STUDIES IN ANAEMIA OF INFANCY AND CHILDHOOD*

THE HAEMOGLOBIN, RED CELL COUNT, AND PACKED CELL VOLUME OF NORMAL ENGLISH INFANTS DURING THE FIRST YEAR OF LIFE

BY

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(RECEIVED FOR PUBLICATION, AUGUST 18, 1949)

The difficulty in establishing a normal standard for the blood picture in infancy is emphasized by the wide range in values recorded by different workers on this subject. Such variations may be due in early work to differences in technique and in later work to the use of different criteria of normality in infancy, to the random selection of infants and the acceptance of such as normals, to racial differences, and to the limitations imposed by a haemoglobin estimation without a corresponding red cell count.

The present work was planned in an attempt to establish normal values for English infants, to account for the disparity between the findings of different workers, and to determine whether all infants should receive prophylactic doses of iron in their first year of life.

Choice of Sample

In the present investigation the term 'normal' was used in a restricted sense and was applied only to those infants who, besides being 'standard' or 'average' and apparently healthy on physical examination, were not subjected to influences likely to produce anaemia during the first year of life. Thus, when infants were being selected for a normal series, those were excluded who were premature, immature at birth, one of a multiple birth, or who weighed less than a minimum of 6 lb. at birth. Also excluded were those who had suffered from any neonatal disease or from any infection during the first year of life.

It was considered necessary to exclude the children of anaemic mothers, although anaemia in the mother during pregnancy does not invariably lead to anaemia in the child. Mackay and Goodfellow

(1931) could find no difference between the haemoglobin levels of infants born of anaemic mothers and of those whose mothers were given protective doses of iron; Strauss (1933), who examined a small number of infants of severely anaemic and of healthy mothers, found a statistical difference between the haemoglobin levels in the two groups and states that 'infants born to mothers suffering from iron deficiency, although exhibiting at birth a normal blood picture, are unable to maintain a normal haemoglobin level during the first year of life.' Parsons (1932) and Parsons and Hickmans (1933) have described the occurrence of congenital nutritional anaemia in infants born to women suffering from an iron deficiency anaemia. Since such infants are a possible source of error, they should not be included in any 'normal' group.

An adequate supply of iron in the diet is essential for the maintenance of a normal blood picture at any age; during infancy, as cows' milk contains less iron than breast milk, the substitution of cows' milk mixtures for breast milk is likely to be detrimental to the child. Prolonged nursing or prolonged cows' milk feeding to the exclusion of a mixed diet must also be avoided. A hypochromic anaemia following such milk diets has long been known and has been given the names of 'milk anaemia' and nutritional anaemia of infants. This anaemia must be prevented in any normal series by the early addition to the infants' diets of foods containing iron and by avoiding any delay in weaning. In the present series breast-feeding was carried out for at least six months, additions to the diet were started at five to six months, and weaning was completed by nine months.

One indication of health in infancy is an average gain in weight: any infant more than 10% below the average weight for its age and birth weight

* The investigations described in this paper were carried out in the years 1937-1939 under the direction of Sir Leonard Parsons, but publication of the results has not hitherto been possible.

should be excluded from a normal series. Although not of itself abnormal, a rapid rate of growth has been recognized as a factor in the production of anaemia in infancy. For instance, in the statistical analysis made by Bradford Hill of Mackay's figures (1933) it was found that from six to twelve months of age the haemoglobin level was correlated with the rate of growth; that babies who made the largest percentage increase in weight over their birth weight tended to have the lowest haemoglobin levels. In the majority of investigations into the normal blood picture in infancy insufficient stress has been laid on this point and it is possible that some anaemic infants may thus have become included in a normal series. The rapidly growing, premature infant frequently develops in the second half-year of its life a low haemoglobin level which, because of its grossness, has been recognized as abnormal; on the other hand, finer shades of anaemia have been overlooked in the small, full-term infant who achieves the average weight for all infants at the end of one year. Thus, like premature infants, small infants, who may be expected to double and treble their birth weight much earlier than large infants, are potential sources of error. In the present investigation infants weighing less than 6 lb. at birth were therefore excluded. It is also possible that the big, breast-fed baby who at one year weighs much more than the average for its birth weight is also suffering from a borderline anaemia similar to that of the rapidly growing small baby. Therefore any large full-term infant of excessive weight at one year of age is another possible source of error and should be excluded from the group of normal infants. In the present series one breast-fed infant was excluded on this account.

In spite of every care being taken to select a normal sample of the infant population there will probably still be some babies who will develop mild hypochromic anaemia without any obvious cause (Guest and Brown, 1936). This hypochromic anaemia, together with that due to known causes at this age, has received the name nutritional anaemia of infancy, the material lacking being ultimately iron, the demand exceeding its supply, and the condition being easily cured by giving suitable doses of iron for several weeks. The anaemia usually remains unrecognized in its early stages and therefore the average blood picture of a group of healthy and apparently normal infants is likely to fall below that of a similar group of infants protected from such a nutritional anaemia by adequate doses of iron (Mackay and Goodfellow, 1931). As the administration of iron, a recognized therapeutic procedure, improves the blood picture in

the unprotected groups of infants, this group should probably be regarded as subnormal and the iron-fed group should not be regarded as 'artificial,' 'supernormal,' or 'abnormal.' The iron-fed group may instead be considered an 'ideal' normal and its blood counts may be compared and contrasted with those of the normal series of infants. In the present investigation such a comparison was made in infants of 12 months of age.

The lack of recognition of borderline cases of anaemia in infancy has been partly due to the custom of obtaining an average picture of the haemoglobin changes in infancy by examining cross-sections of the infant population at different ages. This method obscures any finer changes occurring in individual cases, and although the general trend of the blood count in infancy is represented, such an average gives no indication of the limits of normal at any particular age. Repeated examinations in one individual are of more value in determining the change and limits of normal than are those made at random on a number of individuals. In the present work both methods were used: one group of infants was followed from birth to one year of age, and a second group of infants, examined on a few occasions only, was used in the determination of the average.

