REVIEW OF THE LITERATURE.

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Most people, whether medical or lay, are aware that anaemia is often found associated with pregnancy or the puerperium, yet this is not the impression one would gain from reading the literature on the subject. The literature itself is scanty, and the total number of cases recorded few.

In 1836, Nasse [59] noted a reduction of red blood corpuscles in the blood of pregnant women, and considered it to be physiological, but Channing [15] 1842, in America, was the first to describe a severe form of pregnancy anaemia. There was no publication of note in this country till 1919 when Osler [60] made his survey, and for several years after that there were relatively few cases recorded. With the introduction of liver therapy in Pernicious Anaemia in 1926 by Minot and Murphy [52,53] a new impetus was given to the study of anaemias in general, and the anaemias of pregnancy and the puerperium were, for the first time, more exhaustively investigated. Since then, much more has been written and our conceptions have changed, and are still changing with regard to etiology, classification and treatment.

The historical review divides itself naturally into two periods, from 1842 till 1926, and from 1926 till the present time.

Channing [15], 1842, recognised that severe anaemia could occur in the pregnant or puerperal woman without haemorrhage. He/

He suggested sepsis and nephritis as etiological factors, and reported ten cases, all ending fatally. Lebert, 1853,(60) Gusserow, (60) 1871 wrote of it and Willcocks,(88) 1881, noted a tendency to the chlorotic state in pregnancy. In 1903 Elder and Mathews (27) and Carton (12) and in 1906 Sondern (71) wrote about it, and Sondern pointed out that pregnant women often became anaemic without the usual causes of anaemia such as tuberculosis, syphilis or nephritis. Jungcmann (45) 1914, described a case of Aplastic Anaemia in pregnancy, and two cases of Pernicious Anaemia with pregnancy were recorded by Finley (30) in 1918.

These were the main contributions to the literature till Osler's 'Observations on the severe anaemias of pregnancy and the post-partum state' in 1919 (60). He gave a classification, stressed the necessity for careful blood examinations, and emphasised the fact that some cases with a pernicious blood picture recovered completely without treatment. He stated that, in Cabot's series of twelve hundred cases of Pernicious Anaemia, thirty five began during or shortly after parturition. In the next few years articles appeared more frequently, but the incidence of the condition, as judged by the literature, was still rare. Gram (35) 1920, recorded results of his examination of fifty nine pregnant women showing a 7% - 10% reduction of haemoglobin content, and considered this to be a 'physiological variation/

variation'. Beckmann [6], 1921, found six cases of severe anaemia in sixty thousand labours, while Esch [28] 1921, noted twenty three cases in the German literature of the previous twenty years, with a 50% - 70% mortality. In 1923 Vermelin and Vigneul [83] wrote of it and described one case, and Gallupe and O'Hara [33] in 1924. Bardy [4] 1924, collected sixty eight cases from the literature of Europe and America during thirty eight years. In the same year Hampson and Shackle [37] reported one 'Pernicious' case, Adler [1] eleven cases and Rowland [65] two. Smith [70] recorded eight cases in 1925 and Larrabee [47] seventeen. In his series, eight patients presented a 'pernicious' blood picture, and seven a 'secondary'. One aplastic case died in spite of treatment and one atypical case (Acholuric Jaundice) recovered after splenectomy. He was the first to stress the value of transfusion. This period gives a general impression that more interest is being taken in the subject.

Stimulated by the recent advances in haematology during the last decade, the study of the anaemias of pregnancy and the puerperium has received more prominence, and the types have more often been reported in classified groups, usually (1) 'Pernicious', Macrocytic, Hyperchromic or Haemolytic Anaemias and (2) 'Secondary' Microcytic, Hypochromic or Chlorotic Anaemias.

I shall deal separately with these two groups.

Included in the first is the tropical nutritional anaemia/

anaemia studied in India by Balfour (3) 1927, in one hundred and fifty cases of pregnancy, McSwiney(58) 1927, in forty three cases, Wills and Mehta (93) 1930, in fifty cases and Mitra (54) 1931, in eighty six. Wills further reported her work in 1930 (94) 1931 (89) 1932, (92) 1933 (90) and 1934 (91) and showed that there is no essential difference between this anaemia and the ordinary tropical macrocytic anaemia due to nutritional causes, as they responded not only to liver therapy, but to the addition of an extrinsic factor to the diet in the form of marmite. Many of the cases were associated with Syphilis.

References to the 'Pernicious' type occurring in temperate zones are still scanty. Hoskin and Ceirog-Cadle, (39) 1927, reported one case; Powell and Davy (62) 1928, one case; Evans (29) 1929, two cases, one of which had free hydrochloric acid in the gastric juice and both of which recovered with liver therapy. He stressed the infrequency of the condition, and stated that in Queen Charlotte Hospital (1926-27) there was not a single case among 4,083 confinements. Thomson (81) 1929 also recorded a case. In 1930 Petersen, Field and Morgan (61) described three cases treated with liver and transfusion. They also noted the presence of free hydrochloric acid. Stewart and Harvey (73) 1931 recorded one case. The patient was treated by/

by transfusion followed by iron, and went to full time. Macleod and Wilson [57] 1932, reported a case of sudden onset at six and a half months which became rapidly moribund and died. The post-mortem findings were suggestive of Pernicious Anaemia, but the bone marrow was not examined. In the same year Whitby [85] described three cases and noted that megalocytosis was not so prominent as in Addisonian Anaemia. Wilkinson [87] reported two cases of 'Pernicious' Anaemia of Pregnancy and three cases claimed to be true Pernicious Anaemia associated with pregnancy. Witts [97] wrote of 'the Haemolytic Anaemia of Pregnancy'. Strauss and Castle [76] issued their first report of their 'Studies of Anaemia of Pregnancy'. This was followed by other reports in that [77] and the next year [78] which described their views of the relationship of dietary deficiency and gastric secretion to blood formation during pregnancy. Six cases of the macrocytic type of anaemia were quoted. In 1933 Jones & Tocantins [43] reviewed the subject, and in 1934 Baron [5] and Studdeford [79] each reported a case. In 1935 reviews were made by Davies [24] and Ionesco and Bonciu [41]. Jules and Masterman [44] described a case as one of the Acute Haemolytic Anaemia of Lederer. The literature of 1936 includes one case by Heilbrun [38] one case by Sage [67] and reviews of the condition by Smallwood [69] and Boycott [9]. In that year I [72] recorded thirty cases of 'Pernicious' Anaemia of Pregnancy and the/

the Puerperium, and these will be described in greater detail.

From the literature a fairly definite conception of this type of anaemia may be obtained, but one is struck by the lack of unanimity.

Most writers are agreed that 'Pernicious' Anaemia of Pregnancy and the Puerperium is rare in temperate zones, Beckmann,(6) Esch, (28) Bardy,(4) Larrabee,(47) Evans, (29) Strauss and Castle (78) and others.

It occurs in women between eighteen and forty four years, Castle (78) between twenty and forty, Smallwood (69) while the Pernicious Anaemia age group is forty to sixty.

The patients are usually multiparae (29) Evans Whitby (85) Wilkinson (87) Castle (78) etc., but Witts (97) finds it more common in primiparae.

Reports of the pathology are scanty, but the findings correspond with those of Pernicious Anaemia, Macleod and Wilson (57). At autopsy there were the general changes due to severe anaemia. The liver and spleen were only slightly enlarged, and there was some free iron in the liver. The marrow was not examined, and no blood count had been done. The sternal bone, in the case investigated by Heilbrun (38) showed megaloblastic reaction at biopsy.

Clinically, there is usually a history of progressive pallor, the development of more acute systoms such as fainting collapse/

collapse and sudden oedema between the sixth and eighth months, Larrabee (47) Evans (29) Whitby (85) etc. Sometimes symptoms are only noted after delivery Osler (60), Petersen Field & Morgan (61) etc. Common features of the condition are nausea, vomiting, slight jaundice, dyspnoea, loud haemic murmurs, progressive oedema, albuminuria and pyrexia. Blood cultures are negative. The spleen is palpable in one third of the cases. Coma may supervene. Glossitis is variously reported as being "absent" Cornell (17) "practically never present" Whitby (85) "not occurring". Smallwood (69) "sometimes present", Wilkinson (87) "usually present", Strauss (75). Powell and Davy (62) report achlorhydria, but free hydrochloric acid is recognised to be usually present Evans (29) Whitby (85) Castle (78) and many others. Strauss and Castle (76), however, have shown that there is a temporary derangement of gastric secretion. Retinal haemorrhages are reported by many, but no other evidence of involvement of the nervous system is found. Premature labour tends to occur.

Haematologically, this anaemia is described as hyperchromic and macrocytic, Cornell (17), Evans (29), Castle (78) etc. It is one "which judged by the strictest standards is indistinguishable from Pernicious Anaemia". Davidson & Gulland (22) "quite similar to or identical with Addisonian Anaemia" Rowland (66); "from the haematological standpoint is indis-

tinguishable/

indistinguishable from true Pernicious Anaemia" Whitby and Britton [84] Witts [97] finds the Price-Jones Curve shifted to the right. Cornell [17], Evans [29], Wilkinson [87] and others detail variations from the classical Addisonian picture e.g. absence of true megalocytosis, normal leucocyte count or moderate leucocytosis, only slight reduction of platelets and frequent occurrence of nucleated red cells.

Recorded clinical findings with regard to haemolysis are variable. Cornell [17] states that there is increased fragility of the red blood corpuscles, while Evans [29] and others do not find it. Witts [97] notes increased fragility before delivery and normal after it. The Van den Bergh Reaction is usually a slight indirect positive, but according to Witts [97] there is a definite indirect positive in acute cases. The icteric indices are either normal or slightly increased. Strauss and Castle [78].

The Wassermann Reaction is practically always negative.

The condition responds well to suitable therapy - liver or desiccated hog's stomach with or without initial transfusion according to severity. Reticulocytosis develops, but there is no definite statement as to the common time of its occurrence or the height of the peak reached. Patients remain well without continued administration of specific substance after the blood count has reached normal levels, Whitby [85], Rowland [66] etc. Recurrencies in subsequent pregnancies are considered/

considered unlikely by Larrabee (47), but Reist (63), Evans (29) Whitby (85) etc. quote cases illustrating that this does occur.

Mortality rates of untreated cases varied from 30% - 87% before the introduction of transfusion, but after that the outlook was changed. Larrabee (47) states that among his eight cases of the 'pernicious' type, of four cases not transfused three died, and the other four recovered. After the introduction of transfusion 90% of the patients were cured Wilkinson (87). Since liver and stomach therapy have been used, the prognosis is very good, but in many acute cases and some chronic ones, transfusion must be supplemented, Whitby (85) Smallwood (69) etc. Untreated cases may occasionally so exhaust the haematopoietic tissues that they pass into a hypoplastic or aplastic state, Whitby and Britton (84).

As regards the foetus there is considerable difference of opinion. Aubertin (2) 1923 gives a foetal mortality of about 80%, and states that many infants are under weight and under developed. Whitby (85) 1932 states that many of the children are very feeble, but that there is a reasonable prospect of a living child. Rowland (66) 1933 says that a highly anaemic mother may and usually does bear a child with normal blood, and this is the main impression formed as a result of recent therapeutic advances.

This anaemia appears, therefore, to be allied to Addisonian/

Addisonian Anaemia and possibly due to similar etiological factors which are, however, only temporary in their effects. The variation of descriptions could be explained by the small numbers of cases reported by individual observers.

During the last decade the 'Secondary' Microcytic, Hypochromic, Chlorotic Anaemia of Pregnancy has also received much more attention. The work of Witts (95) (96) (97), Davies (23) and others on Hypochromic Anaemia gave a further incentive.

Among the more important articles were those of Lyon (48) and Galloway (32) in 1929. Lyon found that 32.2% of two hundred pregnant women observed developed anaemia with Hb below 70% by the time of delivery. Galloway studied three hundred and twenty eight patients in some of which the anaemia was severe. In 1930 Moore (55) reported on three hundred cases, Strauss (74) on three, and Bland Goldstein and First (8) on three hundred pregnant women, 72% of whom had a haemoglobin content of 74% or less. Ivy, Morgan and Farrell (42) 1931 advocated the use of large quantities of iron. Mussey, Watkins and Kilroe (56) 1932, recorded eighty two cases, and noted that distinct improvement followed the administration of large doses of iron salts. Thirty of the thirty six cases of Castle and Strauss (78) 1933 were of this type, and Jones and Tocantins (43) mentioned a few illustrative cases in their survey/

survey of the anaemias of pregnancy in that year. In 1934 Kersley and Mitchell [46] reviewed the condition and described three cases and Gibson [34] one case. Boycott [9] Corrigan and Strauss [18] Smallwood [69] and Fullerton [31] 1936 all give critical analyses, and Fullerton reports on his investigation of eleven hundred and sixty six women.

The large number of cases recorded by individual workers emphasises the fact that this is a much more common form of anaemia than that just described. The average age of onset is thirty-two and the patients are usually multiparae. A lack of sense of wellbeing tends to develop at mid-pregnancy, and is followed by progressive exhaustion and pallor. This may be gradual and well tolerated, but after delivery the patient may collapse. In the more severe cases, dyspnoea and oedema often develop. Splenomegaly is sometimes found. Dyspepsia does not appear to be common. Atrophic glossitis was observed in two cases by Strauss [74] but Smallwood [69] stated that it was rarely seen. Brittleness of the nails is sometimes present. Achlorhydria or hypochlorhydria are the usual findings. Of twenty-nine cases analysed by Strauss and Castle [78] seventeen showed achlorhydria, ten hypochlorhydria and two normal gastric acidity. Premature labour is rather common.

The blood picture shows a hypochromic, microcytic anaemia of varying degrees from slight to severe. The haemoglobin is/

is always below 70%. The red cells show moderate anisocytosis, and the Price-Jones Curve a shift to the left. "Leucocytes and platelets are unaffected", Whitby and Britton (84). "Leucocytes and platelets are normal or increased, and there is sometimes a relative polymorphonuclear leucocytosis" Strauss and Castle (78).

The majority of cases respond well to adequate iron therapy, both during and after delivery. Transfusion is only required in exceptional cases. Treatment may usually be discontinued after the blood count has reached normal, though a few cases manifest the features of Idiopathic Hypochromic Anaemia and require continued iron therapy.

Though the mortality is negligible the maternal morbidity is increased in untreated cases. "The foetal mortality rate is higher" Smallwood (69). "The foetus itself is born with a normal blood count," Whitby and Britton (84).

This anaemia, therefore, corresponds haematologically to Idiopathic Hypochromic Anaemia. It first manifests itself during pregnancy, and, though achlorhydria is not constant, it simulates it clinically. The iron deficiency is in most cases temporary. It is sometimes difficult to separate the two anaemias as pregnancy may increase an existing Idiopathic Hypochromic Anaemia, or be the starting point of it.

These two anaemias, the Macrocytic Hyperchromic, and the/

~~the Macrocytic Hyperchromic~~, and the Microcytic Hypochromic have been described, as they are the outstanding types in the literature reviewed. Deficiency of factors essential for the normal maturation of the red blood corpuscles appear to be the main cause of their development. The anaemias of known etiology e.g. those due to haemorrhage, nephritis, puerperal sepsis etc., account for a relatively small proportion Strauss (75).

One must bear in mind that pregnancy may be superimposed on an already existing anaemia. This will be discussed later. It is also generally accepted Nasse (59) Galloway (32), Dieckmann & Wegner (26), Bethell (7) etc., that during pregnancy there is an increased blood volume, both plasma and cells and haemoglobin contributing, the plasma increase being greater. The haemoglobin may be reduced by 15% roughly to 70%, but the total circulating haemoglobin and red cells are actually increased. This allows of adequate gaseous exchange between mother and foetus, and considerable loss of blood volume at confinement with conservation of haemoglobin. Re-adjustments of blood volume occur during the puerperium, and this 'physiological anaemia' is 'cured'.

