BLOOD FORMATION IN INFANCY

PART IV*—THE EARLY ANAEMIA OF PREMATURITY

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In premature infants the post-natal fall in haemoglobin level tends to be exaggerated, so that these infants, although starting life with a cord haemoglobin as high as that of normal infants (see Part III), often develop abnormally low haemoglobin levels during the second month. Usually this early

anaemia of prematurity slowly improves from about the fourth month, but is frequently followed by a second phase of anaemia (Fig. 1). This late anaemia of prematurity, which is characterized by hypo-

chromia of the red cells and a response to iron therapy, does not differ from the hypochromic anaemia common in other infants of over 6 months. It reflects the precarious iron balance during infancy, exaggerated by several factors which bear on the premature infant, such as its smaller initial iron stores, its more rapid growth, and its tendency to receive a purely milk diet for a prolonged period. These facts were established many years ago, Mackay (1935) having first clearly distinguished between the early and late phases of anaemia.

The cause of the early anaemia of prematurity has, however, never been precisely understood. Three different mechanisms have been suggested. (1) That the anaemia is the result of an abnormally high rate of destruction of red cells. (2) That it is the result of the rapidity of body growth outstripping a normal erythropoietic capacity. (3) That it is the result of a functional immaturity of the bone marrow, a dyshaemopoiesis.

Each of these three suggested mechanisms will be

FIG. 1.—Course of haemoglobin level in a premature infant (weight 1,560 g.) from birth to 8 months. Note normal level at birth (cord blood); post-natal fall reaching 9 g. during second month ('early anaemia'); recovery during fourth month, followed by second fall ('late anaemia'). Hypochromia of red cells was present from 4 to 7 months. Iron was exhibited at 5 months with a satisfactory response.

examined in the light of our data. The consensus of current opinion, judging from paediatric textbooks, is that a combination of these factors operates, and that the early anaemia of prematurity cannot be influenced by giving haematinics. We have arrived at different conclusions.

Material and Methods

Since it is known that the lower the birth weight the more marked is the early anaemia of the premature infant, we have confined our attention to the smaller infant, the 31 infants studied all having birth weights below 1,620 g. (3 lb. 9 oz.). The cord was clamped as soon as conveniently possible after birth. Infants were fed initially on breast milk with vitamin supplements; a few became fully breast fed. The majority, when they reached about 2,000 g. (4½ lb.), were gradually changed on to a cow's milk formula. The dried milk from which this formula was made contained small amounts of added iron and ammonium citrate, such that an infant of 2,000 g. received about 2 mg. iron per day. This formula had long been in use for feeding premature infants, and as it was known that anaemia was not prevented thereby it was decided to continue the established feeding practice. All the infants made uneventful progress.

The main study concerns a group of 26 infants, to half of whom additional iron was given, while another five infants received cobalt as well as iron.

Samples of blood were taken at intervals of one to two weeks beginning as soon as steady weight gain had begun, usually in the second or third week. Venous samples (heparinized) only were employed, up to 1 ml. blood being aspirated, usually from a scalp vein. Venous samples offer the following advantages over skin-prick samples: the falsely high haemoglobin values obtained from skin-prick samples are avoided; measurements can be checked; the haematocrit can be measured and from this the mean corpuscular haemoglobin concentration derived, providing an index of iron deficiency. Haematological methods and in particular standards of haemoglobinometry have been detailed in Part I.

Blood volumes were calculated in order to study changes in the total circulating haemoglobin. Mollison, Veall and Cutbush (1950) and Mollison (1951) give data from which the blood volumes of young infants can be calculated from the body weight and venous haematocrit: the method of using their data has been described in Part I. Mollison *et al.* worked with newborn infants, though they showed that their formula for calculating blood volumes agreed well with accepted values for adults. Nevertheless in applying their data to premature infants, we realize that considerable inaccuracy may result. This point will be taken up again in the following section.