Guest and Brown (1936) found that borderline cases of anaemia occurred more often than is commonly realized. This is due to the reliance placed by many investigators on the haemoglobin level alone as an index of anaemia. Guest and Brown state that in the development of nutritional anaemia diminution in the size of the red cells occurs before the fall in haemoglobin level, but that the two changes are additive and both depress the mean content of haemoglobin per cell. They consider that a haemoglobin content of 20 $\gamma\gamma$ or less per cell justifies a diagnosis of anaemia whatever the total haemoglobin. Parsons, Hickmans, and Finch (1937) have shown that the earliest signs of an iron deficiency anaemia in rats are polycythemia and microcytosis with a normal haemoglobin value. Therefore in order to obtain a complete blood picture it is necessary to correlate the haemoglobin with the red cell count and measure the packed cell volume. This was done in the present investigation.

Review of the Literature

Since the end of the last century numerous studies of the blood picture during infancy have been made, and by 1916 a broad outline had been obtained. It was then known that at birth the haemoglobin level and the red cell count were high compared with adult figures and that they became relatively

lower in the second half-year of life. In that year Williamson of Chicago published figures for the haemoglobin level from birth to old age. Using blood obtained from the pulp of the finger he found the average haemoglobin level at birth to be 23.4 g. per 100 ml. of blood, and in the first year of life to be never less than 12.5 g. haemoglobin per 100 ml. of blood (Table 1 and Fig. 1). This is a consistently high level compared with that of most later work, and as Williamson does not mention the minimum birth weight in his series, it may be an erroneously high level. His work has been criticized because of the standard of recrystallized haemoglobin which he used but, as Mugrage and Andresen (1936) point out, 'His values may be high but the general nature of the curve he obtained is significant.' In support of his figures are the findings of Merritt

and Davidson (1933) and of Faxen (1937), which were obtained at monthly intervals from birth and which closely parallel Williamson's figures (Table 1).

In 1918 Appleton, using the method of Palmer and Van Slyke and examining blood from the capillary circulation, determined the haemoglobin level in 103 New York children from birth to two years. Appleton does not mention the birth weights of the children he examined but all appeared healthy and 90% were breast-fed. The curve of haemoglobin averages followed that of Williamson's cases, the absolute amount at birth being 22.6 g. %, but in the latter half of the year falling below Williamson's figures to 12.0 g. % and corresponding closely to that of the majority of later workers (Table 1). It should be noted that Appleton placed all children of ages 6 to 11 months in one age-group

TABLE 1
HAEMOGLOBIN VALUES (%) IN INFANCY AS RECORDED BY VARIOUS AUTHORS

Age	Williamson	Appleton	Drucker	Mackay	Elvehjem	Merritt and Davidson	Mugrage and Andresen	Faxen	Present Author
0-48 hours	169	164		143	160	169	125	168	148
3-7 days	160	135						169	141
8-21 "	155	137	123	130	130		120		130
22-35 "	133	102	99	106		118		130	110
6-8 weeks			87	88	97	95		98	96
9-12 "	99	88	79	74	84		80		86
13-16 "				77	86	91		92	87
17-20 "			83	81	87	93		97	91
21-24 "	99	87		86	88	94	89	99	89
25-28 "				86	86	95		97	90
29-32 "			81	86	84	94		94	88
33-36 "				86	86	92	86	96	86
37-40 "	91	85		86	83	94		95	86
41-44 "				86	82	94		96	85
45-48 "			80	86	83	91		93	82
49-52 "				86	84	90		97	90
53-56 "		to 23 months	84	86	83		85		84
			to 2 years				to 18 months		

100% = 13.8 g. haemoglobin per 100 ml. blood.

and all of 11 to 23 months in another age-group. The inclusion of such a wide range of ages in each group may have produced a false picture of the haemoglobin level as it is from the sixth month onwards that nutritional anaemia is most likely to develop and finer changes that might occur at this time will not be detected by such grouping.

In 1923 and 1924 Drucker investigated methods of obtaining blood from infants and estimated the haemoglobin content and red cell volume in 85 healthy Danish infants aged from two weeks to two years. He found that what had been described by various authors as physiological variations in the haemoglobin level of infants were due to faulty technique. Thus, variations described as being due to the site of the puncture, the time of day, the relationship to meals, and so on, could be abolished by the use of an extremely sharp instrument, in his case a razor. Twenty-eight of these infants were breast-fed and Drucker found no differences between breast-fed and bottle-fed babies nor any between the sexes at this age. The youngest infants he examined were two to three weeks old, and at this age the haemoglobin level was 17.0 g. per 100 ml. of blood. In his cases the lowest haemoglobin level was found between 8 and 12 weeks of age and was 10.9 g. %. It then rose between three and six months to 11.5 g., fell to 11 g. between 9 and 12 months and rose again to 11.6 g. during the second year (Table 1). In this second rise, slight though it is, his figures correspond to those of Monrad and Ormu (quoted by Drucker) obtained in Danish children and are in contrast to Williamson's and Appleton's figures for American children which showed their lowest value in the second year. Unfortunately, Drucker did not make red cell counts in these infants but the figures for cell volume he found at their lowest at 8 to 12 weeks of age, that is, at the same time as the haemoglobin, and that, like the haemoglobin, they rose gradually during the following months.