The main classifications as recorded in the literature are the following:-

Osler (60) 1919.

1./

1. Anaemia from Post-partum Haemorrhage (a) Rapidly fatal.

(b) Following repeated small haemorrhages.

2. The Severe Anaemia of Pregnancy.

3. Post-partum Anaemia.

4. The Acute Anaemia of Post-partum Sepsis.

Larabee [47] 1925.

1. Anaemia with Secondary Blood Picture.

2. Anaemia with Pernicious Blood Picture.

3. Anaemia with Aplastic Blood Picture.

4. Anaemia with Atypical Blood Picture.

Whitby [85] 1932.

1. Pernicious Type:
   - Plastic — High Colour index with definite megalocytosis and signs of blood regeneration.
   - Hypoplastic / Aplastic — High colour index and slight megalocytosis or normocytosis and no evidence of blood regeneration.

2. Iron Deficient or Chlorotic Type: Low colour index and no megalocytosis.

3. Atypical: Dependent on primary blood disease.

Rowland [66] 1933.

1. The Pernicious or Hyperchromic Form.

2. The Secondary or Hypochromic Form.

Kersley and Mitchell [46] 1934.

1. The common microcytic type.

2./

2. The rarer megalocytic or pernicious type.

3. Anaemia due to haemorrhage.

4. Anaemia due to haemolysis following sepsis.

5. The rare acute idiopathic haemolytic anaemia of pregnancy.

Whitby and Britton [84] 1935.

1. Hypochromic Anaemias.

   (a) Idiopathic hypochromic anaemia complicated by pregnancy.
   (b) Hypochromic anaemia induced by pregnancy.

2. Macrocytic Anaemias.

   (a) Macrocytic anaemia complicated by pregnancy.
   (b) Macrocytic anaemia induced by pregnancy.

3. Hypoplastic Anaemia.

4. Haemolytic Anaemias.

   Acute haemolytic anaemia of Lederer.

5. Secondary Anaemia complicated by pregnancy:

   e.g. Streptococcal and Staphylococcal septicaemia, malignant disease, leukaemia, nephritis, haemolytic icterus, hookworm infection, malaria, syphilis.

Smallwood [69] 1936.

A. Physiological Anaemia of Pregnancy - Hydraemia.

B. Deficiency or Anhaematopoietic Anaemia.

   1. Deficiency of Iron (microcytic hypochromic anaemia).

      (a) Hypochromic anaemia induced by pregnancy.

      (b) Idiopathic hypochromic (Witt's) anaemia, complicated or precipitated by pregnancy.

   2. Deficiency of Liver Factor (macrocytic anaemia)

      (a) Deficiency/

(a) Deficiency of extrinsic factor. Tropical macrocytic anaemia, complicated or induced by pregnancy.

(b) Deficiency of intrinsic factor. (i) True Addisonian pernicious anaemia complicated or precipitated by pregnancy; (ii) Pseudo-pernicious anaemia of pregnancy.

C. Erythronoclastic (Haemolytic) Anaemia.

1. Plastic.

2. Hypoplastic.

3. Aplastic.

D. Post-haemorrhagic Anaemia.

1. Ante-partum haemorrhage.

2. Post-partum haemorrhage.

E. The Anaemia of Puerperal Sepsis.

F. Other Anaemias Complicated by Pregnancy.

Streptococcal and staphylococcal septicaemia, malignant disease, leukaemia, nephritis, familial haemolytic icterus, malaria etc.

A STUDY OF 100 CASES OF ANAEMIA IN PREGNANCY AND THE PUERPERIUM.

I N T R O D U C T I O N.

The present investigation began in 1928, when a test was being made of the value of various forms of liver extract in the treatment of Pernicious Anaemia. I was struck by the rapid response to treatment on the part of certain patients whose 'Pernicious Anaemia' appeared to date from a pregnancy, and by the frequency with which women in the Out-Patient Department dated the onset of anaemia and debility from a past pregnancy - a frequency which was greater than one would expect from the literature on the subject. I decided to study a number of cases to determine if the impression gained with regard to frequency was correct, and, if so, to look for any common factors which might indicate an etiology, and a possible line of treatment or even prevention.

The work was done in the wards of Professor Harrington and Professor Hendry, and, in the Out-Patient Department of the Glasgow Royal Infirmary, and in the wards of Professor Cameron, Professor Hendry and Professor Munro Kerr in the Glasgow Royal Maternity Hospital.

I observed one hundred cases of Anaemia. All but two patients (Cases 9,22) were of the hospital class.

Clinical and haematological examinations were made, and response to different forms of treatment noted. In addition blood examinations were carried out on four cases of Hyperemesis Gravidarum, four cases of Eclampsia, five normal pregnant women in/

in the eighth and ninth month and five normal patients in the first week of the puerperium. Thoma ruling was used when counting the red and white cells, and the haemoglobin estimations were made with Haldane standards. The blood films were stained with Leishman's stain, and cresyl blue was used to demonstrate reticulocytes. The red cells were measured with an eye piece micrometer and Price-Jones curves were charted. The effect of exercise and diurnal variations were not considered, because tests were made with the patients at rest and during the day. Under the supervision of Dr. Robert Cruickshank a bacteriological examination of the resting gastric juice was made in a hundred patients, twenty four of whom were suffering from Anaemia of Pregnancy or the Puerperium. Autopsy was performed on one case which died (Case 19). Haemalum and eosin were employed for staining the sections obtained at this examination. Details of the cases investigated are recorded in Volumes 2 and 3.

At this stage I shall deal with my cases under the headings 'Pernicious' and 'Secondary'. Thirty cases belong to the first group, and seventy to the second. These figures give no indication of comparative frequency of the two types, as more attention has been directed to the first group. An analysis of the findings in these cases will be made, and compared with the accepted findings already given. As in the previous part I shall deal first with the 'Pernicious' type.

THIRTY CASES OF 'PERNICIOUS' ANAEMIA IN PREGNANCY AND THE PUERPERIUM.

I. THE 'PERNICIOUS TYPE.

In this series of thirty cases collected during the last nine years:

Fourteen were examined in the Glasgow Royal Infirmary.

(14 in Professor Harrington's Wards (Cases 1, 2,3,4,5,6,23,24,25,26,27,28,29,30).
1 was seen first in Professor Hendry's wards) (Case 6).

Ten were examined in the Glasgow Royal Maternity Hospital

(2 in Professor Cameron's wards (Cases 13,20)
6 in Professor Hendry's Wards (Cases 7,12,14, 19,21,22)
2 in Professor Munro Kerr's Wards (Cases 15, 17).

Five were examined as out-patients at Glasgow Royal Infirmary (Cases 8, 10, 11, 16, 18).

One was examined at a private consultation by Professor Harrington (Case 9).

Five cases were first seen during pregnancy (Cases 6, 12, 19, 21,22)

Twenty five cases were first seen after delivery (Cases 1,2,3,4,5, 7,8,9,10,11,13,14,15,16,17,18,20,23,24,25,26,27,28,29, 30).

Age: The ages varied from twenty one (Case 15) to forty four years (Case 11), the average being thirty three years, and half the number were between thirty and thirty five years. (Cases 4,6,7,8,10,12,16,17,22,24,25,26,27,28,30). The age incidence was earlier than in thirty seven cases of true Pernicious Anaemia affecting female patients seen in Professor Harrington's wards during the last nine years. The age group in them was from twenty six to seventy years, but the average was fifty/

fifty one years.

The Number of Pregnancies: In all but three cases (Cases 15,20,25) the patients were multiparae, the average number of pregnancies being five. Twin pregnancy was associated with this anaemia in two patients. Symptoms became acute during pregnancy in one of the patients (Case 21). The anaemia ran a more chronic course in the other (Case 11) and she was first seen five months after delivery.

Previous Health: Most of these patients were in good health prior to the onset of the anaemia. Four patients (Cases 6,20,29,30) stated that they had always been pale but had been able to lead quite normal lives without symptoms. One patient (Case 22) had had Rheumatic Fever twice in her youth, and suffered from Chronic Valvular Disease of the Heart. One (Case 19) had been subject to seizures suggestive of Petit Mal for two years.

With regard to their previous obstetrical histories nine patients (Cases 1,2,3,5,7,10,19,24,27) stated that there had been no abnormalities. Three others were primiparae, and in one (Case 9) no details were obtained. Among the remaining seventeen patients, single miscarriage had occurred in four cases (Cases 6,8,21,26) and two miscarriages in Case 11. There had been a previous still-birth in case 12 and two in case 18. Case 12 had had three breech births. Nephritis had complicated/

complicated the other pregnancy of Case 22, and Case 29 had developed oedema of the legs in the last month of each pregnancy. Excessive vomiting was present throughout the whole period of each gestation in Case 30.

Puerperal Fever had followed the last delivery in two patients. (Cases 14, 28) and Phlegmasia Alba Dolens after the last child in two (Cases 22,23). Case 13 had had a 'chill with jaundice' after her other child was born, but had made a good recovery.

Patients were questioned with regard to haemorrhage associated with previous pregnancies. Case 17, had been pale since an ante-partum haemorrhage with her fifth child twenty months before. Case 4 had had a severe post-partum haemorrhage after her fifth child six years previously, and recovered satisfactorily. Case 18 had had a post-partum haemorrhage after her eighth child. Case 28 had had a post-partum haemorrhage after her second, eight years before, and had not felt really well since.

Family History: There was no family history of anaemia associated with pregnancy, but in two cases (Case 3,24) a sister had suffered from severe anaemia, and one of these had been treated successfully with liver (Case 24).

Social Conditions: Twenty of the patients were in very poor circumstances. In eight, conditions were fairly satisfactory (Cases 2,3,4,6,13,15,25,29). In Cases 9 and 22 the patients were not/

not of the hospital class. As far as could be ascertained, nuitrition in all but these last two cases was inadequate.

Symptoms: Symptoms of anaemia usually developed between the sixth and the eighth month of pregnancy. This was the time on onset in seventeen cases (Cases, 2,3,4,5,6,9,13, 14,19,20,21,23,25,27,28,29,30). In five patients (Cases 8,11, 15,17,24) symptoms were present during the whole period of gestation, and in four (Cases 7,10,16,22) they began between the third and the sixth month. In one case (Case 3) they followed a miscarriage at three months, and in three (Cases 10, 18,26) they first appeared immediately after delivery at full time.

The mode of onset varied. Usually it was insidious, but less so than in true Pernicious Anaemia. Sometimes the symptoms were slight for several weeks, and then became rapidly worse either shortly before or shortly after delivery (Cases 2, 4,7,12,13,14,17,26). In two cases (20,21) the onset was dramatic in its suddenness with collapse and development of oedema within a few hours. In ten cases several months elapsed before symptoms became sufficiently severe for the patients to seek medical aid (Cases 1, 3, 8, 10, 11, 16, 18, 24, 28, 30) and in one case (Case 23) the interval extended to two years after delivery, during the whole of which period the patient had symptoms of anaemia.

Progressive pallor was usually noticed by patients and friends/

friends, and in four cases (Cases 4,6,24,29) 'jaundice' was observed. Weakness, faintness, and breathlessness were common complaints. Vomiting was often present and was excessive in eleven cases (Cases, 3,7,8,12,13,15,19,22,24,25,30). Sore tongue was complained of by seven patients (Cases 1,3,5,10,12,20,23). There was no history of constipation and diarrhoea was present in only one case (Case 10). Swelling of the feet and legs was a feature in nine cases (Cases 5,6,9,20,21,22,27,28,29). One patient (Case 3) complained of tingling in the limbs. There were no other symptoms referable to disease of the central or peripheral nervous systems. Three patients (Cases 1,10,22) stated that they had lost weight in the course of the illness. In case 1 the loss of weight was noted in the five months after delivery when she had a very painful glossitis and much bilious vomiting. In case 10 it again occurred ~~in~~ after delivery when 'soreness of the mouth' and diarrhoea were accompanying symptoms. Case 22 became progressively thinner in the last five months of pregnancy when vomiting and anorexia were very troublesome.

Special attention was paid to the possible relationship of haemorrhage to the development of symptoms. Ante-partum haemorrhage occurred in three patients (Cases 7,17,23). In Cases 7 and 17, it aggravated the severity of the anaemia already established; in Case 23 it was the starting point of symptoms. Postpartum haemorrhage took place in two cases (Cases 2,28), and in each caused increase of symptoms which had been present for/

for a few months. Haemorrhage, following a miscarriage at three months in Case 3, apparently marked the beginning of the illness. Epistaxis occurred five months after delivery in Case 1, and two weeks after delivery in Case 29, and in each appeared to aggravate the symptoms of anaemia.

Examination.

General: The general physical signs were those of a severe anaemia, - intense pallor of the skin and mucous membranes, asthenia, haemic murmurs etc. - but certain features were of interest.

Nutrition: Although the majority of cases were gravely ill there was no great wasting. Six, however, were thin (Cases 1, 5, 10, 17, 22, 27). Only cases 11 and 22 had complained of loss of weight. Case 5 had a chest condition suggestive of tuberculosis. Case 17 had been previously debilitated. Case 27 had had anorexia for several months.

The Skin: Icteric tingeing of the skin was noted in twenty four patients (Cases 1,2,3,4,6,7,10,12,13,14,15,17,18,19, 20,21,22,23,24,26,27,28,29,30), and of the sclerotics in eighteen (Cases, 2,3,4,6,7,12,13,14,15,17,18,19,21,23,24,26,29,30). Brownish pigmentation of the skin of the face, chest and upper limbs were seen in only four cases (Cases 6,24,27,30). One patient (Case 1) had a purpuric eruption on her legs, and recent epistaxis had occurred in this case.

Oedema: Oedema was present in eight cases (Cases/

(Cases 9,14,19,20,21,22,29,30). In cases, 9 and 21 it was gross and widespread. In Case 21 it was associated with albuninuria and high blood pressure.

Pyrexia: Pyrexia occurred in nineteen cases (Cases 1, 4,6,7,12,13,14,17,19,20,21,22,24,25,26,27,28,29,30). It was usually mild and irregular, but sometimes it was of greater degree, as in Cases 23,24,29. In case 14, the combination of pyrexia and considerable leucocytosis during the first week of the puerperium led to a tentative diagnosis of pelvic sepsis. In only one case (Case 4) could the pyrexia be attributed to sepsis. The patient had a mild pyrexia followed by a further rise of temperature with the development of Phlegmasia Alba Dolens.

The Mouth: Though only seven patients had complained of 'sore tongue' there were definite signs of glossitis in fifteen patients (Cases 1,2,3,5,6,8,10,12,13,14,20,23,24,25,30) and fissuring in other two (Cases 17,18). Dental sepsis was present in ten cases (Cases 2,3,6,7,12,14,16,17,23,26). It is seen from the figures that these did not necessarily occur together. One case (Case 8) had chronic tonsillitis.

Abdomen: There was moderate enlargement of the spleen in 15 cases (Cases 1,2,3,6,12,13,14,18,19,20,22,27,28, 29,30) and of the liver in six (Cases 1,12,13,17,19,30). In another patient (Case 28) there was great enlargement of the liver which extended down to the level of the umbilicus.

Under/

under treatment it returned to normal dimensions.

Gastric Analysis: Of nineteen cases in which fractional gastric analysis was performed free hydrochloric acid was absent in three (Cases 5,6,24); a trace was present in six (Cases 1,2,7,13,14,23); it was present in normal amount in seven (Cases 15,17,20,26,27,28,30); it was copious in three (Cases 4,12,25). Excess of mucus was constantly found, even when the free hydrochloric acid was abundant.

