The onset is usually during the last three months of pregnancy, but in some cases symptoms do not develop until after delivery. In the more acute cases the patient rapidly becomes pale and ill, with dyspnoea and prostration. The skin and mucous membranes are pale and the conjunctivae may become icteric. Usually the spleen is palpable and the liver may also be enlarged. During the stage of red cell destruction the urine contains urobilin and urobilinogen in excess, and in the more severe cases haemoglobinuria may appear. The van den Bergh test shows a positive indirect reaction. The nature of the blood picture depends to some extent upon the state of the bone marrow and its reaction to the blood loss. The anaemia is usually severe. The red cells and haemoglobin are proportionately reduced, so that a colour index of approximately unity is usual. The cells are of average size or contain at most only a few macrocytes in contradistinction to the pernicious-like anaemia of pregnancy, in which well-marked macrocytosis is necessarily an essential feature of the disorder. Anisocytosis and poikilocytosis are present. In those cases in which the bone marrow has remained uninjured polychromasia is well marked and nucleated red cell forms may appear even in untreated cases. This type may be referred to as "plastic." In spite of all this bone marrow activity, however, the degree of anaemia may remain unaltered. A leucocytosis up to 40,000 per c.mm. is usual and immature white cells of the granular series may be seen.

The blood picture is therefore essentially different from that of the pseudo-pernicious anaemia of pregnancy, in which macrocytosis is invariably present, signs of blood regeneration occur only after delivery or as the result of liver treatment, and the white cell count is normal or reduced. In those cases in which bone marrow injury has accompanied the haemolysis of the circulating red cells, signs of regeneration are few or altogether absent, and these may be described as hypoplastic or aplastic forms. The disease is rare, but obstetrical shock following delivery is common and the mortality rate high. Cases that survive the trial of labour may recover spontaneously, especially the plastic forms. The nature of the poison responsible for the haemolysis is unknown. In many cases sepsis seems to have played a part. Pregnancy appears to behave as a predisposing factor, and there is some evidence that the disease may recur in subsequent pregnancies. In the treatment of erythronoclastic anaemia iron and liver are seldom of value, but intravenous blood transfusion, repeated, if necessary, may truly be regarded as a life-saving measure. By providing red cells for immediate use in the circulation, transfusion will tide the patient over a crisis: in most cases it appears to stir up the bone marrow to greater activity, and in a manner that is little understood it stops the haemolytic process.

Conclusion

To sum up the problem, there exist in this country, more especially in hospital patient class practice, mild degrees of hypochromic anaemia of pregnancy which, though seldom dangerous to life, are nevertheless responsible for minor ailments and ill-health in both mother and child, and may be prevented or cured by a generous diet and the exhibition of iron. Occasionally severe and dangerous degrees of anaemia develop during and as a result of pregnancy, especially in the later months of gestation. These conditions demand detailed haematological investigation, accurate diagnosis, and prompt treatment appropriate to the type of anaemia present. A routine haemoglobin estimation at about the seventh month of pregnancy and detailed haematological investigation of all cases showing severe degrees of anaemia should form an essential part of ante-natal supervision.

HYPOCHROMIC ANAEMIAS OF PREGNANCY AND THE PUERPERIUM

BY

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The effects of repeated pregnancies in producing iron-deficiency anaemia have already been discussed (*Journal*, September 12th, page 525). In this communication particular attention will be paid to the problem of hypochromic anaemia occurring during gestation, and the importance of the blood loss at parturition will be dealt with in some detail. During the last century Nasse and Fouassier¹ pointed out the reduction in red cells which takes place in gestation. Since then workers in many countries have contributed studies of the anaemias of pregnancy, and the increased interest in haematology during the past ten years has embraced this field. The work of many authors in America,^{1 2 3 4 5 6 7} Britain,^{8 9 10 11} Germany,^{12 13} Norway,¹⁴ India,¹⁵ and New Zealand,¹⁶ has shown that anaemia often appears in pregnancy and has a widespread geographical distribution. The aetiology of the anaemia has been discussed by Strauss,¹⁷ Strauss and Castle,¹⁸ Witts,¹⁹ Bethell,²⁰ Irving,²¹ Boycott,¹¹ and others; and Richter, Meyer, and Bennett,⁵ Corrigan and Strauss,²² Wills,²³ Toland,²⁴ Irving,²¹ and Bethell²⁰ have studied the effects of treatment. The views held by most authorities are that hypochromic anaemia, often of severe degree, occurs frequently during pregnancy; that its production depends on an iron deficiency due mainly to the supply of iron to the foetus; and that iron therapy is followed by good results.