In 1931 Mackay and Goodfellow published the results of several years' work on the haemoglobin level of London infants from birth to 14 months of age. These figures were revised in 1933. The infants weighed from $5\frac{1}{2}$ to $9\frac{3}{4}$ lb. at birth and were placed in three groups. The first group consisted of infants who were breast-fed up to the age of three months, and after that age consisted of infants who were being given prophylactic doses of iron. This group Mackay called 'normal,' and using the method of Haldane found the haemoglobin to be 19.7 g. % at birth, 10.2 at two to three months, and from approximately five months of age to be 11.8 g. per 100 ml. of blood. Mackay's second group consisted of breast-fed infants who were not treated

with iron. The same low haemoglobin level was found at two to three months in these cases, and there was then a rise from four to eight months to 10.8 g. % followed by a slight fall to 10.4 g. at 9 to 13 months. This rise at four to eight months is similar but not as great as in the first group and is followed by a fall not seen at all in the first group. The third group comprised untreated bottle-fed infants who showed a similar but greater divergence from the normal group. At two to three months of age their haemoglobin level was 9.5 g. %. These three groups all included infants of between 5 and 6 lb. birth weight. Such cases, like premature infants, might well influence adversely any average haemoglobin values. In the first group the prophylactic use of iron should have prevented any fall of haemoglobin due to this factor. It is possible that this effect was produced in the second and third groups: hypochromic anaemia may have been present in some cases and, the haemoglobin value being regarded as a low normal, have escaped detection. Mackay did not make any corresponding red cell counts in her cases; had she done so, cases such as those described above as 'low normals' might have been recognized as masked cases of anaemia. Mackay's group of breast-fed infants given iron showed average haemoglobin values lying at a much lower level than those of Williamson's cases but approximating to those of Drucker in the first six months and to those of Appleton in the second six months of life (Table 1 and Fig. 1).

In 1933 Elvehjem and his co-workers, using a Bausch and Lomb colorimeter, studied the capillary blood of 720 white children up to five years of age in Madison, U.S.A. They excluded from their series premature infants, twins, anaemic children, and those having treatment, but they made no

FIG. 1.—Percentage haemoglobin in infancy according to various authors.

mention of the minimum birth weight in the series. Their results followed the usual trend and the haemoglobin values lay between the lower ones of Mackay and the higher ones of Williamson. At birth the haemoglobin value was 22.2 g. %, at 8 to 12 weeks 11.9 g., and during the remainder of the year it altered only slightly (Table 1). In 1935 they published results in a similar age-group of children who had been given iron and copper by mouth. They found that the characteristic fall of haemoglobin in the first few months still occurred but in the later months the haemoglobin levels were all higher than in the previous series. They concluded that between three months and one year of age the haemoglobin level should lie between 12 and 13.5 g. per 100 ml. of blood and that 'the fact that the values for practically all the untreated infants are lower than the values obtained after therapy forces them to conclude that a large number of children suffer from slight anaemia.' Unfortunately both of their investigations suffered from the same defect as Mackay's work in that there were no red cell counts with which to correlate the haemoglobin findings. Elvehjem and his colleagues agree with Mackay that there is a difference between the haemoglobin values of a group of infants to whom iron is given and one from whom iron is withheld, but neither he nor Mackay has enough data to show in what way this difference develops.

In 1933 Merritt and Davidson, using a modification of Wong's method of estimating haemoglobin and making corresponding counts of the red cells, attempted to follow from birth to one year 73 healthy American infants. Success was achieved in 15 cases and these were examined at monthly intervals throughout the year. The infants were full-term but the minimum birth weight was not stated; they were healthy, mostly breast-fed, and were drawn from a poor and unprivileged population of mixed racial origin. Blood was obtained by puncturing the toe with a Hagedorn needle. The authors do not show findings in individual cases but show maximum, minimum, and mean values in monthly age-groups throughout the year. Although their average was much higher than in Mackay's cases and lay close to that of Williamson, the difference between maximum and minimum counts at each age-period was great. After the high initial value of 23.4 g. of haemoglobin at birth they found that, beginning with the fourth month, the greater number of infants had haemoglobin levels between 13 and 14.9 g. % except in the ninth and twelfth months when the greater percentage lay between 11 and 12.9 g. % (Table 1). The red cell count fell from a mean at birth of 5.95 million per c.mm. to 4.74 million at the second month and

thereafter made only minor fluctuations (Table 2). From the second month onwards the majority of values fell between 4.5 and 4.9 million cells per c.mm. and from the fifth to the eighth month there was 'a dispersion of values suggesting a lability of erythrocyte level under the influence of environmental factors.' In this way they noted some

TABLE 2
RED BLOOD CORPUSCLES (MILLIONS PER C.MM.) IN INFANCY
ACCORDING TO VARIOUS AUTHORS

Age	Merritt and Davidson	Mugrage and Andresen	Faxen	Present Author
0-48 hours	5.95	4.86	5.78	6.54
3-7 days		4.22	5.47	6.30
8-21 "				5.85
22-35 "	5.19		4.70	5.02
6-8 weeks	4.74		3.91	4.53
9-12 "		3.90		4.14
13-16 "	4.65		3.96	4.42
17-20 "	4.61	4.23	4.20	4.91
21-24 "	4.67		4.46	5.03
25-28 "	4.73		4.57	5.14
29-32 "	4.70		4.30	5.07
33-36 "	4.65	4.28	4.41	4.72
37-40 "	4.79		4.43	5.23
41-44 "	4.74		4.45	5.17
45-48 "	4.70		4.53	4.96
49-52 "	4.67		4.58	5.33
53-56 "		4.25 to 18 months		5.41

alteration in the relationship between red cell counts and haemoglobin values but did not show in what way that relationship was changing. It was left to Guest and Brown (1936) to point to the explanation of this change though not to demonstrate its occurrence in apparently healthy children.

In 1936 Guest and Brown of Cincinnati stated that nutritional anaemia might be seen not only in milk-fed infants but also in infants who had been offered a seemingly well-balanced diet. This anaemia was found to improve with a better diet in the case of milk-fed infants or spontaneously in those on a good mixed diet. Nevertheless, they say, the period of transition is a critical one for the infant. Guest and Brown showed that in the development of nutritional anaemia in infants 'diminution in the size of the cells occurs earlier than the decrease in the haemoglobin concentration but the two changes are additive and both depress the mean haemoglobin