Bacteriological examination of the resting gastric juice was carried out in sixteen cases (Table in Vol.) (Cases 1,2,3,4,5,6,7,12,13,17,23,24,25,26,27,30). There was usually an abundant flora, but no haemolytic streptococcus or other specific organism was isolated. The amount of growth on culture appeared to be related to the quantity of free hydrochloric acid present.

Nervous System: Retinal haemorrhages were seen in twelve out of 22 cases examined (Cases 1,3,6,20,21,24,25,26,27, 28,29,30).

There was no other evidence of involvement of the Nervous System except the findings noted in Case 3 and there the possibility of true Pernicious Anaemia has not been disproved.

Urine: The urine contained a trace of albumen (non-catheter specimens) in 5 cases, (Cases 2,20,22,23,27) and abundant albumen in two (Cases 6,15,21). In cases 15 and 21 it was associated with raised blood pressure.

Urobilinogen/

Urobilinogen in slight excess was found in ten cases (Cases 2,14,15,17,18,19,20,21,22,23). Cases 20 and 21 were relatively acute; cases 18 and 23 were relatively chronic; the others belonged to the 'average' group. It was abundant in one case (Case 3), probably one of Pernicious Anaemia.

Indican was present in one case (Case 5). Tuberculosis of the lungs was suspected in this patient, but repeated X-ray examination of the lungs and bacteriological examination of the sputum were negative.

Case 19 had much acetone in the urine associated with excessive vomiting.

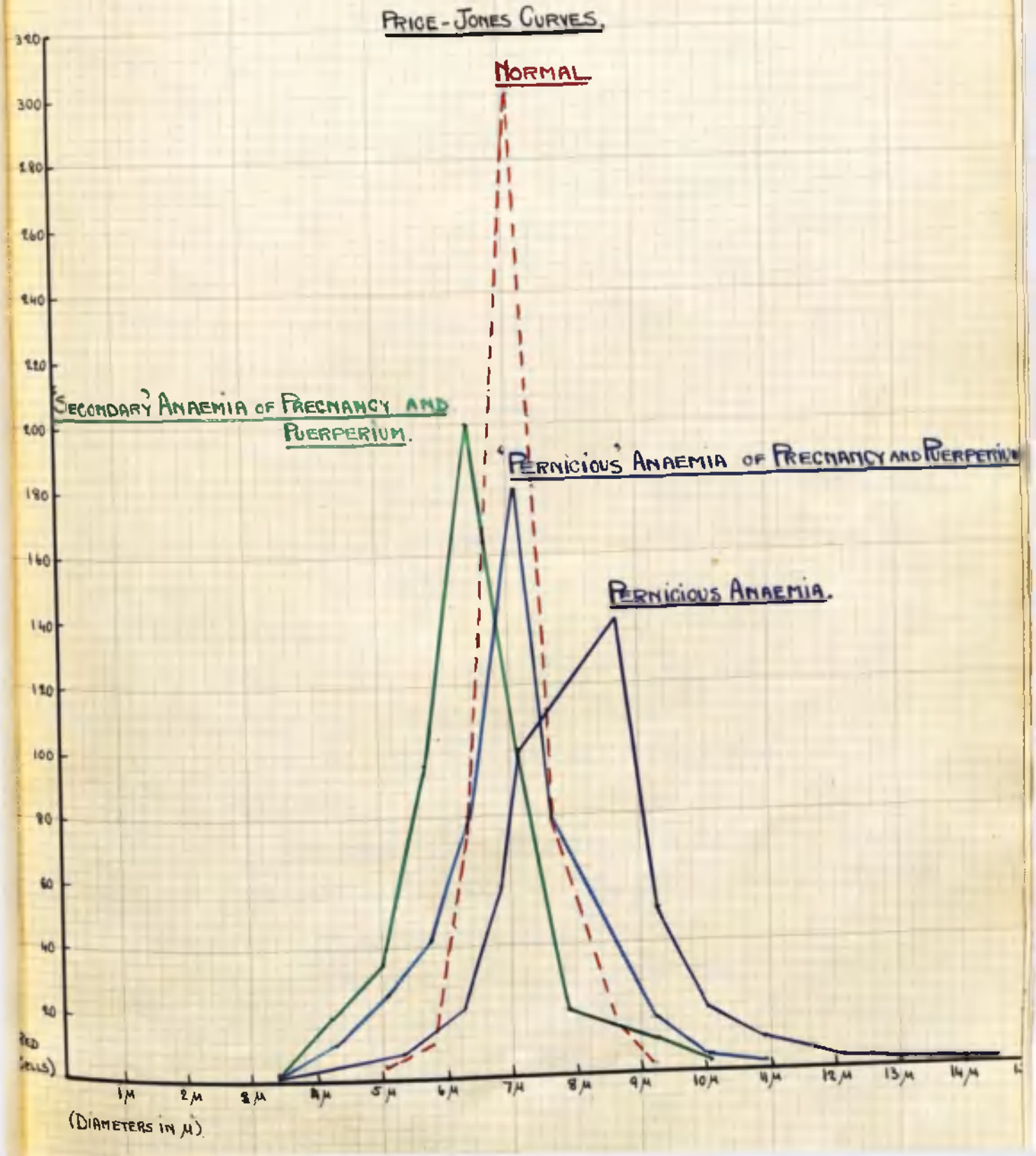
The Blood Examination: The Wassermann Reaction was negative in all the twenty five cases tested (Cases 1,2,3,4, 5,6,7,12,13,14,15,16,17,19,20,21,22,23,24,25,26,27,28,29,30).

The indirect Van den Bergh reaction was tested in twelve patients (Cases 1,2,3,4,6,7,23,24,25,26,27,29). In case 23, a very chronic case, the reading was 2·4 units of bilirubin, but in all the others it gave only a slightly positive reaction. In four cases examined quantitatively the figures were .4 units, ·5 units, 1 unit, and 1·2 units.

The blood fragility was estimated in four cases. In cases 4 and 14, it was normal, and in Cases 13 and 22 slightly decreased.

The main features of the blood picture in untreated cases were there.

There/


PRICE-JONES CURVES.
NORMAL.
SECONDARY ANAEMIA OF PREGNANCY AND PUERPERIUM.
'PERNICIOUS' ANAEMIA OF PREGNANCY AND PUERPERIUM.
PERNICIOUS ANAEMIA.
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
1μ
2μ
3μ
4μ
5μ
6μ
7μ
8μ
9μ
10μ
11μ
12μ
13μ
14μ
(DIAMETERS IN μ)

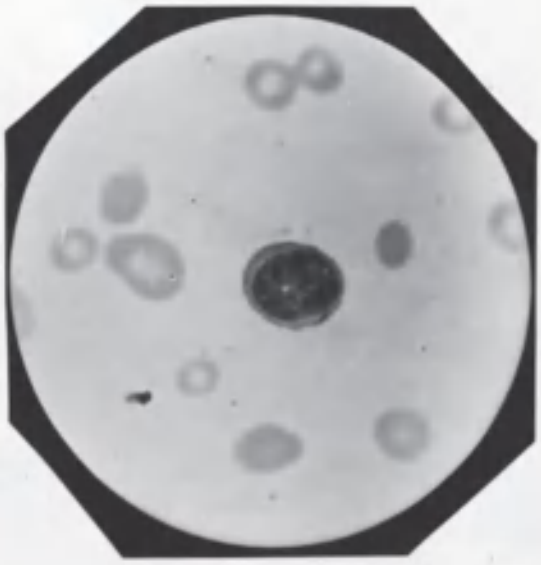
There was usually great reduction of the red blood corpuscles. Of twenty nine cases examined the red blood cell count was under 1,500,000 per c.mm. in fourteen cases (Cases 1, 3,4,12,13,17,19,23,24,25,26,27,28,30) and under 2,000,000 per c.mm. in eight (Cases 2,7,8,14,18,20,21,29). The haemoglobin was also greatly reduced but the average corpuscular content was about normal. The colour index was above unity in seventeen Cases (Cases 1,2,3,5,12,14,15,18,19,21,24,25,26,27,28,29,30) unity in seven cases, (Cases 6,8,10,11,13,16,23) and below unity in five cases (Cases 4,7,17,20,22). In the last group only case 7 was associated with haemorrhage.

Stained blood films showed well stained corpuscles, anisocytosis and many megalocytes, and closely resembled smears of cases of Pernicious Anaemia. On measurement, however, the average red cell diameter was seldom increased. This occurred in six cases (Cases 3,8,24,25,26,28). In Cases 3,5 it was 7.68 μ. 7.64 μ but the others did not exceed 7.42 μ. In six cases (Cases 6, 7,9,17,22,29) it was decreased, the lowest measurement being 6.44 μ. In the remaining 18 cases the average diameters varied from 7·01 to 7·21 μ.

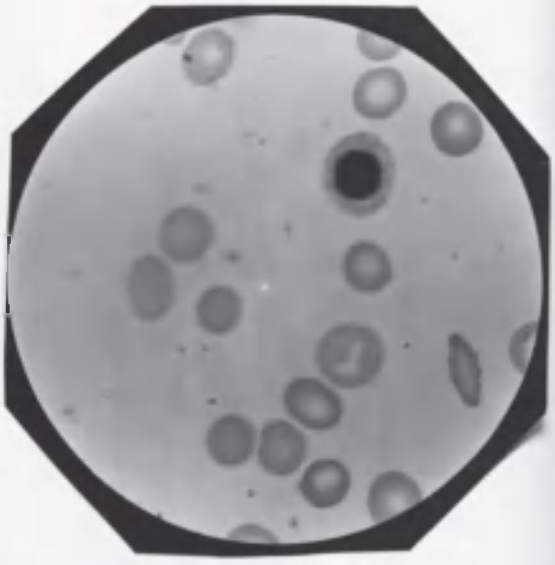
Price-Jones curves were charted in the thirty cases. They all showed broadening of the base, but a shift of the peak to the right or left was uncommon.

Polychromasia was a very prominent feature, but poikilocytosis was not striking except in a few chronic cases (Case/

Nucleated Red Cells and Young Granular White Cells.

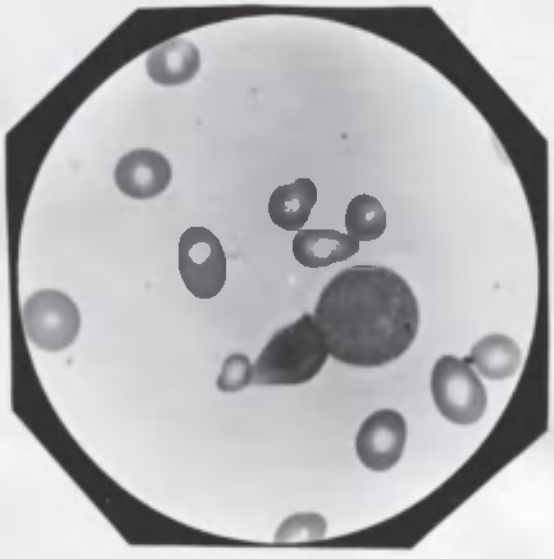


Mecaloblast - Case 13.

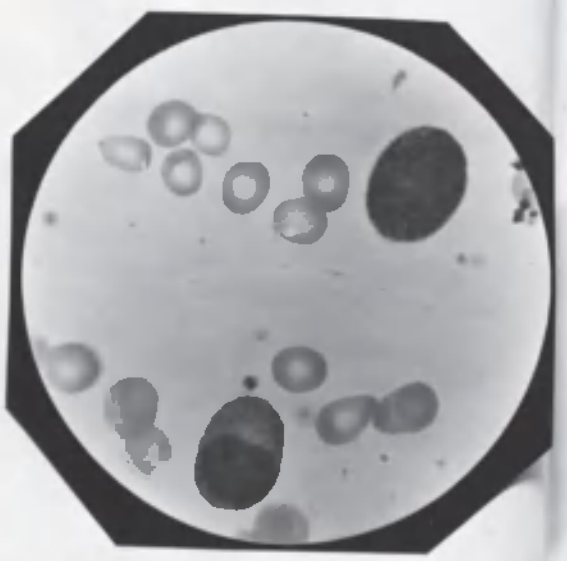


Normoblast - Case 19.

(x 1000)



Normoblast + Myelocyte
Case 18.

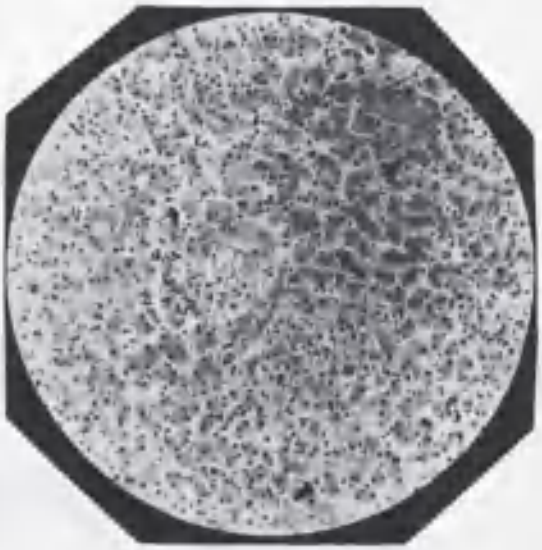


Myelocytes - Case 13.

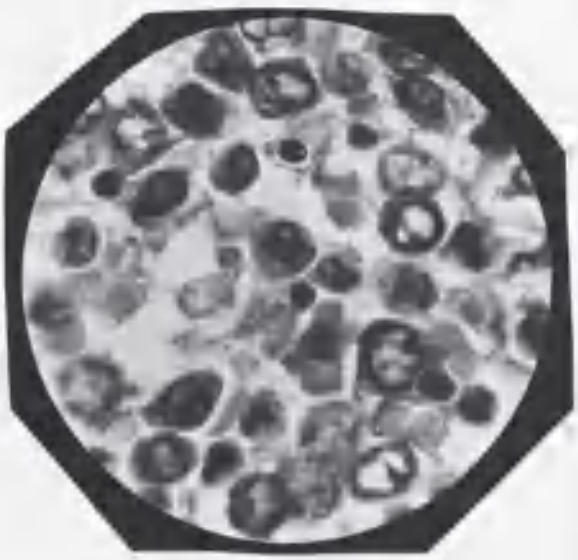
(Case 1,3,5,23,24). The reticulocyte count was often slightly increased (Cases 2,3,20,21,22,23,27,28,30). Nucleated red cells, normoblasts, erythroblasts, and megaloblasts were common (Cases 1, 2,3,4,9,12,13,17,19,20,21,22,23,25,26,27,28,29,30). In Cases 1, 2,9,13,21,27 and 29 they were abundant, varying from 9 to 19 per 200 white cells counted. Nuclear remnants were seen in Cases 13, 14,27.

