THE EARLY ANAEMIA OF PREMATURE INFANTS :

the haemoglobin level of immature babies in the first half-year of life and the effect during the first three months of blood injections and iron therapy

BY

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An anaemic baby is more susceptible to infection than the normal infant^{3, 7} and this is an important factor in the mortality rate of infants of subnormal birth weight. Lichtenstein⁶, from his extensive work with premature babies, concluded that these infants regularly become anaemic in the first months of life although they are not anaemic at birth. The average haemoglobin level of thirty-six premature infants examined by him in the third month of life was about 40 per cent. (ranging between about 30 per cent. and 50 per cent.). He found that healthy full-term babies only exceptionally showed a drop to below 60 per cent. Many others have reached similar conclusions, though usually the number of their cases has been smaller; for example, Kunckel⁴ found in twenty-one premature babies, whose birth weight averaged four pounds, a drop to an average figure of 46 per cent. It has been generally accepted that premature babies at this age drop to much lower levels than full-term babies although they all start extra-uterine life with high haemoglobin levels. The author's observations on premature babies brought to the Queen's Hospital for Children for advice on feeding or management did not contradict these views. It should be borne in mind that the normal full-time infant always shows a considerable drop in haemoglobin level after birth, the lowest level being reached at about two to three months of age. This is followed by a rise in the second three months of life and then, if, as so often happens, a sufficiency of iron is not available, a renewed fall.

Object of investigation and clinical material.

The investigations described in this paper were carried out at the Mothers' Hospital, a maternity hospital in the north-east of London. The babies were either newly-born in-patients, or were attending the hospital welfare centre. The investigation was concerned with the haemoglobin level

during the first twenty-six weeks of life of babies of low birth weight, attention being chiefly focussed on the extent of the drop from birth to about the end of the third month of life, and how an excessive drop might be minimized. The author was not here concerned with the nutritional anaemia due to iron deficiency, so common in the second half-year of life, although babies of low birth weight are particularly likely to develop nutritional anaemia in its severer forms, and in some babies the effects of iron deficiency begin to appear between three and six months of age. This is shown by the fact that iron medication begun by about two months of age will often augment the rise in haemoglobin level normally occurring after this initial fall, i.e., between, say, three and six months of age⁷.

Effect of intramuscular blood injections.—The estimations were made with a Haldane (Price-Jones) haemoglobinometer⁸ from blood taken from a prick in the heel: ninety-one babies weighing less than six pounds at birth and fifty-nine babies of birth weight over six pounds were examined. The first set of investigations was planned to observe the effect of intramuscular blood injections. Human blood serum or citrated human blood, given intramuscularly or by transfusion, appears in many cases to check the excessive drop in haemoglobin and red cells occurring in familial icterus gravis neonatorum and the allied severe anaemia of the new-born, and it was hoped to discover

TABLE 1.
EFFECT OF TREATMENT ON THE EXTENT OF THE DROP IN HAEMOGLOBIN LEVEL AFTER BIRTH.

Birth weight and group.	Average Hb. level.		Lowest average Hb. level.	Age of infants with lowest average.
	At birth.	Eighth day.		
A. CITRATED BLOOD INJECTIONS.				
3, 4 and 5 lb. odd.				
Injected cases ...	142.4 (16)	125.3 (16)	73.0 (8)	10th week
Controls	145.6 (22)	125.4 (20)	74.4 (8)	14th ,,
6 lb. and upwards.				
Injected cases ...	136.6 (22)	124.1 (19)	76.4 (13)	14th ,,
Controls	141.8 (28)	128.3 (27)	74.3 (9)	14th ,,
All birth weights.				
Injected cases ...	139.1 (38)	124.6 (35)	75.1 (21)	14th ,,
Controls	143.5 (50)	127.0 (47)	74.4 (17)	14th ,,
B. IRON THERAPY, started before 45 days old.				
3, 4 and 5 lb. odd.				
Iron cases ...	145.1 (32)	—	74.7 (20)	14th ,,
Controls	—	—	74.0 (21)	14th ,,