There has been a tendency to confine investigations into the incidence of anaemia among women to the period of pregnancy, because it is during this time that large numbers of women present themselves for routine supervision at ante-natal clinics, and so render such investigations easy. It is a more difficult matter to obtain blood examinations in a large series of non-pregnant women who complain of no symptoms of ill-health. The high incidence of anaemia found in practically all series of gravid women has led naturally to the assumption that pregnancy is the cause of the anaemia. Our figures have shown clearly that, while anaemia is frequent among pregnant women, it is only slightly less frequent among non-pregnant women, and the incidence of severe anaemia is actually less in the former group. In addition, there is a greater tendency to perform blood examinations at this rather than at other times, because such symptoms as breathlessness and oedema of the ankles, which are so common in pregnancy, often raise the suspicion of anaemia. The frequency with which anaemia will be found has already been pointed out; it is therefore natural that its relation to pregnancy should have been repeatedly stressed, since the symptomatology of pregnancy tends to make more evident the chronic anaemia so common in women. For these reasons, then, the anaemias of pregnant women have been widely studied, and comparatively little attention has been paid to those of non-pregnant women, apart from the severe cases which form the "idiopathic hypochromic" group.

Fall in Haemoglobin

Practically all authors are agreed that there is a fall in the haemoglobin level in pregnancy, but the degree of this fall and the period of gestation at which it is maximal show considerable variation in different series of cases. Richter, Meyer, and Bennett,⁵ Feldman *et al.*,²⁵ Bland,

Goldstein and First,¹ Kerwin and Collins,⁷ Wills,²³ McGeorge,¹⁶ and Galloway⁴ found that the fall progressed until shortly before term, while the series of cases reported by Strauss and Castle²⁶ showed a slight rise after the end of the second trimester. The results we obtained in investigating 1,166 women during pregnancy and at various times after delivery are shown in Fig. 1. The average haemoglobin level of women seen at different times during pregnancy falls from 83.3 per cent. at the twelfth week to 74.3 per cent. at the thirty-seventh week, and rises to 76.5 at the thirty-ninth week. In addition, it has been demonstrated by several authors^{16 26 27} that a rise in haemoglobin occurs in most cases after delivery. Our data show (Fig. 1) that throughout the first year after delivery the haemoglobin level rises from 74 per cent. within two days after labour to approximately 85 per cent. six to eleven months after delivery, after which the level is stationary. Moreover, ninety-seven untreated women

therapy during pregnancy the increase was 10 per cent. These increases have been arranged in Table I according to the haemoglobin level in gestation. It is seen that the lower the haemoglobin level at this time the greater is the rise which occurs after delivery.

The fall in haemoglobin level during pregnancy is one of the main factors leading to the belief that pregnancy causes an anaemia to develop in many cases as a result of iron transference to the foetus. However, a critical study of the literature leads one to the conclusion that most authors dealing with the hypochromic anaemia of pregnant women have adopted this theory without proper consideration of the possibility that the anaemia existed before gestation. It should be pointed out, however, that Schultz,²⁸ and Mussey, Watkins, and Kilroe,²⁹ thought that severe hypochromic anaemia in pregnancy was really a pre-existing condition. Boycott¹¹ stated that this possibility was difficult to disprove.