Leucocytosis occurred in 7 cases (Cases 6,7,8,14,15, 20,21), a normal leucocyte count (5000-9000 per c.mm.) in 14 cases, (Cases 2,4,5,10,11,12,13,16,17,19,23,25,27,29) and a leucopenia in 8 cases (Cases 1,3,18,22,24,26,28,30). In seven cases there was a relative increase in the number of cells of the granular series (Cases 4,7,8,12,20,21,22), in eleven cases (Cases 2, 5,11,13,14,15,17,18,23,25,27) a normal proportion of granular and non-granular leucocytes, and in twelve cases (Cases 1,3,6,9,10, 16,19,24,26,28,29,30) a relative increase of lymphocytes. The more acute cases often showed a polymorphonuclear leucocytosis, e.g. cases 20 and 21, and the more chronic ones e.g. cases 1 and 24, a leucopenia with a relative lymphocytosis, but these findings were not constant. The appearance of some of the younger cells of the granular series was a common finding (Cases 2,3,4,6,8,11, 12,13,14,16,17,19,20,21,22,23,24,25,27,28,29) and this bore a more definite relationship to the character of the anaemia. In the more acute cases, e.g. cases 2,12,13,20 and 21, there was considerable/

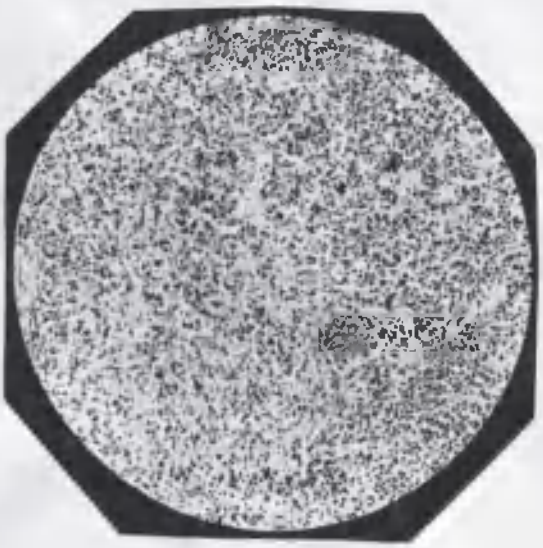
Sections obtained at Autopsy - Case 19.



Liver x 150



Bone Marrow x1000
(Megaloblastic Reaction)



Spleen x 150

Stomach x 100

considerable outpouring of early forms. These young granular cells occurred not only in the cases showing a relative increase of the granular series, but in cases showing a normal proportion of granular and non granular cells, and in cases with a relative lymphocytosis, e.g. cases 2,11,13,14,16,17,19,23,24,27 & 28.

Routine platelet counts were not made, but the stained films showed them to be more numerous than in true Pernicious Anaemia. The numbers appeared to vary with the chronicity of the cases, being more abundant in the more acute cases, e.g. 2,12,13, 20,21.

Pathology.

A post-mortem examination was carried out on Case 19. The general findings were those associated with severe anaemia. Catarrhal changes were present in the gastric mucous membrane. There was no deposit of haemosiderin in the liver or kidneys. The bone marrow showed prominent megaloblastic reaction. (Details in Vol II)

Response to Treatment.

The following varieties of treatment were used:-

Liver by mouth ..... 7 cases (Cases 8,10,11,13,15, 16,18).

Liver Extract by mouth ..... 4 cases (Cases 5,9,12,14).

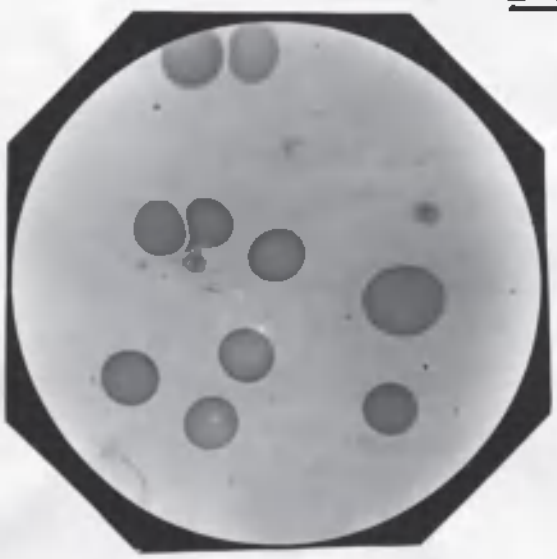
Liver Extract by mouth + Liver by mouth ..... 5 cases (Cases 1,2,3,4,7).

Liver Extract by mouth + Iron by mouth ..... 2 cases (Cases 6,17).

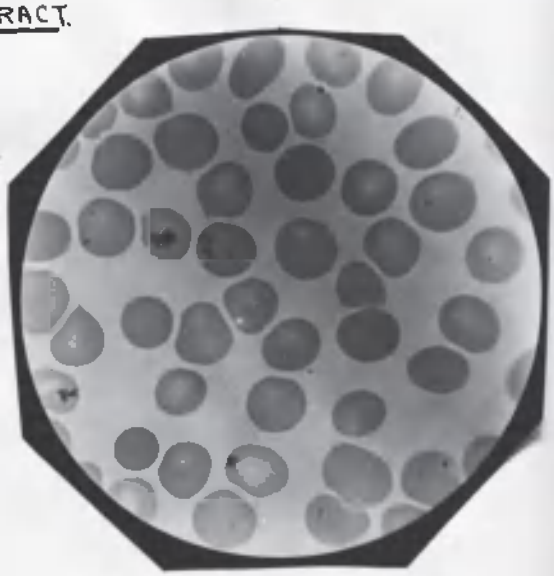
Desiccated/

Effect of Treatment.

Liver Extract.



Case 12.

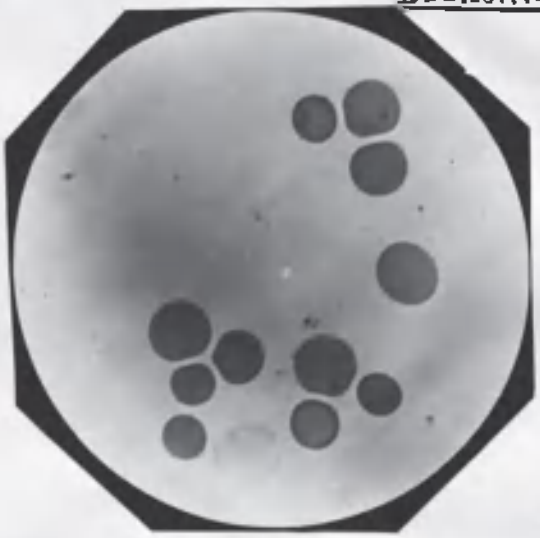


×1000

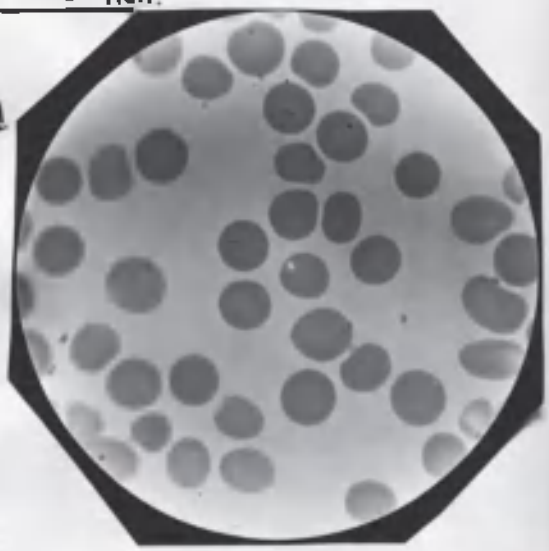
19-2-30

19-3-30

Desiccated Hog's Stomach.



Case 21



×1000.

31-3-31

19-5-31

Desiccated Hog's Stomach by mouth ..... 1 case (Case 21).

Desiccated Hog's Stomach by mouth + Liver Extract by mouth.....3 cases (Cases 19,22,23).

Marmite by mouth + Liver Extract by mouth .....1 case (Case 25).

Liver Extract intromuscular + Liver Extract by mouth + Liver by mouth .....2 cases (Cases 26,27).

Liver Extract intravenously + Liver Extract intromuscularly + Liver Extract by mouth...1 case (Case 24)

Blood Transfusion + Liver Extract by mouth + Iron and Arsenic by injection .....1 case (Case 20).

Blood Transfusion + Liver Extract intravenously + Liver Extract intramuscularly + Liver by mouth.....1 case (Case 27).

Blood Transfusion + Liver Extract intravenously + Liver Extract intramuscularly + Liver Extract by mouth + Liver by mouth .....1 case (Case 28).

Blood Transfusion + Liver Extract intravenously + Liver Extract intramuscularly + Iron by mouth .....1 case (Case 30).

Liver or liver extract by mouth was the usual treatment. In very ill patients intramuscular and intravenous routes were used. Desiccated hog's stomach caused excessive vomiting in several cases, but was well tolerated in one (Case 21). The giving of liver, liver extract and desiccated Hog's Stomach in/

Comparison of Reticulocytosis in Pernicious Anaemia and in 'Pernicious Anaemia of Pregnancy and the Puerperium.

Case	Anaemia.	Initial Count.	Treatment.	Reticulocytosis.
Table I				
Mrs NL.	Pernicious Anaemia	RBC 740.000 per c mm. Hb 16	L.E. B.W.Co. } 1 tube daily	→ 9 on 10th day.
Mrs G.	Pernicious Anaemia	RBC 1.400.000 per c mm. Hb 28	L.E. B.W.Co. } 1 tube daily	→ 12·3 on 12th day.
Mrs MH.	Pernicious Anaemia	RBC 1860.000 per c mm. Hb 48	L.E. B.W.Co. } 1 tube daily	→ 3·6 on 18th day.
Mrs C.	Pernicious Anaemia	RBC 2.160.000 per c mm. Hb 53	Ventriculin P.D.&Co. } 2 tubes daily	→ 12 on 10th day
Mrs B	Pernicious Anaemia	RBC 1.200.000 per c mm. Hb 30	L.E. B.W.Co. } 1 tube daily	→ 4·6 on 9th day
Mrs R	Pernicious Anaemia	RBC 940.000 per c mm. Hb 20	Ventriculin P.D.&Co. } 2 tubes daily	→ 10·2 on 18th day.
C.T.	Pernicious Anaemia	R.B.C. 1.140.000 per c mm. Hb 27	L.E. B.W.Co. } 1 tube daily	→ 12 on 11th day
Mrs E	Pernicious Anaemia	RBC 1.190.000 per c mm. Hb 27	Hepatex (Evans) } 3ss Bid	→ 30 on 11th day
Mrs N	Pernicious Anaemia	R.B.C. 1.940.000 per c mm. Hb 49	Hepatex (Evans) } 3ii Bid	→ 10 on 9th day
H.M.	Pernicious Anaemia	RBC. 1.440.000 per c mm. Hb 44	Hepatex (Evans) } 3ii t.i.d.	→ 15 on 11th day.
2.	'Pernicious' An. of Puerp.	RBC 1680.000 per c mm. Hb 39	L.E. B.W.Co. } 1 tube daily	→ 11·7 on 7th day
4.	'Pernicious' An. of Puerp.	RBC 940.000 per c mm. Hb 14	L.E. B.W.Co. } 1 tube daily	→ 11·6 on 5th day.
6.	'Pernicious' An. of Preg.	RBC 1010.000 per c mm. Hb 20	L.E. B.W.Co. } 1 tube daily	→ 26 on 8th day.
12.	'Pernicious' An. of Puerp.	RBC 1.010.000 per c mm. Hb 21	L.E. Amnous } 3ss Bid	→ 36 on 12th day.
Table II				
13.	'Pernicious' An. of Puerp.	RBC 820000 per c mm. Hb 17	Liver ½ lb. daily.	→ 25 on 7th day.
14.	'Pernicious' An. of Puerp.	RBC 1290.000 per c mm. Hb 30	L.E. B.W.Co. } 1 tube daily	→ 40 on 10th day.
17.	'Pernicious' An. of Puerp.	RBC 1390.000 per c mm. Hb 20	L.E. B.W.Co. } 1 tube daily	→ 20 on 6th day.
18.	'Pernicious' An. of Puerp.	RBC 1550.000 per c mm. Hb 40	Liver ½ lb daily.	→ 20 on 8th day.
21.	'Pernicious' An. of Puerp.	RBC 1680.000 per c mm. Hb 35	Ventriculin P.D.&Co. } 2 tubes daily	→ 24·4 on 7th day.
25.	'Pernicious' An. of Puerp.	RBC 1140.000 per c mm. Hb 30	Hepatex (Evans) } 3ii t.i.d.	→ 15 on 5th day.

in cases with albuminuria and raised blood pressure (Cases 15, 21,22) had no ill effects. Marmite had to be discontinued in two days because of sickness (Case 25). Transfusion was resorted to in emergency in one acute case (Case 20) in a more chronic type (Case 28), where the patient was admitted in extremis, and also in cases where response to liver therapy was unsatisfactory (Cases 27,30). The response to subsequent treatment by liver in these cases was good. In some patients the haemoglobin curve lagged after a few weeks, and these did well on the addition of iron, e.g. Cases 6,17, and 30.

The following features were noted in the response to treatment. The reticulocyte rise was usually earlier, and often higher, than in cases of true Pernicious Anaemia of the same severity treated in Professor Harrington's wards with the same amounts of liver administered by similar routes, e.g. Cases 2,4,12,13,14,17,18,22,23,25 (See comp. Tables I and II.) There was a reticulocytosis of 24·4% on the sixth day of treatment in a case given desiccated hog's stomach (Case 21). A striking output of nucleated red cells and sometimes nuclear fragments (Cabot's rings and Howell-Jolly bodies) often preceded the rise of reticulocytes (Cases 6,12,14,26,28). The red cells and haemoglobin frequently started to rise with the reticulocytes, instead of after the peak. (Cases 2,4,6,12,13,17,20,21,25,26, 28,29). (See comparative charts A & B). As a rule the curves rapidly/

Pernicious Anaemia.

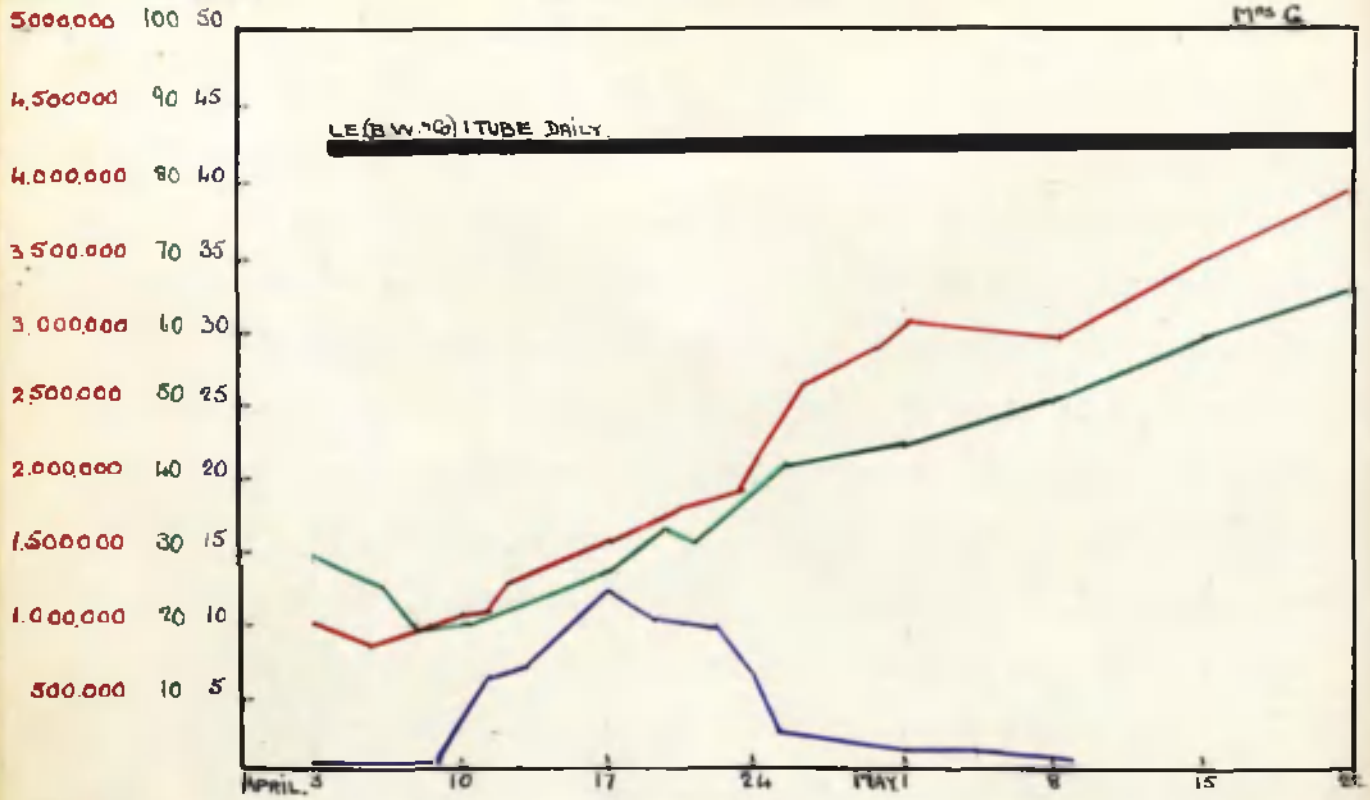


Chart I.

