STUDIES OF THE INCIDENCE, ETIOLOGY AND MORPHOGENESIS OF THE ANAEMIAS OF PREGNANCY.

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SECTION IV PATHOGENESIS OF THE SEVERE ANAEMIAS.

PREFACE.

The investigations on which this thesis is based were carried out in the Research Department, Wards and Ante-natal Clinic of the Royal Maternity and Women's Hospital, Glasgow, during the tenure of the Reid Stewart and McCunn Scholarships.

I have much pleasure in acknowledging my indebtedness to Dr.A.D.T.Govan for his constant encouragement and helpful critism throughout the course of this work. Thanks are also due to Professor R.A.Lennie, Professor D.F.Anderson and Dr.J. Hewitt for permission to investigate cases in their wards of the Glasgow Royal Maternity and Women's Hospital and to Dr.David Smith for permission to study cases in his wards at the Glasgow Royal Infirmary.

STUDIES OF THE INCIDENCE, ETIOLOGY AND MORPHOGENESIS OF THE ANAEMIAS OF PREGNANCY.

INTRODUCTION:-

Anaemia in association with pregnancy is a condition which has been noted from earliest times, but very few serious studies were made until comparatively recently. The first specific reference on this subject is that of Channing (1842) who described ten fatal cases of severe anaemia associated with pregnancy in his "Notes on Anhaemia, principally in its connexions with the puerperal state and functional diseases of the uterus". From then on publications appeared regularly and in increasing numbers. Lebert (1854) and Gusserow (1871) both published eight similar cases with fatal terminations. The next reference to this "rare type of anaemia" was made by Biermer (1872) who noted its resemblance to "progressive pernicious anaemia". The same year Trousseau (1872) drew attention to an iron deficiency anaemia and remarked how it became more apparent during pregnancy. Ehrlich and Lazarus (1898), in describing pernicious anaemia, commented on cases occurring in association with pregnancy and grouped them separately on the grounds of aetiology. But it was left to Osler (1919) to distinguish this anaemia from Addisonian pernicious anaemia by the frequency of its recovery without recurrence.

As in the case of Addisonian pernicious anaemia

this severe and often fatal anaemia of pregnancy was regarded as a haemolytic process (Osler 1919, Minot 1921, Rowland 1924, Allan 1928). With the advent of liver therapy in the treatment of Addisonian pernicious anaemia however interest was rekindled and Brault (1928), Audebert and Fabre (1928) and Devraigne and Laennec(1928) were all able to demonstrate the favourable response to liver by patients suffering from pernicious anaemia of pregnancy. Up to this date then interest appears to have centred around two distinct types of anaemia, one which was apparently due to iron deficiency and a second which showed many of the features of Addisonian pernicious anaemia, including response to liver therapy, but which, unlike that condition did not usually progress beyond the term of pregnancy. It was not until a much later date that any attempt was made to produce a comprehensive classification of anaemias occurring in pregnancy. One of the first of these was published by Smallwood (1936), who based his classification on theories current in the sphere of general medicine. His grouping was as follows:-

(1) <u>Deficiency Anaemia</u>

a) iron deficiency (i) hypochromic type induced by pregnancy.

(ii) idiopathic hypochromic type complicated or precipitated

by pregnancy.

b) deficiency of the anti-anaemic liver principle, which may be due to.

(i) a deficiency of the extrinsic factor as in tropical macrocytic anaemia (Balfour 1927, Wills and Mehta 1929, Wills 1931, 1932, 1933)

(ii) a deficiency of the intrinsic factor due to true Addisonian pernicious anaemia or pernicious anaemia of pregnancy.

(2) Haemolytic Anaemias These anaemias he classifies according to the condition of the bone marrow as:-

a) plastic

b) hypoplastic

c) aplastic

(3) Post Haemorrhagic group: of which the majority are due to antepartum and post partum haemorrhage.

(4) Anaemia of puerperal sepsis.

(5) Other anaemias complicated by pregnancy e.g. leukaemia.

Elliott (1944) followed the method of Smallwood in principle but with minor modifications in detail. He described four groups as follows:-

(1) Deficiency anaemia:-

a) iron deficiency anaemia of pregnancy.

b) anti-anaemic liver principle deficiency.

c) mixed iron and anti-anaemic liver principle deficiency.

(2) Unproved group:-

a) Acute haemolytic anaemia of pregnancy.

b) Protein deficiency anaemia of pregnancy.

c) Vitamin B deficiency anaemia of pregnancy.

(3) Unclassified group of anaemias which do not conform to the above groups yet can be considered as possibly due to pregnancy.

(4) Anaemia complicated by pregnancy including tropical megalocytic anaemia.

Many authors, however, appeared to be dissatisfied with these classifications drawn from general medicine, since practice revealed many discrepancies. Stevenson (1938) for instance used the older terminology of "pernicious" and "secondary" anaemias and these she subdivided as follows:-

(1) Pernicious Anaemia in pregnancy and the puerperuim.

a) Addisonian anaemia

b) Pseudo-pernicious anaemia which, she said, was due to a temporary deficiency of the intrinsic factor and possibly of the extrinsic factor and may be

i) plastic or ii) hypoplastic in type.

(2) Secondary Anaemia.

a) Idiopathic hypochromic anaemia complicated by pregnancy or first manifested in it or in the puerperuim, and due to iron deficiency.

b) Microcytic hypochromic anaemia due to a temporary iron deficiency.

c) Microcytic hypochromic anaemia due to some known cause e.g. haemorrhage, sepsis, nephritis.

(3) "Pernicious Secondary" anaemia combing the morphological features and possibly the aetiological factors of both.

(4) Anaemia associated with other conditions complicated by pregnancy e.g. malaria, syphilis, luikaemia.

Even as late as 1943 Dillon preferred to divide his cases of pregnancy anaemias simply into mild and severe groups. The reasons for this continued indecision in regard to these anaemias are manifold. Firstly, there is a great difficulty in establishing the correct diagnosis by a study of the peripheral blood alone. For instance it has been repeatedly shown that the peripheral blood picture in pernicious anaemia of pregnancy is frequently atypical and often frankly misleading (Stevenson 1936, Abramson 1938, Segerdahl 1941, Miller and Stoddart 1942, Davidson, Davis and Innes 1942 , Lescher 1942, Callender

1944). With this in view Wolff and Limarzi (1946) have classified the anaemias of pregnancy according to the marrow picture. Their classification is therefore much simpler.

(1) Normoblastic erythropoiesis with a more immature type of erythroid development, such as occurs in iron deficiency anaemias.

(2) Megaloblastic erythropoiesis, such as occurs in Addisonian pernicious anaemia, pernicious anaemia of pregnancy and tropical macrocytic anaemia.

(3) Aplastic marrow with marked hypoplasia of all cellular elements, which may be:-

i) primary

ii) secondary, due to chemicals, Roentgen rays etc.

Secondly the causes of anaemia in pregnancy appear to be much more numerous and complicated than in general medical practice. Elsom (1937) claimed to produce a macrocytic anaemia in pregnant women with a diet deficient in vitamin B and lack of this vitamin is mentioned as a cause of anaemia by Elliott in his classification. Bethel (1936) described an anaemia of normal colour index and normal or slightly raised cell volume associated with pregnancy, which he considered was due to a protein deficiency. Experimental evidence adds

weight to this hypothesis (Whipple 1935, Minot 1939, Hahn and Whipple 1939, Miller, Whipple, Robschiet - Robbins 1947 a) b) c)).

Thirdly, as will be shown shortly it is difficult to establish accurate criteria of anaemia owing to the natural hydraemia which occurs in pregnancy.

A study of all these reviews shows that a microcytic hypochromic anaemia is the anaemia commonly occurring in this country associated with pregnancy (Davidson et al 1935, 1942, 1944, Fullerton 1936, 1943, Boycott 1936, Reid and Mackintosh 1937, Hamilton and Wright 1942, Widdowson 1943, MRC report 1943). Investigations carried out in America report similar results (Adair, Dieckmann and Grant 1936, Oberst and Plass 1936, Dillon 1943, Evans 1943, Elliott 1944). In India, however, a macrocytic anaemia is commoner (Wills and Mehta 1929, Wills 1931, 1932, 1933, Mudeliar and Menon 1942).

Prior to recent work pernicious or as it was known "severe anaemia of pregnancy", was regarded as a rare complication (Osler 1919). Beckman (1921) estimated its occurrence as six in sixty thousand deliveries. Evans (1929) found no case of "severe anaemia" out of 4,083 patients. Reid and Mackintosh (1937) did not find one case in a series of 1108 pregnancies. Whitby (1932),

Wilkinson (1932) Bethell (1936) Musser (1940) seldom encountered pernicious anaemia of pregnancy. Stevenson (1938) found thirty cases in Glasgow in six years.

Opinion in regard to both these types of anaemia has tended to alter in recent years with the introduction of more modern and exact methods of investigation, particularly marrow biopsy. Large haemoglobin surveys have been carried out by Davidson and Fullerton in Aberdeen (1935) Davidson et al. in Edinburgh (1942), MRC report (1943) and Roscoe and Donaldson (1946). The reports give the impression that the incidence of anaemia in pregnant women has fallen during the past ten to fifteen years. The percentage of patients with haemoglobin readings less that 70% Haldane has fallen from 17.5% during the year 1935 to 3.9% in the year 1943 in the city of Aberdeen. As stated above many cases hitherto regarded as iron deficiency anaemias were found to be atypical cases of pernicious anaemia of pregnancy (Segerdahl 1941, Miller and Studdert 1942, Davidson, Davis and Innes 1942 b Lescher 1942, Callender 1944). Also Elliott (1944) in a detailed study of a small group of patients suffering from microcytic hypochromic anaemia reported some cases, which did not respond to iron in the way characteristic of non-pregnant cases.

Pernicious anaemia of pregnancy was originally

regarded as a haemolytic anaemia ~~originally~~ (Minot 1921, Rowland 1924, Allan 1928, Witts 1932), but the megaloblastic change in the bone marrow suggests that it is primarily a dyshaemopoietic anaemia, although a haemolytic component may also be present. Swan (1933) and Lescher (1942) report in all, ten cases of so called haemolytic anaemia of pregnancy. Callender (1944) considers these cases to be pernicious anaemia of pregnancy and her figures would suggest that pernicious anaemia of pregnancy is not an uncommon complication. With the introduction of liver therapy and modern methods of investigation it has been shown that true haemolytic anaemia of pregnancy is an extremely rare condition and Bethell (1944) states that no case of true acute haemolytic anaemia of pregnancy has been recorded in the last ten years.

One of the chief difficulties in diagnosing anaemia of pregnancy and one which causes difficulty in assessing the statistical significance of this condition, is the occurrence of a normal hydraemia during the course of pregnancy. Trousseau (1872) was the observer to suggest that such a condition existed in normal pregnancy and that it was the cause of a so called "physiological anaemia", which could be differentiated from a true anaemic state. Many workers using a variety of methods

have verified the occurrence of hydraemia in pregnancy. (Nasse 1876, Meyer 1887, Zunst 1911, Zangemeister 1904, Mahnert 1921 Miller, Kieth and Rowntree 1915) but it was not until 1934, when Dieckmann and Wegner carried out their investigations on normal pregnant women by injecting red dye intravenously, that the condition was absolutely established. They found that the hydraemia became apparent about the third month of pregnancy, was maximal during the 25th to the 25th weeks and tended to become less marked during the last month. At term they estimated that the total blood volume had increased 23%, the plasma volume 25% and the total erythrocyte mass 20%, the 5% discrepancy causing the apparent anaemia.

Oberst and Plass (1936) confirmed these findings in principle. Thomson, Hirsheimer, Gibson and Evans (1938) found higher haemodilution readings in their series. Roscoe and Donaldson (1946) using Evans blue, which they claim gives better results than vital red and is not rapidly removed by the reticulo - endothelial system, produced results which agreed well with those of the preceding authors. Blood volume estimations were carried out on the same patients during the first, second and third trimesters and from the results they had hoped they would be able to determine the normal haemodilution at a given stage of pregnancy and hence the normal haemoglobin etc. — Unfortunately the increase of

TABLE I.

Author.	Hb in grams or % Haldane.	R.B.C. in millions.	Cell Volume in %.
Dieckmann and Wegner	10	3.36	33.11
Bethell.	11.3	3.7	
Watson.	7.7		
Whitby and Britton	10.	4.400	
Evans.	10.1		
Elliot.	65%	3.2	
Roscoe and Donaldson	74%		
Plass and Bogert			32.

blood volume, cell mass and haemoglobin was not constant and no definite conclusion could be drawn from these results. They were able, however, to suggest the normal haemoglobin levels to be expected in the different months of pregnancy for women of each age group. Allowing for a standard deviation of eight, it is obvious that below these levels the condition was one of anaemia and could not in any sense be attributed wholly to hydraemia. Many other authors have suggested lower limits of normality (Table 1). For the purpose of this thesis the figures of Roscoe and Donaldson (1946) have been used.

METHODS.

A. Clinical Methods.

(1) Each patient attending the antenatal clinic attached to the hospital has blood taken off at her first visit, for the estimation of haemoglobin, Kahn and Rhesus tests. Care was taken in withdrawing venous blood without obstruction. The blood was collected in heparin tubes and, with few exceptions, all the investigations were carried out within six hours of withdrawal.

(2) As soon as cases of anaemia were detected they immediately came under direct supervision of the laboratory for further investigation and treatment, and remained under such supervision throughout the whole of pregnancy and the puerperium.

(3) A case record was kept of each patient and, as can be seen from the accompanying specimen card, details of the patient's obstetrical and general medical conditions were recorded in addition to those directly relating to the condition of her blood. By this means it has been possible to assess the statisticalimportance of anaemia per se and to eliminate those changes due to other conditions, such as infections.

(4) Sternal punctures were performed and smears made

according to the technique of Davis, Glasgow. (personal communication).

B. Haematological Estimations.

(1) A sahli haemoglobinometer was used, which was standardised each year using blood of known oxygen capacity and checked at six monthly intervals against a haemin standard. 100% on the scale was found to be equivalent to 16 gms of haemoglobin. From a number of haemoglobinometer tubes, twelve were carefully selected, each tube reading within ± 1.5%. Eight haemoglobinometer pipettes, which had been specially selected because they did not require a correction factor, were used. They were checked and rechecked at regular intervals. After use, pipettes and tubes were washed thoroughly in distilled water, spirit and ether and dried with the use of a pump. Readings were taken 10 mins after setting up and all colour matching was done by daylight.

(2) The same counting chamber with a double platform and improved Neubauer ruling was used throughout the whole survey. Two counts were made on each blood. Three red and three white cell pipettes were used and checked from time to time. Correction factors were added where necessary.

(3) Haematocrit tubes were unobtainable when the work

was commenced and twelve 2 c c haemoglobinometer tubes, which were standardised with the use of a microburette made good substitutes. Later as Wintrobe tubes became available, they were standardised against the original tubes and brought into use. A finely balanced centrifuge, maximum speed 24,000 revs/min. was found to give optimum packing of the cells without haemolysis after 30 mins. spinning. Strict adherence was kept to this time and speed.

(4) Mean cell diameter estimations were made using an Eve's halometer, which was calibrated against a series of blood films from normal healthy males and females.

(5) Red cell fragility tests were carried out according to the method of Creed (1938).

(6) From the above the mean corpuscular volume (M.C.V.) mean corpuscular haemoglobin concentration (M.C.H.C) and mean cell thickness (M.C.T.) were deduced.

C. Staining Methods.

(1) Blood films (a) Leishman

(b) Prussian blue staining reaction for iron according to the technique of Davis & McFadzean (1947).

(c) $\alpha\alpha$ dipyridyl and potassium thiocyanate

reaction for iron (Case 1944)

(d) Dry cresyl blue method for reticulocytes.

(e) Grams stain.

(f) Feulgens reaction for nucleo - proteins.

(2) Marrow films (a) May Grunwald.

(b) Wetcresyl-blue method for reticulocytes.

Davidson (1930) and Currie(1944) both mention the presence of reticulocytes in bone marrow, but neither author gives any details of the method of staining. In the present investigation the common wet procedure was used. It was obviously impossible, however, to make the normal coverslip preparation and the following modification was found to give satisfactory results. One drop of a 1% solution of cresyl blue in normal saline was mixed with one drop of the aspirated material and left for ½ min. The excess stain was poured off and smears were made and stained as before with May Grunwald.

(c) Prussian blue reaction, see above.

(d) $\alpha\alpha$ dipyridyl reaction, see above.

(e) Feulgens reaction.

D. Biochemical Methods.

(1) Plama proteins - total plasma proteins were estimated using the method of Phillips and Van Slyke (1945). A short series done as a check using the method of King (1946) gave results consistently 0.2 gm % higher than the copper sulphate method.

(2) Qualitative and quantitative Van der Bergh estimations were carried out, colour matchings being made in the Lovibond comparator.

(3) Schlesingers test for urobilin in the urine was used and arbitrary standards of fluorescence on a -,+,++ system adopted, as a rough quantitative guide.

(4) Iodine test was used for bile in the urine.

(5) Icteric index was estimated using standard potassium bichromate solution.

(6) Spectroscopic examination of the blood and urine in a case of haemolytic anaemia.

E. Biological methods.

These were employed in a case of haemolytic anaemia in an attempt to detect antibodies in the patient's blood. The various experiments performed will be described in the text of the thesis.

F. Statistical methods.

These are described as required in the text.

GENERAL REVIEW.

1. INTRODUCTION:-

This section deals with the incidence of anaemia among patients attending the ante-natal clinic. It is the result of a survey carried out during the months of April to September 1946 and throughout the whole of 1947. Cases of anaemia admitted directly to the hospital as emergencies are not included in this part of the thesis, as they would raise the incidence of anaemia considerably.

Other factors considered are the significance of age and parity in the causation of anaemia; the seasonal variation in the average monthly haemoglobin and the incidence of other deficiences as well as an iron deficiency.

During six months of 1946 1,180 routine haemoblobin estimations were performed and for 1947 the total was 3,415. Roscoe and Donaldson (1946 a) in a survey of haemoglobin levels divided their patients into age groups and found that with increasing age the lowest normal haemoglobin showed a decline. For instance in the 35 to 40 age group, the lowest normal haemoglobin reading in the eighth month of pregnancy was 74 per cent on the Haldane standard, whereas in the 20 to 25

TABLE II.

	NORMALS.	NORMALS.	ANAEMIA.	ANAEMIA.
SAHLI %	65	60	50	50-
GMS. Hb %	10.4	9.6	8	8-
HALDANE %	71.7	66	55.2	55.2-

TABLE III.

YEAR.	% SEVERE ANAEMIAS	% MODERATE ANAEMIAS	% LOW NORMALS	% NORMALS.
1946	4	17	29	50
1947	4.8	17.8	24.5	52.9

age group the reading was 82 per cent. The standard deviation in all groups was 8. It is obvious that if Roscoe and Donaldson's hypothesis is correct then women in the younger age groups will be in an anaemic state at haemoglobin levels, which would come within the range of normality for older age groups. This is however, a moot point and in the present thesis a haemoglobin level of 70 per cent Haldane is considered the lowest level of normality for all age groups. 70 per cent Haldane (9.66 gms haemoglobin per cent) is equivalent to 60 per cent (9.6 gms haemoglobin per cent) on a Sahli haemoglobinometer, standardised at 100 per cent equivalent to 16 gms haemoglobin. On the Sahli scale therefore it was considered that all women with haemoglobin readings falling within the range 60-65 per cent could be classified as "low normals", to be kept under observation. Below 60 per cent the "anaemias" were divided into "moderate anaemias" with haemoglobin readings above 50 per cent (8 gms haemoglobin per cent) and "severe anaemias" with haemoglobin readings below 50 per cent (Table II).

II. INCIDENCE.

The 1946 and 1947 readings were assessed according to the above standards and the results are shown in Table III. The percentage number of patients

TABLE IV.

INCIDENCE OF SEVERE ANAEMIA.

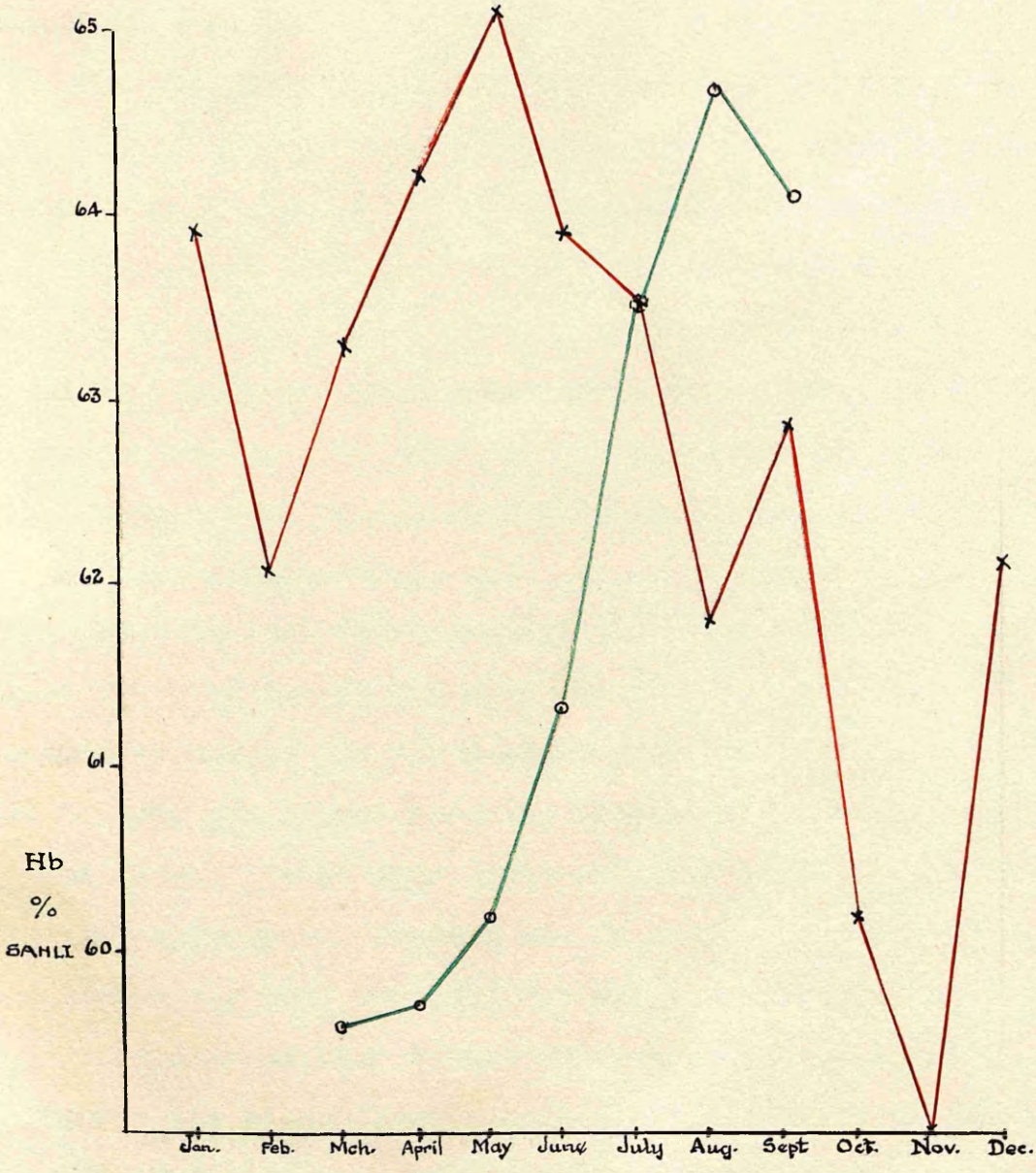
Month	Jan	Feb	Mar	Apr	May	June	July	Aug	Sep	Oct	Nov	Dec.
No of cases	7	17	15	23	8	11	10	20	17	14	18	6

TABLE V.

	NORMALS.	MODERATE.	SEVERE.
AVERAGE AGE - YEARS.	26.8	28.3	30.7
AVERAGE PARITY	2.1	3.5	3.6

CHART I

MONTHLY VARIATIONS IN THE HAEMOGLOBIN AVERAGES DURING 1946 AND 1947.



o——o 1946

×——× 1947.

in each group shows only slight variations in the two years, there being no significant rise or fall in the incidence of anaemia. From the table it will also be seen that one out of every twenty to twenty-five patients attending the clinic was severely anaemic. The incidence of these severe anaemias was considered in the light of various environmental and social factors, in an attempt to find some general correlation which might point to a cause. Although the average monthly haemoglobin readings for each year show a tendency to rise in summer and fall in winter, no correlation could be found between the incidence of severe anaemia and this seasonal variation (Table IV).

This variation was quite regular with the exception of a temporary rise during the Christmas season, but the numbers attending the out-patient department fell during the holiday season and this may account for the alteration in the curve. It is also interesting to note that, whereas the peak haemoglobin reading was in August in 1946, it was reached in May 1947 and fell rapidly thereafter.(Chart.1.)

Age is another factor which might be expected to influence the haemoglobin reading. From table V it can be seen that the women with normal haemoglobin values had an average age of 26.8 years, that those with moderate anaemia showed a rise to 28.3 years, while women

with severe anaemia had the highest average age of 30.7 years. When these figures were examined statistically, the standard deviation in the normal group was 3,237 and in the severe group 2.812. It would therefore appear that the age was a significant factor only in severe anaemia. This of course refers to a direct comparison between established cases and normals and cannot be applied to any other circumstances.

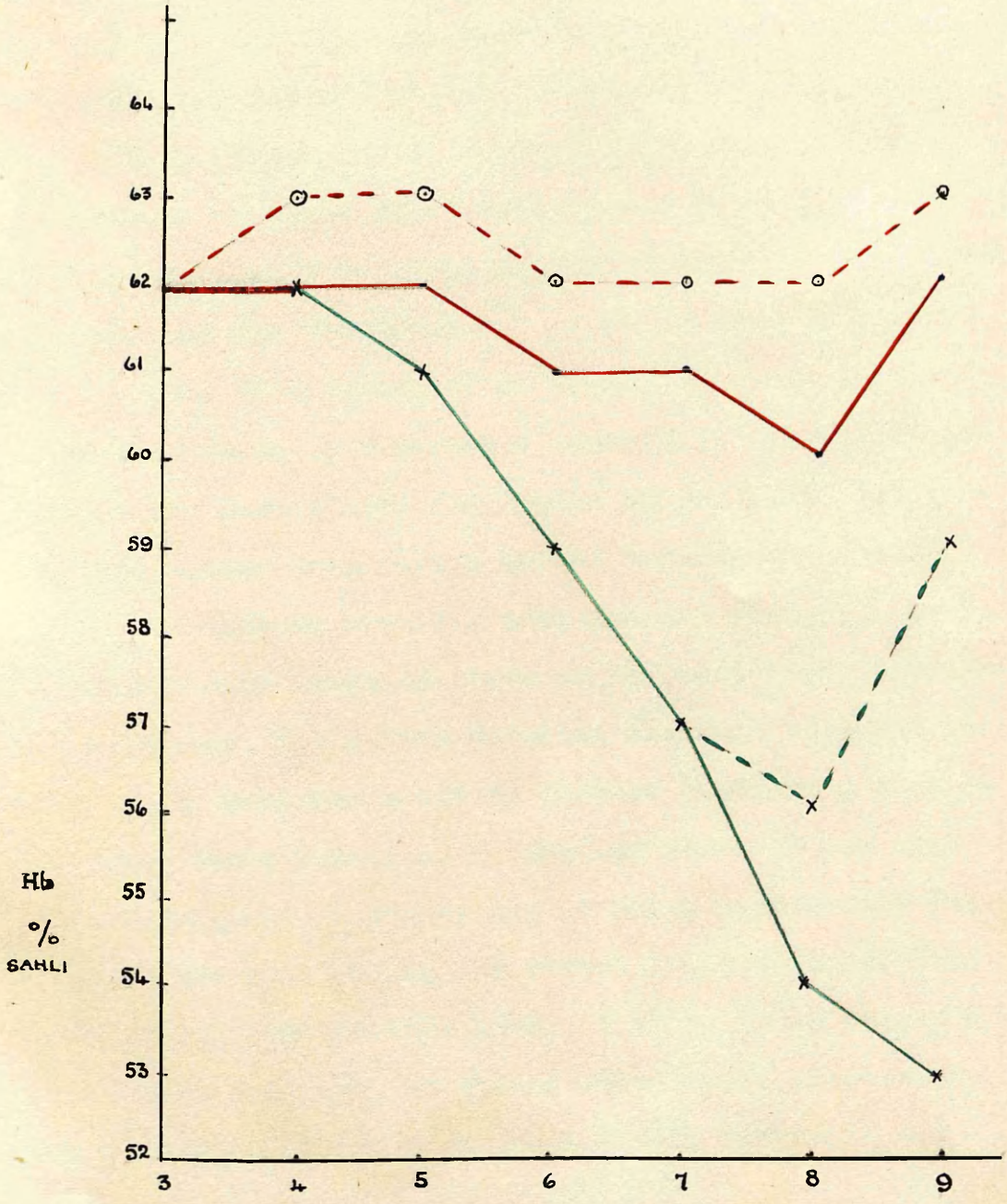
When parity was considered in relation to the haemoglobin reading it was found that the women with normal haemoglobin values had an average parity of 2.1, that the average parity rose to 3.5 in women with moderate anaemia and to 3.6 in women with severe anaemia (Table V). Statistical analysis of these figures, however, showed a standard deviation of 1.698 for the normal women and 2.810 for the severe anaemias. Parity would not therefore appear to be statistically significant as a factor in anaemia.

III LOW NORMALS.

In all types of anaemia it is difficult to obtain clinical material for a study of the genesis of the anaemic state, but it was felt that the group of low normals contained a number of individuals, who might well be in the initial stages of anaemia. A series of 85 patients were selected during 1947 from this group. The

CHART II

CURVE SHOWING THE VARIATIONS IN THE "LOW NORMAL" GROUP AND THE EFFECT OF IRON THERAPY IN PATIENTS WHO BECOME ANAEMIC



average duration of pregnancy was 5.4 months, with individual variations between 4 and 7 months. Monthly haemoglobin readings were made as usual, but whenever a patient's haemoglobin showed a tendency to fall, the haemoglobin readings were made every fortnight. The haemoglobin in these cases was allowed to fall to 55 per cent Sahli, i.e. a definite anaemia developed, before iron therapy was commenced.

From this series of 85 women, three groups could be eventually demarcated (Chart 11). It was found that if the haemoglobin fell below 58 per cent Sahli, the fall became progressive and no improvement could be looked for without specific anti-anaemic therapy. Sixty of the patients remained above 58 per cent Sahli throughout pregnancy, but a more detailed analysis revealed that these sixty patients could be further subdivided into 44 patients, whose haemoglobin remained above 60 per cent Sahli throughout pregnancy and 16 whose haemoglobin fell below 60 per cent during the second trimester, but rose above 60 per cent towards term. A third group showed a progressive fall and, as stated above, were allowed to deteriorate to 55 per cent Sahli before treatment was commenced.

Analysing this control group of "low normals" by the above method, it was found that four patients

or 4.7 per cent improved, fifty-six patients or 65.9 per cent showed no change and 25 patients or 29.4 per cent deteriorated (Table VI). Of the deteriorations 12 per cent occurred during the sixth month of pregnancy, 24 per cent during the seventh month, 44 per cent during the eighth month and 20 per cent during the ninth month, showing that the tendency to develop anaemia was most manifest during the eighth month. All the deteriorations on reaching levels below 55 per cent Sahli were given iron (Ferri et ammon. cit gr. $\overline{xxx}$ t.i.d. or Ferrous sulph. gr.$\overline{v}$ t.i.d., whichever the patient could tolerate best). Nineteen of the patients received treatment for at least one month and they showed an average rise in haemoglobin of 6.3% during the first month of therapy. The results are recorded graphically (Chart II).

Variations occurred in the haemoglobin readings taken in individual patients throughout pregnancy; a fact which has been demonstrated by many authors, who showed that the haemoglobin tended to fall gradually as pregnancy advanced, reaching a minimum about the eighth month and sometimes rising towards term (Kuhnel 1926, McGeorge 1935, Boycott 1936, Oberst and Plass 1936, Thomson, Hirsheimer, Gibson and Evans 1938, Dieckmann and Wegner 1943, Meyer - Wedell 1943, Roscoe and Donaldson 1946 (b)). Reference to the analysis of the

three groups of low normals will show that the second group of sixteen patients could not be considered anaemic although their haemoglobin level fell. These cases are similar to those reported by the authors mentioned above and they provide criteria for estimating the progress of any particular patient. The maximum fall of haemoglobin recorded in these patients was 4 per cent Sahli, and therefore from this, it seems reasonable to assume that any variation from the original level of haemoglobin in low normals within ± 5 per cent Sahli at any one time should not be considered significant.

Some doubt may be felt as to the validity of this statement in view of the fact that the patients of this group were first seen at various stages of pregnancy. It is a well known fact that hydraemia appears about the third month of pregnancy, reaches a maximum during the 25th to 35th week and tends to become less marked during the last month (Dieckmann and Wegner 1936, Oberst and Plass 1936, Thomson, Hirsheimer, Gibson and Evans 1938, Roscoe and Donaldson 1946). Now some of the patients in this series came to clinic as early as the 4th month of pregnancy, while others delayed their first visit till the 7th month and the degree of hydraemia and therefore the original haemoglobin reading would vary markedly in individual patients. Thus a low normal patient with a

haemoglobin reading equal to 60 per cent Sahli at the 4th month of pregnancy might possibly show a lower reading at the 7th month, due to the development of hydraemia and, had she reported for the first time then, she would have been considered anaemic. It was thought advisable to examine the figures statistically to see whether the month when the original haemoglobin reading was taken was significant or not. This was found to be 4.8 months in the patients who deteriorated and 5.6 months in those who maintained their original haemoglobin reading. The standard deviation was 1.25. It can therefore be said that it was not statistically significant whether the first haemoglobin estimation was made during the 4th or the 7th month.

Further it was felt that patients in this series with haemoglobin readings nearer 60 per cent Sahli might be more liable to become anaemic than patients with haemoglobin readings slightly higher, but less than 65 per cent Sahli. However, on analysing the original haemoglobin readings it was found that the average original haemoglobin readings of the twenty five patients who deteriorated was 61.5 per cent Sahli, compared with an average of 61.8 per cent in the remainder. The standard deviation was 1.1. Thus it would appear that

the development of anaemia by patients of the "low normal" group is independent of the original haemoglobin reading within the range of that group.

The individual ages in whole series of low normals varied from seventeen to forty four years. Of the total, forty fell within the group 17 to 24 years. Roscoe and Donaldson (1946 (a)) state that a gradient in haemoglobin exists in relation to age. Two corollaries arise from this hypothesis. Firstly, the lowest normal haemoglobin in a young pregnant woman will always be higher than that in an older. Further, this means that an anaemic state can be said to exist in these young women at haemoglobin levels, which would be considered normal for older age groups. If these hypotheses are correct then it would be logical to expect a higher incidence of anaemia to develop in the group of forty young pregnant women of this series. In fact only eight of this group deteriorated and became definitely anaemic, whereas seventeen of the remaining forty five in the older age groups showed a progressive fall in haemoglobin. Expressed on a percentage basis, 20 per cent of young pregnant women in the low normal haemoglobin level group (60 - 65 per cent Sahli) deteriorate and become anaemic, but in older age groups this figure becomes 38 per cent. There is therefore no

preponderance of young pregnant women among those tending to develop anaemia. In addition the average age of the twenty five patients, who deteriorated was 28.6 years compared with an age of 26.6 years in those who maintained their haemoglobin level. On statistical analysis the standard deviation was 3.4. It is therefore apparent that age is not in any way a significant factor in the development of anaemia in low normal patients.

Parity was examined next to see if it might be important. The average parity of the deteriorations was 2.4 whereas the average parity of those who maintained or improved their haemoglobin was 2.1. The standard deviation was 1.25. It is obvious from this that parity was not statistically significant either.

It is quite apparent that pregnancy per se is not a cause for anaemia in normal patients, since only a percentage of "low normals" in any age group developed an anaemic process. It has also been shown than anaemia most commonly appears during the latter part of pregnancy when the demands of the foetus are greatest. From this one might conclude that the factor determining whether anaemia will develop in any individual of the low normal haemoglobin group, is that of her own stores of iron. Coons (1932) showed that high storage rates occurred in the mother early in pregnancy though foetal increments

were greatest during the last three months. In an attempt to discover concomitant factors, which might affect the storage of iron in these women, a survey was made of their medical history and condition in the early months of pregnancy. It was found that twelve of the twenty-five patients, who deteriorated or 48 per cent had suffered from some form of mild gastro-intestinal upset during the early months of pregnancy, such as nausea, constipation, morning sickness and anorexia; whereas only twenty out of those who maintained themselves or 33 per cent had this history. (Table VII) These figures would therefore appear to be significant and, following this point a step further, it was seen that of the twenty-five deteriorations, the twelve who had a history of gastro-intestinal upset early in pregnancy developed anaemia at an average duration of pregnancy of 7.25 months, whereas the remaining thirteen, with a negative history, developed anaemia at 8.3 months. These figures were analysed statistically. The standard deviation was 0.87. In addition three of these patients with a history of gastro-intestinal upset suffered from infections later in pregnancy, but the incidence of infection was just as high in those patients who did not become anaemic. It is important to emphasise also that the infections

in all cases were of mild degree and were treated at the out-patient department. Therefore it would appear that gastro-intestinal upset in the early months of pregnancy plays a part in the development of anaemia in the later months or that it hastens the onset of the anaemia. It is possible that it affects the storage of iron.

Of the remaining thirteen patients in this group, twelve had no history of any significant abnormality in the early months of pregnancy and one can only conclude that there was a relative deficiency prior to pregnancy and that possibly the intake of haemotinic factors was deficient throughout pregnancy. This possibility will have to be investigated at some future date by means of a social survey.

Since it seems that almost a third of the "low normal" patients attending the out-patient department of this hospital will become anaemic, it was considered worth while to try out small groups of twenty-five patients on various supplements to see what effect they would have on the incidence of anaemia (Table VI).

(1) Twenty five otherwise normal patients, in the low normal haemoglobin group, averaging 5-6 months pregnant were given iron as before for periods averaging two to three months and not less than one month. 40 per cent of the patients improved, 52 per

cent showed no change and 8 per cent deteriorated. i.e. two patients out of the twenty five deteriorated. Deterioration commenced at the 7th month, was relieved slightly during the 8th month, when the dose of iron was increased, but fell again during the last month. Neither anaemia was severe.

(2) Twenty five similar patients, averaging 6 months pregnant, were given 150 mgm daily of vitamin C for one month, then 50 mgm. daily for periods averaging two to three months. 16 per cent of the patients improved, 72 per cent showed no change, 12 per cent deteriorated i.e. three patients deteriorated. One of the patients, who deteriorated developed a pyuria and the fall in haemoglobin dated from that. The three cases were put on iron and they showed an average increase of 9 per cent haemoglobin during the first month of iron therapy.

(3) A similar group, averaging 5.8 months pregnant, were given special dietary advice. They were supervised by the dietician, who saw them every visit and advised them as to what foods they should take and how they should be cooked. In addition a letter was given to the patient to take to her butcher asking him to co-operate by giving the patient priority liver and kidney. On an average most patients received ½ lb of liver each week for periods not less than one month. Of this group,

32 per cent improved, 52 per cent showed no change and 16 per cent deteriorated. The deteriorations were given iron and the average haemoglobin increase in the first month was 13 per cent Sahli.

(4) The last group consisted of thirty similar patients, averaging 6 months pregnant. These patients were given marmite 1 dram three times daily. Treatment was only carried out for one month, because at the end of that time the patients complained of nausea. The haemoglobin was taken at two-weekly intervals and the patients who showed a slight drop in haemoglobin, were asked to report back to confirm an anaemia, should it occur. No improvement was found after one month's therapy. 80 per cent of the patients showed no change and 20 per cent deteriorated. They were given iron as before and after one month's therapy, the haemoglobin had risen 11 per cent on the average.

The results of therapy in these four subsidiary groups are shown in table VI, the control group of "low normals" being used as a standard of comparison. Although the numbers are small, several tentative conclusions may be drawn. Firstly, the control group showed the highest percentage deterioration and the lowest percentage improvement. Secondly the best results were obtained with iron therapy, which reduced the percentage

deterioration by more than one third and increased the percentage improvement eight times compared with the control series. Further, vitamin C appeared to reduce the incidence of deterioration, while a special diet had more effect on the percentage improvement.

The apparent maintainance of the haemoglobin levels by the administration of vitamin C may be due to its ability to increase the absorption and effective utilization of the iron. It has been shown that vitamin C by its reducing action converts iron compounds into a form which is readily absorbed (Powell 1944). A condition of anaemia however, due to a deficiency of vitamin C has been produced experimentally in animals (Meyer and McCormack 1928, Metier et al.1940). Whether such a condition, due solely to a vitamin C deficiency, exists in man has not been definitely proved (McMillan and Inglis 1944). None of the patients in the low normal series showed any signs of clinical scurvy and it would therefore be even less likely for anaemia to develop due to a sub-clinical deficiency of that vitamin.

The failure of special diet to prevent deterioration in the haemoglobin levels in one group of patients, while increasing them in another, suggest that there is an inability on the part of the first group to absorb or utilise iron from the diet and that

the diet was relatively deficient in some substance necessary for these processes.

The results with marmite were extremely disappointing and the haemoglobin values approximated too closely to the control series to be of any significance.

When deterioration occurred in all four groups iron therapy was commenced, as in the control group. The average haemoglobin rise during the first month of therapy was calculated for each group. It was interesting to note that patients in the marmite and special diet groups showed a higher average increase for the month on iron than the control patients, suggesting that previous treatment with other haemotinic factors, such as vitamin B complex or anti-anaemic liver principle, may enhance the rate of regeneration of haemoglobin when iron is given.

IV ANAEMIAS.

During 1946 patients with a definite anaemia i.e. with haemoglobin readings below 60 per cent were treated empirically with iron at the antenatal clinic, to establish the value of this form of therapy, when applied to out-patients. Haemoglobin readings were made at monthly intervals, unless there was evidence of deterioration, when readings were made weekly. In addition, if the initial haemoglobin was very low

i.e. below 45 per cent or if the patient seemed likely to prove unsatisfactory, readings were made at fortnightly intervals.

In all, 140 cases were treated by this method the average period of treatment being 2.2 months. For statistical purposes,no patient receiving less than one month's treatment was included in the group and once the haemoglobin reached normal levels, no further account was taken of the readings in the analysis, though for clinical purposes the patient still continued to attend at monthly intervals. The average duration of pregnancy was 5.6 months with individual variations from 3 to 8 months.

No attempt was made to grade the severity of the anaemia initially, but the average haemoglobin reading in these patients was 51 per cent Sahli. Out of the whole group only ten patients required to be admitted to hospital and, of these ten, four admissions were made because of some complaint other than anaemia. Eventually the patients were found to fall into three groups namely.

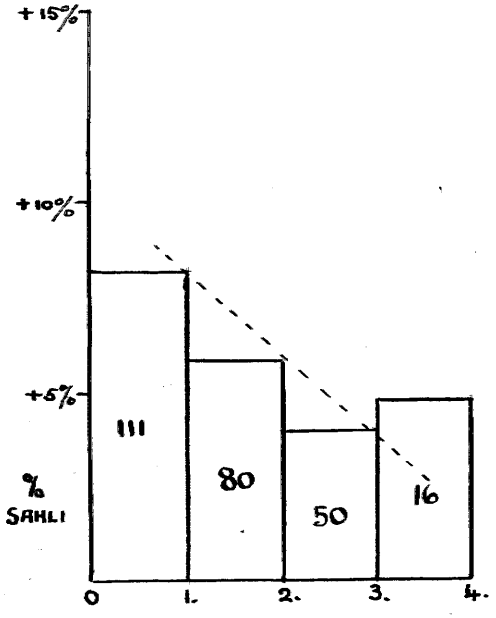
A. Those who respond to treatment, 112 in all or 80.0 per cent of the total.

