytes falling to normal in another 10 days. This is the most convincing, or rather the least doubtful, case in the literature; Evans himself gave the opinion that there was no evidence of haemolysis. The red cell fragility was normal at the height of the anaemia. Hampson and Shackle (1924) are also quoted by Witts; reference to their original description shows no features even suggestive of an haemolytic anaemia; the cases has been referred to in the discussion on macrocytic anaemia of pregnancy. Minot (1921) described a case with jaundice, splenomegaly, increased red cell fragility, reticulocyte count persistently above 20 per cent; and Larabee (1925) a similar case of "atypical anaemia of pregnancy cured by

splenectomy"; both these cases had the features of haemolytic anaemia, but the more reasonable diagnosis seems to be acholuric jaundice complicated by pregnancy. Witts had to go back to the year 1914 to find his best case.description as reported by Jungmann. As the original publication is not available, the description given here is taken from Witts. The findings of the cases are reproduced in graphic form in Fig. 74.

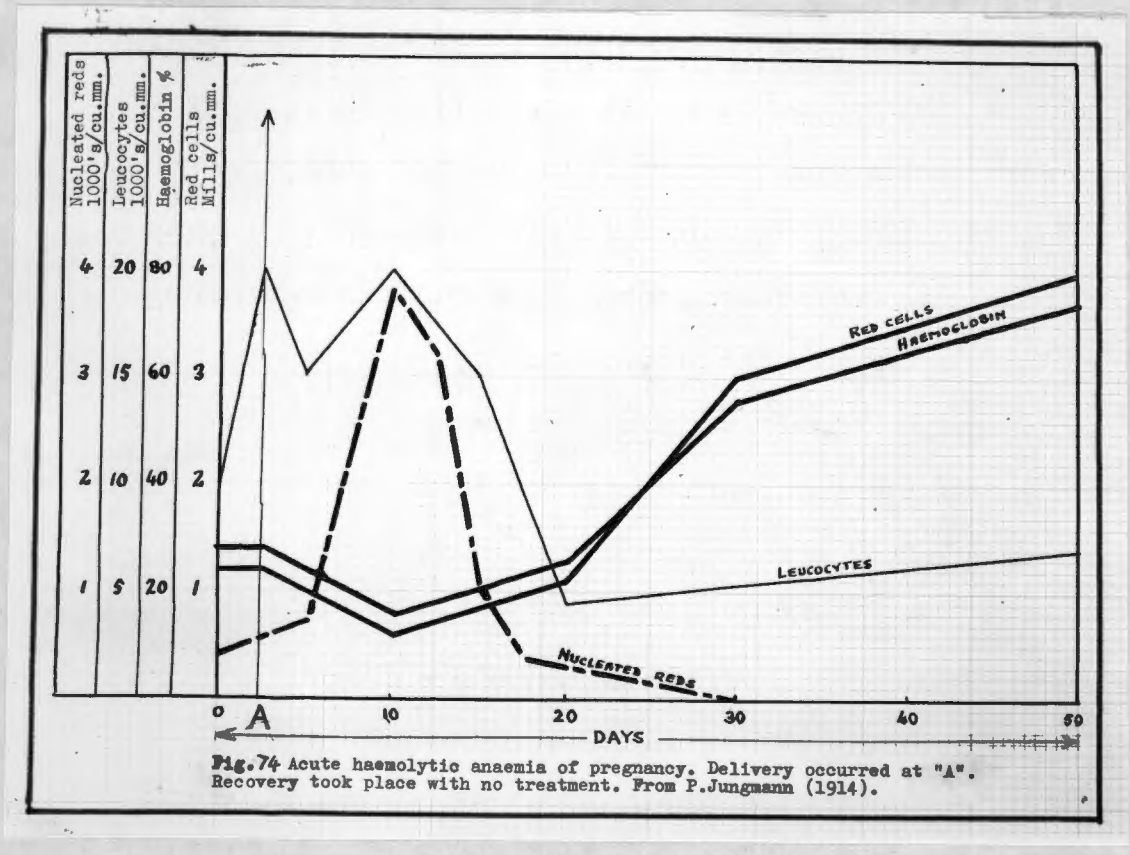


Fig.74 Acute haemolytic anaemia of pregnancy. Delivery occurred at "A". Recovery took place with no treatment. From P.Jungmann (1914).

Fig. 74.

The condition spontaneously recovered after parturition. As the graph shows, many of the features of acute haemolytic anaemia are present, including the high leucocytic count, high nucleated red count, and progressive advance of the anaemia followed by steady recovery. These features alone however cannot allow of the case being accepted with any degree of certainty as a case of acute haemolytic anaemia of pregnancy.

A case of the author's (unpublished) can be presented as a case not dissimilar from that of Jungmann, but which was in fact of quite a different nature. The findings are reproduced in graphic form in Fig. 75. When first seen, a

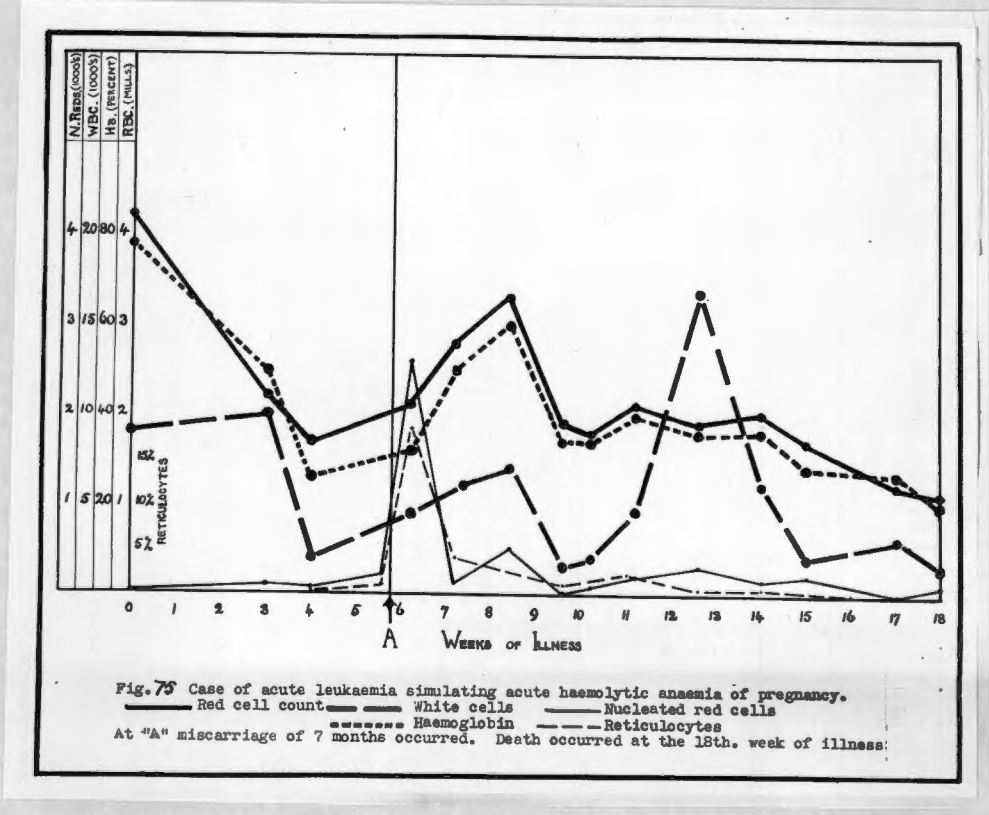


Fig. 75 Case of acute leukaemia simulating acute haemolytic anaemia of pregnancy.
——— Red cell count — — — White cells ——— Nucleated red cells
- - - - - - - Haemoglobin — — — Reticulocytes
At "A" miscarriage of 7 months occurred. Death occurred at the 18th. week of illness.

Fig. 75.

diagnosis of acute aleukaemic leukaemia in a pregnant woman was made with confidence; there was a recent history of rapidly progressive anaemia with severe purpura, there was sternal tenderness, the white cells were reduced, with many premature forms. The condition steadily became worse, and 2 weeks later a miscarriage occurred. On the third day after the miscarriage, a remarkable change took place in the blood picture, as the chart shows. There was a great outpouring of nucleated red cells and some premature whites, reticulocytes rose to 18 per cent; the total white cell count did not rise. Thereafter, for three weeks, improvement took place, and at the end of the third week postpartum, the red cells were 3.00 million, haemoglobin 60 per cent, white cells 7,000, reticulocytes 2 per cent, there were no abnormal red or white cells in the circulation. At this stage, the blood picture was comparable with the blood picture of Jungmann's case at the 50th day postpartum. From then on, however, the condition relapsed, and the patient died 9 weeks later with the leukaemic picture again. Transfusions had no good effect.

The least doubtful of the cases accepted by Witts as acute haemolytic anaemia are those of Evans (1929) and Jungmann (1914). A search of the literature since the publication of Witts has failed to reveal a single case

record which conforms in any way with the definition of haemolytic anaemia. The only mention in modern publications of haemolytic anaemia of pregnancy has been found in text-books of haematology, for instance, that of Whitby and Britton (1937).

There is no doubt that conditions occur which simulate in greater or less degree the usual description of acute haemolytic anaemia of pregnancy. In the first place, it is possible to see acute haemolytic anaemia during pregnancy but not due to pregnancy; a haemolytic crisis of acholuric jaundice may occur during pregnancy, acute haemolytic anaemia such as follows the use of the sulphanilamides (Elliott, 1939) or other drugs, or acute haemolytic anaemia due to subtertian malaria may also occur. Such causes unassociated directly with pregnancy should always be sought in a suspected case. Secondly, there are many blood conditions which simulate haemolytic anaemia, for instance acute leukaemia, which can occur coincidentally with pregnancy.

THE CONCLUSIONS regarding acute haemolytic anaemia of pregnancy are that if it ever occurs, it does so extremely rarely. Acute haemolytic anaemia occurring during pregnancy is probably due to ther causes not connected at all with the pregnancy. It is significant that in the literature of the

last 10 years, not one example of acute haemolytic anaemia of pregnancy has been found amongst the very numerous descriptions of types of pregnancy anaemia.

In the classification of anaemia of pregnancy, acute haemolytic anaemia if proved, should be put into the group "Anaemia complicated by pregnancy".

HYPOPLASTIC ANAEMIA OF PREGNANCY

No strict definition of this type of anaemia of pregnancy can be given. It is a traditional and probably non-existent type. The term is generally applied to an anaemia, assumed to have been originated by pregnancy, which fails to return spontaneously to normal after parturition within a reasonable period. The "reasonable period" is variously stated to be from a matter of months to years. Some of the cases respond to no treatment, some to liver, some to iron and some to blood transfusions. The failure to respond spontaneously, or the failure to respond to any treatment at all, is responsible for the term hypoplastic, which refers to the supposed state of the bone marrow.