'Pernicious' Anaemia of the Puerperium.

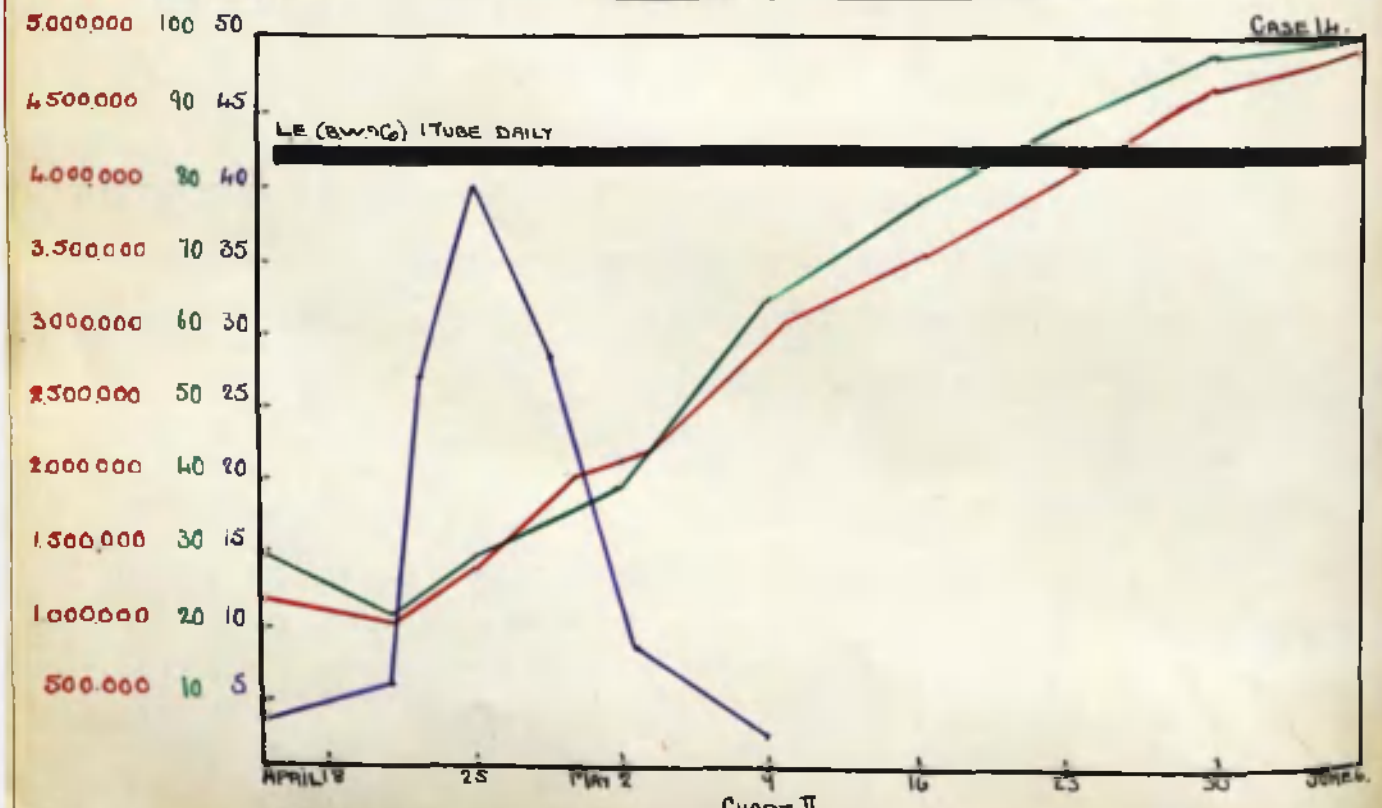


Chart II.

rapidly reached normal levels, sometimes in about four weeks from the commencement of treatment (Cases 2,14,20). The cases of recent origin (Cases 2,6,12,13,14,17,20,22,29) usually responded more rapidly than those which first came under observation several months after the onset of symptoms (Cases 1,3,23,24,28). Some fairly early cases, however, reacted slowly to treatment (Cases 25,26,27,30.)

The Delivery - The Life of the Mother - The Life of the Child.

The following were the findings in the five cases first seen during pregnancy:-

Case	When first seen.	Delivery	Treatment.	Response before Delivery	Child	Mother.
(6)	At 7 months	At 7½ months Spontaneous. Normal.	Liver extract by mouth.	Reticulocytosis of 26% on 8th day. R.B.C. 10,000,000 Hb 20% to R.B.C. 1,810,000 Hb 24%	Weakly, surviving.	Survived.
(12)	At 8½ months	2 days later Spontaneous. Normal.	Liver extract by mouth.	-	Weakly, surviving.	Survived.
(19)	At 8 months	At 8½ months Spontaneous.N.	Ventriculin. Liver extract by mouth (Vomiting).	-	Stillborn	Died 4 days after delivery

(21/

Case	When first seen.	Delivery	Treat-ment.	Response before Delivery.	Child	Mother.
(21)	At 7 months.	4 days Induced N.	Ventri-culin	Reticulocytes 4.6% on 3rd day, and 14.6% on 5th day.	Twins still-born.	Survived.
(22)	At 8½ months	At full time. Spontan-eous.N.	Ventri-culin (Vomit-ing.)	-	Still born.	Survived.

Among the thirty cases there was one miscarriage at three months with excessive haemorrhage (Case 3). Premature labour occurred between 7½ and 8½ months in eight cases (Cases 6,7,14,17,20,21,28). Ante-partum haemorrhage was present in three cases (Cases 7,17,23). Post-partum haemorrhage followed two deliveries (Cases 2 and 28). Deliveries were otherwise normal, and excessive haemorrhage was not present.

Two patients died (Cases 9 and 19). Case 9 was moribund when first seen. Case 19 was extremely ill, and vomiting interfered with the oral administration of desiccated hog's stomach and liver extract. Parenteral routes were not then employed. No transfusion was given.

Five children (Cases 7,19,20,21,22) were still-born and another weakly child died in a few days (Case 6). Of these, five were born prematurely; one delicate infant born at full time (Case 12), and one premature child with malaena neonatorum (Case 14) survived. All the other infants were apparently healthy.

Subsequent/

Subsequent Histories.

It has been difficult to record the subsequent histories accurately because of irregular attendance as out-patients.

Specific therapy was discontinued at four to sixteen weeks after the beginning of treatment (Cases 1,2,3,4,12,13,14, 22,23,24,25,26,27,28,29) and patients are known to have kept well for periods extending up to four years (Case 22).

Normal pregnancy occurred later in two cases (Cases 22, 26) without further treatment. There was recurrence of anaemia with a subsequent pregnancy in eight cases (Cases 1,3,22,25,27, 28,29,30). Two of these (Cases 1 and 3) attended regularly, and with treatment carried on till term and had normal confinements. Two are at present under treatment (Cases 29,30). Four were extremely ill, and were transfused elsewhere in emergency. One case (Case 28) recovered, and three (Cases 22,25,27) died.

The anaemia which recurred in Case 1 was of the 'Pernicious' type. In Case 3 it was hypochromic after one delivery, and 'Pernicious' after another. In Case 29 it is hypochromic. Case 30 is not under my care.

THE 'PERNICIOUS' TYPE - DISCUSSION.

From 1928 to 1934 I examined thirty cases of 'Pernicious' Anaemia of Pregnancy and the Puerperium. If my experience is any indication of its frequency, this anaemia is more common than the literature would lead one to believe, and it must be considered as an important complication of pregnancy and the puerperium. It may be that my experience is exceptional, but some possible explanations of the small numbers recorded by others present themselves. Urgent obstetrical situations associated with shock may overshadow the clinical picture of anaemia; various sets of signs and symptoms found in this anaemia may lead to wrong diagnosis, e.g. 'Nephritis', Cardiac Disease', 'Toxaemia of Pregnancy', 'Puerperal Sepsis'; overtaxed hospital conditions and poor home conditions may prevent adequate blood examinations. The old belief that the anaemias of pregnancy cured themselves in time without treatment may be responsible for lack of interest. The fact, however, that many of my patients were ill for periods varying from several months to two years after delivery, and then presented themselves for treatment in extremis, is a strong argument against expectant treatment.

Of my thirty cases, twenty-eight were of hospital class. Most of my work was among this class, but I was in close touch with obstetricians who attended the better class type, and I learned from them that the condition was seldom found among their/

private patients.

All the twenty eight patients were under-nourished, and enquiry into their home conditions made it clear that a full and proper diet was not economically possible. One of the other patients (Case 22) was troubled with sickness, vomiting and anorexia, prior to the onset of the anaemia. It would seem as if nutritional deficiency was at least a predisposing factor in the causation or aggravation of the anaemia.

This anaemia has been labelled the 'Pernicious' Anaemia of Pregnancy and the Puerperium, because of its close similarity to true Pernicious Anaemia, but there are certain points of difference.

It develops during the child bearing period and therefore occurs in an earlier age group than true Pernicious Anaemia.

There is no evidence of familial incidence.

Symptoms begin between the sixth and eighth month in the majority of cases. In some they are present throughout pregnancy. In others they appear for the first time after delivery.

It is usually relatively insidious in development, but more rapid than true Pernicious Anaemia. It may become acute, and is sometimes fulminating.

Oedema is often present and occasionally gross.

Glossitis/

Glossitis and dental sepsis are common, but are not necessarily found together.

Occasionally there is achlorhydria or hyperchlorhydria but the common finding is hypochlorhydria. The hydrochloric acid may be diminished during the illness and return to normal levels after recovery. Gastric catarrh is common.

Unlike Pernicious Anaemia the nervous system is not involved except for retinal haemorrhages which are common. In case 3 the general megalocytosis, leukopenia with relative lymphocytosis, persistent achlorhydria and tendency to relapse are suggestive of true Addisonian Anaemia.

Haemolysis is a common feature, but is not so striking as in true Pernicious Anaemia. Icteric tingeing of the skin and sclerotics is usually found. Excess of urobilinogen in the urine is slight and not constant. It was abundant in case 3. A weakly positive indirect Van den Bergh reaction, often within normal limits, is common. The blood fragility in the few cases tested was not increased. Post mortem findings (1 case) show no haemosiderin reaction in the liver or kidneys.

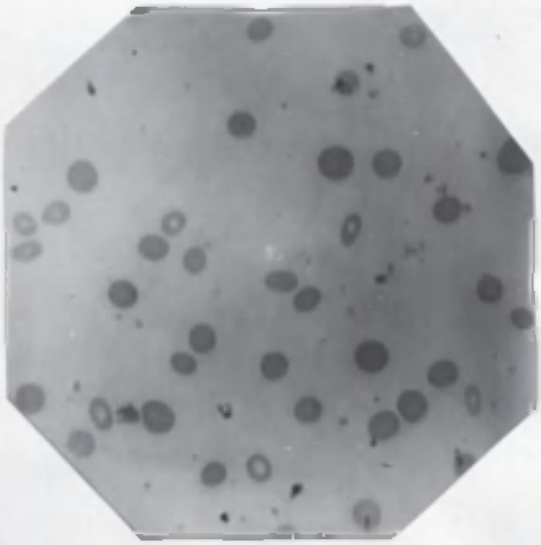
This is a megaloblastic anaemia, but while its general haematolical features are similar to Pernicious Anaemia, it differs in certain respects. The anaemia is usually intense with more or less parallel reduction of red cells and haemoglobin giving a colour index of near unity. Stained films show anisocytosis/

anisocytosis with many large red cells, but there is not one constant blood picture. The variations can be classified according to the chronicity of the anaemia. (1) There are acute forms showing evidence of marrow activity which is reflected in the peripheral blood by leucocytosis or normal leucocyte count with many young granular forms, slight increase of reticulocytes, polychromasia nucleated red cells, (normoblasts, erythroblasts and megaloblasts) and nuclear remnants, before treatment is started. The colour index is unity or a little less even in cases without haemorrhage. Poikilocytosis is not a striking feature. Though the Price-Jones curve shows a broadened base the average red cell diameter is normal or a little less. Platelets are fairly abundant. (2) The average case shows a colour index of near unity, a normal leucocyte count with increase of the cells of the granular series including both old and young forms, anisocytosis - but an average red cell diameter of about normal, polychromasia, a slightly increased reticulocyte count, and a few nucleated red cells. (3) The more chronic cases resemble Pernicious Anaemia closely and have a high colour index, leucopenia with relative lymphocytosis, occasional nucleated red cells, no increase of reticulocytes, poikilocytosis, anisocytosis with a general megalocytosis and shift to the right of the Price-Jones curve. Platelets are scanty. Even these cases, however, often have a bigger proportion of young granular leucocytes than is usually found in Addisonian Anaemia.

In/

Change of Blood Picture.

Case 6.



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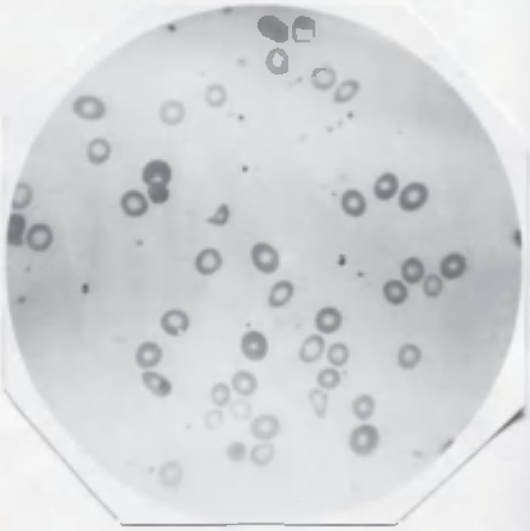


22-10-'29.

R.B.C. 1010.000 per c. mm.
W.B.C 10.000 per c. mm.
Hb. 20 | C.I=1.

30-11-'29.

R.B.C. 2820.000 per c. mm.
W.B.C 6.400 per c. mm.
Hb. 32 | C.I=0.

In the peripheral blood there are signs of abeyance of the normal marrow function of red cell production, and reversion to the megaloblastic type of blood formation. There was megaloblastic reaction of the bone marrow in the one case which went to autopsy.

Though the blood picture reflects marrow depression, the degrees of this are variable, and in most cases some activity is evidenced by the appearance of young granular leucocytes, polychromasic cells, many normoblasts as well as megaloblasts and fairly numerous platelets.

As a rule this anaemia responds to treatment by liver, liver extract by mouth or parenterally or desiccated hog's stomach. The response is usually earlier and more rapid than in true Pernicious anaemia (and this is further evidence of the relatively active state of the bone marrow). Sometimes initial transfusion is necessary, and sometimes transfusion is necessary later because of unsatisfactory response to other therapy, but even then the subsequent response to liver is evident. Where the haemoglobin lags behind the red cells during recovery the addition of iron gives good results.