The bone marrow was examined in a number of cases by means of tibial aspiration. From the total count of nucleated cells and the proportion of erythroid cells, the marrow erythroid count was measured. This we

have found to be a useful yardstick of erythropoietic activity (see Parts I and II).

The Rate of Destruction of Red Cells after Birth in the Premature Infant

The mean life-span of the red cells of a premature infant can at present only be estimated by indirect means. The fact that neonatal jaundice is often particularly marked in premature infants has often been cited as evidence of haemolysis. Recent studies have not agreed as to whether the degree and persistence of bilirubinaemia is in fact abnormal in premature infants (Obrinsky, Allen and Anderson, 1954; Billing, Cole and Lathe, 1954), but in any case, as Billing *et al.* emphasize, bilirubinaemia in these infants must be largely ascribed to hepatic insufficiency.

There is some evidence (Mollison, 1951) that amongst the red cell population of the full-term infant there may be a small proportion having a somewhat shorter life-span than the 120 days of the normal red cell. It is more than likely that the same applies in the smaller premature infants, some of whose red cells must date from an early period of foetal life. The question is whether such a factor, if it exists, is of sufficient magnitude to contribute significantly to the early anaemia of the premature infant.

In order to gain an answer, even if an imperfect one, to this question, we have estimated the rate of decline of the total haemoglobin during the first few weeks of life in each of the infants of our series. From bone marrow studies to be described later in this paper, it is clear that in premature infants as in normal infants, erythropoiesis is at a low ebb during the first few weeks of life. Therefore it would be expected that the rate of decline of total haemoglobin would be largely determined by the rate of red cell destruction. Suppose the average life-span of the premature infant's red cells to differ little from the normal value of 120 days, then the total haemoglobin present at birth would decline at such a rate that all would have disappeared by the 120th day. By comparing the observed rate of decline of the total haemoglobin with the expected rate, some idea can be gained of whether the rate of destruction of red cells is or is not appreciably greater than normal.

This has been done for an individual infant in Fig. 2. In this case it will be seen that the haemoglobin declined at about the calculated rate during the first month of life. Similar curves were constructed for all 26 infants of the series. In two cases the observed rate of decline of haemoglobin during the first month appreciably exceeded the expected

FIG. 2.—Rate of destruction of red cells in a premature infant (weight 1,460 g.). Line X represents the expected rate of decline of total haemoglobin, assuming that new blood formation is negligible and that the mean life-span of the red cells is 120 days. During the first 30 days the observed decline in total haemoglobin proceeded at the expected rate.

rate; in the remaining 24 the observed rate was equal to, or more often considerably less than the expected rate.

The many assumptions implicit in this quantitative approach to the problem obviously make it justifiable to draw only very rough conclusions as to the life-span of the red cells in these cases. We have, for instance, assumed that blood volume comprises the same fraction of body weight in premature as in normal infants, although the scantiness of subcutaneous fat in premature infants presumably means that in them the blood volume actually comprises a somewhat larger fraction. If so, then the total haemoglobin in the early weeks of life will have been estimated too low, and consequently our observed rates of decline of total haemoglobin will be too low. This may explain why the observed rates of decline of total haemoglobin were in some cases less than the expected rate. Nevertheless, after making reasonable allowance for this factor, we conclude that the rate of red cell destruction in the premature infant is unlikely to be much greater than normal, and that therefore excessive red cell destruction is not a major factor in the early anaemia of prematurity.

Since completion of our own studies on this subject, those of Schulman, Smith and Stern (1954) have been published. They have with enviable skill succeeded in measuring blood volumes in premature infants between 1 and 94 days old. Their curve relating blood volume to venous haematocrit in

premature infants agrees reasonably well with that given by Mollison (1951) for full-term infants and utilized by us for calculating blood volumes in premature infants. Thus the results of Schulman *et al.* on this point provide support for the validity of our approach.