content per cell.' In anaemic infants they found that with a low haemoglobin level, microcytosis and hypochromia, the red cell count might be normal, low or high. They state that a 'haemoglobin content' of 20 $\gamma\gamma$ or less per cell justifies the diagnosis of anaemia whatever the total haemoglobin; in some cases the haemoglobin level might be as high as 11 g. % yet it would be found that iron medication produced an improvement in the total blood picture. The fact that anaemia might be present with a normal, a low, or a high red cell count helps to explain the wider dispersion about the mean of the red cell values in Merritt and Davidson's series from the fifth to the eighth month. In other words it is probable that there were included in Merritt and Davidson's series some infants who were actually developing a mild anaemia but in whom such changes were not gross enough to warrant their exclusion from the series. During their study of anaemic infants Guest and Brown tested at intervals of approximately three months a considerable number of infants who were being studied closely from birth through their early years. From data thus obtained they attempted to define the normal limits of variability of the red cell count, the total haemoglobin and the haemoglobin content per cell in order to define the borderline of clinically significant anaemia. Their results showed that at one time or another from six months to 2½ years of age the red cells of the majority of healthy infants showed minor alterations of the same pattern as in the development of anaemia. By their method they demonstrated that borderline anaemia occurred much more frequently among seemingly normal infants than is generally appreciated. Moreover, they found that anaemia, when it was recognized in routine clinical work, was usually severe.

In 1936 Mugrage and Andresen made volumetric measurements as well as red cell and haemoglobin estimations on 533 American children, mostly of white parentage, from birth to 13 years. They did not state the birth weights of these infants and only a few were breast-fed. Blood was obtained from the umbilical cord in the newborn, by sinus puncture in the infant, and venipuncture in the older child. Their curve of haemoglobin lay below that of Merritt and Davidson but did not fall as low as Mackay's for normal infants until between 8 and 18 months. At birth their mean haemoglobin value was 17.4 g.; between two and four months 11.4 g.; between four and eight months 12.29 g.; and between 8 and 18 months 11.73 g. % (Table 1). Compared with Merritt and Davidson's figures Mugrage and Andresen's red cell counts were low: at birth 4.88 million cells per c.mm., at two to four months 3.90 million, and thereafter the number

slowly increased until at 12 years of age the count reached 4.66 million cells per c.mm. (Table 2 and Fig. 2). For packed cell volume they give the

FIG. 2.—Red cell count in infancy according to various authors.

following figures: in cord blood, 53.18%; from two to four months, 34.18%; from four to eight months a value slightly higher and rising after 18 months to 43.8% at 12 years (Table 3 and Fig. 3). They found the mean corpuscular haemoglobin to be 35.1 $\gamma\gamma$ in cord blood, 27.5 $\gamma\gamma$ at 8 to 12 months and equal to adult values at seven years. The mean

TABLE 3
HAEMATOCRIT VALUES IN INFANCY
ACCORDING TO VARIOUS AUTHORS

Age	Mugrage and Andresen	Drucker	Present Author
0-48 hours	53.18		62.65
3-7 days	43.28		58.61
8-21 "		54.8	54.04
22-35 "		41.8	45.51
6-8 weeks		37.9	38.95
9-12 "	34.18	35.7	34.25
13-16 "			34.66
17-20 "	37.37	37.9	36.27
21-24 "			36.09
25-28 "			36.98
29-32 "			36.26
33-36 "	36.81	38.1	35.61
37-40 "			36.59
41-44 "		38.3	36.35
45-48 "			34.87
49-52 "			38.00
53-56 "			35.00
	36.28 to 18 months	38.8 to 2 years	

corpuscular volume in the cord blood was 108.9 cubic μ , at 12 to 18 months 85.3 cubic μ , and in older children it lay between 89.2 and 93.3 cubic μ , the values for men and women respectively. The mean corpuscular haemoglobin concentration they found to vary little, between 32 and 33.8%.

Before 1937, when Faxen published his work in Sweden, there had been in all investigations some defects in the selection of normal infants. The 374 infants examined from birth to one year of age by Faxen fulfilled all the requirements for normality. Capillary blood was examined and was obtained by pricking the finger tip with an ordinary stilette. Several infants had more than one count made on them during their first year; one had six successive counts, five had five counts and six had four, but the majority had three, two, or only one count made on them. Each of these counts was, from a statistical point of view, regarded as an isolated count and thus Faxen's figures represent the average blood picture of the normal infant community in Sweden. His values for haemoglobin and red cells lie within a very narrow range, but unfortunately his results lack completeness in that he did not measure the volume of packed red cells. After the initial fall of haemoglobin from 23.2 g. % at birth to 12.7 g. at three months a rise to 13.7 g. at five months followed (Table 1 and Fig. 1). These figures were very much higher than Drucker's figures for Danish infants, than Mackay's figures for an artificial normal (i.e. iron-fed) English group, and than Elvehjem's figures for a similar artificial normal group in America. On the other hand they lay close to the findings of Merritt and Davidson on children in New York. Drucker's and Merritt and Davidson's figures showed a fall between the ninth and twelfth months whereas Faxen's figures did not alter. Faxen's red cell count, with an initial value of 5.78 million cells per c.mm., ran parallel to Mugrage and Andresen's but fell below Merritt and Davidson's counts at two to three months and reached a minimum of 3.9 million per c.mm. It then rose until at five months it reached 4.5 million cells per c.mm. and then approximated closely to Merritt and Davidson's counts (Table 2 and Fig. 2). Faxen says that 'the individual variation shows no certain changes in the different ages, but may be somewhat greater in early infancy than at later ages.'

