THE BLOOD IN INFANCY

BY

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Introduction

In view of the vast amount of work which has been done on the study of the blood picture in the infant and young child, it might seem superfluous to add to the number of communications. The story has already been told by so many workers, and with such apparent unanimity on the general features, that there would seem little reason to doubt the main conclusions. However, it is always worth while reviewing afresh even a question considered settled, if it can be done from a new angle. If this is possible, additional light may be shed on some aspect of the problem so that a different, and perhaps a more correct, conception of the processes at work is obtained. It is because of this that I consider some observations which I have been making during the past two or three years are worthy of publication.

In the past, for example, conclusions regarding the formation and destruction of blood have been drawn for the most part from a consideration of the percentage concentration of the haemoglobin and red corpuscles in the circulating blood. Such a method does not reveal the total amount of haemoglobin or number of red blood cells in the body, which knowledge is essential for a correct estimate of haemopoiesis. It must be admitted, of course, that in the case of a constituent of the body like blood, which normally bears a definite relationship to body weight, the percentage concentration of its constituents may permit of fairly reliable conclusions in an individual of constant weight, as, e.g. the full-grown adult. Nevertheless, it has long been appreciated that rapid variations in body weight, both in the adult and in the child, either in consequence of dehydration or oedema, give rise to anomalous readings and thus to false conclusions; but so far as I am aware, the variations in weight of the normally growing child have never been taken into consideration. It is true that the variations in weight during the process of natural growth of the infant are not so rapid as they are during the development of oedema after renal disease, or of dehydration from an acute enteritis. The variations in weight from growth, however, are considerable, especially during the early months of life. During the first six months the average child doubles its weight, and, therefore, should double its quota of blood.

That there is a want of correlation between body growth and blood formation in the early weeks of life is suggested from the fall in the concentration of the haemoglobin and red cells, but from observations on the concentration of haemoglobin and red cells alone it is impossible to say whether this is due to a lag in blood formation, or to an increased rate of destruction of blood, any more than that the variations in haemoglobin and red cell concentrations in the presence of dehydration or oedema point to abnormalities in the processes of formation and destruction of blood. The correct answer to what is happening can only be obtained from a knowledge of the nature of the change, if any, in the total amount of blood (haemoglobin and red cells). The importance of this conception was first pointed out to me by Dr. Robb-Smith, who suggested that it would be interesting to see how the absolute amount of haemoglobin and total number of red cells in the circulating blood behaved during the neonatal period, for in this way the key to the solution of the much discussed problem of excessive haemolysis might be obtained.

Material. Since 1941, through the kind co-operation of Prof. Chassar Moir, I have had the opportunity of studying the blood picture in the newborn in his Department at the Radcliffe Infirmary, Oxford, and of following the course of events in these children throughout their first year of life. In addition, I have collected isolated observations in a large number of infants under my own care in the Children's Department of the same hospital. To Dr. R. G. Macfarlane I am indebted for much advice and for most of the blood examinations, which were carried out by his technicians. This help was so arranged that, as a rule, the blood examinations were performed by one individual so that some general constancy in standards was maintained.

The blood in the foetus was obtained from the umbilical cord immediately after delivery and before pulsation had ceased. In the newborn infant blood was obtained either by heel puncture or from a scalp vein. There tends to be a slightly greater concentration of haemoglobin and of red cells in the capillary blood as obtained by heel puncture, but the differences are so slight (fig. 1) that it has been deemed justifiable not to differentiate between them and to take either venous blood or capillary blood as representative of the state of matters at any

particular age. In the older infant blood was always obtained by heel puncture, and if this was taken up in heparinized pipettes and collected in heparinized tubes, ample amounts could always be obtained for comprehensive analysis.

The haemoglobin was estimated by Haldane's method, the colour standards employed always

FIG. 1.—Comparison of average haemoglobin and red-cell concentrations in capillary and venous blood in newborn infant.

having been recently tested at the National Physical Laboratory. The reticulocytes were enumerated by the 'wet process.'

Results. Like previous workers, I have found a gradual fall in haemoglobin and red cell concentrations during the early weeks of life. This fall most observers have found to continue till about the age of twelve to fourteen weeks, after which there ensues a slight recovery extending to the end of the first year. Around both of these phenomena, however, there is much controversy. Is the early fall in haemoglobin and red cells due to an abnormal degree of haemolysis, and can the recovery during the later period of infancy be influenced by the administration of additional iron in the diet? These are two of the chief points at issue, and it is to these two problems that our new angle of approach is mainly directed.

Part I: The Neonatal Period

INCREASED HAEMOLYSIS OR DEFICIENT FORMATION?
As I have just stated, I was able to corroborate the

decline in haemoglobin and red-cell concentrations during the early weeks of life. This phenomenon, if not explicitly declared, is tacitly assumed to indicate an increased rate of destruction with a resultant actual diminution in the amount of blood. Indeed, it is generally assumed that the child is born with more blood than he requires for an independent existence, and so there results immediately after birth an increased destruction of blood (an abnormal degree of haemolysis) to compensate for the altered conditions of post-natal life, viz.: the greater amount of O_2 available from the institution of respiration. It is this increased haemolysis, too, which is fairly generally credited as the reason for the development of jaundice (so-called icterus neonatorum) which attacks the great majority of children during the first week of life.