Rates of decline of total red cell mass were also derived by Schulman *et al.* from their blood volume determinations, and the conclusion was reached that the mean red cell life in premature infants was slightly shorter than normal, with values from 77 to 98 days in contrast to the normal 120 days. These authors finally concluded that while red cell survival in premature infants is probably slightly diminished, this effect is insufficient to account for the production of anaemia, though it may contribute towards it. These conclusions thus differ little from our own.

The Effect of Body Growth

Most thriving premature infants grow nearly as fast as does a foetus of like gestational age; many achieve this standard and not a few surpass it. When the infants of our series reached a weight of about 1,800 g. (4 lb.) the rate of weight gain was usually 1.5–2% per day, such rates being often maintained for several weeks. For comparison, a 2% daily weight gain by an infant of 4.5 kg. (10 lb.) is equivalent to a weekly weight gain of 630 g. (22½ oz.), a rate which is never sustained by a normal infant.

It can be calculated that with a growth rate of 2% per day the daily production of haemoglobin needed to maintain a constant level of 11 g./100 ml. would be 0.14 g./kg. body weight, over and above the amount necessary to replace effete red cells. To maintain the haemoglobin concentration at a somewhat lower level of 8 g./100 ml. would require the daily formation of 0.10 g./kg., i.e., only 70% as much.

It is of interest to compare these figures with some other estimates of the body's capacity to synthesize haemoglobin. For instance, Heath (1933) studied the rate of increase in haemoglobin of a group of adults under treatment with iron for severe hypochromic anaemia: the mean rise of haemoglobin was from 20% to 70% in 30 days. Taking the blood volume of a severely anaemic subject as 60 ml./kg., this rate of rise in haemoglobin concentration is equivalent to a daily increment in total haemoglobin of 0.16 g./kg.

From the data of other authors who have treated severe iron deficiency anaemia in children by means of oral iron (Josephs, 1953), intravenous iron (Dickstein, Wolman, Tan, Slaughter, Butson and Cohen, 1952), or iron and ascorbic acid (Gorten and

Bradley, 1954) values have been similarly derived for the rate of haemoglobin synthesis, expressed as the number of grams of circulating haemoglobin formed per day per kilogram body weight. In these three studies this figure has varied from 0.10 to 0.20 with an average value of 0.15 g./kg.

Such a comparison shows (1) that the growth of the premature infant itself requires the formation of haemoglobin in amounts which are of the same order (in proportion to size) as are produced by the body under the stimulus of iron medication in iron deficiency anaemia; (2) that the lower the haemoglobin concentration in the blood, the smaller the amount of erythropoiesis needed to maintain this concentration during growth. Therefore, if erythropoiesis be insufficient to maintain a normal haemoglobin concentration, the concentration will continue to fall until a level is eventually reached where haemoglobin requirements become balanced by haemoglobin formation.

If rapid growth were the factor mainly responsible for the early anaemia of prematurity, we should expect that the rate of growth would largely determine the degree of anaemia. Accordingly we have assessed the rate of growth in terms of the number of days taken by an infant to double its birth weight, and compared this with the lowest haemoglobin reached. No correlation between rate of growth and degree of anaemia was found. We conclude that rate of growth does not by itself adequately account for the anaemia.

The high rate of growth does, however, necessarily imply that once anaemia has developed in a premature infant from whatever cause, then its correction is likely to be slow. This point is illustrated by the case shown in Fig. 3, where the haemoglobin concentration fell steadily until it reached 8 g./100 ml. on the 58th day. By then erythropoiesis had become active, as shown by the rise in the marrow erythroid count, and the total haemoglobin began to increase. Nevertheless the haemoglobin concentration, on account of the rapid growth of this infant (1.5% per day at this period), fell rather than rose, and from the 80th to the 120th day was still only slowly rising towards a normal level.

We conclude that the rapid growth of the premature infant is not the main cause of the early anaemia, but that it is an important factor in prolonging it.