Reference to the literature of published cases, alleged to be of this type, gives no evidence to justify the type in any classification of anaemia of pregnancy. The

cases have usually been very incompletely investigated, but from the facts available they appear to be either some blood condition which has been aggravated by pregnancy, or complicated by pregnancy, or cases of iron deficiency or pernicious anaemia of pregnancy which have taken longer than usual to return to normal after parturition. The variable time after parturition that the intrinsic gastric factor, for instance, returns after pregnancy during which macrocytic anaemia has occurred, has already been referred to. It is significant that most of the cases described were reported before ten years ago, that is, before the days of modern haematological methods.

PROTEIN DEFICIENCY ANAEMIA OF PREGNANCY

This condition has been discussed under the heading macrocytic anaemia of pregnancy.

VITAMIN B DEFICIENCY ANAEMIA OF PREGNANCY

This condition has been discussed under the heading of macrocytic anaemia of pregnancy. The existence of this and the protein deficiency group has not been confirmed.

UNCLASSIFIED GROUP OF ANAEMIA OF PREGNANCY

Whilst the clinical and haematological characters of

some forms of pregnancy anaemia are constant and readily recognised, for example, physiologic anaemia, iron deficiency anaemia and macrocytic anaemia of pregnancy, there are many cases which in one respect or more do not conform to any one of such types. Many if not all of the cases, for instance, described as acute haemolytic anaemia of pregnancy do not even have the characteristics of haemolytic anaemia, and the few that do are, on the evidence, more probably haemolytic anaemia complicated by pregnancy. To call a condition, in which there is from case to case no constancy of clinical or haematological characteristics by a title which is descriptive of a very definite entity, is misleading and retards improvement in the knowledge of the subject.

The group "unclassified" is intended to include all cases which do not conform to recognisable clinical entities. This is admittedly a vague method of differentiation but serves to stimulate investigation into the details of exceptional cases. One of the purposes of the present investigation was to study in detail certain haematological characteristics of the blood in normal pregnancy and in pregnancy associated with anaemia. The results have been mainly of negative value, but have demonstrated the peculiar behaviour of the fragility of the red cell during pregnancy. The significance of this behaviour is to be discussed later, but at this stage it is relevant to draw attention to one

illustrative case.

Case 20 (Figs. 17 and 45) had some of the features of an iron deficiency type of anaemia of pregnancy. Had the red cell fragility not been done, the case could have been regarded as of such a type although the mean corpuscular volume was high (74 cu.μ.) for the degree of anaemia. The fragility, however, was found to be considerably increased, returning to normal after parturition. This was not a usual feature of the iron deficiency type. It suggested the possibility of the factor of intravascular haemolysis as being responsible wholly or in part for the anaemia. There was no persistent rise of reticulocytes in the face of a severe degree of anaemia, no jaundice, no spleen; these exceptional features must exclude it from the haemolytic group. Rather than include it in the iron deficiency group, where it is at once labelled as a type, is it not better to include it in the unclassified group until further investigation explains the unusual features of the case? In this case, for instance, investigation of the urinary and faecal urobilin excretion might have furnished important information bearing on the nature ofthe anaemia. Case 22 (Figs. 21 and 42) is another exceptional case. It responded to neither iron nor liver during pregnancy, but returned spontaneously to normal after parturition. The reticulocytes were possibly spontaneously just over normal, the fragility was normal.

On the evidence the case cannot be classified.

The inclusion of an unclassified group of anaemia of pregnancy is a confession of ignorance, but acts as a stimulus to further investigation which will allow of a particular case either being retained as a case of anaemia of pregnancy of a special type, or of its being placed in the final group in this classification of "anaemia complicated by pregnancy".

4. ANAEMIA COMPLICATED BY PREGNANCY

In every case of anaemia, mild or severe, occurring during pregnancy, the possibility of the pregnancy being coincidental must be considered. A person suffering from any particular blood disease may become pregnant, or a pregnant woman may develope any blood disease or disorder during her pregnancy. Only the commoner types will be considered here.

ANAEMIA OF HAEMORRHAGE

Occult haemorrhage, especially from the gastro-intestinal tract, may insiduously produce an anemia during pregnancy. A woman who has haemorrhoids is more likely to bleed during pregnancy. Case 29 (Figs. 26 and 41) is an example of such an anaemia; it was interesting that the red cell fragility in this case afforded a clue indicating that the case was not one of anaemia due to pregnancy. Haematologically it is impossible in many cases to differentiate between the blood pictures of iron deficiency anaemias and of chronic blood loss. Other lesions, such as ulcer, diaphragmatic hernia, may be the source of occult continuous haemorrhage.

DYSHAEMOPOIETIC ANAEMIA

ADDISONIAN PERNICIOUS ANAEMIA

Wilkinson (1932) described 3 cases of pregnancy occurring in Addisonian pernicious anaemia. In most cases the diagnosis is not difficult. The older age, the regular occurrence of achylia gastrica, the presence of nerve complications, and the permanent liver requirements differentiate it from the pernicious anaemia of pregnancy due to temporary inhibition of P-A factor. It must, however, be remembered, that true Addisonian pernicious anaemia may pass through a temporary phase of spontaneous improvement after parturition. It is therefore necessary to make regular observations of the blood of apparent cases of pernicious anaemia of pregnancy for many months after parturition.

IRON DEFICIENCY ANAEMIA

The subject of pre-existing anaemia in cases of iron deficiency anaemia of pregnancy has been fully discussed. It was concluded that an iron deficiency anaemia of pregnancy was more than an aggravation of a pre-existing anaemia of the same type. There must however be cases of pregnancy

occurring in persons suffering from idiopathic hypochromic anaemia; in such cases, it has been pointed out by Castle and Strauss (1932b) that there need no necessarily be an aggravation of the anemia during pregnancy, provided the patient is kept on an adequate diet.

TROPICAL MEGALOCYTIC ANAEMIA

The effect of pregnancy on tropical megalocytic anaemia has been discussed.

HAEMOLYTIC ANAEMIAS

The view is held by the author, that it is probable, on the evidence available, that cases of true haemolytic anaemia occurring during pregnancy are not "due to" pregnancy, but are cases of haemolytic icterus or other recognised form of haemolytic anaemia with pregnancy occurring coincidentally. Attention is once more drawn to two reported cases, that of Minot (1921), and that of Larabee (1925), both of which cannot be excluded from the category of haemolytic icterus.

VARIOUS

Acute leukaemia occurring during pregnancy has been

described (Hampson and Shackle, 1924, Richter, Meyer and Bennett, 1934), simulating some form of pregnancy anaemia. The case charted graphically in Fig. 75 is an example of an acute leukaemia having at one stage features resembling acute haemolytic anaemia. With modern methods of haematological technique, including examination of the sternal bone marrow, the diagnostic difficulties should not be great.

Aplastic anaemia, purpura haemorrhagica, "splenic anaemia", may present problems of differential diagnosis occasionally.

CONCLUSIONS REGARDING CLASSIFICATION.

The following classification of anaemia occurring during pregnancy is suggested, not as the most scientific, but as the most reasonable and the most conducive to stimulating further researches.

1. PHYSIOLOGIC ANAEMIA
2. DEFICIENCY ANAEMIA OF PREGNANCY
    - A. Iron deficiency anaemia
    - B. Macrocytic or pernicious anaemia
    - C. Mixed iron deficiency and pernicious anaemia
3. UNPROVEN GROUP

Includes acute haemolytic, hypoplastic, protein deficiency and vitamin B deficiency anaemia of pregnancy.

4. UNCLASSIFIED GROUP

Includes cases which do not conform to the above groups of physiologic anaemia and dyshaemopoietic anaemia of pregnancy, nor to the unproven group, and yet which, on the available evidence can reasonably be considered as possibly due to pregnancy. Examples have already been quoted.

5. ANAEMIA COMPLICATED BY PREGNANCY

Includes any blood disease or disorder with pregnancy occurring incidentally.

As a matter of interest, two additional classifications are appended, mainly of historical interest. They are an indication of the trend of haematological thought at the time they were published.

The first is that of Osler (1919) :

1. Anaemia from small repeated haemorrhage.
2. Severe anaemia of pregnancy. The cases quoted by Osler in the original publication are frequently re-quoted as cases of haemolytic anaemia of pregnancy.
3. Severe postpartum anaemia without haemorrhage.
4. Acute anaemia of postpartum sepsis.

The classification of Osler makes no attempt to explain the different types on a pathological basis; it is a purely clinical classification.

The second is that of Alder (1924) :

1. Anaemia with pregnancy
   (a) Chlorosis
   (b) Post-haemorrhagic
   (c) Congenital haemolytic icterus
   (d) True pernicious anaemia
   (e) Leukaemia
2. Anaemia due to pregnancy
   (a) Physiologic
   (b) Pernicious type. This type was regarded as an exaggeration of the physiologic anaemia, the word pernicious indicating severe.

The classification of Alder recognises the hydraemia effect and attempts to make all anaemias in pregnancy either an exaggeration of the physiologic, or coincidental with pregnancy.

SYMPTOMATOLOGY

The symptoms of anaemia of pregnancy are those common to any form of anaemia, namely, shortness of breath on exertion, swelling of ankles, faintness and giddiness, and pallor. These symptoms may appear at any stage of the pregnancy but usually are first noticed not before the sixth month.

Purpuric manifestations are described, but usually in cases in which the diagnosis of anaemia of pregnancy is in question. Retinal haemorrhages are found in the pernicious anaemia of pregnancy, but generalised purpura and haemorrhagic tendency should suggest the possibility of a blood disorder not due to pregnancy but complicated by pregnancy.

Splenomegaly of moderate degree is fairly common in either the iron deficiency anaemia or the pernicious anaemia of pregnancy. Glossitis is not infrequent. Nerve degeneration however does not occur and the presence of symptoms or signs of nerve lesion indicate a revision of the diagnosis of anaemia of pregnancy.

A peculiar "watery" complexion is common, probably due to the association of anaemia with hydraemia.

There is therefore no symptomatology specific for the anaemia of pregnancy.

ETIOLOGICAL FACTORS IN PREGNANCY ANAEMIA

ETIOLOGICAL FACTORS IN PREGNANCY ANAEMIA

Factors specially related to the iron deficiency anaemia and pernicious anaemia of pregnancy have been discussed under the headings of gastric hydrochloric acid, the effect of diet and social conditions, pre-existing anaemia, iron metabolism, and experimental work on the pernicious anaemia of pregnancy. Certain factors, more generally related to the etiology of anaemia in pregnancy, remain to be considered.