FIG. 1.—Haemoglobin levels in 1,166 women during and after pregnancy. The figures along the curve show the number of women examined at that particular stage.

seen during pregnancy and again about one year after delivery showed an average increase in haemoglobin of 8.6 per cent. In fifty-four women who received iron

TABLE I.—Changes in Haemoglobin Level between Pregnancy and One Year after Delivery.

Haemoglobin level in pregnancy ...		<50	50-59	60-69	70-79	80-89	90-99
Iron therapy in pregnancy: 54 cases	Number of cases	1	2	9	13	23	6
	Average change in Hb	+22.0	+36.0	+14.0	+15.1	+6.1	-2.8
No therapy: 97 cases	Number of cases	—	4	16	39	25	13
	Average change in Hb	—	+12.3	+16.1	+11.6	+5.5	-5.0
Combined series: 151 cases	Number of cases	1	6	25	52	48	19
	Average change in Hb	+22.0	+20.2	+15.4	+12.5	+5.8	-4.3

Physiological Hydraemia

A factor of great importance in anaemic states during pregnancy is the physiological hydraemia or dilution of the blood. Dieckmann and Wegner³⁰ have constructed a table summarizing many of the published results. In all but two of the ten series in which the blood volumes of pregnant and non-pregnant women were compared, there was an increase in the former group. When it is considered that these results are stated in terms of percentage of body weight, which shows gains of 20 to 30 lb. during gestation,³¹ the absolute increases in blood volume are still more striking. Similar results have been shown by Dieckmann and Wegner,³⁰ Feldman *et al.*,²⁵ Oberst and Plass,³² and Richter, Meyer, and Bennett.⁵ These studies indicate that the increase is particularly in the plasma volume, although in some cases there is a gain in total cell volume. Calculations from the data of Dieckmann and Wegner³³ for women during the eleventh to sixteenth, twenty-seventh to thirtieth, and thirty-sixth to fortieth

weeks of gestation show that the average amount of total circulating haemoglobin is practically the same at these three periods. According to these authors, the volume of the blood plasma has increased by 25 per cent. at term. Individual cases of theirs showed all degrees of change between a slight reduction in the plasma volume and an increase of over 100 per cent. It is generally held that this hydraemia becomes less towards the end of pregnancy and still less very soon after delivery, but the time at which it disappears completely has not been clearly established. It is evident, therefore, that the increased incidence of anaemia and the fall in haemoglobin level can be explained *prima facie* on the basis of blood dilution at least as satisfactorily as by the presumption of an iron deficiency due to transference of iron from mother to foetus.

Several authors have failed to realize that, although a fall in haemoglobin may be prevented or transformed into a rise by iron treatment of a group of pregnant women, this does not constitute proof that the fall which otherwise occurs is due to the development of iron deficiency and

three months the change over that period was divided by two or three, respectively, and the result taken as the change which would take place in each month. Similar calculations were applied in a series of women who received no therapy. Both groups are representative of the total series of 819 pregnant women examined, and contain, therefore, few cases of severe anaemia. It is seen that while the upper curve shows a rise of almost 8 per cent., the lower curve falls, so that the difference at term exceeds 13 per cent.

Changes in Colour Index

We must conclude, then, that before the hypothesis that severe hypochromic anaemia develops frequently during an uncomplicated pregnancy can be accepted, arguments other than those already discussed are necessary. For example, a definite fall in the colour index during pregnancy would be strong presumptive evidence of iron deficiency. It is possible to calculate colour indices from the charts of Strauss and Castle,²⁶ compiled from data on haemoglobin estimations and red cell counts

FIG. 2.