B. Those who showed no response to treatment, but maintained their original haemoglobin level.

CHART III

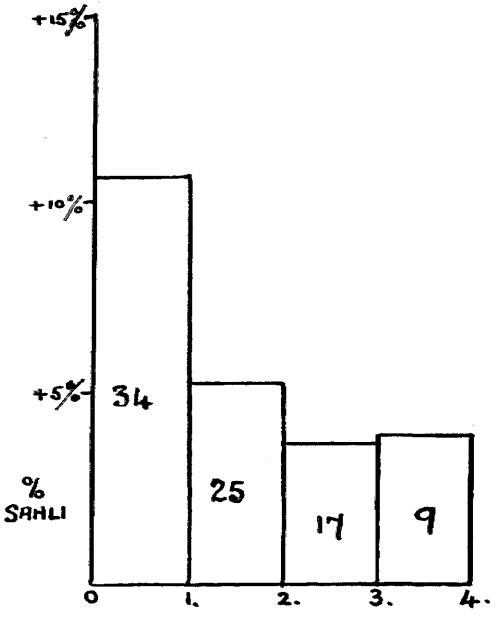
IIIa WHOLE SERIES

MONTHLY INCREMENTS OF 140 PATIENTS TREATED WITH IRON AS OUT-PATIENTS



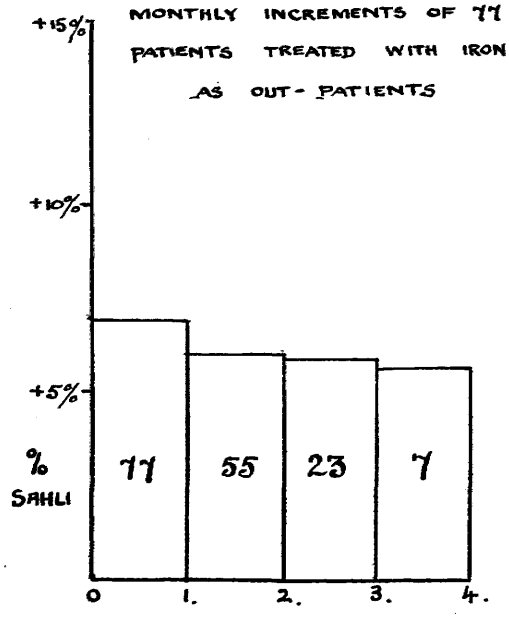
IIIb ALL SEVERE ANAEMIAS

MONTHLY INCREMENTS OF 34 PATIENTS TREATED WITH IRON AS OUT-PATIENTS



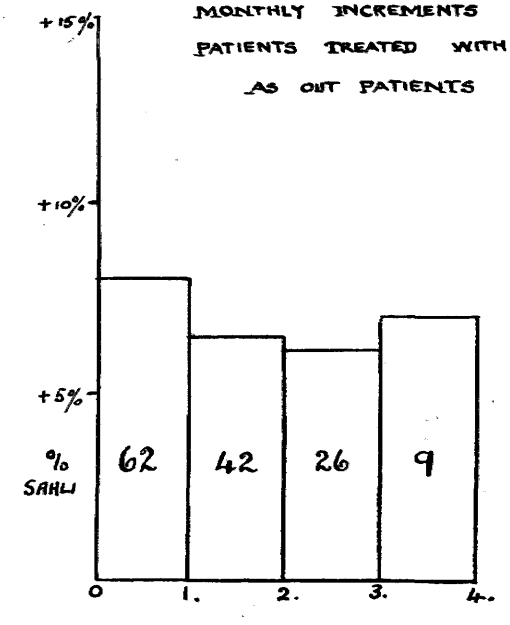
IIIc ALL MODERATE ANAEMIAS

MONTHLY INCREMENTS OF 77 PATIENTS TREATED WITH IRON AS OUT-PATIENTS



IIId PURE ANAEMIAS

MONTHLY INCREMENTS OF 62 PATIENTS TREATED WITH IRON AS OUT PATIENTS



This group was formed of 26 patients or 18.6 per cent.

C. Two cases who deteriorated.

For the present, attention will be confined to group A.

Group A.

The patients in this group showed an average rise in haemoglobin of 5.8 per cent Sahli per month, and the average haemoglobin rose from 51 per cent Sahli at the beginning of treatment to a final reading at the end of treatment of 65 per cent Sahli. In order to guage the response to treatment; the average haemoglobin for the whole group was charted in a graph (Chart 3a). From this graph it will be seen that the greatest rise in haemoglobin occurred during the first month (8.2 per cent). In the succeeding two months the increase was much less striking and was indeed almost exactly halved, 4 per cent. In those cases requiring treatment for four months it was found that in the final month, the curve tended to rise slightly to 4.9 per cent. With the exception of this month, the curve for this group is a straight line and in this respect they resemble anaemias in non-pregnant women (Whitby and Britton 1946).

Preliminary sub-divisions into moderate and

severe grades revealed marked differences in the nature and degree of response to treatment in these grades. In the moderate anaemias the average increase of haemoglobin per month was 5.7 per cent Sahli and the total average increase of haemoglobin from beginning to end of treatment was 13.9 per cent Sahli. The response in relation to duration of treatment is diagrammatrically represented in chart 3c. From this it will be seen that the increase does not vary very much from month to month. There is a slight curve with a fall in the later months of treatment.

In the severe grade, the average monthly rise was 6.2 per cent and the total average haemoglobin rise from beginning to end of treatment was 17 per cent Sahli. A monthly graph of the response in these patients showed a very distinct difference from that in the "moderate" group. During the first month the haemoglobin increased by 10.8 per cent but in the following month this figure was exactly halved and in the third month the increase was still less. A slightly greater increase was recorded in the 4th month of treatment. Chart 3b. represents these changes.

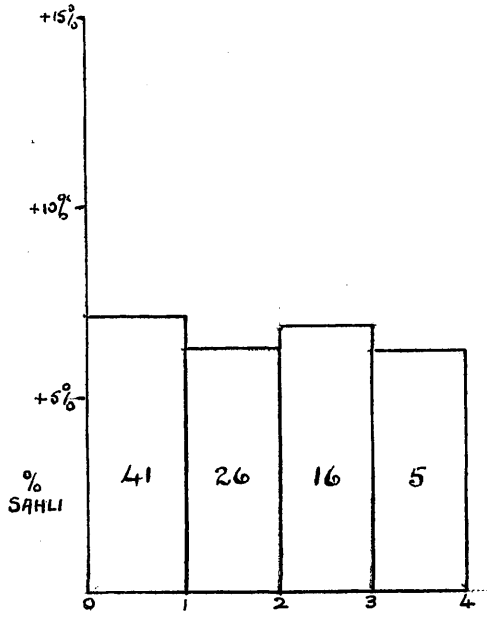
In both of these groups the curves as depicted in graphs /3c and 3b are atypical when compared with

those for anaemias in non-pregnant women (Whitby and Britton 1946). In the latter, the rate of haemoglobin regeneration is said to be inversely proportional to the haemoglobin level. Examination of the details of clinical history of patients in Group A revealed that they could be further sub-divided. Of the total, 62 patients had symptoms which could be attributed solely to the anaemic process, 36 had some form of mild gastro-intestinal disorder, 10 suffered from a mild intercurrent infection and 4 developed hypertension during the course of treatment.

The patients with mild infection and hypertension showed an average increase in haemoglobin per month, which approximated too closely to that of the whole series to be of any significance and as the numbers were small, no further analysis could be made.

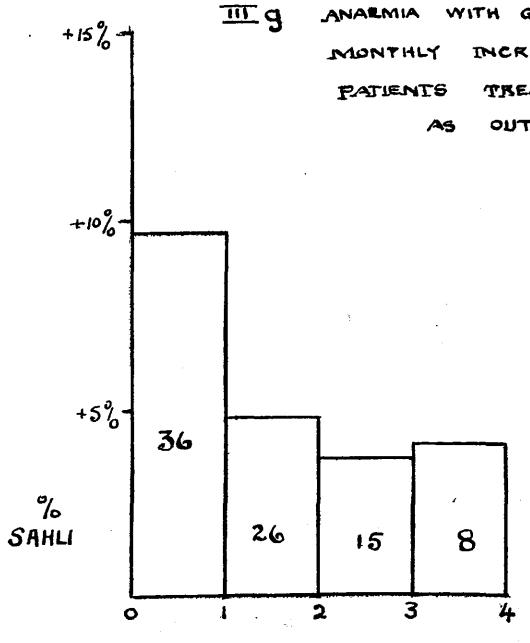
As stated above, 62 patients could be regarded as "pure anaemias", in that anaemia was the only apparent complicating factor in the pregnancy. The curve of the average monthly increases (Chart 3d) was rather similar to that of Chart 3c, which, as will be remembered, was constructed from all the moderate anaemias in Group A. The curve however, was at a higher level and during the fourth month of treatment, it tended to rise instead of falling as in Chart 3c.

III e PURE ANAEMIAS WITH Hb ABOVE 50% SAHLI
MONTHLY INCREMENTS OF 41
PATIENTS TREATED WITH IRON
AS OUT - PATIENTS



III f PURE ANAEMIAS WITH Hb BELOW 50% SAHLI
MONTHLY INCREMENTS OF 21
PATIENTS TREATED WITH IRON
AS OUT - PATIENTS.

III g ANAEMIA WITH GASTRO-INTESTINAL UPSET
MONTHLY INCREMENTS OF 36
PATIENTS TREATED WITH IRON
AS OUT - PATIENTS

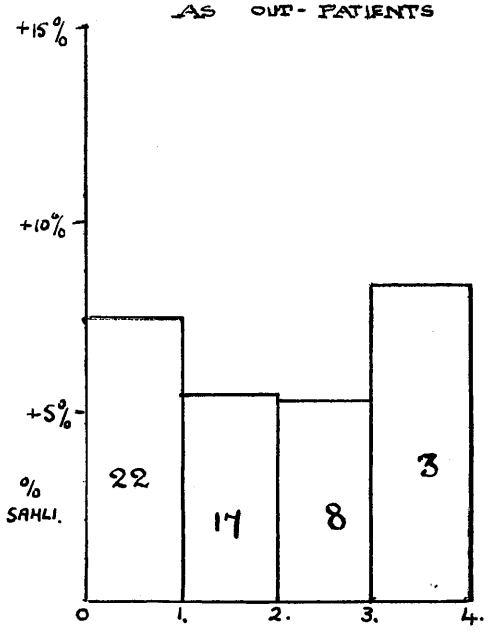


Of these 62 patients, 41 suffered from a moderate degree of anaemia, and the remainder had haemoglobin readings less than 50 per cent Sahli. As can be seen from Chart 3e, the curve of monthly haemoglobin increments was almost the same as that of Chart 3c, for all moderate anaemias in Group A patients. Chart 3f shows the response of severe "pure anaemias" and the curve is parallel to that for the whole of Group A (see Chart 3a) but runs at a slightly higher level.

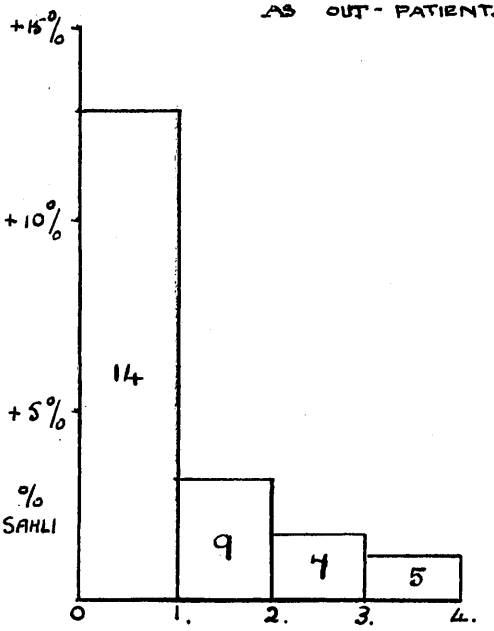
From all of the foregoing it will be evident that in the case of "pure" anaemias complicating pregnancy the response to iron therapy is comparable to that in non pregnant women. As a general observation, it may be noted that the response to therapy in the moderate group, although not so striking initially is maintained more steadily than in the severe group. By the second month of treatment, however, the haemoglobin level of most of the patients in the severe grades had risen above 50 per cent and their response thereafter could not be expected to differ much from that in the initially moderate grades.

Investigation of the 36 patients suffering from gastro-intestinal disorder as well as anaemia was conducted along similar lines. The average increase per month for this series was charted as before (3g). It can be seen that the curve is steeper and almost L shaped.

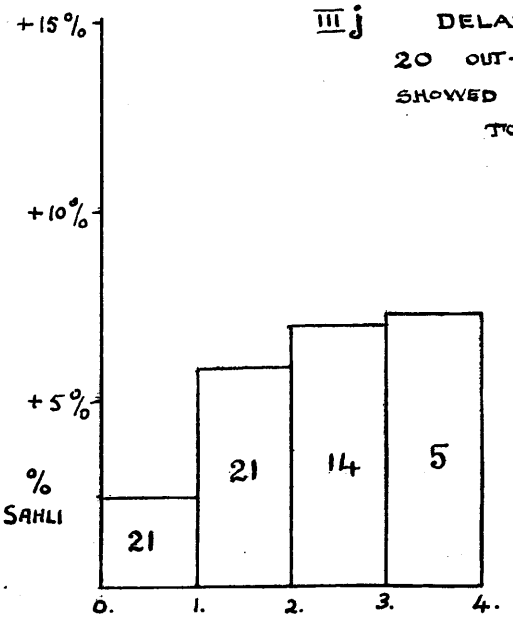
III h MODERATE ANAEMIA WITH GASTRO-INTESTINAL UPSET
MONTHLY INCREMENTS OF 22
PATIENTS TREATED WITH IRON
AS OUT-PATIENTS



III i SEVERE ANAEMIA WITH GASTRO-INTESTINAL UPSET
MONTHLY INCREMENTS OF 14
PATIENTS TREATED WITH IRON
AS OUT-PATIENTS



III j DELAYED GROUP
20 OUT-PATIENTS WHO
SHOWED A DELAYED RESPONSE
TO IRON THERAPY



This change in the shape of the curve became even more apparent when the patients were graded according to the severity of their anaemia. Moderate anaemia was present in 22 and it was severe in 14. The graph for the patients with moderate anaemia was very similar to that of the moderate anaemias without gastro-intestinal upset. The initial haemoglobin rise was 7.4 per cent Sahli and in the 1st month, fell slightly to 5.4 per cent and 5.3 per cent Sahli during the 2nd and 3rd months and rose again during the last month (Chart 3h). There were only 3 patients in this latter group so the rise is of doubtful significance. It would therefore appear that mild gastro intestinal upset, as a further complication to moderate anaemia in a pregnant woman, has little influence on the course of iron therapy. When the 14 cases of severe anaemia with symptoms of mild gastro intestinal upset were analysed as above, the "curve" was not striking and completely atypical (Chart 3i). The average haemoglobin increase during the first month was the highest recorded for the whole series viz. 12.9 per cent Sahli, but thereafter, treatment with iron seemed to have little, if any, effect on the haemoglobin levels of these patients, as the haemoglobin increments during the 2nd, 3rd and 4th months were 3.1 per cent, 1.7per cent and 1.4 per cent Sahli respectively. These

fourteen cases would therefore account for the apparent inadequate response of the 34 severe anaemias analysed originally and would modify the graph accordingly in this series (Chart 3b). Because of their very satisfactory response to iron therapy in the first month, they naturally fall into the class of cases that are regarded as having improved, but when haemoglobin readings were repeated during the 2nd 3rd and 4th months, it was found that little further improvement occurred despite the continuance of iron therapy i.e. a "plateau" in haemoglobin levels had been reached. Several tentative conclusions can be drawn from these results. Firstly these 14 patients probably had an iron deficiency or they would not have shown such a striking response to iron therapy initially. Since this response was higher in the 1st month than that shown by the series of 20 "pure anaemias", at similar haemoglobin levels, the iron was probably absorbed efficiently, i.e. the gastro-intestinal complaint whether it was morning sickness, heartburn, nausea or constipation did not prevent the absorption of iron. Thirdly, when the "plateau" was reached and no further improvement occurred, two hypothesis can be postulated,

(a) that a break occurred in the "mechanism" of iron absorption, transportation or utilization or

(b) that the iron deficiency having been rectified and the body stores satisfied another deficiency had become apparent. These hypothesis will be discussed later in this thesis.

When the response to treatment was being considered in the 112 patients, who improved as a result of iron therapy, it was noted that 20 of the patients showed a delayed response to iron. During the first month the improvement in each case and the average for the group was less than ± 5 per cent Sahli. Thereafter the haemoglobin rose satisfactorily, 18 of the patients reaching normal haemoglobin levels before delivery. The incidence of "pure anaemias", cases complicated by gastro intestinal upset and by infection was found to be the same in this series as for the whole group. (Table VII.) Therefore the cases occurred proportionately throughout and in no way would upset previous observations. The incidence of severe anaemia was 20 per cent compared with 30 per cent in the whole series but as the numbers in this group were small, this is of doubtful significance. The average duration of pregnancy at the first visit to the clinic was approximately that of the whole series. Thus it would appear that neither the incidence of mild gastro intestinal upset, infection or of severe anaemia or the

duration of pregnancy could supply significant cause for the delayed response to therapy. The average haemoglobin increase per month was calculated as before and a graph drawn (Chart 3j). It will be seen that the average rise in haemoglobin during the 1st month was 2.5 per cent, that it rose sharply to 5.9 per cent in the 2nd month and thereafter by gentle rises to 7.2 per cent at the 4th month. Why this delay in response should occur is difficult to say. No obvious cause could be found but before any opinion can be given investigations will have to be carried out on a larger series of patients of various grades of anaemia including studies of their gastric secretion by routine test meal examinations, of their rate of absorption of iron by plasma iron estimations and of their haemopoiesis by marrow biopsy.

GROUP B.

As stated previously this group consisted of twenty six patients who failed to respond to iron therapy. Although at first sight they might all be classified as "resistant" to treatment, closer scrutiny suggested possible reasons for their apparent resistance in many of the cases.

Thirteen of the cases received treatment for only one month, and as has already been noted under Group A, many cases of anaemia show a delay in response during the

first month of treatment. It does not appear justifiable therefore, to state that there was definite resistance to treatment in these patients.

Of the remainder, five cases had some complaint in addition to anaemia. Two patients had moderately severe infections necessitating confinement to bed and, as has been shown by Pepper 1927, Wintrobe 1942, Saifi and Vaughan 1944, Cartwright et al.1946, these patients do not respond to iron therapy while the infective process is active. In these cases the infection persisted over a period of several months and would account for the failure to respond to iron. Of the remaining three, two patients, one of whom was severely anaemic, had mild gastro intestinal disorders and the third, a mild pyuria. All three were treated as out-patients. In the case of the patient with severe anaemia one might reasonably have expected a modified response to therapy with the L-shaped curve of increments shown by similar patients in group A, but none of the three should have been completely resistant to treatment.

A third group of three patients with no other complaint beyohd anaemia, failed to respond to iron therapy, even when continued over a period of several months. All had complete investigations of their

peripheral blood, but in each case the picture was that of a normocytic hypochromic anaemia. One of these patients was admitted to hospital and responded to iron therapy soon after admission. It is interesting to note that this patient deteriorated after leaving hospital and in a succeeding pregnancy her haemoglobin was reduced to 45 per cent Sahli and her bone marrow contained megaloblasts.

These three groups account for twenty one of the twenty six patients. The remaining five must be omitted for several reasons. Three were unco-operative and it is doubtful if they took the iron mixture prescribed regularly. The remaining two had initial haemoglobin readings of 55 per cent and 57 per cent respectively and although neither showed an increase of more than 5 per cent over the whole period of treatment, it was nevertheless sufficient to lift them into the range of low normals, in which case they might be incapable of further response.

Thus of the total of twenty six patients six could be definitely described as "resistant" to treatment.

GROUP C.

Of the two patients who deteriorated one showed no response to iron therapy and developed diarrhoea and vomiting in the 9th month of pregnancy, deteriorating

thereafter. The other patient received iron as an out-patient for two months, during which time the haemoglobin fell 8 per cent. She was admitted to hospital a week before term and was given iron in large doses, but no improvement was recorded though the blood picture was typical of a microcytic hypochromic anaemia.

In view of the severe gastro intestinal disorder in the first case, it is not certain if this patient was resistant to iron therapy. The second patient obviously was, and this brings the total of patients resistant to iron therapy up to seven.

DISCUSSION.

The incidence of anaemia in pregnant women would appear to vary considerably throughout Great Britain. Recent surveys have shown estimations as low as 3.9 per cent in Aberdeen (Fullerton et al 1944) and as high as 16.8 per cent in London (Hamilton and Wright 1942). Even reports from the same area vary. In a survey of women attending a London ante-natal clinic (Thomas 1942) found a 50 per cent incidence of anaemiaamong his patients in the later months of pregnancy. In the Edinburgh survey 1942 Davidson et al estimated the incidence of anaemia as 24 per cent, but a more recent survey would suggest that this figure is too high (Davidson et al 1944).

In 1943 a general survey of the whole of Great Britain was carried out by the Medical Research Council. The results of this survey published in 1945, show an average incidence of anaemia of 6.7 per cent among pregnant women.

None of the recent surveys has covered an industrial area comparable with Glasgow and Clydeside. Although several series were reported prior to 1939, these may not be applicable owing to changed circumstances as a result of the war and its aftermath. Of these Boycott (1936) in a survey of 222 patients attending an ante-natal clinic found 11 per cent of the women had haemoglobin readings less than 70 per cent Haldane. Meyer - Weddell (1943) reviewed a series of 105 women attending a London clinic between 1936 and 1939 and reported a 16 per cent incidence of anaemia. Whereas Reid and Mackintosh (1937) in a very much larger survey, including 1100 women, gave the figure as 10.2 per cent.

The most recent surveys have dealt with semi-industrial areas or certain classes in industrial areas. The surveys of Davidson et al 1942 and 1944 and Fullerton et al 1944 belong to the former, whereas the survey of Hamilton and Wright 1942, which dealt with the upper artisan and lower middle classes was an example of the latter.

The results of the present survey show a high incidence of anaemia. Taking 100 per cent Haldane as equivalent to 13.8 gms haemoglobin per cent and converting the Sahli reading to a Haldane, it can be said that 17.6 per cent of the women had haemoglobin readings less that 70 per cent Haldane. Reference to the group of "low normals" however, will reveal that 29.4 per cent of the patients in this group ultimately became anaemic and a further 18.8 per cent had readings below 60 per cent at one time in their pregnancy though they did not develop anaemia. It will be seen that of all the women attending the clinic for the first time, which on the average is between the fifth and sixth month of pregnancy, those with haemoglobin readings less than 60 per cent, diagnosed as anaemias, will not include the 29.4 per cent who ultimately became anaemic, but may include the 18.8 per cent, who temporarily showed haemoglobin readings below 60 per cent. From these results it can be deduced that 10.6 per cent of the "low normal group will develop anaemia and this correction added to the original estimation gives an amended figure of 20.1 per cent i.e. 20.1 per cent of the patients seen for the first time at clinic are likely to be, or will become anaemia.

Three large surveys have been carried out in

recent years and the results as well as varying from the above, differ widely from each other. (Davidson et al 1942 and 1944) (Fullerton et al 1944) (Hamilton and Wright 1942) Davidson et al and Hamilton and Wright dealt with patients outwith the class attending the out-patient department in Glasgow, and in many ways their results are not comparable with those in Glasgow. Fullerton on the other hand, drew his patients from the poorer classes and with the standardisation of diet and income which has occurred in recent years, it might have been expected that his series would have been comparable. If this was so, then any difference between the patients in Aberdeen and Glasgow would be environmental and Glasgow's slums are certainly worse than Aberdeen's. However, it is generally admitted that although diet is standardised in principle, there are marked regional variations. The question of social circumstances is obviously important and a survey, economic, dietary and social of the patients attending the out-patient departments is in progress. So far it can be said that of a small series, selected at random, of patients attending the out-patient department, the average income per head, after rent, coal, gas, insurance commitments etc., have been deducted, is 25/3, with values ranging from 12/- to 45/-. Since

the value of money is generally regarded as only one third of what it was pre-war, these figures cannot be compared directly with those of McCance et al (1938). Possibly their lowest income group of 6/- per head will be comparable with the 12/- per head group of the patients at present attending the out-patient department.

Most war-time surveys show a diminished incidence of anaemia as compared with pre-war years (Davidson et al 1935, Fullerton et al 1944, Davidson et al 1942, and Davidson et al 1944). In Aberdeen, Fullerton repeated the survey of 1935. The results showed a striking decrease in the incidence of anaemia among pregnant women. The average haemoglobin had risen from 78.1 per cent Haldane to 82.6 per cent and only 3.9 per cent of the women now had readings below 70 per cent Haldane, compared with 17.5 per cent before. In Edinburgh 1942, Davidson found that of 570 pregnant women 24 per cent had haemoglobin readings below 70 per cent Haldane and only two years later, the same observers were able to report an average rise in haemoglobin of 9.8 per cent over the previous reading. This second group was smaller and the incidence of anaemia was not given, but they were able to say that the increase in the average haemoglobin reading was mainly due to an improvement in the women with haemoglobin readings less than 70 per

cent Haldane, i.e. the degree of anaemia was less severe in 1944.

Conflicting reports have been made by observers in other parts of the country. Reid and Mackintosh(1937) in a survey of 1100 women in London found an incidence of anaemia of 10.2 per cent. Kay and Alston (1941) in a survey of 2205 women in the years 1936 to 1939 gave the figure as 5.3 per cent. Other reports have been published but the numbers studied have been rather small to have any general application (Mackay 1935, McCance 1938, Meyer-Weddell 1943, Boycott 1936, Sinclair 1942). The Medical Research Council reviewed all these surveys and published a report (1945) of the haemoglobin levels in Great Britain in 1943. Their results for pregnant women showed a mean haemoglobin reading higher than those of Aberdeen 1935 and Edinburgh 1942, agreeing closely with those of Edinburgh 1944 and slightly below the optimal pre-war readings of McCance (1938).

In short, it would appear that the incidence of anaemia in poorer class women attending ante-natal clinics has fallen since 1942, but it would appear to have increased at the same time among the artisan classes. The majority of the authors are of the opinion that the introduction of the national wheat loaf has raised the iron intake of the poorer classes (Davidson

et al 1944) Fullerton et al 1944) whereas rationing has restricted the diet of the artisan classes. (Hamilton and Wright 1942).

Concomitant with the introduction of the national wheat meal loaf between the years of Davidson's surveys in Edinburgh, it was felt that there might be another factor which would prove significant. During 1944, forces were being massed in North Africa, the Mediterranean, in Italy and on the south coast of England for the invasion of Europe. Many men were therefore away from home and it was thought that a consequent decline in the birth rate over that period might reduce the incidence of anaemia at that time. When the registrar general's reports for 1936 to 1946 were studied, however, they showed that for Scotland, the birth rate had remained fairly steady from 1937 onwards till 1944, when it began to rise slowly, whereas in England, the birth rate had been rising steadily from 1941 onwards. From these findings it would appear that the birth rate had no bearing on the incidence of anaemia in the mothers.

No pre-war survey on which to base a comparison is available for Glasgow and therefore no conclusion can be drawn as to the rise or fall in the incidence of anaemia in the class of mothers taken for this survey. Certainly environmental conditions are no better in Glasgow since

the war; if anything they are worse. Diet may be a factor as supported by (Fullerton, 1944 Davidson, 1944). However it can be said that during the years 1946 and 1947 the incidence of anaemia was static in Glasgow, that the levels at which it remained were far from satisfactory, and that the incidence of severe anaemia was exceptionally high. Probably environment plays the major part in such conditions, but proof of this awaits the completion of our survey mentioned previously.

Though the incidence of anaemia during 1946 and 1947 was fairly constant, it has been shown that the average monthly haemoglobin reading tended to rise in summer time and fall in winter. Why the peak of this curve should occur in August, 1946 and in May, 1947 is difficult to explain, but it is interesting to note that in July, August, and September, 1947, the weather was exceptionally warm, to the extent of being oppressive to some of these women living in closely populated districts of the city. In a survey of haemoglobin levels in school children in 1942, 1943, and 1944 Davidson et.al (1944) publish a graph of the haemoglobin readings taken in the same children in March, June and December, 1943. It is interesting to note that for 1943 the average reading for June is higher than either that of March or December i.e. a similar peak was reached in the summer time.

The significance of age and parity as factors in the causation of anaemia in pregnant women has long been a problem for discussion. Mackay (1935) thought that age had no influence on the incidence of anaemia, Davidson (1935) found that the percentage of anaemias rose during the child-bearing period as the age rose. Boycott (1936) and Reid and Mackintosh (1937) agreed with MacKay. On the other hand Fullerton (1936 (a)) was of the opinion that the average haemoglobin of non-pregnant and pregnant women fell gradually throughout re-productive life, and that this downward gradient was parallel in each group, the pregnant women having readings 5 per cent below the non-pregnant due to the existance of hydraemia. After the menopause he found that the haemoglobin rose once more and approximated in both groups. In a more recent survey, Fullerton et.al(1944) found no decrease in the average haemoglobin level in the older age groups, and in this revised opinion he agreed with Davidson et.al. (1942). The Medical Research Council survey for 1943 (1945) however, found results similar to those of Davidson (1935). With such a variety of opinions expressed even by the same authors, it is difficult to come to any conclusion when the literature is reviewed. More recent work by Roscoe and Donaldson (1946 a & b) would suggest that older women show a relatively greater

increase in plasma during pregnancy, which may account for the lower average haemoglobin readings obtained in the older age groups. Their series of patients was small however and larger numbers will have to be investigated. In the present survey age did not appear to be a factor in moderate anaemia and was only significant in the severe anaemias. With this point in view, it is interesting to note that surveys with a high incidence of anaemia such as Davidson (1935) and Fullerton (1936) showed a relationship between the levels and age. The survey of Davidson (1942) is an exception, however.

More agreement is reached regarding the significance of parity. Reid and Mackintosh (1937) were of the opinion that parity played a part in the development of anaemia after the fifth pregnancy and where social conditions were poor, its effect might become apparent in earlier pregnancies. Davidson (1935) however considered parity to have no influence on haemoglobin levels and Fullerton (1936 a) stated that parity was really an effect of age. Recent surveys such as those of the Medical Research Council (1945) Fullerton et.al (1944) and Roscoe and Donaldson (1946) revealed no correlation between haemoglobin levels and parity. In our present survey it has been shown that women with normal haemoglobin values had an average parity of 2.1, that the average parity rose to

3.5 in women with moderate anaemia and to 3.6 in women with severe anaemia. Statistical analysis of these figures showed that the differences in the average parity of the various haemoglobin groups were not significant and therefore parity did not appear to be a factor in the causation of the anaemia.

By now it will be seen that many factors such as diet, environment, social habits, age parity, etc., have to be considered when reviewing the aetiology of hypochromic anaemia of pregnancy. The majority of authors are of the opinion that dietary deficiency does play a part in determining the incidence of anaemia in pregnancy (Davidson and Fullerton 1933, Reid and Mackintosh 1937. McCance 1938, Hamilton and Wright 1942). On the other hand Watson (1938) considered that as a factor diet was unimportant.

An inadequate diet inevitably results in a diminished iron intake which is now generally accepted as a factor in the causation of both idiopathic hypochromic anaemia and hypochromic anaemia of pregnancy. Numerous authors have published papers on the dietary iron requirements during pregnancy. Coons (1932) calculated that 14.7mgm. of iron were necessary as a daily intake to give a positive balance of 3.16 mgm.

Ohlson and Daum (1935) agreed with these results, but McCance et.al (1938) considered values as high as 20 mgm. daily were necessary. More recently the National Research Council U.S.A.(1947) put the daily requirement at 15 mgm. Lower threshold values have however been proposed. Farrar and Goldhamer (1936) kept two women in positive iron balance for long periods on daily intakes of 5.2 mgms. and Kyer and Bethell (1936) were able to maintain the haemoglobin levels of healthy young women during the last three months of pregnancy on a diet supplying only 7.1mgm of iron daily. However, no account was taken of the iron stores which, according to Coons (1932) are laid down during the earlier months and may have released the necessary iron while the haemoglobin level was maintained. From the practical aspect Davidson and Fullerton (1938) were able to show that the majority of women in their series were in negative iron balance and their diets were low in animal protein. The average daily intake was 7.71 mgm and according to Elvehjem (1933) and Shackleton and McCance (1936) only 75 per cent of this intake was available and of that only a possible 50 per cent could be absorbed.

It has been shown by many authors that the incidence of anaemia in certain parts of the country

has fallen (Davidson et al.1935, Fullerton 1944, Davidson et.al 1942 and 1944). This improvement has been attributed to the introduction of the national loaf, which has raised the iron intake in the country (McCance and Widdowson 1940). Klatsein (1940) and Fuhr and Steenbock (1943) have shown, however, that where there is an upset in the calcium, phosphorus ratio and especially when there is an increased amount of phytic acid in the diet the absorption of iron is less; but when vitamin D is given, optional absorption of iron is maintained. It would therefore be interesting to correlate the incidence of anaemia not only with the iron intake but also with reference to the calcium, phosphorus and vitamin D intake. Results of this from our social survey are not as yet available, but it is interesting to note that the average daily iron intake of eight women attending the out-patient department at present is 16.7 mgms. This value according to the generally accepted standards is very satisfactory but despite this, the incidence of anaemia in Glasgow appears to be much higher than in the rest of the country. It may be that some dietary imbalance, such as that suggested above is present. However, further investigation is required before any definite opinion can be given.

Of the patients in the "low normal group" who were given special dietary advice during their pregnancy, it has been shown that 32 per cent improved, 52 per cent showed no change, and 16 per cent deteriorated. The patients were seen on the average between the fifth and sixth months of pregnancy and remained under supervision till term. Comparing the results in this group with a similar control group it was shown that special diet increased the percentage improvement, but did not prevent the appearance of anaemia. It would therefore appear that diet alone in the later months is not sufficient to correct an anaemic state and this would further suggest that the storage arrangements in the early months of pregnancy have been upset.

Little attention has been paid in recent surveys of anaemia of pregnancy to the health of the patient during the early months of gestation. Strauss and Castle (1932, 1933) were the pioneers to investigate the relationship of gastric function and anaemia of pregnancy. They showed that the pH of the upper intestinal tract was a factor in the absorption of iron; that 75 per cent of their cases of anaemia showed a hypochlorhydria during pregnancy and 80 per cent of these showed an increased secretion of hydrochloric acid in the puerperium. They also demonstrated that

a maximal fall in haemoglobin occurred when the diet was inadequate and hypochlorhydria present. Davies and Shelly (1934) confirmed these results, but Bethell et al (1938) found no correlation between the degree of anaemia and the amount of free acid secreted. In the present survey it has been shown that gastro-intestinal disorders in the early months of pregnancy occurred in 48 per cent of the patients in "low normal" group who deteriorated, whereas only 33 per cent of the patients who maintained their haemoglobin levels gave this history. These figures were statistically analysed and found to be significant. Further, The Combined Textbook of Obstetrics and Gynaecology (1944) states that up to 50 per cent of pregnant women suffer from morning sickness in the early months of pregnancy. A history of gastro - intestinal upset in the early months of pregnancy was given by 36 patients suffering from anaemia in the later months. Of these 22 had a moderate degree of anaemia and responded well to iron therapy. The remaining 14 however failed to maintain their initial response and their haemoglobin level became static despite continued treatment. So far as one could judge, the severity of the gastro-intestinal upset was of the same order in both groups. This

suggests that the storage of iron in the second group of the patients was already deficient before pregnancy commenced. The results would further suggest that dietary deficiency per se is responsible for anaemia in a small percentage of women during the later months of pregnancy and that the severity of the anaemia is increased by gastro-intestinal disorder in the early months. Finally it would seem that gastro-intestinal disorder in the early months of pregnancy of itself may be responsible for many cases of moderate anaemia. The failure of the cases of severe anaemia to maintain their response to iron therapy suggests that their dietary deficiency is not altogether one of simple diminished iron intake, but is possibly a more complicated process involving other haematinic factors. Thus the importance of gastro-intestinal disorders in the early months of pregnancy when the rate of maternal iron storage is, or ought to be, at its maximum (Coons 1932) should not be underestimated and the results of the present survey suggest that mild gastro-intestinal upset in the early months of pregnancy appears to be a determining factor in the development of anaemia in the later months.

Finally in considering the aetiology of hypochromic anaemia of pregnancy, the question of

pregnancy itself as factor must be considered and here the greatest diversity of opinion occurs. Most reviews avoid this difficulty by subdividing the anaemia into a) hypochromic anaemia induced by pregnancy and b) pre-existing idiopathic hypochromic anaemia complicated by pregnancy (Smallwood 1936, Elliot 1944, Stevenson 1936, Whitby and Britton 1946) and give no indication of the incidence of either. Without the knowledge of the haemoglobin reading before the onset of pregnancy it is difficult to come to any conclusion. Elliot (1944) suggested that a return to normal haemoglobin levels within a few weeks of delivery may indicate that the haemoglobin percentage was normal before pregnancy and therefore the existence of anaemia during pregnancy could only be related to the pregnancy. Whitby and Britton (1946) state that any distinction made between the two is mainly theoretical and that both types are clinically similar except that idiopathic hypochromic anaemia complicated by pregnancy tends to occur in older women and to be more constantly associated with achlorhydria. Fullerton (1936a) is of the opinion that in the majority of cases the anaemia antedates the pregnancy. He calculated the total iron requirements of foetus, placenta, uterus, increased body tissues, blood loss at parturition and 7 months lactation as 905 mgm of

iron (Coons 1936, Macy and Hunscher 1934). This he stated was equivalent to sixteen menstrual periods with a loss of 57 mgm of iron at each period. Since normal menstrual loss may vary up to 78 mgm. of iron, he suggested that in some cases menstruation might cause a greater strain on the iron reserves than pregnancy (Fowler and Barer 1935, Barer and Fowler 1936). He further estimated the expected fall in haemoglobin in the case of a normal woman who retained no iron at all from her food during pregnancy and he found the maximum fall in haemoglobin, which the "iron demand" of pregnancy could cause was from 100 per cent to 78 per cent Haldane. He therefore said that "in the most unfavourable conditions which probably do not exist, only a moderate degree of anaemia can develop from uncomplicated pregnancy" (1936b). In support of this hypothesis he was further able to show that, allowing for the hydraemia of pregnancy the haemoglobin levels of pregnant and non-pregnant women were the same for each age group. i.e. The incidence of anaemia in pregnant women is no greater than that of the non-pregnant; it is only more apparent.

The results published by the Medical Research Council (1945) of a survey of haemoglobin levels in Great Britain show a greater incidence of anaemia

among parous women than among nulliparae and the authors suggest that in the case of parous women the demands of pregnancy could not be fully met. These findings therefore are not in agreement with those of Fullerton above.

Also, in the present survey, it has been possible to demonstrate the appearance of moderate anaemia at the eighth month of pregnancy in 29.4 per cent of the patients who had haemoglobin readings at the lower range of normality when 5.4 months pregnant. In two instances the haemoglobin reading fell as low as 51 per cent Sahli (8.16 gms. haemoglobin per cent) before treatment could be commenced and a further two patients, who developed mild pyuria, which was treated at the out-patient department, reached levels of 48 per cent and 47 per cent Sahli (7.72 gms haemoglobin per cent). All four cases responded to iron therapy. According to the standards here two of these cases could be regarded as "severe anaemias", but since minor complications did arise in these patients, they unfortunately cannot be considered. Of the other two patients, who had "uncomplicated pregnancies" it can be said that moderate anaemia did develop and though conditions in Glasgow are bad, they are probably not "the most unfavourable". The results would suggest that the

added strain of pregnancy in many women whose Hb readings come within the low-normal range is sufficient to cause anaemia in the later months. It is probable that such low-normal cases are really examples of deficient iron storage, but this point will require further investigation via dietary and biochemical analyses.

The response to iron therapy has been recorded in three groups of patients viz. a low normal group, a group of moderate anaemias and a group of severe anaemias. Considering the normal group first it must be said that innumerable papers have been published by various authors claiming a rise in haemoglobin levels as compared with a fall in a similar control series (Toland 1936, Corrigan and Strauss 1936, Hamilton and Wright 1942, Lobate 1939, Linder and Massey 1939). Others have failed to note this improvement (Adair and Dieckmann 1936, Evans 1943. Meyer-Weddell 1943, Roscoe and Donaldson 1946(b)). In the present survey the number of patients who received iron is small and therefore no definite conclusion can be drawn, but it is interesting to note that 40 per cent of the low normal patients registered an improvement, compared with 4.7 per cent of the control series. The improvement on iron fell within the range of 60 to 75 per cent Sahli or 9.6 to 12 gms haemoglobin per cent. Though iron therapy was continued no higher

reading was recorded. The prophylactic value of iron therapy in this group could also be demonstrated. Only 8 per cent of the treated cases deteriorated whereas 29.4 per cent of the control group became anaemic, and as a result of this finding all patients at the ante-natal clinic with haemoglobin readings falling within the "low normal" range are now regarded as potentially anaemic and are treated with iron routinely.

Sixty three patients with moderate anaemia were treated with iron. The response in these cases was satisfactory, only two of the seven resistant cases of the whole series fell within this group and one of these was the patient who responded to iron therapy after admission to hospital. The average rise in haemoglobin for the moderate anaemias during the first month of therapy was 7.3 per cent Sahli and in each succeeding month a further rise of approximately 6 per cent was recorded.

The response to iron therapy in the case of severe anaemias was not so satisfactory. Five of the resistant cases fell within this group and as has already been shown 14 of the patients in this group, who had mild gastro-intestinal disorders as complicating factors, only partially responded to the iron. Of the remaining 21 "pure anaemias" in this group the reponse

was satisfactory, the haemoglobin reading rising 9 per cent Sahli in the first month of therapy, and by successive steps of 6 per cent per month thereafter.

It will therefore be seen that the response to iron therapy in the 140 patients surveyed, was by no means 100 per cent. In general, however, it may be said to be satisfactory although not so good as that reported by some authors (Stevenson 1936, Adair et al 1936, Smallwood 1936, Dillon 1943, Wolff and Limarzi 1946, Whitby and Britton 1946). In our series as the anaemia became more severe the number of resistant cases increased. The blood picture was examined in the latter cases and was found to be normocytic or microcytic and hypochromic in every instance. Several authors have reported similarly resistant cases and a few have suggested a possible cause for the resistance. Elliot (1944) in a survey of 28 anaemic women found that some of his cases did not show a characteristic response to iron. Minot and Heath (1932) described a few cases which did not respond satisfactorily and they considered this was due to a hypochlorhydria. Bethell (1936) found a few cases resistant to iron therapy and he suggested that they may be due to a protein deficiency.

A further possibility has to be considered in view of the recent work regarding the peripheral blood

picture of pernicious anaemia of pregnancy. Numerous cases showing atypical blood picture have been recorded. (Stevenson 1936, Abramson 1938, Segerdhal 1941, Miller and Studdert 1942, Davidson, Davis and Innes 1942 (b) Lescher 1942, Callender 1944). Many cases previously regarded as iron deficiency anaemias, on account of a microcytic or normocytic hypochromic blood picture have now, by modern haematological methods been proved to be actual cases of pernicious anaemia of pregnancy. It is obvious that this group of cases resistant to iron therapy require further investigation along the lines suggested by the above authors and also with regard to their relationship to simple iron deficiency anaemia of pregnancy.

Twenty five patients in the "low normal" group were given vitamin C in large doses during the later months of pregnancy, and the results were compared with those of a similar control group. Vitamin C appeared to reduce the incidence of deterioration, only 12 per cent of the patients in this group developing anaemia, as compared with 29.4 per cent of the control group. In this respect vitamin C was almost as effective as iron, which, given to a similar group, showed an 8 per cent deterioration. When improvement with vitamin C therapy was considered, the results were not so satisfactory as

those obtained with iron; only 16 per cent improved as compared with 40 per cent in the group receiving iron. It has been suggested by Powell (1944) that vitamin C by its reducing action renders more iron available for absorption and to this fact the maintainance of the haemoglobin level in this group could be attributed. A pure vitamin C deficiency anaemia has been produced experimentally in animals (Meyer and McCormack 1928, Metier et al 1940) but whether such a condition, due solely to a vitamin C deficiency, exists in man, is doubtful (McMillan and Inglis 1944, Crandon, Lund and Dill 1940). Certainly our patients showed no clinical evidence of a deficiency and, since all the patients in the low normal group, who deteriorated, responded spontaneously to iron therapy, it is more likely that a mild iron deficiency was the factor. Meyer Weddell (1942) reported ten cases of probable vitamin C deficiency anaemia occurring during pregnancy, but all these cases had failed or showed only a modified response to iron and liver therapy. Young et al (1946) reported on the plasma ascorbic acid levels in pregnant women at various periods of their pregnancy and in the puerperium. They found no evidence of any general state of deficiency of this vitamin, and from our results also it would appear and there was no evidence to show that

such a deficiency existed in patients in the low normal group.

Summary.

(1) A survey of 4,595 routine haemoglobin estimations in patients attending the ante-natal clinic for the first time has been carried out and the incidence of anaemia determined.

(2) The haemoglobin level in normal pregnant women is variable, with a basic value of 60 per cent Sahli or 70 per cent Haldane.

(3) 85 women in the "low normal group" i.e. with haemoglobin readings above or near the basic level were followed throughout pregnancy. Almost one third of these patients developed anaemia and a smaller number might temporarily have been regarded as anaemic. From these facts a correction factor was deduced for the total incidence of anaemia and an ammended figure suggested. The results show that 20.1 per cent of all women attending the out-patient department were anaemic i.e. had haemoglobin readings less than 70 per cent Haldane and of these 4.6 per cent were severely anaemic. The literature has been reviewed and the high incidence of anaemia in Glasgow stressed.

(4) The significance of age, parity, environment, social habits, diet etc., as factors in the causation of the anaemia have been discussed. Age was found to be significant as a factor only in severe anaemia and

parity did not appear to be significant at all. Dietary deficiences before and during the early months of gestation; were probably responsible for increasing the severity of an anaemia, which became apparent in the later months.

(5) Gastro-intestinal disorder in the early months of gestation was apparently responsible for many cases of moderate anaemia in the later months. Where dietary deficiences also existed, the anaemia was severe and did not react in the usual manner to iron therapy.

(6) The response to iron therapy in 140 cases of anaemia seen at the ante-natal clinic and followed right through their pregnancies has been shown. The majority responded satisfactorily to iron therapy. Seven,however, were resistant and 14 showed a modified response. In the first group no definite aetiological cause for the "resistance" to therapy could be found whereas in the second group of 14 severe anaemias, all the patients gave a history of gastro-intestinal disorder in the early months of pregnancy and this may have altered their ability to deal with iron.

(7) In an attempt to determine what part minor dietary deficiences might play in the development of anaemia in patients of the "low normal" group, 105 patients from this group were given adjuvant treatment in the later months of their pregnancies and their

progress was noted, as compared with the control group of 85 untreated "low normal" patients. They were divided into four groups receiving iron, vitamin C, enhanced diet and marmite. The best results were obtained in the group receiving iron where the deteriorations were reduced by two thirds and the improvements increased nine times as compared with the control group. Vitamin C reduced the number of deteriorations by more than half but had little effect on the improvement rate. Enhanced diet was able to raise the haemoglobin level in six times the number of patients but had no effect on the number of deteriorations. The results with marmite approximated too closely to those of the control group for any conclusion to be drawn. It is suggested that an iron deficiency was probably present in some of these patients; that vitamin C made more iron available for absorption and thus prevented a number of the deteriorations and that enhanced diet by increasing the total iron intake remedied that deficiency in patients who were able to absorb iron, but could not prevent deterioration in those who were not.