RED CELL FRAGILITY IN RELATION TO PREGNANCY ANAEMIA

Very few observations of red cell fragility in anaemia of pregnancy have been recorded. Records that are available lose much of their significance, either on account of the tests used being technically insufficiently standardised to give accurate results, or on account of the incompleteness of the other haematological investigations which have been done in each case.

Evans (1929), describing his second case which has been discussed under the heading of acute haemolytic anaemia of pregnancy, states that "haemolysis ceased at 0.5 grammes per cent sodium chloride concentration". As the patient was very anaemic, having a haemoglobin of 12 per cent, the slope of the

fragility curve would have been very flat, bringing the 50 per cent haemolysis mark well into the limits of normal. No information is given by Evans as to the point at which haemolysis commenced, so that even a rough curve cannot be constructed. The case is quoted as an example indicating the need for accurate test technique. The case of Larabee (1925) definitely had increased fragility, as haemolysis began at 0.575 and was complete at 0.400 grammes per cent sodium chloride concentration; the case, however, had all the features of an acholuric jaundice, including response to splenectomy. The case of Minot (1921) was of similar type. Stevenson (1938) stated that in the 30 cases of alleged pernicious anaemia of pregnancy described by her, the fragility was "normal in the cases examined". Witts (1932), from an analysis of cases in the literature which he accepted as cases of haemolytic anaemia of pregnancy, came to the conclusion that "fragility is usually increased as long as the foetus is in utero; after delivery, fragility returns to normal even though the anaemia persists". Whilst it cannot be agreed that the cases quoted by Witts were examples of haemolytic anaemia of pregnancy, his conclusions happen to be nearest to those of the present investigations! The fragility in the cases quoted was definitely increased, but very much more grossly than in the cases of the present series. The following table summarises Witts' quotation :

TABLE XII (Fig. 76.)

GRAMMES PER CENT NaCl CONCENTRATION	
Haemolysis commenced	Haemolysis complete
0.600	0.400
0.900	0.425
0.720	0.400
0.500	0.450
0.520	0.420
0.540	0.320

In all the examples included in Table XII, no figures are given for the postpartum reading of fragility, but they were all stated to be normal. In three other examples quoted, of cases seen postpartum, the figures given are 0.500/ ? , 0.470/0.430 and 0.600/ ? . Witts does not comment upon the fact that in the cases of Table XII the postpartum fragility was normal, whereas in these latter three, alleged to be a similar type of condition, the postpartum fragility was increased. Unfortunately, the literature from which Witts obtained his information is not available, with the exception of the two cases of Larabee and Minot, already referred to. As neither of these cases is acceptable as anaemia of pregnancy, one wonders how many of the remaining ones can be accepted. Cassells (1938) examined the fragility in various blood conditions including pregnancy. His findings

have been charted in Fig. 3. In the four cases of anaemia of pregnancy, he noted the failure of the curve of fragility to make the shift to the left that usually occurs in cases of anaemia except acholuric jaundice. Up to the time of the present investigation no series of cases of normal pregnancy had been investigated from the point of view ofthe red cell fragility.

From the literature, then, the behaviour of the red cell fragility in normal pregnancy is unknown, and its behaviour in anaemia of pregnancy has not been reliably investigated except for the series of 4 cases included in Cassells series. Witts' conclusions lose much of their significance as the diagnosis in the cases quoted is open to doubt.

The findings in the present investigation have been presented, and may be summarised as follows:

There is a tendency in anaemia of pregnancy for the fragility to remain within normal limits or even to increase slightly, even in the severest degrees of anaemia. In the majority of anaemias, except acholuric jaundice, the fragility is reduced the greater the grade of anaemia. There is a fair degree of correlation between cell thickness and median corpuscular fragility in pregnancy anaemia, but

the correlation is not of a close enough degree to exclude factors other than cell dimensions as being responsible for the alteration in fragility. There is no evidence of a persistently raised reticulocyte percentage, even in the cases with the grossest alterations in fragility, and no evidence of an increased serum bilirubin content even in the severest anaemia.

These are the facts. What is the significance of these observed facts?

The factors affecting the resistance of the red cells to haemolysis in hypotonic saline solution have been summarised by Dacie and Vaughan (1938). They are :

A. Intrinsic factors.

(a) Red cell dimensions. Haden (1934) originally suggested that red cell fragility varied proportionately with the red cell thickness. Thick red cells, known as spherocytes, are more fragile than thin red cells. A red cell placed in hypotonic saline solution assumes a spherical shape before it bursts. The spherical shape of a thick red cell puts it nearer the bursting point. Vaughan (1937) confirmed Haden's views. The present investigation has shown that in anaemia of pregnancy there is some correlation between the cell thickness and the fragility (Fig. 28) but as the correlation is not close there must be other factors concerned.

(b) Chemical composition of cell and membrane. Erickson, Williams, Hummel, Lee and Macy (1937) and Williams, Erickson, Bernstein, Hummel and Macy (1937) found no relation between the protein content of the red cell and its fragility. Dacie and Vaughan (1938) and others have found no correlation between haemoglobin content and fragility. Studying the chemistry of the red cell membrane, Erickson et al found no relation between fragility and phospholipoid-cholesterol ratio. These negative finds are of interest, but cannot be interpreted as excluding the factor of the composition of the red cell in the problem of its fragility.

B. Extrinsic factors.

These include any physico-chemical process affecting the ionic content of the cell.

(a) The chemistry of the blood plasma. Clearly, alterations in the constitution of the blood plasma may affect the constitution of the red cell. In normal pregnancy, various alterations occur in the plasma. The serum protein at term has been shown to be about 7 per cent below the level of the first trimester, the range of fall being 0.3 to 15 per cent (Dieckmann and Wegner, 1934d). There is a still further decrease for the first few days postpartum, after which it returns to normal. The total serum protein increases, being

about 18 per cent over normal at term. Dieckmann and Wegner point out that the fall in protein percentage cannot be solely accounted for by simple dilution, since the total protein is increased. They suggested certain intrinsic changes in the protein during pregnancy. Sure, Kik and Walker (1929) and Van Donk et al (1934) have shown the fall in percentage protein during pregnancy in the rat.

The relationship of fragility to the serum protein level is difficult to assess. The weight of evidence is against there being any relation, as it is known that gross changes in the serum protein need not be associated with changes in fragility. Unless the serum protein in pregnancy undergoes some peculiar change, as yet unknown, it is improbably that the alterations in serum protein level in pregnancy have anything to do with the red cell fragility.

The fibrin content per cent of the blood increases considerably during pregnancy, reaching a maximum of about 40 per cent above normal at term, and a little higher for a week or two postpartum (Dieckmann and Wegner, 1934d). As it remains high after parturition for a much longer period than the fragility remains shifted, it is unlikely to influence the fragility.

The cholesterol content of the blood during pregnancy increases, the increase varying in degree from case to case

and at different times in the same case (Dieckmann and Wegner, 1934f). There is no evidence available to indicate the behaviour of the fragility in other conditions in which the blood cholesterol is raised. The relationship of cholesterol content to fragility must remain unsettled on the present evidence.

(b) Oxygen and carbon dioxide content of the blood. It has been demonstrated that the fragility increases as the carbon dioxide content increases, and diminishes as the oxygen content increases (Dacie and Vaughan, 1938). It is known that in pregnancy the carbon dioxide content is decreased (Dieckmann and Wegner, 1934e) but this is of no significance, as with the technique used for testing fragility, the blood is fully oxygenated before the test.

(c) Temperature of haemolytic solution. As the temperature is standardised during the test, this can have no influence in the test.

(d) Hydrogen ion concentration. The pH of the blood in pregnancy remains unchanged (Dieckmann and Wegner, 1934e). It can play no part in the changes in fragility.

(e) Degree of anaemia. In the description of the technique of the fragility test used in this investigation,

the effect of a reduction in the volume of packed red cells on the red cell fragility was discussed. The smaller the volume of packed cells, the more electroyte is added to the haemolytic system with each drop of blood. This is partly responsible for the shift to the left of the fragility curve that occurs in most cases of anaemia. Is it possible that the slight alterations in electrolyte content that occur in pregnancy, and the blood diluting effect of the hydraemia of pregnancy (which is very variable in amount in different cases), are responsible for the different behaviour of the red cells of anaemia or pregnancy from other types of anaemia? There are so many variables to be considered in a discussion of such a question that without investigating these variables individually in a series of cases, no answer can be given. One factor which can be discussed fully is the electrolyte content.

(f) Electrolyte content of the plasma. The total electrolyte content can be determined by estimation of the conductivity of the serum. The conductivity is expressed in terms of sodium chloride concentration per cent. The average normal value for non-pregnant women is 0.800 grammes per cent. This does not mean that there is 0.800 grammes per cent sodium chloride. Of this amount, 0.550 to 0.650 grammes per cent is actually sodium chloride, the balance being

other salts. As all the electrolytes together are concerned in the ionic balance between the plasma and the red cells, they are also to be considered as a whole in considerations of the resistance of the red cells to hypotonic solutions of salt. The total electrolyte content of the plasma in pregnancy has been estimated by determination of the conductivity by Dieckmann and Wegner (1934e) who found that the mean value for 52 estimations from the 36th week to full term was 0.771. grammes per cent sodium chloride with a range of 0.750 to 0.795. The actual sodium chloride percentage of the plasma is unchanged from normal during pregnancy, so that the fall from 0.800 in non-pregnant states to 0.771 mean value in pregnancy indicates a fall in electrolytes other than sodium chloride.

Can this fall in total electrolyte, from the equivalent of 0.800 grammes per cent sodium chloride in the non-pregnant state to 0.771 grammes per cent in the pregnant state account for the behaviour of the red cell fragility in cases of anaemia of pregnancy? Will the smaller amount of electrolyte present in a drop of blood from a pregnant woman affect the result of the test to any appreciable degree? These questions can be answered mathematically, the answers to both being in the negative. The calculation is as follows:

The drop of blood added to each saline dilution in the test is dropped from a standard pipette dropping 22 drops to the cc. The volume of one drop is therefore approximately 0.05 cc. The effect of the electrolyte content in the case of (a) mild anaemia and (b) of severe anaemia requires to be known.

(a) Volume of packed red cells 35 per cent, that is, a case of mild anaemia if from a non-pregnant woman, but actually normal for pregnancy. 0.05 cc of blood contains 65/100 x 0.05 cc plasma, that is, 0.0325 cc. The total electrolyte in this amount of plasma for (1) the non-pregnant state is $\frac{0.800 \times 0.0325}{100}$ grammes = 0.0002600 = 0.260 mg, and (2) for the pregnant state is $\frac{0.771 \times 0.0325}{100}$ grammes = 0.000251 = 0.251 mg.