From the above review it will be seen that there have been numerous investigations into the blood picture in infancy but certain deficiencies can be found in each survey, either in the quality of the infants selected or in the completeness of the examinations made. It is only in recent years that the adverse effect of a low birth weight on the blood

picture of infants has been recognized and, though all workers agree on the necessity for selecting healthy full-term infants for their survey, Faxen has been the only one to regard a minimum birth weight as one of the essentials of normality. The results of the majority of workers may thus have been affected by the accidental inclusion of infants who, because of a relatively low birth weight or a very rapid gain in weight, may have been suffering from a mild anaemia. Mackay's group of breast-fed infants and infants fed in the later months with iron, together with a similar group of Elvehjem's, constitute artificial normal groups, the development of anaemia presumably having been prevented by the addition of iron to the diet. Even so, Mackay's and Elvehjem's figures for haemoglobin, approximately 86% and 88% in the second six months of life, were much below Faxen's average of 95%. Where red cell counts were made in addition to haemoglobin estimations there is a close approximation between the results of different workers; Merritt and Davidson's figures were high at birth but after the fall at two to three months their findings and those of Faxen and Mugrage and Andresen were almost identical. Volumetric findings were recorded by Drucker and Mugrage and Andresen. All of Drucker's cases were full-term and of 'approximately normal' weight but only one-third were breast-fed. Few of Mugrage and Andresen's cases were breast-fed and the minimum birth weight was not stated. In both of these investigations the grouping of the cases was such that all but gross changes occurring in the blood during the first year of life would probably be overlooked. In spite of this it is noteworthy that, except for a lower initial haematocrit reading in Mugrage and Andresen's cases, subsequent readings lie closely parallel to those of the present series with Drucker's findings at a slightly higher level (Table 3 and Fig. 3).

FIG. 3.—Haematocrit values in infancy as recorded by Drucker, Mugrage and Andresen, and the author.

No author shows the individual changes occurring in a sufficient number of normal infants throughout their first year of life to state with authority the limits of the normal blood picture in infancy. With regard to random observations, Faxen's figures may be taken as a criterion of the average in apparently healthy infants. Had he obtained similar results in a control group fed prophylactically with iron it might have been possible to state that his results were not only average but normal for this age.

Material and Method

The infants used in this investigation numbered 249. They were drawn from the population of Birmingham and its suburbs and were mainly the children of artisans with families of one or two. A few came from a poorer working class but most of these babies soon ceased attending. As regards racial differences, the population of this part of England is not a floating one and although there appeared an occasional Scottish or Irish woman amongst the mothers, it is considered that the sample was as purely English as could be obtained. The infants were brought to the clinic at least once a month for blood examinations and 33 continued to attend throughout their first year. Some infants were brought on one or two occasions only. They could not give as valuable information on the changes in the normal blood picture during the first year as did those examined on many occasions but, with the latter, they formed a cross-section of the infant community and from them an average blood picture was obtained.

A clinical examination especially for the purposes of this investigation was not carried out on the mothers as they had all been examined at ante-natal clinics and were delivered at one of the maternity homes of the City of Birmingham Public Health Department. There were no cases of obvious anaemia amongst them although, when seen in the present survey, eight mothers said that they were or had been 'anaemic.' Six had had pyelitis and three albuminuria during pregnancy. A number had received iron during pregnancy.

Twins and infants weighing less than 6 lb. at birth were excluded from the present survey. All but five infants were born within two weeks of the expected date. Of these five, one who was four weeks and two who were three weeks premature were not seen after three weeks of age; another, three weeks premature, was not seen after three months; and the other, although born three weeks before term, weighed 7 lb. 8 oz. at birth and so was regarded as mature and examined at intervals throughout the first year.

Neonatal disease did not appear in the infants selected but the occurrence of pneumonia, pink disease, measles, and other infectious fevers during the later months meant the exclusion of the affected infants after the event. In addition, children who had had more than one attack of bronchitis were excluded. As the majority of the infants had one or two minor illnesses in their first year, those who had not ceased to gain weight were regarded as normal. In this way were included a number of infants who had had more than one cold, three who had had

one attack of bronchitis, and five who had had mild gastro-enteritis.

Infants were excluded if at any time their weight fell more than 10% below the average for their age and birth weight. One breast-fed infant and seven artificially fed infants weighed at one year over 10% more than their expected weight, but these were not excluded from the series representing a cross-section of the community; the breast-fed infant was excluded from the breast-fed normal series when its weight became excessive.

Most of the infants were breast-fed for the first three months. After that time most of them were artificially fed while some were partly breast-fed and partly artificially fed. In all cases orange juice and cod liver oil or their equivalents were started at about two months of age. Additions to milk feeds were begun at five or six months and were increased until at nine months the infant was fully weaned and was taking approximately one and a half pints of cows' milk daily with cereals, fruit, vegetables, egg, fish, and small amounts of liver. The quantity and variety of foods were increased during the next three months so that at one year of age the infant was on a well-balanced mixed diet. Prophylactic doses of iron were given to certain infants in an attempt to protect them from nutritional anaemia and so create an 'ideal normal' series. A number of mothers succeeded in giving their infants sufficient iron for not less than three months. The findings in these infants were compared at 12 months with those in babies who were not given iron at all during their first year.

No special attention was paid to the time of day at which the samples of blood were taken, although the majority were collected in the morning. Usually a particular child was seen always at the same time of day so that the counts of each individual were presumably comparable throughout. It is noteworthy, however, that Drucker (1923) did not find that the time of day or the relation to meals affected the results in any way.

The following routine was used for collecting blood from the infants. The baby's heel was warmed in a bowl of warm water, dried, cleaned with ether, and pricked by means of a sharp spring-lancet. This produced a free flow of blood which was collected into a small tube of total capacity 0.25 ml. containing two or three particles of dry heparin and a small piece of shot. About 0.1 ml. of blood was obtained and thoroughly mixed with the heparin and the tube was corked with a rubber bung. The use of heparin in tubes allowed ease of transport and the duplication of estimations on the one sample.