There are, however, several theoretical considerations which argue against such a sequence of events. In the first place, expansion of the lung is not a sudden event with rapid availability of the alveolar surface. On the contrary, it is a gradual process which requires several weeks for its completion. In the second place, after birth the child is deprived of the extra-medullary haemopoietic tissue on which it was chiefly dependent during foetal life. It would, therefore, seem more logical to advance the hypothesis that the child had an undue need to conserve its red cells, at least until respiration is fully established and medullary haemopoiesis well under way. My own observations support such a contention.

BLOOD QUOTA IN FOETUS. In so far as can be gauged from a study of the percentage concentration of haemoglobin and red cells, there is no support for the idea that the child has relatively more blood during its ante-natal existence than it has during post-natal life. In eleven children of varying degrees of maturity I have compared the haemoglobin and red cell concentrations of foetal blood with those present during post-natal life. The cord blood, withdrawn immediately after delivery and before pulsation had ceased, was taken to represent the state of affairs during foetal life, and after birth the blood was examined at ages varying between two hours and five days. The findings, detailed in table 1, reveal that, without exception, the concentration is increased after birth, the increase within the first few hours of life in both haemoglobin and red cells varying between 13 and 70 per cent., and the haematocrit readings between 10 and 75 per cent. If the conclusion which such a change usually suggests is drawn from these findings, then it seems probable that there is a call for rather more oxygen carriers than for fewer during the critical neonatal period. It would be idle to suggest that such a finding results from an absolute increase in the number of red cells during so short a period of time (as little as five hours) and the explanation of the phenomenon is almost certainly merely an increase in concentration of the blood. Such an increase might result in part from loss of weight due to dehydration which takes place after birth. But that this is the whole explanation is improbable,

TABLE 1
Hb AND RED CELL CONCENTRATIONS AND
HAEMATOCRIT READINGS IN CORD BLOOD
AND IMMEDIATELY AFTER BIRTH

Name and age	Duration of pregnancy	Haemotocrit reading	Haemoglobin concentration %	Red cell concentration per cu. mm.	Presence of jaundice
R. C.B. 4½ hrs.	38/52	57	130 160	mill. 4.8 6.4	
K. C.B. 3 days	37/52	55	120 136	4.1 5.4	+
C. C.B. 1½ hrs. 2 days	40/52		110+ 110+ 130	3.7 6.6 5.8	+
A. C.B. 5 hrs. 4 days	38/52	40 70	100 170 125	3.6 5.8 5.0	+
J. C.B. 2 hrs. 10 days	40/52	54 68 63	130 180 140	4.8 6.1 5.5	+
W. C.B. 17 hrs.	41/52	50 66	114 150	4.2 5.6	—
R. C.B. 19 hrs.	40/52	57 75	120 160	4.1 5.9	—
D. C.B. 4 days	37/52	44 50	105 100	3.0 4.5	—
S. C.B. 4 days	35/52	44 55	104	3.5	+
S. C.B. 5 hrs. 5 days	40/52	61 66	130 180 150	4.7 5.2 6.1	—
W. C.B. 7 hrs.	36/52	45 60	100 160	4.2 5.7	
S. C.B. hrs. 5 days	45/52	52 70	115 175 170	5.7 5.7 6.1	—

since the increased concentration is much greater than what could occur in this way. For example, the loss of 1 lb., which, by the way, would be an abnormally high figure and in any case would be spread over two or three days, would only account for a change in concentration of some 12 per cent., whereas we have seen that an actual concentration of some 70 per cent. may occur during the first five hours of life. The phenomenon is to me at present inexplicable, but it reveals how dangerous it is to conclude from the red-cell and haemoglobin concentrations during the early hours and days of life, and probably at all ages, what is happening so far as blood formation and blood destruction are concerned.

PERIOD OF MOST RAPID DECLINE IN CONCENTRATION OF BLOOD. In support of the view that there occurs increased haemolysis during the neonatal

period, and that this is the cause of icterus neonatorum, it is usually stated that the most rapid decline in the red-cell and haemoglobin concentrations occurs during the earliest days of life (first ten days). This, however, has not been my experience. For the special study of this particular question I have available a set of observations made on almost every day of life during the first two months. The findings in this series are shown in fig. 2. These reveal that the most rapid decline occurs during the second week of life, a point which must have an important bearing on our views regarding icterus of the newborn. During the first week the fall in concentration of red cells amounts to 3.6 per cent., or 0.5 per cent. per day, during the second week to 15 per cent., or 2.0 per cent. per day, i.e. four times as much, and during the period from the third to the eighth weeks inclusive to 4.4 per cent. or, 1 per cent. per day, i.e. only one-fifth of what occurred during the first week and one-twentieth of what occurred during the second week.