(b) Volume of packed red cells 20 per cent, that is, a case of severe anaemia from either a pregnant or a non-pregnant woman. 0.05 cc of blood contains 80/100 x 0.05 cc plasma, that is, 0.04 cc. The total electrolyte in this amount of plasma for (1) the non-pregnant state is $\frac{0.800 \times 0.04}{100}$ grammes = 0.320 mg, and (2) for the pregnant state is $\frac{0.771 \times 0.04}{100}$ = 0.308 mg.

In carrying out the fragility test, one cc of each saline dilution is used. The effect of one drop of blood can readily be estimated. Consider, for example, the effect

on the tube containing a sodium chloride concentration of 0.400 grammes per cent.

In 1 cc of this concentration, there is 0.004 grammes of sodium chloride. To this is added (1) a drop of non-pregnancy blood with a volume of packed red cells of 35 per cent; this drop has been shown to contain 0.00026 grammes NaCl; the mixture of saline and blood now has a sodium chloride content of 0.004 + 0.00026 = 0.00426 grammes in 1.05 cc of fluid, which can be calculated to be a concentration of 0.406 grammes NaCl per cent, (2) a drop of pregnancy blood with a volume of packed red cells of 35 per cent; this drop contains 0.000251 grammes NaCl; the mixture of saline and blood now has a sodium chloride content of 0.004 + 0.000251 = 0.004251 grammes in 1.05 cc of fluid, which can be calculated to be a concentration of 0.405 grammes NaCl per cent, (3) a drop of non-pregnancy blood with a volume of packed red cells of 20 per cent; this drop contains 0.00032 grammes NaCl; the mixture of saline and blood now has a sodium chloride content of 0.004 + 0.00032 = 0.00432 grammes in 1.05 cc fluid, which can be calculated to be a concentration of 0.411 grammes NaCl per cent, and (4) a drop of pregnancy blood with a volume of packed red cells of 20 per cent; this drop contains 0.000308 grammes sodium chloride; the mixture of saline and blood now has a sodium chloride content of 0.004 + 0.000308 = 0.004308 grammes in 1.05 cc of fluid, which can be calculated to be a

concentration of 0.410 grammes NaCl per cent.

Therefore the greatest difference possible, for mild or severe anaemia, in the electrolyte concentration of the mixture of saline and blood, for pregnancy and non-pregnancy blood is 0.001 grammes per cent, provided the volume of packed red cells is equal in each case. This difference is insignificant. It has been demonstrated that the median corpuscular fragility in cases of pregnancy anaemia is very much more than 0.001 grammes NaCl per cent greater than other types of anaemia with equivalent volume of packed red cells. The procedure of "correction for anaemia" described in the technique of the fragility test reduces the volume of packed red cells to a common figure.

It is therefore apparent that the reduction in electrolyte content of the plasma during pregnancy is not the factor which is responsible for the failure of the fragility curve to "shift to the left" in pregnancy anaemia, as it does in other types of anaemia except acholuric jaundice.

As a corollary to this conclusion, it can be stated that the dilution of theblood due to hydraemia of pregnancy is not responsible for the behaviour of the fragility in cases of pregnancy anaemia, since the only probable way in

which dilution would affect the test would be by reduction in the percentage of electrolyte in the plasma.

C. Haemolysins

Circulating haemolysins have been demonstrated as causes of haemolytic anaemia. Damashek and Schwartz (1938) showed them to be present in three cases of acute haemolytic anaemia, and Damashek, Schwartz and Gross (1938) produced all the features of haemolytic anaemia, including the spherocytosis, by injecting haemolytic serum into guinea pigs. The primary factor, in their opinion, was the circulating haemolysin, and the observed changes in the blood picture were all secondary, including the spherocytosis.

In the case of pregnancy, it was suggested in 1908 by Hofbauer that anaemia occurring during pregnancy was due to a circulating "syncytial" haemolysin. Whilst such a theory is very difficult to disprove, it is highly improbable that such a haemolysin, or any other sort of haemolysin, is responsible.

The apparent implication of the behaviour of the fragility in anaemia of pregnancy is that there may be a factor of haemolysis responsible. For various reasons, this is unlikely. In the cases under investigation, the

reticulocyte percentage was never raised above normal save for the occasions when a crisis occurred after some form of treatment had been instituted; had active haemolysis been responsiblefor the anaemia, a raised reticulocyte count would have been expected, especially in the more severely anaemic cases, and especially in those with a fragility to the right of normal. The normal level of plasma bilirubin in all the cases under investigation is no argument against there being a haemolytic factor. A normal liver is well able, by its excretory function, to maintain the level of bilirubin in the blood at normal in the face of considerable haemolysis. If intravascular haemolysis, due either to a circulating haemolysis or to some abnormality of the red cell, were a usual phenomenon in pregnancy, then frank cases of haemolytic anaemia would occur with fair frequency. It has been argued that it is very doubtful whether there is such an entity as haemolytic anaemia of pregnancy.

THE CONCLUSIONS regarding the observed facts of the behaviour of the red cell fragility in pregnancy, namely, the increase sometimes noted in cases of anaemia, or at least the failure of the curve to "shift to the left", does not imply intravascular haemolysis. The cause of the peculiar behaviour of the fragility is unknown, but may be due to changes in the red cell membrane or to physico-chemical alterations in theblood plasma during pregnancy. The blood

diluting effect of the hydraemia of pregnancy is probably not the reason for the fragility changes, nor is the lowered electrolyte content of the plasma in pregnancy responsible.

Further investigation of haemoglobin metabolism in normal pregnancy and in anaemia of pregnancy of various types is necessary. In particular, the study of the faecal and urinary urobilin excretion would give valuable information regarding the anaemias of pregnancy.

THE INFLUENCE OF PARITY AND AGE

There is insufficient material in the present investigation to form any opinion on the influence of parity and age on pregnancy anaemia.

The reports in the literature generally do not favour parity as affecting the incidence of anaemia of pregnancy. Davidson, Fullerton and Campbell (1935), Fullerton (1936a), Reid and Mackintosh (1937b), Boycott (1936), Moore (1930), Galloway (1929) and Mackay (1931), in analysing large series of cases are of this opinion. Gottlieb and Goodall (1936), however, investigating 200 cases gave the opinion that hypochromic anaemia occurred especially in multipara with rapidly succeeding pregnancies. Linder and Massey (1939) found a slightly lowered average haemoglobin per cent in the multiparous than the less multiparous groups of their series.

There are very few reports on the effect of age. Fullerton (1936a) showed graphically that the degree of anaemia is greater in pregnancy occurring in the later years of child bearing life, but at the same time he showed that age for age, the degree of anaemia amongst the non-pregnant women of the same area became greater towards the menopause andthen lessened after the menopause (Fig. 56) The general opinion is that age itself has no bearing on the degree of anaemia.

TOXAEMIA OF PREGNANCY AND ANAEMIA

The more reliable investigations do not favour any relationship between toxaemia and anaemia. Adair et al (1936), Boycott (1936) Reid and Mackintosh (1937b) in large surveys found no relationship. The observations of Linder and Massey (1939) of the haemoglobin per cent of pregnant women in Cape Town showed a grand mean of 12.4 grammes per cent amongst 213 European and Coloured women. The average for the Coloured was very slightly less than the average for the European. This very good haemoglobin is surprising considering the poor social conditions under which the patients lived, and is interesting because it is the haemoglobin per cent level of a group of women with an extremely high incidence of toxaemia of pregnancy.

Moore and Pillman-Williams (1936), Moore (1929, 1930),

and O'Sullivan (1932) thought there was some relationship between toxaemia and anaemia, but their series of cases were unsatisfactorily controlled.

There is therefore no reason to consider that there is any relationship between toxaemia and anaemia of pregnancy.

GENERAL INCIDENCE OF ANAEMIA OF PREGNANCY

Boycott (1936) has summarised the results of surveys of haemoglobin percentage estimations on pregnant women for different parts of the world. The series of Davidson, Fullerton and Campbell (1935) from Aberdeen, of Galloway (1929), Lyon (1929), Bland et al (1930a, 1930b), Richter et al (1934), Adair et al (1936), Labate (1939), Watson (1938) and Kerwin and Collins (1926) from the United States, of Stevenson (1938) from Edinburgh, of Boycott (1936), Reid and Mackintosh (1937a), Mackay (1935), Evans (1929) from London, McGeorge (1935) from New Zealand, and Linder and Massey (1939) from Cape Town have been referred to and indicate an incidence of anaemia, that is an incidence of haemoglobin percentage below 70 to 75 Haldane, varying between 10 and 60 per cent for the different series. Social conditions to a certain extent affect the incidence. The indidence in Aberdeen is greater than the incidence in London. Cape Town, with an average haemoglobin of 12.4

grammes per cent, is better than figures from Great Britain and from many parts of the United States, in spite of the fact that the investigation was of a very poor community. New Zealand, with 16 per cent of the 100 cases below 75 per cent, was better than most European figures.

Many of the results are fallacious. Pohl (1928) reported an incidence of severe anaemia of 22 cases in 14,400 deliveries in Zurich, Beckmann (1921) an incidence of 6 severe anaemias in 60,000 deliveries in Vienna; Evans (1929) no cases in 4083 deliveries at Queen Charlotte's Hospital, London. In each of these reports, it is certain that many cases were not diagnosed, as the diagnosis depended on the anaemic appearance of the patient, there being no routine haemoglobin estimation in the series.

Additional reports, not referred to previously in this investigation, are those of Jerlov (1927) from Denmark with 24 per cent of 1143 women having a haemoglobin under 70 per cent, Schultz (1933) with 3 per cent of 567 women anaemic in a middle class German population, and Adamson and Smith (1935) from Canada with 20 per cent of 116 cases under 74 per cent haemoglobin.

Detailed analysis of all these reports serves no useful purpose, except to indicate that the haemoglobin

level is lowered in pregnancy, and that the grade of lowering varies in different communities and different countries. Exact comparisons are made difficult on account of the different methods of haemoglobin estimation; many of the series do not state the class of patient investigated, or if they do, no idea is given as to the standard of living amongst them.

THE INFLUENCE OF ANAEMIA OF PREGNANCY ON MATERNAL AND INFANTILE HEALTH

The majority of investigations into the effect of anaemia of pregnancy on the health of the mother and infant have been concerned either with iron deficiency anaemias only, or with large groups of cases in which iron deficiency anaemias predominate. The effect of macrocytic or pernicious anaemia of pregnancy has been very incompletely investigated and will be discussed in a separate section.

MATERNAL EFFECTS

MORTALITY FROM ANAEMIA. Isolated reports of death apparently due to anaemia of pregnancy appear from time to time. Large scale investigations have been carried out which tend to indicate a very low mortality. Douglas and McKinlay (1935) in an analysis of figures from Scotland for the years 1928 to 1932 found 19 out of 2527 maternal deaths ascribed to anaemia. They were of opinion that very few of these 19 deaths appeared on the evidence to be actually due to anaemia. Reid and Mackintosh (1937b) found no greater mortality amongst anaemic than amongst normal pregnant women in London.