CLINICAL RECORD CARD.

THE GLASGOW ROYAL MATERNITY AND WOMEN'S HOSPITAL

DIAGNOSIS

NAME

AGE PARITY DATE FIRST SEEN.

L. M. P. DUE

OBSTETRICAL HISTORY:-

FAMILY HISTORY:-

CLINICAL FINDINGS:-

Skin, Appendages, Soft Tissues.
- Purpura
- Positive Tourniquet Test.
- Koilonychia.
- Other Abnormality.

C. V. S.
- Dyspnoea.
- Angina.
- Palpitation.
- Syncope.
- Systolic Murmur.
- Other Abnormality.

Alimentary System.
- Cheilosis.
- Stomatitis.
- Glossitis.
- Dysphagia.
- Dyspepsia.
- Achlorhydria.
- Diarrhoea.
- Steatorrhoea.
- Thirst.

Respiratory System.
1.

Urinary System
1.

Nervous System.
1.

Reticulo-Endothelial System.
- Splenomegaly.
- Adenopathy.
- Other Abnormality.

Bones.
- Sternal Tenderness.
- Other Abnormality.

Abnormal Blood Loss.

Dietetic Deficiency.

Response to Treatment
1. Crude Liver.
2. Pure Liver.
3. Iron.
4. Vitamins.
5. Other treatment.
6. No response.

Summary of Lab. Findings.
1. R. B. C.
2. Hb.
3. W. B. C.
4. P. C. V.
5. M. C. V.
6. M. C. H. C.
7. Reticulocytes.
8. Platelets.
9. Fragility.
10. Bilirubin.
11. W. R.
12. Film
13. Marrow.

SPECIMEN COPY.

CLINICAL SURVEY.

INTRODUCTION:-

In this survey a complete clinical record of 104 patients was kept. From the specimen record card it can be seen that this included a record of the patient's obstetrical history, her family history, her previous history and her present condition. When she first appeared at our haematological clinic her complaints, if any, were noted, but since she already knew she was "bloodless" by the time she reported to the laboratory, less attention was paid to these secondary complaints than to the initial complaint made to the nurse at the ante-natal clinic. In addition to the obstetrical examination a full clinical examination of each system including cardio-vascular system, respiratory system, central nervous system, alimentary system and urinary system was carried out. Records were kept of the laboratory findings and the response to treatment. The back of the report card was used for progress notes including details of her labour, the puerperium and the baby.

Of the 104 patients selected, 44 were moderate anaemias i.e. had haemoglobin readings between 50 per cent and 59 per cent Sahli and the remainder were severe anaemias with haemoglobin readings below 50 per cent

Sahli. The cases were reviewed in respect of symptoms and signs. The striking feature in all these cases was the number of patients who had no complaint to make at all and who stated they felt perfectly well. It is obvious therefore that the majority of these patients would not have been recognised as anaemic, had it not been for the routine ante-natal haemoglobin estimation. Of the moderate anaemias only 34 per cent of the patients complained of any symptom which could be related to anaemia, and in the severe group this figure was exactly doubled 68 per cent. Only after questioning would a further 46 per cent of the moderate anaemias and 23.7 per cent of the severe anaemias admit to feeling not "quite well". In other words, after questioning the patients further, nine of the moderate anaemias and five of the severe anaemias still maintained they felt well.

Reviewing the symptomatology of the patients in both groups, it was found that the commonest complaint was that of tiredness. 59 per cent of the moderately anaemic patients had this complaint and 80 per cent of the severely anaemic, but in the 14 per cent of the latter the degree was more marked. The same number of patients in each group complained of breathlessness and fewer of dizziness, weakness, palpitation and syncope. Approximately one third of the patients in each group

had complaints relating to the gastro-intestinal system. Anorexia, heartburn, nausea and vomiting were more common than lower bowel dysfunction and constipation occurred more frequently than diarrhoea. In the severe group 11 per cent of the patients gave a history of intermittent attacks of diarrhoea, whereas none of the moderately anaemic patients had this complaint. Half of the severely anaemic and 43 per cent of the moderately anaemic patients complained of exceptional thirst, due to a "dryness" of the mouth and from one third to one half of the patients in both groups had headache or sleeplessness, or experienced "spots before the eyes". Urinary complications occurred equally in both groups in one out of every seven pregnancies, but respiratory infections were less frequent in the moderately anaemic group.

On examination of the patients, pallor of the face was noted more frequently than pallor of the mucous membranes. But here it must be said that cases with high blood pressure with anaemia, had often well injected mucosae and frequently good colour, making it impossible to estimate the degree of anaemia on clinical examination. In these cases, only when the blood pressure fell, did the anaemia become apparent. Cheilosis, glossitis and koilonychia occurred in that order and more frequently in the severe anaemias. Twelve cases or 20 per cent of

the patients in this group had cheilosis, as compared with 6.8 per cent of the moderate anaemias; 14 per cent of the severely anaemic patients complained of glossitis, but on examination a further 21 per cent of the patients had tongues that were smooth or very red and fissured. One case of actual glossitis occurred in the moderate anaemias and an atrophic tongue was noted in three other patients of this group. Only seven cases of koilonychia were noted in the whole series, six in the severe anaemias and one in the moderate anaemias. Oedema occurred in 24 per cent of the severe anaemias, in 8 per cent of which it was marked. Only 16 per cent of the moderately anaemic patients had oedema and in no instance was it marked. A ventriculo-systolic murmur was noted in nine of the severe anaemias.

On the bases of symptoms and signs however, it was seen that three main groups could be distinguished.

A. Anaemias.

B. Anaemias with toxaemia.

C. Anaemia with jaundice.

Group A:-

The majority of the patients fell into this group. Altogether, including the 104 moderate and severe anaemias mentioned previously, category B patients admitted directly to hospital and category A patients who were admitted

directly to hospital from the ante-natal clinic without attending the haematological clinic, 151 of the total number of patients seen, fell into this group. Of these, 44 were the moderate anaemias considered previously, and 107 were severe anaemias. It was found that the incidence of signs and symptoms recorded above for the whole group of anaemias was the same for this group depending on whether the anaemia was moderate or severe, except in four instances.

Two patients out of the whole series surveyed were found to be typical cases of pernicious anaemia of pregnancy. The patients, whose ages were 44 years and 31 years respectively, were seen in their ninth month of pregnancy. They gave histories of increasing weakness, lassitude, breathlessness etc., dating from the sixth month of pregnancy and gradually becoming worse. In one patient gastro-intestinal upset was present; the other complained of heartburn, but, on further questioning, it was found she had been having a very inadequate diet which excluded milk completely. This latter patient also complained of frequent epistaxis. Oedema was present in each case, though not to a marked degree. Both patients complained of glossitis, dryness of the throat and marked thirst, one of the patients complaining of a hoarseness which affected

her speech.

Both patients were very ill and were admitted to hospital directly. Pallor was marked and was the typical "lemon - yellow" colour noted by Stevenson (1936). The mucous membranes were blanched. Cheilosis and Koilonychia were absent. Tachycardia was present and one patient had a ventriculo-systolic murmur. The spleen was enlarged and could be felt one finger breadth below the costal margin in one case. One of the patients, the older of the two women, had a chronic bronchitis present as a complicating factor. Examination of the urine revealed no abnormality in either case.

From the above findings it will be seen that in these two cases of confirmed pernicious anaemia of pregnancy the symptomatology did not vary considerably from that of the other severe anaemias described, except that the symptoms were more marked; the patients were obviously ill and in one case the splenic enlargement and epistaxis were not typical, while the marked degree of glossitis and hoarseness of the voice in the latter were not found in any of the other severe anaemias.

The remaining two anaemias in group A which require special attention were two cases of haemolytic anaemia. As both of these cases differed widely in their symptomatology, they will have to be considered

separately. The first patient, a married woman, age 28 years, had seen service with the W.A.A.F. in Italy and was demobbed on account of the present pregnancy. Her health remained excellent till the sixth month when she complained of pain in the left hypochondrium, followed a week later by swelling of the ankles, a slight yellowish pallor of the skin, dyspnoea, and extreme weakness. She became rapidly very ill and was admitted to a nursing home. A diagnosis of pernicious anaemia of pregnancy was made and treatment with anahaemin, 2 c.c daily, oral liver and iron was commenced. Her condition improved clinically; the oedema disappeared, but she still felt weak and stated she had felt no life since admission to the home. After six weeks, when progress seemed to have come to a standstill, she was admitted to hospital for further investigation.

On examination she was very thin. Her temperature was normal, but the pulse rate was slightly elevated. She looked anaemic and the skin had a faint icteric tinge. The mucosae were pale. There was no glossitis, cheilosis, koilonychia, etc., nor were there any symptoms relating to the gastro-intestinal tract. The cardiac borders were within normal limits and a ventriculo-systolic murmur could be heard at all areas. Her blood pressure was normal, no oedema could be

detected and the lymphatic glands were not enlarged to palpation. The striking feature of the whole examination was the size of the spleen. It could be felt four finger-breadths below the costal margin and was slightly tender on deep pressure. The liver was not enlarged to palpation. The uterus was six months size and no foetal heart could be heard. A diagnosis of haemolytic anaemia was confirmed by examination of the peripheral blood and bone marrow. These findings will be discussed later.

The second case of haemolytic anaemia was seen after delivery. The patient, a young unmarried girl aged 21 years, was admitted to hospital at term with a severe pre-eclamptic toxaemia. Labour was induced surgicallyand 25 hours later she delivered herself spontaneously of a female, mature live child weighing 5½ lbs. Haemorrhage was moderate. Her blood pressure remained elevated till the fourth day when it fell to 140/90 and only then was her pallor noted. She became rapidly anaemic within the next two days, and had a moderately severe epistaxis. Blood transfusion was necessary and had to be repeated seven days later. Although she was pyrexial and coliform bacilli were found in the urine on culture, blood culture was negative. Jaundice was not noted clinically but was present in the plasma. The spleen was enlarged and

the liver edge which could be felt one inch below the costal margin, was tender to palpation. The diagnosis of a haemolytic anaemia was confirmed by laboratory findings, which will be discussed later in the text. It is sufficient to note here the similarity that exists clinically between pernicious anaemia of pregnancy and a haemolytic anaemia complicating pregnancy, where the jaundice, as here, is not marked and the splenic enlargement not typical.

GROUP B:-

Altogether 29 patients were included in this group. Of these 10 were anaemias who developed toxaemia in the course of therapy, 7 were toxaemias complicated by anaemia and 12 were cases of anaemia who presented a clinical picture very similar to that of pre-eclamptic toxaemia.

In the first two groups the toxaemia was the major factor in each case and the majority of patients were admitted to hospital because of it, though two patients were admitted to hospital initially because of severe anaemia and developed toxaemia while in the wards.

The remaining twelve cases are interesting however. Three were treated antenatally in the wards of the hospital, two paid one visit to the haematological

clinic and the remaining seven were admitted directly to hospital as pre-eclamptic toxaemias. Thus five cases were examined personally before delivery and had sternal punctures done. The records were available for the other seven and a blood picture was available in every case before delivery. It was found that these twelve cases fell into two clinical groups depending on the severity of the anaemia. The nine patients who received no treatment had no complaint to make at all apart from oedema, which was only present to a marked degree in three cases. All were severe anaemias with haemoglobin readings averaging 40 per cent Sahli and ranging between 33 per cent and 48 per cent. The two patients who were seen personally had no complaint to make originally and it was only after repeated questioning that they would admit to feeling "slightly tired". The blood pressure was raised in every instance and the readings ranged from 175/100 to 140/90. With the exception of two patients who had pyuria due to a coliform infection, only a trace of albumen could be detected in the urine. Pallor was noted in the two patients examined personally, who had haemoglobin readings of 33 per cent and 37 per cent Sahli; the mucosae were pale and cheilosis was present in one. Both had oedema of the feet and ankles, but apart from that clinical examination was otherwise

negative.

Of the nine patients, one was surgically induced on admission to hospital and a second was delivered at home while awaiting admission. Of the remainder the blood pressure became normal within 24 hours of admission in three, within 48 hours in two and within a week in two. All the patients were delivered before treatment was commenced and it was not till the third day of the puerperium that these patients complained of any symptoms relative to anaemia. Four patients with initial haemoglobin readings of less that 40 per cent Sahli complained of extreme weakness after delivery and felt dizzy even when sitting up in bed. Pallor was marked, oedema had disappeared, and in one case the spleen was palpably enlarged.

Of the three cases treated antenatally two were admitted as "pre-eclamptic toxaemias", the third as "oedema and anaemia". In all three the blood pressure was raised, readings from 160/90 to 140/80 being recorded. Oedema was marked extending right up on to the abdominal wall and in one patient even the face and hands were markedly swollen. In this patient pallor was not marked and despite the severe anaemia (haemoglobin equal to 24 per cent Sahli) the mucous membranes were moderately coloured. Only a trace of

albumen was found in the urines and this cleared up soon after admission. All three patients were very severe anaemias with haemoglobin readings varying from 32 per cent to 23 per cent Sahli. They gave histories of increasing weakness and tiredness with the development of oedema of one month's duration. One patient was able to relate her symptoms to an attack of diarrhoea and vomiting one month previously. She and another patient had been having an inadequate diet, but the third patient, who came from the Outer Hebrides had a good dietary intake except for the absolute exclusion of green vegetables in winter and oatmeal which had become scarce since rationing. All three women belonged to the older age group, their ages ranging from 36 to 39 years. Two were primigravidae and the third was a para four.

As before the blood pressure fell and the albumenuria cleared up after admission, but the oedema which was gross in these three cases took longer to disappear. The peripheral blood picture and marrow picture were examined in each case before therapy was commenced.

It will be seen that a close similarity exists between the nine milder cases mentioned previously, the three severe cases above and cases of pre-eclamptic

TABLE VIII

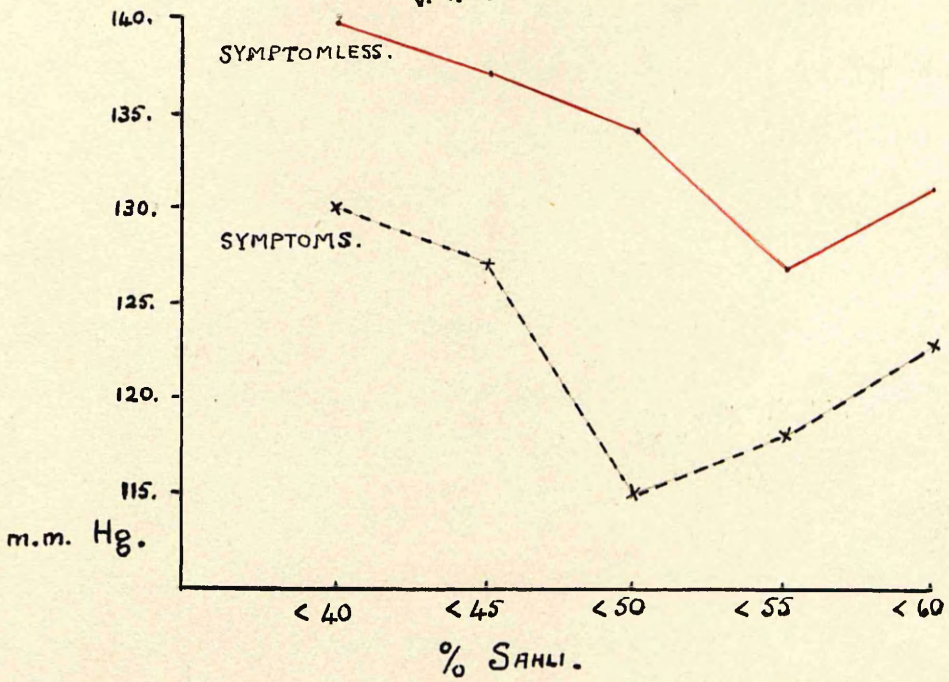
Anaemia simulating Toxaemia.	Toxaemia.
1. B.P. not so high and systolic more than diastolic, high pulse pressure.	1. B.P. high, particularly diastolic, pulse pressure, raised but not so marked relatively.
2. B.P. falls soon after admission.	2. B.P. remains high or falls only slowly.
3. Oedema more marked.	3. Oedema not always marked.
4. Albumen a trace.	4. Albumen usually estimates.
5. Anaemia severe, but may be symptomless.	5. Normal Hb. or moderately anaemic.
6. Untreated anaemia marked in puerperium.	6. -

toxaemia. However several distinguishing features are apparent (Table VIII). Firstly, in anaemia simulating toxaemia the blood pressure is usually not as high as in a pure toxaemia and when it is raised the systolic blood pressure would appear to be relatively higher than the diastolic, giving therefore a greater pulse volume. Also, the blood pressure tends to fall soon after admission to hospital. Secondly oedema is relatively more marked and may be the only complaint which the patient has. Thirdly albumenuria is not a prominent feature in anaemia simulating toxaemia; the albumen is present in the urine as a trace usually and clears up soon after admission. Finally the anaemia may or may not be an obvious feature. It has been shown that in this group the majority of the patients with severe anaemia did not complain and did not look anaemic till after delivery, when in the third day of the puerperium and thereafter when post partum haemodilution was maximal (Oberst and Plass 1936, Crawford, 1940) the symptoms became proportional to the degree of anaemia. Haematologically and biochemically, features peculiar to this group of anaemias were found, but these will be discussed in a later section of the thesis.

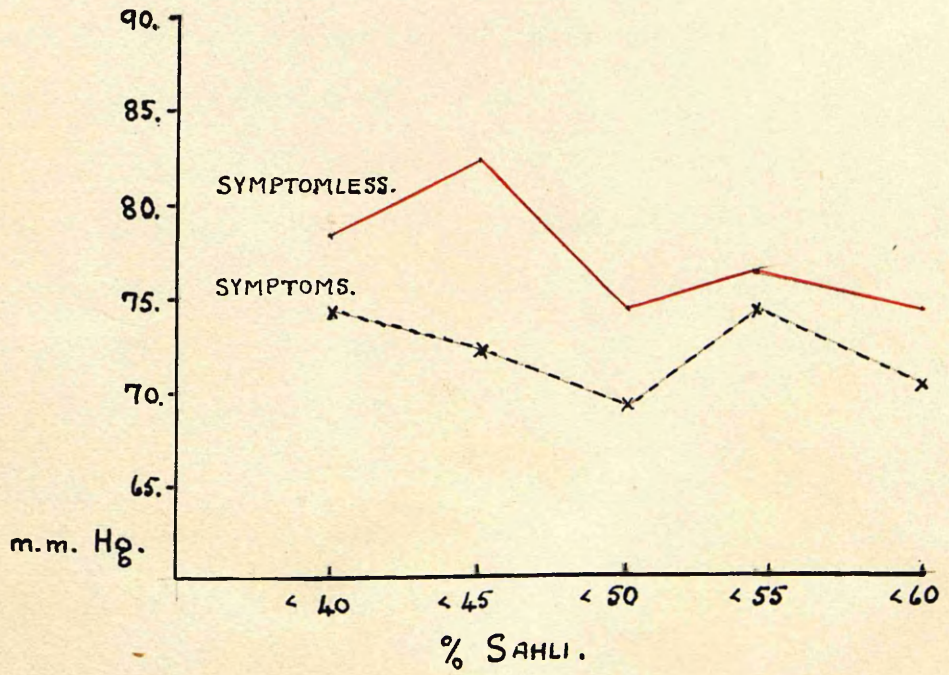
The absence of symptoms in nine out of twelve patients in this group of severe anaemias would suggest

CHART V

V.A. SYSTOLIC BLOOD PRESSURES.



V.B. DIASTOLIC BLOOD PRESSURES



that the raised blood pressure was possibly the factor which prevented the patient from appreciating her anaemic state. If this is true, the raised blood pressure might be regarded as a compensatory reaction of the body to the anaemic state. It was therefore decided to analyse the anaemias in group A and find the average blood pressure systolic and diastolic of the patients with and without symptoms in each haemoglobin group. The results are shown in Chart(V (a) and (b)). It will be seen that the curves for those with and without symptoms are parallel, but the curve for the latter is definitely higher and this holds for both systolic and diastolic readings. Hence it would appear that patients with anaemia, who are asymptomatic, have on the average a higher blood pressure than those who have symptoms and that this occurs irrespective of the degree of anaemia. Further as the anaemia becomes more severe the number of cases without symptoms in each group is gradually reduced and finally includes the cases of anaemia simulating toxaemia described above.

GROUP C:-

Stevenson (1936) first stated that a number of her cases of hypochromic anaemia of pregnancy showed signs of "haemolysis" viz. positive Van den Bergh, excess urobilinogen in the urine and she was unable to explain,

"why the signs of haemolysis are so slight in the "pernicious" group and why they are present in some cases of the "secondary" group". On this account she felt that the hypochromic anaemia of pregnancy might not be a single group of anaemias.

In the course of treatment of patients with hypochromic anaemia at the haematological clinic, it was noted that the plasma of a number of the patients attending was jaundiced and gave a positive Van den Bergh reaction. These patients were also found to have increased urobilinogen in the urine, but the red cell fragility was normal. As the pregnancy advanced and the anaemia responded to treatment the "jaundice" tended to clear up, but would reappear again if the patient developed a gastro-intestinal upset or an infection, such as a cold or pyuria. Some connection therefore appeared to exist between the jaundice, the anaemia and the incidence of complications as mentioned above.

At the same time it was noted that several of the bloods taken off routinely at the ante-natal clinic for haemoglobin estimation had jaundiced plasma and that the haemoglobin in these cases was usually normal. It was therefore decided to follow these patients right through their pregnancy with monthly estimations of

their haemoglobin, icteric index, Van den Bergh urobilinogen and bilirubin excretion. A total of 1,890 clinic bloods were observed and of these 112 or 5.9 per cent were found to give positive Van den Bergh reactions. Of the original 112, some did not report back and ultimately only 70 patients could be followed right through their pregnancies.

The normal patient attending the clinic has an icteric index of 2 to 3 and a Van den Bergh reaction, which is negative directly and indirectly, whereas the 70 patients followed up, had either a direct or an indirect Van den Bergh. However, when these 70 cases were reviewed it was found that seventeen patients who had a negative direct and a positive indirect Van den Bergh which was insufficient to estimate, showed no correlation between the three factors. viz, jaundice, anaemia and complication. This would suggest that an indirect Van den Bergh insufficient to estimate is not significant in relation to the occurrence of anaemia and it may occur normally in a pregnant woman. Certainly, in the seventeen cases followed each month, the pregnancy was normal in every respect. Finally therefore, the numbers were reduced to 53 patients who had either a positive immediate or delayed direct Van den Bergh or a plasma bilirubin estimating more than

0.8 mg. per cent. These patients could then be divided into three groups:-

(a) 20 patients who were already anaemic.

(b) 21 patients who developed anaemia.

(c) 12 patients who did not become anaemic.

Considering the anaemic patients first, it was found that the average time of the first appearance at clinic was 6.7 months and that the average haemoglobin for the group was 55.2 per cent. The majority of the patients were "quite well" when they reported for a second blood test a month later, but they gave a history or were found to have some complicating factor in the pregnancy. 55 per cent of the patients complained of a gastro-intestinal disorder, which was either an acute attack lasting a week or so, or persistent morning sickness lasting months. Two of these patients required special attention. One patient developed severe sickness and malaise, became clinically jaundiced with a plasma bilirubin estimating at 14 mg per cent and was ultimately diagnosed as an acute hepatitis. This patient became very anaemic, but made a good recovery and responded well to iron therapy. The second patient came to clinic complaining of swelling of the abdomen and persistent vomiting. She was sent for an X-Ray and

told to report back in three days time. During this time, she became very much worse, the abdomen was tense and tender; sickness persisted and she was very dehydrated. The jaundice had increased; the anaemia was more marked and she had oliguria. Laparotomy was performed and at the operation, she was found to have a twisted ovarian cyst. She made an uneventful recovery; the jaundice which had estimated 2.8 mg. of bilirubin per cent cleared up and the haemoglobin which fell from 55 per cent at the first visit to 38 per cent ultimately, reached normal levels after two months iron therapy. Both these patients were clinically jaundiced and at the height of their illnesses bile was detected in the urine in each case.

A further 15 per cent of the patients in this group gave histories or still had signs of a mild pre-eclamptic toxaemia. Only one patient required admission to hospital on this account and she was dismissed "well" two weeks later. One patient had an active tuberculous infection and one patient was a cardiac. The remaining four patients or 20 per cent gave no history whatsoever and apart from the anaemia no other abnormality could be found.

Eight patients in this group were given iron and responded satisfactorily. The average rise in haemoglobin was 12 per cent. A further seven patients showed

spontaneous improvements. The remaining six patients showed little change in their anaemic state.

(b). In this group the average initial haemoglobin was 63.9 per cent, the majority of the patients falling within the "low normal" range. The average time of the first appearance at clinic was 4.8 months i.e. considerably earlier than the previous group, and 75 per cent of the patients still had symptoms relating to the complication when they were seen for the first time. All these patients ultimately became anaemic and the average time of appearance of the anaemia was 6.2 months, i.e. approximately the average time of appearance of the first group, who were already anaemic (Table IX.). The average and ultimate haemoglobin level for the second group was 51.9 per cent Sahli giving an average drop of 12 per cent Sahli.

The complicating factors in this group were examined as before and the results showed that 52.4 per cent of the patients had gastro-intestinal upset; 23.8 per cent had an infection, 9.5 per cent had toxaemia; one case was a cardiac, 4.8 per cent, and the remaining two cases or 9.5 per cent had no factor present as a complication. These two patients had therefore a latent jaundice; they developed anaemia later and no apparent cause could be found for either condition.

Seven of the patients in this group, who became

TABLE IX.

	Time of Jaundice (months)	Time of Anaemia (months.)
Group B.	4.8	6.2
Group A.	-	6.7

anaemic were given iron therapy and the average rise in the haemoglobin was 12 per cent. Two patients showed spontaneous improvements in their anaemic condition without iron, nine patients developed moderate anaemia, two tending to rise before term and three patients became progressively worse, developing severe anaemia before term.

(c) This group consisted of 12 patients seen for the first time in their pregnancies at an average of 6.4 months and with a haemoglobin reading of 67 per cent i.e. higher than in the previous groups. Five patients in this group who were seen at an earlier month of gestation than the average for the group did "deteriorate" within the range of normality i.e. the haemoglobin reading fell more than 5 per cent Sahli, but still remained above the basic level of normality. The remaining seven patients, who showed no significant deterioration, were not seen until 7.9 months pregnant. Four of these patients had no history of any complication early in pregnancy. Their symptoms were all of recent origin. Two patients had no symptoms whatsoever, and the remaining patient who was seen in the ninth month of her pregnancy, gave a history of sickness, early in pregnancy. Whether she had been anaemic before, and had shown spontaneous improvement, as nine of the cases in

the whole series did, is difficult to say, but it is a possibility.

From the findings in this group, the following tentative suggestions can be made. Firstly, the higher the original haemoglobin reading, the less chance there is of the patient becoming anaemic. Secondly, if the complicating factor occurs early in pregnancy, even a patient with a high normal haemoglobin reading may show a significant drop in the haemoglobin reading within the range of "normality". Finally, if the complicating factor arises in the later months of pregnancy, there is less tendency for a patient with a high normal haemoglobin reading to show any significant change in the level.

It is obvious that, despite the apparent correlation between the complicating factor, jaundice and anaemia, the question arises whether these cases are not really cases of familial non-haemolytic jaundice as described by Gilbert et.al(1907) Weber (1917) Van den Bergh (1933) Rozendal et.al.(1935) Meulengracht (1939) Damashek and Singer (1941) Alwell et al (1946) and Barrie (1946). In other words, that the jaundice was a constitutional inadequacy, that it was common to these patients and bore no relation to the complicating factor and the anaemia. Such did not appear to be the

TABLE X.

	No.	+++	++	+	(+)		% positive urobilinogen
Hydramnios.	.2	1			1		50
Pre-eclampsia.	44	1	4	5	8	26	23
Infection.	31	4	2	6	8	11	39
Intra-uterine Death.	2			1		1	50
Ante-partum Haemorrhage.	5				2	3	0
Vomiting.	2	1	-	1			100
Anaemia(severe)	25	6	6	3	8	2	60
Thrombosis.	1				1		0
Obstetric.	22			2	5	15	9
Cardiac.	1				1		0

case, however, since the jaundice had already cleared up in thirty two of the patients in the series by the time of delivery, while in another twelve patients the complicating factors which apparently caused this metabolic upset, were still active. Further, in eight patients who had an exacerbation of their gastro-intestinal upset, infection etc. the whole process was followed out closely. The complicating factor and the jaundice appeared initially, the fall in the haemoglobin level not occurring till a later date, when in most of the patients the symptoms had improved. The jaundice usually cleared quickly, but the urinary urobilinogen remained above normal levels, sometimes for months. From these findings it would appear that a definite relationship exists between the complication, the jaundice and the anaemia and the striking feature of the whole investigation is that such minor complications, treated at the ante-natal clinic, should have such a significant effect upon a pregnant woman.

In an attempt to establish the normal urobilinogen excretion of a pregnant woman, every routine urine sent to the laboratory for bacteriological examination, during one month, was tested. In all 135 urines were examined. The results are shown in Table X. Only urines giving definite positive results have been regarded as

TABLE XI.

45 patients from the wards of Royal Infirmary.

	No.	+++	++	+	(+)	-	% positive urobilinogen
Cardiac.	6	2		1	1	2	50%
Pernicious Anaemia.	3	1			1	1	33%
Chronic Disease.	3						0%
Acute Infections.	8		1	2	1	4	38%
Diabetes Thyrotoxicosis	7		1	1	2	3	29%
High B.P. Kidney Disease.	3					3	0%
Disease of Gastro-intestinal Tract.	4			1	1	2	25%
Miscellaneous.	11			4	1	6	36%

significant. It will be seen that of twenty two patients admitted on purely obstetrical grounds, only two had positive urobilinogen tests and neither was strongly positive. Similar results were found in cases of anti-partum haemorrhage, while at the other extreme excessive vomiting, severe anaemia, infection and pre-eclampsia showed a higher percentage of positive results in that order.

For comparative purposes 45 urines from patients in the wards of the Glasgow Royal Infirmary were examined and the results are shown in table XI . Only three patients in this series gave strongly positive results; two were cardiacs, in the terminal stages of cardiac congestive failure and the third was a severe Addisonian Pernicious Anaemia.

From these results it would appear that, if increased urobilinogen in the urine can be taken as evidence of a metabolic upset (haemolysis having been ruled out) then the same disease is more liable to cause a greater upset in the metabolism of a pregnant woman than in the non-pregnant. Hence the significance of minor complications in patients attending the ante-natal clinic and their relationship to jaundice and subsequent anaemia.

This group of 53 patients possibly forms one of

the groups of hypochromic anaemia with jaundice to which Stevenson (1936) referred. In addition, jaundice has been noted in the two cases of haemolytic anaemia mentioned previously. In the three severe cases of anaemia simulating toxaemia, jaundice was present initially, but disappeared with treatment and finally jaundice has been observed to occur in cases of anaemia undergoing treatment. These three groups of jaundice and anaemia will be considered in a later section with reference to the pathogenesis of the anaemia.

So far in this section the immediate history of the patient has been considered. It is obvious, however, that a patient will relate her symptoms to her previous state of health and her complaints will be proportional to the actual divergence from that state. In other words, it seemed probable that a patient whose previous health was good would be more likely to complain of symptoms of anaemia during her pregnancy, than a patient who had been anaemic before. It has been shown that only 34 per cent of the moderate anaemias complained of any symptom which could be related to anaemia and in the severe group the figure was 68 per cent. Only after further questioning would a further 46 per cent of the moderate anaemias and 23.7 per cent of the severe anaemias admit to feeling not "quite well". In other words, after questioning the

patients further, nine of the moderate anaemias and five of the severe anaemias still maintained they felt well. It is conceivable that a patient with moderate anaemia, who follows the regime advised at clinic and rests every afternoon, may not appreciate the extra "burden" of anaemia and may relate any minor symptoms solely to the pregnancy. On the other hand, it is difficult to believe that a woman with severe anaemia should make no relative complaint, unless she had been anaemic for years and having adjusted her mode of life to that state, she ultimately did not recognise it as such. In support of this argument it was interesting to note that three of the five severe anaemias, who had no complaint gave a history ofhaving had anaemia at some previous date, whereas only two of the nine cases with moderate anaemia gave this history. Therefore the hypothesis is probably true that these women had been anaemic for some time and, having adjusted their mode of life accordingly, they no longer recognised its existence.

When the patient's family history was considered the results showed a family history of anaemia in 20 per cent of the patients with haemoglobin less than 50 per cent Sahli and an incidence of 16 per cent in those with haemoglobin more than 50 per cent. Of the severe anaemias in four instances the relative had pernicious anaemia, in

TABLE XII.

Personal History of Anaemia

	No history of anaemia.	Anaemia dating from pregnancy.	Anaemia dating from menstrual flow.	Anaemia from other blood loss	Anaemia ideopathic in origin.
Moderate %	72.7	9.1	6.8	2.3	9.1
Severe %	43	33	7	3	14

two cases the mother had pernicious anaemia, in one a father, and in the fourth a maternal aunt had died as a result of it. No case of pernicious anaemia had occurred among the relatives of the moderately anaemic women.

The patient's own histories were examined with reference to the incidence of pernicious anaemia and the results are shown in Table XII . It can be seen that 27.3 per cent of the patients in the moderate group gave a history of anaemia previously, as compared with 57 per cent in the severe group, the ratio being almost 1 to 2. When the histories were analysed further according to whether the anaemia dated from a previous pregnancy, excessive menstrual loss, anaemia due to other blood loss, and anaemia idiopathic in origin, the results showed that in the latter three groups the incidence was approximately the same in the moderate and severe anaemias, but in the first group i.e. anaemia dating from a previous pregnancy, the percentage incidence in the severe group was three times that of the moderate group. This means that the higher incidence of a history of anaemia prior to pregnancy in the severe group was due solely to an increase in the number of patients in this group who were able to relate their anaemia to a previous pregnancy.

DISCUSSION.

Having stressed the high incidence of anaemia in Glasgow in our initial survey, it is of further importance to note a large number of these anaemic women do not complain of any symptoms relative to their anaemic state. The results of the clinical survey show that only one third of the moderately anaemic and two thirds of the severely anaemic patients made any complaint. More detailed questioning however did elicit symptoms from many patients, but it must be emphasised that these were not spontaneous. Adair, Dieckmann and Grant (1936) Hamilton and Wright (1942) and Dillon (1943) reported cases of asymptomatic anaemia in pregnant women, but the anaemia was only of mild degree. No mention is made in the literature of the asymptomatic severe anaemia which occurred in a high percentage of our patients. Many authors however (Smallwood 1936, Boycott 1936, Stevenson 1936, Whitby and Britton 1946) have stressed the insidious nature of hypochromic anaemia of pregnancy and have stated that patients did not complain unduly until the haemoglobin level had fallen to 7 g. per cent.

Of the patients who did not complain, the average time of appearance of symptoms was at 4.3 months of the pregnancy. The patients had the usual signs and symptoms of anaemia, the difference between the moderate and

severe anaemias being mainly one of degree. In addition to the common signs of anaemia gastro-intestinal upset occurred fairly frequently. In the moderate anaemias this was usually a complaint of heartburn, nausea, occasional vomiting, anorexia and constipation. The severe anaemias showed similar features but more cases of diarrhoea occurred in this group. In contrast to these findings Smallwood (1936) stated that few patients with severe hypochromic anaemia of pregnancy had dyspepsia. One of the common signs of anaemia, which was most constant in our patients, was pallor of the mucosae. More commonly pallor of the complexion was noted. Clinical diagnosis in these cases was therefore less reliable and, as stated previously, many cases with high blood pressure and anaemia had well injected mucosae. It was also interesting to note that trophic changes such as cheilosis, glossitis and koilonychia had a higher incidence in the severe anaemias. Oedema was also a marked feature in many cases of severe anaemia, whereas no instance of gross oedema could be found in the group of moderate anaemias (that is patients with haemoglobin readings above 50 per cent Sahli).

More has been written about the clinical picture of pernicious anaemia of pregnancy. In both of our cases symptoms of anaemia developed, during the sixth month of

pregnancy and became propressively worse. Cases of pernicious anaemia of pregnancy of rapid onset in the later months of gestation, have been reported in the literature however, most of the patients becoming severely anaemic immediately after delivery (Smallwood 1936, Stevenson 1936, Lescher 1942, Callender 1944). Others have reported cases dating from early pregnancy (Naegeli 1912, Osler 1919, Vermelin and Vigneul 1921, Drexel 1926, Pohl 1928, Batisweiler 1933, Ionescue and Bonciu, 1935, Onhauser and Mitchell 1939). Thirteen patients of Davidson, Davis and Innes (1942) had histories dating from the second trimester, but the condition did not really become marked in these cases until the last two months of pregnancy.

In the two cases surveyed in the present series the ~~present~~ symptoms were more severe than in the other group of severe anaemias. Both patients had the typical "lemonish pallor" reported by most authors, rather than the 'pearly white' appearance described first by Gallupe and O'Hara (1924) and later quoted by Callender (1944). In this respect however it must be noted that some of our cases of severe anaemia had a similar "lemonish pallor". This will be discussed later with reference to aetiology. Gastro-intestinal upset occurred in both of our cases but Callender (1944) found that only 30 per

cent of her patients had this complaint (that is a similar incidence as that found in our severe group of anaemias). One of our patients had repeated epistaxis and it is interesting to note that purpura, haemorrhages from the mucous membranes and retinal haemorrhages have been reported quite frequently in cases of pernicious anaemia of pregnancy (Stevenson 1936, Smallwood 1936, Miller and Studdert 1942, Lescher 1942, Callender 1944). Epistaxis did not occur in any of our severe microcytic anaemias reported here. Trophic changes in the form of severe glossitis were present in both of our cases of pernicious anaemia of pregnancy. Trophic lesions were also present in the microcytic group of anaemias, especially the severe cases, but the changes were mainly those of koilonychia, and cheilosis and glossitis, when present, were only of very mild degree. Most reports of pernicious anaemia of pregnancy regard glossitis as a fairly common feature (Naegeli 1931, Stevenson 1936, Abramson 1938, Segerdahl 1941, Miller and Studdert 1942). Lescher (1942) however, only noted four cases of glossitis in his series; Callender (1944) stated that it occurred less constantly than in true Addisonian pernicious anaemia, and Smallwood (1936) did not regard it as a common feature at all. Enlargement of the spleen was only noted in one of our cases. Stevenson (1936) noted

enlargement of the spleen in half of her patients, but Lescher (1942) Callender (1944) reported an enlarged spleen in only a third of their cases. None of our severe anaemias showed any palpable splenic enlargement. Oedema was present in both of our cases of pernicious anaemia of pregnancy, but not to the marked degree shown by a few of the severe anaemias or the three severe cases of anaemia simulating toxaemia.

Pernicious anaemia of pregnancy can occur at any age within the childbearing period (Stevenson 1936, Lescher 1942, Callender 1944). Smallwood (1936) agreed with these authors, but he thought parity might also be a factor. In this, however, he has received little support. (Davidson, Davis, and Innes 1942 (b) Lescher 1942 Callender 1944). Both patients in the present series were multiparae this being their third and sixth pregnancy respectively.

Few cases of haemolytic anaemia of pregnancy have been published in the recent literature (Swan 1933, Lescher 1942). Bethell (1944) stated that none of the cases published in the last ten years could be regarded as pure haemolytic anaemias of pregnancy. Lescher (1942) divided his series of seventeen cases into nine cases of pernicious anaemia of pregnancy and eight cases of so called haemolytic anaemia of pregnancy. The latter he

defined as an anaemia of rapid onset, quickly becoming severe with icteric colour of the skin and plasma. As will be shown later the two cases of haemolytic anaemia reported here probably differed in aetiology. Their symptomatology certainly varied. In the first case the initial complaint was that of pain in the left hypochondrium, a complaint which is fairly frequent in acholuric jaundice. Swelling of the ankles, dyspnoea, icteric colour of the skin appeared within a week, probably when the anaemia had become established. This rapid onset was not typical of the cases of pernicious anaemia described here, but as stated, cases of rapid onset in the latter have been reported (Smallwood 1936, Stevenson 1936, Lescher 1942, Callender 1944). The degree of anaemia in this case was ultimately as severe but no trophic changes were noted and no gastro-intestinal upset was present, as in the two cases of pernicious anaemia of pregnancy. Splenic enlargement in this case was striking and reached a size not seen in any of the other anaemias. The second case of haemolytic anaemia had as rapid an onset, but it occurred in the puerperium. This patient was pyrexial, but the infection did not appear to be sufficient to account for such a high temperature. She was extremely pale, icterus of the complexion not being noted though the plasma was

jaundiced. Epistaxis occurred, as also it did in one of the cases of pernicious anaemia of pregnancy. Splenic and hepatic enlargement were noted but not to a marked degree and the splenic enlargement was certainly not as remarkable as that noted in the first case of haemolytic anaemia. Swan (1933) described two cases of haemolytic anaemia of pregnancy. Each bore a resemblance clinically to the cases mentioned above but haematologically and biochemically differences were noted.

Little need be said about the clinical picture in cases of toxaemia, who have a complicating anaemia, except to stress the fact that the majority of these patients have no symptoms whatsoever relative to their anaemia. Further clinical examination is often misleading; pallor is often not noticeable and frequently the mucous membranes are well injected. Only when the blood pressure falls as in the majority of patients in the first few days of the puerperium do the symptoms of anaemia appear.

Anaemic patients may develop toxaemia, but the number who do is small. Only ten of the patients in this large series surveyed developed toxaemia and of these, four could no longer be regarded as anaemic when they developed their toxaemia, and another two had almost reached normal levels. These two patients became more anaemic again as a result of the toxaemia. Thus the

incidence of toxaemia developing in severely anaemic women in the wards or attending the out-patient department of this hospital is 2.2 per cent, whereas the incidence of toxaemia in hospital patients in 1946 was 22.5 per cent. In this respect it is interesting to note that in Madras, where anaemia is unduly common in pregnant women (over 70 per cent of them are anaemic by western standards), macrocytic anaemia is more common than pre-eclamptic toxaemia (Mudaliar and Menon 1942). These authors were only able to report 103 cases of pre-eclamptic toxaemia in 1,200 admissions to the ante-natal wards.

In conjunction with our figures these facts would tend to suggest that toxaemia rarely develops in cases of anaemia and it might almost be said that anaemia is a deterrant factor in the development of toxaemia of pregnancy. Anaemia occurring in the course of toxaemia, however, is not uncommon and in this case the anaemia would appear to evolve as a result of the original disease.

As early as 1912 Naegeli reported a case of anaemia in pregnancy which resembled pre-eclamptic toxaemia, but had only a trace of albumen in the urine. Since then similar reports have been published by Beckman (1921) and Callender (1944). Numerous authors

have noted the tendency to misdiagnosis in these cases (Smallwood 1936, Stevenson 1936, Miller and Studdert 1942, Callender 1944). In the present survey, twelve such cases were "discovered" by the routine haemoglobin estimation and by the time the results were obtained and the patients traced, six of them had already been admitted to hospital and diagnosed as "pre-eclamptic toxaemias", and one was sent home to rest while awaiting a bed. In these cases it was impossible to estimate the duration of anaemia because the patients had no complaint to make at all. Apart from oedema which was marked in three instances, a raised blood pressure in which the systolic was raised more than the diastolic, and a trace of albumen in the urine, examination in these cases was otherwise negative. Clinically the record cards showed no note of anaemia. All these seven patients were at term, but a further two cases who reported to clinic in their ninth month were seen at the haematological clinic and examined personally before delivery. One of these patients was interesting; a young married woman of 24 years, she had been seen a year previously under exactly the same circumstances. At that time she had been admitted to the ante-natal wards as a "pre-eclamptic toxaemia". The blood pressure then was 150/100, but fell to normal levels soon after admission;

oedema was marked and only a trace of albumen was found in the urine. As now, she made no complaint relative to her anaemia, but on further questioning she did admit she felt "tired". Clinically, her condition at that time was substantially the same as in the present pregnancy, namely pallor and oedema, but with this exception that trophic changes had now appeared. On examination she was found to have quite a marked cheilosis but glossitis and koilonychia were absent. After dismissal from hospital a year ago, she did not continue treatment nor did she report back to the post-natal clinic. In all probability therefore she was probably still anaemic when she became pregnant again and this may explain the appearance of cheilosis this pregnancy.

The other patient examined ante-natally presented a similar picture. She also admitted symptoms after further questioning. Pallor in her case was less marked however and this would have made diagnosis all the more difficult.

Such negative findings with reference to anaemia make it difficult to compare and contrast these cases but in regard to their history all followed a similar course. As stated, serial blood pressure readings were not obtained in two cases, in the first because the patient was induced immediately; in the second

because the patient delivered herself at home while awaiting admission. These two cases however showed the typical features of the group, namely lack of signs and symptoms of anaemia, a moderately high blood pressure, a trace of albumen, varying grades of oedema and finally the appearance of signs and symptoms in the puerperium. On this account, therefore, they have been included in the group. In all remaining seven patients the blood pressure fell to normal levels within a week, and in the majority within forty-eight hours. Albumenuria disappeared as rapidly and the oedema afterwards. Symptoms of anaemia did not appear, however, till after delivery and in four patients who had haemoglobin readings less than 40 per cent before delivery, the symptoms were marked.