In the case of haemoglobin the same general trend is observed but the percentage falls are not identical. During the first week the fall in haemoglobin is almost equal with that of red cells, being 3 per cent. for the seven days or 0.4 per cent. per day, as against 0.5 per cent. per day for the red cells. During the second week, however, the fall in haemoglobin amounts to 23 per cent., or 3.3 per cent. per day, that is, close on 100 per cent. more than in the case of the red cells; and during the period of the third to the eighth weeks inclusive the fall in haemoglobin amounts to 15.3 per cent., or 0.4 per cent. per day, which is 300 per cent. more than that of the red cells.

CHANGE IN SIZE OF RED CELL AFTER BIRTH. This want of harmony in the behaviour of the haemoglobin and red cells might at first sight cast doubt on the reliability of the findings, but it is possible to advance another explanation and one which we think is of special significance. One of the most marked alterations which the blood undergoes in the change-over from foetal to natal life is the diminution in the size of the red cell and, therefore, in the amount of the contained haemoglobin. I regret that I did not make actual measurements of the size of the red cell during this important transition period. I did not at a sufficiently early period in my study appreciate the importance of this factor. However, from the blood counts and haematocrit readings it is possible to form an estimate of the mean corpuscular volume (M.C.V.) and of the mean corpuscular haemoglobin content (M.C.H.), and this I have done in a fairly comprehensive series of infants, in which both cord blood immediately after delivery, and venous and capillary blood at various ages, were examined. The findings are shown graphically in figs. 3, 4, and 5 which supply data for foetus of varying degrees of maturity and for children of varying ages. From these computations it would appear that immediately after birth there results a marked diminution in both the mean corpuscular volume and mean corpuscular haemoglobin content, but no alteration—as is to be

FIG. 2.—Daily average Hb and red cell counts during first four weeks of life.

FIG. 3.—Mean corpuscular volume in foetus and newborn child.

FIG. 4.—Mean corpuscular haemoglobin in foetus and newborn child.

FIG. 5.—Mean corpuscular haemoglobin concentration in foetus and newborn child.

expected—in the mean corpuscular haemoglobin concentration (M.C.H.C.). It will be noted that the maturity of the foetus has little or no influence on the size of the red cell or on its quota of haemoglobin.

It seems to us that it is in this alteration in size of the red cell, and, therefore, in the amount of its contained haemoglobin, that the explanation of the want of harmony in the rates of fall of haemoglobin and red-cell concentrations is to be found. As the foetal red cells are destroyed they are replaced by others of a smaller size but with the same M.C.H.C., so that there is a change in the relationship between red cells and haemoglobin. Moreover, as time progresses, an increasingly greater proportion of the larger foetal cells are replaced by the smaller and more mature cells, so that the alteration in the relationship between the red-cell and haemoglobin concentrations should increase, which, as we have observed, is just what happens. These findings would seem to allow of only one conclusion, viz.: that during this period, whatever the degree of destruction, new blood formation is not inconsiderable. Were it otherwise it is difficult to see how this change in the relative quantities of haemoglobin and red cells could arise.

TOTAL BLOOD HAEMOGLOBIN AND RED CELLS. Although the above observations strongly suggest that there occurs considerable new-blood formation during the neonatal period, no true idea of the extent to which this occurs can be obtained from observations of the haemoglobin and red-cell concentrations alone. In our introductory paragraphs we have already drawn attention to the limitations of such a method of study of the problem, and it was for these reasons that we decided to investigate the variations in the total blood volume during this period.

FIG. 6.—Showing percentage of Hb and total Hb in full-time normal infants.

FIG. 7.—Showing Hb percentage and total Hb in normal full-time children receiving additional iron.

We did not find it possible to estimate the blood volume directly. In the foetus and the newborn direct methods are not feasible and so we have been able to make our estimations only indirectly from the weight of the child at the time of the blood examination. We have assumed that for every pound weight there are 40 c.cm. of blood, and, from the blood volume so computed and the haemoglobin percentage (100 per cent. representing 14.8 g. haemoglobin) and red-cell concentration, we have estimated the total blood haemoglobin content in grammes and the red-cell content in millions to the 10^{13} power. The findings are shown graphically in figs. 6, 7, 8, and 9. These graphs show that while there would seem to be an absolute diminution in the amount of blood (expressed in total g. of haemoglobin and millions of red cells) during the early weeks of life, it is neither so marked nor so prolonged as the percentage concentration readings suggest. In all the charts, except in that showing the trend of total haemoglobin in the case of children receiving additional iron, the lowest estimate in total blood is observed during the second month of life, whereas the graphs for percentage concentrations show the lowest readings during the third and fourth months of life. These graphs of total amounts seem to us to reflect a truer perspective in the balance between destruction and formation. We have already remarked on the post-natal disappearance of much of the haematopoietic tissue on which the foetus had depended, and it is, therefore, not surprising that in the early days and weeks of life production lags behind and is not able to compensate for even the normal loss.