not entirely to blood dilution unless it is definitely shown that none of the women suffered from iron deficiency prior to the pregnancy. A woman with hypochromic anaemia who becomes pregnant will respond to iron therapy quite satisfactorily, and the resulting increase in haemoglobin formation may entirely mask the fall which hydraemia would produce. Therefore, the changes in the haemoglobin level during iron treatment of a gravid woman suffering from hypochromic anaemia depend on the resultant of two factors: new haemoglobin formation, tending to cause a rise, and hydraemia, tending to cause a fall. It should also be noted that the unsatisfactory results of iron therapy sometimes seen in pregnancy are due to the fact that the rise in the haemoglobin percentage which occurs represents, not the difference at the beginning and at the end of treatment, but the difference between the level at the end of treatment and one which at that time might have been considerably lower than the initial value as a result of increased hydraemia. This point is well illustrated by Fig. 2, in which the changes in haemoglobin level in a series of women treated with ferrous sulphate (9 grains daily) have been calculated from month to month during gestation. In cases where haemoglobin estimations were made at an interval of two or

in 200 women. At 100 days' gestation the average colour index was 0.87 and at 250 days it was again 0.87. Bland, Goldstein, and First²⁷ give figures for the haemoglobin and red cells of fifty women seen during pregnancy and again two to six months after delivery. The average colour index at both times was 0.94, although the average haemoglobin level in pregnancy was 14.6 per cent. less than that after delivery. The fact that the reductions in haemoglobin and red cells observed during pregnancy were exactly proportional in both these series is much more in favour of a purely hydraemic process than a deficiency of iron resulting from gestation. It is, however, possible that the response to a marked degree of hydraemia is an increased production of red cells by the bone marrow. If the iron reserves are very low, these new cells will be poorly haemoglobinized and will cause a lowering of the colour index. Thus it is theoretically possible that a fall in the haemoglobin concentration and in the colour index might occur in the presence of an increased amount of circulating haemoglobin. In other words, signs of an iron-deficiency anaemia could develop although the amount of iron in the circulation had actually increased. Although it is probable that the supply of iron to the foetus is a factor which would accentuate this relative iron deficiency,

it will be shown later that its effect can only be slight. Thus even the development of anaemia with lowering of the colour index cannot be taken as definite evidence that the maternal iron content has been reduced by the demands of the foetus.

It is of more importance, however, to realize that before cases of hypochromic anaemia can be attributed to the iron demands of the foetus, a fall in the colour index during pregnancy must be shown. Moreover, this fall should occur particularly during the last trimester, when the iron supply to the foetus is at a maximum and the degree of hydraemia may be decreasing. In the series of cases described by Boycott¹¹ as hypochromic anaemias of pregnancy, the colour index was low initially but did not decrease significantly as gestation progressed. It is therefore probable that in these cases some degree of hypochromic anaemia antedated the pregnancy. Reports of cases of hypochromic anaemia during pregnancy, proved by blood examination to have had no previous anaemia, have not been found in the literature. On the contrary, the histories of published cases³⁴ lead one to suspect strongly that anaemia had been present for several years.

Pre-existing Anaemia

In support of their contention that a true iron-deficiency anaemia had occurred during gestation, Strauss and Castle²⁶ stressed the fact that their cases did not improve significantly after delivery. The number of their cases, however, was small. As has been pointed out by Boycott,¹¹ the degree of blood loss at parturition is such a variable factor that a large series of cases is necessary before any conclusions can be drawn regarding the changes in haemoglobin level during the puerperium. Moreover, our data indicate (Table I) that the rise in haemoglobin during the first year after delivery varies inversely with the haemoglobin level during pregnancy. We may conclude, therefore, that there appears to be no real evidence to support the view that the severe hypochromic anaemias of gestation are due to the iron demands of uncomplicated pregnancy. It appears much more probable that such anaemias antedate the pregnancy and apparently are rendered more severe by hydraemia.