Improvement can occur with suitable treatment during pregnancy, but the results are more dramatic after delivery.

Once normal levels of blood curves have been reached treatment can be discontinued, but the possibility of recurrence in/

in a severe form in a subsequent pregnancy, must be remembered.

Premature labour is common.

The maternal mortality in untreated cases is high.

There is a high incidence of still birth, but the majority of the children are born healthy, even though the mother is grossly anaemic.

One of the main purposes of this work was, as I have already stated, to look for common factors which might indicate etiology and mode of treatment.

Before discussing my own results I shall first deal with the historical views of causation.

Osler (60) attributed this anaemia to a haemolytic agent caused by the metabolism of pregnancy. or the catabolism of the post-partum state. Rowland (65) quoting Hofbauer's work described a haemolysin from the ectodermal cells of the chorion which caused a physiological anaemia in the early months of pregnancy. In the later months an antihaemolysin was produced. If this latter failed to develop progressive anaemia resulted. Although these theories are not now accepted, some writers, e.g. Wilkinson (87) Witts (97) still refer to the condition as the Haemolytic Anaemia of Pregnancy.

Few writers have stressed sepsis as one of the possible causes. Gulland (36) described a case of 'Pernicious Anaemia' seen in the puerperium in which treatment by mercurochrome was "brilliantly successful". "The patient was very/

very ill, could not take arsenic and was running a high swinging temperature without any discoverable cause. A single injection of mercurochrome brought the fever to an end, and the patient began at once to improve.------Probably she was suffering from a septicaemia in addition to the pernicious anaemia, although the blood culture was negative".

Castle and his co-workers[13] [14] believe that, for normal red cell maturation beyond the megaloblastic stage in the bone marrow, a substance is produced by the interaction of an intrinsic factor found in the gastric juice and extrinsic factor supplied mainly in the form of meat proteins. In Pernicious Anaemia the intrinsic factor is lacking, and anaemia with an embryonic or megaloblastic type of red cell formation results. Remission of this anaemia is brought about by administration of gastric secretion containing this factor by desiccated hog's stomach Brower and Simpson [10] Sharp [68] Sturgis and Isaacs[80] Wilkinson [86] or by liver or kidney which either contain this factor or store the elaborated substance necessary for marrow stipulation.

Deficiency of the extrinsic factor (contained in Marmite) has been shown by Wills [93] and others to produce a tropical Macrocytic Anaemia in many Indian women during pregnancy.

Strauss and Castle [76] [77] [78] have shown that there is a temporary derangement of gastric secretion in pregnancy, and consider/

consider that there is a temporary lack of the specific intrinsic factor in 'Pernicious' Anaemia of Pregnancy and the Puerperium.

I shall now consider some of the main features of my cases already detailed.

(1) Multiparity appeared to play a part in causation, the average number of pregnancies being five.

(2) There was no supporting evidence of sepsis as a cause. In a few cases previous or present puerperal sepsis may have been a predisposing factor, but it seldom occurred in my series. Many had carious teeth and gingivitis, but this is a common finding in the class of patient being considered. In many cases there was a high normal leucocyte count and in some a leucocytosis. A moderate increase of leucocytes is normal in late pregnancy and in the puerperium.(84) Moreover, a leucocytosis could be considered to be evidence of marrow activity in response to the severe anaemia, or at a later stage in response to treatment. The bacteriological examination of the resting juice resulted in findings similar to those of Davidson(21), in true Pernicious Anaemia. There was a high bacterial content, but no specific organism was isolated. In the control cases many patients with an equally abundant flora were not anaemic.

(3) Haemolysis. though present, was not excessive in my series. One wonders if the amount of haemolysis demonstrated could be/

be accounted for by an increased tendency to lysis in young reticulocytes in the circulation, but, according to Valentine[82], there is no proof that they are more fragile than ordinary red blood cells.

It has been a common belief that Pernicious Anaemia is due to blood destruction and depression of haematopoietic function. Cornell 1927 [17] stated that the relative influence of these two processes was by no means clearly defined, and he quoted Schneider who regarded the increased urobilin and urobilinogen excretion as an expression not of 'immediate haemolysis' but of the 'heaped-up pigment in the portal system'. Whitby and Britton 1935[84] stated that all the indirect evidence of blood destruction was found in the disease, but that probably the findings were the result of accumulation of pigment derived from the ordinary slow destruction of red cells. 'Pernicious' Anaemia of Pregnancy and the Puerperium develops more rapidly than true Pernicious Anaemia. Possibly two factors account for the relatively slight evidence of haemolysis found in it:- (a) The rapid marrow depression will quickly result in fewer red cells in the circulation to be haemolysed; (b) The shorter time of development will not allow of such great storage of pigment.

(4) Poor Nutrition was a common feature either because of deficient diet, or because of anorexia or vomiting.

This/

This suggests insufficiency of the extrinsic factor as a possible cause of the anaemia. But though defective nutrition is very widespread in this class of community, 'Pernicious' Anaemia of Pregnancy and the Puerperium is a relatively uncommon condition. The four cases of Hyperemesis Gravidarum which I examined did not show it. There must, therefore, be an individual determining factor.

(5) Gastric analysis showed evidence of abnormal gastric secretion. Though free hydrochloric acid was often found, in the vast majority of cases it was diminished. Excess of mucus was very common even when the acidity was fairly high.

(6) The blood picture closely simulated that of true Pernicious Anaemia. In untreated cases it reflected greater activity of the bone marrow than is found in Pernicious Anaemia except in an occasional case during a spontaneous remission. The degrees of marrow depression were related to the chronicity of the anaemia.

An added iron deficiency sometimes complicated the picture.

(7) Response to treatment gave certain data:-

(a) A nutritious diet alone did not appear to be a satisfactory form of treatment. Several cases had been resident in the Maternity Hospital for two weeks before they were first examined by me. Marmite was not/

not tolerated by my patients, and therefore its effect was not tested.

(b) The condition responded to liver therapy and to desiccated hog's stomach.

(c) The addition of iron was sometimes necessary because of the low haemoglobin content of the red cells initially, in the course of recovery (with liver extract etc.) or in a later pregnancy.

(d) Response and recovery with specific treatment were more rapid than in true Pernicious Anaemia.

(e) Treatment could be finally discontinued after the blood curves had reached normal levels.

(8) Recurrence during subsequent pregnancy was a definite danger.

SUMMARY and CONCLUSIONS.

1. Thirty cases of 'Pernicious' Anaemia of Pregnancy and the Puerperium have been described. Of these two may have been cases of Pernicious Anaemia, first manifested in pregnancy. (Cases 3 & 24)

2. The condition is a definite entity, is more common than is generally believed, and forms an important complication of pregnancy and the puerperium.

3. The main features of the Anaemia are:-

(1) It develops most often in the second half of pregnancy.

(2) Multiparity is usually associated with it.

(3)/

(3) Defective nutrition is common.

(4) Glossitis is present in fully half the cases.

(5) There is abnormal gastric secretion.

(6) Retinal haemorrhages occur in more than half the cases.

(7) Haemolysis is relatively slight.

(8) The blood picture resembles that of Pernicious Anaemia, but shows important differences.

(9) It responds to liver or to liver extract by mouth or parenterally, or to desiccated hog's stomach.
A nutritious mixed diet is essential.
Iron is sometimes necessary in addition.
Transfusion is indicated as a temporary measure, in some severe cases.

(10) Response to treatment occurs before delivery, but is more dramatic after delivery.

(11) Treatment may be discontinued after the blood curves have reached normal levels.

(12) There is definite possibility of recurrence in subsequent pregnancy, and sometimes in a more severe form.

(13) There is a high mortality rate in untreated cases.

(14) The incidence of prematurity and still-births is high. a few children are weakly, but the majority are born healthy.

(15/

(15) It would appear there is temporary lack or insufficiency of the intrinsic factor in the gastric juice. Insufficient specific substance is elaborated, and a megaloblastic anaemia results. Dietary deficiency of the extrinsic factor probably plays a part by causing incomplete utilisation of the already reduced intrinsic factor.

(16) Proper attention to diet and ante-natal care would stay its development, and might even prevent its occurrence.

4. The condition differs from Pernicious Anaemia as follows:-

(1) It occurs at an earlier age.

(2) Multiparity is a predisposing cause.

(3) Poor nutrition is common.

(4) It is more rapid in development.

(5) Achlorhydria is uncommon, but the gastric secretion is abnormal.

(6) Retinal haemorrhages are the only signs of involvement of the nervous system.

(7) Haemolysis is relatively slight.

(8) The blood picture reflects a more plastic marrow, and varies with the chronicity of the illness. The red cells are sometimes deficient in haemoglobin.

(9) Response to suitable therapy is usually more rapid.

(10) Maintenance treatment is not required.

SEVENTY CASES OF 'SECONDARY' ANAEMIA IN PREGNANCY AND THE PUERPERIUM.

2. THE 'SECONDARY' TYPE.

I have examined seventy cases (Cases 31 to 100) of this type of anaemia. Forty four were examined as out-patients at Glasgow Royal Infirmary, seven in Professor Harrington's Wards in Glasgow Royal Infirmary, one in Professor Hendry's wards in Glasgow Royal Infirmary, seventeen in Professor Hendry's wards in Glasgow Royal Maternity Hospital, and one in Professor Munro Kerr's wards in Glasgow Royal Maternity Hospital. Fourteen (31 to 44) were ante-natal cases and fifty-six (45 to 100) were post-natal.

Many of these did not require indoor hospital treatment, and in consequence the records are incomplete. In eighteen (Cases 83 to 100) only initial blood counts were obtained, and in my analysis of the group I shall deal only with the remaining fifty-two.

Age: There was considerable variation in age, the youngest patient being twenty and the oldest forty-five. The average age was thirty-one.

Number of Pregnancies: Most of the patients were multiparae, only seven (Cases 32,47,59,61,68,81,82) being primiparae. The average number of pregnancies was five. There was twin pregnancy in three cases (Cases 49,71,75).

Previous Health: Splenic Anaemia had been previously diagnosed in Case 33. Case 56 suffered from Chronic Bronchitis. Two patients (Cases 66 and 72) had Mitral Stenosis.

The/

The previous obstetrical histories revealed that miscarriage had occurred with earlier pregnancies in five cases (Cases 33,34,39,60,65) and still-births in one (Case 62). Two patients (Cases 42 and 46) had had Puerperal Sepsis. Three (Cases 40,46,74) stated that they had had 'Kidney Trouble'. Four (Cases 51,64,77,78) have histories of pallor during and after delivery with previous pregnancies. Cases 51 and 77 had not properly recovered from these illnesses. Two patients (Cases 62 and 70) had had previous haemorrhages. Case 62 had had a post partum haemorrhage, but had recovered satisfactorily. Case 70 had had one ante-partum haemorrhage with one child and a post-partum haemorrhage with another and had been debilitated since then.

Social Conditions: All but two cases (Cases 72 and 78) were in poor circumstances and were unable to obtain adequate nourishment.

Symptoms:

Time of Onset: Symptoms began during the first month of pregnancy in twenty four cases (Cases 32,34,38,39,40,41,42, 43,45,49,50,51,52,53,64,66,67,70,71,73,74,77,78,82) at mid-pregnancy in seven cases (Cases 31,36,37,46,69,72,75), in the last three months of pregnancy in four cases (Cases 33,35, 44,47), after delivery in fourteen cases (Cases 48,55,56,59, 60,61,62,63,65,68,76,79,80,81) and after a miscarriage in three cases (Cases 54,57,58).

Mode/

Mode of Onset: Apart from the acute post-haemorrhagic cases symptoms developed insidiously.

The main complaints were of progressive weakness, breathlessness, and inability to perform ordinary household duties. Oedema was seldom noted. Sickness and vomiting were common and excessive vomiting occurred in six cases (Cases 52,53,67,71,72,73).

Haemorrhage occurred in ten cases. There was ante-natal haemorrhage in four cases (Cases 32,36,60,68). In Case 32 symptoms of anaemia preceded the haemorrhage and were aggravated by it. There was post-partum haemorrhage in five cases (Cases 48,61,63,77,78). In Cases 77 and 78 it increased the severity of symptoms already present. Haemorrhage following a miscarriage was the apparent cause in Case 57.

Puerperal Sepsis was present in two cases examined (Cases 49 and 54).

Pyelitis was associated with three cases (Cases 31, 34,74).

Hydramnios was present in two cases (Cases 27 and 75)

Examination:

The patients were usually thin and ill-looking, and presented various degrees of pallor of the skin and mucous membranes. Often the pallor was intense. In eighteen patients Cases 26,41,43,45,46,47,51,55,63,64,67,70,71,72,73,78,79,82) there was icteric tingeing of the skin, but the sclerotics were bluish/

bluish white. In two the skin had a greenish tint suggestive of Chlorosis (Cases 59 and 62)

Glossitis: There was glossitis usually of an atrophic type in seventeen patients (Cases 31,34,36,37,39,46,47,48,49,52, 53,57,58,60,61,62,65).

Gastric Analysis: This was carried out in fifteen patients, (Cases 45,46,55,56,64,65,67,68,69,70,71,74,79,80,82). There was achlorhydria in all but two cases (Cases 70 and 71). In case 70 the acidity curves were normal. In Case 71 there was hyperchlorhydria. Gastric catarrh was the usual finding. In eight cases (Cases 42,45,46,58,64,67,70,71) the resting juice was examined bacteriologically. A mixed flora was found in all cases, sometimes abundant, sometimes scanty. In Case 71, where free hydrochloric acid was copious, there was no growth or culture.

Urine: The urine was examined in thirty-three cases. In thirteen cases it was clear. Albumen was present in ten cases in small amounts in seven cases (Cases 33,34,41,56,73,74,78) and abundant in three Cases (Cases 31,34 and 37). There was excess of urobilinogen in eleven cases (Cases 36,43,64,65,67, 68,70,71,72,78,79).

Wassermann Reaction: The Wassermann Reaction was tested in twenty cases. It was negative in eighteen (Cases 31,33,36, 37,40,42,46,47,56,58,64,67,69,71,72,73,78,82) and weakly positive in two (Cases 44 and 45).

The/

The Blood Picture: As a rule there was reduction of the red cells and haemoglobin, but the latter was reduced to a greater degree, so that the colour index was low, often between .5 and .6. Occasionally the number of red cells was normal or even slightly increased, while the haemoglobin was decreased. The degree of anaemia was variable. In the majority of cases the red cells count was between two and three millions per c.mm. and the haemoglobin between 25% and 50%.

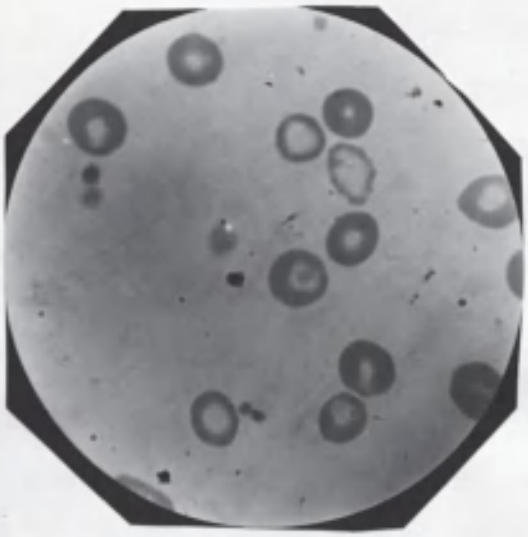
Stained films showed ring staining and general microcytosis, but, in most cases, there was considerable anisocytosis, with a fair number of large red cells, which were often polychromasic. Poikilocytosis was usually slight. Nucleated red cells were scanty. A megaloblast was noted in two cases (Cases 32 and 46), and a normoblast in one (Case 45)

Price-Jones curves were charted in ten cases (Cases 45,46,55,64,67,69,70,71,82). They all showed broadening of the base and a shift to the left. The average red cell diameter varied from 6.28 μ. to 6.79 μ.