MORBIDITY RATE. The evidence indicates that there is

possibly a higher incidence of puerperal sepsis amongst women who were anaemic during pregnancy. Reid and Mackintosh (1937b) followed up 1094 cases, some anaemic, some not, and were very dubious about there being any difference between the two groups. Labate (1939) gave a morbidity rate of 15 per cent amongst women treated with iron during pregnancy, and of 20 per cent amongst an untreated series. His criteria of morbidity were unusually strict, but were the same for the two series, and therefore his argument is valid that the incidence of sepsis is not much increased by anaemia. Mackay (1935) thought there may be a slightly greater incidence of puerperal sepsis amongst the anaemic group.

POSTPARTUM HAEMORRHAGE. There is no evidence to indicate that the incidence of postpartum haemorrhage is greater amongst anaemic pregnant women. Fullerton (1936b) is definitely of this opinion. In the present series, one case had severe postpartum haemorrhage although not severely anaemic during pregnancy. None of the severely anaemic cases lost morethan the usual amount of blood at delivery. Reid and Mackintosh (1937b) concur.

POSTPARTUM ANAEMIA. This subject has been fully discussed under the heading of "pre-existing" anaemia.

FOETAL EFFECTS

Reid and Mackintosh (1937b) noted a slightly higher still birth rate amongst the anaemic than amongst the non-anaemic group. King (1929) noted that in hookworm anaemia the incidence of abortions increased. Otherwise there are no references based on observed facts to foetal death rate. The general opinion is that the effect is very slight.

INFANTILE EFFECT

THE BLOOD PICTURE

Clinical investigation of theblood of infants born of anaemic mothers shows that as a rule theblood is normal at birth, but that anaemia developes within a few months of birth.

Strauss (1933, 1935) examined the blood of infants born of three groups of mothers, a group of 6 with no anaemia the haemoglobin being 70 per cent at term, a group of 6 with anaemia untreated until after parturition with haemoglobin under 45 per cent at term, and a group of 3 with an average haemoglobin of 35 per cent at the end of the second trimester when treatment was instituted to raise the haemoglobin at term to an average of 66 per cent.

In the second group, iron treatment was continued through the lactating period. In each group (Fig. 77) the blood of the infants at 48 hours was normal. At one year, the blood of the first group was normal, of the second group averaged only 40 per cent haemoglobin, and of the third group was normal. Strauss considered it unlikely that the

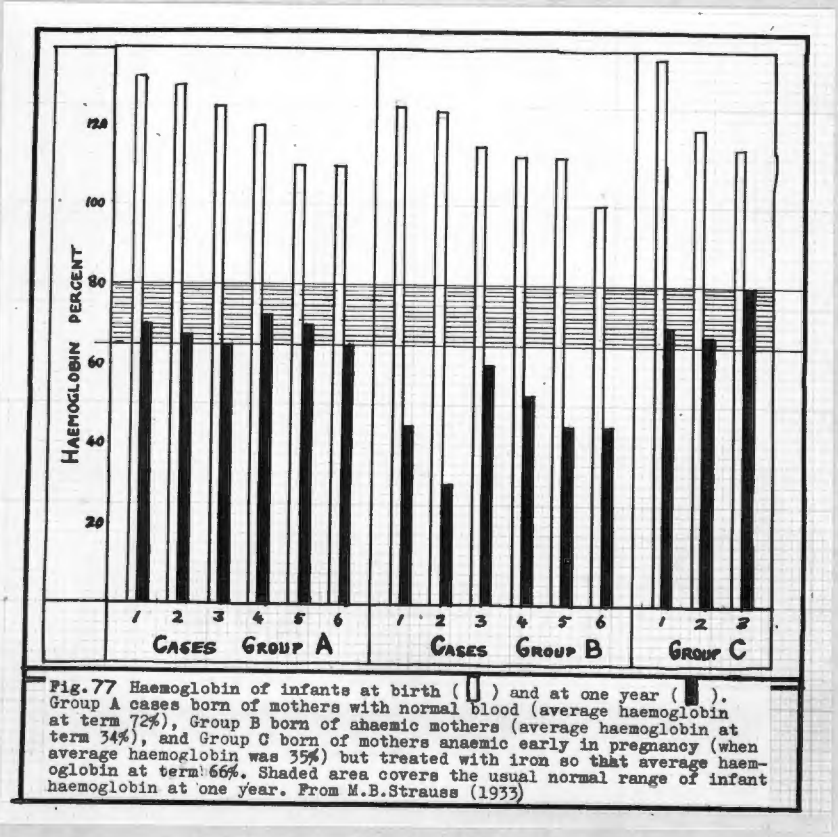


Fig. 77 Haemoglobin of infants at birth (▯) and at one year (▮). Group A cases born of mothers with normal blood (average haemoglobin at term 72%), Group B born of ahaemic mothers (average haemoglobin at term 34%), and Group C born of mothers anaemic early in pregnancy (when average haemoglobin was 35%) but treated with iron so that average haemoglobin at term 66%. Shaded area covers the usual normal range of infant haemoglobin at one year. From M.B.Strauss (1933)

Fig. 77.

anaemia was due to a congenital weakness of the haemopoietic system as suggested by Parsons (1932) because it is preventable andtreatable; nor was it due to iron poor

milk because the mothers were taking adequate iron during the lactating period. Strauss was of opinion that the anaemia was due to deficient iron storage in the foetal liver. This postulation of a liver with deficient iron store is confirmed by direct investigation. Toverud (1935) found that the iron content of livers of infants dying soon after birth and born of anaemic mothers was moderately decreased in 8 of 12 cases examined. He had no control series of findings in cases born of non-anaemic mothers. Alt (1938), experimenting on rats, studied the newborn rats of mothers made anaemic by iron poor diet. The newborn rats showed various grades of effect. If the deprivation of iron to the mother had not been too strict, the newborn haemoglobin percentage was normal, but the liver stores were reduced; more complete deprivation of iron resulted in a reduction of haemoglobin percentage and a greater reduction in foetal liver iron storage. The second litter newborns showed similar but grosser effects. Many of the anaemic newborns died, but of those that lived, the haemoglobin was near normal in 3 or 4 weeks time. Alt's work demonstrates thereforethat reduction of foetal liver iron stores precedes the development of anaemia. More indirect evidence of the effect on the infant of deficient iron storage is the observation of Abt and Nagel (1932) that premature infants regularly become anaemic at 3 to 4 months of age; it is a likely probability that as

the foetal iron stores are laid down mainly in the last month or two (Hugonenq, 1899) the premature infant is born with less iron stored in its liver than the full-term infant and therefore becomes anaemic later.

Mackay (1931) investigated 1090 infants and 168 mothers in the East Endof London and considered it probable that immaturity and maternal anaemia predisposed to anaemia in the infant. She should find no proof that administration of iron to the mother would prevent the development of anaemia in the infant, but admitted that her series was too small and that the iron was taken irregularly and in too small dosage. 9 grains of iron and ammonium citrateto the infant daily cured the anaemia. Mackay drew attention to an important practical point of technique; the ear blood of an infant might have an haemoglobin percentage 5 to 24 per cent (average 10 per cent) higher than the heel blood, this being the finding of Drucker (1923) as well. Drucker found the ear blood might be minus 3 to plus 32 per cent different from the heel blood. Parsons (1932, 1936) argues that the haemoglobin at birth, whilst usually normal in the case of infants born of anaemic mothers, may in extreme cases of iron deficiency anaemia of the mother, be low at birth. He agrees that the delayed appearance of the anaemia in the infant is therule. Gottlieb and Strean (1939) examined

the blood of 50 infants born of mothers untreated with iron, and of 50 infants born of mothers treated with iron. At birth, the haemoglobin of the two groups was 120 and 110 per cent respectively, and at 32 weeks 51 and 82 per cent respectively, thus confirming the results of Strauss with work on a larger scale. Smallwood (1936) confirmed the general view.

Fullerton (1937), on the other hand, found no relationship between the degree of maternal and infantile anaemia, but his conclusions have never been confirmed.

MORTALITY AND MORBIDITY.

Mackay (1931) found that in her series, cure of the infantile anaemia with administration of iron reduced the morbidity rate and improved growth. Reid and Mackintosh (1937b) found a definitely higher morbidity and mortality amongst the anaemic infants than amongst the non-anaemic ones.

SUMMARY OF MORBID INFLUENCE OF PREGNANCY HYPOCHROMIC ANAEMIA

Maternal mortality is probably not increased.

Maternal morbidity (puerperal sepsis) rate is very slightly higher than in the non-anaemic group.

Complications of labour are not increased.

Still-birth rate may be slightly increased.

Infants born of even the most severely anaemic mothers are rarely if ever anaemic at birth, but develope anaemia, probably due to deficient iron storage in the foetal liver, during the first year of life. This anaemia is preventable by treating the mother with iron.

Infants born of anaemic mothers definitely have a higher morbidity and mortality rate during the first year than infants born of non-anaemic mothers. The infantile anaemia is treatable with iron.

INFLUENCE OF PERNICIOUS ANAEMIA OF PREGNANCY.

Discussion on the effect of maternal pregnancy anaemia of pernicious type on the infant must necessarily be speculative, as the facts on which to base a discussion are scanty.

Ritter and Crocker (1939) describe a case of pregnancy anaemia which could possible be accepted as a case of macrocytic anaemia of pregnancy, and which responded temporarily during pregnancy to liver injection treatment. Haemoglobin at 6 months was 20 per cent, colour index

constantly 1.05 to 1.3. A full term infant was born, with the mother still moderately anaemic, and at 2 weeks of age the haemoglobin of the infant was 2 0 per cent, red cells 0.96 million, colour index 1.0; at 4 months, having had continuous liver treatment, unfortunately uncontrolled with reticulocyte counts, haemoglobin 78 per cent red cells 3.77 million. The case was very incompletely investigated, but it does suggest the possibility that infants born of mothers suffering from macrocytic anaemia are anaemic at birth. No other cases can be found in the literature in which the state of theblood of the infant has been observed, the mother having had the pernicious type of anaemia of pregnancy. It would be absurd to come to any definite conclusions on the observation of a single case, and that one doubtful.