RELATION BETWEEN HAEMOLYSIS AND ICTERUS NEONATORUM. Since the fall in the haemoglobin

FIG. 8.—Percentage of red blood cells and total red blood cells in normal full-time child.

FIG. 9.—Red cells per c.mm. and total red cells in million to power in full-time children receiving additional iron.

and red-cell concentrations is more marked during the second than during the first week of life, it is unlikely that this plays the chief rôle in the production of icterus neonatorum, which usually sets in on the second or third day of life. And the fact that there is little or no difference between the rates of fall in icteric and non-icteric infants renders such an association still less likely (see figs. 10 and 11). The blood in twenty newborn infants, seven of whom developed clinical jaundice, was examined as soon after birth as possible and on every alternate day

till due for discharge from hospital, usually the tenth or eleventh day of life. The haemoglobin and red-cell concentrations were determined and the total haemoglobin and red-cell content computed from the weight of the child at the time of the examination.

FIG. 10.—Daily haemoglobin percentage and total amount in icteric and non-icteric infants.

FIG. 11.—Red cells in millions per c.mm., and total amounts in icteric and non-icteric infants.

The means of the findings are shown graphically in figs. 10 and 11. The similarity of the trend of the curves in the two groups—icteric and non-icteric—is striking. During the first seven days the percentage fall in the haemoglobin and red-cell concentrations is identical in both groups of infants, but when we consider the percentage fall in the total amounts of haemoglobin and red cells it is slightly greater in the case of the infants who did not develop jaundice (table 2).

TABLE 2
PERCENTAGE FALL IN Hb AND RED CELLS
DURING THE FIRST SEVEN DAYS OF LIFE

Nature of case	No. of cases	Haemoglobin		Red cells	
		% concentration.	Total in g.	mill. per c.mm.	Total mill. 1013-power.
Non-icteric	13	3	8.9	5.3	10
Icteric	7	3	7.7	5.3	8.5

FRAGILITY OF RED BLOOD CORPUSCLE TO HYPOTONIC SALINE. In order to find support for the contention that excessive haemolysis occurs during the early days of life, many workers have studied the resistance of the red cell in the newborn to hypotonic saline solutions. On this question, however, there prevails great diversity of opinion. This, I think, is due to the fact that hardly any two observers have employed the same technique and that not one of them has taken into consideration such extrinsic factors as the CO₂ content of the blood and the relative amounts of cells and plasma. It is well known that venous blood is more fragile than arterial blood, with capillary blood occupying an intermediate position. Little wonder, therefore, when venous blood, e.g. from the cord in the foetus or the longitudinal sinus in the newborn, is compared with capillary blood in the older infant, that some workers have concluded that the red cell in the foetus and the newly born is more fragile than during later infancy. And again, the proportion of plasma to cells will influence the final saline content of the mixture, so that tests in which plasma and cells are not controlled by haematocrit readings and reduced to a constant proportion, as recommended by Dacie and Vaughan (1938) are quite unreliable. We have drawn attention to the very different haematocrit readings in foetal blood and that of the newly born so that unless this factor is taken into consideration the results are not comparable.

I (1945) have investigated the resistance of the red cell to hypotonic saline in close on 100 samples of blood, including that of the foetus, the newborn, and the older child. I have found that the blood of the foetus shows a slightly diminished resistance, but in the case of the newborn child the resistance of the red cell is increased, a characteristic which persists for some months. Such a finding suggests that

Nature is rather attempting to conserve the red cells, possibly until haemopoiesis is fully established, which, as we have already hinted, would seem necessary during the rapidly developing period of neonatal existence.

PRESENCE OF NUCLEATED RED CELLS AND RETICULOCYTES DURING NEONATAL PERIOD. Moreover, if haemolysis were excessive during the neonatal period, one would expect the usual consequences of such a process, viz., a rise in premature cells in the circulating blood, yet so far as nucleated red cells are concerned there is absolutely no evidence of such a process, and in the case of reticulocytes the evidence is equivocal. In figs. 12 and 13 the proportion of these two types of cell in the foetus of varying degrees of maturity and in the newborn of different ages is shown. So far as nucleated red cells are concerned it is seen that there is a steady fall in their proportion during foetal life and that, unless during the first few hours of life, they are hardly ever seen in the post-natal state. The only case in which these were observed after the first day of life was an Rh+ child whose mother was Rh-. The reticulocytes also fall during the later weeks of foetal life, but after birth there occurs a temporary rise on the third and fourth days. This might be taken to indicate the presence of increased haemolysis, but the rise is very slight and only affects a minority of infants, so that it is questionable if any significance can be attached to it.