The leucocyte count was within normal limits in thirty cases. There was a moderate leucocytosis in sixteen, and a leucopenia in six. Differential white cell counts were done in twenty-nine cases. In fourteen there was a relative increase of granular cells (Cases 31,33,37,39,42,43,64,67,69, 71,72,73,75,80). In six cases there was a relative increase of the lymphocytes (Cases 45,47,48,49,51,82). In nine cases the/

Iron Therapy - Moderate Dosage - (Old Treatment)

Case 47.



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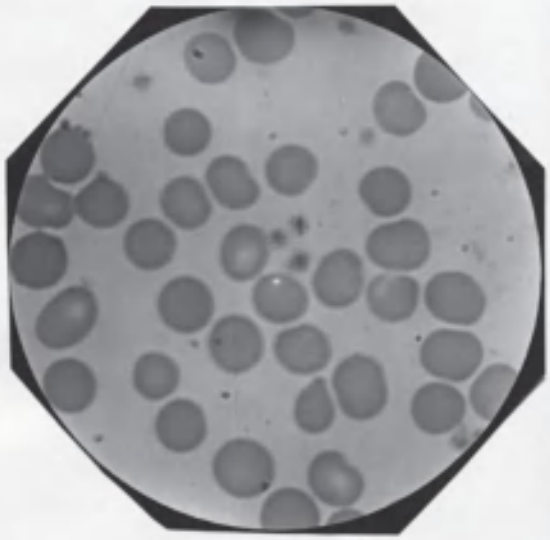


17-1-30

RBC 3230000 /cu.c.mm.
WBC 6400 /cu.c.mm.
Ne. 25%.

30-5-30

RBC 4.530.000 /cu.c.mm.
WBC 9.000 /cu.c.mm.
Ne 60%.

the the types of white cell were present in normal proportions (Cases 46,53,54,60,63,65,70,78,79). Very few young granular forms were seen.

Treatment: Iron by mouth in moderate dosage, e.g., Iron and ammonium citrate gr.10 t.i.d. or reduced iron gr.2 t.i.d. was given in twenty-five cases, (Cases 1,33,35,36,40,48,50,51,52, 53,55,56,57,58,59,60,61,63,65,68,69,70,71,72,73). Iron by mouth in moderate dosage + dilute hydrochloric acid, as described by Mettier and Minot (49), was given in three cases (Cases 42,64, 67). Iron by mouth in moderate dosage + liver, as advocated by Cheney and Niemand (16) and later by Richter, Meyer and Bennett (64), was given in four cases, (Cases 34,41,45,47). Iron by mouth in moderate dosage + iron and arsenic by injection (iron citrate and sodium arsenate) + tryptophan and histidine by injection as described by us (20) was given in two cases (Cases 64 and 67). Iron by mouth in massive doses, e.g. iron and ammonium citrate gr. 20.t.i.d., as used by Witts (96) Davies (23) Dameshek (20) Ivy Morgan and Farrell (42) was given in ten cases (Cases 44,74,75,76,77,78,79,80,81,82.) Iron in massive doses + liver was given in one case (Case 43).

The response to treatment by iron by mouth in moderate dosage, e.g. 10 gr. of iron and ammonium citrate t.i.d., was often disappointing. Even after several months of treatment it was difficult to raise the haemoglobin above 60%, e.g. Case 47. A few cases, however, gave satisfactory results, e.g. Cases/

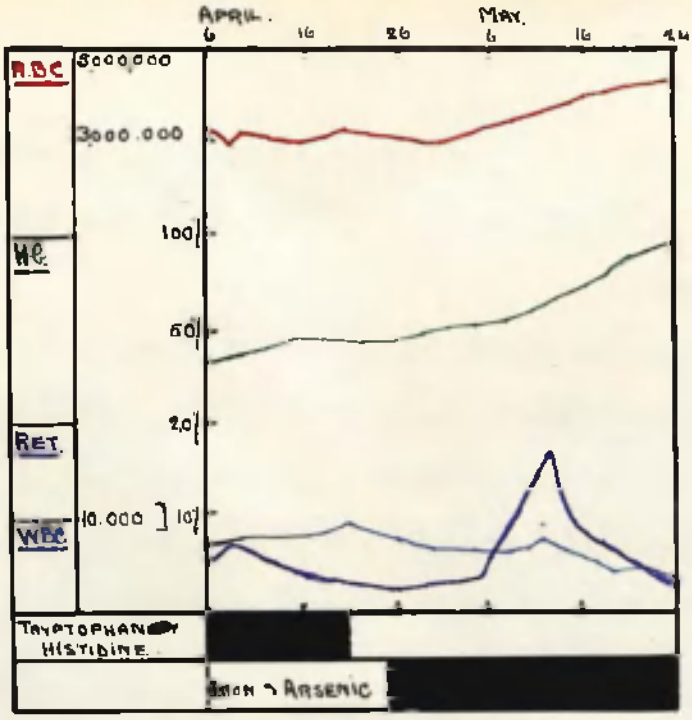


CHART III. CASE 67

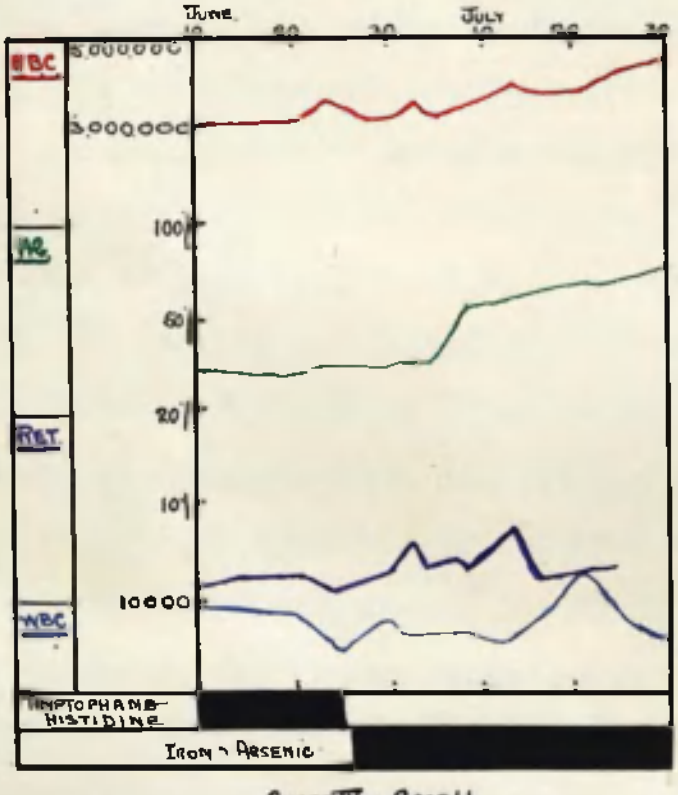


CHART IV - CASE 64

Cases 35 and 46. In the few cases where dilute hydrochloric acid was given in addition the results were poor. There was no outstanding benefit from the giving of liver as well as iron, but it appeared to be helpful in cases 34 and 41. It was not given in any of the post-haemorrhagic cases. Tryptophan and histidine did not improve the blood picture in the two cases tested (Cases 64 and 67), but the subsequent administration of iron in ordinary dosage had excellent results, and was associated with moderate reticulocytosis. The giving of iron in massive doses produced dramatic improvement, e.g. cases 79 and 80 where the haemoglobin rose from about 50% to 90% in five weeks with 20 gr. iron and ammonium citrate t.i.d.

The Delivery - The Life of the Mother - The Life of the Child:

Figures are not available, but premature labour was uncommon. There were two miscarriages (Cases 57 and 58). Haemorrhage occurred in eleven cases as already detailed.

There were no maternal deaths in the series.

There were seven still-births (Cases 32,33,49,68,75, 79,81) and two miscarriages (Cases 57 and 58). One child died shortly after delivery. (Case 66).

Subsequent Histories:

Very few cases have been followed up.

Relapse in subsequent pregnancy occurred in cases 47 and 64, neither of which had been treated with massive doses of/

of iron, and whose blood had not reached satisfactory levels after the previous anaemia. In case 47, after several years of anaemia the clinical picture is suggestive of a Plummer-Vinson Syndrome.

Cases 79 and 80 were given massive iron therapy for five weeks and kept well for nine months after cessation of treatment.

THE "SECONDARY" TYPE - DISCUSSION.

My notes of this group of cases are too scanty to allow me to generalise, but I think they show that the 'Secondary' Anaemia of Pregnancy and the Puerperium has characteristic features.

The patients were as a rule very debilitated, but not so gravely ill as in the 'Pernicious' group.

It differed from Idiopathic Hypochromic Anaemia in that icteric tingeing of the skin, and slight excess of urobilinogen in the urine were sometimes present. These were noted in the same patients in cases 36,43,64,67,70, 71,72,78,79. This association is hardly likely to be coincident, and further investigation of the indirect evidence of haemolysis is required.

There was glossitis in only one third of the cases.

Achlorhydria was usual, but not constant and hyperchlordria occurred. Gastric catarrh was common. No specific organism was isolated from the resting gastric juice.

The blood picture was that of a microcytic hypochromic anaemia of considerable severity. The striking appearance of anisocytosis with a proportion of large red cells was confirmed by Price-Jones curves. The apparent macrocytosis with some polychromasia, often gave a picture like Pernicious Anaemia in some fields of the stained films. Nucleated/

Nucleated red cells and young granular white cells were uncommon. The leucocytes varied in number, but were most often within normal limits.

Iron in massive doses was the most successful form of treatment.

Relapse occurred during subsequent pregnancy in two cases, neither of whom had made a satisfactory response to previous treatment. Two patients, after successful treatment of the anaemia, kept well for nine months without maintenance iron therapy.

Reference to the literature reveals that some writers do not consider this type of anaemia to be due to pregnancy. Mills 1931 (50) says "Pregnancy is not the cause of the anaemia, but the added burden which reduces the haemoglobin level to a point incompatible with the pursuit of the ordinary duties of life". Fullerton 1936 (31) concludes "Where hypochromic anaemia in pregnancy is marked, anaemia has probably existed before the pregnancy, but has been made more apparent by physiological hydraemia. The conception that uncomplicated pregnancy frequently produces a severe degree of anaemia should be discarded". The foetus, however, draws on the mother for its body building materials during the whole period of gestation, and according to Hugounenq (40), obtains two/

two thirds of its iron supply in the last three months. The work of Bunge (11) shows that the livers of young animals contain relatively much more iron than the livers of adult animals. In the experimental work of Ivy, Morgan and Farrell (42) all their gastrectomised dogs which became pregnant developed a severe 'secondary' anaemia, while normal dogs fed on the same diet did not become anaemic during pregnancy. Minot and Heath (51) have demonstrated a more satisfactory response to iron in cases of hypochromic anaemia with free hydrochloric acid in their stomach contents than in comparable cases with achlorhydria. Davies and Shelley (25) have shown that there may be a temporary achlorhydria associated with gastric disfunction during pregnancy. Strauss and Castle (78) in their studies of anaemia in pregnancy conclude that "The hypochromic anaemia of pregnancy is due either to a direct dietary deficiency or to a deficiency conditioned by gastric anacidity, hypoacidity or associated defects in the presence of the fetal demand for blood-building materials, and may be completely relieved, either during or after pregnancy, by the administration of iron in large doses."

The impressions I gained with regard to etiology were:-

One third of my patients developed the symptoms in the last three months of pregnancy or just after delivery and/

and may have been related to the iron drain by the foetus. Almost half the patients dated their symptoms from the first month of pregnancy, and some stated that they had been pale since a previous pregnancy. This suggested pre-existing anaemia which had been increased in severity by the metabolic upset of gestation.

Frequent child-bearing seemed to play a part in causation.

Infection was not important.

Haemorrhage apparently caused or aggravated the anaemia in a fifth of the cases.

Excess Vomiting, Albuminuria, Hydramnios were all present in a few cases, but I was unable to decide whether their presence was accidental; if not, whether they were the cause or the result of the anaemia was difficult to assess.

Gastric secretion was abnormal, but again I was left in doubt as to whether this preceded or followed the anaemia.

Poor previous health - Splenic Anaemia, Chronic Bronchitis, Mitral Stenosis, may have predisposed to its development in the few cases in which they were found.

All but two of my patients were undernourished, and in eighteen (Cases, 35,39,40,41,42,46,51,55,58,59,64,65,69, 76,79,80,81,82) inadequate nutrition was the only explanation

I/

I could offer for the anaemia.

It seems to me that this type of anaemia may develop by a combination of several factors, the physiological iron drain of pregnancy, poor dietary and abnormal gastric secretion, and that Idiopathic Hypochromic Anaemia may be increased in severity or make its first appearance during pregnancy.

SUMMARY and CONCLUSIONS.

1. Seventy cases of the 'Secondary' Anaemia in Pregnancy and the Puerperium have been described.

2. The condition is much more common than the 'Pernicious' type, and as a rule is not such a serious complication of pregnancy, but may be in the acute post-haemorrhagic cases. If not efficiency treated, however, it leads to a state of chronic ill-health which may predispose to other illnesses, and render the patient unfit for the strain of subsequent pregnancy.

3. The main etiological features appear to be:-
   (1) The strain of repeated child-bearing.
   (2) Dietary deficiency.
   (3) Abnormal gastric secretion with poor absorptive powers.

4. The anaemia may appear at any stage or pregnancy or immediately after delivery.

5. It is a microcytic hypochromic anaemia resembling Idiopathic Hypochromic Anaemia, but differing from it in the following features:-
   (1) It usually occurs at an earlier age.
   (2) While achlorhydria is common, hyperchlorhydria is/

is sometimes found.

(3) Icteric tingeing of the skin, and slight excess of urobilinogen in the urine are fairly common.

(4) There is often anisocytosis with a considerable number of large polychromasic cells. Leucocytes are sometimes increased.

(5) While massive iron therapy is usually the most satisfactory form of treatment, the addition of liver is sometimes helpful.

(6) Some cases recover very rapidly and remain well without maintenance iron therapy.

Some relapse in subsequent pregannoy.

6. There is a high incidence of still-birth and miscarriage.

7. As in 'Pernicious' Anaemia of Pregnancy and the Puerperium, preventive treatment has great possibilities.

8. It may be that this is not a single type of anaemia but rather a group of anaemias included in which are cases of true Idiopathic Hypochromic Anaemia, many cases closely resembling it, and a few which in certain features are like the 'Pernicious' group.

ECLAMPSIA AND HYPEREMESIS GRAVIDARUM.

ECLAMPSIA and HYPEREMESIS GRAVIDARUM.

The blood was examined in four cases of Eclampsia (Cases A_1, A_2, A_3, A_4), and in four cases of Hyperemesis Gravidarum (Cases B_1, B_2, B_3, B_4). Some points are summarised in the following table.

Case	Glossitis.	Anaemia	Colour Index.	Blood Film.	Leucocytes.
A_1	-	Moderately Severe	Above unity	Anisocytosis with megalocytes	Increased.
A_2	+	Moderately Severe	Below unity	Anisocytosis with megalocytes	Reduced.
A_3	-	Slight	Above unity	Fairly normal	Increased
A_4	+	-	Above unity	Normal	Normal
B_1	-	Moderate	Below unity	Anisocytosis with megalocytes	Normal
B_2	-	-	Unity	Normal	Normal
B_3	+	-	Unity	Normal	Normal
B_4	-	-	Below Unity	Normal	Increased

The numbers are too small to draw conclusions, but it was noted that:-

(1)/

(1) Glossitis occurred in two cases of Eclampsia and one case of Hyperemesis Gravidarum with and without anaemia.