The quantitative aspect of the problem may now conveniently be discussed on the basis of the figures presented in the previous paper. Taking 550 mg. as the total "iron demand" and 280 days as the duration of gestation, we find that in order to satisfy this demand a woman needs to achieve a positive iron balance of just under 2 mg. daily. This represents roughly a retention of slightly less than one-half of the "available iron" contained in the average dietary of women of the poor classes. It may be deduced, therefore, that in many cases some loss of maternal iron occurs during gestation. If, however, over the whole of pregnancy only 1 mg. of iron is retained daily, then 270 mg. will be deducted from the maternal iron content. The total change in the haemoglobin level resulting from this loss would be a fall from 100 to 90 per cent.* This hypothetical case probably represents fairly accurately the iron deficit in a woman with gastric hypofunction taking an iron-poor diet. If throughout pregnancy no dietary iron whatsoever be retained, the haemoglobin level would fall from 100 per cent. to 78 per cent. These calculations presume a complete absence of maternal iron reserves, a condition which probably never arises. Since the supply and demand of iron over the whole period of pregnancy have been considered, it is irrelevant to object that iron transference to the foetus is not a uniform process but becomes increased towards the end of gestation.

* In this and the following calculations the blood volume is taken as 5 litres and 100 per cent. haemoglobin as equivalent to 50 mg. of iron per cent.

It is therefore clear that even in circumstances which are as unfavourable as possible and which probably never exist, only a moderate degree of anaemia can develop as a result of the iron demands of uncomplicated pregnancy. Moreover, the above calculations apply only to the total effect of pregnancy—that is, the effect on the maternal organism at term. Most of the published cases of the hypochromic anaemia of pregnancy have had marked anaemia at or before the end of the second trimester. At this stage the iron content of the foetus is probably slightly less than 100 mg.³⁵ and one may take 180 mg. to represent approximately the total iron loss. In the absence of any retention of dietary iron, this loss would be accounted for by a fall in the maternal haemoglobin from 100 to 93 per cent.

Consideration of the problem from a quantitative point of view thus supports our previous conclusion—namely, that cases of severe hypochromic anaemia in pregnancy are cases of pre-existing anaemia rendered apparently more severe by blood dilution. This contention is supported also by the results of repeated haemoglobin estimations in a series of twenty-one women first seen when gestation had lasted for an average period of 6.9 months. All of them had haemoglobin percentages of less than 70 at this time, and therefore, as a group, they suffered from iron deficiency. After a further two months, during which iron transference to the foetus was presumably at a maximum, the haemoglobin level of the group had risen by 5 per cent. Bland, Goldstein, and First¹ found that 58 per cent. of forty-five women in whom the red cell count was below 3.5 millions before the end of the second trimester showed definite improvement before term. These findings are probably due to an early reduction in hydraemia, and are certainly strong evidence against an increase in anaemia.

Blood Loss at Parturition

The effect of repeated pregnancies in the production of hypochromic anaemia has already been discussed. In this connexion it was pointed out that while about 350 c.cm. of blood represented the average haemorrhage at parturition, very wide variations existed. Published figures^{4, 5, 36} range from 75 to 1,020 c.cm. It is obviously important to distinguish clearly between the sudden blood loss of parturition and the iron transference to the foetus, which takes place over a period of nine months and is therefore compensated, at least to a large extent, by the absorption of dietary iron. Such acute blood loss may bring about severe hypochromic anaemia, since the iron reserves in the class of women under consideration must be low in many cases. Consideration of a hypothetical case will make it clear that, with the average dietary taken by the poor women in this city, little haemoglobin regeneration is possible following haemorrhage. If 2.5 mg. of dietary iron be retained daily during six months' lactation, the gain in iron at the end of this period would be 270 mg. (total retention of 450 mg. less 180 mg. iron loss during lactation). In a case in which post-partum haemorrhage has reduced the haemoglobin level to 50 per cent., complete utilization of 270 mg. of iron in haemoglobin synthesis would produce a rise in the haemoglobin up to 61 per cent. The resumption of menstruation after six months' lactation will in many cases either prevent a further rise in haemoglobin level or produce a gradual fall. Thus it is probable that the frequency with which a history of anaemia dates back to a previous pregnancy is usually due to excessive blood loss at parturition and not to the supply of iron to the foetus.