Haemoglobin, red cell, and haematocrit estimations were carried out on each sample. The haemoglobin was estimated by the method of Haldane, and eight Haldane pipettes and diluting tubes were used throughout the investigation. Heparinized blood was drawn up to the 0.02 ml. mark on a Haldane pipette and washed into distilled water in a diluting tube. Coal gas was then blown over the surface of the haemolysed blood for two minutes, and the blood diluted with distilled water to match the standard. Haemoglobin dilutions were matched against artificial daylight and the result was

expressed as a percentage, 100% being equivalent to 13.8 g. of haemoglobin per 100 ml. of blood. For the red cell count six standard red cell pipettes and one Hawksley's 'improved Neubauer' counting chamber were used over the whole period. Heparinized blood was drawn up to the 0.5 mark, and then Hayem's diluting fluid up to the 101 mark. The cells in 80 squares, each of 1/400 sq. mm. area, were counted on each side of the counting chamber and the average taken. Calculation then gave the average red cell count per ml. of blood. In the latter part of the investigation duplicate red cell counts were made on the same sample of blood and the average taken. For packing the red cells a special high-speed centrifuge made by Baird and Tatlock, with tubes graduated from 0 to 100 with an internal diameter of 1 mm., was used. The tubes were 5 cm. long, of thick glass, and were open at both ends; they were inserted into accurately fitting brass containers with rubber stoppers at each end and with a screw cap to ensure that the close fit of tube against rubber was maintained. The tubes were centrifuged at 8,000 revolutions per minute until packing was complete. Results were expressed as the percentage of packed red cells per unit volume of blood.

In an investigation such as the present the potential sources of error are many. It has been stated by various authors that capillary blood obtained from different parts of the body at the same time, for instance from the heel and the lobe of the ear, may show considerable variations, but Drucker (1923) considers that this is due to faulty methods of obtaining blood. It has also been stated that blood from one part of the body may vary widely at different times, but Drucker did not confirm this in children over one month of age. In the present investigation the heel was used instead of the ear because of its convenience and because physical conditions could be kept constant more easily. Throughout the survey care was taken to ensure continual sharpness of the lancet as Drucker showed that bluntness leads to greater variations and higher values. As dilutions were not made at the time of collection of the blood, dry heparin, which does not affect the osmotic equilibrium of cells and plasma, was used as an anticoagulant. Throughout the investigation dilutions were usually made within two or three hours of collection, but in a few cases the heparinized blood was left in the corked tubes overnight. Comparative counts showed that such a delay did not introduce any recognizable error.

It was realized that errors in estimating haemoglobin might arise from variations in the Haldane pipettes, in the diluting tubes, or in the standard haemoglobin tube; in counting the red cells they might arise from variations in the red cell pipettes or from the counting chamber; and, in measuring the volume of packed cells, from variations in the haematocrit tubes.

All glassware used in this investigation was supplied by Messrs. Hawkesley and Sons, Ltd., and was used with their guarantee of accuracy. The one haemoglobin standard was guaranteed accurate at the beginning of the investigation and was tested again at the end of the investigation and found still to be accurate.

Manipulative technique was standardized and kept

unaltered so that the personal error might remain at a minimum. As the technical work was never delegated the personal error is presumed to have remained the same throughout and to have affected the results equally. In repeated estimations on the same sample of blood it was found that the range of error in reading haemoglobin and haematocrit values and in counting red cells was in each case $\pm 2\%$. Such an error, of significance in a solitary estimation, may be presumed to operate equally about the mean where a sufficient number of estimations are made on a group of infants or when a statistical analysis is made of a smaller number of such estimations.

Results of the Present Investigation

The present work may be divided into two main sections. This paper is the first section and deals with an analysis of approximately 1,200 blood counts made on 249 infants, and with the establishment of mean values for the haemoglobin, red cell count, and haematocrit at ages ranging from birth to 13 months.

The 249 infants, alike in all other respects, differed from one another in one important particular, that of feeding. According to the method of feeding the infants were placed in one of four groups. The first group consisted of all the infants in the survey whether they were breast-fed, artificially fed, fed on a mixture of breast milk and cows' milk or given iron as a prophylactic measure. This group formed a cross-section of the healthy infant population. The second group consisted of all cases who were breast-fed from birth to at least six months of age. This group was regarded as the true normal of the infant population. The third group consisted of all infants who were artificially fed from birth: in addition, any infants who had been completely weaned before the age of three months (90 days) were added to this group after they reached the age of six months. Readings in this group were compared and contrasted with those of the breast-fed group. The fourth group consisted of a small number of infants of approximately 12 months of age who had been given adequate prophylactic doses of iron for at least three months. This last group formed an 'ideal normal' for one year of age and was used as a criterion of the normality of the breast-fed and artificially fed groups of the same age.

In the first three feeding groups, the blood counts were arranged in age-groups from birth to 13 months. The grouping was 0 to 48 hours, 3 to 7 days, 8 to 21 days, 22 to 35 days, 36 to 56 days, and thereafter consisted of periods of four weeks. The mean values and their standard errors for haemoglobin, red cell count, and haematocrit were calculated from the readings obtained in each age-group within each feeding group and alterations in these values during the first year of life were observed. From these absolute values were calculated the mean corpuscular haemoglobin, the mean corpuscular volume, and the mean corpuscular haemoglobin concentration. The colour index was calculated from the red cell count and the haemoglobin value expressed as a percentage where 100% corresponded to 13.8 g. of haemoglobin per 100 ml. of blood. The values so obtained in the group of breast-fed infants have been

taken as an arbitrary standard and with them have been compared the results from other methods of feeding and the findings of other workers.

Haemoglobin. Table 4 shows the mean values, with their standard errors, of the haemoglobin of the group

TABLE 4
HAEMOGLOBIN VALUES IN BREAST-FED INFANTS

Age	Number of Cases	Haemoglobin		
		Percentage Haldane (100% = 13.8 g.)		G. per 100 ml. blood
		Mean	Standard Error	
0-48 hours	87	148.66	1.29	20.5
3-7 days	100	141.32	1.20	19.4
8-21 "	96	130.77	1.22	18.0
22-35 "	33	110.03	2.09	15.2
6-8 weeks	27	96.11	2.31	13.3
9-12 "	32	86.00	2.12	11.8
13-16 "	24	87.38	2.45	12.0
17-20 "	14	91.14	3.21	12.6
21-24 "	9	89.78	4.00	12.4
25-28 "	11	90.00	3.62	12.4
29-32 "	10	88.40	3.62	12.2
33-36 "	8	86.00	4.00	11.8
37-40 "	8	86.13	4.00	11.8
41-44 "	5	85.20	4.90	11.7
45-48 "	6	82.17	4.54	11.3
49-52 "	5	90.80	5.37	12.5
53-56 "	4	84.50	6.00	11.7

of breast-fed infants from birth to 13 months of age. The means are expressed as g. per 100 ml. blood and as the equivalent percentage Haldane. The number of cases in each age-group decreased rapidly after the first three weeks so that from the seventeenth week onwards the number was less than ten. In the statistical analysis of these figures corrections were made for the use of such small numbers. At birth the haemoglobin level was high, 20.5 g. per 100 ml. blood or 148.6% Haldane: it then fell rapidly and steadily to a minimum of 11.8 g. or 86% at two to three months of age: thereafter it rose slightly to a second lower maximum of 12.6 g. or 91% at four to five months and then fell slightly again to an average of 11.7 g. or 85% (range 11.3 to 12.4 g. or 82% to 90%).