These cases might explain in part the number of cases of pernicious anaemia of pregnancy which have been reported to develop suddenly in the puerperium (Smallwood 1936, Stevenson 1936, Lescher 1942, Callender 1944). The haematology and biochemistry of these patients will be discussed in a later section. It is sufficient to state here that an asymptomatic severe anaemia can occur antenatally, that it rapidly becomes apparent clinically in the puerperium and hence leads to the erroneus assumption that the anaemia itself is of rapid origin.

Analysing the cases with and without complaints it was shown that patients with no complaints showed a higher average blood pressure than patients with complaints and this was a constant feature in all haemoglobin groups. On these findings it has been suggested that a raised blood pressure may prevent a patient from fully appreciating her anaemic state and it was further suggested that this may be a compensatory reaction of the body. Middleton and Weggers (1944) experimenting with dogs have shown that small doses of renin increase the blood pressure and the cardiac output per minute. Thus the circulation time is reduced and the same number of red blood cells, circulating more frequently, can deliver more oxygen to the tissues. This, occurring in an anaemic patient, where the symptoms depend on the reduced oxygination of the tissues, would explain the absence of symptoms in such a case. The nine cases of asymptomatic severe anaemia may therefore, be examples of such a condition. When these patients are put to bed, there is less demand for oxygen by the tissues and hence the compensatory mechanism is withdrawn, as evidenced by the fall in blood pressure. Subsequent to labour with its extra demands on the patient the total number of red blood cells is reduced by the blood loss and the blood is

further diluted by the temporary hydraemia which occurs during the first days of the puerperium (Oberst and Plass 1936, Crawford 1940, Skajaa, Schwartz and Dieckmann 1929, Dieckmann 1933, Plass and Bogert 1924). Thus the tissues are served with oxygen less efficiently and symptoms of anaemia appear.

Though a large number of pregnant women have been surveyed, only a small number of patients showed these phenomena and it is therefore difficult to come to any definite conclusion as to the significant factors in these cases. It is interesting to note that the same woman showed the same clinical, and, as will be shown later, the same haematological features in two consecutive pregnancies. Further it was found that the majority of the women were in their twenties. The average age for the whole group was 29.9 years and, comparing this with the average age of 30.7 years for all the severe anaemias it is slightly less. However, the numbers, as yet, are too small to come to any definite conclusion.

The three very severe anaemias with haemoglobin readings between 32 and 23 per cent Sahli, who presented a clinical picture resembling pre-eclamptic toxaemia, came first to ante-natal clinic and were admitted directly to hospital, two, as stated, being diagnosed as

"toxaemias". The features in these cases were gross oedema, moderately high blood pressure as before, and albuminuria present as a trace. These patients had symptoms of anaemia, however, suggesting that the "compensatory mechanism" was ineffective against such a marked degree of anaemia. All the patients were pale, two markedly so, but the third was only moderately pale despite the fact that her haemoglobin was 24 per cent Sahli. It is apparent, therefore that the diagnosis of anaemia could be made more easily in these cases, but, despite this, the striking features were the gross oedema and the moderately high blood pressure.

Symptoms of anaemia dated from the eighth month of pregnancy, that is, later than the two cases of pernicious anaemia of pregnancy, but not as "late" as the nine asymptomatic cases. Apart from the usual symptoms of anaemia, one patient gave a history of acute gastro-intestinal upset from which, she said, her symptoms dated. Trophic changes were observed in two of the patients namely cheilosis, glossitis, and koilonychia in one and koilonychia in the second. All three patients had a sub-clinical jaundice although the skin did not show an icteric colouring. The spleen was enlarged in one case. Thus apart

from the gross oedema and the koilonychia observed in two of the patients, these cases resemble clinically those of pernicious anaemia. Similarity in the haematological and morphological characters will be discussed later.

As has been stated previously the cases of jaundice and anaemia reviewed in this section only represent three groups showing this syndrome. Two of these groups have already been discussed viz (a) two cases of haemolytic anaemia and (b) three cases of severe anaemia simulating toxaemia where the jaundice was noted initially on admission to hospital. The third group (c) consisted of fifty-three patients who developed jaundice as a result of a complication during pregnancy, of whom forty one became anaemic. A fourth group (d) will be discussed in a later section.

During the period covered by the survey, blood from 1,890 patients was examined. Of these cases 404 were anaemic. The incidence therefore of anaemia with jaundiced plasma as a presenting sign was 10.1 per cent of all anaemias and 2.1 per cent of all out-patients during the period of survey. Nine of these patients improved spontaneously leaving a group of thirty-two or 1.7 per cent of all patients who would have remained anaemic had treatment not been given. Reports of jaundice and anaemia as a result of

infection in non-pregnant patients can be found in the literature (Pepper 1927, Wintrobe 1942, Saifi and Vaughan 1939 and 1944). Saifi and Vaughan (1939 and 1944) carried out quantitative urobilinogen excretion tests in ten non-pregnant patients with chronic infections giving rise to anaemia and they decided that the anaemia was not due to an increased blood destruction. In their cases the plasma bilirubin was never more than normal and ranged from 0.2 mg. to 0.4 mg. per cent, whether the infection were acute or chronic, but where the infection was mild e.g. boils, no anaemia developed in ten cases despite the prolonged history. In our series, all the infections, with the exception of two of the gastro-intestinal upsets and one of the toxaemias were mild, and yet anaemia developed in the majority of patients and every case showed either a direct Van den Bergh or plasma bilirubin estimations of more than 0.8 mg. per cent. Further, it has been shown already that the same infection occurring in pregnant and non-pregnant patients gives rise to a greater increase in urobilinogen excretion in the former patients and it was suggested this could be taken as evidence of a greater metabolic upset. Certainly these findings in comparison with those of Vaughan and Saifi (1944) would suggest that minor infections etc. were more important in the pregnant woman than in the non-

pregnant as causative factors in the development of anaemia.

When the fifty three patients were analysed they were found to fall into three groups. The first group of twenty patients were seen on the average at 6.7 months of their pregnancies and they all had an anaemia as well as a sub-clinical jaundice. In the majority of the cases the original complication had improved and the patients had no complaints to make at the time of their first visit to clinic. In contrast to these, the second group of twenty-one patients were seen at an earlier period of their pregnancy, namely 4.8 months. At this time sub-clinical jaundice was present, but they were not anaemic. Of these, 75 per cent still had symptoms of the initial complication when they were first seen and though by 6.2 months the clinical symptoms had disappeared, they had all become anaemic by that time. In other words the second group of twenty-one patients presented a picture at 6.2 months similar to that of the first group and this would further suggest that had the first group been seen earlier in their pregnancies when the majority of them still had symptoms relating to the complicating factor, they would have presented a similar picture of jaundice without anaemia. If this assumption is correct,

then both groups of patients are probably examples of the same pathological condition and the differences observed are due to variations in the relative time of the initial examination in each group.

The above findings would also suggest that the anaemia appears on the average 1.4 months after the development of the complication and the jaundice, and further proof that this was the correct sequence of events was obtained. Eight of the fifty-three patients, who developed anaemia following jaundice associated with infection, had a recurrence of their infection later in pregnancy. Prior to this their anaemia had improved, but with the recurrence of infection, sub-clinical jaundice re-developed and their haemoglobin fell rapidly. With recovery the jaundice cleared as before, but the anaemia and urinary urobilinogen took longer to disappear. Four patients, however, reached normal haemoglobin levels before delivery.

A condition known as familial non-haemolytic jaundice does exist and many cases have been reported in the literature (Gilbert et al 1907, Weber 1917, Van den Bergh 1933, Rozendal et al 1935, Meulengracht 1939, Damashek and Singer 1941, Alwell et al 1946, and Barrie 1946). The question therefore arises whether the jaundice observed in our cases could be examples of

non-haemolytic familial jaundice and merely coincidental. We have however been able to demonstrate a definite correlation between the complicating factor and the jaundice and anaemia viz. jaundice re-appeared when the complicating factor recurred and anaemia developed subsequently. Also the majority of the patients who improved on iron or spontaneously, had no jaundice in the later months.

The last group of twelve patients had higher haemoglobin readings and though they developed jaundice, they did not become anaemic. However a significant drop in the haemoglobin level i.e. more than 5 per cent, but still within the range of normality, as based on the present standards, was noted in four patients who developed a complication in the early months of pregnancy. Thus, it would appear that in a pregnant woman where the initial haemoglobin is high, a metabolic upset, as evidenced by the appearance of jaundice, occurs as a result of a mild complication, but this is insufficient to cause an anaemia. Where the complication occurs in the early months a significant drop in the haemoglobin level may be observed, but in the cases surveyed here the fall in haemoglobin did not reach anaemic levels.

Finally, in the second group of patients in this series who were not initially anaemic, but became so, it

was interesting to note that the majority of these patients belonged to the "low normal" group and the average initial haemoglobin reading of these patients was 63.9 per cent Sahli. Compared with an average initial haemoglobin reading of 67 per cent in the group of twelve, who did not deteriorate, it seems possible that the initial haemoglobin level may be a factor in determining whether the patient becomes anaemic or not. It does not appear a factor in the development of jaundice, however, but a larger series of patients from all haemoglobin groups would have to be surveyed and their reactions to minor complications in pregnancy noted, before any opinion could be ventured about the significance of the metabolic upset. It is interesting to note that three of the patients in this series were cardiacs, one was already anaemic when seen, a second developed anaemia and the third who had an original haemoglobin reading of 67 per cent Sahli showed a significant fall in haemoglobin to 60 per cent, but did not become anaemic. No other cause for the latent jaundice and subsequent "anaemia" could be found. With proper rest the jaundice cleared in two patients and the haemoglobin was normal before delivery. The third patient who has a plasma bilirubin of 2.8 mg. per cent and a urinary urobilinogen + + + , is at present awaiting admission to hospital before

delivery. Her cardiac condition has become progressively worse though she is still managing to do her housework at home. These findings in comparison with those observed in non-pregnant patients, who only showed a + + + urobilinogen excretion when complete cardiac decompensation had occurred, are therefore very interesting and may prove to be of prognostic value. Why anaemia should develop in these cases is a problem to be solved. It may be that a hepatic congestion due to the cardiac condition causes the metabolic upset, which ultimately results in an anaemia.

Finally, with reference to the significance of minor complications during pregnancy as a causative factor of anaemia in patients of the "low normal" group, it should be stated that the above findings corroborate the results of the statistical analysis namely that gastro-intestinal disorders in the early months of pregnancy in patients of the "low normal" group played a significant part in the development of anaemia in the later months.

In conclusion, stress must be laid on the importance of an adequate history of the patient's own previous health and that of her family. It has been shown that in three out of five of the severe anaemias who made no complaint even after further questioning,

there was a history of anaemia for some years previously and on these grounds it has been suggested that the anaemia having become "chronic" the patient was no longer able to appreciate its significance. In addition when an analysis of the previous history of all cases was made it was found that 57 per cent of the severe anaemias gave a history of anaemia compared with only 27.3 per cent of the moderate anaemias. Closer scrutiny of these figures showed that the high percentage in the severe group was due solely to a rise in the number of patients in this group who could relate the onset of their anaemia to a previous pregnancy. In the literature little reference can be found as to the significance of a previous history of anaemia in these patients. Fullerton (1936) showed that as a result of an antepartum haemorrhage or a postpartum haemorrhage a patient can be put in a negative iron balance from which she will not make a spontaneous recovery; and he stresses this as an important factor in the incidence of anaemia in subsequent pregnancies.

When the patient's family history was considered with reference to the degree of the anaemia in the patient, it was found that the incidence of a family history of anaemia varied little in either group viz. 20 per cent of the severe anaemias and 16 per

cent of the moderate anaemias. With reference to a history of Addisonian pernicious anaemia, however, the results were striking. Four instances of Addisonian pernicious anaemia in members of the families of the severe anaemias were noted, whereas not one case of Addisonian pernicious anaemia occurred in the families of the moderate anaemias. On the other hand, however, no family history of anaemia at all could be elicited in the two typical cases of pernicious anaemia of pregnancy, nor in either of the haemolytic anaemias. Callender (1944) has reviewed the incidence of Addisonian pernicious anaemia in families of patients suffering from pernicious anaemia of pregnancy and she states that only three instances of this have been recorded in the literature (Schmidt 1918, Miller and Studdert 1942, Callender 1944). Since one of the four severe anaemias mentioned above was found after examination of her bone marrow to be an atypical case of pernicious anaemia of pregnancy and as her maternal aunt had died as a result of Addisonian pernicious anaemia, she can therefore be added to Callender's list of four patients.

SUMMARY.

(1) A complete clinical examination of 104 pregnant women all suffering from anaemia has been carried out. Of these patients, 44 were moderate anaemias and the remainder were severe.

(2) The striking feature in all the cases was the number of patients who made no spontaneous complaint. Only one third of the moderate and two third of the severe anaemias made any initial complaint. Further questioning however revealed that another 46 per cent of the moderate and 23.7 per cent of the severe anaemias did have symptoms relative to anaemia.

(3) The symptomatology of these patients has been reviewed and the results show that the symptoms usually dated from the fourth month of pregnancy. The patients had the usual signs of anaemia, the difference between the moderate and severe anaemias being one of degree, but in addition one third of the patients in both groups complained of gastro-intestinal disorders, of which diarrhoea occurred more often in the severe anaemias. Trophic changes and oedema were observed more frequently in the severe group, koilonychia and cheilosis being more

frequent than glossitis.

(4) The clinical picture in two cases of typical pernicious anaemia of pregnancy has been discussed and it has been shown that the symptoms were more severe in these cases and developed during the sixth month of pregnancy. Gastro-intestinal upset was common to both patients who also showed a marked degree of glossitis. Splenic enlargement was found in one of the cases.

(5) Two cases of haemolytic anaemia have been reported, one occurring during the sixth month of pregnancy, the other in the puerperium. Both patients presented a different clinical picture; pain in the left hypochondrium, severe anaemia without trophic changes, slight icterus and splenic enlargement being the picture presented by one as compared with epistaxis, severe anaemia, pyrexia, splenic and hepatic enlargement in the other.

(6) Anaemia with reference to toxaemia has been discussed and it has been shown that anaemia resulting from a toxaemia is fairly common, whereas the incidence of toxaemia occurring in anaemic patients is only 2.2 per cent. A few cases of anaemia simulate toxaemia and even when the

anaemia is severe clinical signs and symptoms of anaemia may be absent. An explanation of the sudden appearance of symptoms after delivery has been given, namely hydraemia and lowered blood pressure. It has been suggested that this may account for some of the cases of pernicious anaemia of pregnancy reported as developing rapidly in the puerperium. When the anaemia is very severe, that is, less than 33 per cent Sahli (5.3 g. haemoglobin per cent) symptoms of anaemia do appear despite the raised blood pressure, yet a mistaken diagnosis of toxaemia can be made. Several points in the differential diagnosis of anaemia simulating toxaemia and a true toxaemia which were noted in this survey, have therefore been made.

(7) Jaundice in relation to anaemia in pregnancy has been discussed. Four types have been found and three have been discussed. Commonly the jaundice has been shown to occur in the plasma, as a result of a minor infection etc., during pregnancy, and anaemia has been found to result in patients in the "low normal" group. In this respect also it has been suggested that minor infections are more prejudicial to

the pregnant woman and, especially with reference to the development of anaemia, if they occur in the early months of pregnancy. Jaundice occurring in two cases of haemolytic anaemia and in three cases of very severe anaemia simulating toxaemia has been mentioned and will be referred to later.

(8) With reference to the patient's own and her family history, it has been shown that, when a patient has been anaemic for years, she may no longer complain of any symptoms relative to anaemia, that, where the anaemia is severe, more patients are able to relate their anaemia to a previous pregnancy, and that, irrespective of the degree of anaemia, about one out of every five patients gave a family history of anaemia. Where, however, the anaemia was severe, one out of every fifteen gave a family history of Addisonian pernicious anaemia. One patient who was a case of atypical pernicious anaemia of pregnancy gave a family history of Addisonian pernicious anaemia.

TABLE. XXVII.

SERIES.	% SPONT. DELIVERY.	% DELAYED LABOUR.	% ASSISTED DELIVERY.	% CAESARIAN SECTION.	% MISCARRIAGE.	% TWINS.	% PREMATURE DELIVERY.	HAEMORRHAGE % NORMAL.	% MODERATE.	% BRISK.	PUERPERIUM % NORMAL.	% MILD COMPLICATION.	% MOD. COMPLICATION.	% DEATH.	BABY % NORMAL.	% MILD COMPLICATION.	% MOD. COMPLICATION.	% STILLBIRTH.	% NEONATAL DEATH.
LOW NORMAL CONTROL. 85	89	22	62	6		3		55	40	5	73	16	11		89	9	2		
LOW NORMAL.																			
IRON. 25	88	4	4		4		4	33	38	29	88	12			92	4			4
VITAMIN C. 25	84	8	8	8		4		44	44	12	88	4	8		84	8	8		
DIET. 25	85	8	4	4	8	8		50	31	12	69	23	8		75	18		3·5	3·5
MARMITE. 30	81	8	4	15		8		56	40	4	88	4	8		82	7	7		4
TREATED ANAEMIAS 1946 140	75	17	11	5	1·5	4		59	31	10	81	17	2		83	12	2	1·5	1·5
CONTROL ANAEMIAS 1946 83	84	19	8	4		1	2	64	30	6	73	22	5		78	14	2		6
TREATED SEVERE ANAEMIAS 1947 58	77	20	20			3		40	44	16	65	25	10		93	5		2	
CONTROL SEVERE ANAEMIAS 1947 53	79	7·5	7·5	2	11	5·5	11	61	28	11	55	26	19		74	9		8	9

Anaemia in relation to maternal and foetal morbidity and mortality.

While it is obvious that anaemia is important in regard to the general health of the mother during pregnancy it is also necessary to consider at least three points relating to events at term and in the puerperium viz:-(a) The nature of the labour and the incidence of complications (b) The health of the mother in the puerperium and (c) The prognosis for the baby.

In order to establish criteria in these circumstances several groups of patients were compared and contrasted. The group of 140 patients in 1946 already under consideration were compared with 83 untreated patients with haemoglobin readings of less than 60 per cent Sahli at term. Both series, however, consisted mainly of cases of moderate anaemia and it was important to assess the influence of the various grades of anaemia, two groups of patients had to be selected from those seen during 1947. These consisted of 58 treated unselected severe cases of anaemia, and a similar series of 53 untreated cases. The collected results are shown in Table XXVII.

No difference could be found between the treated and untreated cases in regard to the duration of labour,

the incidence of spontaneous as compared with instrumental delivery, or the number of Caesarian sections performed. The incidence of plural pregnancy was fairly constant in each grade of anaemia, whether treated or untreated and therefore in these cases did not appear to bear any relationship to the incidence of anaemia nor did it effect the statistical analysis.

It is difficult to estimate the amount of blood lost by a woman during the 2nd and 3rd stages of labour. Three arbitrary standards of estimation are used in the hospital and the doctor in charge of each case, reports whether the blood loss is "normal", "moderate" or "brisk". It is obvious that personal variations introduce considerable error, when an attempt, such as this is, made to assess the blood loss. However, it can be said that severe post-partum haemorrhage does not appear to occur more frequently in patients suffering from anaemia, but when it does occur in such a patient, the prognosis is worse and immediate replacement is usually necessary. From table XXVII it will be seen that of the untreated cases 6 per cent of all the anaemias in 1946 and 11 per cent of the severe anaemias had "brisk" haemorrhage after delivery, whereas the treated cases showed figures of 10 per cent and 16 per cent respectively. At first glance, it would therefore appear that the untreated

cases showed less tendency to bleed. Further investigation of these untreated cases reveals that 34 per cent of the cases were delivered on district, whereas the majority of all the treated cases were delivered in hospital and received some form of analgaesia. Also the incidence of instrumental deliveries is higher in hospital cases. These two factors would therefore account for this apparent anomaly.

No maternal death occurred in either the treated or control series. Maternal morbidity was fairly frequent and three grades were recognised: viz "normal puerperium", "mild" and "moderately severe" complications of the puerperium. From the table it will be seen that the puerperium was normal in more than 80 per cent of the anaemias treated during 1946 and on the average in all the treated "low normals". The control groups showed readings nearer 70 per cent, but when the severe anaemias, both treated and untreated were considered the difference was striking. In the former group 65 per cent had an normal puerperium and in the latter 55 per cent. The corollary follows when the incidence of complications was considered. The untreated severe anaemias showed the highest incidence; 19 per cent of the patients were affected whereas treatment in this group, reduced the incidence by almost a half. From the above, it can

therefore be said that the presence of anaemia prejudices an expectant mother by rendering her more liable to develop complications in the puerperium. Further, a definite relationship exists between the degree of the anaemia and the incidence of complications and thirdly specific treatment antenatally by alleviating the anaemic state reduces the incidence of complications in the puerperium.

The miscarriage rate appeared to be higher in the untreated severe group. This is probably fallacious. Six cases miscarried but in two of these the anaemia was due to or had been aggravated by accidental haemorrhage which was bound to lead to foetal asphyxia.

The difference in the incidence of prematurity in the various groups, however, appears to be significant. In the severe untreated group, 6 patients had premature deliveries i.e. 11 per cent incidence. None of these 6 patients had suffered from any form of antenatal bleeding and therefore no other factor beyond the anaemia could be found to account for the premature birth of these infants. No cases of prematurity occurred in the treated severe group. Only one occurred in the control group of low normals and two in the control group of 140 treated anaemic patients in 1946. It is also interesting to note that the baby in the normal group throve and

developed normally, whereas 4 of the 6 babies born prematurely of severely anaemic mothers and both babies born of anaemic mothers in 1946 were still born, or died within a few days of delivery.

This factor of prematurity alone is well known to influence the neonatal mortality and morbidity rates. Information culled from a study of these rates showed very marked differences between the various groups. From table XXVII it will be seen that of the "low normal patients", one baby was a still born anencephalic and 4 babies died within a few days of delivery. Of the neonatal deaths, two were twins, one died of aphyxia and the other was a hydrocephalic. The two remaining neonatal deaths were due to hydronephrosis and intussusception. Ample cause for death, apart from "anaemia" in the mother, could therefore be given for all but one of these babies and this would reduce the combined still-birth and neonatal mortality rate for the whole series of low normals from 2.6 per cent to 0.5 per cent. This figure was 3 per cent for the series of 140 patients treated for anaemia in 1946; one neonatal death was due to erythroblastosis foetalis and so the actual combined rate for the group is 1.5 per cent. A slightly higher percentage was obtained for the control series of untreated anaemias in 1946. As

mentioned before two premature babies born in this group, died soon after delivery. Omitting two neonatal deaths in this group, due to erythroblastosis, the actual combined still birth and neonatal death rate was 3 per cent. There were no still births or neonatal deaths in the severe anaemias who received treatment during 1947. In striking contrast, the combined rate for the untreated controls was 17 per cent. In other words 9 babies of 47 viable pregnancies died in this group. At this juncture it is necessary to emphasise that the 47 mothers were cases of "anaemia" and had never suffered from bleeding, accidental or otherwise. The six cases mentioned previously when considering miscarriages are not included. Of these 9 babies, 4 were still births, two occurring in twins, a third in a case of toxaemia and the fourth was a premature delivery. Of the neonatal deaths, 3 occurred in premature babies, a fourth baby lived a few hours after a difficult labour and at postmortem was found to have a cerebral haemorrhage. The fifth baby had asphyxia pallida and died six days after delivery of a bronchopneumonia. Difficulty arises, however, when an attempt is made to estimate the influences, if any, which anaemia in the mother may have on the still-birth or neonatal mortality rate. The hospital statistics for 1946 show that one third of the premature deliveries and one seventh of

the still-births were due to toxaemia in the mother; that delayed labour accounts for one fifth of the still births and twin pregnancies formed 5.5 per cent of the premature deliveries. It can be seen therefore that the presence of toxaemia, twins and delayed labour as secondary complications cannot be disregarded. No pelvic abnormality was present in the one case of delayed labour in this series. Irregular uterine contractions were stated to be the cause of the delay and it is conceivable that inefficient oxygenation of actively contracting muscle, due to the existing anaemia, might well effect the contractability of that muscle. In view of this fact, this case has not been discarded though still births and neonatal deaths occurring in cases of toxaemia and plural pregnancy have been ruled out. This gives a corrected still birth and neonatal mortality rate of 5 out of 47 deliveries or 10.6 per cent.

In regard to those babies who survived, it is difficult to reach any conclusion and to obtain a standard on which to base the general health, the state of nutrition etc., Birth weight may vary considerably depending on the presence or absence of oedema and it is not always the fat baby which is the healthiest. However, it is interesting to note that the babies of mothers treated for anaemia during 1946 were 14 oz.

TABLE XXVIII.

GROUP.	Treated Anaemias. 1946.	Control Anaemias 1946.	Severe Anaemias. 1947.	Control Anaemias 1947.	Low Normals 1946.
Average weight of baby.	7 lbs. 14 oz.	7 lbs.	7 lbs. 8 oz.	7 lbs.	7 lbs. 6 oz.
Average Duration of Labour.	15 hrs.	17 hrs.	16 hrs.	10 hrs.	15 hrs.

heavier on the average than the babies in the control series. As a further check, a similar analysis was carried out in 1947 with the treated and untreated severe anaemias. It was found again that the birth weight in the treated cases was ½ lb heavier than that in the control series (Table XXVIII) The average birth weight of babies whose mothers belonged to the "low normal" series is shown alongside for comparison. This reading was between that of the treated and untreated groups.

The health of the baby, while it was in hospital or under supervision of the district staff, was graded, as for the mother, depending on the incidence of mild or moderately severe complications. As the figures in table XXVIIshow, complications during the first ten days of neonatal life show no correlation with the degree of anaemia in the mother. It has been shown, however, by several observers that though these babies are not born anaemic, their stores of iron are reduced and they therefore tend to develop anaemia when about three months old.(Parsons 1947).

Discussion.

The prognosis for the mother and child in labour and in the puerperium has been considered with reference to the various grades of anaemia. From the results it would appear that anaemia has no influence on the duration of labour, the mode of delivery or the incidence of severe haemorrhage. These results are in agreement with those reported by Waitby and Britton (1944), but Smallwood (1936) considered that labour was longer in cases of anaemia and Meyer-Weddel (1943) stated that while severe haemorrhage was not common in iron deficiency anaemias, it did occur in cases of vitamin C deficiency anaemia and pernicious anaemia of pregnancy. In our series, the incidence of intra and post-partum haemorrhage was no greater than that observed in non-anaemic cases. When haemorrhage occurred, however, the effects were obviously greater in regard to morbidity in the puerperium.

A definite relationship was found to exist between the degree of anaemia and the incidence of maternal complications. For example, 19 per cent of the patients with severe anaemia, who received no treatment antenatally, developed moderately severe complications in the puerperium compared with only 10 per cent in the treated group. Similar results were obtained in the

group of 140 patients treated during 1946 who showed a figure of 2 per cent, compared with 5 per cent in the untreated control group. As the 1946 series contained a greater percentage of moderate anaemias, it is obvious that the incidence of maternal morbidity is in proportion to the degree of anaemia. Equally satisfactory reports, as a result of therapy, have been made by Smallwood (1936), Dillon (1943) and Paine and Dameshek (1944).

Since haemorrhage associated with a "miscarriage" resulting in anaemia is a common finding, it is very difficult to say whether the anaemia existed previously or whether it was a significant factor in the aetiology of miscarriage. In the present series, six miscarriages occurred and in two the anaemia definitely appeared to be due to haemorrhage. Stevenson (1936) reported only one miscarriage in her series, but Smallwood (1936) mentioned miscarriage with reference to the prognosis in anaemia of pregnancy.

On the other hand, the incidence of premature deliveries in anaemic mothers did appear to be significant. In the severe untreated anaemias, the incidence was 11 per cent, whereas no premature deliveries occurred in the treated patients with severe anaemia; one occured in the treated low normal

group and two in the untreated low normal control group. Premature deliveries are frequently recorded in previous reviews e.g. Stevenson (1936) reported eight, Meyer - Wedell (1943) four and Callender (1944) six in both treated and untreated patients. Since the group of severe anaemias in the present series only includes patients, who responded satisfactorily to treatment, the absence of premature delivery in this group is all the more significant, when compared with the severe untreated anaemias.

As prematurity itself influences the neonatal mortality and morbidity rates, it is not surprising that the findings with reference to the prognosis for the baby were all the more significant. In the low normal group the corrected combined still birth and neonatal death rate was 0.5 per cent. This figure was 1.5 per cent in the 140 mixed moderate and severe anaemias treated during 1946 and 3 per cent in the control group. No still births or neonatal deaths occurred in the severe anaemias treated during 1947, but in striking contrast, the combined corrected rate in the control group of severe anaemias was 10.6 per cent. From the percentages in the control groups it is obvious that as the anaemia becomes more severe, the still birth rate and neonatal death rate increase

in the untreated cases. Again, most of the still birth and neonatal deaths reported in the literature have been expressed as percentages of the whole series examined. No distinction has been made between the treated and untreated patients, possibly because figures for such a large series of untreated severe anaemias have not been available elsewhere. Originally, however, the still birth rate and neonatal death rate was high, but with improved antenatal care, these figures have decreased. Stevenson (1936) reported five still births and one neonatal death among thirty babies, whose mothers had pernicious anaemia of pregnancy. Callender (1944) reported only two foetal deaths in the twenty five cases which she observed. In the fifty-eight severe anaemias in this group of iron deficiency and pernicious anaemia of pregnancy, who reached normal haemoglobin levels before delivery, it is therefore significant that no still birth or neonatal death was recorded.

With regard to the babies that survived it has been shown in both series observed during 1946 and 1947 that the babies of mothers treated for anaemia were definitely heavier than the babies born of untreated mothers. Whether this can be taken as an indication that these babies were healthier is controversial, and

when the neonatal morbidity rates were compared in the treated and untreated groups, no correlation was possible between the degree of anaemia in the mother and the incidence of complications in the baby.

At present in connection with our post-natal haematological clinic routine blood examinations are being performed on the babies of anaemic mothers during the first three months of life. No conclusions can be drawn as yet, but Parsons (1946) has stated that there is a tendency for anaemia to develop about the third month in these babies.

Pathogenesis of the Severe Anaemias.

Since the initial haemoglobin survey in 1946 revealed a high incidence of severe anaemia in the women attending the ante-natal clinic, it was decided to carry out a more thorough investigation of these cases during 1947. Where possible, complete blood and urine investigation, including haemoglobin, red count, white count, haematocrit, mean cell diameter, icteric index, Van den Bergh, plasma protein and urinary urobilinogen and bilirubin estimations were performed at weekly intervals. Cases attending as out patients, were not seen so regularly, but the above investigations were carried out at least once a month. Forty eight patients, all with severe anaemia, were followed throughout pregnancy, repeated marrow punctures being performed in most. In all 67 marrow punctures were done. In addition, the peripheral blood picture was examined at regular intervals in other 74 patients and biochemical estimations, as mentioned above, performed. A further 33 patients were seen just before term, or had attended irregularly and in their case it was impossible to carry out repetitive tests ante-natally although they were studied fully during the puerperium. This, therefore, brings the total number of cases studied to 148. As before the cases were considered in three

groups namely (a) Cases of anaemia.

(b) Cases of anaemia and toxaemia.

(c) Cases of anaemia and jaundice.

The first group of anaemias, as stated before, consisted of 107 patients of whom two were haemolytic anaemias and two were cases of pernicious anaemia of pregnancy. Four other patients had pernicious anaemia of pregnancy, but they had received liver therapy from their own doctors before admission to hospital. Special reference will be made to these eight cases later in the text.Of the remaining patients 26 were seen just before term or had attended irregularly and it was impossible to carry out a complete investigation in these cases, or to determine the response to therapy. The marrow picture and blood count were obtained in four of these patients, however, and though the blood picture was hypochromic in every instance, megaloblasts were found in the marrows of three of the patients, the percentage varying from 6.5 per cent to 10 per cent. The patient who was found to have 10 per cent megaloblasts in her marrow was six months pregnant. She had collapsed at her work on the morning of admission and she had had slight vaginal staining but no significant blood loss. She miscarried within 24 hours, blood loss fortunately being slight. After delivery, the

TABLE XIII.

	Hb. % Sahli	R.B.C. Mill.	P.C.V. %	M.C.V. μ^3	M.C.H.C. %
Before treatment.	38	3.26	29	91	21
6 weeks after delivery	55	4.00	36	87	25

haemoglobin was found to be 26 per cent Sahli and the red blood cell count was 2.33 million, yet six weeks later on iron therapy alone, the haemoglobin estimated 60 per cent Sahli and the red count 3.8 million. The other three patients had normal deliveries. The average blood counts before delivery and six weeks later are shown, iron being the only form of therapy (Table XIII).

The remaining 73 severe anaemias have been further divided according to the treatment given. Of these patients 51 received iron alone, 13 received iron and small doses of folic acid, three were given a blood transfusion and the remainder formed a miscellaneous group where the treatment was varied.

Of the 51 patients who received iron alone three were admitted to hospital immediately, as they had haemoglobin readings less than 35 per cent Sahli. Forty eight patients were therefore, initially treated as out-patients and of these, fifteen had ultimately to be admitted, as they showed no response to therapy. Treatment with iron was continued with these patients in hospital and they can therefore be considered with the original three very severe anaemias.

The peripheral blood picture in the eighteen patients admitted to hospital was that of a microcytic or normocytic hypochromic anaemia in every instance.

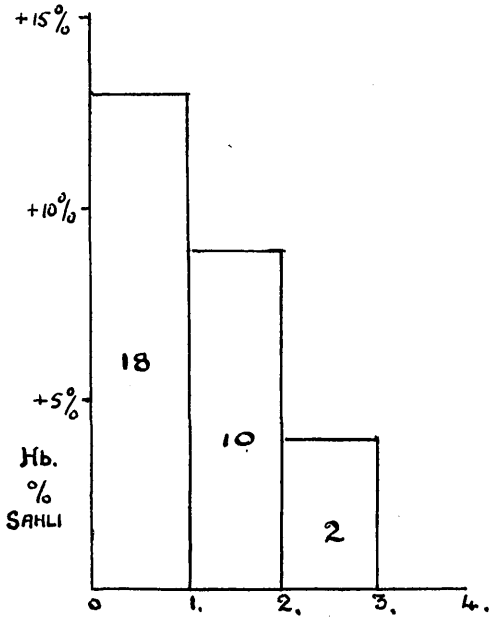
The average haemoglobin was 39 per cent, but values between 49 and 23 per cent were recorded. The average red blood cell count was 3.73 million with variations between 4.32 and 2.71. The mean cell volume, mean corpuscular haemoglobin concentration and mean cell diameter averages were 74 μ^3, 22 per cent and 7.0μ respectively. Plasma proteins averaged 5.5 g per cent and the Van den Bergh estimations were all negative. Only thirteen of the patients had weekly urinary urobilinogen estimations carried out and of these positive results were obtained in ten of the patients initially. With treatment, all but one were considerably reduced or were negative. This one patient was ultimately found to have an intra-uterine death, and absorption of haemoglobin due to haemorrhage in utero may have caused the increased pigment excretion. In general therefore, it can be said that the increased urinary urobilinogen decreases with effective treatment of the anaemic condition. Most of the eighteen patients in the group showed a very satisfactory response to iron therapy, even those who had failed to respond to iron as out patients. During the first month of therapy the haemoglobin rose 13 per cent Sahli during the second month 9 per cent and only 4 per cent in the third month, in one case observed over that period of time. The

TABLE XIV.

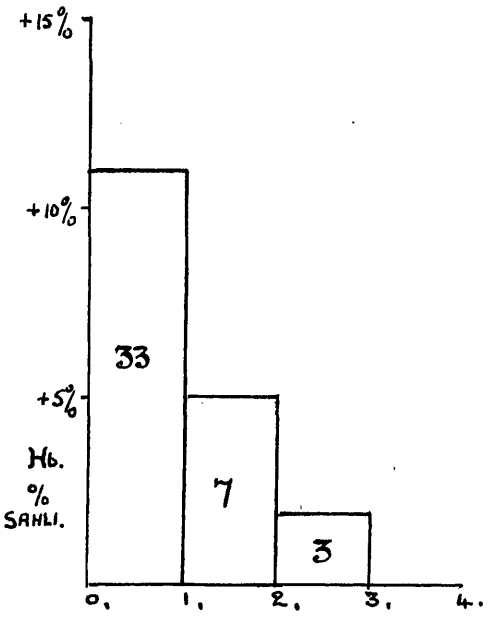
Marrow	Megaloblast %	Normoblast %	Myeloid %	Reticulocytes %	% Reticulated normoblasts	Marrow iron
Before treatment	5.1	31.9	53	1.7	0.5	0
After treatment	2.8	31	52	2	0.4	+ +
Blood.	**Hb. %**	**R.B.C. Mill.**	**P.C.V. %**	**M.C.V. μ^3**	**M.C.H.C. %**	**Plasma protein. g. %**
Before treatment	33	3.49	26	73	21	5.2
After treatment	66	3.84	38	99	28	5.3

CHART IV

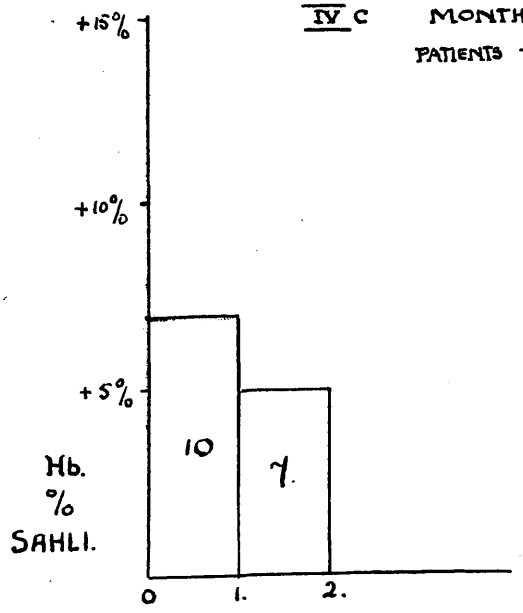
IV a MONTHLY INCREMENTS OF 18 PATIENTS TREATED WITH IRON IN HOSPITAL



IV b MONTHLY INCREMENTS OF 33 PATIENTS TREATED WITH IRON AS OUT-PATIENTS



IV c MONTHLY INCREMENTS OF 10 PATIENTS TREATED WITH IRON AND FOLIC ACID AS OUT PATIENTS.



ultimate haemoglobin reading for the group was therefore 55 per cent Sahli. This curve shows much higher monthly increments than that observed in the group of severe anaemias receiving treatment as out-patients (Chart 4a and Chart 3f Section I). Also it should be remembered that the majority of these patients had failed to respond to iron therapy initially when they attended as out-patients.

Three of the eighteen patients, it will be remembered, were admitted to hospital direct and all three responded to iron therapy. Of the remaining fifteen, eight responded to iron therapy, but seven showed only a partial response. Altogether then, eleven patients appeared to be suffering from an anaemia which responded to iron therapy, while seven had an anaemia fundamentally resistant to iron therapy. Of the first group of eleven patients five had sternal punctures and on examination of the marrow showed a rather similar picture. In four of these patients a differential count of the initial marrow smears showed 5.1 per cent megaloblasts, but with iron therapy this fell to 2.8 per cent (Table XIV).

The normoblast count was 31.9 per cent, the myeloid series 53 per cent and there was very little change in the number of these cells as a result of

iron therapy. The marrow was stained for reticulocytes and the percentage of reticulated red blood cells and erythroblasts were counted. The figures in these patients were 1.7 per cent and 0.5 per cent respectively. Following treatment there was little alteration in these percentages. The marrow was stained for iron and using the potassium ferrocyanide method, no free iron could be demonstrated in the initial marrow smears, but after therapy, iron staining bodies, similar to these described by McFadzean and Davis (1947) were seen in one of the two cases examined. The other patient gave a negative iron reaction in her marrow, but she had just recovered from a moderately severe attack of pyelitis and this may have altered the storage of iron in the marrow (Cartwright et al 1947). The average haemoglobin, red cells counts etc., for this group of patients are shown (Table XIV). The improvement on iron therapy alone is quite remarkable. None of the patients was delivered when all these examinations were made and this is important because, as will be shown later, delivery has an effect on the cell counts and on the marrow picture.

The fifth patient in this group of patients who were admitted to hospital and improved on iron therapy, had failed to respond as an out-patient. Yet when her marrow was examined it was found to be normoblastic.

TABLE XV.

Marrow	Megaloblast. %	Normoblast %	Myeloid %	Reticulocytes %	% Reticulated normoblasts	Marrow iron.
Before treatment	1.7	20	69	2.1	.5	0
After treatment	4.1	18	66	1.3	.2	+

Blood.	Hb. %	R.B.C. Mill.	P.C.V. %	M.C.V. μ^3	M.C.H.C. %	Plasma protein. g.%
Before treatment	37	3.49	27	77	22	5.5
After treatment	50	3.94	33	84	25	5.0

The peripheral blood picture was normocytic hypochromic, the haemoglobin having risen from 40 per cent to 46 per cent Sahli as an out-patient. The plasma proteins, originally 5 g. per cent fell to 4.5 g. per cent during treatment with iron in hospital. The haemoglobin ultimately reached 63 per cent Sahli before delivery, the plasma proteins having reached their original level by that time too. The marrow showed a high percentage of cells of the normoblastic series, namely 32 per cent and the myeloid series constituted 52 per cent. Apart from the social circumstances, which were very poor in this case, no apparent reason for the failure to respond to iron, given for two months before admission, could be found.

The second group of seven patients were seen as early in their pregnancy as the first group i.e. in the sixth month. Despite continued treatment, these patients did not show any further improvement beyond the blood levels shown in Table XV. The marrow counts were made as before and it will be seen that though the percentage of megaloblasts was low in these cases initially, the percentage of cells of the normoblastic series was also low, namely 20 per cent. After treatment with iron in hospital the megaloblasts increased to 4.1 per cent instead of falling as in the first group and the

normoblasts showed very little change, remaining at their initial low level. The marrow reticulocytes and the reticulated erythroblasts showed a decrease in the second smears. The cases in this group, who had been given iron as out-patients, without any response being obtained, had small quantities of free iron lying outside the cells, whereas the marrows of the untreated patients showed a negative iron reaction. After iron therapy all the patients showed the same "iron staining bodies" as the case mentioned in the first group, but here the number of "bodies" was fewer. The blood levels in this group were the same or even slightly higher than the first group originally, but the ultimate count was far below that of the first four patients.

Comparing these two groups of patients with megaloblasts in their marrow smears, it can be seen that apart from the ultimate differences in the peripheral blood pictures, the variations in the marrow pictures were striking and indeed the initial marrow picture itself would seem to provide an indication of how the patients would respond to iron therapy in hospital. It has been shown that the seven cases who only showed a partial response to therapy had a low percentage of cells belonging to the normoblastic series initially and, despite treatment, this remained the same. Less

stress can be laid on the percentage of megaloblasts, because though low initially, which at first would have been considered an advantage, the megaloblast count rose in these patients. Marrow reticulocytes were the same in both groups, but a fall was noted in the second group as a result of therapy, as compared with a maintainance of the original level in the first. Marrow "iron inclusion bodies" were maximal in the case of the former group; all the latter cases had "inclusions", but to a lesser degree.

So far only patients admitted to hospital and given iron have been considered. Of the 51 patients given iron alone, there are therefore a further 33 who were treated as out-patients and responded well. The average initial haemoglobin in these patients was 43 per cent Sahli i.e. slightly higher than either of the hospital treated groups. However, the red cell count was the same, namely 3.55 million and the haematocrit, mean cell volume, mean corpuscular haemoglobin concentration and mean cell diameter were 27 per cent 77 μ^3, 22 per cent and 6.8 μ, showing therefore very little variation from the previous groups. The initial plasma protein estimations averaged 5.5 g. per cent, which was also the average figure for the hospital cases. Substantially therefore, there would

appear to be very little difference in the initial peripheral blood picture of these patients and of those who failed to respond to treatment as out-patients. Unfortunately marrow pictures were not performed in these cases, but possibly they might have revealed marrows with a fairly high percentage of the normoblastic series. The urobilinogen excretion was followed in eight of these patients. Only three positive results were obtained initially and the last estimation, made before delivery in each case, showed a considerable decrease in two of these patients, all the others being negative. One patient in this series developed a mild urinary infection which was treated effectively at the ante-natal clinic. The urobilinogen estimated a trace the week before pus was detected in the urine, was positive the next week when pus was detectable and remained positive a week later though examination of the urine for pus was negative. Patients in this group who received treatment for one month only, had an ultimate haemoglobin value of 53.0 per cent Sahli, whereas patients receiving treatment for two months or more had an average haemoglobin of 59 per cent before term. As before the monthly increments were calculated and they were found to be 11 per cent in the first month, 5 per cent in the second and 2 per cent in the

TABLE XVI.

IRON DEFICIENCY ANAEMIAS TREATED AS OUT-PATIENTS.

	Hb. %	R.B.C. Mill.	P.C.V. %	M.C.V. μ^3	M.C.H.C. %	M.C.D. μ	Plasma protein. g.%
Before treatment.	43	3.55	27	77	22	6.8	5.5
After treatment.	57	4.07	36.5	91	25	7.6	5.1

third. These average monthly increases are less than those of the patients receiving treatment in hospital, but are slightly higher than those of the group of severe anaemias reported in the general review (Chart 4b and Chart 3f, Section I). In this respect, however, it must be stated that the patients considered here are those who responded satisfactorily to iron therapy and do not include the patients in the miscellaneous group who only showed a partial response and were given other treatments. The initial and final blood counts in the thirty three patients have been compiled in a table for comparison (Table XVI). It will be seen that the blood picture was no longer microcytic though still slightly hypochromic. The striking feature in all the cases, however, apart from the improvement in the blood picture was the fall in plasma proteins. The average drop was 0.4 g. per cent. In view of this fact weekly plasma protein estimations were performed in a series of hospital patients and the results will be discussed later on in the section. Summarising the results in these patients it can be said that.