Some interesting points regarding the effect of the blood loss at parturition are illustrated by our findings. Thirty-four women were examined within a few days of term, within forty-eight hours after delivery, and again on the ninth day of the puerperium. The average haemoglobin

levels at these three times were 75.4, 69.9, and 74.7 per cent. Since the physiological hydraemia becomes less during the latter part of pregnancy, and still less after delivery, the fall in haemoglobin level occurring just after labour must be due to the blood loss at parturition. Actually seven out of the thirty-four cases showed a rise forty-eight hours after delivery, while in twenty-seven the haemoglobin fell in varying degree, the maximum fall being 28 per cent. Between forty-eight hours and the ninth day after delivery no case showed a fall, and the average rise in haemoglobin was 4.8 per cent. This rise is due to progressive decrease in hydraemia and to haemoglobin regeneration following the haemorrhage of parturition.

Since hydraemia becomes less before term and during the puerperium, it might be deduced that the difference in haemoglobin level during pregnancy and a few days after delivery would indicate the extent of the blood loss at parturition, and therefore might give a clue as to the probable course of the haemoglobin level during the first few weeks of the puerperium. We have data on fifteen women to illustrate this point, and while one cannot draw definite conclusions from such a small number the results are at least suggestive. Seven of the fifteen showed a fall in haemoglobin or a rise of less than 5 per cent. between pregnancy and a few days after delivery. In these the rise which occurred between pregnancy and a few weeks after delivery was 6 per cent. In this group the blood loss at parturition was probably severe, since reduction in the physiological hydraemia resulted in little or no change in the haemoglobin level shortly after delivery. Consequently the further reduction in hydraemia during the puerperium produced only a slight rise in haemoglobin above the level in pregnancy. Eight of the fifteen showed a rise of 5 per cent. or more between pregnancy and the first few days of the puerperium. In these blood loss at parturition was probably slight, and the average rise in the haemoglobin level between pregnancy and a few weeks after delivery was 21 per cent.

Conclusions

1. The average haemoglobin levels of poor women fell during pregnancy up to the thirty-seventh week of gestation, and then rose slightly before delivery.
2. A rise in the haemoglobin level occurred from forty-eight hours post partum to six to eleven months after delivery.
3. Even in women of the poor classes the transference of iron from the mother to the uterus and its contents is compensated wholly or to a large extent by dietary iron.
4. In cases where this demand exceeds the retention of dietary iron, the degree of maternal iron deficiency which results is only slight.
5. Where hypochromic anaemia in pregnancy is marked, anaemia has probably existed before the pregnancy, but has been made more apparent by physiological hydraemia.
6. Therefore, the conception that uncomplicated pregnancy frequently produces a severe degree of hypochromic anaemia should be discarded.
7. The blood loss at parturition varies greatly in degree and often produces severe hypochromic anaemia.

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PREVENTIVE MEASURES IN DERMATOLOGY*

BY

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The discussion which I have the privilege of opening concerns "Preventive Measures in Dermatology." At the first hearing that phrase has a novel sound, but I am not introducing yet another subdivision of the science and art of medicine: 450 years before Christ the writer or writers of the early chapters of Leviticus were concerned with the prevention of a disease which has cutaneous manifestations. The whole fifty-nine verses of the thirteenth chapter of Leviticus are devoted to the differential diagnosis of leprosy, the isolation of the patient once the disease has been diagnosed, and the purification of his clothing. One could quote several relevant examples of the preventive measures which have been taken in former centuries, but I will merely refer to the introduction of the quarantine system by the Venetians in A.D. 1403 in order to prevent the spread of bubonic plague—a disease which is inoculated through the skin by the bite of an infected flea; to the Turkish custom described in 1717 by Lady Wortley Montague¹ whereby persons were inoculated with variolous matter and after having developed a mild attack of smallpox were immune to the disease; and to Jenner's work on variola and vaccinia.

I have mentioned these few well-known facts to emphasize that although it was not until the middle of the

* Read in opening a discussion in the Section of Dermatology at the Annual Meeting of the British Medical Association, Oxford, 1936.