NOTE: Figures in brackets indicate the number of cases in each group.

if blood injections would have a comparable effect in premature babies. Babies were therefore given on the first, second or third day of life an intramuscular injection of 15 c.c. of human blood with one c.c. of one per cent. citrate solution, the blood being taken usually from the mother but occasionally from the father. Haemoglobin estimations were made by the author on the first and the eighth day of life, and subsequently in the fourth, sixth, tenth, fourteenth, eighteenth, twenty-second, and twenty-sixth week, whenever possible. The results are shown in table 1. The lowest average haemoglobin value was reached in each weight group in the tenth or fourteenth week. Babies under six pounds at birth dropped to an average figure of 73 per cent., whereas their controls dropped to 74.4 per cent.; the corresponding figures for babies over six pounds at birth were 76.4 per cent. and 74.3 per cent., and for both sets combined 75.1 per cent. and 74.4 per cent. Taking all the cases together the difference between injected cases and controls was therefore less than one per cent., so it must be concluded that injections of blood, as here given, did not diminish the drop in haemoglobin level occurring in the first three months of life. Comparison of the haemoglobin levels in four pairs of twins, one of each pair having had the injection of blood, led to the same conclusion. Yet one surprising fact emerged, namely, that there was very little difference between the lowest level reached by the bigger babies and the smaller babies respectively.

Effect of iron medication.—In a search for some cause for this unexpected result, it seemed necessary to make sure that iron administration played no part in minimizing the drop in the small babies, since most of the babies who continued to attend were given iron before one-and-a-half months old. There seemed various reasons against the hypothesis that iron deficiency played any part in this early anaemia of premature infants⁹, for, unlike the nutritional anaemia of later infancy, it is not a hypochromic anaemia, and moreover, investigations have shown that the iron store in the liver increases up to two months of age². Since, however, several workers^{1, 5} have claimed that iron, or iron in conjunction with some other medication, is beneficial in such cases, the question needed investigation.

Since a single blood injection was evidently without effect in this connection, this factor was ignored, and cases were analyzed on the basis of their iron medication. Table 1 shows a comparison between the lowest haemoglobin level reached by babies given iron and ammonium citrate from under forty-five days old (usually $4\frac{1}{2}$ – $6\frac{3}{4}$ grains daily) and a group of babies who received no iron during the period under consideration². All these infants were under six pounds at birth. The average minimum haemoglobin level in both groups was again very close, namely, 74.7 per cent. and 74.0 per cent. in the fourteenth week; a difference of less than one per cent. Thus these figures negative any prophylactic influence of iron in this connection.

Extent of drop in haemoglobin level in babies of different birth weights.—It looked, therefore, as if an attempt was being made to prevent an excessive drop in haemoglobin level in babies whose drop was not excessive. In order to compare larger numbers, babies of similar birth weight were grouped together, irrespective of whether or not they received blood injections, or the age of starting iron treatment, since both these factors were without influence on the haemoglobin level in the first three months of life.

Table 2 shows the average haemoglobin level at birth, and the lowest average reached by babies of different birth weights. It will be seen that with one exception the lowest average figure reached by each group varies with the birth weight, the babies three to four pounds at birth drop lowest, those of eight pounds and upwards drop least, but nevertheless the difference is small, only about six per cent. between the lowest level reached by these two groups at opposite extremes of birth weight. It is true that the total drop from birth of the three pound babies is considerably more than that of the eight and nine pound babies, because they start higher; the tiny babies dropped 80·8 per cent. as compared with a drop of 59·2 per cent. in the eight and nine pounders, a difference of 21·6 per cent.

TABLE 2.