The Erythropoietic Capacity of the Marrow in the Premature Infant

Our earlier studies of the myelogram in normal infants during the first three months of life (see

FIG. 3.—Course of total haemoglobin, haemoglobin concentration in g. %, and marrow erythroid count in a premature infant. Note that the erythropoietic activity of the marrow increases only slowly, so that the decline in haemoglobin concentration is not arrested until this has fallen below 9 g. %. From the 60th day the total haemoglobin increases, but owing to the rapid growth of the infant (weight tripled by 110th day) there is only a very slow rise in haemoglobin concentration.

Part II) have revealed a simple pattern. Erythropoietic activity, as gauged by the marrow erythroid count, is high at birth but falls rapidly to a very low level which persists for about two months, by which time the haemoglobin has usually fallen to about 11 g./100 ml. This lowered level stimulates erythropoiesis, the marrow erythroid count gradually rising to a value comparable with that found in normal adults. The lower the haemoglobin falls, the greater the stimulus to the marrow (see Fig. 6 of Part II).

In order to discover whether erythropoiesis follows a similar pattern in premature infants, we have examined marrow samples from infants in our series on 29 occasions, at ages ranging from 26 to 99 days. In 21 instances this examination was made during the second month of life. The marrow has been studied with a view to answering two questions. (1) Do the numbers of the different types of cell and their morphology differ in the premature infant from the normal infant? (2) Does anaemia stimulate erythropoietic activity in the premature as in the normal infant?

The Myelogram in the Premature Infant. We can summarize the results of 29 marrow examinations by stating that we have observed no difference whatever between the morphology of the various

types of cells seen in the marrow of the premature and the normal infant. Megaloblastic erythropoiesis was never seen, and the haemoglobinization and nuclear maturation of the normoblasts followed the pattern seen alike in normal infants and in normal adults.

Two studies of the marrow picture in premature infants have been previously published. Lichtenstein and Nordenson (1939) described various irregularities of maturation of the normoblasts, which (although no normal infants were examined as controls) they interpreted as evidence of a functional insufficiency of the marrow. This work has often been quoted in support of the view that haemopoietic immaturity is the cause of the early anaemia of prematurity, a view for which our findings provide no support. Joppich (1948) examined the marrow of 12 premature infants at ages from 2 to 4 months; he found no sign of abnormal haemopoiesis, the majority of specimens showing active erythropoiesis.

The Erythropoietic Response of the Marrow to Anaemia. By relating the marrow erythroid count to the haemoglobin level of the blood we find that in the premature infant erythropoiesis increases as the haemoglobin level falls, although the response is a sluggish one. An individual case set out in Fig. 3 illustrates this point. The marrow of this

infant was examined on three occasions. On the 26th day, when the haemoglobin was 13.4 g./100 ml., the marrow erythroid count was 300/c.mm., showing that erythropoiesis was at a very low level. By the 33rd day the haemoglobin had fallen to 12.1 g./100 ml. and the marrow erythroid count had risen to 6,000/c.mm., still a low count. By the 54th day the haemoglobin had fallen below 9 g./100 ml. and now the marrow erythroid count had risen to 37,000/c.mm. indicating active erythropoiesis, and at the same time the reticulocytes, previously below 2%, rose to 5%. At this point the total haemoglobin started to rise and the fall in haemoglobin concentration was arrested.

A comparable pattern was found in other individual premature infants studied; the erythropoietic response to a falling haemoglobin concentration did not occur until a time lag of some two weeks after the haemoglobin had fallen below 11 g./100 ml. and therefore the fall in haemoglobin was not arrested until levels of 10 g./100 ml. or less had been reached.