EXPERIMENTAL APPROACH TO THE PROBLEM. Goldbloom and Gottlieb (1930) have attempted to solve the problem of increased haemolysis during the neonatal period by experiments on the guinea-pig. Guinea-pigs were placed in chambers under minus (reduced) pressure to simulate the hypothetical conditions of life *in utero*. These authors found that in consequence of this procedure both haemoglobin and red cells rose by 30 per cent. They state that, when the guinea-pigs were removed from the chamber, which was considered analogous to birth, the haemoglobin and red-cell values fell, reaching the normal level within five days, and that at the same time the icteric index rose at once from nil to 1.5 units. It was also noted that the marrow became hyperplastic during the period the animals were under the influence of diminished atmospheric pressure. These authors lay great stress on their findings and certainly at first sight it does look as if the experimental conditions and those pertaining to our problem are identical. But a scrutiny of the experimental protocols raises doubts regarding their accepted significance. For instance, in three of the eleven experiments the plasma bilirubin was raised while the animals were still in the chamber, and in the other eight animals, although the plasma bilirubin was not noted to be raised till after their removal from the influence of the diminished atmospheric pressure, the maximum level was observed immediately after removal from the chamber and it fell rapidly thereafter. This is, of course, exactly the opposite of what obtains during infancy, when the plasma bilirubin almost invariably rises after birth. There is also

FIG. 12.—Showing proportion of nucleated red cells in blood of foetus and newborn during neonatal period.

the fact already noted (p. 196) that the red-cell and haemoglobin concentrations also rise. It would seem, therefore, that the increased haemolysis in Goldbloom and Gottlieb's experiments is related to hyperpoiesis (the greater the number of red cells the greater will be the number undergoing natural death or haemolysis at any particular moment), and that the fall in red-cell concentration is due more to a slowing down of haemopoiesis due to a return to a normal state of the hyperplastic marrow after removal of the stimulus (rarified atmosphere) than to any increased haemolysis. Indeed, these experimental findings are exactly parallel with the clinical changes

described in individuals resident at high altitudes (Hurtado, 1932 and 1937; and Monge, 1937) but they are certainly not analogous to what obtains in the newborn child.

Part 2: The Blood during Later Infancy

THE EFFECT OF THE ADMINISTRATION OF IRON. It has always been recognized that the concentration of haemoglobin and red cells is less during the latter part of the first year of life than during later childhood and adult life. With the fall during the neonatal period the haemoglobin may reach a reading between 60 and 70 per cent. and the reds a level of 3.5 million per c.mm., but with the recovery, which sets in during the third and fourth months, readings

FIG. 13.—Percentage of reticulocytes in blood of foetus and in newborn child.

of between 70 and 80 per cent. of haemoglobin and of 4.5 million red cells per c.mm. are reached. Details of the findings in my examples of full-time children are given in tables 3 and 4, and the averages of both full-time and premature children are represented graphically in figs. 14 and 15.

Until 1931 this lower level of haemoglobin and red cells during later infancy was considered physiological and thus unalterable. But in that year Helen Mackay (1931) stated that by the addition of an iron salt to the infant's diet the haemoglobin could be raised 5 or 10 per cent. higher, and naturally she postulated that the lower level was the consequence of a nutritional defect, a view which would seem to be fairly generally accepted.

There is no doubt that in what we consider the natural food of the infant (breast milk)—and the same is equally true of the substitute food (cow's milk)—there is an insufficient amount of iron to supply the child's current needs. On the basis that Nature seldom makes mistakes, it is generally held that she circumvents this shortage of iron in the infant's diet by sending the child into the world with a store of iron in the liver, a store which is said to be laid down for the most part during the last three months of pregnancy. It was by this device that, in spite of the dietary deficiency, the full-time child was considered to be satisfactorily provided for, but doubts prevailed regarding the case of the premature child. Indeed, it is almost universally taught that the premature infant, unless given additional iron, will develop anaemia. My researches, however, raise doubt concerning the validity of such a doctrine.

We do not know how long Nature intends breast milk to be the sole means of nourishment, but if we are correct in assuming that it should be continued till the appearance of teeth, as is done to-day, then we should desire strong proof that all the child's nutritional requirements are not being supplied. Yet on the strength of the work of Helen Mackay and her collaborators very far-reaching conclusions have been drawn not only regarding the provisions of Nature but also concerning the incidence of anaemia in infancy and childhood. I have not, in surveys undertaken in such diverse localities as Glasgow, the east end of London (1937), and the city of Oxford, been able to detect the widespread anaemia which Mackay (1942) and some other observers have found.