The interest of the problem of the effect on the infant's blood in the case of pernicious anaemia of pregnancy centres around the ability of the foetus to manufacture its own P-A factor. Experimental work on this subject is confusing. Wintrobe, Kinsey, Blount and Trager (1937) found that pig foetal liver, at all stages of development, was of no value in the treatment of Addisonian pernicious anaemia. Goldhamer, Isaacs and Sturgis (1934) found that human foetal liver at 8 months gave a slight reticulocyte response when given to a case of pernicious

anaemia. Foetal bovine liver has been variously shown to be ineffective (Berglund, Watkins and Johnson, 1927) weakly effective (Bence, 1933), or nearly as effective as adult liver (Wigodsky, Richter and Ivy, 1939). The trend of evidence, however, is against the normal foetus being able to make its own P-A factor, at least in any quantity. If P-A factor is necessary for foetal haematopoiesis, then, seeing that the foetus normally has no stores of the factor, it must be entirely dependent on the mother for its supply of the factor; as the factor is lacking in the mother, it must also be lacking in the foetus and it is natural to expect that the infant would be born anaemic.

The problem must remain unsettled until further investigated.

GENERAL SUMMARY AND CONCLUSIONS

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RESULTS AND CONCLUSIONS FROM PRESENT INVESTIGATION

GENERAL OUTLINE

The object of this investigation was to study in detail certain haematological characteristics in normal pregnancy, and to compare with these standards the findings in anaemia of pregnancy.

The haematological character specially to be studied was the fragility of the red cell. Fragility of the red cell envolves a knowledge of the cell size. Therefore full haematological investigation was carried out in each case.

The haematological course through pregnancy and in many cases into the puerperium was followed, and detailed study of response to treatment made.

From the findings, the need for re-classification of the anaemias of pregnancy was seen to be apparent, and suggestions have been made for the necessary modification of the classification.

SELECTION OF CASES

Cases were arbitrarily selected as "normal" or "anaemic" according as the haemoglobin was above or below 80 per cent Haldane. No case with symptoms or signs that could not be explained by pregnancy or anaemia was accepted. The investigation showed that in pregnancy no arbitrary standards can be laid down, each case having to be decided on its merits.

HAEMATOLOGICAL FINDINGS

A. NORMAL GROUP (20 CASES).

Haemoglobin and red cells were within the normal limits for the non-pregnant state.

Mean corpuscular volume was normal with one exception. The readings fell between 73 and 88 cu.mu, the exception being 62 cu.mu.

Median corpuscular fragility was normal, with slight tendency to "shift to the left" after parturition.

Mean cell diameter in the 14 cases tested was within normal limits, the readings being 6.7 to 7.7 mu.

Variability per cent and standard deviation were above normal in nearly half the cases. In some instances this was apparently the effect of recently administered iron, but in others appeared to be a natural feature of the blood picture in pregnancy.

Colour index was below the accepted normal of 0.9 to 1.05 in several cases.

It is suggested that cases with low colour index and greater than normal degree of anisocytosis as expressed by variability and standard deviation are not physiological in spite of their having haemoglobin percentages which are within the normal range.

B. ANAEMIC GROUP (28 CASES).

No cases of macrocytic anaemia were found. The observations and remarks now given are almost without exception concerned with the iron deficiency type of anaemia.

According to the haemoglobin level, the majority were only moderately anaemic with haemoglobin between 60 and 76 per cent. A number had haemoglobin below 60 per cent, the lowest being 32 per cent.

The colour index was low in the majority, but 12 of the less anaemic cases, with haemoglobin over 60 per cent, had colour index of 0.9 to 1.0.

Mean corpuscular volume was 58 to 98 cu.mu, with the majority below 80 cu.mu.

Mean corpuscular diameter in 6 out of 18 measured was below 6.76 mu.

Variability per cent and standard deviation were above normal in most instances, but in some of the less anaemic

cases were within normal limits. In one case, variability and standard deviation were normal with a haemoglobin of 65 per cent, and colour index of 0.9.

It is suggested that cases with haemoglobin lower than accepted normal may not be truly anaemic if their colour index and variability and standard deviation are normal. Such low haemoglobin percentages may be the result of hydraemia.

Median corpuscular fragility and its relationship to pregnancy anaemia has received special attention in this investigation. From the literature, it has been seen that very little reliable information can be obtained, due either to the coarseness of the technique of thetests used, or to the serious doubts that have to be expressed of the diagnosis of the anaemia being due to the pregnancy. This investigation has shown that even in cases of severe anaemia of pregnancy there is a failure of the median corpuscular fragility and the fragility curve to "shift to the left" as happens in most anaemias except acholuric jaundice. There is a tendency to shift to the left after parturition. In some cases there is actually during pregnancy an increase in fragility to beyond normal limits. There is a rough correlation between MCF and MCT/MCD ratio, but not close enough to exclude factors other than red cell dimensions as being responsible for the peculiar behaviour

of the fragility.

The cause of the behaviour of the fragility has clearly been shown not to be the lowering of electrolyte percentage that occurs during pregnancy. Quantitative changes in the plasma protein, fibrin and cholesterol cannot be excluded but are improbable factors. By indirect argument, the change in fragility is probably not due to the dilution of the blood by hydraemia of pregnancy. It is speculative to suggest that physico-chemical changes in the constitution of the red cell are responsible. It must be admitted that the cause of the phenomenon is unknown.

The significance is uncertain. There is no evidence to justify it as indicating intravascular haemolysis, as even in those cases in which there was an actual increase in fragility, the reticulocyte counts were normal apart from the rises following one or other form of treatment.

Investigation of the faecal and urinary urobilin excretion should help in solving the problem of the cause of the alteration in fragility.

FOLLOW-UP RECORDS

The existence of an iron deficiency anaemia occurring

during pregnancy is confirmed. The condition is as a rule diagnosable on the blood picture and on the response to treatment.

The trend in most cases of pregnancy for the haemoglobin percentage and the red cell count to fall as pregnancy advances is confirmed, but in some cases spontaneous rise of haemoglobin occurs. This spontaneous rise may be differentiated from the rise due to iron treatment by the absence of reticulocyte crises.

Postpartum anaemia does not necessarily result if iron is not given during pregnancy to anaemic cases. Nevertheless, the evidence of this investigation strongly favours administration of iron in any anaemic or doubtfully anaemic case with a blood picture compatible with an iron deficiency anaemia.

The severest anaemia need not have a complicated delivery. In particular, anaemia does not predispose to postpartum haemorrhage.

Spontaneous postpartum improvement in the blood picture is the rule. This improvement is probably speeded up in anaemic cases by the administration of iron postpartum.

No examples of macrocytic anaemia were found in this series. It is not surprising therefore that liver treatment in the few cases in which it was used was ineffective.

The investigation does however include cases which do not conform to the characters of either iron deficiency or macrocytic anaemia of pregnancy in one or more features. A plea is made to name these "unclassified" or other such non-committal title until more is known of them, rather than name them "hypoplastic" or "haemolytic". A name such as haemolytic which has a particular haematological definition should not be applied to conditions which differ in any one feature from that definition.

The safety and value of large volume blood transfusions is demonstrated.

NORMAL STANDARDS

Information regarding normal haematological standards for pregnancy has had to be gained from the literature, as the series of 20 cases studied is too small to give any significant results.

Haemoglobin percentage and red cell count usually fall during pregnancy due chiefly to the physiological

increase in blood volume that occurs in the majority of cases. The average increase of blood volume amounts to 25 per cent over normal, but an appreciable number of cases show very little if any rise. Therefore the blood diluting effect of the hydraemia of pregnancy must vary considerably from case to case. The haemoglobin and red cell count fall as a rule 10 to 15 per cent during pregnancy, whether the pre-pregnancy levels were normal or not. There appears to be some inverse correlation between haemoglobin percentage and degree of increase of blood volume in the few series investigated, but the correlation has many exceptions. The lowest acceptable value for normal haemoglobin in pregnancy is 70 per cent Haldane, although many observers consider that this figure is too low. The lowest acceptable red cell count is 3.3 to 3.4 million per cu.mm; it is important that the fall in red cells should be proportionate to the fall in haemoglobin, the colour index remaining near unity.

The volume of packed red cells decreases to a minimum normal value of 32 per cent. The mean corpuscular volume may increase up to a maximum of 100 cu.mu.

The reticulocytes, according to most observers, remain normal, but there is some difference of opinion on this point, and the matter requires further investigation. The plasma bilirubin remains normal.

The little investigation that has been done on the red cell diameters in normal pregnancy tends to confirm the observation that a raised variability per cent and a raised standard deviation indicate a non-physiological condition, even though the mean cell diameter be normal. Similarly, the trend of opinion is that the colour index should be normal. These conclusions are open to criticism.

The median corpuscular fragility in normal pregnancy has not previously been investigated. Hence no additional observations are available.

The conclusions regarding the blood picture in pregnancy arethat many features have to betaken into consideration before the blood can be stated to be normal or abnormal. A case with a haemoglobin of 70 per cent, a colour index of 1.0, MCD 7.1 mu, variability and standard deviation normal, is probably the result of blood dilution by an abnormal grade of hydraemia. A case with a higher haemoglobin but with colour index low, and an increased variability and standard deviation may be anaemic.

CLASSIFICATION OF ANAEMIA OCCURRING DURING PREGNANCY

On the evidence afforded by the literature and by

the present investigation, the following classification of anaemia occurring during pregnancy is suggested.

1. PHYSIOLOGIC ANAEMIA OF PREGNANCY

The fall of haemoglobin percentage and red cell count that occurs in normal pregnancy is called the physiologic anaemia of pregnancy. A normal initial blood count should be postulated. The cause of the fall is mainly the increase in blood volume, but another factor is the demand of the foetus for iron, greatest during the last trimester. Attention has already been drawn to the need for the colour index, M.C.D, variability and standard deviation to be normal.

2. DEFICIENCY ANAEMIAS OF PREGNANCY

A. IRON DEFICIENCY ANAEMIA

There is general agreement on the existence of an iron deficiency anaemia which occurs with fair frequency in pregnancy. It may be mild or severe, is identical in haematological characters with any other form of iron deficiency anaemia, and responds to iron treatment with characteristic reticulocyte crisis and temporary increase in anisocytosis. The rise of haemoglobin percentage that follows the administration of iron need not necessarily be due to the iron, as an appreciable number of cases show a

spontaneous rise of haemoglobin as pregnancy advances. Adequate dosage of iron is essential. Iron and ammonium citrate 90 grains daily, ferrous sulphate 9 to 15 grains daily, Blaud's pill 45 grains daily are adequate doses. Ferrous sulphate is said to cause less gastro-intestinal upset than the other forms of iron. In all these particulars, the description is that of any form of iron deficiency anaemia.