The response of the marrow to anaemia is also illustrated in Fig. 4, which shows that there is in general an inverse relation between the marrow erythroid count and the haemoglobin concentration of the blood, the unbroken line roughly indicating the trends of the data for premature infants. The broken line is taken from a comparable series of observations on normal infants (Fig. 6 of Part II). At first sight it appears as if in premature infants erythropoiesis is less sensitive to the stimulus of anaemia, since within the range of haemoglobin 11 to 13 g./100 ml. the marrow erythroid counts tend to be higher in the normal than in the premature infants. This apparent difference can be accounted for by the time lag which elapses between the stimulus provoked by an anaemia and the ability of the marrow to increase erythropoiesis, a delay which means that the more rapid the rate of fall of the haemoglobin level, the lower that level will have reached by the time erythropoiesis increases. Thus the faster rate of decline of the haemoglobin level in the premature infant, occasioned by its rapid growth, exaggerates the effect of the time lag before erythropoiesis mounts.

This time lag is not peculiar to the premature infant, because we have observed the same effect in full-term infants. In two normal infants we were able to study the result of an acute anaemia resulting from a considerable haemorrhage just after birth, such that the haemoglobin was reduced to below 10 g./100 ml. on the first day of life. Erythropoiesis, as gauged by the marrow picture and by the reticulocytes, remained at a low ebb for two to

FIG. 4.—Relation of marrow erythroid count to haemoglobin level in blood of premature infants. The unbroken line roughly indicates the trend, which shows that erythropoiesis tends to be at a low level until the haemoglobin falls below 11 g. %. For comparison, the trend in normal infants is represented by a broken line (see text).

three weeks in each case, the haemoglobin level consequently continuing to fall during this period. By contrast, an acute post-haemorrhagic anaemia in an adult is known to be followed by a marrow and reticulocyte response within four to six days. The relative insensitivity of the marrow to anaemia seen in the premature infant thus seems to be a general characteristic of early infancy.

The Mechanism of the Early Anaemia of Prematurity

The facts so far presented lead to the following account of the early anaemia of prematurity.

The premature infant, like the normal infant, shows suppression of erythropoiesis shortly after birth. As a result the haemoglobin concentration falls, due to breakdown of red cells at an approximately normal rate. When the haemoglobin approaches a level of 11 to 12 g. erythropoiesis is stimulated, but this stimulus takes some two weeks to produce any appreciable effect in the blood. During this period the infant's haemoglobin level therefore continues to fall, and at a rate which is decidedly faster in the premature than in the normal infant, mainly because of the greater rate of growth of the premature infant. Thus the post-natal fall in haemoglobin is arrested at a level which is well below the normal level of about 11 g. %. The same high rate of growth thereafter makes correction of the anaemia inevitably slow.

It is worth noting that even in normal infants the post-natal fall of haemoglobin may sometimes carry this to levels as low as 9 g. by the seventh week (see Part III), but the lower rate of growth of normal infants allows this anaemia to be corrected quickly.

These views on the mechanism of the early anaemia of prematurity receive further support from the results of giving first iron and secondly cobalt to premature infants.

The Effect of Prophylactic Iron on the Early Anaemia of Prematurity

The effect of iron in the anaemia of prematurity has been the subject of numerous studies, but few of these have made a clear distinction between the effect of iron in the early and the late phase of the anaemia. Merritt and Davidson (1934) found that whether or not premature infants were given iron from shortly after birth, the haemoglobin fell to a level of about 11 g. by the second month, while in the iron-treated group the haemoglobin then tended to rise slowly; in the untreated group it fell further. Comparable results were obtained in a study by Magnusson (1935): in both an iron-treated and a control group the haemoglobin fell to 65% at

11 weeks; thereafter the treated group showed a rapid rise of haemoglobin, whereas in the controls it remained at about 65% over the next three months. Blackfan and Diamond (1944) reached a different conclusion, that iron medication is without influence on the course of the haemoglobin curve, at least during the first three months of life. Schulman *et al.* (1954) likewise infer that since about four months elapse before the haemoglobin mass at birth is regained, iron medication is unnecessary before the third or fourth month.