RELATION BETWEEN BIRTH WEIGHT, THE AVERAGE HAEMOGLOBIN LEVEL AT BIRTH, AND THE LOWEST HAEMOGLOBIN LEVEL REACHED IN THE FIRST FOUR MONTHS OF LIFE.

Birth weight.	Average Hb. level.	No. of cases.	Lowest Hb. level.	No. of cases.	Age of infants with lowest average.
3 lb. to 4 lb. ...	153·0	5	72·2	6	14th week
4 lb. to 5 lb. ...	148·7	12	73·3	12	10th "
5 lb. to 6 lb. ...	146·6	33	76·0	20	14th "
6 lb. to 7 lb. ...	142·1	32	74·0	8	14th "
7 lb. to 8 lb. ...	140·8	44	75·2	9	14th "
8 lb. and upwards	137·8	30	78·6	5	14th "

The average haemoglobin level at birth in babies of different birth weights.—The average haemoglobin level at birth is in inverse order to the birth weight; the babies weighing three to four pounds at birth averaged 153 per cent. on the first day of life, those of eight pounds and over, about 138 per cent. The author has already published figures for the average haemoglobin value at birth of babies weighing five pounds and over when born⁹, and those now given (which incorporate the first set of figures) are for the most part lower. This is apparently due to the selection of cases; in the first series the babies were all rigidly selected as healthy and normal in every way, whereas in this second series, though no babies obviously ill were included, there were a proportion who were subnormal in vigour and general progress. Individual haemoglobin levels at birth showed very wide variation. In apparently

normal babies under six pounds at birth the maximum figure was 179 per cent. and minimum 105 per cent.; in babies over six pounds at birth maximum and minimum were 174 per cent. and 110 per cent. respectively.

The haemoglobin curve for babies under six pounds at birth.—The average haemoglobin levels during the first six months of life of babies of three to five pounds at birth and those of five to six pounds at birth

TABLE 3.

THE HAEMOGLOBIN LEVEL DURING THE FIRST SIX MONTHS OF LIFE OF BABIES WEIGHING FIVE POUNDS AND UNDER AT BIRTH.

(Figures on which chart is based.)

Age :	1st day	8th day	4th wk.	6th wk.	10th wk.	14th wk.	18th wk.	22nd wk.	26th wk.
Birth weight 3 and 4 lb. odd	149.9	127.9	100.1	82.1	73.4	74.4	77.8	77.3	81.7
No. of cases ...	17	23	21	20	19	14	13	4	12
Birth weight 5 lb. odd	146.6	130.0	102.7	85.1	76.3	76.0	78.5	78.3	80.8
No. of cases ...	33	46	25	30	22	20	24	15	14

are shown in the chart and in table 3. The smaller babies start higher, but from the eighth day until the twenty-second week are consistently slightly lower than the larger babies. At the end of the sixth month (twenty-sixth week) both groups averaged just over 80 per cent. in spite of the fact that iron medication in some cases is known to have been irregular. All babies were ordered iron from the fourteenth week of life, if they were not having it before.

Possible influence of general management and feeding.—After this digression regarding haemoglobin values at birth and the haemoglobin curve in immature babies, the factors which may have prevented the premature and immature babies in this series from showing any marked anaemia by the tenth or fourteenth week of life may be considered. There was nothing unusual in the type of feeding given to these children, unless it be that they were not given highly diluted feeds. Whenever possible they were given breast milk, feeding being started within a few hours of birth. The smaller premature babies and twins were given the milk of other mothers during the first weeks of life if no milk was available from the infant's own mother. If artificial feeding was employed, it was usually dried milk (half cream and later full cream), sugar and water, in the calorie concentration of 20 calories to each ounce. Whenever possible the calorie allowance reached 50 calories

per pound body weight by about one week old, sometimes before, and was subsequently further raised according to the appetite and rate of progress of the infants. Water was given between feeds as and when the baby would take it. Cod-liver oil emulsion and orange juice were started within the first few weeks of life. Thus these babies, on the whole, underwent no long period of underfeeding such as is frequently the lot of premature infants, nor were they given the very dilute feeds often associated with underfeeding. It is possible that both these factors played their part in the results here considered. Premature infants brought up to children's hospitals often after a period of much mismanagement give a different impression of the prognosis as regards life from that obtained in a maternity hospital, provided that the babies are adequately fed and kept warm from birth. Naturally the amount of illness suffered by these two groups also varies widely.