Four years ago (1942), in a discussion on nutritional anaemia at the Royal Society of Medicine, in a communication entitled *The Blood as an Index*

TABLE 3
AVERAGE RED CELLS IN A TREATED (RECEIVED IRON) AND A CONTROL GROUP OF CHILDREN, ACCORDING TO AGE

Age in months	Without iron			With iron			Size of difference
	No.	Mean	C.V.	No.	Mean	C.V.	
0-1	7	5.514 $\pm$ 0.159	7.65	8	5.76 $\pm$ 0.414	20.30	P=0.9
1-2	7	4.657 $\pm$ 0.218	12.39	15	4.413 $\pm$ 0.136	11.90	P=<0.4>0.3 (n.s.)
2-3	7	4.143 $\pm$ 0.244	15.57	16	3.869 $\pm$ 0.113	11.708	P=<0.1>0.05 (n.s.)
3-4	8	4.113 $\pm$ 0.122	8.36	15	3.913 $\pm$ 0.085	8.43	P=<0.7>0.6 (n.s.)
4-5	8	4.288 $\pm$ 0.104	6.88	16	4.38 $\pm$ 0.094	8.607	P=<0.4>0.3 (n.s.)
5-6	10	4.220 $\pm$ 0.081	6.09	12	4.36 $\pm$ 0.075	6.078	P=<0.3>0.2 (n.s.)
6-7	9	4.467 $\pm$ 0.096	6.42	13	4.39 $\pm$ 0.114	9.362	P=<0.7>0.6 (n.s.)
7-8	11	4.273 $\pm$ 0.057	4.45	15	4.31 $\pm$ 0.127	11.38	P=<0.3>0.2 (n.s.)
8-9	7	4.257 $\pm$ 0.174	10.83	16	4.23 $\pm$ 0.096	9.031	P=<0.3>0.2 (n.s.)
9-10	7	4.171 $\pm$ 0.099	6.30	15	4.16 $\pm$ 0.092	8.53	P=<0.9>0.8 (n.s.)
10-11	11	4.345 $\pm$ 0.164	12.54	16	4.23 $\pm$ 0.085	7.99	P=0.8 (n.s.)
11-12	7	4.443 $\pm$ 0.180	10.71	16	4.025 $\pm$ 0.104	10.31	P=<0.6>0.5 (n.s.)
12-13	13	4.354 $\pm$ 0.140	11.621	13	4.307 $\pm$ 0.043	3.60	P=<0.02>0.01 (sig.)

n.s. = not significant.

sig. = significant.

TABLE 4
AVERAGE HAEMOGLOBIN IN A TREATED (RECEIVED IRON) AND A CONTROL GROUP OF CHILDREN, ACCORDING TO AGE

Age in months	Without iron			With iron			Size of difference
	No.	Mean	C.V.	No.	Mean	C.V.	
0-1	7	122.0 $\pm$ 5.45	11.8	8	123.50 $\pm$ 10.63	24.31	P=<0.7>0.6 (n.s.)
1-2	8	95.0 $\pm$ 5.68	16.9	15	89.9 $\pm$ 3.01	13.0	P=<0.4>0.3 (n.s.)
2-3	7	84.6 $\pm$ 6.51	20.4	16	74.1 $\pm$ 2.28	12.3	P=<0.3>0.2 (n.s.)
3-4	8	78.0 $\pm$ 3.19	11.6	15	76.5 $\pm$ 1.51	7.6	P=<0.2>0.1 (n.s.)
4-5	8	80.5 $\pm$ 2.26	7.9	17	83.4 $\pm$ 1.84	9.1	P=<0.6>0.5 (n.s.)
5-6	10	81.0 $\pm$ 1.09	4.2	12	83.2 $\pm$ 1.49	6.2	P=<0.3>0.2 (n.s.)
6-7	9	82.2 $\pm$ 1.90	6.9	13	83.4 $\pm$ 1.54	6.7	P=<0.7>0.6 (n.s.)
7-8	11	76.7 $\pm$ 2.29	9.9	15	80.9 $\pm$ 2.38	11.4	P=<0.9>0.8 (n.s.)
8-9	8	77.0 $\pm$ 1.46	5.4	16	81.0 $\pm$ 2.25	11.1	P=<0.9>0.8 (n.s.)
9-10	7	80.6 $\pm$ 1.29	4.2	15	79.9 $\pm$ 2.24	10.9	P=<0.9>0.8 (n.s.)
10-11	11	79.1 $\pm$ 2.83	11.9	16	80.0 $\pm$ 1.93	9.7	P=<0.5>0.6 (n.s.)
11-12	8	74.4 $\pm$ 2.75	10.5	16	77.1 $\pm$ 2.73	14.1	P=<0.05>0.02 (border-line sig.)
12-13	13	75.8 $\pm$ 2.12	10.1	13	83.2 $\pm$ 1.72	7.4	P=<0.8>0.7 (n.s.)

n.s. = not significant.

sig. = significant.

FIG. 14.—Haemoglobin percentage concentrations in full-term and premature children with and without additional iron.

FIG. 15.—Red-cell concentrations in full-term and premature children with and without additional iron.

of Health, I put forward the thesis that it is fallacious to look upon the concentration of the haemoglobin and red cells in the blood as a direct measure of the health of the individual.