These values agree, after the age of six months, with those of Mackay and the majority of other workers, but lie at a lower level than those of Williamson, Merritt and Davidson, and Faxen (Fig. 1 and Table 1).

A statistical examination of the results showed that the falling values of haemoglobin in the age-groups from birth to two to three months were highly significant but that the subsequent rise as shown in Table 4 and Fig. 1 was not significant.

Table 5 shows the mean values, with their standard errors, of the haemoglobin of the group of artificially-fed infants from birth to 13 months of age. The age-groups up to 12 weeks contained 10 cases or less, from 13 to

40 weeks between 20 and 32 cases and from 41 to 56 weeks approximately 10 cases. Fig. 4 is a graphical representation of these results compared with those of the breast-fed group. Comparison of Tables 4 and 5 and an examination of Fig. 4 show that the haemoglobin

FIG. 4.—Percentage haemoglobin in breast-fed and artificially fed cases.

values for breast-fed and artificially fed infants are extremely close, that their curves are virtually parallel, and that the artificially fed group lies at the lower level.

Table 6 shows the mean values, with their standard errors, of the haemoglobin from birth to 13 months of all infants, whatever the type of feeding. Fig. 5 depicts these findings compared with those of breast-fed infants. The numbers in each age-group were much greater than in the breast-fed and artificially fed groups: up to three weeks of age the groups contained between 129 and 141 cases, from 3 to 40 weeks between 40 and 72 cases, and from 41 to 56 weeks between 19 and 28 cases.

TABLE 5
HAEMOGLOBIN VALUES IN ARTIFICIALLY FED INFANTS

Age	Number of Cases	Haemoglobin	
		Percentage Haldane (100% = 13.8 g.)	
		Mean	Standard Error
0-48 hours	9	146.11	4.00
3-7 days	8	147.88	4.24
8-21 "	10	135.40	3.79
22-35 "	4	113.50	6.00
6-8 weeks	5	94.60	5.37
9-12 "	6	81.33	4.90
13-16 "	32	86.88	2.12
17-20 "	31	88.45	2.12
21-24 "	29	89.86	2.23
25-28 "	28	87.75	2.27
29-32 "	28	85.57	2.27
33-36 "	24	84.83	2.45
37-40 "	20	87.00	2.68
41-44 "	14	84.14	3.21
45-48 "	13	83.53	3.33
49-52 "	9	87.56	4.00
53-56 "	11	81.64	3.62

TABLE 6
HAEMOGLOBIN VALUES IN ALL CASES

Age	Number of Cases	Haemoglobin	
		Percentage Haldane (100% = 13.8 g.)	
		Mean	Standard Error
0-48 hours	129	149.60	1.06
3-7 days	141	143.81	1.01
8-21 "	134	131.72	1.03
22-35 "	56	110.50	1.60
6-8 weeks	51	95.16	1.68
9-12 "	72	85.49	1.41
13-16 "	65	87.42	1.49
17-20 "	56	89.23	1.59
21-24 "	53	89.72	1.65
25-28 "	49	88.67	1.71
29-32 "	57	86.37	1.57
33-36 "	45	85.62	1.77
37-40 "	40	86.50	1.90
41-44 "	28	84.96	2.27
45-48 "	27	83.41	2.31
49-52 "	20	86.90	2.68
53-56 "	19	82.32	2.75

Comparison of Tables 6 and 4 and an examination of Fig. 5 show that the same remarks apply to this group of infants, a cross-section of the healthy infant population, as to the artificially fed group, i.e. that its haemoglobin

FIG. 5.—Percentage haemoglobin in breast-fed cases and all cases.

values lie extremely close to but at a lower level than those of the breast-fed group.

Comparison of Figs. 4 and 5 show that the mean haemoglobin values in 'all cases' lie between those of the artificially fed group and those of the breast-fed group. This observation is supported by statistical analysis in which it was shown that there was a characteristic range of values associated with each age whatever the method of feeding but the actual value within this range was dependent upon the method of feeding. At any particular age the differences between the various methods of feeding were too small to be statistically significant but they were consistent enough to be highly significant when the mean was taken for each method over the whole range of age-groups. This was demonstrated graphically by the parallelism of the curves in the three methods of feeding. In other words, in a group of healthy infants the method of feeding produces small but significant effects on the haemoglobin level. Artificially fed infants have the lowest average haemoglobin values. Slightly higher values are found in partly breast-fed infants and slightly higher values still are found in fully breast-fed infants. The values in the artificially fed group were well within the accepted lower limits of normal and at no time did this group come under the suspicion of anaemia.

At approximately 12 months of age the haemoglobin values of a small group of infants who had been given adequate prophylactic doses of iron for at least three months were compared with those of a group of breast-fed infants and also with those of a group of artificially fed infants of the same age. Table 7, showing the mean haemoglobin values with their standard errors, makes this comparison clear and includes also the values for the red cell count and the haematocrit. The one statistically significant difference in these blood findings is in the haemoglobin means of artificially fed and iron-fed infants. The difference between these means is 10.5 which has a standard error of 3.68 so that the odds against this difference being due to chance lie between 100 and 1,000 to 1. No other difference is significant, either for the red blood corpuscles, the haematocrit or the remaining haemoglobin means, but there is some indication that increasing iron intake influences all three characteristics as the three sets of means are consistent in showing slight increases in the order artificially fed, breast-fed, iron-fed.