The anaemia has been shown to be more than a simple aggravation by the hydraemia of pregnancy of a pre-existing anaemia. Known factors conditioning the development of an iron deficiency anaemia in pregnancy are the temporary reduction in gastric hydrochloric acid that is known to take place in most cases, and which reduces the absorption of haemopoietic material; and a diet with iron content adequate to maintain the blood at normal levels apart from pregnancy but inadequate during pregnancy on account of the reduced absorption from the intestinal tract and the demands of the foetus. Iron metabolism studies prove the increased iron requirements during pregnancy. Social conditions are a factor in the production of this type of anaemia of pregnancy probably on account of the poor diet that goes with poor social conditions. Poor social conditions are not necessarily a concomitant of a low haemoglobin level amongst a population,

as shown by the satisfactory average haemoglobin level of poor class pregnant women in Cape Town.

B. MACROCYTIC OR PERNICIOUS ANAEMIA OF PREGNANCY

No examples of this type are included in the present investigation.

This type has been proved as a clinical entity but is rare. The characters must conform to those of a macrocytic anaemia, although the macrocytosis is usually less than in the case of true pernicious anaemia. No case should be accepted without either mean corpuscular volume or mean cell diameter readings. The observation of a few macrocytes in a blood film does not justify the diagnosis of a macrocytic anaemia. As a diagnostic point, the blood must respond to liver administration, and the reticulocyte response should be demonstrated. The lack may apparently be of either intrinsic or extrinsic factor.

Following parturition the intrinsic factor returns. There is some difference of opinion as to how long the return may be delayed. If P-A factor has to be administered permanently after parturition, the case cannot be accepted as one of pernicious anaemia of pregnancy. It is obviously important to follow up the case for an adequate period after

the blood has returned to normal after parturition, in order to rule out the possibility of the improvement post-partum being a spontaneous fluctuation of a true pernicious anaemia. This is the only type of anaemia of pregnancy that is known to respond to liver treatment.

C. MIXED IRON DEFICIENCY AND PERNICIOUS ANAEMIA

This type of anaemia has been shown to exist, and its treatment is with iron and liver.

3. UNPROVEN GROUP

The "unproven" group includes cases which are still regarded as clinical entities by some authorities, but which have never been satisfactorily proved as such. The evidence is not strong enough to place them in the "~~ana~~emia complicated by ~~anaemia~~ pregnancy" group. Haemolytic anaemia of pregnancy, hypoplastic anaemia, protein deficiency anaemia, vitamin B deficiency anaemia are examples belonging to this group.

Haemolytic anaemia of pregnancy is a very doubtful entity. The cases described in the literature as haemolytic are either definitely not haemolytic at all or very doubtfully haemolytic on the features presented, or if haemolytic are probably better described as cases of acholuric jaundice

complicated by pregnancy. The cases which are haemolytic have not been reported for the last ten years.

Hypoplastic is a vague and unscientific term applied to cases which fail to respond to any treatment in any satisfactory manner, but which in the authors' opinions can be ascribed to pregnancy past or present. The term is haematologically meaningless.

Vitamin B deficiency anaemia and protein deficiency anaemia have not been confirmed as entities.

4. UNCLASSIFIED GROUP

In this group are included any cases which justifiably appear to be in some way due to pregnancy, and yet which do not conform to the features of one of the recognised types. Examples have been cited. These cases will eventually either be placed in a special group of anaemia of pregnancy, or into the group of anaemia complicated by pregnancy.

5. ANAEMIA COMPLICATED BY PREGNANCY

Pregnancy may occur in any type of blood disorder. Attention has been drawn to those disorders which are particularly liable to be confused with anaemia due to pregnancy.

EFFECT OF ANAEMIA ON MATERNAL AND INFANTILE HEALTH

The present study did not include any investigation of the effect of anaemia of pregnancy on the maternal and infantile health. The discussion of the topic is based entirely on published reports.

The effect of hypochromic anaemia has been summarised as follows:

Maternal mortality is probably not increased. Maternal morbidity, as judged by the puerperal fever rate, has a slightly higher incidence amongst anaemic than amongst non-anaemic pregnant women. Complications of labour are not increased.

The still birth rate is probably slightly increased. Infants born of even the most severely anaemic mothers are rarely if ever anaemic at birth, but develope anaemia during the first year of life. This anaemia is due to deficient storage of iron in the foetal liver, and is preventable by administration of iron to the mother during the last trimester. Administration of iron to the mother during the lactating period does not prevent its development. There is a definitely higher morbidity and mortality rate amongst infants born of anaemic mothers, unless the infantile anaemia

is treated by administration of iron to the infant.

The effect of macrocytic or pernicious anaemia of pregnancy on maternal and infantile health can only be speculatively considered, as the matter has not been investigated satisfactorily. On experimental evidence, it seems reasonable to deduce that infants born of mothers suffering from this type of pregnancy anaemia should be born anaemic. There is no clinical proof or disproof of such a deduction.

THE FUTURE

It is fitting to conclude this thesis with suggestions for future enquiry into the subject of anaemia of pregnancy. Two fundamental physiological associations of pregnancy are the increase of blood volume, and the changes in the metabolism of iron and its product haemoglobin conditioned by the demands of the foetus. The technical difficulties connected with the investigation of these matters is responsible for their having been neglected as part of the routine investigation ofcases of anaemia of pregnancy.

The factor of blood volume varies so much from case to case, that it ought to be known for each individual case investigated in order to make it possible to determine the degree of diluting effect of the hydraemia.

Iron metabolism has been studied only in connection with normal pregnancy. The intake, absorption and excretion of iron during pregnancy anaemia requires detailed study. Study of haemoglobin metabolism by determination of the excretion of haemoglobin break-down products such as urobilin and the porphyrins will go far towards deciding the disputed subject of intravascular haemolysis during normal or anaemic pregnancy. In this connection, the simple matter of the

behaviour of the reticulocytes during normal and anaemic pregnancy should be settled.

The detailed study of individual cases is the method of study of the future. The method of mass survey has in the past served a useful purpose, but has the disadvantage that it obscures knowledge of the less common forms of anaemia in that such cases are lost in the general pool. It is only by a more detailed investigation of both the common and the exceptional cases that the classification of the anaemias of pregnancy will be placed upon a more reasonable basis than at present exists.

REFERENCES

REFERENCES

Abt, A.F., and Nagel, B.R. (1932). J.A.M.A. 98.2270.

Adair, F.L., Dieckmann, W.J., and Grant, K. (1936). Am.Jnl Obstets and Gyn. 32.560.

* Atkin, I. (1938) Lancet, 1.434.

Alder, A. (1924). Zeitsch.f.Geburtsh.u.Gynak. 87.505. Quoted by Pepper (1929).

Allan, W. (1928). Surg.,Gyn., and Obstets, 47.669.

Alt, H.L., (1938). Am. Jnl Dis.Childh. 56.975.

Arzt, F. (1930). Am.Jnl Obstets and Gyn. 20.382.

Balfour, M.I. (1927). Ind.Med.Gaz. 62.491.

Barnum, G.G., and Woodward, J.C. (1938). 111.1749.

Beckmann, M. (1921). Monat.f.Geburtsh.u.Gynak. 56.119. Quoted by Stevenson (1938).

Beebe, R.T., and Lewis, G.E. (1931). Am.Jnl Med.Sci. 181.796.

Bence, J. (1933). Zeitschr.f.klin.Med. 126.127. Quoted by Wintrobe, Kinsey, Blount and Trager (1937).

Bethell, F.H. (1936). J.A.M.A. 107.564.

Berglund, H., Watkins, C.H., and Johnson, R. (1927). Proc. Soc.Exp.Biol. and Med. 25.834.

Bland, P.B., Goldstein, L., and First, A. (1930a). Am.Jnl Med.Sci. 179.48.

Bland, P.B., Goldstein, L., and First, A. (1930b). Surg., Gyn., and Obstets. 50.954

Boycott, J.A. (1936). Lancet, 1.1165.

* Adamson, J.D., and Smith, F.H. (1932). Canad.Med.Assoc.J. 26.669.

Bunge, G. (1889). Hoppe-Seyl.Zeitschr. 13.399. Quoted by Mackay (1931)

Burwell, C.S., (1936). South.Med.Jnl, 29.1194.

Burwell, C.S. (1938). Arch. Int.Med. 62.979.

Cassells, D.A.K. (1938) Jnl Path. and Bact. 47.603.

Castle, W.B., Heath, C.W., and Strauss, M.B. (1931). Am. Jnl.Med.Sci. 182.741

Channing, W. (1842). New Engl. Jnl Med. and Surg. 1.157. Quoted by Evans (1929).

Coons, C.M. (1932). Jnl Biol. Chem. 97.215.

Coons, C.M. (1935). Oklohama Agric. Exptal. State Bull. No.223. Quoted by Fullerton (1936a).

Corrigan, J.C., and Strauss, M.B. (1936). J.A.M.A. 106.1088.

Creed, E. (1938) Jnl Path. and Bact. 47.603.

Dacie, J.V., and Vaughan, J.M. (1938) Jnl. Path. and Bact. 46.341

Damashek, W., and Schwartz, S.O. (1938). New Engl. Jnl Med. 218.75.

Damashek, W., Schwartz, S.O., and Gross, S. (1938). Am. Jnl Med.Sci. 196.769.

Davidson, L.S.P., and Fullerton, H.W. (1933). B.M.J. 1.685.

Davidson, L.S.P., Fullerton, H.W., and Campbell, R.M. (1935). B.M.J. 2.195.

Davies, D.T., and Shelley, V. (1934). Lancet, 2.1094.

Davis, M., and Walker, E.W. (1934). New Engl. Jnl Med. 210.1310.

Dieckmann, W.J., and Wegner, C.K. (1934a). ArchInt.Med. 53.71.

Dieckmann, W.J. and Wegner, C.K. (1934b). Arch.Int.Med. 53.189.

Dieckmann, W.J., and Wegner, C.K. (1934c). Arch.Int.Med. 53.345.

Dieckmann, W.J., and Wegner, C.K. (1934d). Arch. Int.Med.53.353.

Dieckmann, W.J., and Wegner, C.K. (1934e). Arch.Int.Med. 53.527.

Dieckmann, W.J., and Wegner, C.K. (1934f). Arch.Int.Med. 53.540.

Douglas, C.A., and McKinlay, P.L. (1935). Report on Maternal Mortality in Scotland. Edinburgh. Page 8.

Dragstedt, C.A., Bradley, J.D., and Mead, F.B. (1931). Proc. Soc. Exptal Biol. and Med. 33.58.

Dragstedt, C.A., Bradley, J.D., and Mullenix, R.B. (1933). Am.Jnl Phys. 105.443.

Drucker, P. (1923). Act. Pediatr. 3.1. Quoted by Mackay (1931).

Elliott, G.A. (1939). S.A. Med. Jnl., 13.641.

Elsom, K.O. (1935). Jnl. Clin.Investig. 14.40.

Elsom, K.O. (1937). Jnl Clin. Investig. 16.463.

Elvehjem, C.A., Hart, E.B., and Sherman, W.C. (1933). Jnl Biol. Chem. 103.61.