On the assumption that the only purpose of giving iron to premature infants is to prevent iron deficiency developing after the first trimester, the commonest current practice is probably for it to be given only from about the sixth week or later.

In order to clarify the matter we have followed the course of the haemoglobin level in a group of 13 premature infants given iron from shortly after birth, and compared results with those from a control group of 13 premature infants. There are two main differences between this and previous studies. First, only small premature babies (with birth weights below 1,620 g., 3 lb. 9 oz.) have been included, so that results are not diluted by data from larger infants who may never develop anaemia. Secondly, treated and control groups were carefully matched as regards birth weight. In each group there was one case with a weight of 1,000 to 1,200 g., seven cases with a weight of 1,200 to 1,400 g., and five cases with weights of 1,400 to 1,620 g. However, it happened that there were six twins in the treated group and no twins in the control group (see Appendix).

Iron was given as a solution of ferrous sulphate ($\text{FeSO}_4 \cdot 7 \text{H}_2\text{O}$) in doses of 60 mg. (1 grain) thrice daily. This was begun during the second or third week. The control group received iron in the same dosage, but starting only after the haemoglobin level had fallen to 11 g., usually at about the sixth week.

Results are shown in Fig. 5. The haemoglobin curves of treated and control groups run together until the 50th day, by which time the haemoglobin has fallen to 10 g. From here the two curves diverge; in the treated group the haemoglobin slowly rises, whereas in the control group it continues to fall, reaching 9.4 g. at the 70th day before starting to rise slowly. Thus between the 50th and 80th days the haemoglobin levels of the treated group averaged 1 g. 100 ml. higher than the controls.

The data were analysed statistically (see Appendix); the average haemoglobin level of the treated infants between 60 and 100 days was significantly higher than that of the controls.

The effect of iron can also be seen upon the

FIG. 5.—Effect of iron on the early anaemia of prematurity. The treated group of 13 infants (birth weights, 1,170-1,620 g.) received iron from about the second week; the 13 controls did not. In the treated group the fall in haemoglobin level is arrested sooner.

lowest level to which the haemoglobin fell in the two groups; in four of the 13 treated cases the haemoglobin never fell below 10 g.

LOWEST LEVEL OF HAEMOGLOBIN (G./100 ML.)

	Below 8.0	8.0-8.9	9.0-9.9	10.0—
Treated, 13 cases . .	—	3	6	4
Controls, 13 cases	1	5	7	—

We conclude that iron exhibited from about the third week can, to a small but appreciable degree, mitigate the early anaemia of prematurity. The post-natal fall in haemoglobin level is checked earlier, so that very low haemoglobin levels are less likely to be reached in the third month. The subsequent rise in haemoglobin also occurs earlier, so that treated cases tend to regain normal levels sooner.

The mechanism by which iron produces its effect is obscure. No question of iron deficiency, in the sense of depletion of the body's iron stores, arises as early as the 50th day, the time when the effect of the iron exhibited is becoming apparent, for at this stage the total circulating haemoglobin is usually much less than was present at birth (see Fig. 2). Furthermore, the mean corpuscular haemoglobin concentration has always remained normal throughout the first trimester in the smallest premature

FIG. 6.—Effect of cobalt on the early anaemia of prematurity. Co-Fe represents five premature infants (weights below 1,530 g.) given cobalt and iron from about the second week.

Fe represents 13 premature infants (weights below 1,620 g.) given iron alone from about the second week.

N is an average normal infant.

The course of the haemoglobin level in the cobalt-treated group is comparable to that of a normal infant.

infants. From time to time workers in other fields have suggested that iron has a stimulant effect upon haemoglobin synthesis even in the absence of iron deficiency: this is referred to in a recent review by Josephs (1953). As already pointed out, the rapid rate of growth of a premature infant means that haemoglobin synthesis can only exceed by a small margin the amount needed to maintain the haemoglobin concentration constant. It follows that a small increase in the rate of haemoglobin synthesis would have a disproportionately large effect upon the haemoglobin concentration.