My attention had been first drawn to this matter during a research (1909) on the blood in rickets, when I found that, both in experimental rickets in the dog and in spontaneous rickets in the child, the concentration of the haemoglobin and red cells was increased. I found, for example, higher haemoglobin and red-cell levels in rachitic children resident in the Glasgow slum than in the healthy children of the wealthy citizens living under good conditions in the suburbs. I was inclined to ascribe this state of affairs to the fact that the rachitic child was confined in a badly ventilated house and thus required additional oxygen carriers, just as is the case in the individual living at a high altitude in a rarified atmosphere. One is here tempted to recall the observation of Dobbs (1942) that nurses evacuated from London to the country at the beginning of the war showed a fall in the haemoglobin level. This phenomenon Dobbs attributed to less satisfactory dietetic conditions in the country than in the town, but in my view it may possibly have been due to the result of improved atmospheric conditions and a consequent lesser demand for oxygen carriers. Is it not possible that in this way also we can account for the different haemoglobin levels in childhood, in women, and in men? In this order we can express the relative expenditure of muscular energy, and

thus the relative amount of oxygen required and the consequent relative amount of oxygen carriers.

For some years, too, I (1942) had been studying the effect of the administration of iron to normal individuals, apparently concurrently but unknowingly with my American colleagues, Fowler and Barer (1941). We all came to the same conclusion—that it was impossible to increase, unless very temporarily, the haemoglobin level in the healthy individual by the administration of iron.

For these reasons I was pleased to have the opportunity, provided by Prof. Chassar Moir and Dr. R. G. Macfarlane, to contrast the blood curves in full-time healthy infants, and also in premature but otherwise healthy babies, with and without iron added to their diet. I began observations on many infants, but a considerable number of the mothers failed to co-operate for a sufficient length of time, and I have been left with twenty-six full-time, and ten premature children. I was particularly anxious to study this problem in a series of twins, as they would seem to provide the most uniform material for test-case and control, but unfortunately it was here that co-operation was least satisfactory, and my material is insufficient for analysis.

I found no radical difference between the sexes, and so for purposes of simplification have combined the sexes on the graphs. For the differentiation between full-time and premature babies, I have depended on the duration of pregnancy and have not adopted the more recent index—birth weight—

as indicating the degree of maturity. In most instances the mothers had attended the ante-natal clinic at the hospital, and thus there was a fair measure of certainty regarding the duration of pregnancy. All the premature babies in my series receiving additional iron had a birth weight under $5\frac{1}{2}$ lb. (they ranged from 2.9 to 5.2 lb.) and thus would be considered immature by modern classification; but, by an unfortunate coincidence, of the five premature babies chosen as controls—that is, not given additional iron—three had birth weights above $5\frac{1}{2}$ lb. However, a comparison between the three over $5\frac{1}{2}$ lb. and the two under $5\frac{1}{2}$ lb. reveals no radical difference in the trend of the various curves, so that there seems no disadvantage in adopting the time factor rather than the weight factor.

I examined fewer infants than Helen Mackay; but all the children were healthy and the administration of iron was begun within ten days of birth. I usually started with daily doses of 20 mg. of iron in the form of ferrous sulphate, and gradually increased the amount to 60 mg., and in some cases to 120 mg. per day. In Helen Mackay's (1931) series the children were selected from her outpatient clinic and 'in many cases were ill and in the majority of instances were underweight and underfed.' Moreover, they were not infrequently five months, and in some instances were eight months old, when they first came under observation. Mackay states that the daily dose of iron in her cases varied between 60 and 120 mg. per day and was given in the form of ferri et ammon. citrate.

Figure 16, showing the average weight curves, reveals the satisfactory and almost equal rate of growth in all the various groups of children in my series. The parallelism of the average weights of the full-time children receiving added iron and those not so treated is striking. Those not receiving iron start at a slightly lower level but they do not lag behind those receiving iron. In the case of the premature children, those receiving iron started at a much lower level than those not receiving iron, and their rate of increase is certainly more rapid, but the rate of growth of those not receiving iron is quite as good as that of the normal full-time child.

The percentage concentration of haemoglobin and red cells in full-time children with and without additional iron are given in tables 3 and 4. These tables were compiled from my findings by Dr. Russell of the Department of Social Medicine, Oxford, and from the statistical analysis there emerges no significant differences between the two groups. In the graphic representation of the means of the two groups, shown in figs. 14 and 15, it will be seen that in the group receiving iron there is a more rapid recovery, specially marked in the case of the red cells, and by the age of five months higher haemoglobin and red-cell concentrations are reached in the group of children receiving added iron than is the case in the control series of children. But this higher level is only temporary and is not sustained, so that by the end of their first year, although the

FIG. 16.—Average weight curves of full-term and premature children with and without iron.

administration of iron had been without intermission, there is no difference between them. This recalls what I, and also Fowler and Barer, have found to be the result of the administration of iron to healthy older children and adults, viz., a temporary stimulating effect on haemopoiesis, but one to which the body soon becomes acclimatized.