THE HAEMOGLOBIN LEVEL DURING THE FIRST SIX MONTHS OF LIFE OF BABIES WEIGHING FIVE POUNDS AND UNDER FIVE POUNDS AT BIRTH.

Haemoglobin levels in babies with pathological conditions.—May it be that it is primarily the general health and well-being of the infant which determines the extent of this early drop in haemoglobin level? On this point the present investigation does not provide sufficient material to reach any final conclusion, but several cases are suggestive. From the various tables

given in this paper six babies were excluded because they had definite pathological symptoms. The clinical records are as follows:—

- M. S., birth weight 2 lb. 5 oz. Suffered from repeated cyanotic attacks and abdominal distension, necessitating underfeeding; poor gain in weight. Died at about ten weeks old. Haemoglobin in tenth week 35 per cent. (average in tenth week for babies three pounds odd at birth was 73·4 per cent.).
- J. B., birth weight 2 lb. 6 oz. Suffered from oedema, abdominal distension and otorrhoea; poor gain in first ten weeks of life. Haemoglobin in tenth week 47 per cent. (average in tenth week for three-pound babies 73·4 per cent.). Good progress thereafter. Haemoglobin rose to 86 per cent. by six months old (with iron medication).
- A. T., birth weight 3 lb. 2 oz. Suffered from cyanotic attacks. Haemoglobin in tenth week 58 per cent. (average in tenth week for three-pound babies, 73·4 per cent.).
- J. T., birth weight 4 lb. 7 oz. Suffered from sclerema. Haemoglobin on the first day of life 115 per cent. Haemoglobin of twin on first day 170 per cent. (Average haemoglobin of babies four pounds odd at birth 148·7 per cent.).
- D. J., birth weight 4 lb. 6 oz. Suffered from oedema. Lowest haemoglobin level reached is unknown, as estimations were not done at the requisite ages, but in the eighteenth week the haemoglobin was 69 per cent. (average for babies four pounds odd at birth 77 per cent.).
- M. G., birth weight 5 lb. 14 oz. Suffered from oedema. Lowest haemoglobin level reached is unknown, as no estimations were made after the sixth week when it was 75 per cent. (average for babies weighing at birth five pounds odd was 85 per cent. at this age).

Thus every one of these six cases, excluded as having definitely pathological conditions, showed haemoglobin levels considerably below the average. Of four patients whose haemoglobin levels were available at the tenth or fourteenth week, three dropped to 35 per cent., 47 per cent. and 58 per cent. respectively. No other premature or immature child in the present series dropped below 63 per cent. It is true that the two babies who dropped below 50 per cent. were both under three pounds at birth (i.e., were more immature than any babies included in our series), nevertheless they both had in addition symptoms of severe pathological conditions.

Some babies were included although they could not be passed as absolutely normal. Five are noted as taking poorly during the first week of life or longer, so that there was considerable difficulty with the feeding; of these, three had haemoglobin levels well below the average. Three are noted as having 'shock' or 'white asphyxia' at birth, but making a rapid recovery. Of these, none showed especially low haemoglobin values, though one dropped more rapidly than usual. One baby suffered from abdominal distension in the early days and its drop was lower than average.

Discussion.