(1) Of all patients showing a microcytic hypochromic anaemia in their peripheral blood, approximately 15 per cent do not respond to iron therapy in the manner expected.

(2) No difference could be detected between the peripheral blood picture of these patients who responded satisfactorily.

(3) Apart from one patient among those who responded to treatment, whose marrow contained only normoblasts, all patients of both groups showed megaloblasts in their marrow smears.

(4) The percentage of megaloblasts was initially greater in the patients who responded to iron therapy than in the refractory cases (1.7 per cent).

(5) The normoblast percentage in the initial marrow smear appeared to be more significant than that of the megaloblasts. In the patients responding to iron the normoblasts averaged 31.9 per cent with a low level of 28 per cent, whereas in the refractory group the average percentage was 20 per cent with a high level of 30.5 per cent.

(6) It would appear from the figures that if the initial marrow smear contains more than 30 per cent normoblasts and 3 per cent megaloblasts, the patient is likely to improve with iron therapy. Exceptions to the latter figure occur. It may be necessary to admit these patients to hospital before improvement is noted.

(7) During treatment the percentage of megaloblasts fell in the first group, averaging 2.8. The normoblasts remained stationary at 31 per cent. In the second refractory group the megaloblasts increased to 4.1 per cent and the normoblasts fell to 18 per cent.

(8) The percentage of reticulated cells, nucleated and non-nucleated, was initially the same in both groups, but during the course of treatment the percentage fell in the refractory group.

(9) Iron deposits formed in the marrow during treatment in both groups, but they were much more numerous in those patients who responded to iron therapy.

(The cases reported in this section are detailed in protacol I).

It is not easy to treat a woman with pernicious anaemia of pregnancy as an out-patient even though the disease is in its early stages. Liver injections mean the patient reporting back at regular intervals, usually twice a week, and many of our patients come fairly long distances. Oral liver on the other hand is "difficult to take" and patients failed to take treatment unless they were supervised in the wards of the hospital. Folic acid, however, is easy to take,

unlike iron it does not cause any gastro-intestinal upset and the patient can carry on treatment at home without reporting back to clinic more than necessary. Its one drawback is the expense. As eleven of the twelve patients whose marrows were examined showed the presence of megaloblasts and these cases occurred in 53 severe anaemias treated with iron, which gives an incidence of 21.5 per cent, it was decided to give folic acid in small doses to 13 out-patients who had a severe anaemia. In this way the value of folic acid as an empirical prophylactic agent in these possible early cases of pernicious anaemia of pregnancy might be estimated. In other words, it was hoped that the cases treated with folic acid and iron would show a greater response to therapy than those given iron alone, and also that the number of resistant cases requiring admission to hospital would be less in this group.

Ten patients were given folic acid 5 mgm.daily in addition to iron for a period of one month. They were asked to report back at weekly intervals for haemoglobin estimations and at the beginning and end of the month blood was withdrawn for complete investigation. Thereafter iron was given alone and if the patient was not delivered after a second four weekly period a third complete blood investigation was made. The

results of this investigation were disappointing, the haemoglobin average rose only 7 per cent in the first month, (Chart 4c) the average red blood cell count showed no significant improvement, the haematocrit rose from 29 per cent to 33 per cent however and the blood picture was no longer microcytic although it still was hypochromic. The plasma protein average before and after one month's treatment was 5.3 g.per cent. Seven patients were observed during the second four weekly period when they showed an average increase of 5 per cent. One patient in this group was interesting however. She had an original haemoglobin of 45 per cent Sahli, a red cell count of 2.92 million and a haematocrit reading 28.5 per cent. The mean cell volume was 98 μ^3, the mean cell haemoglobin concentration 25 per cent, the mean cell diameter 7.4 μ and the plasma proteins estimated 5.8 g. per cent. After one month's therapy the haemoglobin had risen to 50 per cent, the red cell count to 3.19 million and the haematocrit to 31.5 per cent. The plasma proteins however had fallen to 5.6 g.per cent. On iron alone during the next eight weeks the haemoglobin rose to 57 per cent Sahli in the first fortnight, but fell gradually thereafter to 52 per cent Sahli when the red cell count was 3.39 million. The patient was then

given a test dose of 4 cc. of plexan intramuscularly and though the reticulocytes remained at 1 per cent, daily estimations being made, the red cell count had risen to 3.97 million and the haematocrit from 31 to 32.5 per cent a week later. The haemoglobin reading remained unchanged. Unfortunately this patient delivered herself within the next two days and no further investigation could be made. In all probability she was an early case of pernicious anaemia of pregnancy and folic acid even in small doses prevented her from being absolutely resistant. Apart from this one case however, no significant indication was found in this group for the giving of folic acid daily in 5 mgm.doses as an empirical prophylactic.

A further three patients were given folic acid 10 mg. daily. All showed very satisfactory responses, the haemoglobin rising 11 per cent in the first month. The numbers in this series were unfortunately too few and therefore no conclusions could be drawn, but it is interesting that even here the first monthly haemoglobin increment was not as high as that found in patients treated with iron alone in hospital.

This group is rather small to allow any definite conclusion to be drawn, but at least it can be said that there seems no justification for giving folic acid

empirically to outpatients with severe anaemia. Relatively large doses require to be given before any satisfactory response is obtained, but even with such doses the results are not so good as those obtained by hospitalisation and iron therapy.

The third group of patients, receiving a different treatment antenatally, consisted of three patients who were given a blood transfusion. The first patient was admitted in the sixth month of her pregnancy having lost a considerable quantity of blood in the previous week from bleeding haemorrhoids. On admission she looked very pale and ill. Her haemoglobin was 22 per cent Sahli. A blood transfusion, one pint of packed cells was given and thereafter iron therapy was commenced. The results were remarkable. Within a month the haemoglobin was 55 per cent Sahli, and the red cell count 3.32 million. In such a case as this treatment with blood transfusion proved to be very successful.

The second patient to receive blood was admitted from the ante-natal clinic when 36 weeks pregnant with a haemoglobin of 38 per cent Sahli, a red cell count of 3.8 million and a haematocrit of 26 per cent. The blood picture was that of a microcytic hypochromic anaemia and her plasma proteins

were 4.5 g. per cent. On admission she was very oedematous;no albumen was found in the urine and the blood pressure was 150/90. A sternal puncture was performed and the marrow differential count showed only 1 per cent megaloblasts and 20.5 per cent cells of the normoblastic series. No reticulocytes, nor reticulated erythroblasts were present in the marrow. She therefore appeared to belong to the group of anaemias, who only show a partial reponse to iron therapy even when in hospital. Iron, however, was given for one week but no improvement occurred in the haemoglobin level. As she was near term it was decided to see what the effect of transfusion would be in such a case and she was given one pint of packed cells of the same group as her own. Thirty six hours after the transfusion she had symptoms very similar to a pre-eclamptic state. She complained of not feeling well, had dimness of vision and severe headache. Morphia gr.$\frac{1}{4}$ was given and the next morning her symptoms had disappeared. Her haemoglobin which previously had been 145/95 to 145/100 had fallen to 126/86, on the morning after the appearance of these symptoms, but it rose again the next day to its original level and remained so till delivery. The haemoglobin rose to 48 per cent Sahli as a result of the transfusion, remained stationary during the next two weeks though iron

therapy was continued and only showed a rise of 6 per cent in the third week at the end of which period she went into labour and had a normal spontaneous delivery. Apart from the usual risks of transfusion in a pregnant woman such as infection, rhesus incompatability etc., there would appear to be another factor in this woman's case which may be the upset in the blood volume, blood pressure balance. Clinically this patient resembled the group of anaemias who similate toxaemia, though the fall in blood pressure after admission was not so striking. Whether the symptoms of pre-eclampsia and the fall in blood pressure noted the next morning were the result of the transfusion is difficult to say, but certainly it can be said that the transfusion did not provide a dramatic stimulus to haemoglobin production. The total rise in haemoglobin including that due to the transfusion itself in the subsequent weeks was 16 per cent Sahli whereas the average rise in the haemoglobin of all eighteen anaemias admitted to hospital during the first month was 13 per cent. Hence where there is time available before delivery for treatment of the anaemia, almost as good results were obtained with iron therapy as in this one case that was transfused.

The third patient to receive blood was admitted just before term with a haemoglobin of 22 per cent

Sahli, a red blood cell count of 4.08 million and a haematocrit of 21.5 per cent. The blood picture was that of a very severe microcytic hypochromic anaemia. The mean cell diameter was 6.6 u and the plasma proteins were 5.3 g. per cent. Transfusion before delivery was considered advisable at that time and the patient was given one pint of packed cells of similar group to her own. Two hours after completion of the transfusion she complained of left-sided abdominal pain colicky in nature. Her bowels moved repeatedly, but apart from the actual diarrhoea, the stools appeared quite normal. She became progressively worse and died eight hours later. Clinically the condition was not like that of an incompatable transfusion, nor cardiac congestive failure. The donor's blood was rechecked with the patients blood and no imcompatability was found. Unfortunately permission for a post mortem examination was not granted in this case and the actual cause of death was never really confirmed.

In conclusion it is apparent in view of the excellent results obtained in the first case, that blood transfusion has a place in the therapy of anaemias of pregnancy as an emergency measure. Before administering a transfusion however it would appear than an examination of the bone marrow is advisable. The fatal

outcome in the third case suggests that there are additional hazards as yet unknown to be considered in these cases of anaemia before transfusion is attempted.

The last group of anaemias to be considered consisted of 6 patients. All were given iron but in addition three received folic acid, one liver by injection and the remaining two thyroid. All three patients who had folic acid failed to respond to iron therapy as out-patients and one had only shown a partial response after admission to hospital. Initial marrow punctures were performed in all three cases, two as out-patients after failure to respond to iron therapy and the third before any treatment was given at all. In the first two patients the percentages of megaloblasts were 23 per cent and 15.7 per cent. Marrow reticulocytes were present in both and a few "inclusions" giving a positive iron reaction were seen in the marrow of the patient with the higher megaloblastic count but not in the other case. This latter film however showed a few blue patches of an iron staining substance lying outside the cells.

Both patients were given 20 mg. of folic acid daily, and in addition the first with 6.8 per cent megaloblasts in the marrow, was admitted to hospital. This patient showed a reticulocyte response of 3.5 per

cent on the sixth day, after admission. Two weeks later sternal puncture was repeated and the megaloblasts were found to have fallen to 2.6 per cent and the normoblasts had risen to 29.6 per cent. Thus with folic acid the normoblastic series which had been originally low (23 per cent) rose as a result of therapy, a fact which was not observed in the cases treated with iron. The marrow was stained for iron as before and a slight increase in the number of "inclusion bodies" in the cells was noted.

The marrow of the third patient examined before treatment started showed 25 per cent megoblasts and 26.8 per cent normoblasts, reticulocytes numbered 2 per cent and reticulated erythroblasts 0.8 per cent. No iron staining deposits could be found in the marrow. This patient was given iron as an out-patient but failed to show any response. She was therefore admitted to hospital and given iron as before. After two weeks the haemoglobin rose from 43 per cent to 51 per cent, but thereafter showed no further improvement. Three weeks after admission a second puncture was performed and a marrow differential count showed that the megaloblasts had risen to 4.8 per cent, the normoblasts showed little change and no reticulocytes or reticulated erythroblasts could be found in the bone marrow. Iron

staining "inclusion bodies" were fairly frequent. They therefore would appear to belong to the group of anaemias who only partially respond to iron therapy after admission to hospital. The same dose of folic acid was given to this patient when she ceased to respond to iron therapy, but the response was poor, the reticulocytes never exceeding one per cent in the peripheral blood.

The peripheral blood picture was microcytic in one case and normocytic in the other two, and all were hypochromic. During treatment the peripheral blood was slow in showing any definite improvement. A significant rise in haemoglobin (i.e. more than 5 per cent Sahli) was noted in only two cases viz. the patient treated wholly as an out-patient and the patient who received iron initially in hospital. Even in these cases the rise in haemoglobin was delayed for two weeks. All three, however, showed a marked increase in red cell population, approximately 1 million in each case. Concurrent with this, the haematocrit increased by approximately 5 per cent. No change was noted in the plasma proteins. After the patients reached a satisfactory level, it was found that theyrequired 10 mg. folic acid daily as a maintenance dose.

Summary. 1. In contrast to those cases receiving

folic acid empirically these cases of severe anaemia responded satisfactorily. This alone suggests that they constitute a definite type of anaemia.

2. In their response to iron therapy and their marrow pictures they correspond to the group of patients who proved refractory to iron even when admitted to hospital. It will be noted however that in one case the megaloblasts (6.8 per cent) were above the standard set for this type of case. However, it has been shown that these refractory anaemias show an increased per centage of megaloblasts when given iron and this may account for the abnormal number in this particular case.

3. Folic acid therapy caused a diminution in the number of megaloblasts and an increase in the normoblasts. This change occurred before any alteration was noted in the peripheral blood.

4. It seems likely from the action of folic acid on these patients that they should be considered as atypical cases of pernicious anaemia in whom there is a considerable degree of iron deficiency.

Two patients who failed to respond to iron as out-patients were given thyroid gr.$\frac{1}{2}$ t.i.d. in addition to iron, in the hope that by increasing the metabolism their appetite might be stimulated and the dietary intake increased. One patient was observed in hospital; the other was an out-

TABLE XVII.

BLOOD AND MARROW PICTURES IN UNTREATED TYPICAL PERNICIOUS ANAEMIA OF PREGNANCY.

	Hb. %	R.B.C. Milli	W.B.C.	P.C.V. %	M.C.V. μ^3	C.H.M.C. %	M.C.D μ.
BLOOD	37	1.78	4.200	20.5	118	29	7.7

	NORMOBLAST %	MEGALOBLAST %	RETICULATED CELLS %
MARROW	7	13	0.5 or less.

patient. No improvement was observed and a sternal puncture performed in one of these patients showed the presence of megaloblasts. This patient ultimately responded to crude liver by injection.

The last patient to be considered in this group had proved resistant to iron therapy given to her for two months as an out-patient. As before, the blood picture was normocytic hypochromic. A test dose of 4 c.c. of a crude liver extract was given empirically. Seven days later her reticulocytes had risen to 3.5 per cent but the initial improvement in the blood picture was not striking. Three weeks later, however, a definite improvement was noted and thereafter it continued. Before delivery the haemoglobin had risen from 45 per cent to 62 per cent Sahli.

Two typical cases of pernicious anaemia of pregnancy were investigated in the course of this survey. One patient delivered herself two days after admission; the other was seen four weeks before term. Blood counts revealed a very severe degree of anaemia in both patients, the average haemoglobin, red blood cells, white blood cells, haematocrit, mean cell volume, mean corpuscular haemoglobin concentration, mean cell diameter being 37 per cent, 1.78 million, 4,200, 20.5 per cent, 118 μ^3, 29 per cent and 7.7 μ respectively (Table XVII).

Sternal punctures were performed in both patients before and after delivery. In the initial films numerous indeterminate smear cells were present which made a proper differential count difficult. Counts, however, showed that the percentages of megaloblasts and normoblasts were relatively low, namely 7 per cent and 13 per cent respectively. In other words one out of every three cells belonging to the erythrocyte series was a megaloblast. Marrow reticulocytes were scanty and a very few iron staining deposits were seen lying outside the cells. The Van den Bergh was negative in the patient who delivered herself soon after admission and a specimen of urine was not obtained for examination. In the other, the Van den Bergh was biphasic and the urine gave a very strongly positive urobilinogen. This patient was given crude parenteral liver, the initial dose being 4 c.c. followed by 2 cc. daily, and iron by mouth, but she proved resistant to this form of therapy and nine days later, 2 pints of packed cells were given. Daily reticulocytes which have been less than 1 per cent showed no tendency to rise after transfusion. Delivery ensued two weeks later, labour lasted forty hours and delivery was spontaneous, but the child which weighed 5½ lbs., was still-born. A second blood transfusion was given after labour and treatment with liver and iron

was continued as before. Within four days the reticulocyte count began to rise and reached a maximum of 12 per cent on the 18th day of the puerperium. Thereafter progress was very satisfactory, weekly liver injections were given for two months after dismissal, then discontinued. The patient was seen a year later when her blood picture was normal in every respect.

The second patient, despite her severe anaemia, had an uneventful delivery, the baby weighed 5 lbs.3-oz. and appeared quite healthy at birth. This patient developed a urinary infection with associated pyrexia two days after delivery, and treatment with sulphadiazine and penicillin was commenced. Blood culture was negative, however, and the temperature fell within four days. The reticulocytes again showed a rise, in this case three days after delivery. Treatment only with iron had been given, and, as it was hoped to compare the effect of folic acid in this case, iron was given till the reticulocyte count settled. Instead, however, the reticulocytes increased during the first week of the puerperium, reaching 9 per cent on the 7th, 8th and 9th days. At this time a repeat sternal puncture was performed and the change in the marrow picture was quite remarkable. Fewer smear cells were present. The normoblastic series was now 27.3 per cent of the total

and the megaloblasts 10 per cent. The marrow reticulocytes were 7 per cent and the reticulated erythroblasts 4 per cent. Numerous "iron staining inclusion bodies" were present in the red blood cells and late normoblasts. The urine at this stage also gave a very strong positive test for urobilinogen. The blood picture was even more macrocytic with a haemoglobin of 25 per cent, a red cell count of 1.28 million and a haematocrit of 18 per cent. Treatment with folic acid was therefore commenced, 20 mg. daily being given. The result was dramatic; within two days the reticulocytes were 17 per cent and within seven days 30 per cent. Megaloblasts were present in the peripheral blood during the crisis. Twelve days after commencing therapy the haemoglobin was 47 per cent and the red cell count 2.23 million, the urinary urobilinogen was negative, and the plasma proteins 5.1 g. per cent. Because of exceptional home circumstances the patient was allowed home to continue treatment. Since then, however, she has refused to report back to hospital and though reports say she feels well, no further examination of her blood has been possible.

It is difficult to say whether the results with folic acid and liver in these two cases are comparable or not. Before delivery, the first patient was certainly refractory to parenteral liver even in its

crude form. Blood transfusions had to be given as supplies of oral liver did not arrive in time. The second transfusion in her case may therefore have depressed the erythropoietic response in the puerperium by raising the haemoglobin level and decreasing the state of anoxaemia in the bone marrow sinusoids. Or secondly, she may still have remained refractory to the liver in the early days of the puerperium and this may account for the delayed rise in the reticulocytes. Certainly, however, it can be said that the initial response to folic acid therapy in the second patient was very satisfactory, but whether this improvement was maintained we do not know.

Other four cases of pernicious anaemia of pregnancy were seen during 1946 and 1947. They had all received liver therapy from their own doctors and the peripheral blood pictures and marrow films were therefore modified accordingly. As none of the patients had received iron regularly this deficiency was once again more apparent. Of the four patients three were seen antenatally and the fourth after delivery. Sternal punctures were performed in all four patients, but as these were done at varying times in the course of treatment it is better that each case be considered separately in order that the complete picture may be

TABLE XVIII.

Marrow.	Megaloblast %	Normoblast %	Myeloid %	Reticulocytes %	% Reticulated normoblasts	Marrow iron.
On admission	4	38.7	52.3	9	3	0
After 8 wks iron therapy.	5.6	18.6	67.8	5	0	+

Blood	Hb. %	R.B.C. Mill.	P.C.V. %	M.C.V. μ^3	M.C.H.C. %	Plasma protein
On admission	24	2.99	22	74	17	5.2
After 8 wks iron therapy	53	4.16	30.5	80	26	4.7

obtained:-

Case (1). This patient was seen two months previously at the Royal Infirmary when she was told she had pernicious anaemia of pregnancy and liver injections were advised. These were given regularly, initially three per week and then twice weekly in 2 cc.doses. The peripheral blood count and initial marrow differential count are shown in Table XVIII. The megaloblasts were present in moderate numbers only and the normoblasts had a high percentage. Marrow reticulocytes and reticulated erythroblasts were high and no iron "inclusions" were seen. The blood picture was typical of an "iron deficiency anaemia" and the plasma proteins slightly below the average. After eight weeks' iron therapy in hospital without any liver being given, the results were striking. The blood picture was now slightly below normal standards, the cell size, volume and concentration of haemoglobin being normal or nearly so. The only abnormal finding in the blood examinations made, was the low plasma protein value of 4.7 mg.per cent. When the marrow results were compared it was obvious that, instead of approaching "normality", a further divergence had occurred, namely, the percentage megaloblasts had increased, the percentage normoblasts and reticulocytes

decreased and no reticulated erythroblasts could be found. "Iron staining inclusion bodies" had now appeared.

From the description above it is obvious that by withdrawing the liver therapy and giving iron to this patient a marrow and a peripheral blood picture similar to the ultimate pictures presented by the anaemias, who showed only a modified response to iron therapy in hospital, has been produced. The corollary should therefore hold that a deficiency of the "liver factor" was also present in these hospital patients. Folic acid has been shown to increase the normoblasts and reduce the megaloblasts (three cases mentioned previously). Work, therefore awaits to be done with liver therapy to prove that it also is effective in producing a more normal marrow. One further point should be mentioned here. It has been shown that folic acid therapy in these "early cases of pernicious anaemia of pregnancy" had its initial effect on the marrow and a delayed influence on the blood picture. In this patient withdrawal of liver had its initial effect on the marrow which could not be called "healthy", yet the blood picture was almost normal and, as yet, showed no evidence of a deficiency of the erythrocyte maturation factor.

TABLE XIX.

Marrow	Megaloblast %	Normoblast %	Myeloid %	Reticulocytes %	% Reticulated normoblasts.	Marrow iron
On admission	-	-	-	-	-	-
After 2 wks iron therapy	2.1	17.7	72	5	.5	0

Blood	% Hb	Mill. R.B.C.	% P.C.V.	% M.C.V.	% M.C.H.C.	Plasma protein. g. %
On admission	32	2.93	21.5	73	20	4.8
After 2 wks iron therapy	50	2.81	33	117	24	5

Case (2). This patient had been in her local hospital, when five months pregnant, on account of anaemia. A diagnosis of pernicious anaemia of pregnancy was made then and treatment with liver and iron was given. After dismissal she did not have any further treatment and three months later she was seen at clinic here and admitted to hospital with a severe "microcytic hypochromic anaemia" (Table XIX). The plasma proteins in her case were exceptionally low, 4.8 g. per cent. Treatment with iron was given as before and a sternal puncture was performed two weeks later. The differential count showed fewer megaloblasts than in the first case, but also fewer normoblasts. The marrow reticulocytes were still fairly high and no "iron inclusion bodies" were seen. The blood picture taken at this time was now definitely macrocytic and less hypochromic. Several points can therefore be made. Firstly that where treatment with liver has been insufficient the percentage of normoblastic cells in the marrow is low. Secondly the iron deficiency is the dominant factor in the peripheral blood, but where previous liver therapy has been inadequate, the blood picture reveals the latent erythrocyte maturation factor deficiency at an earlier date when iron alone is given (two weeks in this case, whereas the blood picture was still "normal" after eight weeks in the previous case).

TABLE XX.

Marrow	Megaloblast %	Normoblast %	Myeloid %	Reticulocytes %	Reticulated normoblasts. %	Marrow iron. g. %
On admission	-	-	-	-	-	-
After 1 wk liver and iron.	5	18	72	0	0	0
Blood.	**Hb. %**	**R.B.C. Mill.**	**P.C.V. %**	**M.C.V. μ^3**	**M.C.H.C. %**	**M.C.D. μ.**
On admission	31	1.89	22	116	22	6.9
After 1 wk iron therapy.	34	2.1	-	-	-	7

These findings would suggest that the first patient had been able to store her erythrocyte maturation factor, which had been given in the form of liver therapy, and utilise it to advantage during the eight weeks she was in hospital on iron alone. Thirdly no "inclusion bodies" were found in the marrow in this case after two weeks iron therapy. They would therefore seem to appear sometime between two weeks and eight weeks, as in the previous case. Finally the plasma proteins in this case had risen slightly when this estimation was made. Iron therapy was continued for another week before delivery and by that time the plasma proteins had dropped to 3.9 g.per cent. This patient had therefore developed a "typical macrocytic blood picture" and it is interesting to note that weekly urobilinogen estimations of the urine increased as the erythrocyte maturation factor deficiency became more apparent.

Case (3). This patient was admitted in labour. She had been ineffectively treated with iron and liver elsewhere. Her original count is shown; the blood picture was macrocytic (Table XX). Crude liver by injection and iron were given and a week after delivery the sternal puncture, and second blood count were made. The percentage of normoblasts was again low, the megaloblasts being moderately high. No reticulocytes were found in

the marrow but when the peripheral blood was examined the reticulocytes estimated 9 per cent. No "inclusion bodies" were seen but a few iron staining masses were found lying free outside the cells.

Case (4). This patient was also admitted in labour. She attended the clinic and though routine blood counts were done, her own doctor wished to continue treatment. Treatment with pure liver by injection and iron was given and before admission the blood count was normal. Unfortunately liver therapy was not continued after admission, which may account for the low percentage of cells of the normoblastic series which were found in the marrow when sternal puncture was peformed a week after delivery. The marrow reticulocytes were only 1 per cent, but, possibly this may be due to the fact that this patient was really no longer anaemic. Only a very few iron "inclusions" were seen in the marrow, which would suggest that where iron and liver therapy are combined this phenomenum does not exist to any great extent. Summarising these results it can be stated:-

(1). Typical cases of pernicious anaemia of pregnancy do occur but they are less common than the atypical cases described previously.

(2). Apart from the differences in the degree of

anaemia and the peripheral blood picture in the untreated typical and atypical cases the marrow smears also showed contrasting features. Firstly the number of indeterminate smear cells was higher in the typical cases. Secondly, the initial percentage of cells of the normoblastic series was even lower than the initial percentage in those cases who only partially responded to iron therapy and thirdly the percentage of megaloblasts was slightly higher in these typical cases than in the atypical. Marrow reticulocytes and reticulated erythroblasts were also low.

(3). It seems possible in view of the contrast between the typical and atypical cases that typical pernicious anaemia of pregnancy may represent a specific type of anaemia.

(4). However, the sequema of events following the administration of iron to patients previously diagnosed as pernicious anaemia of pregnancy, suggests that this is not so. These patients had received liver for varying periods and on admission the peripheral blood picture was that of the atypical cases. All showed an apparent microcytic hypochromic anaemia. The marrow smears contained a fairly high percentage of normoblasts depending apparently on the intensiveness of previous liver therapy. Iron was given to these

patients on admission and the blood picture gradually changed. At one stage the appearance of the peripheral blood and marrow resembled that in the cases who showed only a partial response to iron. "Iron - inclusions" began to appear in the marrow and the normoblast percentage fell steadily. Eventually the peripheral blood showed a typical picture of macrocytic hyperchromic anaemia.

(5). Whether or not the "typical" cases of pernicious anaemia of pregnancy represent a distinct syndrome, it seems fairly certain, from the megaloblastic reaction in almost all other cases of anaemia examined, that the "atypical" cases develop out of ordinary severe iron deficiency anaemias.

(6). Finally, a case of typical pernicious anaemia of pregnancy which proved resistant to crude liver parenterally antenatally, showed a satisfactory response in the puerperium. Also the second case followed showed a tendency to spontaneous remission in the puerperium as evidenced by the reticulocytosis of 9 per cent before folic acid was given and also by the increase of the normoblasts in the bone marrow from 13 per cent to 27.3 per cent. It is doubtful however if this patient would have reached such satisfactory levels without folic acid therapy, as she was extremely

anaemic and, despite the changes observed in the marrow cells and the reticulocytosis, it is doubtful if this response would have been sustained.

The last of the special group of anaemias to be considered are the haemolytic anaemias. The clinical pictures have been described and it has been shown that they varied considerably. Haematologically and biochemically they also varied and must therefore be considered separately.

On admission the first patient was thought to be a case of pernicious anaemia of pregnancy. The blood picture was that of a typical macrocytic anaemia namely the haemoglobin was 35 per cent, the red cells 1.44 million, the packed cell volume 20 per cent, the mean cell volume 139 μ^3, the mean corpuscular haemoglobin concentration 28 per cent and the mean cell diameter 7.8μ. However, when the mean corpuscular average thickness was calculated it was found to be 2.78 μ, compared with the normal 1.7 to 2.5 μ (Price - Jones, Vaughan and Goddart 1935) and with 2.2 μ which is the figure quoted by Haden (1934) for Addisonian pernicious anaemia. The white cell count was 6,000 and a differential count showed no abnormality. Platelets estimated 350,000 and the reticulocytes were 16 per cent. The plasma proteins were 4.2 g. per cent, the

icteric index was 7, the Van den Bergh reaction was weakly positive directly and indirectly and the urine contained + of urobilinogen. In view of these findings a red cell fragility test was carried out and haemolysis was found to begin at 0.7 per cent and to be complete at 0.45 per cent sodium chloride, the normal values being 0.42 per cent to 0.48 per cent (Haden 1934). The clotting time, the bleeding time and the capilliary fragility were normal however.

When the marrow picture was examined it was found to be macronormoblastic. Haemopoiesis was active and numerous "inclusion bodies" were present similar to those described by Pappenheimer (1945) and McFadzean and Davis (1947) and also similar to the "inclusion bodies" noted previously in the marrows of our atypical pernicious anaemias of pregnancy after iron therapy.

A test dose of 4 c.c. of anahaemin was given to this patient and daily reticulocyte counts showed only slight variations, remaining at their initial high value. No improvement was noted after 7 days despite the continuously raised reticulocyte count. Proteolysed liver 1 ounce daily was therefore commenced and was continued throughout her stay in hospital. Two days later the patient appeared to be going into labour and it was decided to give her a blood transfusion. Fresh

blood of the same group o and rhesus CDe, CDe was cross-matched and read after five minutes and one hour at 0°C. 15°C., and 37°C. No agglutination occurred and transfusion was therefore commenced. The blood was administered slowly by the drip method and after 250 c.c. had been given, the patient had a severe rigor. Though the transfusion was immediately discontinued the patient began to complain of pain in the renal angles. She became very breathless and jaundice appeared rapidly. Two pints of 5 per cent glucose saline were given slowly. The urinary output was 16 oz. in the next 24 hours and the urine contained numerous casts, both granular and hyaline; a few red cells, white cells and epithelial casts were seen. Further analysis revealed the presence of bile in the urine, the urobilinogen was strongly positive, but no haemoglobinuria or methaemoglobinuria was detected. The blood was very jaundiced, the icteric index being 80. The Van den Bergh was positive directly and the plasma bilirubin estimated 19 mg. per cent. The blood urea was 24 mg. per cent;methaemalbuminaemia was not detected on spectroscopic examination of the blood. As a result of the "haemolytic crisis" the haemoglobin fell to 27 per cent Sahli and the red cells to 1.20 million with a haematocrit reading 15.5 per cent. The reticulocytes

rose to 20 per cent. The blood film showed even more marked polychromasic macrocytes, containing nuclear fragments and "inclusion bodies" which gave a positive iron reaction in addition to staining with Leishman. Numerous normoblasts were also seen in the peripheral blood.

Labour commenced 24 hours later and lasted 10 hours, when the patient delivered herself of a macerated foetus of 6½ months size. To prevent further blood loss and, as the placenta was not immediately delivered, a general anaesthetic was administered and the placenta and membranes removed manually. Thereafter the condition improved. The spleen continued to enlarge and on the second day of the puerperium the lower pole could be felt at the level of the iliac crest. On the third day her temperature rose to 101°F and penicillin 20,000 units three hourly was commenced. A fall in temperature to normal occurred within 24 hours however. By the eighth day of the puerperium reticulocytes reached a peak of 20 per cent and the haemoglobin was 38 per cent. Progress thereafter was very satisfactory; the haemoglobin was 57 per cent and the red cells 3.00 million a month later. The blood picture was still macrocytic; the reticulocytes were 4 per cent, the plasma was still jaundiced with an icteric index of 12 and a plasma bilirubin estimation of

1 mg. per cent. The red cell fragility was still raised haemolysis beginning at 0.65 per cent and complete at 0.4 per cent sodium chloride . The patient reported back a year later. Her health had been good and she had no complaints. She was still taking Hepamino, but had discontinued iron therapy. Her count showed little change from the above; the haemoglobin was 57 per cent and the red cells were 3.20 million. Sub-clinical jaundice was present. The direct Van den Bergh was negative, but the plasma bilirubin estimated 3.6 mg.per cent. The red cell fragility was still raised and showed no change. The urinary urobilinogen was however negative. On examination of the patient the lower pole of the spleen could just be tipped under the costal margin. No other abnormality could be found.

Fundamentally the condition in this patient is the result of two processes; one blood destruction, recognised by the spherocytosis, the increased fragility, the positive indirect Van den Bergh, the increased plasma bilirubin and urinary urobilinogen and the other blood formation with reticulocytosis, polychromosia, nucleated red cells and nuclear fragments.

It was necessary to determine whether the destruction of the red cells was a result of some congenital abnormality in the cells or the reticulo-

endothelial system, or whether a circulating haemolysin was present in the blood. The following procedures were carried out in an attempt to demonstrate the presence of a haemolysin. Blood was taken with all precautions against haemolysis, no constriction being applied to the arm. 10 c.c. of blood was transferred to a sterile heparinised bottle and the cells allowed to settle.

(1). The patient's cells were put up against her plasma and left in the refrigerator at 0°c., at room temperature at 15°c. and in the incubator at 37°c. Agglutination occurred only at 0°c., thus demonstrating the presence of cold agglutinins.

(2). The patient's cells were put up against the patient's plasma and haemolysis occurred equally after 12 hours at 0°c., 15°c. and 37°c.

(3). The patient's cells were washed with normal saline centrifuging being carried out at low speeds and for short durations. The washed cells were put up against the patient's plasma as before and haemolysis occurred again as in (2).

(4). When the patients washed cells were put up against plasma of a similar group haemolysis occurred as before.

(5). When the control cells were put up against the patient's plasma, no haemolysis occurred after 12 hours

except a very doubtful trace in the tube at 37 C.

(6). The plasma was heated at 56 C. for half an hour, which according to Dacie (1938), Ham (1937) and Lescher and Osborn (1939) will destroy a haemolysin. The cells were resuspended in the heated plasma and complement was added. Three tubes were set up as before and read after 12 hours. No haemolysis occurred except a trace in the tube at 37 C.

These experiments were repeated a year later when the patient reported back and similar results were found except that washing of the patient's cells then appeared to increase the haemolysis. Haemolysis occurred with the patient's cells and control plasma, and again only a trace was noted in the tube at 37 C., when the control cells and patient's plasma were put up.

(7). A Coomb's test was performed on the patient's washed cells when she was in hospital and again a year later. The results were negative.

(8). Finally, though the patient gave no family history of anaemia, her nearest living relatives were examined. Unfortunately, both her parents were dead but a maternal aunt and the patient's only sister were available. No abnormality was found on examination of their blood. The haemoglobin etc., was normal, there was no jaundice, the fragility of the red blood cells was within normal limits

and the reticulocytes were less than 1 per cent.

Summarising these results,

(1) It seems unlikely that an iso-immune body was the cause of the haemolysis, as the Coomb's test in that case would have been positive. Also no haemolysis of the control cells occurred, except at 37°C. and after twelve hours when a faint trace was reported, but this is of doubtful significance.

(2) The inherent factor instead, would appear to be in the cells, which have already been shown to be spherocytic and excessively fragile in the higher saline dilutions. Also haemolysis occurred equally when the patient's cells were resuspended in her own and in the control plasma.

(3) It is difficult, however, to explain the absence of haemolysis when the patient's cells were resuspended in her own heated plasma. This result was obtained on both occasions. It would tend to suggest that a haemolysin was present and that it had been destroyed by heating, but it would not explain the haemolysis that occurs when the patient's cells are suspended in control plasma.

(4) The absence of any abnormality in the blood of near relatives should be noted.

(5) Finally, the persistence of increased fragility and

spherocytosis one year after delivery must be taken into account in the final analysis.

The second patient was not seen until the fifth day of the puerperium when her haemoglobin was 25 per cent, the red count 1.20 million, the packed cell volume 13 per cent, the mean cell volume 109 μ^3, the mean corpuscular haemoglobin concentration 31 per cent, and the mean cell diameter 7.6 μ. From these values the mean corpuscular average thickness was calculated and was found to be 2.26 μ which is not typical of a haemolytic anaemia with spherocytosis, where the mean corpuscular average thickness is nearer 3.0 μ.(Haden 1934). The white cells were 13,000 and a differential count showed that this was due to a polymorphonuclear leucocytosis. The reticulocytes were 7 per cent. The blood picture was therefore macrocytic and normochromic. The film showed considerable anisocytosis, fairly numerous large polychromasic cells could be seen and occasional normoblasts and erythroblasts were found in the peripheral blood. No megaloblasts were seen however. Biochemical analysis of the blood was carried out; the plasma proteins were 4.6 g.per cent, the blood urea 17 mg. per cent, the plasma was icteric and the Van den Bergh was positive directly. The red cell fragility was increased, haemolysis commencing at 0.65 per cent and complete at 0.45 per cent sodium chloride.

At this time the patient was pyrexial. Penicillin therapy had been commenced, but when coliform bacilli were obtained as a heavy growth from the cervical swab and urine culture, sulphonamides were given. A coliform septicaemia is not likely to give rise to a haemolytic anaemia but it was considered advisable to do a blood culture. This was negative.

As stated in the clinical section, a blood transfusion was given initially when the patient came under supervision. Iron therapy was also commenced. During the next seven days the blood levels, which were estimated every second day, gradually fell, yet the reticulocytes remained high. The jaundice still persisted and the Van den Bergh remained positive directly. On the twelfth day of the puerperium the patient had a second epistaxis; she looked suddenly much worse and it was found that the haemoglobin had dropped to 13 per cent Sahli and the red blood cells to 0.70 million. The haematocrit was now 12 per cent, the white blood cells 28,000, and the reticulocyte count had risen from 14 per cent to 21 per cent within 24 hours. The peripheral blood film showed numerous erythroblasts and macronormoblasts, no megaloblasts were seen. A second transfusion was given and the improvement was dramatic. The reticulocytes fell to 7 per cent within 36 hours and

thereafter rose to a maximum of 14 per cent as the patient gradually began to improve. Within two weeks, the haemoglobin had risen to 49 per cent and the red count to 2.28 million; the reticulocytes were 3 per cent. It was decided to watch the effect of a test dose of liver in such a case; 4 c.c. of a crude liver extract were therefore given. The reticulocytes rose to 5 per cent the following day, remained at that level for 4 days and then fell, i.e. not a very marked reticulocyte response, which would possibly indicate that this was not a case of pernicious anaemia of pregnancy, but suggesting that in such a case where haemopoiesis was rapid, liver therapy would be a useful adjuvant.

Biochemical analysis of the blood at this time showed a negative Van den Bergh, both directly and indirectly, the icteric index was normal, the plasma proteins 5.4 g.per cent and the red cell fragility was now normal.

The patient was seen a year later when her blood picture was normal, jaundice was absent, and the red cell fragility was normal. Clinical examination revealed no abnormality and the patient felt well.

This patient was seen at the very beginning of the present survey before material was available to

carry out all the investigation performed on the previous case. The salient features in this case, however, which point to a diagnosis of haemolytic anaemia are:

(1) The two haemolytic crises, the second of which was most dramatic in appearance.

(2) The blood examinations which revealed a jaundice, an ever-increasing anaemia, a rising reticulocyte count, and an increased fragility of the red blood cells.

(3) The absence of megaloblasts in the peripheral blood picture during the second haemolytic crisis.

(4) The poor reticulocyte response to the test dose of liver.

Several factors have to be considered with reference to the cause of the haemolysis.

(1) Sepsis may cause a haemolytic anaemia but the anaemia is usually hypochromic and the reticulocytosis slight. Increased fragility of the red blood cells is uncommon. Moreover in this case it is unlikely that a coliform infection of the uterus and urinary tract could have caused such a marked degree of anaemia.

(2) The pre-eclamptic toxaemia may be a causative factor.

(3) Finally when no other cause is apparent, pregnancy itself must be considered a factor.

TABLE XXI.

7 cases of Anaemia and Toxaemia.

	Hb. %	RBC Mill.	PCV %	MCV μ^3	MCHC %	MCD μ.	Plasma proteins. g.%	Blood picture.
Average for 6 cases.	44	3.82	27	72	24	6.5	4.6	Microcytic hypochromic.
7th case	44	3.22	26	81	27	6.3	3.2	Normocytic normochromic.

TABLE XXII.

10 cases of Anaemia who developed Toxaemia.

		Hb. %	RBC Mill.	PCV %	MCV μ^3	MCHC %	MCD μ.	Plasma protein g %
6 patients responding to iron.	Before treatment	45	3.91	30	80	23	6.9	5.7
	After treatment	57	4.24	36	85	24	7.2	5.6
4 no response		39	3.29	28	87	22	6.9	5.3

GROUP B.

As stated in the clinical section, 29 cases were included in this group of "anaemias and toxaemia". Of these, seven were cases of pre-eclamptic toxaemia who had an anaemia, ten were cases of anaemia who developed a toxaemia, and twelve were cases of anaemia simulating a toxaemia.

The above figure of seven cases of pre-eclamptic toxaemia, who had an anaemia, cannot be taken as the figure for the incidence of anaemia in toxaemic patients. Many patients with pre-eclamptic toxaemia have been found to be anaemic, but in few is there an opportunity to investigate them haematologically still less to observe the effects of treatment. In these seven patients, however, this was possible. All were admitted to hospital on account of their pre-eclamptic toxaemia, having had a routine blood test taken at the ante-natal clinic. The blood picture in six of the cases was that of a microcytic hypochromic anaemia, but in the seventh patient it was normocytic and normochromic.(Table XXI). In this patient it was interesting to note that though the plasma proteins were 3.6 g. per cent, the lowest figure recorded in the group, no oedema was present. Sternal punctures were not performed because of the existing toxaemia. All the patients were given iron

in hospital for periods of at least two weeks but the results were not striking. Only four patients showed any improvement. No difference could be found in the blood picture or plasma proteins between those who improved with iron and those who failed to respond. In those who responded, the results were very satisfactory and corresponded to the changes shown by other cases of anaemia admitted to hospital, a haemoglobin rise of 12-14 per cent Sahli being recorded within a month. It is possible that some of the apparent improvement in these cases may have been due to blood volume changes. Two of the patients showed a marked anaemia one week after delivery although they had suffered no undue blood loss. In addition, one of the patients who improved showed a sudden rise in haematocrit from 27 per cent to 31 per cent within four days. Reticulocytes however, only estimated 3 per cent and it is difficult to believe that such a steep rise in haemoglobin etc., could result from so small a reticulocyte response. Before further investigations could be carried out this patient had an eclamptic fit. It is possible therefore that the changes recorded in the blood were the result of haemoconcentration and could be taken as a "warning" of pending eclampsia.

No reason could be found to account for the

lack of response in the remaining three patients, but without examination of the marrow it is impossible to state definitely what kind of "anaemic" process was at work. It is obvious therefore that more investigation of these cases is required, especially by marrow biopsy, to determine whether the anaemia is due to a hypoplasia of the bone marrow as a result of the toxaemia, or a deficiency state of one of the haemopoietic factors. One striking feature of the cases surveyed was the low plasma protein value, the average initial value for all the cases here being 4.4 g. per cent as compared with an average of 5.5 g. per cent in the "anaemias".

Of the 10 cases of anaemia who developed a toxaemia it will be remembered that 4 could no longer be regarded as anaemic when they developed their toxaemia and another 2 were responding to treatment. The remainder showed no response whatever to iron therapy. The initial and ultimate blood levels in the patients who were responding to therapy and the initial blood levels in the remainder who showed no response have been tabulated (Table XXII). It will be seen that the anaemia was less severe initially in those who responded to iron therapy before developing toxaemia and also that the plasma proteins were higher in this group too. i.e. the plasma protein level of the

patients who showed no response to iron therapy and ultimately developed toxaemia was lower initially (5.3 g. per cent). When the toxaemia had developed it was noted that a further fall in plasma proteins occurred in these patients (4.7 g. per cent), i.e. the figure now approached that observed in cases of toxaemia with anaemia (4.6 g. per cent).

Whether these changes in the plasma protein estimations are essentially blood volume changes is difficult to say. If this were so then absence of a similar drop in the haemoglobin etc., could be explained by an increase in the haemoglobin production. Unfortunately daily reticulocyte counts were not carried out in these cases to determine if this were so. Alternatively the "toxaemic process" through its action on the liver may exert a greater influence, when the "stores" of protein, as evidenced by the plasma protein level, are low. It may in its initial stages prevent the anaemia from responding to treatment and ultimately establish a picture of severe anaemia, low plasma proteins and toxaemia. One of the four resistant cases who developed toxaemia is interesting. Before delivery her blood count was the only one to deteriorate as a result of the toxaemia, the haemoglobin falling from 42 per cent to 37 per cent and the red count from 3.50

TABLE XXIII.

9 untreated cases of Anaemia simulating Toxaemia.

	Hb.	R.B.C.	P.C.V.	M.C.V.	M.C.H.C.	M.C.D.	Plasma protein.
Initial.	39	3.71	27	76	20	6.5	5.5
One week after delivery.	38	3.42	27	80	20	6.9	5.2

TABLE XXIV.

3 severe Anaemias simulating Toxaemia.

BLOOD.	Hb.	R.B.C.	P.C.V.	M.C.V.	M.C.H.C.	M.C.D.	Plasma protein.	Urobilin.	Plasma Bilirubin.
	26	3.14	19.5	62	21	6.9	4.4	+ + +	1.0 mg.