The Effect of Cobalt

If we are correct in our conclusion that the main cause of the excessive post-natal fall in the haemoglobin level of premature infants is the slowness of the response of erythropoiesis to the stimulus of anaemia, it follows that the anaemia could be prevented only by causing erythropoiesis to be stimulated earlier and before anaemia has developed. The single agent with claims to possess the property of stimulating the marrow directly is cobalt. We shall not here refer at length to the literature on the haematological effects of cobalt, for this has been

done in recent papers from this country (Coles and James, 1954), the U.S.A. (Rohn, Bond and Klotz, 1953) and Germany (Schmöger, 1953). There is now good evidence that in man as in animals cobalt is capable of stimulating erythropoiesis, although its mode of action remains obscure.

In giving cobalt to premature infants we have combined it with iron, partly on the grounds that if erythropoiesis is to be stimulated it is sensible to provide additional iron for haemoglobin synthesis, partly because we had already shown that iron was itself capable of mitigating the anaemia of these infants. The following mixture has been given:

FeSO ₄ , 7 H ₂ O	..	..	..	60 mg.
Co(NO ₃) ₂ , 6 H ₂ O	..	..	..	15 mg.
Glucose	..	..	..	0.6 g.
Dilute hypophosphorus acid	..	..	..	0.1 ml.
Water to	..	..	..	4 ml.

These amounts, which are equivalent to 12 mg. iron and 3 mg. cobalt, have been given thrice daily to infants irrespective of size, in courses of up to seven weeks.

A group of five premature infants, with birth weights between 1,330 and 1,530 g., were given cobalt and iron from the second or third week, and their blood picture followed in detail.

In general we have fully confirmed the striking effect of cobalt upon erythropoiesis. These effects were usually obvious within one week of exhibiting cobalt. Reticulocytes rose sharply with levels up to 13%, and in some instances normoblasts appeared in very large numbers, up to 7,000/c.mm. These signs of exceptionally energetic erythropoiesis have been the more striking in that they have occurred at a time when the haemoglobin level in the blood was still high, 15 g. or more, when erythropoiesis is ordinarily at a low ebb.

The marrow was examined in three of these premature infants between the 23rd and 37th days when the haemoglobin level lay between 11 and 15 g./100 ml. At this haemoglobin level we should from past experience have anticipated a low level of erythropoiesis (see Fig. 4), yet when cobalt had been exhibited erythropoiesis was active, with the high average marrow erythroid count of 70,000/c.mm. In other respects the myelograms were normal.

The increased output of haemoglobin in the infants given cobalt can be seen most simply by comparing the haemoglobin curves of the group of premature infants treated with cobalt and iron from the second or third weeks, with a group treated with iron alone. Results are shown in Fig. 6, where it will be seen that the cobalt-treated group followed

a course closely similar to that of a normal infant, with haemoglobin values well above those of the control group. Since it was found that the cobalt-treated group grew fully as fast as the controls there was clear evidence of increased haemoglobin output in the former.

These results show that by the early administration of cobalt to premature infants erythropoiesis can be stimulated at a time when it is otherwise at a low ebb. In this way the rapid post-natal fall in haemoglobin can be slowed, and the early anaemia of prematurity largely prevented.

Coles and James (1954) have also studied the effect of cobalt on the anaemia of prematurity, observing a large series of infants for up to one year. Their study, although not particularly directed to the early anaemia of prematurity, led them to conclude that cobalt, given in the early weeks of life, was of value in preventing this anaemia. No toxic effects were noted by these workers, using dosages equivalent to 2.5-5 mg. cobalt daily.

Quilligan (1954) gave cobalt in doses equivalent to 10 mg. cobalt daily to 16 premature infants. The treated group showed higher haemoglobin values than the controls, but grew less rapidly.