The case histories of the patients quoted above, showing that ten out of fifteen immature babies who had pathological symptoms, severe or slight, developed haemoglobin levels well below the average, at least suggest that it is some factor or factors associated with the general health which bring about the very low haemoglobin levels noted by so many authors in premature babies in the first three months of life. Such a suggestion, of course, does not elucidate the actual cause of the excessive drops. In the normal infant during the first two months of life—the period when the haemoglobin level is falling—it seems probable that two factors are acting: increased haemolysis and decreased red cell formation⁹. When, in the second quarter year of life, the haemoglobin is rising, there has already come about an augmentation in the rate of red cell production. Is an excessive drop in an immature baby usually due to excessive haemolysis, or to a delay in the age of augmentation of red cell formation to beyond the normal, or to a combination of these factors? And if these factors operate what is the mechanism of the changes? So far these questions are unsettled. Another theory has been put forward by Sanpaolesi¹⁰ which is that hydraemia plays an important rôle. He found in twelve premature infants a loss in the total solids of the blood in the second month of life which reached its maximum in the third month, with a parallel decrease in red cells and haemoglobin. There was not, however, any alteration in the weight curves to indicate water retention. So far as the author is aware this work has not yet been confirmed. From Sanpaolesi's work presumably a loss of solid elements must be supposed rather than an increase of fluid in the third month of life or else a change in the relative amount of water in the circulation and in the tissues. If there is a loss from the body of solid elements of the blood without change in the blood volume, the low blood cell counts would still indicate that the total number of corpuscles in circulation in the body was subnormal. The observations recorded in this paper throw no light on these points, though it is interesting that the four babies excluded from the tables in this paper because they had suffered from oedema did show subnormal haemoglobin levels. There exists no definite knowledge at the present time of the cause of oedema in new born babies, though excessive cooling of the body appears to predispose to this condition.

Summary.

Observations were made at the Mothers' Hospital, London, on the haemoglobin level of 150 infants during the first half year of life. The main object in view was to obtain information regarding the fall in haemoglobin level during the first two to three months of babies of low birth weight. Of the babies examined, 39 were under five pounds in weight at birth, 52 were five to six pounds, and 59 were six pounds and upwards. Estimations were made with a Haldane (Price-Jones) haemoglobinometer on blood obtained

from a prick in the heel. When babies showing symptoms of definitely pathological conditions in the early days of life were excluded, it was found that the lowest average haemoglobin level reached in the first half year of life by the babies weighing three pounds odd at birth (72.2 per cent.) was only six per cent. lower than that of those weighing eight and nine pounds at birth (78.6 per cent.); the total drop of the three-pound group was, however, considerably greater than that of the eight and nine-pound group because they started life with a higher average haemoglobin level, thus these immature babies dropped 80.8 per cent. as compared with a drop of 59.2 per cent. in the big babies.

No influence on the extent of the drop in haemoglobin level in the first two to three months of life was observed as a result of giving an intramuscular injection of 15 c.c. of citrated human blood within the first three days of life, nor from the administration of iron and ammonium citrate by mouth.

Figures are given for the average haemoglobin level during the first six months of life of babies weighing at birth three and four pounds and five pounds respectively. Not one of these babies dropped below 63 per cent. The three and four pounders started with a higher haemoglobin level than the five pounders, but from the eighth day until the twenty-second were consistently slightly lower than the bigger babies. Babies showing symptoms of any severe pathological condition in the early weeks of life were excluded from these groups. It is suggested that premature and immature babies whose general health and progress have been satisfactory from birth do not usually show any severe anaemia during the first three months of life. The mechanism which brings about an excessive fall in haemoglobin remains unexplained—possibly excessive haemolysis, diminished red cell production and hydraemia may all play their part in varying degree.

The investigation involved the resident medical staff of the Mothers' Hospital, who gave all the citrated blood injections, in much extra work. The author's sincere thanks are due to all those medical officers who have held office during 1933 and 1934 for their generous co-operation, as well as to the nursing staff for their unvarying assistance. Her thanks are also due to Miss Lorel Goodfellow for her help in the analysis of the figures.

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