As in the case of the full-term child, so in that of the premature child there is little difference in haemoglobin and red-cell concentrations in the group receiving additional iron and in the control group not receiving iron. The more rapid recovery, particularly of the red cells, after the neonatal fall is also apparent in the premature children receiving iron, but here again the superiority is only temporary, and by the time the children are one year old there is no significant difference between the groups (figs. 14 and 15).

Nor are any radical differences in the rate of blood formation apparent between the children receiving additional iron and those not so treated, when we study the total blood haemoglobin and red-cell contents. This we have attempted, as already mentioned, by computing from the blood counts and the body weights the total haemoglobin and red-cell contents. The average figures are shown in figs. 17 and 18, which reveal an almost uninterrupted rise in all (prematures and full-term alike) after the preliminary neonatal fall. In the case of the full-term children, those receiving iron present consistently—but only slightly—higher total

FIG. 17.—Average total Hb in grammes in full-term and premature child.

FIG. 18.—Total red cells in full-term and premature child with and without iron.

FIG. 19.—Hb in grammes per lb. weight in full-term and premature child with and without iron.

FIG. 20.—Red cells in millions to 10^{13} power per lb. weight in full-term and premature child with and without iron.

haemoglobin and red-cell values than those not receiving iron, but by the time the children are one year old there is no significant difference between the two groups. Most remarkable is the behaviour of the curves in the case of the premature children. In those not receiving additional iron the total amounts of haemoglobin and number of red cells is little different from that of the full-time child not receiving iron, and in the group receiving additional iron there did not occur any apparent diminution in total haemoglobin and reds during the neonatal period. The most striking feature of these charts is the steady and satisfactory formation of blood in all the groups.

BLOOD HAEMOGLOBIN AND RED CELLS PER LB. WEIGHT. During my analysis of the findings it occurred to me that it would be interesting to refer the amount of blood haemoglobin and number of red cells to body weight. This relationship is shown in figs. 19 and 20, in which haemoglobin and red cells are expressed in amount per lb. weight. The similarity of the curves of the various groups (full-time and premature alike) is striking. Unless in the case of haemoglobin in the premature children, which runs at a slightly lower level than in the full-time children, there is no radical difference between them.

A survey of the above findings leads to the conclusion that iron is not necessary as an adjunct to the diet of the normal infant for normal blood formation, that its administration does not lead to any improvement in the state of the blood, unless temporarily immediately after its presentation, when it seems to exert merely an irritating effect on the haemopoietic tissue just as it does in the case of the normal adult. Nor does there seem any evidence that additional iron is necessary even in the case of the premature child.

Conclusions

1. The haemoglobin and red-cell concentrations are lower in the foetus than in the child.
2. The haemoglobin and red-cell concentrations increase considerably within the first few hours after birth. For this no adequate explanation can be given.
3. After the initial post-natal increase in haemoglobin and red-cell concentrations, there is a gradual fall during the first three months of life.
4. This post-natal fall in haemoglobin and red-cell concentrations is most rapid during the second week of life.
5. The fall in the haemoglobin and the red cells during this period is not absolutely parallel: the fall in haemoglobin concentration is more marked than the fall in the red-cell concentration and causes a change in their relative proportions.
6. The change in proportion of haemoglobin and red cells is due to a change in the size of the red cell—which is smaller during post-natal than during antenatal life—and it indicates considerable new blood formation.
7. The total haemoglobin and red-cell contents

of the circulation show the same trend as the haemoglobin and red-cell concentrations, but the fall in the total amounts is less marked and continues for a shorter period.

8. There is no evidence of increased haemolysis during the neonatal period, in fact, rather the reverse.

9. Increased haemolysis is, therefore, not the prime factor in the causation of icterus neonatorum.

10. The fragility of the red cell in the newly born is diminished in comparison with that during foetal life and later childhood.

11. Nucleated red cells and reticulocytes, while abundant during foetal life, rapidly disappear from the circulation in the newborn child. Their persistence suggests some abnormality, e.g. the presence of the Rh factor.

12. Goldbloom and Gottlieb's experiments with the guinea-pig in a rarified atmosphere reproduce the results from living at a high altitude, but they are not comparable with those due to the change-over from foetal to post-natal existence.

13. The administration of iron to the diet of the full-time and premature healthy child causes a slightly earlier and higher post-neonatal rise in both haemoglobin and red-cell concentrations than occurs without any medication.

14. The improvement in the haemoglobin and red-cell concentrations from the administration of iron in the full-time and premature healthy infant is only temporary: by the time the children are one year old there is no statistical difference between the blood pictures of the treated and the untreated infant.

15. Estimations of total haemoglobin and red cells in the full-time and premature healthy infant reveal a progressive increase in the amount of haemoglobin and number of red cells from the second month of life, and show that the increase in both haemoglobin and red cells is identical in infants receiving additional iron and in those not receiving additional iron.

16. The effect of iron added to the diet of the normal infant, full-time and premature, would seem to be the same as in the case of the healthy older child and adult, viz., a temporary irritation of haemopoietic tissue.

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