Elvehjem, C.A., Hart, E.B., and Sherman, W.C. (1934) Jnl. Biol.Chem. 107.383.

Erickson, B.N., Williams, H.H., Hummel, F.C., Lee, P., and Macy, I.G. (1937). Jnl.Biol.Chem. 118.569.

Esch, P. (1921). Zentbl.Gynak. 45.341. Quoted by Evans (1929).

Evans, W. (1929). Lancet, 1.14.

Feldman, H., van Donk, E.C., Steenbock, H., and Schneiders, E.F. (1936). Am.Jnl.Phys. 69.115.

Fullerton, H.W. (1936a). B.M.J. 2.523.

Fullerton, H.W. (1936b). B.M.J. 2.577.

Fullerton, H.W. (1937). Arch.Dis.Childh. 12.91.

Galloway, C.E. (1929). J.A.M.A. 93.1695.

Gibson, J.G., and Evans, W.A. (1937). Jnl.Clin.Invest. 16.301.

Goldhamer, S.M., Isaacs, F., and Sturgis, C.C. (1934).Am. Jnl.Med.Sci. 188.193.

Goodall, J.R., and Gottlieb, R. (1936). Canad.Med.Assoc.Jnl, 35.50.

Gottlieb, R., and Strean, G.J. (1939). Surg.Gyn. and Obstets, 68.869

Haden, R.L. (1934). Am.Jnl.Med.Sci. 188.441.

Hampson, A.C., and Schakle, J.W. (1924) Guy's Hosp. Ref. 74.193.

Haslewood, G.A.D., and King, E.J. (1937). Biochem. Jnl. 31.920.

Heath, C.W., Strauss, M.B., and Castle, W.B. (1932). Jnl Clin.Invest. 11.1293.

Hofbauer, J. (1908). Zentrlbl.f.Gynak. 32.1469. Quoted by Strauss and Castle (1932b).

Hoskin, T.J., and Ceirog-Cadle, E. (1927). Lancet, 1.433.

Hugonenq, M.L. (1899). Comp.Rend.Soc.Paris, 51.337. Quoted by Mackay (1931).

Ivy, A.C., Morgan, J.E., and Farrell, J.I. (1931). Surg. Gyn. and Obstets, 53.611.

Jacobs, M.H., and Parpart, A.K. (1931). Biol.Bull. 60.95.

Jerlov, E. (1927). Act.Obst.et Gyn.Scand. 8.356. Quoted by Boycott (1936).

Jerlov, E. (1929). Act.Obst.et Gyn.Scand. 8.11. Quoted by Corrigan and Strauss (1936).

Jungmann, P. (1914). Munch.Med.Woch. 41.414. Quoted by Witts (1932).

Keith, N.M., Rowntree, L.G., and Geraghty, J.T. (1915). Arch.Int.Med. 16.54.

Kersley, G.D., and Mitchell, D.A. (1934). B.M.J. 2.720.

Kervin, W., and Collins, L.L. (1926). Am.Jnl.Med.Sci. 172.548.

King, E.L. (1929). Am. Jnl Obstets and Gyn. 18.569.

Kuhnel, P. (1927). Zeitschr.f.Geburtsh.u.Gynak. 90.511. Quoted by Adair, Dieckmann, and Grant (1936).

Labate, J.S. (1939). Am.Jnl.Obstets and Gyn. 38.48.

Labate, J.S. (1940). Am.Jnl.Obstets and Gyn. 39.87.

Larabee, R.C. (1925). Am.Jnl.Med.Sci. 170.371.

Linder, G.C., and Massey, P.J.H. (1939). Jnl.Obst.and Gyn. Brit.Emp. 46.885.

Lull, C.B. (1937). Med.Clin.N.Amer. 21.1185.

Lyon, E.C. (1929). J.A .M.A. 102.11.

Mackay, H.M.M. (1931). M.R.C. Report. No. 157

Mackay, H.M.M. (1935). Lancet, 2.1431.

McGeorge, M. (1935). Jnl.Obst. and Gyn.Brit.Emp. 42.1027.

MacSwiney, S.A. (1927). Ind.Med.Gaz. 62.487.

Maison, G.L., and Ivy, A.C. (19). Proc.Soc.Exptal Biol. and Med.

Minot, G.R. (1921). Med.Clin.N.Amer. 4.1733.

Minot, G.R., and Mettier, S.K. (1931). Am.Jnl.Med.Sci. 181.25.

Mogenson, E. (1938). "The size of the red blood cell". Copenhagen.

Moore, J.H. (1929). Am.Jnl Obstets and Gyn. 19.

Moore, J.H. (1930). Am.Jnl.Obstets and Gyn. 20.254.

Moore, J., and Pillman-Williams, E.M. (1936). B.M.J. 2.528.

Mussey, R.D., Watkins, C.H., and Kilroe, J.C. (1932). Am. Jnl. Obstets and Gyn. 24.179.

Nicholas, J.S. (1928). Am.Jnl.Phys. 83.499.

Oberst, F.W., and Plass, E.D. (1936). Am.Jnl.Obstets and Gyn. 31.61.

Osler, W. (1919). B.M.J. 1.1.

Osgood, E.E., and Haskins, H.D. (1927). Arch.Int.Med. 39.643.

O'Sullivan, H. (1932). Lancet, 2.1326.

Parsons, L.G. (1932). Act. Pediatr. 13.378. Quoted by Alt (1938).

Parsons, L.G. (1936). B.M.J. 1.1009.

Pepper, O.H.P. (1929). Med.Clin.N.Amer. 12.925.

Paterson, R., Field, H., and Morgan, H.S. (1930). J.A.M.A. 94.839.

Plass, E.D., and Bogert, L.J. (1924). Bull.J.H.Hosp. 35.361.

Pohl, A. (1928). Zentralbl.f.Gynak. 52.1384. Quoted by Boycott (1936).

Ponder, E. (1934). "The mammalian red cell and the properties of haemolytic systems.". Berlin. Quoted by Vaughan (1937).

Price-Jones, C.J. (1933). "The Diameter of red blood cells". London.

Price-Jones, C.J. Vaughan, J.M. and Goddard, H.M. (1935). Jnl.Path. and Bact. 40.503.

Reid, W.J.S., and Mackintosh, J.M. (1937a). Lancet, 1.43.

Reid, W.J.S., and Mackintosh, J.M. (1937b). Lancet, 2.1389.

Richter, O., Meyer, A.E., and Bennett, J.P. (1934). Am.Jnl Obstets and Gyn. 28.543.

Ritter, J.A., and Crocker, W.J. (1939). Am.Jnl.Obst. and Gyn. 38.239.

Rowland, V.C. (1924). J.A.M.A. 82.372.

Rowland, V.C. (1933). J.A.M.A. 100.537.

Sacks, A. (1936). J.A.M.A. 107.564.

Schultz, W. (1933). Much.med.Woch. 80.679. Quoted by Boycott (1936).

Schackleton, L.R.B., and McCance, R.A. (1936). Biochem.Jnl. 30.582.

Skajaa, K. (1929). Act. Obstet.et Gyn.Scand. 8.371. Quoted Dieckmann and Wegner (1934b).

Smallwood, W.C. (1936). B.M.J. 2.573.

Smith, C.T. (1925). Surg.Gyn. and Obstets, 40.223.

Stevenson, E.M.K. (1938) Edin.Med.Jnl, 45.81.

Strauss, M.B. (1930). Am.Jnl.Med.Sci. 180.818.

Strauss, M.B. (1935). Internat. Clinics. 4.56.

Strauss, M.B. (1933). Jnl.Clin.Invest. 12.345.

Strauss, M.B., and Castle, W.B. (1932a). Am.Jnl.Med.Sci. 184.655.

Strauss, M.B., and Castle, W.B. (1932b). Am.Jnl.Med.Sci. 184.663.

Strauss, M.B., and Castle, W.B. (1933). Am.Jnl.Med.Sci. 185.539.

Studdiford, W.E. (1934). Am.Jnl.Obstets and Gyn. 28.539.

Sure, B. Kik, M.C., and Walker, D.G. (1929). Jnl.Nutr. 1.299.

Thomson, K.J., and Cohen, M.E. (1939). J.A.M.A. 112.1556.

Thomson, K.J., Hirscheimer, A., Gibson, J.G.H., and Evans, W.A. (1938) Am. Jnl. Obstets and Gyn. 36.48.

Thomson, K.J. and Cohen, M.E. (1936). Jnl.Clin.Invest. 15.607.

Toverud, K.U. (1935). Act. Pediatr. 17.136. Quoted by Alt (1938).

Vaughan, J.M. (1936). "The Anaemias". London.

Vaughan, J.M. (1937). Jnl.Path. and Bact. 45.561.

Vaughan, J.M., and Haslewood, G.A.D. (1938). Lancet, 1.133.

Van Donk, E.C., Feldman, H., and Steenbock, H. (1934) Am.Jnl.Phys. 107.616.

Watson, H.G. (1938). Am.Jnl.Obstets and Gyn. 35.106.

Whitby, L.E.H. (1932). Jnl. Obstets and Gyn.Brit.Emp. 39.267.

Whitby, L.E.H., and Hynes, M. (1935). Jnl.Path. and Bact. 40.219.

Whitby, L.E.H., and Britton, C.J.C. (1937). "Disorders of the Blood". London.

Widdowson, E.M., and McCance, R.A. (1936). Jnl.Hyg. 36.13.

Wigodsky, H.S., Richter, O., and Ivy, A.C. (1939). Am.Jnl. Med.Sci. 197.750.

Wilkinson, J.F. (1932). Jnl. Obstets and Gyn. Brit.Emp. 39.293.

Willcocks, F. (1881). Lancet, 2.944.

Williams, H.H., Erickson, B.N., Bernstein, S., Hummel, F.C., and Macy, I.G. (1937). Jnl.Biol.Chem. 118.599.

Wills, L. (1931). B.M.J. 1.1059.

Wills, L. (1933). Lancet, 1.1283.

Wills, L., and Mehta, M.M. (1930). Ind.Jnl.Med.Res. 17.777.

Wills, L., and Talpade, S.N. (1930). Ind.Jnl.Med.Res. 18.283.

Wills, L., and Evans, B. (1938). Lancet, 2.416.

Wintrobe, M.M. (1930). Arch.Int.Med. 45.287.

Wintrobe, M.M. (1932). Jnl.Clin.Invest. 17.899.

Wintrobe, M.M., Kinsey, R.E., Blount, R.C., and Trager, W. (1937). Am.Jnl.Med.Sci. 193.449.

Witts, L.J. (1932). Lancet, 1.653.

Witts, L.J. (1936). Lancet, 1.1.

Zeidberg, L.D. (1929). Am.Jnl.Phys. 90.172.

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