MARROW.	Megaloblast Series	Normoblast Series	Myeloid Series	Reticulocytes		Marrow Iron
				Nucleated	Non nucleated	
	4.8	25	61	-	-	-

to 2.69 million. In addition she had developed a definite sub-clinical jaundice with a biphasic Van den Bergh and a plasma bilirubin estimating 2.4 mgs. per cent. Labour had to be induced because of the severe pre-eclampsia. After delivery the blood picture became definitely macrocytic and her marrow contained 12.6 per cent megaloblasts, i.e. she now presented a typical picture of pernicious anaemia of pregnancy. This case will be discussed later with reference to the development of jaundice in the course of therapy.

Of the 12 cases of anaemia, who simulated a toxaemia it will be remembered that nine of the patients with a less severe degree of anaemia were delivered before therapy could be instituted, but the remaining three cases were investigated and treated antenatally. The average figure for the initial blood levels in the nine untreated cases are shown in table XXIII. Clinically these patients resembled the cases, seven in number, who had a true toxaemia complicated by anaemia. The degree of anaemia however was more marked in the former than in the latter. Oedema was more prominent in this group also, although the plasma proteins were initially higher, namely 5.2 g. per cent compared with 4.6 g. per cent in the cases of true toxaemia. Two of these patients were investigated rather more fully

than the remainder. Their initial haemoglobin levels were 33% . and 37% . per cent respectively. On the third day of the puerperium these values fell. The haemoglobin readings became 23 per cent and 32 per cent and the plasma proteins 4.3 g. per cent and 4.75 g. per cent. By this time these patients complained of symptoms of anaemia but it is interesting to note that the oedema had completely disappeared although the plasma proteins were still very low. Sternal puncture was performed before delivery on the patient with the higher haemoglobin (37 per cent). The marrow was found to contain 2.4 per cent megaloblasts, 22.3 per cent normoblasts, 1 per cent reticulocytes and no reticulated nucleated cells. No iron deposits could be seen. The marrow of the other patient (initial haemoglobin 33 per cent) was examined on the fourth day of the puerperium. During the 4 days after delivery the patient had had iron therapy, since it is customary in this hospital to give iron therapy to all patients routinely in the post-natal wards. This marrow contained 2.5 per cent megaloblasts, 34.7 per cent normoblasts, 5 per cent reticulocytes and 0.5 per cent reticulated normoblasts. A small number of iron staining "inclusions" were seen in the erythrocytes. Apart from the percentage of megaloblasts which was the same for each, the

normoblasts and reticulated nucleated and non-nucleated cells estimated 34.7 per cent, 5 per cent and 0.5 per cent respectively as compared with 22.3 per cent, 1 per cent and 0 per cent in the case examined before delivery. Whether the increase in the normoblastic series and in number of reticulated cells in the second case is due to the termination of the pregnancy and the prompt institution of iron therapy in the puerperium is not absolutely proved, as a sternal puncture would have been necessary in the same patient before and after delivery, but in view of the fact that the reticulocytes in the peripheral blood estimated only 1.5 per cent before delivery in this case and were 6.5 per cent on the fourth day of the puerperium when the marrow was examined, it can be said that the difference in the two marrow pictures was probably significant.

Since this second patient, whose marrow was examined in the puerperium appeared to be responding to iron alone, no further treatment was given. For comparison purposes the first patient, who was the less anaemic of the two, that is had an initial haemoglobin of 37 per cent Sahli, was given iron and folic acid 20 mg. daily after delivery. The reticulocytes reached a peak of 10 per cent, as compared with 6.5 per cent in the previous case, on the sixth day of the puerperium;

by three weeks the haemoglobin was 54 per cent Sahli, whereas it took the second patient 6 weeks to reach this figure on iron alone. A repeat sternal puncture was performed in the first patient seventeen days after commencing the iron and folic acid and the changes in the marrow picture were even more significant. The percentage of megaloblasts had fallen to 2.1 per cent, the normoblasts had risen to 32 per cent and the reticulated nucleated and non-nucleated cells estimated 1.3 per cent and 8 per cent respectively. From these results it would appear that the greater improvement shown by the first patient was due to the folic acid. The second marrow smear was stained for iron as before, and though iron had been given in this case for three weeks only a very few "inclusion bodies" were seen.

Of the remaining 7 patients it was only possible to interview two patients after they had left hospital. The results in these 2 patients, especially when compared with a third case, show in a striking manner the effect of diet and breast feeding. The first patient had an initial haemoglobin reading of 37 per cent before labour. She breast fed her baby and despite iron therapy, her haemoglobin six weeks later had fallen to 34 per cent. It is necessary at this point to explain that, in this hospital, cases

of toxaemia are placed on one of three diets according to which unit they are sent. The main feature of these diets is a variation in protein, in one unit the toxaemia patients have a high protein diet: in another low protein; an in a third a normal balanced diet. This first case had a low protein diet. The second case had an initial haemoglobin of 38 per cent and six weeks after delivery it was up to 71 per cent. This patient had a balanced diet while in hospital and did not breast feed her baby. The third patient, who breast fed her baby had an initial haemoglobin of 48 per cent, but showed a rise to 63 per cent within a week of delivery. She, however, had a high protein diet in addition to the usual iron therapy.

The remaining three patients in this group of anaemias simulating toxaemia, were very severe anaemias. All had haemoglobins less than 33 per cent Sahli and the average was 26 per cent. The results are shown in table XXIV. It will be seen that these three patients had the most severe degree of anaemia noted in the whole of the group B. cases. In addition on biochemical analysis the plasma proteins were exceptionally low, the reading being 3.45 g. per cent in one patient; all had delayed positive and positive indirect Van den Bergh reactions, the plasma bilirubin estimating 1 mg. per cent and the urines gave a strong positive result for urobilinogen. Again despite

the microcytic hypochromic blood picture, which was marked in these patients, the marrows contained 4.8 per cent megaloblasts, the normoblast series tended to be low, namely 25 per cent and no marrow reticulated cells were found. No iron therapy had been given and no iron staining "inclusion bodies" were seen. Various treatments were given and the response to therapy in each case will therefore be considered separately.

(1) The first patient was given iron alone for 2 weeks before delivery. During that time the haemoglobin rose from 24 per cent to 31 per cent, and the haematocrit from 18 per cent to 24.5 per cent, the red cells showing no change. The plasma proteins fell from 5.3 g. per cent to 4.1 g. per cent and then rose to 4.6 g. per cent. The jaundice cleared up but the urinary urobilinogen still remained positive though to a lesser degree. Delivery was normal, the baby appeared quite healthy and a week later the haemoglobin, red cells, haematocrit, mean cell volume, mean copuscular haemoglobin concentrating mean cell diameter and plasma proteins were 35 per cent, 3.19 million, 28 per cent, 88u , 20 per cent, 7.3 u and 5.4 g. per cent. The jaundice had gone and the urinary urobilinogen was only a trace. The marrow picture now showed a drop in

the percentage of megaloblasts from 7.3 per cent to 4.5 per cent, in the percentage of normoblasts from 33.5 per cent to 28.5 per cent and the appearance of reticulated red blood cells and normoblasts which estimated 6 per cent and 1.5 per cent respectively. A few iron staining "inclusion bodies" were seen.

The second patient was given iron for a period of three weeks when improvement appeared to have ceased, the haemoglobin having risen from 23 per cent to 35 per cent, the red count from 2.81 to 3.22 million and the haematocrit from 19 per cent to 27.5 per cent. As in the previous case the jaundice had cleared after one week in hospital and the urinary urobilinogen only estimated a trace. 2 c.c. of a crude liver extract were given intramuscularly every day. As was noted with folic acid in these cases "resistant to iron", who have megaloblasts in their bone marrow, no improvement in the puerpheral blood picture was observed until after two weeks therapy when the haemoglobin rose to 44 per cent, the red cells to 3.42 million and the haematocrit to 32.5 per cent. Liver therapy was discontinued after three weeks, but the haemoglobin etc. continued to rise and reached values of 58 per cent, 4.39 million and 38 per cent before delivery, eight weeks after admission to hospital.

(3) The last patient was similar in every respect to the previous cases except that her plasma proteins were very low viz. 3.45 g. per cent. Since the symptoms dated from a very acute attack of diarrhoea and vomiting, it was felt that a dietary deficiency may have been a factor in her case. She was given a protein hydrolysate, Casahydrol daily, in addition to iron therapy. Within a week the haemoglobin had risen from 32 per cent to 40 per cent Sahli, the haematocrit from 21.5 per cent to 26 per cent but the red cells showed a slight fall from 3.31 million to 2.95 million. The reticulocytes reached a peak of 7 per cent on the fifth day of treatment, the plasma proteins rose from 3.45 g. per cent to 4.7 g.per cent, the jaundice disappeared and the urinary urobilinogen only estimated a trace. Delivery occurred thirteen days after commencing therapy and was spontaneous, but the child had an asphyxia pallida and required special nursing. The birth weight was 7 lbs. In view of the low plasma protein in the mother, the baby's plasma proteins were estimated two weeks after delivery when it had quite recovered from the asphyxia pallida; they were found to be 5.0 g. per cent.

Casahydrol therapy and iron were given as before to the mother in the puerperium. Three days after delivery the plasma proteins were 4.6 g. per cent, but

at nine days they were only 4.75 g. per cent despite the large amount of protein given. Further questioning however, revealed that despite instructions, the mother had commenced to breast feed her baby. Breast feeding was therefore discontinued and within another week the plasma proteins estimated 5.1 g. per cent. The haemoglobin at this time was 57 per cent the red blood cells 3.92 million and the haematocrit 33.5 per cent. A repeat sternal puncture at this time showed the megaloblasts had fallen from 6 per cent to 2.8 per cent, the normoblast series had risen from 20.2 per cent to 23.8 per cent and the marrow reticulated red blood cells and normoblasts were 2.5 per cent and 0.5 per cent respectively. Only a few iron staining "inclusion bodies" could be seen in the cells.

The initial marrow pictures in all three of these severe anaemias showed a number of indeterminate smear cells similar to those seeh in the marrows of the untreated typical pernicious anaemias of pregnancy, though not so numerous. In addition the third patient with the exceptionally low plasma proteins had a very fatty marrow and numerous fat spaces were present throughout the whole smear. These disappeared as a result of therapy.

Thus from a survey of twelve cases of anaemia

simulating toxaemia, it has been shown that all five cases investigated by repetitive blood counts and marrow punctures were cases of atypical pernicious anaemia of pregnancy. Probably from the initial marrow pictures, which showed a low percentage of cells of the normoblastic series and no reticulated nucleated or non-nucleated cells, they were cases that would have ultimately proved to be "iron resistant". One case, at least was so.

Two groups could be easily defined. Firstly, a group of nine severe anaemias, seen just before term with moderately low plasma proteins and no jaundice. All may go through their pregnancy, labour and the puerperium unrecognised as anaemias or labelled mild toxaemia. With the routine iron therapy, they do respond in the puerperium, but the response was found to be slower than it was, in a similar case given folic acid and iron. The other group consisted of three very severe anaemias, who were seen earlier in their pregnancies and who presented a picture of severe anaemia, low plasma proteins, jaundice and very strongly positive urinary urobilinogen estimations, which clear up soon after admission to hospital. These patients require treatment for their anaemia. Very satisfactory results were obtained in two patients, one treated with liver after she had proved resistant to iron and the other

treated with iron and a protein hydrolysate. The detrimentery result of breast feeding in the case of a mother with low plasma protein levels has been shown and it was further interesting to note that the offspring in this instance had also low plasma proteins.

Summarising the results in group B i.e. the "anaemias and toxaemias", it can be stated that.

(1) The incidence of anaemia in cases of toxaemia is fairly high, but the opportunities of investigating and treating these cases are few. The peripheral blood picture, which in the main was microcytic and hypochromic showed no striking features, but the plasma protein levels were noted to be exceptionally low. Assessment of the response to treatment is complicated by variations in the blood volume, and although four of our patients showed a satisfactory response, it was probable that the rise in haemoglobin in two at least was due to haemoconcentration.

(2) On the other hand, the incidence of toxaemia developing in cases of anaemia is low and it has been shown that six of the ten cases who developed toxaemia were responding satisfactorily to treatment when the toxaemia appeared. These patients had a higher blood count and plasma protein estimation than the cases of anaemia who showed no response at all. The latter

patients, with one exception, maintained their blood levels when the toxaemia developed but showed a further drop in plasma proteins to the level noted in the seven cases of anaemia and toxaemia. It has been suggested that blood volume changes may be responsible for this modification of the peripheral blood picture after the onset of the toxaemia or that reduction in the plasma proteins and failure to respond to treatment are actual parts of the toxaemic process. The one exception noted above did deteriorate, developed a sub-clinical jaundice and ultimately after delivery presented a picture of typical pernicious anaemia of pregnancy, confirmed by marrow puncture.

(3) Obviously, further investigation by marrow biopsy of these two groups of patients is required before any pronouncement can be made on the actual anaemic process at work.

(4) The last group to be considered consisted of twelve cases of anaemia who resembled the toxaemias clinically, but were found on examination to be more anaemic. In nine of these patients where the anaemia was less severe, the plasma proteins were higher than those occurring in the seven toxaemias with anaemia, but in the remaining three in addition to the very severe anaemia, the plasma proteins were low i.e. less than that of

toxaemias with anaemia, sub clinical jaundice was noted and an increased excretion of urobilinogen in the urine observed.

(5) Complete investigation of five of these twelve patients revealed that despite the microcytic hypochromic blood picture all five were atypical cases of pernicious anaemia of pregnancy. The response to iron therapy alone, iron and a protein hydrolysate, iron and liver, and iron and folic acid have been compared during pregnancy and in the puerperium. Though the cases are few, it can be said that the latter three groups gave better results than those obtained with iron alone. The patient who had liver therapy before delivery had a haemoglobin of 60 per cent, three weeks later; the patient on cashydrol and iron had a haemoglobin of 76 per cent six weeks later and the patient on folic and iron had a haemoglobin of 64 per cent four weeks later. These findings would suggest that the best results were obtained with cashydrol, but a larger series of patients would have to be compared.

(6) As stated the initial marrow pictures showed megaloblasts varying from 1 per cent to 7.3 per cent, the percentage of cells of the normoblast series was low, no reticulocytes or reticulated erythroblasts could be seen and iron staining "inclusion bodies"

were absent. After delivery with folic acid and cashydrol the megaloblasts in the marrow decreased, the normoblasts increased, reticulated cells appeared and a very few iron "inclusions" were noted. No report is available for the changes noted in the marrow as a result of liver therapy, but on iron alone similar changes were noted, except that in one case where the normoblasts had been high two weeks before delivery, a drop in the percentage was noted on the seventh day of the puerperium.

(7) The three cases with very severe anaemia had a greater number of indeterminate smear cells than usual. These were similar to those noted in the cases of typical pernicious anaemia of pregnancy although not as numerous.

(8) The detrimental effect of breast feeding has been demonstrated in two cases in this group and the value of extra protein, one in the form of a protein hydrolysate and the other as a high protein diet has been shown.

(The individual case records are shown in protocal II).

GROUP C.

Only the last group of patients showing the syndrome "jaundice and anaemia" have now to be

considered, namely jaundice appearing in the course of therapy. It will be remembered with reference to Group A that of the eighteen patients admitted to hospital and given iron alone, seven only showed a partial response i.e. a plateau was reached in the blood levels above which no improvement occurred on iron therapy alone. In the present group of five patients similar findings were observed, but, concurrent with the cessation of improvement, a sub-clinical jaundice began to appear. Reference was made to one of the cases quoted here when considering the anaemic cases in Group B, who developed toxaemia. The remaining four who have not been mentioned previously attended as outpatients, and, because of their gross anaemia, were admitted directly to hospital. All were given iron therapy. At this period two of the four patients showed sub-clinical jaundice but this cleared up with treatment. Improvement was noted in all four. One of these patients was only four months pregnant and her case will be referred to at length later. In the other three, first seen during the 8th or 9th month, the response to iron was only partial and after a short time ceased altogether. At this juncture sub-clinical jaundice reappeared. Marrow smears were made in all three initially and in two when

TABLE XXV.

	3 cases.		1. Toxaemia.		Case treated early in pregnancy.		
	Initially	Jaundice	Initially	Jaundice	Initially	Improved	Jaundice.
Hb.	33	49	42	37	39	65	50
R.B.C.	3.5	3.3	3.5	2.69	3.69	4.61	3.59
P.C.V.	26	31.5	33	25	28.5	33.5	29
M.C.V.	71	94	97	93	77	73	81
M.C.H.C.	21	25	23	24	22	31	31
M.C.D.	6.7	7.1	6.9	7.2	6.9	7.5	7.0
Plasma protein.	5.5	5.2	6.0	5.0	5.2	4.2	4.65

TABLE XXV. (Contd).

	3 cases		1. Toxaemia.		Case treated early in pregnancy.		
	Initially	Jaundice	Initially	Jaundice	Initially	Improved	Jaundice
Urobilinogen	0	+ +	0	+ + +	0	0	+ + +
Van den Bergh	0	1.5	0	2.4	0	0	.8
Megaloblast	3.2	7.2	-	12.6	2.8	5.4	-
Normoblast	18.5	22.9	-	11.2	17.8	14.8	-
Myeloid series	58	59	-	60.4	65.6	65.4	-
Reticulocytes	2.1	3.0	-	1.5	0.5	0	-
Reticulated normoblasts	0.2	1.5	-	.75	0	0	-
"Inclusion bodies"	0	+ +	-	+ +	0	(+)	-

jaundice appeared. The results of blood and marrow examinations are given in Table XXV. It will be seen that the bone marrow picture resembles that of the "iron resistant" atypical cases of pernicious anaemia of pregnancy described in Group A with the exception that the megaloblasts were more plentiful - 3.1 per cent as compared with 1.7 per cent. Normoblasts tended to be somewhat fewer. Reticulated cells were scanty and no iron staining "inclusions" could be found. By the time jaundice appeared, the haemoglobin had risen to 49 per cent, but the red blood cells had fallen to 3.3, while the haematocrit had increased to 31.5. The peripheral blood was therefore tending to become macrocytic and less hypochromic. The plasma proteins fell to 5.0 grams per cent, the Van den Bergh gave a delayed direct reaction with a plasma bilirubin estimating 1.5 mg. per cent and the urinary urobilinogen was now strongly positive. When the marrow was examined it was found that the megaloblasts had shown a three-fold increase and were now 7.2 per cent, the normoblastic series showed little change, the percentage of reticulated cells had increased, and numerous iron staining "inclusion bodies" could be seen in the red blood cells, the late normoblasts and the monocytes.

The fourth patient of this group was admitted

to hospital when four months pregnant and was given iron for four weeks. She responded well and the haemoglobin reached normal levels. During the next three months, as an out-patient attending clinic, she became gradually anaemic again despite iron therapy. At eight months she was admitted to hospital suffering from anaemia and a sub-clinical jaundice. In Table XXV the results of some of the blood examinations in this case are given. The three columns show her initial blood count, her blood after improvement with iron therapy, and the blood when jaundice appeared. Unfortunately it was only possible to make two marrow smears in this case, one initially and one when the anaemia appeared to improve. It is interesting to note, however, that despite the improvement in the peripheral blood picture, her marrow showed an increase in the percentage of megaloblasts and a decrease in the normoblasts.

The patient who had toxaemia had an initial blood count taken at clinic before she developed her toxaemia a month later. She had been given iron therapy as an out-patient and again in the ante-natal wards of the hospital, and, although she was not seen personally till the ninth month of per pregnancy, her blood count and biochemical results were available. A marrow smear was made in this case on the seventh day of the

puerperium. Her results are shown on Table XXV. It will be seen that the marrow picture is similar to that of the other patients in this group. In other words, from her blood and marrow pictures it would appear that delivery had had very little effect on her response to iron therapy, that is, she showed no tendency to a spontaneous remission in the puerperium and this was further corroborated by the fact that, though her reticulocytes were estimated daily during this time, they did not estimate more than 1 per cent. In fact, her blood count became so low (haemoglobin of 20 per cent, red blood cells of 1.61 million, and a haematocrit of 15 per cent) that a blood transfusion, two pints of packed cells, had to be given on the fifth day of the puerperium. Follwing the transfusion, the reticulocytes rose to a maximum of 3 per cent but reached their original low level within a week, the blood levels having also shown a significant drop by that time. Thus, two weeks after delivery, this patient had shown no real attempt at a spontaneous recovery and it was decided to investigate the response to folic acid therapy in this case also. Treatment with 20 mg.daily was therefore commenced and the result was dramatic. Within three days the reticulocytes were 4 per cent and they reached a peak of 17 per cent seven days after

commencing therapy. The jaundice which had cleared before giving folic acid reappeared after folic acid therapy was commenced and remained. The plasma bilirubin estimated 1.6 mg. per cent a fortnight later when the haemoglobin was 50 per cent, the red blood cells 4.26 million, and the haematocrit 34 per cent.

The remaining four patients in this group were all given cystine in doses varying from 2.5 gms. daily to 7 gms daily, the rationale being that if the jaundice were due to a liver "dysfunction" which might also be responsible for the lack of further improvement in the anaemic state, it might improve by the addition of one of the essential amino acids. Hence the reason for the giving of the varying amounts of cystine to the following patients.
(1) The first patient received 2.5 g. daily in addition to iron. Unfortunately on the sixth day of treatment she went into labour and delivered herself spontaneously. A blood examination made the next day gave a negative Van den Bergh and the urinary urobilinogen was also negative. However, since delivery had intervened the disappearance of the jaundice cannot be fully attributed to the cystine. As in the previous case, this patient also failed to respond to continued iron therapy after delivery, the reticulocytes remaining less than one per cent. The red count was 2.2 million, the haemoglobin

36 per cent Sahli and the haematocrit 23.5 per cent on the seventh day of the puerperium. A repeat marrow puncture was performed at this time and it showed that, as a result of delivery or the cystine therapy, the megaloblasts had fallen from 11.1 per cent to 8.3 per cent, the normoblasts which were 24.3 per cent showed very little change, the marrow reticulocytes and the reticulated erythroblasts had increased, however, and were now 3 per cent and 2 per cent respectively and fewer iron staining "inclusion bodies" were present. Thus, despite the failure to show improvement in the peripheral blood, definite changes, which, as will be shown, can be taken as indicative of improvement, were observed in the bone marrow in this case. Treatment with folic acid 20 mg. daily was therefore commenced. The reticulocytes reached a peak of 11 per cent on the fourth day of therapy and in this case it was interesting to note that jaundice did not reappear when folic acid therapy was commenced. However, folic acid seemed to be less effective in this patient, as two weeks after commencing therapy, the haemoglobin was only 47 per cent, the red blood count 2.42 million and the haematocrit 29.5 per cent. She was allowed home to continue folic acid and iron therapy, but failed to report back for further treatment as she said she

felt well.

(2) The second patient to receive cystine was given 4 g. daily for one week, at the end of which time her Van den Bergh and urinary urobilinogen were negative. No change occurred in the peripheral blood picture and the plasma proteins remained the same (5.0 g.per cent). Folic acid therapy 20 mgm. daily was therefore commenced; the reticulocytes increased to 2.5 per cent and in two weeks the haemoglobin rose from 45 per cent to 50 per cent, the red blood count from 3.25 million to 3.77 million, while the haematocrit and plasma proteins remained unchanged. The Van den Bergh was positive indirectly at one estimation during the period, the plasma bilirubin only estimated 0.8 g. per cent however. Since the response to folic acid appeared to be so poor in this case it was decided to give proteolysed liver and compare its effect. No increased rate of improvement occurred however, the reticulocytes remained "elevated" reaching 3 per cent on two occasions in the next week and after 7 days treatment, the red cells were unchanged, the haemoglobin had risen to 55 per cent Sahli, and the haematocrit to 33 per cent. Delivery ensued thereafter, and was normal except for a breech presentation. Eight days later the mother and child, having progressed satisfactorily, were dismissed from hospital, the

mother's haemoglobin being 63 per cent Sahli, her red count 4.11 million and haematocrit 41 per cent.

(3) The third patient was given 6 g. of cystine daily for a period of one week. The jaundice and the increased urinary urobilinogen disappeared as before, but in addition the anaemia began to improve once more. A repeat sternal puncture was performed after giving cystine in this case and the results of the blood and marrow counts are shown in Table XXVI. It will be seen that the improvement in the blood levels is considerable, the haemoglobin rising from 56 per cent Sahli to 67 per cent Sahli, the red count from 3.90 to 4.41 million and the haematocrit from 39 per cent to 42.5 per cent. The tendency was for the blood picture to become less macrocytic again and the mean cell diameter fell from 7.4 to 7.2 μ. As further proof that these changes were not due to blood volume changes, but an actual haemopoietic response, the reticulocytes rose again after commencing cystine, reaching a maximum of 5 per cent on the fifth day. Since the anaemia was only of moderate degree at this stage, a 5 per cent reticulocyte response is very satisfactory. The plasma proteins estimated before and after cystine therapy, also showed a rise, from 5.0 g. per cent to 5.3 g. per cent. The marrow picture examined after the course of cystine was completed, differs considerably

from the other three marrows examined when the patients were jaundiced. Instead of the increase in megaloblasts noted in these cases the megaloblasts were reduced in this case, the normoblasts were low in both however, but the reticulocytes were higher in the present case and iron staining "inclusion bodies" were less numerous. The patient was allowed home at this stage. Improvement continued; before delivery, her haemoglobin was 80 per cent Sahli and 87 per cent on the eighth day of the puerperium. Jaundice was noted in the plasma on one occasion after giving cystine, but this was only temporary.

(4) The last case to receive cystine was the patient who responded to iron therapy in hospital, when four months pregnant, became anaemic again after dismissal and ultimately developed jaundice in her ninth month. She was admitted to hospital and given cystine 7 g. daily. The jaundice and urinary urobilinogen cleared as before but on the sixth day of therapy the indirect Van den Bergh was again positive, the plasma bilirubin estimating 0.8 mg. per cent. At first there seemed no apparent reason for the reappearance of the jaundice until examination of a second catheter specimen of urine at this time revealed that in addition to the mild bacilluria she had shown initially on admission, the urine

now contained numerous pus cells and coliform bacilli, though the patient herself had no symptoms relative to this complication. It has already been shown that mild infections in pregnancy are liable to cause a sub-clinical jaundice and in all probability the urinary infection here supplies the reason for the reappearance of the jaundice. Despite this however, after one week's course of cystine, the haemoglobin had risen from 47 per cent to 56 per cent Sahli, the red count from 3.38 to 3.62 million, the haematocrit remained unchanged at 33 per cent, and the blood picture therefore tended to become less macrocytic. The reticulocytes rose again in this case reaching a maximum of four per cent on the fifth day of therapy. No rise was noted in the plasma protein levels, instead a slight fall from 5.1 g. per cent to 5.0 g. per cent was observed. During the next week iron therapy alone was continued, the haemoglobin rising to 59 per cent, but the red blood count remaining unchanged. Jaundice still persisted. Delivery ensued thereafter. The patient developed a mild B. proteus uterine infection. She refused to remain in hospital for treatment for this and her anaemia and she dismissed herself irregularly. Before dismissal however her Van den Bergh was negative and the urine contained only + of urobilinogen. Her haemoglobin had fallen to 47 per

cent Sahli and the red count to 3.31 million.

Reviewing the results obtained in this last group it is possible to say that.

(1) A definite correlation appears to exist in these five cases between the appearance of jaundice and the cessation of the response to iron therapy in hospital.

(2) When these features were observed the peripheral blood showed the following changes, namely the haemoglobin and haematocrit rose and the red blood count fell. The blood picture therefore tended to become more macrocytic and less hypochromic. At the same time the plasma proteins fell.

(3) The marrow changes consist of an increase in the percentage of megaloblasts, no change in the percentage cells of the normoblastic series, which were originally low, a rise in the reticulated cells and a very marked increase in the number of iron staining "inclusion bodies".

(4) The results of the administration of cystine in varying amounts to these patients has been shown. Optimal results were obtained with 6 g. or more daily, a rise in the blood levels and the disappearance of jaundice being observed in two cases and a definite reticulocyte response being noted. With amounts less than this jaundice definitely disappeared in one case

and the disappearance in the other case was probably due to the cystine.

(5) After cystine therapy given in optimum doses for one week, striking changes were observed in the marrow of one patient in comparison with the picture obtained in the three other patients at the time of development of the jaundice. It has therefore been suggested that these changes observed were due to the administration of cystine i.e. that the cystine in this patient was able to reduce the megaloblasts, increase the number of reticulated cells and decrease the number of iron staining "inclusion bodies". Similar marrow changes were observed in another patient who received only 2.5 g. of cystine daily but as delivery intervened in her case less stress can be laid on the effect of cystine in this instance.

(6) The administration of folic acid to a patient who had received sub-optimal doses of cystine daily for one week, i.e. a case where the jaundice had cleared but the blood levels remained unchanged, resulted in a further improvement in the haemoglobin and red blood count. The response was not dramatic however, and treatment was changed to proteolysed liver after two weeks with no better results.

(7) Two cases were given folic acid in the puerperium. From the blood pictures a week after delivery both

appeared to be showing no spontaneous improvement. Definite changes, however, were observed in the marrow of the first patient who had received cystine previously, but the second patient, who had a toxaemia in addition, showed no changes in her marrow indicative of improvement.

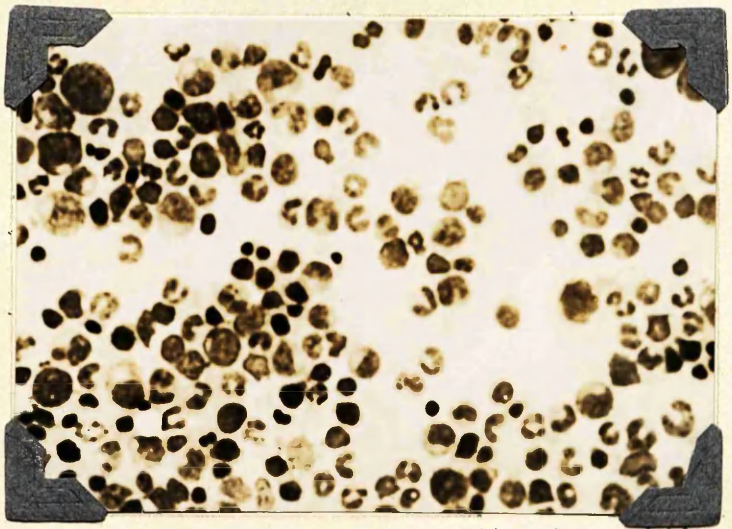
(8) The response to folic acid therapy was very satisfactory in one of these patients, namely the patient who had toxaemia, but the response in the second patient, who had been given cystine, was less acceptible and a "follow up" of this patient was not possible.

Jaundice was noted in two patients with very severe anaemia admitted just before term, the haemoglobin readings being 33 per cent and 29 per cent respectively. The blood pictures were microcytic and hypochromic and the marrows contained 2.7 per cent and 6 per cent megaloblasts, 25 per cent and 39.5 per cent normoblasts, no reticulated cells and no iron staining "inclusions". Both patients were delivered before any conclusion could be reached as to their response to therapy but in the puerperium they both responded to iron therapy. It is difficult to say to which group these two patients belong. The second patient with the high percentage of cells of the normoblastic series in her marrow had had iron therapy for four days before

she came under observation and this may account for the high percentage normoblasts observed in the marrow smear. If this were so, then possibly they both were cases of atypical pernicious anaemia of pregnancy, who could have only shown a partial response to iron therapy antenatally, but now respond in the puerperium.

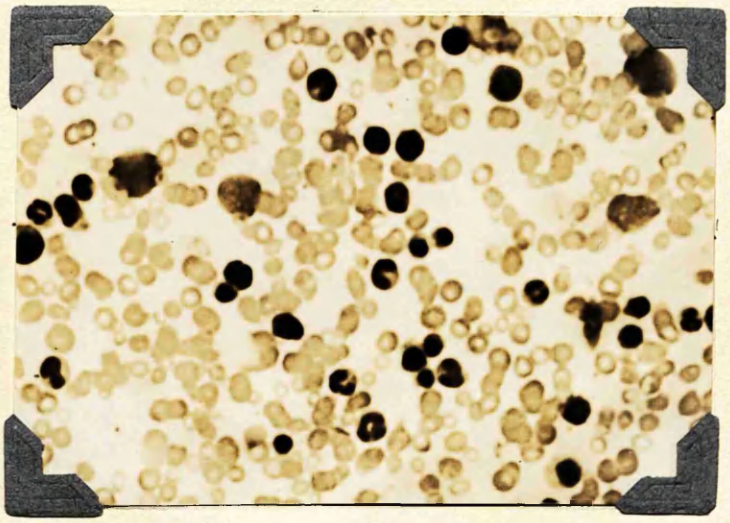
(The individual results of the cases in this group are shown in protocol III).

PLATE 1.



Iron deficiency anaemia in the transitional phase showing megaloblasts in the marrow.

PLATE 11.



Marrow of the same patient after iron therapy.

DISCUSSION.

By now it will be obvious that although typical pernicious anaemia of pregnancy is a rarity (we were only able to examine six such cases in a survey of more than 5000 pregnant women) atypical cases are much more common. Further, as the peripheral blood picture is atypical, so is the clinical presentation i.e. cases of atypical pernicious anaemia of pregnancy were found to occur in all three groups, namely, anaemia, toxaemia and anaemia, and jaundice and anaemia.

The classification of these cases is obviously difficult. All previous reviews of pernicious anaemia of pregnancy have dealt with established cases, but the striking feature of this whole survey has been the high percentage of anaemic patients showing megaloblasts in their marrow smears. The response to treatment, however, indicate that these megaloblasts do not have the same significance as these occurring in non-pregnant cases of anaemia. Cases of severe microcytic hypochromic anaemia were found to have relatively large numbers of megaloblasts in their marrow.(Plate I). It has been found that most of these cases respond to iron therapy alone, if the diagnosis is made at an early stage, as it is in this hospital by means of the initial routine haemoglobin estimation at ante-natal clinic (Plate II).

The remainder show only a partial response i.e. have a plateau like response and constitute a group of atypical cases of pernicious anaemia of pregnancy. Owing to this discrepancy, existing between the marrow in pernicious anaemia of pregnancy and that in Addisonian pernicious anaemia, any classification must be based on the response to treatment. For this reason therefore, the anaemias who respond satisfactorily to iron therapy alone have been regarded as iron deficiency anaemias though it is true some of them may be in the "transitional" phase, a phase which at this stage is reversible with iron therapy alone. The remaining cases who only partially respond to iron therapy that is develop a "plateau", constitute therefore our group of atypical pernicious anaemia of pregnancy.

Considering the iron deficiency anaemias first it is obvious from the low mean cell volume, corpuscular haemoglobin concentration and cell diameter that the iron deficiency is marked in these severe anaemias. Elliot (1944) reported haemoglobin readings as low as 28 per cent and mean cell volumes of 58 μ^3. We have found equally low results. It is common for the initial mean cell diameter to estimate somewhere between 6.2 and 6.7 μ, but, unlike Elliott's cases and those of Boycott (1936) the original blood film in our untreated patients

PLATE III. x 600

BEFORE

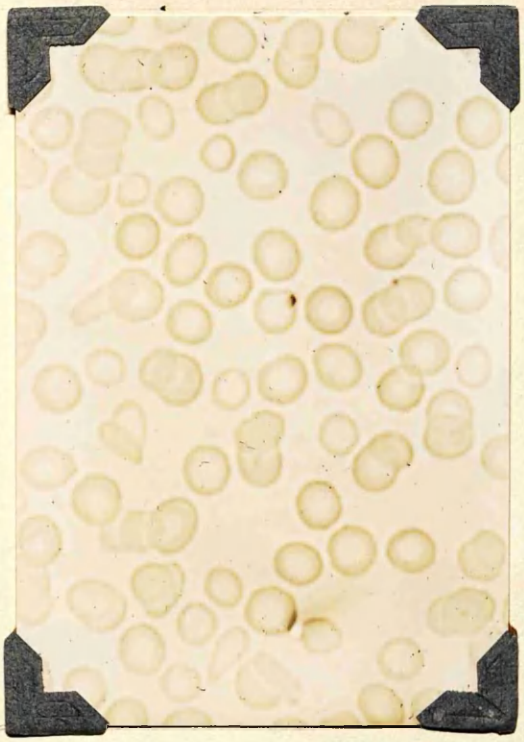
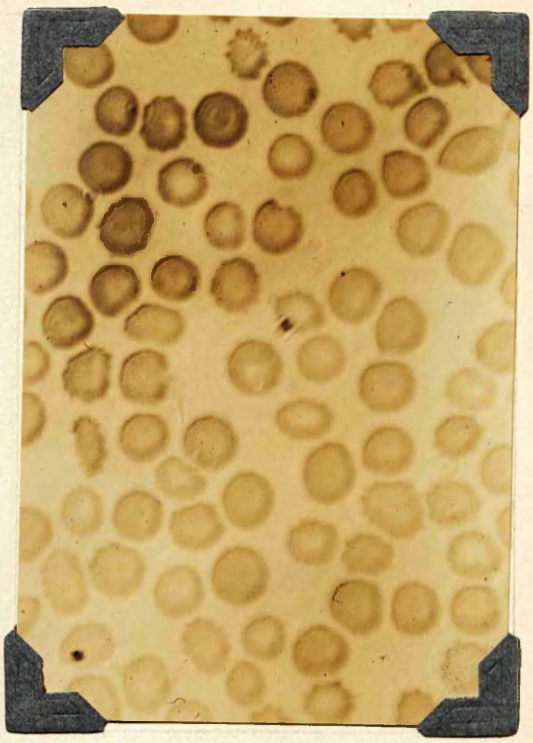


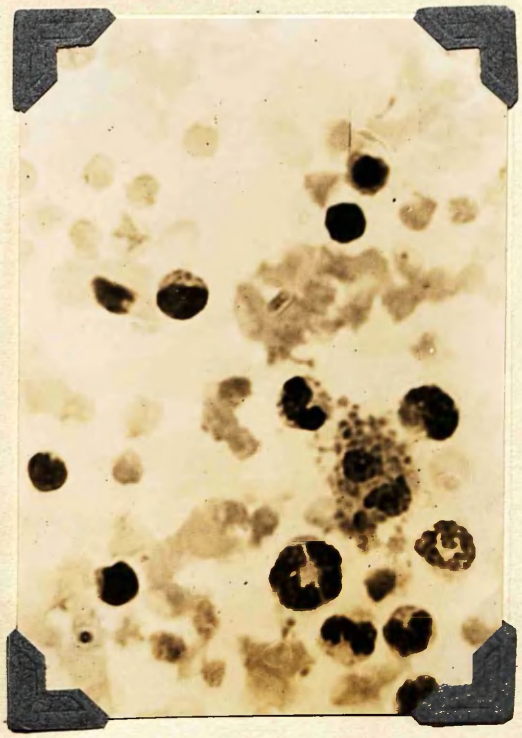
PLATE IV. x 600.

AFTER



Iron deficiency anaemia - blood picture before and after treatment.

PLATE V.
x400.



Normoblastic marrow of the same patient.

did not show much anisocytosis, the main features being the marked degree of microcytosis and ring staining (plates III and IV). Stevenson (1936) reported similar results. Various authors have suggested various standards of normality for the red cell count during pregnancy. Dieckmann and Wegner 1936 found the average figure to be 3.36 millions; Elliott's (1944) figure of 3.2 is close to this, but Bethell (1936) suggested 3.7 millions. Meyer-Weddell (1943) investigating anaemias found that the red cell count was diminished only in cases of pernicious anaemia of pregnancy and vitamin C deficiency. In the present series of iron deficiency anaemias, the average red blood count was 3.49 millions with variations between 4.5 and 2.99 millions. From this it can be seen that the red cell count is not a reliable guide to diagnosis either of anaemia in general or of particular types of anaemia of pregnancy.

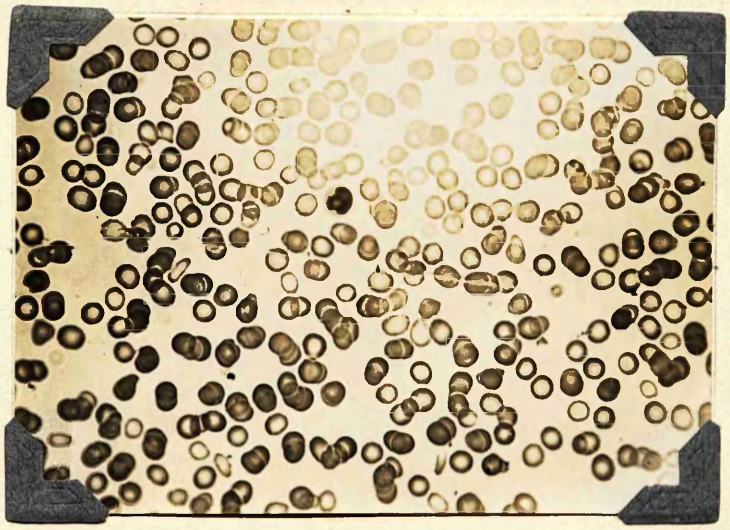
The changes in response to iron therapy were in the reverse order of those which Schwartz and Flowers (1946) demonstrated in the development of anaemia. The first change noted was a rise in haemoglobin, the average increase during the first month being 10 per cent Sahli in out-patients and 13 per cent Sahli in in-patients. At the same time, the red blood cell count rose and there was an increase in the mean cell volume

and mean cell diameter. Little change, however, was noted in the mean corpuscular haemoglobin concentration and only in rare cases did it approach normal before delivery. The blood film also showed typical changes. With the commencement of therapy anisocytosis became marked and large polychromasic cells were fairly frequent. The rise in haemoglobin as a result of iron therapy is small in these cases however, when compared with the response to iron therapy observed in post-haemorrhagic anaemias of pregnancy i.e. in cases of post-partum haemorrhage, incomplete abortion etc. A small series of these post-haemorrhagic anaemias, twenty five in number were followed. They showed an average rise in haemoglobin of 10 per cent Sahli per week and this appeared to be independent of whether the patients were given iron alone or iron plus liver, contrary to the statements of Stevenson (1936). Examination of their marrows showed a completely normoblastic picture when anaemia had not ante-dated the haemorrhage. Further work in this latter group is necessary, but the results so far show that either the absorption, mobilization and utilization of iron during pregnancy is slow or that part of the iron is being deviated to the foetus. Further work here is indicated to determine which factor is the more important.

In the present survey, where most of the work was concentrated on the patients who failed to respond to iron therapy and on the reasons for this failure, the type of haemopoiesis in the patients who improved satisfactorily on iron as out-patients, was not fully investigated. A large series of marrow examinations would be required before this could be established. It is significant, however, that in patients who responded to iron therapy in hospital, the marrow contained large numbers of megaloblasts as well as normoblasts. The percentage of the latter type of cell, however, was still high - usually above 30 per cent. This latter finding would appear to be the determining factor in the response to iron therapy. It possibly could be taken as an indication of the marrow activity i.e. a severe anaemia of pregnancy will respond to iron despite the presence of megaloblasts in the bone marrow, other conditions such as bed rest, good nursing etc. being available. It is not possible to supply the latter conditions in many working class homes and this may explain the lack of response in out-patients, who ultimately improved after admission to hospital.

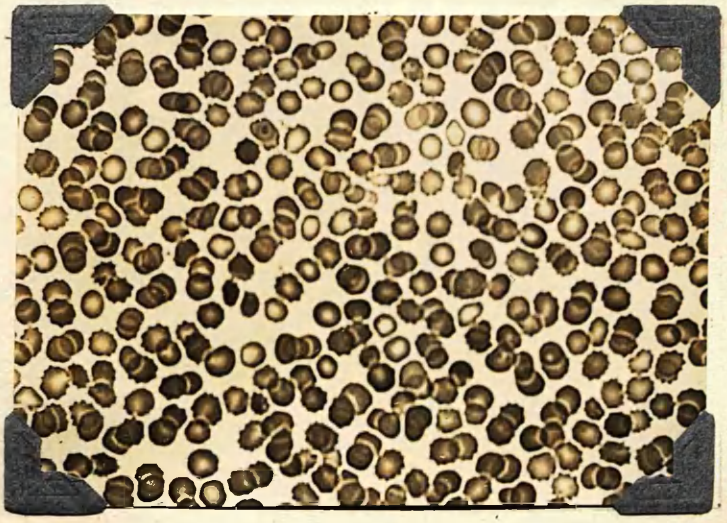
Finally, in considering the iron deficiency anaemias it must be stated that despite the apparent specificity of iron therapy in one patient, who had a

PLATE VI. x 200.



Blood film of atypical pernicious anaemia of pregnancy before iron therapy.

PLATE VII. x 200.



Blood film of atypical pernicious anaemia of pregnancy at plateau level.

Good film. Normal cells

normoblastic bone marrow (Plate V) no satisfactory improvement was obtained with iron therapy, when she was treated as an out-patient although it was definitely ascertained that she had been taking her tonic. Improvement on admission to hospital was immediate, no additional therapy apart from the iron being given. It has been suggested that the social conditions in this case were at fault. For example, the patient was in a very bad nervous state. When she first attended clinic she could not control the tremor of her limbs at rest and she stated she could not sleep at night. As a result of treatment in hospital, these symptoms completely disappeared and her clinical condition improved considerably, as did her blood.

Of all the patients with severe anaemia showing a microcytic hypochromic blood picture in pregnancy, it has been shown that 15 per cent will not respond to iron therapy even after admission to hospital. The addition of acid hydrochlor dil. to the iron therapy also failed to produce any improvement in these patients contrary to the findings of Kellog (1936) Schultz (1940) Hahn (1937, 1945) and Cartwright (1947). The blood picture in these patients has been shown to be indistinguishable from that of the iron deficiency anaemias who do respond (Plate VI), the only differentiating features being found in the bone

marrow. It has been shown that megaloblasts are found in the marrow of patients who, according to their response to treatment are obviously cases of iron deficiency anaemia. The megaloblasts therefore cease to be diagnostic of pernicious anaemia of pregnancy, and, contrary to what might be expected the percentage of megaloblasts was found to be less in the atypical cases of pernicious anaemia of pregnancy than in severe cases of iron deficiency anaemia. What seemed to be more important was the low percentage of cells of the normoblast series observed initially. There therefore appeared to be a hypoplasia of all the red cell series, whether megaloblastic or normoblastic. With treatment on iron alone the former increased and the latter decreased whereas in the "iron deficiency anaemias" the reverse was true. Also the reticulated cells disappeared from the marrow in the resistant cases. In other words, despite the partial improvement in the blood towards its "plateau" level as a result of iron therapy (Plate VII), the marrow picture had become more abnormal, showing less activity of the normoblast series as compared with the megaloblast series.