(2) Anaemia was not constantly found in either, and the type of anaemia varied.

(3) Excessive vomiting occurred without development of anaemia as judged by blood counts, but it is probable that dehydration masked an actual reduction of red cells and haemoglobin.

NORMAL CASES.

TEN NORMAL CASES.

Five cases (C_1, C_2, C_3, C_4, C_5.) were seen during the last two months of pregnancy, and five (C_6, C_7, C_8, C_9, C_{10}.) the last eight days of the puerperium.

Blood examinations were made as detailed in Vol. III. The numbers are too small for conclusions to be drawn, but the findings are of value in comparing my figures in the cases of anaemia with these normal cases investigated using the same technique.

1. The red cell counts and haemoglobin percentages were within the accepted normal limits. The leucocyte figures were normal or slightly increased both before and after delivery.

2. Stained films presented normal features.

3. Price-Jones curves showed no broadening of the bases. The average red cell diameters varied from 6·9 μ to 7·16 μ before delivery and from 6·9 u to 7·24 μ after delivery. The average before delivery was 7·06 μ, and after delivery 7·13 u. The average for the ten cases was 7·1 μ.

4. The differential counts of white cells demonstrated normal proportions of granular and non-granular cells in seven cases, an increase of the granular cells in Cases C_6 and C_9 but no very young forms, and a slight lymphocytosis in Case C_8.

IN CONCLUSION - A GENERAL SURVEY.

This investigation seems to me to have confirmed my early impression that medical literature fails to emphasise the frequency and importance of anaemia as a complication of pregnancy and the puerperium. That I was able to examine almost one hundred cases in six years is an indication that the complication is common, and yet I feel that even this work does not give a real picture of its frequency and seriousness. The majority of the patients were seen during the routine work of one medical unit in the wards and out-patient department of the Glasgow Royal Infirmary, and the others as cases of special interest which I was asked to examine in the Glasgow Royal Maternity Hospital. They were not collected at a special clinic for 'Anaemia', and they in no way represent the frequency of anaemia among patients in the Maternity Hospital.

I have dealt more fully with the 'Pernicious' Anaemia of Pregnancy and the Puerperium, in order to show that the general impression that this type of anaemia is an absolute rarity, and if untreated will probably cure itself, is quite erroneous. My thirty cases are clear proof that it is not so rare, and their histories show that expectant treatment is dangerous.

This type of anaemia closely resembles Addisonian Anaemia, but it is usually more acute in its onset and the blood picture indicates a more active bone marrow. It is cured by the administration of the anti-anaemic factor present in liver, and maintenance treatment, except in the special circumstances which

I/

I have detailed, is as a rule unnecessary. The recognition and treatment of this anaemia in its early stages will save some of our patients from becoming chronic invalids, and may actually prevent a fatal issue.

With regard to the 'Secondary' Anaemia of Pregnancy and the Puerperium, I feel that my work is incomplete, and several points require further study.

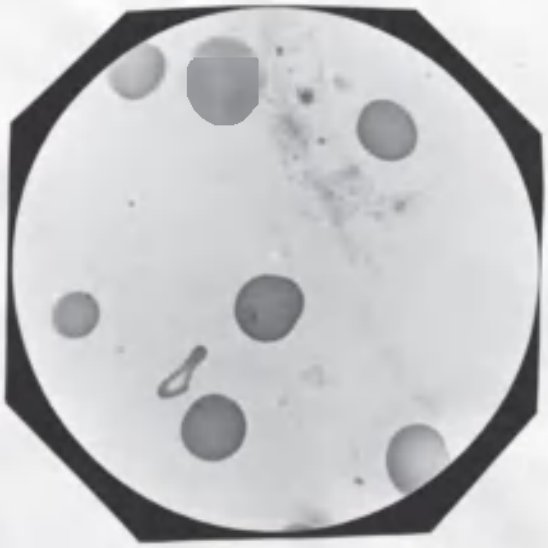
This anaemia resembles Idiopathic Hypochromic Anaemia. It is cured by massive doses of iron, and maintenance treatment is usually not necessary. I am not completely convinced that this is a single group of anaemias. The signs of haemolysis were so definite in certain of my cases that I could not dismiss them as being purely coincidental. I have been unable so far to explain their occurrence, and I feel that further work should be done to seek an explanation.

It is simpler for purposes of description to divide these anaemias into 'Pernicious' and 'Secondary' groups, but I am becoming more and more convinced that the anaemias of pregnancy and the puerperium cannot always be separated into water-tight compartments. They present varying blood pictures. At the one end a megalocytic hyperchromic anaemia resembling Pernicious Anaemia; at the other a microcytic hypochromic anaemia similar to Idiopathic Hypochromic Anaemia; and an intermediate group whose blood picture is a mixture of both, sometimes more closely resembling/

Representative Series of Puerperal Anaemias.

- some approaching Pernicious Anamia
- some approaching Idiopathic Hypochromic Anaemia.

No.1.

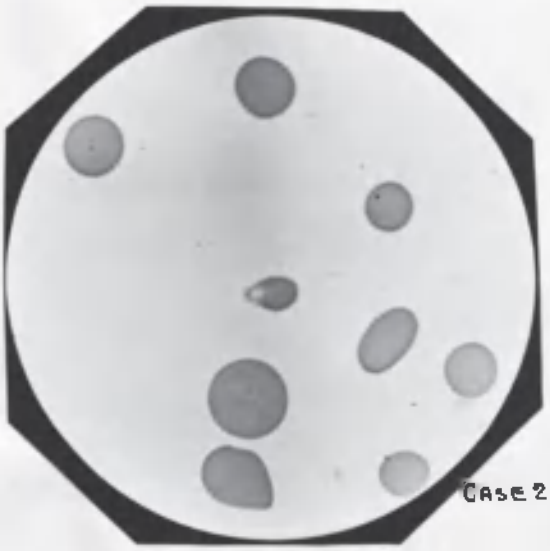


Pernicious Anaemia

(Not Associated with Preg. or Puerp.)

(x 1000)

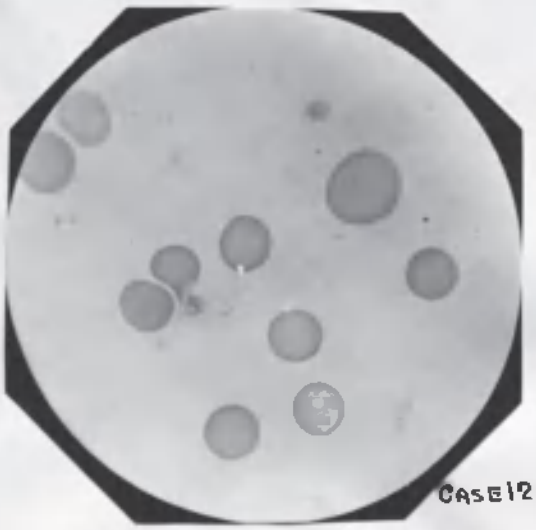
No 2.



Case 24.

'Pernicious' Anaemia of Puerperium Chronic.

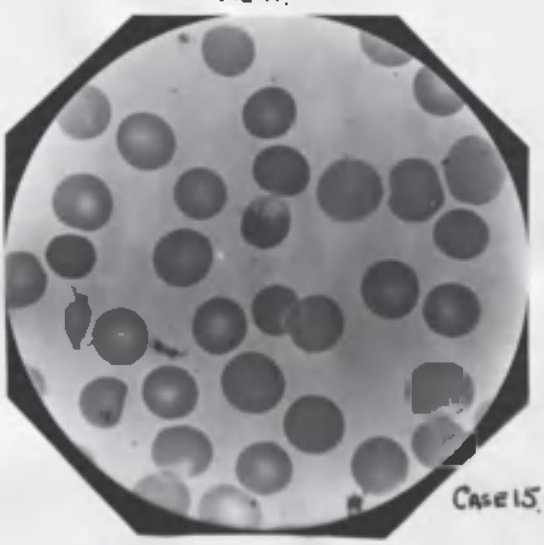
No.3.



Case 12.

'Pernicious Anaemia' of Puerperium Acute.

No 4.

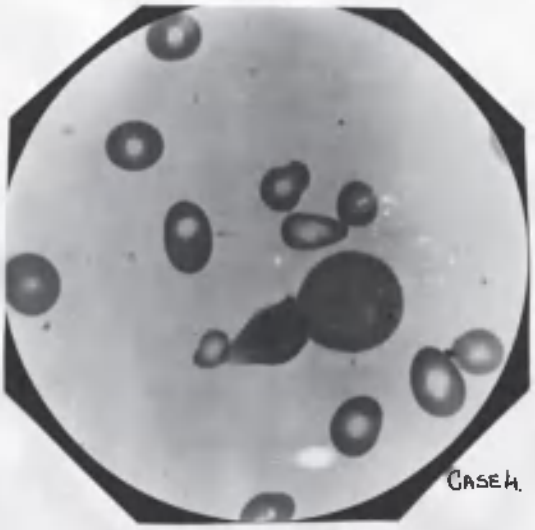


Case 15.

'Pernicious' Anaemia of Puerperium Eclampsia.

(SERIES CONTINUED)

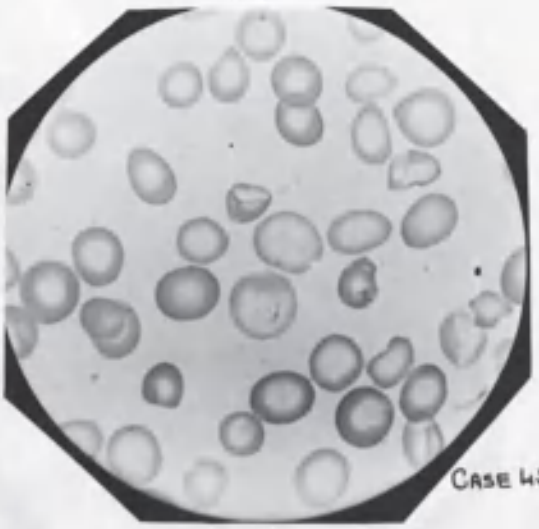
No.5.



CASE 4.

'PERNICIOUS' ANAEMIA OF PUERPERIUM.
C.I < 1 ON ADMISSION. (×1000)

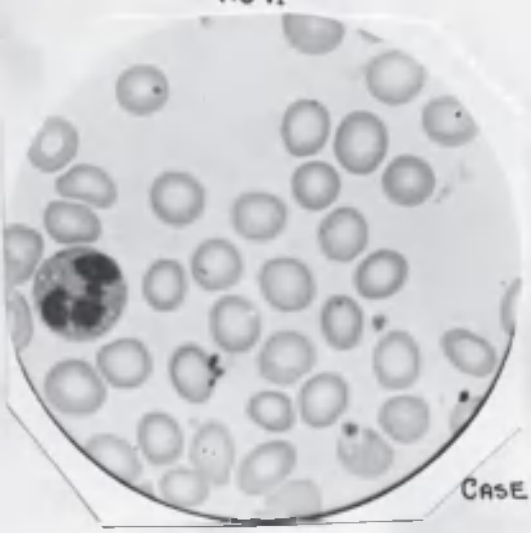
No6.



CASE 45.

'SECONDARY' PUERPERAL ANAEMIA
(N.B. MEGALOCYTES)

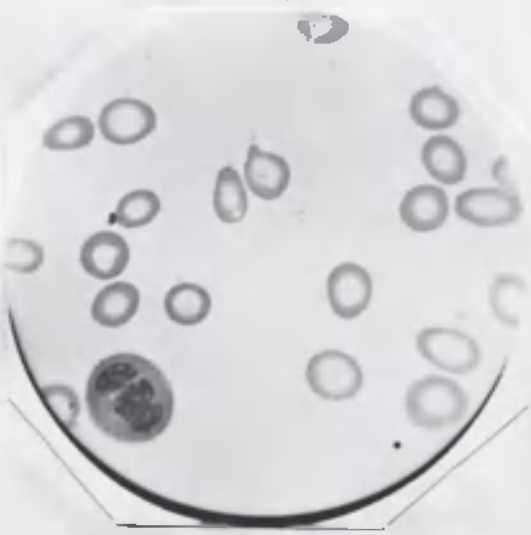
No7.



CASE 46.

'SECONDARY' PUERPERAL ANAEMIA.

No8.



IDIOPATHIC HYPOCHROMIC ANAEMIA.
(NOT ASSOCIATED WITH PREG OR PUERP.)

resembling the one sometimes the other. The more acute forms of the 'Pernicious' group tend to have no general megalocytosis, and, at times, a rather low colour index. Some cases of the 'Secondary' group have so many large cells in the stained films, that isolated fields are suggestive of Pernicious Anaemia. (N.B Series 1-8)

In the course of this investigation certain questions have arisen, which I have been unable to answer. The most important are related to haemolysis. I have not explained to my own satisfaction why the signs of haemolysis are so slight in the 'Pernicious' group, and why they are present in some cases of the 'Secondary' group. In the treatment of the 'Pernicious' group one should have investigated more fully the possibility of deficiency of the extrinsic factor as a cause, and this might have been done by treating some of the patients with marmite.

The classification of the anaemias of pregnancy and the puerperium observed in my cases is:-

1. 'Pernicious' Anaemia in Pregnancy and the Puerperium.

   (1) Addisonian Anaemia first manifested in pregnancy of the puerperium, and due to deficiency of the intrinsic factor.

   (2) Pseudo-pernicious Anaemia of Pregnancy and the Puerperium in temperate zones due to temporary deficiency of the intrinsic factor, and possibly of the extrinsic factor.

   (a)/

(a) Plastic.

(b) Hypoplastic.

2. 'Secondary' Anaemia in Pregnancy and the Puerperium.

(1) Idiopathic Hypochromic Anaemia first manifested in pregnancy or the puerperium, and due to iron deficiency.

(2) Microcytic Hypochromic Anaemia of Pregnancy and the Puerperium, due to temporary iron deficiency.

(3) Microcytic Hypochromic Anaemia in Pregnancy or the Puerperium due to some known cause such as Haemorrhage, Sepsis, Nephritis.

3. A 'Pernicious-Secondary' group combining morphological and possibly etiological factors of both.

The following is a more comprehensive classification of Anaemia in Pregnancy and the Puerperium based on a survey of the literature, in addition to my own findings.

1. 'Pernicious' Anaemia:

(1) Addisonian Anaemia complicated by pregnancy, or first manifested in pregnancy or the puerperium, and due to deficiency of the intrinsic factor.

(2) Pseudo-pernicious Anaemia of Pregnancy and the Puerperium in temperate zones due to temporary deficiency of the intrinsic factor, and possibly of the extrinsic factor.

(a)/

(a) Plastic.

(b) Hypoplastic.

(3) Tropical Macrocytic Anaemia in pregnancy and the puerperium, due to deficiency of the extrinsic factor.

2. 'Secondary' Anaemia.

(1) Idiopathic Hypochromic Anaemia complicated by pregnancy, or first manifested in it or in the puerperium, and due to iron deficiency.

(2) Microcytic Hypochromic Anaemia of Pregnancy and the Puerperium, due to temporary iron deficiency.

(3) Microcytic Hypochromic Anaemia in pregnancy or the puerperium, due to some known cause, e.g. Haemorrhage, Sepsis, Nephritis.

3. 'Pernicious-Secondary' Anaemia combining morphological and possibly etiological factors of both.

4. Various types of anaemia associated with some condition other than pregnancy e.g. Malaria, Syphilis, Tuberculosis, Neoplasm, Leukaemia.

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