Toxic Effects of Cobalt. One of the premature infants treated with cobalt developed signs of thyroid disorder. This infant was started on the cobalt-iron mixture on the 13th day, and thrived until aged 9 weeks. The abdomen then became distended with gas and feeds were no longer taken well. A suggestion of exophthalmos was noticeable. A moderately large goitre, 6 cm. in width, became obvious. The cobalt-iron mixture was stopped and within four days the infant began again to feed well and to gain weight. Within three weeks the goitre had disappeared.

On the eighth day, after omitting the cobalt, measurement of radio-iodine uptake by the thyroid gave a value of 38% of the dose. At 72 hours after ingestion of the radio-iodine 2.2% of the dose was present as protein-bound iodine in the plasma. These values lie near the upper range of normal for older children or adults, implying that thyroid function was not at this stage depressed.

Following this episode it was recalled that another infant in the series, who had received cobalt for about six weeks, had developed a mild and transient exophthalmos, although no goitre had been noticed.

Evidence has since come from two further sources that in children and infants cobalt can produce effects upon the thyroid. Gross, Kriss and Spaet (1954) treated children with sickle-cell anaemia giving cobalt in doses of 2.5 to 3 mg./kg./day;

within six to eight weeks three of four children developed goitres with clinical or laboratory evidence of hypothyroidism. McBryde (1954) reported thyroid enlargement developing in a premature infant given cobalt, 5 mg./day, for six weeks.

It is thus clear that cobalt is a potentially goitrogenic agent. Although cobalt given to premature infants will prevent their becoming anaemic, we consider it unjustifiable to expose these infants to the risk of interference with thyroid function.

Summary and Conclusions

The early anaemia of premature infants is due mainly to the slow response of erythropoiesis to the stimulus of anaemia.

This slow response is not peculiar to premature infants, but in them its consequence is exaggerated by the rapidity of their growth.

Rapid growth also has the effect of prolonging the anaemia once this has developed.

There is no evidence that an abnormal rate of red cell destruction, if it occurs, contributes significantly to the production of anaemia.

Marrow studies reveal no differences between the myelograms of premature and normal infants.

Iron, if given from about the third week, mitigates the anaemia but does not always prevent it. Iron is well tolerated and there seems good reason to give it to the smaller premature infants from about the third or fourth week.

If cobalt is given in addition to prophylactic iron, a striking increase in erythropoiesis can be provoked, sufficient in most cases to prevent anaemia developing. However, the effects which cobalt may have upon the thyroid make it unjustifiable to administer it routinely to premature infants.

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APPENDIX

With the assistance of MARTIN J. POLLARD, M.A., B.Sc.

Statistical Analysis of the Effect of Oval Iron on the Haemoglobin Level of Premature Infants

An average value for the haemoglobin level was calculated for each infant separately from observations in the age ranges 40-60 days and 60-100 days.

It happened that there were six twins amongst the 13 treated infants and no twins in the control group. Therefore a statistical analysis was performed comparing the controls with the treated infants, first including the six twins and secondly excluding them.

The following table gives the mean haemoglobin values, the standard errors for those treated and control groups, the corresponding values for 't' and the significance level (P).

The analysis shows that in the age group 40-60 days there is no significant difference between the treated and control groups whether twins are included or not. In the age group 60-100 days the difference is highly

Age range (days)	Including Twins		Excluding Twins	
	40-60	60-100	40-60	60-100
<i>Treated</i>				
Number	13		7	
Mean of average Hb values	10.215	10.418	10.710	10.803
Standard error	0.763	0.687	0.398	0.725
<i>Controls</i>				
Number	13		13	
Mean of average Hb values	10.097	9.700	10.097	9.700
Standard error	0.912	0.577	0.912	0.577
t	0.358	2.887	1.679	3.733
Degrees of freedom	24		18	
Significance level (P)	>0.1		>0.05	

significant ($p=0.005$), both including and excluding the twins.