The clinical features in these cases of atypical pernicious anaemia of pregnancy are very variable, and the diagnosis can only be confirmed by sternal puncture.

In the present survey three main clinical groups were defined, all of whom presented the same marrow picture and all of whom responded in a like manner to treatment. The first group complained of symptoms of anaemia and clinically were indistinguishable from cases of severe iron deficiency anaemia. The second group showed signs of apparent toxaemia, namely hypertension and oedema, but albuminuria was absent or only slight. Of twelve cases, five were investigated thoroughly and, though the peripheral blood picture was microcytic and hypochromic in every case, a diagnosis of atypical pernicious anaemia of pregnancy was made on the strength of the initial marrow smear. One of these patients was put on iron therapy alone and the fact that she, too, only partially improved gave support to our original diagnosis. A third group, five in number, complained of symptoms of anaemia, but in addition a sub-clinical jaundice was present. Here, too, a diagnosis of atypical pernicious anaemia of pregnancy was made as a result of the initial marrow smear, and, as has been shown, all five developed a "plateau" in blood levels beyond which they did not improve on iron alone.

Altogether therefore, including the cases mentioned above and others in whom the effect of various treatments was tried, a diagnosis of atypical pernicious

anaemia of pregnancy has been confirmed by sternal puncture in twenty-four cases, and a similar diagnosis is suggested in another three as a result of therapeutic tests. Hence it would appear that, including the cases of "anaemia and toxaemia" and "anaemia and jaundice" this condition was more common than was originally expected. Since the clinical presentation varied so considerably in each group, however, despite the similarity noted in the marrow smears, a comparison of the various haematological findings in each group was necessary to determine, if possible, wherein the difference lay.

Examination of the peripheral blood picture revealed little difference between these groups though the cases of toxaemia and anaemia in whom the diagnosis of atypical pernicious anaemia of pregnancy was confirmed by sternal puncture did have a lower haemoglobin etc., than the remaining cases in this group. However, as these cases were only notified because the anaemia was severe, the others in the group having been diagnosed as pre-eclamptic toxaemias and treated accordingly, the blood levels of the five patients investigated cannot be taken as indicative of this group as a whole. Certainly, however, it can be said of these cases of anaemia and toxaemia, that when the toxaemia is gross and symptoms

relative to anaemia are present in addition to those considered "typical" of toxaemia, the anaemia in these cases is likely to be very severe. With this exception the blood levels were substantially the same in all groups. All were originally microcytic and hypochromic in each group and as a result of iron therapy tended to become macrocytic. Two cases in the group of jaundice and anaemia did develop a definite macrocytic anaemia in the puerperium and were given folic acid. Hence it would appear that, in this group, there is a greater tendency for atypical pernicious anaemia of pregnancy to become "typical" as a result of iron therapy. Initially, therefore, no distinction could be made between these groups on the grounds of severity of the anaemia or peripheral cellular changes. There was, however, a difference in the plasma protein level of the "toxaemic" patients, when compared with individuals of the other groups. Although the plasma proteins diminished in the other groups as a result of iron therapy the average never fell below 5.0 grams per cent which was the initial average for the toxaemic group. Treatment with iron therapy alone in the latter group also caused a fall in plasma proteins to 4.3 g. per cent. The lowest plasma protein recorded in the whole survey was in this group and was noted in a patient on admission, namely

3.45 g. per cent. Thus it would appear that the cases of atypical pernicious anaemia of pregnancy simulating toxaemia have an exceptionally low plasma protein estimation in comparison with the other groups.

The only other distinguishing change noted in the peripheral blood was the occurrence of jaundice in the third group of patients. It may be remembered that during the treatment of the cases of atypical pernicious anaemia of pregnancy in Group A (the anaemias) with iron, the urine, which initially did not contain any urobilinogen, became strongly positive as the haemoglobin approached the "plateau" level. This finding would appear to be in accordance with the development of a sub-clinical jaundice in the Group C patients, and possibly the same pathological process is at work in each case, though to a more marked degree in Group C. Reviewing the findings obtained so far in relation to the development of this jaundice, it has also been shown that by withdrawing liver therapy and giving iron to patients with typical pernicious anaemia of pregnancy, who had received liver but no iron therapy previously, the urinary urobilinogen excretion became strongly positive. In some way, therefore, the increased pigment excretion would appear to be linked to a state of rapid haemoglobin formation in a patient in whom there is also a latent

deficiency of the anti-anaemic liver principle, as these findings were not noted in cases treated with liver and iron from the outset. In view of the response to cystine observed in the Group C patients an upset in liver metabolism is suggested as the cause of the apparent upset in pigment metabolism. However, before this conclusion can be reached, haemolysis must be ruled out. Firstly, a routine red cell fragility test was carried out on these patients. Haemolysis was found to begin between 0.5 and 0.45 and be complete at 0.35 per cent sodium chloride. At first these figures suggested that a haemolytic process was occurring but a series carried out on twenty normal patients attending the antenatal clinic, using the same method, gave similar results. These findings are in accordance with those of Elliott (1944) who also reported a shift to the right in the fragility of the red blood cells during pregnancy and, since our experiments were carried out on venous blood, this might explain the slightly higher figures obtained, (Whitby and Britton 1946). Attempts were made next to discover a haemolysin and experiments, similar to those described for the first case of haemolytic anaemia, were made. No haemolysin was found, however, and the Coombs' test was negative. From these results, therefore, it appeared that the increased pigment in the blood and

urine was not due to a haemolytic process. If the increased plasma bilirubin is taken as evidence of an upset in liver metabolism (Maclagan 1944, Higgins et al 1944, Sherlock 1945) then three hypotheses arise. Firstly, that the administration of iron to these very severe anaemias where the reserve stores are probably low, places extra demands on the liver which appears to be mainly concerned with the modification, the storage, and the transportation of the absorbed iron to the bone marrow (Hahn and Whipple 1936, Hahn 1937, Bogniard and Whipple 1932 and Hahn et al 1938). More recent work by Laufberger (1937), Hahn and Bale (1941), Libet and Elliott (1944), and Grannick (1942 1946) reveal the complex mechanism involved in this process and Grannick and Hahn (1944) have shown the speed at which this process can act. e.g. dogs injected with iron intravenously were sacrificed one hour later and by that time 40 per cent of the total injected iron had been taken up by the liver, the amounts in the spleen being negligible. Similar findings were reported by Copp and Greenberg (1946). It is obvious, therefore, from the above findings that extra demands are placed on the liver at this time. Miller and Whipple (1940) and Himsworth and Glynn (1944) have shown that reduction of the protein in the diet, especially if it is accompanied by a high fat intake leads to fatty

infiltration and cirrhosis of the liver or to acute necrosis on the other hand, the former being due to a deficiency of the essential amino acid choline (McHenry and Patterson 1944) and the latter to a deficiency of the essential amino acid cystine (Glynn, Himsworth, and Neuberger 1945). If, therefore, protein is deviated to some other purpose, e.g. haemoglobin production, then it is possible, in view of the above experiments, that the functions of the liver may be altered and the first sign of this interference may well be a rise in the plasma bilirubin. That body protein can be depleted to produce haemoglobin has been shown experimentally by Miller, Whipple and Robschiet - Robbins (1947). In our patients here a definite fall in the plasma protein levels was observed as a result of giving iron, the figure noted for the Group C patients being 0.6 g. Hence a protein deficiency may have existed in these patients and may have been responsible for the development of jaundice. It is obvious, however, that in the above hypothesis we have no actual proof that organic change has occurred in the liver and until such a condition can be demonstrated by liver biopsy it can only be tentatively suggested that an upset in liver metabolism is the cause of the appearance of jaundice and the failure of the anaemia to improve further.

The second hypothesis, and one which appears less likely, is that due to the increase in the haemoglobin etc., as a result of the partial response to iron therapy, a greater amount of haemoglobin is circulating in the peripheral blood. Therefore more haemoglobin is broken down daily and more pigment, namely, bilirubin is produced. If, as before, the liver is unable to deal with this increased production of bilirubin, then sub-clinical jaundice will appear.

A third possibility is that the marrow is hypoplastic and unable to utilise the circulating pigment. Supportive evidence for this hypothesis is given by the marrow picture which showed low percentages of megaloblasts and normoblasts originally. However, it was found that the megaloblasts increased after iron had been given i.e. that the marrow was possibly more active when the jaundice appeared. In view of this and also of the subsequent results obtained in the therapeutic tests with cystine, the fault is more likely to be in the liver.

If a deficiency of an essential amino acid is the cause of the jaundice, then the addition of that acid to the diet should cause the jaundice to disappear. Madden et al. (1939) stated that not one amino acid influences haemoglobin production, but from their experiments, it appeared that cystine nearly qualified as a "key amino

acid" in the production of globin. The following year Miller and Whipple (1940) demonstrated the protective action of methionine and showed that due to its methyl (CH_3) and sulphydril (S.H) groups, it could replace both choline and cystine. Methionine would therefore have been the ideal amino acid to use in these cases. Unfortunately, we were unable to obtain sufficient supplies. Cystine, on the other hand, was available and, as has been shown by Rose et al.(1937) and Beattie and Marshall (1944), one molecule of cystine in a mixture will spare two molecules of methionine when methionine is present in minimal doses. This "methionine sparing effect of cystine" is temporary and moreover, there is evidence that an excess of cystine may be harmful (Witts 1947). Hence the reason for giving cystine for one week only.

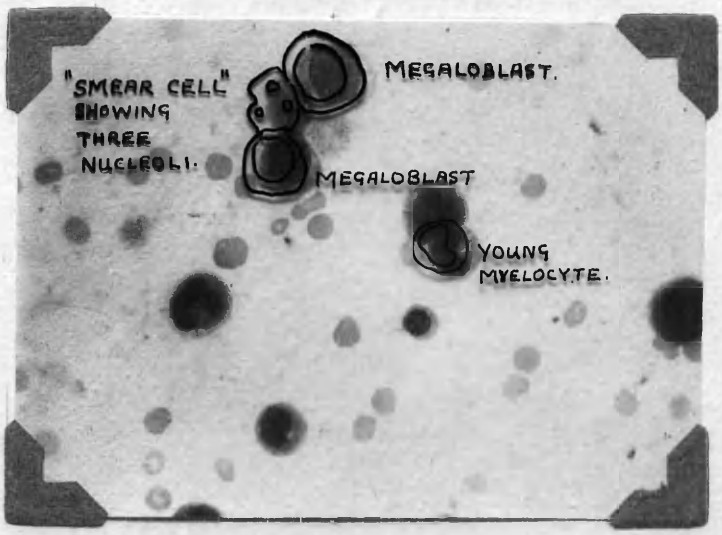
As has already been shown in the four cases who were given cystine, the jaundice disappeared as a result of therapy and where larger doses were given there seemed to be an actual haemopoietic response. However, the number of cases treated so far, is small, but the results would suggest that an upset in liver metabolism is possibly the cause of the jaundice and the failure of the anaemia to respond to further iron therapy. Minor degrees of this occurred in the

atypical pernicious anaemias of pregnancy of Group A, as evidenced by the increased excretion of urobilinogen. In view of this, therefore, it would be advisable to give a high protein diet in addition to iron to these patients.

It will be remembered that two patients in Group C had a latent jaundice on admission to hospital, that this cleared up soon after admission and re-appeared when the anaemia ceased to improve. In addition, two patients who were admitted just before term and appeared to belong to this group, had an initial jaundice. The cause of this initial jaundice is still obscure. It may be due to a dietary deficiency, e.g. low protein intake, which is partially remedied on admission to hospital, but reappears again as described above when the demands for protein are increased.

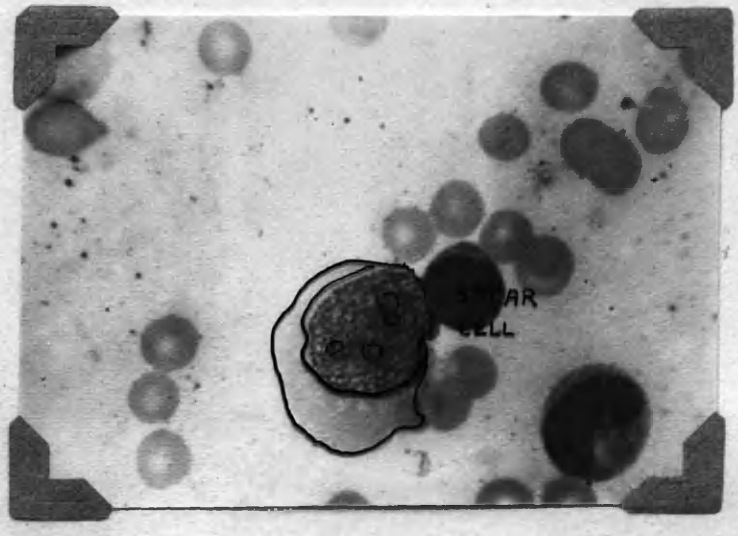
A similar explanation can also be given for the initial jaundice noted in the three severe cases of "anaemia and toxaemia". Here the plasma proteins were very low initially and a protein deficiency might well be the cause of the upset in the liver metabolism. One of these patients was delivered two weeks after admission, the second was given a protein hydrolysate in addition to iron, while the third was given liver immediately the haemoglobin stopped improving. It has therefore been

PLATE VIII. x 400.



Smear cell and megaloblasts from a case of atypical pernicious anaemia of pregnancy.

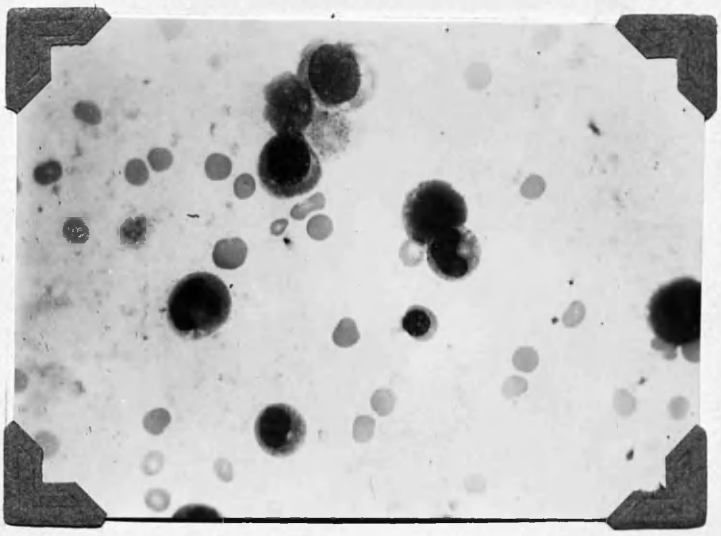
PLATE IX. x 800.



Smear cell showing 4 nucleoli and reticulated nucleus staining with cresyl blue.

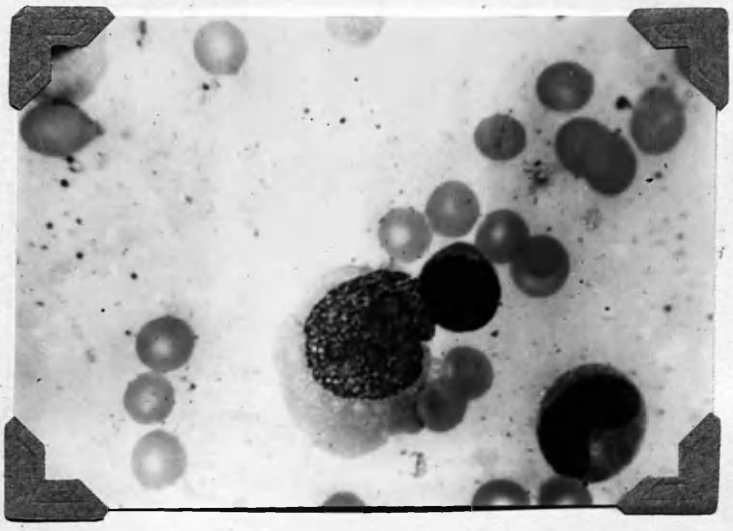
Jenata's cells

PLATE VIII. x 400.



Smear cell and megaloblasts from a case of atypical pernicious anaemia of pregnancy.

PLATE IX. x 800.



Smear cell showing 4 nucleoli and reticulated nucleus staining with cresyl blue.

Jennata's cells

impossible to say, as yet, whether jaundice would ultimately have developed in these very severe anaemias simulating toxaemia. In view of the low plasma proteins it is probable that such would have occurred had these patients been left sufficiently long on iron alone.

Having discussed the variations in the peripheral blood noted in the three groups of "atypical pernicious anaemias of pregnancy", the minor details noted in the bone marrow must now be considered. It must be remembered, however, that the marrow pictures were very similar in all groups.

It has already been mentioned that a differential count of the initial marrow smears of the three severe anaemias simulating toxaemia was made difficult by the number of "smear cells" which were present (Plate VIII). These cells, which were more frequent in the two untreated typical cases of pernicious anaemia of pregnancy, had a large fine reticulated nucleus, with three or four nucleoli. Usually the nuclei were seen without any surrounding cytoplasm hence the name smear cells, but careful searching of the fields revealed that where the cytoplasm was attached it was clear blue, deeper in colour than the cytoplasm of the promegaloblast, but not as dark as that of the pro-erythroblast. When the marrow was stained with cresyl blue then counter - stained, the

PLATE X. x 100.

Fat spaces - before treatment.

PLATE Xl. x 100.

Same marrow - after treatment.

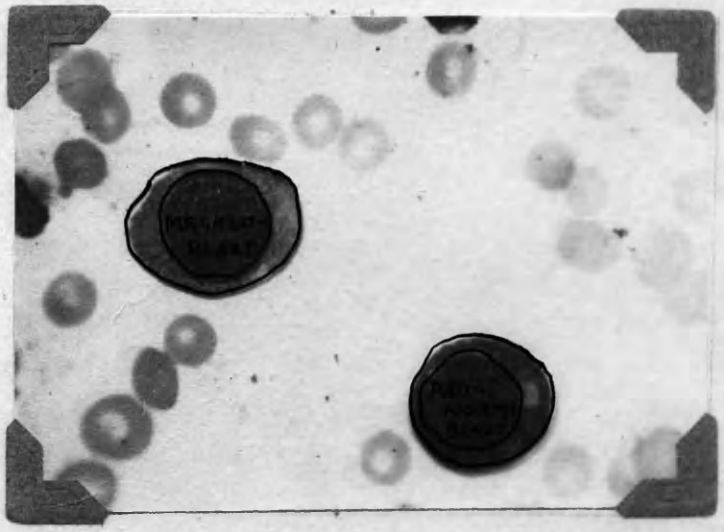
chromatic network of the nuclei became very distinct and the nucleoli stained a clear sky-blue colour (Plate IX). From their structure these cells appeared to be red cell precursors. However, this was not definite and possibly they are similar to the cells described by Rohr (1940) as "large proliferated reticulum cells" and by Gallender (1944) as "haemocytoblasts". Whatever their nomenclature, they were obviously primitive cells. They were present in the marrow smears of all anaemias examined, but occurred most frequently in Group B patients, whose condition simulated toxaemia, and in typical cases of pernicious anaemia of pregnancy, especially the latter. In this respect therefore the marrow in Group B patients bore a greater resemblance to typical pernicious anaemia of pregnancy than did Group A and C.

Numerous fat spaces were found in the marrow smear of one of the Group B patients, but this was not a marked feature in other patients of this Group or in typical cases of pernicious anaemia of pregnancy. It is interesting to note, however, that this patient had very low plasma proteins and, that after treatment with cashydrol and iron for five weeks, a second marrow smear showed no fat spaces whatsoever (Plates X and XI).

Unfortunately only a limited comparison of this group after treatment with typical pernicious anaemias

of pregnancy is possible. Those patients treated with iron alone were not re-examined until the puerperium and the remaining patients were given specific anti-pernicious therapy which radically altered their marrow picture. With regard to iron therapy only the marrow picture of the patients in Group A and C can be considered. It has been shown that the initial marrow picture in Groups A, B, and C was substantially the same, with the exception of the "smear" cells noted in Group B above. The megaloblasts and normoblasts were present in relatively small numbers - approximately 2 per cent and 20 per cent respectively. A second marrow examination in Groups A and C after iron therapy, showed striking changes with a tendency to approach the marrow picture of typical pernicious anaemia. Megaloblasts had increased and more mature forms showing early haemoglobinisation were present, instead of the promegaloblasts and early basophilic types of the first marrow smear. In other words iron therapy appeared to increase the maturation rate of the megaloblasts, although it did not alter the morphogenesis. These changes were more marked in Group C where the percentage of megaloblasts was higher, and thus the marrow in these cases of anaemia with sub-clinical jaundice eventually bore a greater resemblance to that of typical pernicious anaemia than did the other

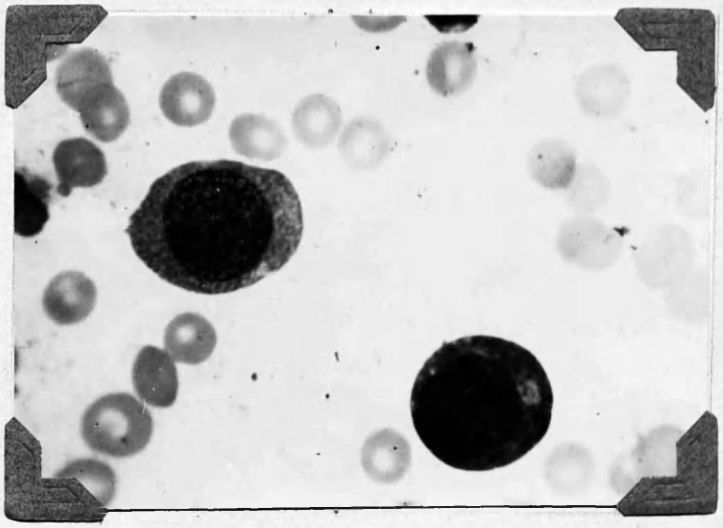
PLATE X11. x 800.



Early megaloblast and pronormoblast

from a dimorphic marrow.

PLATE X11. x 800.



Early megaloblast and pronormoblast

from a dimorphic marrow.

groups. Smear cells, however, were not so plentiful. The appearances were similar to those described by Davidson, Davis and Innes (1942a) as a "dimorphic marrow" (Plate XII).

It is interesting to note that as the marrow of the patients with jaundice and anaemia tended to become more typical of that shown by pernicious anaemia of pregnancy as a result of iron therapy, so a similar tendency for the blood picture to become more macrocytic was observed in this group. It may be that, in view of what has been said previously in relation to the development of jaundice, the possible upset in liver function in this group is responsible for this tendency to develop into a typical pernicious anaemia of pregnancy.

So far only the changes in the megaloblasts as a result of iron therapy have been noted. Changes also occurred in the normoblastic series in which the percentage of cells fell and the cytoplasm of the more mature cells became less basophilic, due to the rectification of the iron deficiency and ultimate increase in available haemoglobin. No significant change was observed in the white cells. A few giant forms were seen with irregularly shaped nuclei, but otherwise no abnormality was seen.

From the foregoing survey of the blood and marrow in atypical pernicious anaemia of pregnancy it is possible to suggest reasons why the clinical presentation of this anaemia is so varied. It will be remembered that the survey carried out during 1946(Section I Chart 3i) revealed a group of 14 severe anaemias with symptoms relating to the gastro-intestinal tract, who only partially responded to iron therapy and developed a "plateau curve" similar to that of the present cases. In the clinical section it has been shown that gastro-intestinal upset was a frequent complaint in cases of atypical pernicious anaemia of pregnancy and a gastric analysis carried out on ten patients in this group revealed that achlorhydria occurred in six (in one instance it was not histamine fast), hypochlorhydria occurred in three and only one patient had a normal gastric acidity. From these findings therefore it is possible that a diminished dietary intake, a diminished absorption of the necessary foods, coupled with increased foetal demands are the important aetiological factors in this anaemia. These factors may lead to various deficiencies and the clinical features will depend on which deficiency is most marked. Thus iron deficiency was initially the most marked feature in all the cases of atypical pernicious anaemia of pregnancy and this was

seen in the blood and in the bone marrow. Secondly, where there was a general protein deficiency, the plasma proteins were lower, oedema developed, the systolic blood pressure rose and a picture very similar to pre-eclamptic toxaemia was presented. Thirdly, it has been suggested that when a deficiency of an essential amino acid occurred or an unbalanced diet renders an increase in that amino acid essential, an upset in liver metabolism may ensue and the patient may develop a sub-clinical jaundice.

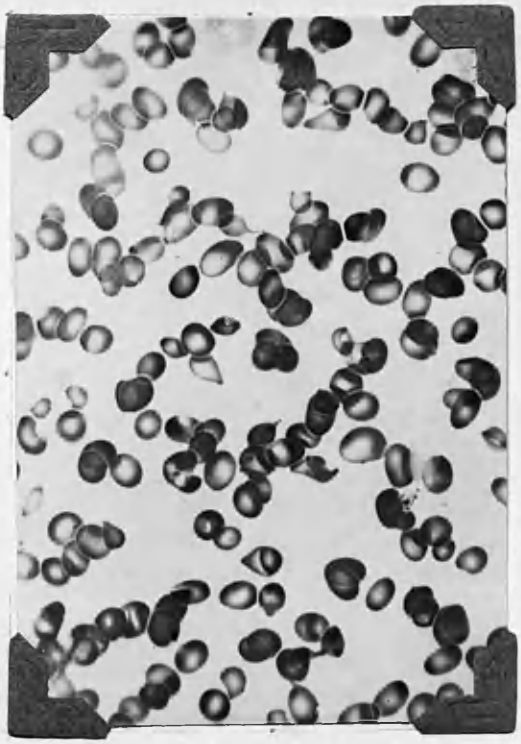
Unlike the cases of ordinary iron deficiency, anaemia with megaloblasts in their bone marrow, this anaemia is not reversible with iron therapy. It will not respond fully to iron therapy even in hospital, though it will respond slowly in the puerperium, showing that foetal demands do play an important part. Other latent deficiencies must therefore be rectified in addition to that of iron, before normal blood levels can be reached. In the treatment of these cases we have tried to treat the obvious deficiency in each group and the findings so far would suggest that equally good results were obtained by this method, as by giving liver and folic acid empirically. Recent work tends to show that present theories regarding liver extract or folic acid are over simplified and that the same marrow picture may be produced by very varying dietary

deficiences. For example Moosnick et al (1945) and Davis and Brown (1947) have shown that a megaloblastic anaemia may be refractory to parenteral liver therapy on account of the fatty state of the liver and that choline corrected this dysfunction. On the other hand Spies et al.(1945) Vilter, Spies and Koch (1945), Moore et al(1945), Spies (1946) and Berry and Spies (1946) have suggested that by giving oral liver which liberates folic acid from its conjugates in the intestinal tract or by giving folic acid itself, the liver may be bi-passed and the haematinic substances supplied to the liver direct. A more recent report by Doan (1946), who quoted a case of megaloblastic anaemia complicated by hepatic cirrhosis, which was refractory to folic acid would appear to contradict the findings of the above authors. Moreover, a haemopoietic response to thymine has now been demonstrated in Addisonian pernicious anaemia, nutritional macrocytic anaemia and pernicious anaemia of pregnancy (Berry and Spies 1946), though this response is less than that following folic acid and liver extract. (Spies and Stone 1947). Thus from an original hypothesis by Castle postulating a single "erythrocyte maturation factor", the theory of the cell formation has now expanded to include a complex system of inter-related substances, and Berry and Spies (1946) reviewing the

subject suggest that all the anti-anaemic factors may be linked to the synthesis of nucleic acid. In their opinion each factor may act in a similar overall manner, but possibly by different routes.

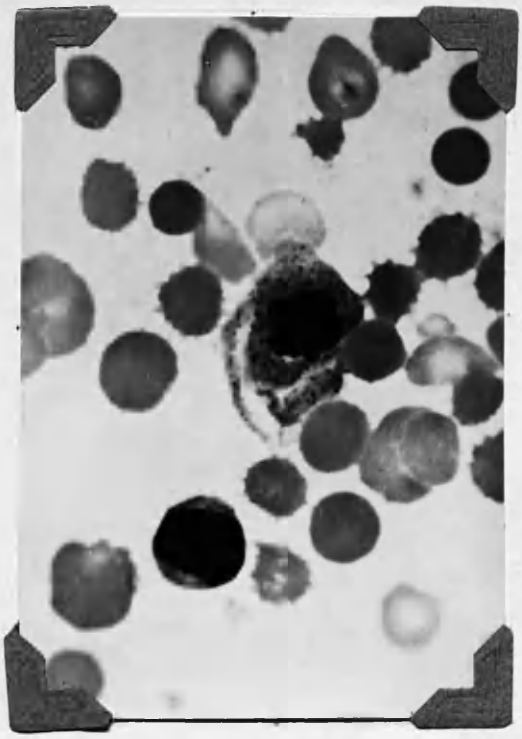
So far, we have only been able to investigate eight patients with typical pernicious anaemia of pregnancy and of these, four had already been treated and the blood and marrow pictures modified accordingly before they came under observation and a further two were atypical cases which had become typical as a result of giving iron therapy. Of the untreated cases it can be said that the anaemia was more severe than in the atypical case. The haemoglobin was low, as in the atypical cases but the red cells were also reduced. Thus a typical macrocytic hyperchromic blood picture was produced similar to that described by Heilbrun (1936) Doan (1938) Ungley (1938) Miller and Studdert (1942). Callender (1944) made her diagnosis of this anaemia by marrow biopsy or the presence of typical megaloblasts in the peripheral blood and hence atypical cases were included in her series, but in no instance did she find a mean cell volume lower than 80.2 μ^3 . The mean cell diameter in the two untreated patients was 8.2 μ and 7.2 μ ~~and 7.8 μ~~. In the latter case this rose to 7.8 μ after delivery. Callender (1944) found the majority of

PLATE X111. x 400.



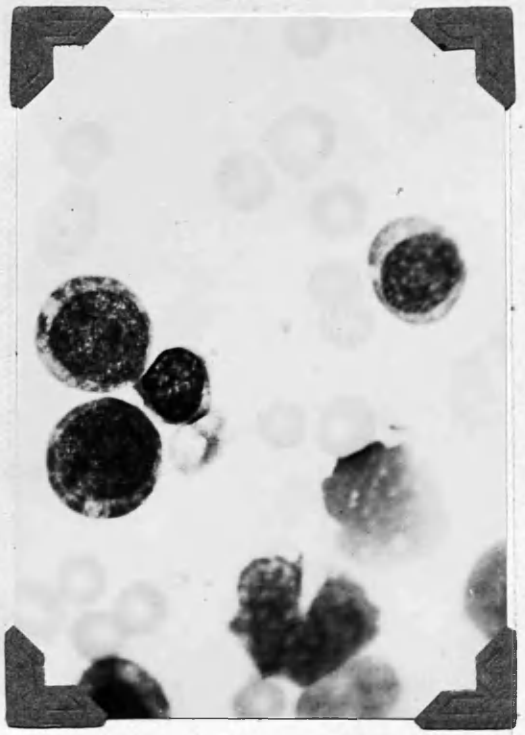
Blood film - typical pernicious anaemia of pregnancy.

PLATE X1V. x 800.



Blood film showing a megaloblast in mitosis.

PLATE XV.
x 800.



Marrow - typical pernicious anaemia of pregnancy showing megaloblasts and a pronormoblast.(see coloured plate).

her patients within the normal range. Segerdahl (1941) only reported two cases with mean cell diameters less than 7.2 μ, whereas Stevenson (1936) reported a shift to the right in six of her patients. The red cell fragility in the present cases was normal and this is an agreement with Filo (1931), Stevenson (1938), Neilsen (1941) and Callender (1944). On the other hand Miller and Studdart (1942) found the fragility slightly raised in three of their cases and Minot (1921) Vermelin and Vigneul (1921), and Devraigne and Laennec (1928) have reported a definite increase in the fragility. Unlike the cases of atypical pernicious anaemia of pregnancy, reported previously, anisocytosis was common, poikilocytosis was marked and nucleated red cells could be seen in the peripheral blood (Plate XIII). During a reticulocyte crisis, as a result of giving folic acid, these features became more marked and megaloblasts in mitosis were seen in the peripheral blood (Plate XIV). Similar findings have been reported by Callender (1944) and Stevenson (1936), but Davidson, Davis and Innes (1942 b) considered the anisocytosis, etc. to be less than that observed in Addisonian pernicious anaemia and Paine and Dameshek (1944) said it was only moderate. Leucopenia was present in the case which proved resistant to parenteral liver before delivery, but after delivery

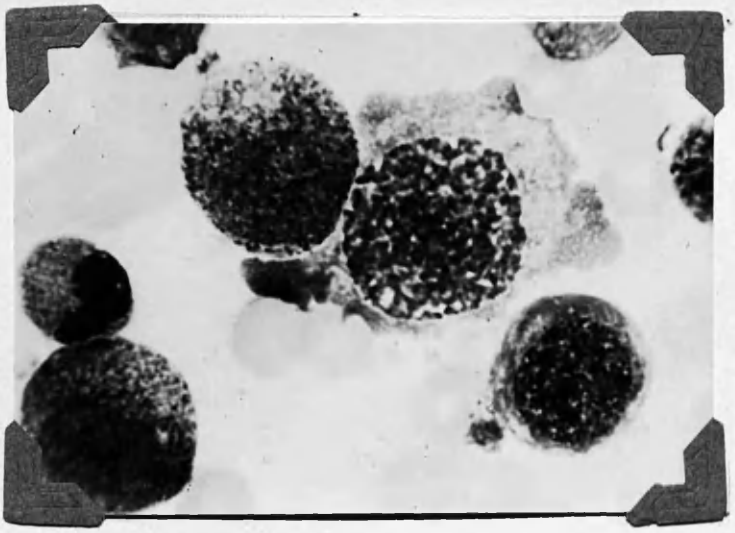
the number of myelocytes in the peripheral blood increased and a few hypersegmented forms typical of Addisonian pernicious anaemia could be seen. The occurrence of these cells in pernicious anaemia of pregnancy has been described by Callender (1944). The reticulocytes were initially low in our cases. This agrees with the findings of Callender (1944), but Stevenson (1936) found them slightly raised and she stated that the rise after treatment appeared earlier than in Addisonian pernicious anaemia. In two of our cases the reticulocytes showed a spontaneous increase in the puerperium and when folic acid was given after the reticulocyte rise has ceased, the response was almost immediate.

Biochemically a slight rise in plasma bilirubin has been reported by Peterson, Field and Morgan (1930). Heilbrun (1936) Abramson 1938 and Stevenson (1938). Callender (1944) reported on the results of eleven estimations; none was more than 0.8 mg. per cent. The plasma bilirubin was 0.4mg per cent in one of our untreated cases and negative in the other; it was more than 1 mg. per cent in the two atypical cases of jaundice and anaemia, who became typical, and was negative in the cases who had received liver therapy before they came under observation. In these patients, however, the

urinary urobilinogen increased as a result of the withdrawal of liver and the giving of iron. The plasma proteins were low in the untreated cases, the lowest level recorded being 3.8 g. per cent. Where liver therapy had been given the readings were higher initially, namely 5.0 g. per cent, but they ultimately fell to 4.3 g. per cent, when iron alone was given in hospital. Test meals were performed in three of these patients. Complete achlorhydria was noted in one, hypochlorhydria in the second and in the third a normal curve was obtained. Stevenson (1936) found the acid secretion reduced in the majority of her patients but Callender (1944) and Davidson, Davis and Innes (1942 b) did not find this a constant feature. In comparison with the cases of atypical pernicious anaemia of pregnancy mentioned previously, achlorhydria would appear to be less frequent in the typical cases, as compared with the atypical, but as only three cases have been investigated in this group so far, these findings await confirmation.

With reference to the marrow picture several features have already been mentioned, which help to differentiate the typical from the atypical cases. For instance the "smear" cells are found to be much more numerous and more mature haemoglobinised

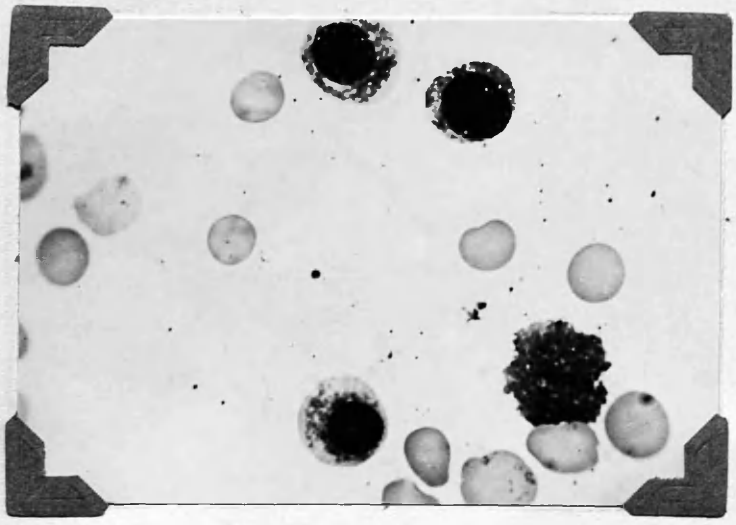
PLATE XV1. x 800.



Marrow typical pernicious anaemia of pregnancy showing promegaloblast and megaloblast. (see coloured plate).

Yes.

PLATE XV11. x 800.



Marrow - typical pernicious anaemia of pregnancy showing haemoglobinised reticulated megaloblasts. — ?

megaloblasts are found. However, it has been shown that a mixed megaloblastic and normoblastic reaction is still present in the marrow of these typical cases, the normoblastic percentage being lower than that observed in the atypical cases and the megaloblast percentage higher. (Plate XV). A similar "mixed reaction" has been noted by Stevenson (1936) Lescher 1942 and Callender (1944). The picture is very similar to that of Addisonian pernicious anaemia and the majority of authors are of this opinion. (Nielsen 1941, Davidson, Davis and Innes 1942b, Miller and Studdert 1942, Lescher 1942), Rohr (1940) and Segerdahl (1941), however, distinguish it from Addisonian pernicious anaemia. They stated that fewer promegaloblasts and basophilic megaloblasts are found and that the erythropoiesis is more mature. In the present cases early cells were just as common as in Addisonian pernicious anaemia. Promegaloblasts of the type described by Callender (1944) with a wide rim of light blue cytoplasm and a nucleus with a pink reticulate structure with three or four nucleoli, were more common than the usual type with the deeply basophilic cytoplasm (Plate XVI). Basophilic megaloblasts, however, were frequent and a few multi-nucleated irregular forms were seen. When the marrow was stained with cresyl blue, the reticulum in the

haemoglobinised cells showed up very clearly. In the normoblastic series reticulum was evident in the intermediate normoblasts or late erythroblasts. As will be seen from Plate XVII, the reticulum was concentrated more round the nucleus, leaving the periphery clear. Similar findings were observed in the megaloblastic series where cells as early as intermediate megaloblasts showed this reticulum. Vital staining of all the marrow smears was performed and the impression gained was that where haemoglobinisation of the red cell series was satisfactory, the reticulum was more apparent. Admittedly the basophilic staining of the cytoplasm may obscure any vital staining of the reticulum and attempts were therefore made to examine the vital stained smears without counter-staining them, but the results were not satisfactory. Cellular definition was not clear and it was very difficult to differentiate the various types. At first, when it was observed that the percentage of reticulated, nucleated and non-nucleated cells fell in the Group A anaemias on reaching plateau levels, it was thought that a correlation could be made between the degree of marrow activity and the percentage of reticulated cells. However, it has been shown that the percentage of reticulated cells rises in the Group C cases, when they reach plateau level and

also that the percentage is high in cases of typical pernicious anaemia. As a close similarity has been noted in these marrows, another explanation will have to be sought. Earlier haemoglobinisation may account for the raised percentage of nucleated cells possessing reticulum, but it does not explain the presence of increased numbers of ordinary reticulocytes.

From the differences noted in the blood and marrow it would first appear that typical pernicious anaemia of pregnancy is a separate entity, but it has also been shown that atypical cases can become typical and that by withdrawing liver and giving iron therapy to partially treated typical cases, an atypical picture can be produced. Hence it is suggested that the various types of anaemia in pregnancy are not definite entities and that one may progress to another, i.e. the iron deficiency anaemia may pass through a "transitional phase" after which it will not respond to iron therapy alone, thus becoming a case of atypical pernicious anaemia of pregnancy, where there is only a partial lack of production or utilisation of the anti-anaemic factor" (or factors). If this condition is left untreated or some added strain such as labour, toxaemia, etc. arises, then it is likely to pass on to typical pernicious anaemia of pregnancy. Clinical evidence that such can occur in the

macrocytic anaemias of pregnancy in India has been presented by Mudaliar and Menon (1942) and morphologically our results would support their opinion.

Finally in considering the aetiology of pernicious anaemia of pregnancy, the above findings would suggest that it is a dyshaemopoietic anaemia and not due to a haemolysis, as originally suggested by Osler (1919) Rowland (1924) and Witts (1932). Endocrine influences may play a part, but no positive evidence that such can occur has so far been produced.(Myer, Stewart, Thewlis and Rusch 1937, Dodds, Noble and Smith 1934, Dodds and Noble 1935, Dodds, Noble, Scarf and Williams 1937). Gastro-intestinal upset has been shown to be significant in the development of an iron deficiency anaemia. Further, when it accompanies a severe anaemia, the response to iron therapy is only partial. It seems likely from this that the gastro-intestinal disorder acts by further reducing a diet already deficient, or by altering or arresting, temporarily at least, the secretion of Castle's intrinsic factor. Both of these mechanisms of course may come into play. Finally it has been suggested that the cases refractory to liver therapy reported in the literature are really cases of achrestic anaemia. Only one of our patients proved refractory to parenteral liver and we were unfortunately not able to watch the

effect of either oral liver or folic acid in this case.

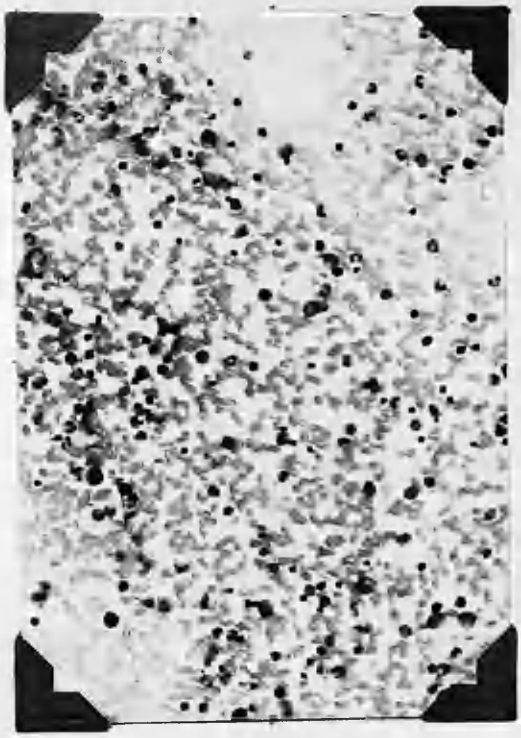
The last group of anaemias to be considered are the two cases of haemolytic anaemia reported in this present survey. In the first patient, the fundamental features demonstrated were the spherocytosis and the increased red cell fragility. Originally these two findings occurring in a case such as this, together with a family history of such a condition, were considered pathognemonic of a congenital haemolytic anaemia (Minkowski 1900, Chauffard 1907, Naegeli 1931). However Damashaek and Schwartz 1938 have shown that by injecting varying amounts of anti-guinea pig sera into guinea pigs, the various types of haemolytic anaemia are produced depending on the amount injected. For example, the smallest quantity injected produced a condition equivalent to congenital haemolytic anaemia. Two factors have therefore to be decided in this case. Firstly, whether the phenomena of spherocytosis and increased red cell fragility were a congenital abnormality of the cell, or, secondly, whether they were due to a haemolysin circulating in the blood.

Apart from the lack of a family history of haemolytic anaemia, the clinical history, the spherocytosis, the increased fragility, the persistence of the condition a year later, the inability to

demonstrate a haemolysin and the negative Coomb's test all point to a diagnosis of congenital haemolytic anaemia aggravated or appearing for the first time as a result of the pregnancy. Threefindings, however, appear to contradict the above, viz. The definite relationship between the pregnancy and the onset of haemolysis and the immediate improvement after the delivery. Secondly, the haemolytic crisis noted after transfusion though, by all the known laboratory methods, the blood seemed compatible, and thirdly, the absence of haemolysis noted in vitro, when the cells were resuspended in the patients own plasma after it had been heated to 56° C. Dacie (1941) also noted the absence of haemolysis after heating the plasma in thirteen cases of congenital haemolytic anaemia. He suggested therefore that, during the circulation of the blood, the red blood cells adsorbed lysolecithin and therefore, when the plasma and cells are incubated together, only a small amount of lysolecithin in the plasma is necessary to produce haemolysis. Lysolecithin is destroyed by heating to 56° C. (Singer 1940). Hence, when the cells are resuspended in the heated plasma, there is insufficient lysolecithin present to cause haemolysis. Bergenhem and Fahreus (1936) first discovered lysolecithin and postulated that it was the

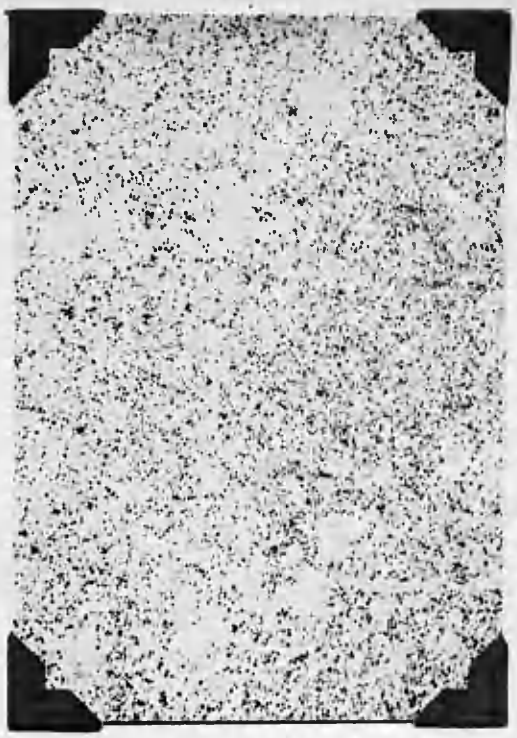
factor in congenital haemolytic anaemia. They suggested that, as incubation of the plasma increased the lysolecithin content and therefore increased the haemolysis, so stagnation of the blood in the spleen would increase the haemolysis. This work has been carried a stage further by Singer (1940), who demonstrated an increased lysolecithin content in the splenic vein of dogs and in blood taken from varicose veins of a patient. If these findings are correct, then it is obvious that the placental sinuses are an ideal site for the incubation of lysolecithin and only after delivery, when this site is removed, would the haemolysis be reduced and the anaemia respond to treatment, a result which actually happened in our patient. Thus two of the apparent contradictory findings have been explained. As to the cause of the haemolytic crisis as a result of the transfusion, we were able to give no explanation. Loutit and Mollison (1946) state that in cases of acquired haemolytic anaemia transfused cells are eliminated more rapidly than in the congenital type. Despite this, however, the above findings point more conclusively towards a diagnosis of congenital haemolytic anaemia where the degree of haemolysis, possibly due to the increased lysolecithin content of the blood, is increased as a result of the pregnancy.

PLATE XVIII. - x-200.



Haemolytic anaemia in crisis nucleated red cells. (blood).

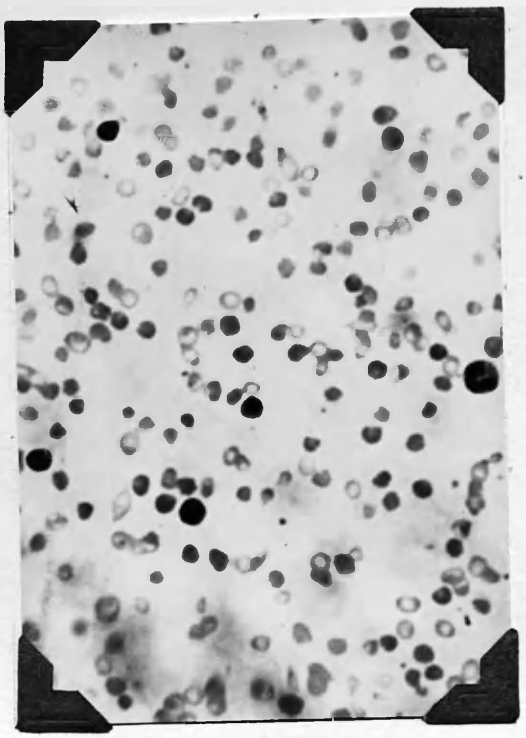
PLATE XIX.a) x 150.



Haemolytic anaemia in crisis pink layer.

PLATE XIX.b).

x 100.



Erythroblastosis foetalis - pink layer.

With reference to the second case, the difficulty that arises here is to prove that this was an actual haemolytic anaemia and not pernicious anaemia of pregnancy appearing suddenly in the puerperium. Most of the cases of haemolytic anaemia reported in the recent literature (Swan 1933, Lescher 1942) have been regarded as actual cases of pernicious anaemia of pregnancy (Callender 1944, Bethell 1944). Lescher (1942) made his diagnosis of a haemolytic anaemia on account of the raised reticulocytes, the positive Van den Bergh and the remarkable response to blood transfusion. At the same time he noted a megaloblastic reaction in most of his cases and observed that the fragility was normal. In the present case, however, more definite indications of a haemolytic process were obtained, namely, two haemolytic crises occurred and, during the second, the patient was under close observation. Within thirty six hours a dramatic fall in the blood levels was observed, which could only be explained by a blood destruction. At this time the peripheral blood contained many nucleated cells (Plate XVIII) and using a technique which has also been applied with advantage elsewhere, it was possible to "concentrate" the nucleated cells and examine them more closely:-

2 c.c. of oxalated blood were placed in the

haemoglobinometer tubes, which were used originally as haematocrit tubes. The blood was spun, as described before for the haematocrit estimation. When the tube was removed, it was found that due to the oxalate, the white cells formed a layer at the foot of the tube. On top of the red cells, however, a pink layer could be seen and this was noted whenever the blood contained a large number of nucleated red cells and reticulocytes. It was found in cases of erythroblastosis foetalis, in both haemolytic anaemias described, in some of the newborn babies and in pernicious anaemias of pregnancy responding to folic acid or liver during the reticulocyte crisis. The depth of the pink layer, which was proportional to the percentage of nucleated cells and reticulocytes present in the peripheral blood varied from 1-3 per cent on the haematocrit scale. The cells could easily be pipetted off and resuspended in the plasma. Films were made as before and the concentrations of nucleated cells observed can be seen in Plates XIX. The reticulocyte counts of the pink layer estimated between 20 and 60 per cent.

Thus it was possible to say in this instance without searching innumerable fields that no megaloblasts were seen in the peripheral blood during the haemolytic crisis. In contrast to this finding, the pink layer

examined in cases of pernicious anaemia of pregnancy during a reticulocyte response contained numerous megaloblasts a few early some intermediate, and more late. Hence, by this means it is possible without a marrow biopsy to determine the nature of the earlier cells of the red blood cell series. One other interesting point was this, that, though the majority of the white blood cells were found at the bottom of the haematocrit tube, a few early myelocytes were found in the pink layer which also contained a high percentage of platelets.

A third finding in favour of a haemolytic process in the present case was the definite increase in the fragility of the red blood cells, haemolysis being noted at 0.65 per cent sodium chloride. In this case however, the increased fragility was of a temporary nature, as a normal result was obtained two weeks later, and again a year later, when the patient reported back, In common with the cases reported by Lescher (1942), this patient also showed a high reticulocyte count, a positive Van den Bergh, and a very satisfactory response to the second blood transfusion. In addition, a test dose of 4 c.c. of a crude liver extract was given parenterally while she was still very anaemic, but the reticulocytes only rose from 3 per cent to 5 per cent

for 4 days, a finding which is also against a diagnosis of pernicious anaemia of pregnancy.

From the above results, therefore, a diagnosis of a haemolytic anaemia would appear the more likely. Since there was no report of a family history of haemolytic anaemia in this case, and since spherocytosis was not observed, and the signs of haemolysis were of a temporary nature, it seems more likely that the haemolytic process was acquired rather than congenital in origin. The question of a coliform infection being the cause of the haemolysis has been discussed, but it seems unlikely. The remaining factors which should be mentioned are the toxaemia, which was present before delivery, and finally the pregnancy itself. Since experiments to detect a haemolysin were not carried out in this case, it is impossible to go further into the aetiology of the haemolytic process, but it appears to be related in some way to the pregnancy or to the puerperium and, as such, could be called a haemolytic anaemia of pregnancy or the puerperium.

Before completing a survey of the pathogenesis of the severe anaemias of pregnancy, two subjects which have been mentioned in relation to every type of anaemia should be considered, namely, the plasma protein levels in relation to oedema and haemoglobin production, and

secondly, the presence of iron staining "bodies" in the red blood cells of the marrow.

With reference to the plasma protein levels it has been shown that a fall occurs when iron is given and the haemoglobin increases, but in resistant cases, where no response is observed, the plasma protein levels remain unchanged. It was decided, therefore, to follow the plasma protein levels more closely in a small series of patients to see what the effect of iron therapy was. Sixteen patients, who were admitted to hospital and given iron therapy, were therefore selected. None of the patients was suffering from toxaemia. The majority of the patients showed a maximal fall in the plasma protein levels at the end of a week, thereafter a slow increase occurred. A few cases, however, did not reach minimal values till three or four weeks, and one case, a pernicious anaemia of pregnancy, who had been treated with liver previously by her own doctor, and was now showing a marked iron deficiency, only reached a minimal value of 4.5 g. per cent at the end of six weeks.

Oedema was present in all these patients on admission to hospital. After a few days rest in bed with iron therapy, the oedema had clinically disappeared in ten out of the twelve cases and had diminished

TABLE XXVI.

Plasma proteins in relation to Hb. production and oedema.

	Plasma Proteins g. %.		Hb % Sahli.	
	Before.	After.	Before.	After.
Oedema (7)	5.28	4.25	34	39
Oedema (9)	5.39	4.79	32	46

considerably in the remaining two, that is, the oedema disappeared as the plasma proteins fell. The average haemoglobin and plasma protein readings before and at the time of the minimal plasma protein reading, have been tabulated and correlated with the degree of oedema observed initially. The results are shown in Table XXVI. This shows that, irrespective of the degree of oedema, the plasma proteins were practically the same in each group originally, but when iron therapy was given, the seven cases with marked oedema showed a greater fall in plasma proteins and a smaller rise in the percentage haemoglobin i.e. the plasma proteins fell 1.03 g. per cent as compared with 0.5 g. per cent and the haemoglobin rose 5 per cent as compared with 14 per cent in the cases with mild oedema. These findings would suggest that the administration of iron to these patients had caused the fall in the plasma protein levels and that the protein had been withdrawn from the plasma to produce haemoglobin. Since a greater fall in plasma proteins was noted in the oedematous patients, the withdrawal of protein is probably indirect in nature. In these patients the oedema had disappeared clinically in all but two, when the basic level of 4.25 g. per cent was recorded, yet the reading is far below the "oedema level" of Moore and Van Slyke (1930). In fact the majority of our anaemic patients

and the baby born of the mother who showed the gross protein deficiency were below the "critical level", stated by the above authors to be 5.5 g. per cent. Moreover, a routine examination of the plasma protein levels of sixty of the normal ante-natal patients gave an average reading of 5.78 g. per cent, which is not much above the "critical level". This figure is lower that the results reported at any time during pregnancy by Rinehart (1946). It is obvious therefore that the "oedema level" is lowered in pregnancy and this may occur as a result of a) an alteration in the make-up of the plasma proteins themselves or b) an altered osmotic balance between the plasma and tissues. Further study of the blood amino acids and blood volume changes in these oedematous patients is necessary before any definite opinion can be vouched on this subject, however.

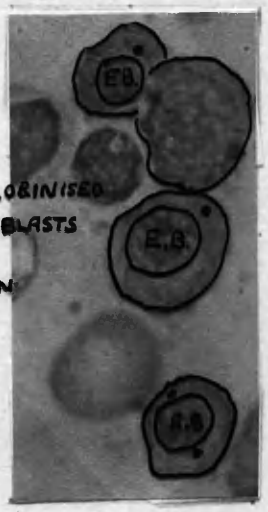
From what has been said previously concerning the value of a high protein diet in anaemias with toxaemia, if not during pregnancy, then certainly in the puerperium, it can be further added here that a high protein diet in addition to iron therapy would be advantageous in the treatment of an "iron deficiency" anaemia if oedema is present. From the definite results obtained so far in two patients and from a clinical impression obtained in several others, it can be said that breast feeding is

detrimental to the recovery from anaemia in cases belonging to Group B, i.e. cases of toxaemia with anaemia and anaemia simulating toxaemia, who have been shown to have low plasma proteins, should not breast feed their babies.

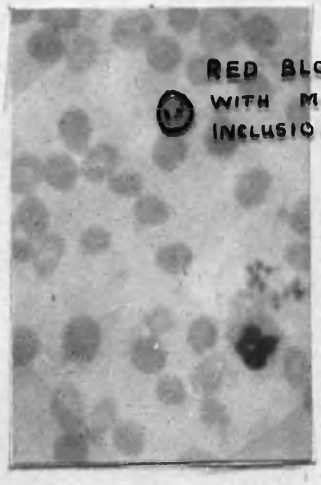
Iron staining "inclusion bodies" were first noted in the bone marrow of the first case of haemolytic anaemia. They were also observed in the blood at the time of the haemolytic crisis. The bodies which were mostly cocoid in shape were first observed in the smear stained with May Grunwald, but on further examination they gave a positive iron reaction with potassium ferrocyanide and hydrochloric acid, a negative Feulgen reaction and failed to stain with Gram or with Gomori's stain for phosphatase. In their morphology and staining reactions they therefore resemble the inclusions described by Pappenheimer et.al.(1945) and McFadzean and Davis(1947). Marrow preparations from this patient were examined by Professor Davis who confirmed the apparent similarity with those observed by him.

In the course of investigating the response to iron therapy in cases of atypical pernicious anaemia of pregnancy, similar bodies were observed in the marrows after treatment with iron had been given. They also gave a positive iron reaction with potassium ferrocyanide and

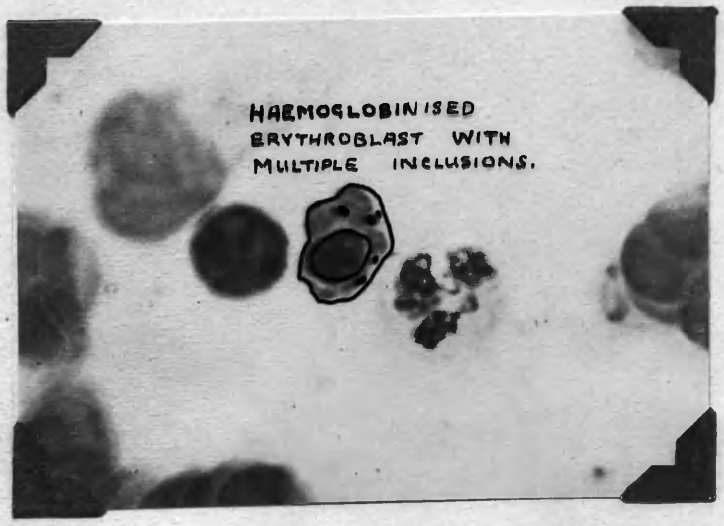
PLATE XX. x 800.



Inclusion bodies in the marrow from a case of atypical pernicious anaemia of pregnancy.

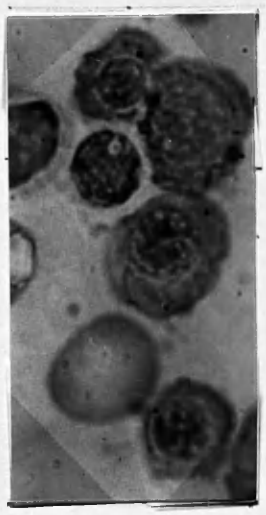


Inclusion bodies in the peripheral blood from a case of haemolytic anaemia.

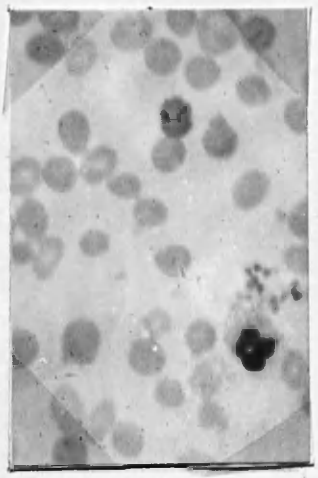


Inclusion bodies from the pink layer - erythroblastosis foetalis.

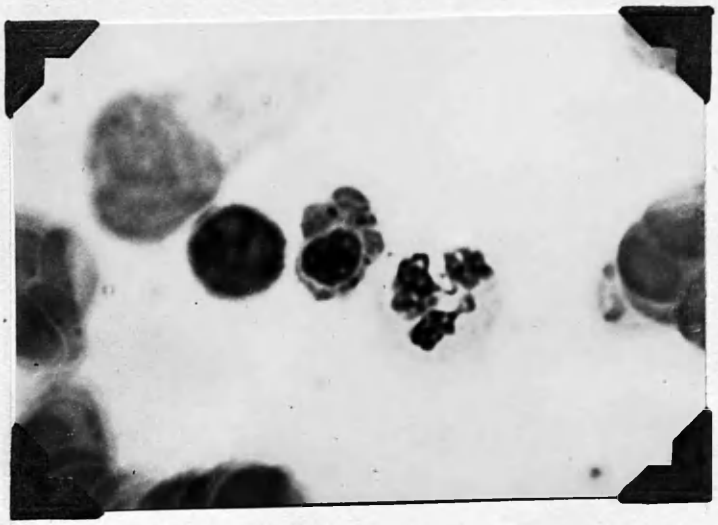
PLATE XX. x 800.



Inclusion bodies in the marrow from a case of atypical pernicious anaemia of pregnancy.



Inclusion bodies in the peripheral blood from a case of haemolytic anaemia.



Inclusion bodies from the pink layer - erythroblastosis foetalis.

hydrochloric acid, a negative Feulgen reaction, and they failed to stain with Gram. As before they were mainly coccoid in shape and of variable size.

In addition, inclusion bodies were found in the peripheral blood of babies with erythroblastic foetalis and during the reticulocyte crisis observed in the cases of pernicious anaemia of pregnancy undergoing treatment with folic acid.

Inclusion bodies observed in all these various conditions showed a marked similarity. In the red cells they were usually found at the periphery, anything from one to six inclusions occurring in a single cell. In the peripheral blood, except during a haemolytic crisis, only a few inclusions could be seen and normally only one or two were present in each cell. In the marrow, however, they were seen more frequently in the red cells and in the later normoblasts and megaloblasts. In the nucleated cells they were found in the cytoplasm in close relation to the nucleus, but definitely separated from it. A few rod-shaped forms were seen and occasionally diploids (Pappenheimer 1945), but the large crescent-shaped masses quoted by McFadzean and Davis (1947) were not observed. A few inclusions were also seen in the monocytes of the marrow; none were observed in any of the cells of the myeloid series, but occasionally large "colloidal

looking" masses, often quadrilateral in shape and giving a positive iron reaction, were seen lying free outside the marrow cells. These were more common in the marrows of the patients with atypical pernicious anaemia of pregnancy, who had failed to respond to iron therapy as out-patients. Similar masses were described by McFadzean and Davis (1947) and they presumed that they were due to rupture of a cell containing the iron staining material. In our cases, however, iron staining inclusions were not observed in the majority of patients, who showed this phenomenum.

Since the presence or absence of inclusion bodies in the marrow seemed to be related to the course of the anaemia and the treatment adopted, every marrow smear examined was stained for iron. Summarising the results of these examinations it was found that:-

(1) No iron staining bodies were found either inside or outside the marrow cells in the untreated cases.

(2) When iron therapy was given to patients with an iron deficiency anaemia in the transitional phase, i.e. with a few megaloblasts in the bone marrow, numerous inclusion bodies were observed in the marrow cells even when the blood count had reached normal levels.

(3) Similar results were obtained when iron was given to patients with atypical pernicious anaemia of pregnancy

though the inclusion bodies appeared less numerous in these cases.

(4) Cases of typical pernicious anaemia of pregnancy who had received both liver and iron therapy showed no inclusion bodies in the marrow. Where liver had been given alone previously, the iron deficiency being untreated, iron alone was given in hospital. After two weeks' iron therapy no inclusion bodies were seen in the marrow, but by eight weeks they had appeared and were very numerous. In comparison with the findings observed in cases of atypical pernicious anaemia of pregnancy who had inclusion bodies in their initial marrow smear when iron had been given for only three or four days, it would appear that the administration of liver had delayed the appearance of the inclusion bodies in the cases mentioned above.

(5) When folic acid was given to patients with atypical pernicious anaemia of pregnancy, who had failed to respond to iron therapy and had numerous inclusion bodies in their marrow smears, the number of inclusion bodies decreased as the marrows became less megaloblastic.

(6) Similar results were noted after cystine therapy in a Group C patient and after cashydrol in a Group B patient, but in the latter instance delivery had

intervened before a second sternal puncture was made and may therefore have modified the marrow picture.

From the above findings two hypotheses can be made. Firstly all the atypical pernicious anaemias of pregnancy given iron had a very gross iron deficiency anaemia in addition to the latent deficiency of the anti-anaemic factor or factors. They respond rapidly to iron therapy as shown by the initial rise in haemoglobin and the appearance of iron in the marrow four days after commencing therapy. Thus more iron is now available to the marrow for haemoglobin formation and may act as a stimulus to produce new cells. On account of the latent erythrocyte maturation factor deficiency, however, this may become more difficult and ultimately impossible, that is, at the time of appearance of the plateau in the blood levels. Despite this, however, the process of iron absorption, mobilization, and transportation to the bone marrow may continue and the presence of the inclusion bodies in the late normoblasts and red blood cells may be the result of a "protective mechanism" of the body to make available as much iron as possible. In other words, they are due to a deficiency of the erythrocyte maturation factor in the marrow in the presence of excess iron.

The second hypothesis is that the rapid

transportation of iron to the bone marrow resulting in rapid haemoglobin formation in the presence of a relative deficiency of the erythrocyte maturation factor results in an abnormal haemoglobin anabolism.

Since the inclusions were not observed in the marrows when iron and liver were given together and since folic acid therapy was able to reduce the number of inclusions, it would appear that deficiency of the erythrocyte maturation factor plays a definite part in the appearance of these bodies. Cystine and cashydrol were also able to reduce the number of inclusion bodies. Their action was possibly indirect, due to their effect on liver metabolism, but, equally well, they may have in some way provided the necessary protein to combine with the iron of the inclusion bodies and thus form haemoglobin.

Pappenheimer et al (1945) and McFadzean and Davis (1947) have discussed the aetiology of these bodies. The former authors, after extensice studies, proved almost conclusively that they were neither an artefact nor intra-erythrocytic parasites. They suggested that they were probably identical with the siderocytes of Gruneberg (1941), but they were unable to say that they were identical with the siderocytes of Case (1943, 1945,1946), although they often occurred in the same cells. McFadzean and Davis (1947) found similar results and they stated

that their inclusion bodies did not stain with the $\alpha\alpha$ dipyridyl technique of Case (1944) and in their opinion they considered them to be distinct from Pappenheimer bodies. These authors were able to demonstrate an increase in the number of inclusion bodies in cases of acquired haemolytic anaemia after splenectomy. They suggested therefore that the red cell containing inclusion bodies was a defective cell and normally it was eliminated rapidly from the circulation by the spleen; hence the increase after splenectomy. In their opinion the defect lay in the haemoglobinisation, which was usually defective when the inclusion bodies were multiple or large in size. Our results agree in principle with those of the above authors, but would suggest that the defective haemoglobinisation is due to a relative deficiency of the erythrocyte maturation factor.

Since it has been shown that the pink layer consists mainly of young cells, reticulocytes and normoblasts and since inclusion bodies have been shown to occur in young nucleated red cells, whereas the siderocytes of Case (1945) occur in ageing cells, it was decided to stain the pink layer and the bottom layer, which consists mainly of old crenated cells, with $\alpha\alpha$ dipyridyl and potassium ferrocyanide. Five

cases of erythroblastosis foetalis, the first case of haemolytic anaemia and three cases of atypical and typical pernicious anaemia of pregnancy during a reticulocyte crisis were examined.

Considering the results with potassium ferrocyanide first, in the pink layer of blood from babies with erythroblastosis, 12 per cent of the cells contained inclusion bodies, less than one per cent was observed in the cases of pernicious anaemia of pregnancy during the reticulocyte crisis and in the one case of haemolytic anaemia. No iron staining inclusion bodies were seen in the bottom layer.

With $\alpha\alpha$ dipyridyl, however, numerous siderocytes were seen in the bottom layer and these appeared to be increased when the blood was slightly haemolysed. Only a few siderocytes were found in the top layer and again these were observed when the blood was slightly haemolysed. As a result of these findings, the following experiment was carried out:-

5 c.c.s of normal fresh oxalated blood was obtained as before and fresh blood films were made. The blood was then partially haemolysed by putting it in an ice-chest for half an hour, after which it was removed and allowed to warm up to room termperature. Films were made an hour later and again twenty-four hours

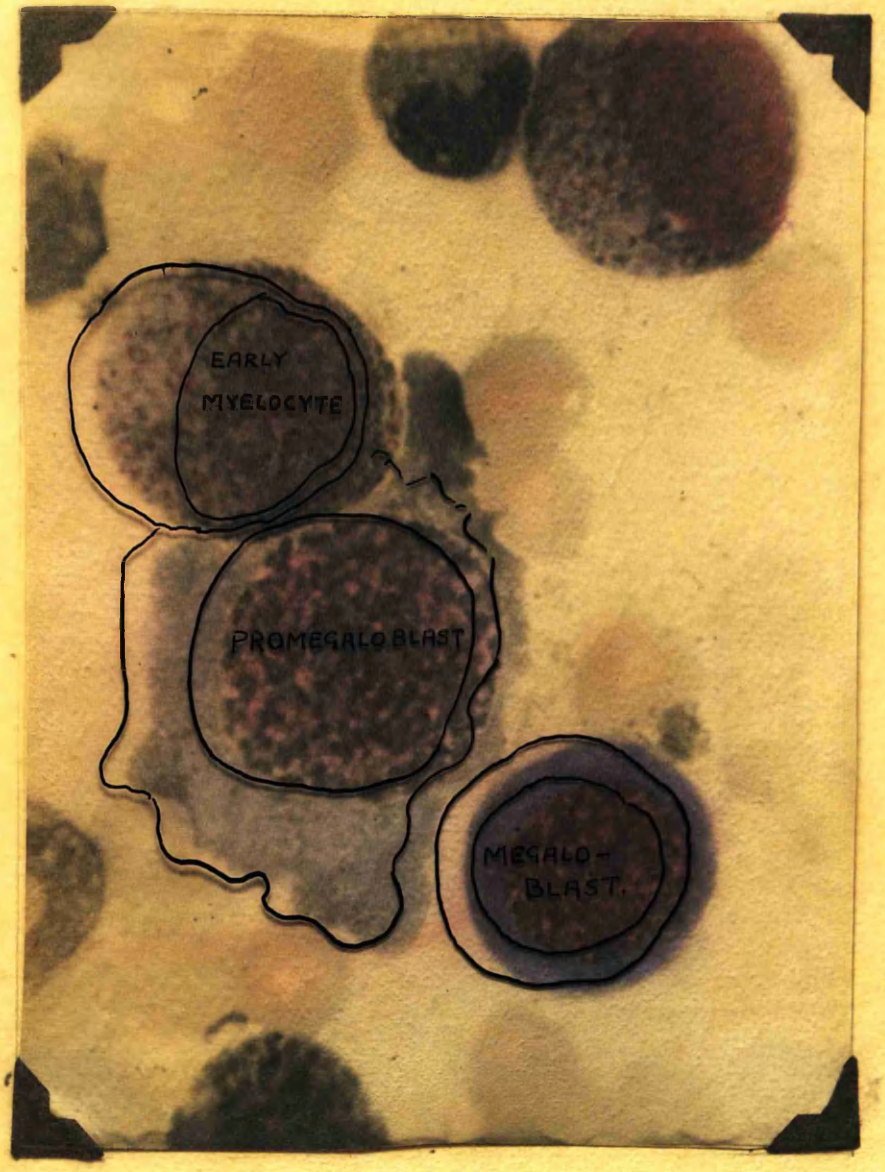
later. Numerous siderocytes, typical of those described by Case (1943) were observed in the films made after twenty-four hours, but were not found in any of the others. With potassium ferrocyanide and hydrochloric acid no inclusion bodies were observed in any of the films. These findings would therefore suggest that haemolysis has a bearing on the appearance of "siderocytes" and that inclusion bodies have a completely separate identity.

Summary:-

(1) 48 patients all with severe anaemia have been followed throughout pregnancy, repeated marrow punctures being performed where possible. A further 74 were seen at regular intervals and biochemical and haematological findings were recorded as for the first group. A remainder of 33 patients with severe anaemia were seen just before delivery and could be followed only in the puerperium. The survey therefore includes 148 patients with severe anaemia.

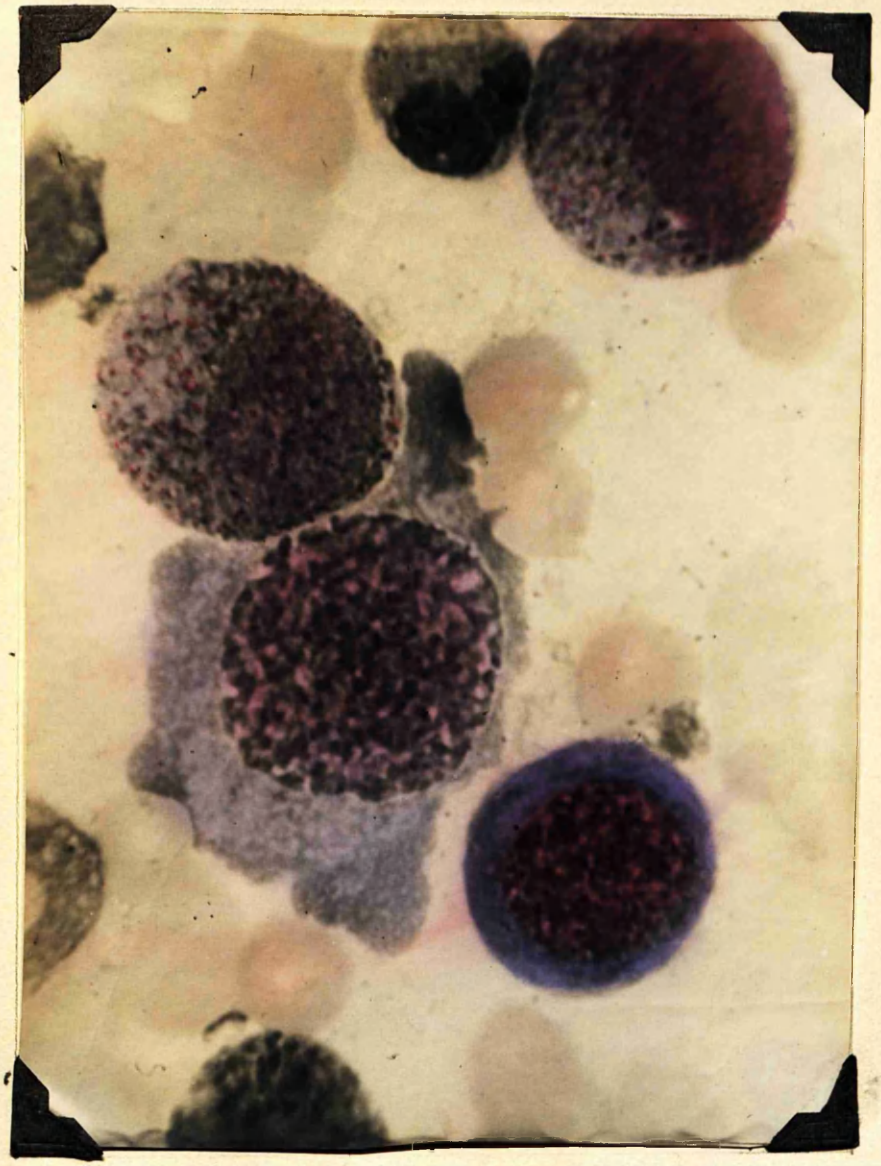
(2) Eight cases of typical pernicious anaemia of pregnancy were diagnosed. Six of these presented the usual blood picture when first seen, but, in two cases, the peripheral blood picture was originally that of a severe iron deficiency anaemia and the features of pernicious anaemia of pregnancy developed only at a later date. The changes in the peripheral blood in

COLOURED PLATE.



Showing a promegaloblast with pale blue cytoplasm and below an early megaloblast.

COLOURED PLATE.



Showing a promegaloblast with pale blue cytoplasm and below an early megaloblast.

all of these cases were similar to those of Addisonian pernicious anaemia, namely - macrocytosis, hyperchromia, anisocytosis, poikilocytosis, a low reticulocyte count and a normal fragility. The plasma proteins were low and, in the two cases, who originally appeared to be severe iron deficiency anaemias, the plasma was jaundiced. Morphologically the marrow was dimorphic, numerous smear cells were present and the degree of haemoglobinisation of the late normoblasts and megaloblasts was marked. The megaloblast percentage was high, the normoblast low, and the percentage of reticulated cells in untreated cases was low. The response to liver and folic acid therapy in these cases has been described and the effect of substituting iron for liver therapy has been observed in the partially treated cases.

(3) Cases of atypical pernicious anaemia of pregnancy are much more common. Altogether 27 cases were proved to belong to this group, 24 by sternal puncture, and 3 by therapeutic tests. Clinically these cases can be divided into three groups, namely anaemias, anaemias and toxaemia characterised by low plasma proteins, and anaemia and jaundice characterised by the development of a sub-clinical jaundice in the course of therapy. The peripheral blood picture in these three groups is

essentially the same and cannot be differentiated from that of the iron deficiency anaemias. An initial diagnosis in these cases depends on the bone marrow picture, which shows approximately 2 per cent megaloblasts and 20 per cent normoblasts. The latter figure, which is intermediate between that of the iron deficiency anaemias and the cases of typical pernicious anaemia of pregnancy, is the more significant. The response to iron therapy is the same in each group. Originally satisfactory, it levels out, giving a typical plateau curve beyond which no improvement will occur on iron therapy alone. The effect of various treatments in each group has been discussed with reference to the aetiological factors and it has so far been found that equally good results were obtained by treating the obvious deficiency as by giving liver or folic acid empirically. The importance of gastro-intestinal upset as a factor in this type of anaemia has been stressed and results in accordance with those noted in previous sections have been obtained.

(4) The remainder of the patients investigated before delivery have been regarded as iron deficiency anaemias. It has been shown, however, that many of these patients may have megaloblasts in their bone marrow and from these findings it has been concluded that megaloblasts

occurring in the marrows of cases with a severe microcytic hypochromic anaemia of pregnancy have not the significance of the megaloblasts seen in the marrows of non-pregnant patients. Instead, the significant feature appears to be the percentage of normoblasts. If this is more than 30 per cent initially, the anaemia will respond satisfactorily to iron therapy, if necessarily after admission to hospital or with the administration of acid hydrochlor. dil. in addition to the iron. The marrow picture in these cases appears to be active, reticulated cells are numerous both before and after iron therapy, and, in the second smear taken when the blood levels are normal, the percentage of megaloblasts has decreased while the normoblasts remain unchanged. Biochemically the plasma proteins are low, but not as low as in the atypical cases of pernicious anaemia of pregnancy. The Van den Bergh is negative and the cases which showed urobilinogenuria originally, clear up as a result of iron therapy.

(5) It has been shown that these three groups of anaemias are not distinct entities but that one may develop into another. However, definite stages have been recognised and the value of marrow biopsy as a guide to prognosis in these cases has been shown.

(6) Two cases of haemolytic anaemia, appearing for

the first time in relation to a pregnancy, have been described. The first would appear to be a case of congenital haemolytic anaemia with a haemolytic crisis occurring as a result of the pregnancy. The second case, which was investigated less fully, appears to be of the acquired type and the findings would suggest that it was a true case of a haemolytic anaemia of the puerperium.

(7) The plasma proteins have been discussed in relation to oedema and haemoglobin production. A fall in plasma proteins has been observed in all cases given iron therapy and it has been suggested that this is a process designed to provide the necessary protein for the increased haemoglobin production. Though the plasma proteins fall far below the "critical level" during treatment, oedema, when present, tended to disappear, and it has been suggested that there is an altered osmotic balance between the plasma and tissues during pregnancy.

(8) Iron staining inclusion bodies were found in the marrow cells of cases of iron deficiency anaemia and pernicious anaemia of pregnancy, typical and atypical, after iron therapy. Morphologically identical bodies have been observed in the peripheral blood of all cases of pernicious anaemia of pregnancy during reticulocyte

crises. They were also found in the peripheral blood of cases of erythroblastosis foetalis and in the marrow and blood of a case of congenital haemolytic anaemia. The inclusion bodies have similar staining reactions to the Pappenheimer bodies, but are distinct from the siderocytes of Case, which would appear to be related to haemolysis, rather than a defect in the haemoglobinisation of the red cell.

(9) Finally, by examination of the pink layer, a method has been devised whereby the nucleated cells in the peripheral blood, observed during a haemolytic crisis or a reticulocyte response in a severe pernicious anaemia of pregnancy, can be scrutinised more easily. By this means, too, the young cells could be pipetted off and specific tests applied where necessary.

In conclusion we would suggest the following classification of the anaemias of pregnancy, which agrees with Elliott (1944) in principle.

I. Deficiency Anaemias.

(1) Iron deficiency anaemia
- a) microcytic hypochromic anaemia with a normoblastic marrow, which responds satisfactorily to iron therapy.
- b) microcytic hypochromic

anaemia in the transitional stage with a marrow showing a relatively high percentage of megaloblasts in addition to a high percentage of normoblasts. This anaemia will respond to iron therapy.

(2). Atypical pernicious anaemia of pregnancy. The blood picture is microcytic hypochromic, but the marrow contains a small percentage of megaloblasts in addition to a relatively low percentage of normoblasts i.e. In this anaemia the iron deficiency is apparent, but there is also a latent deficiency of the "erythrocyte maturation factor".

(3) Typical pernicious anaemia of pregnancy, with a macrocytic hyperchromic blood picture and a marrow showing a high percentage of megaloblasts and a low percentage of normoblasts.

II. Unproved group:-

(1) Acute haemolytic anaemia of pregnancy.

(2) Protein deficiency anaemia of pregnancy.

(3) Vitamin B deficiency anaemia of pregnancy.

III. Anaemia complicated by pregnancy.

IV. Post-haemorrhagic anaemias.

V. Anaemia secondary to other complications e.g. infection toxaemia, leukaemia etc.,

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PROTOCOL I.

CASE No.	EXAM. No.	Blood. Hb.	R.B.C.	P.C.V.	M.C.V.	M.C.H.C.	V.d.B. u.		MARROW. Mgb.	NB.	M.S.	Ret.	R.E.B.	I.B.
CASES RESPONDING TO IRON														
211	1.	25	3.11	24	77	17	0	++	7.7	28.1	49.9	2	.5	-
	2.	57	3.69	43	111	21	0	Tr.	2.7	36.3	43.3	3	.5	++
	3.	74	3.42	39	114	30	0	0	6.0	23.6	55.8	1	.3	++
167	1.	30	3.53	24	68	20	0	+	3.5		61.5	0	0	0
171	1.	30	3.38	25.5	75	19	0	-	5.5	37.7	45.5	3	1	Tr.
	2.	64	4.1	36	38	28	0	0	-	-	-	-	-	-
232	1.	48	3.95	30.5	73	26	0	+++	3.5	30.5	56.25	2	.3	0.
	2.	55	4.31	35	81	25	0	+	2.75	25	60.5	1	.3	0.
CASES SHOWING PARTIAL RESPONSE TO IRON.														
78	1.	36	3.49	27	77	21	0	-	1.5	11	81.5	3.5	.5	Tr.
	2.	51	4.20	33	79	25	0	+	-	-	-	-	-	-
241	1.	41	4.38	31.5	72	21	0	Tr	1.5	30.5	58	.5	0	0
164	1.	43	3.68	30.5	82	22	-	-	4.5	24.5	52	0	0	0
	2.	30	4.05	33	81	24	-	-	-	-	-	-	-	-
124	1.	45	4.39	31	71	23	0	0	-	-	-	-	-	-
	2.	40	3.72	28	75	23	0	-	.7	15.7	75	1.5	.3	Tr.
	3.	63	4.33	38.5	89	26	0	Tr.	2.3	15.3	73	1.3	0	Tr.
214	1.	23	2.71	17.5	65	21	0	-	2.6	16.8	71.0	7	1.5	0 .
	2.	25	3.84	35.5	92	25	0	+	2	11.6	74.4	4	.3	Tr.
252	1.	43	3.32	30.	90	23	0	+	2.3	26.8	64.5	2	.8	0 .
	2.	51	3.52	32.5	91	29	0	0	4.8	28	59	0	0	+ .
195	1.	37	4.06	28.5	70	21	0	Tr.	2		20.5	70	1.5	.3	0.
	2.	45	3.88	29.5	76	24	0	Tr.	-	-	-	-	-	-
MISCELLANEOUS GROUP.														
60.	1.	56	3.05	35	111	29	0	-	6.8	23	58.5	3	.5	Tr.
	2.	55	3.51	34	95	26	-	-	2.6	29.6	49	2	-	+
	3.	51	3.90	32.5	83	25	0	-	3	19	73	1	0	Tr.

202.	1.	38	4.19	27	64	23	-	-	-	-	-	-	-	-
	2.	51	4.86	37.5	77	22	0	0	5	26	55	3.5	1.5	Tr.
69	1.	23	2.63	21	80	17	0	-	2.4	15.7	76.6	4	.3	-
10	1.	65	3.4	33	97	31	-	-	-	-	-	-	-	-
	2.	57	3.37	35	104	26	0	+	0	24.5	67	1.5	.3	0
134	1	37	3.39	26.5	78	22	0	-	1	20.5	77	0	0	Tr.
201	1.	45	3.19	31	97	23	0	Tr.	6.5	39	49	2	0	Tr.
41	1.	44	3.82	32	84	22	0	-	3	37	35	0	0	0
2	1.	48	3.16	32	103	24	0	0	2	25	69	4	1	0
21	1	42	3.3	29	90	23	0	-	2	23	63	.3	.3	0
1.	1.	40	3.39	33	100	19	0	-	0	23	69	.3	.3	Tr.
			Post haemorrhagic group.											
135	1	31	2.64	24	91	21	0	-	3	37	54	7	1.5	0
3	1	29	1.80	18	100	19	-	-	0	30	65	-	-	-
5	1	20	1.19	13.5	113	23	0	-	0	16.5	76.5	-	-	-
89	1	17	1.69	14	83	19	0	-	0	24	73	1	.5	Tr.
7	1	26	2.33	20	87	20.8	0	-	10	25	53	-	-	-
			Typical Pernicious Anaemia.											
145	1	43	1.93	20	103	34	0	-	7	13	59.7	.5	.3	Tr.
	2	25	1.28	18	140	27	0	+++	10	27.3	55.5	7	4	++
	3	47	2.23	-	-	-	-	-	-	-	-	-	-	-
9	1	31	1.63	21.5	132	23	+	-	++	No count.				
	2	39	2.11	25.5	121	21	-	-	-	Fewer megaloblasts.				
131	1	24	2.99	22	74	17	0	-	4	38.7	52.3	9	3	0
	2	53	4.16	30.5	80	26	0	++	5.6	18.6	67.8	5	0	+
45	1	61	5.23	29.5	75	25	0	-	1	14.5	74	1	.3	Tr
237	1	50	2.81	33	117	24	+	++	2.1	17.7	61.8	5	.5	0
11	1	31	1.89	22	116	22	-	-	5	18	72	0	0	0

II Anaemia and Toxaemia.

AL.		Blood. Hb.	R.B.C.	P.C.V.	M.C.V.	M.C.H.C.	V.d.	B. u	Marrow. Mgb.	NB.	M.S.	Ret.	Reb.	LB.
261	1	32	3.31	21.5	65	24	1.0	+++	6	20.2	63	.5	0	0
	2	57	3.92	33.5	85	27	0	Tr	2.8	23.8	59.2	2.5	.5	Tr.
28	1	23	2.54	20.5	82	17.5	0	-	2.5	34.7	48.8	5	.5	Tr.
	2	26	2.85	29	105	14.4	0	-	-	-	-	-	-	-
260	1	34	3.62	23.5	65	23	0	++	2.4	22.3	68.8	1	0	0
	2	54	4.00	34.5	86	25	0	0	2.1	32.0	48.2	8	1.3	Tr.
181	1	23	2.81	19	68	19	0.8	++	1	21.3	68.8	0	0	0
	2	35	3.22	27.5	85	20	0	Tr	-	-	-	-	-	-
236	1	24	3.31	18	54	21	1.0	+++	7.3	33.5	52	0	0	0
	2	35	3.19	28	88	20	0	Tr	4.5	28.5	55.8	6	1.5	Tr.

III Anaemia and Jaundice.

217	1	39	3.69	28.5	77	22	0	0	2.8	17.8	65.6	.5	-	0
	2	48	4.17	36	86	22	0	0	5.4	14.8	65.4	0	-	Tr.
103	1	42	3.5	33	97	23	-	-	-	-	-	-	-	-
	2	37	2.69	25	93	24	2.4	+++	-	-	-	-	-	-
	3	32	2.22	20	90	26	0	+	12.6	11.2	60.4	1.5	.8	++
	4	50	4.26	34	80	24	+	Tr	Jaundice re-appeared when Folic acid given.					
255	1	46	3.99	31.5	79	23	1.2		3.5	28.8	62.5	.5	0	Tr.
	2	67	4.41	42.5	96	25	0	Tr	1.7	18.7	70.7	3.5	.8	+
238	1	33	3.43	23	67	23	1.2	Tr	2.7	25	68.7	0	0	0
156	1	38	3.89	25.5	65	24	1.2	+++	3.4	12.6	75.8	2	0	+
	2	43	2.53	28	111	25	0	++	11.1	27.6	50.7	0	0	++
	3	36	2.4	23	185	28	0	0	8.3	24.3	61.3	3	2	+
	4	47	2.42	29.5	122	25	0	0	-	-	-	-	-	-
245	1	28	3.15	22.5	71	20	0	-	2.8	14.3	59.3	4	.6	0
	2	49	3.05	32	106	24	1.2	Tr	3.3	18.3	66.8	6	3	++
116	1	29	3.15	26	73	17	+	++	6	39.5	45	0	0	0