TABLE 7
BLOOD FINDINGS AT APPROXIMATELY 12 MONTHS OF AGE

Method of Feeding	Number of Cases	Haemoglobin		Red Blood Corpuscles		Haematocrit	
		Mean	Standard Error	Mean	Standard Error	Mean	Standard Error
Artificially Fed	13	82.9	2.43	5.14	0.11	36.12	0.80
Breast-Fed	10	87.3	2.77	5.21	0.12	36.75	0.91
Iron-Fed	10	93.4	2.77	5.45	0.12	38.95	0.91

In Table 1 are shown the haemoglobin values (expressed as percentages) during the first year of life as recorded by various authors. It may be seen that the high level at birth and the subsequent fall in haemoglobin values are common to all workers whereas the slight rise and slighter second fall as seen in the present series are not shown by all. Individual variations in the general pattern are great: for instance, at birth the lowest value for haemoglobin is 125% (Mugrage and Andresen), the highest 160% to 170% (Williamson, Appleton, Elvehjem, Merritt and Davidson, and Faxen), with the values of Mackay and the present author lying midway between these extremes at approximately 145%. (Drucker's figure of 123% for his earliest age-group at two to three weeks of age cannot justly be compared with results in infants a few hours to a few days old.) There appears to be no convincing explanation of this great variation in the haemoglobin values at birth. Mugrage and Andresen's low value may possibly be explained by the fact that the blood was obtained from the umbilical cord at birth before the flow had stopped; all other workers obtained blood from the capillary circulation of the infant, and in some cases stasis in the capillaries may have led to an abnormally high count being recorded. The 20% difference between the figures for English children at birth and those of American and Swedish children still remains unexplained. It is possible that racial differences may account for the disparity or the time at which the umbilical cord is tied. For the remainder of the first year of life the fluctuations of the haemoglobin level as found by different workers may follow one of three types of curve (Fig. 1). In the first type there is a steady fall throughout the first year to the lowest level at 12 months of age (Williamson and Appleton); in the second type an initial fall to two or three months of age is followed by a slight rise which is

maintained to 12 months of age (Mackay, Faxen, Elvehjem's iron-fed group): in the third type the fall and rise is followed by a second slight fall (Drucker, Elvehjem's untreated group, Merritt and Davidson, Mugrage and Andresen, the present author).

In trying to account for the above differences an explanation of the first type of curve may be found in the method of grouping followed by Williamson and Appleton. Both these authors grouped cases aged from two weeks to two months in one group and those aged from three months to five months in the next group. Any finer changes occurring at, say, four-weekly intervals would be lost in such a grouping and any minimum occurring, say, at two to three months of age would be offset by higher values at earlier and later ages. Mugrage and Andresen, who grouped cases aged from two to four months together, found the average haemoglobin values for the first year of life at their lowest at this age. In the present series of cases where serial counts were made on individual infants at four-weekly intervals the minimum was found to occur from six weeks to four months of age. Any curve, therefore, constructed from the mean of a number of individuals may not reflect the extent of this primary fall, the minimum being offset by higher values occurring in other cases at the same age. The second and third types of curve are alike in showing a primary fall followed by a rise. In the second group, comprising Mackay's and Faxen's groups and Elvehjem's group of infants treated with iron, this rise is maintained throughout the remainder of the year. In Mackay's series a second fall is probably prevented by the fact that the infants chosen to constitute the normal were given prophylactic doses of iron from the third month onwards, so that the development of an undetected anaemia in an apparently healthy group of children was presumably prevented. Elvehjem's group of treated

TABLE 8
RED BLOOD CORPUSCLES (MILLIONS PER C.MM.) IN INFANCY

Age	Breast-Fed Infants			Artificially Fed Infants			All Cases		
	No. of Cases	Mean	Standard Error	No. of Cases	Mean	Standard Error	No. of Cases	Mean	Standard Error
0-48 hours	87	6.54	0.06	9	6.40	0.20	129	6.60	0.05
3-7 days	100	6.30	0.06	8	6.66	0.21	141	6.39	0.05
8-21 "	96	5.85	0.06	10	6.05	0.19	134	5.85	0.05
22-35 "	33	5.02	0.10	4	5.19	0.30	56	5.02	0.08
6-8 weeks	27	4.53	0.11	5	4.45	0.26	51	4.47	0.08
9-12 "	32	4.14	0.10	6	3.92	0.24	72	4.14	0.07
13-16 "	24	4.42	0.12	32	4.66	0.10	65	4.56	0.07
17-20 "	14	4.91	0.16	31	4.94	0.10	56	4.93	0.08
21-24 "	9	5.03	0.20	29	5.19	0.11	53	5.12	0.08
25-28 "	11	5.14	0.18	28	5.18	0.11	49	5.19	0.08
29-32 "	10	5.07	0.18	28	5.18	0.11	57	5.11	0.08
33-36 "	8	4.72	0.20	24	5.28	0.12	45	5.12	0.09
37-40 "	8	5.23	0.20	20	5.49	0.13	40	5.29	0.09
41-44 "	5	5.17	0.24	14	5.28	0.16	28	5.20	0.11
45-48 "	6	4.96	0.22	13	5.26	0.16	27	5.14	0.11
49-52 "	5	5.33	0.26	9	5.38	0.20	20	5.33	0.13
53-56 "	4	5.41	0.30	11	5.36	0.18	19	5.30	0.14

infants was probably protected in a similar manner. Faxen's group of infants was not protected in this way but his selection of healthy infants was more strict, particular stress being laid on a minimum birth weight of 3,000 g., on breast-feeding, on freedom from sickness during the first year of life, and on the early addition of iron-containing foods to a milk diet. Even so he found that the diameter of the red cells in healthy children in the second half-year of life showed 'a slight change in the direction of hypochromatic anaemia' and 'the relatively low percentage of haemoglobin per blood corpuscle in the second half-year is associated with the marked predisposition to hypochromatic anaemias occurring at this age.'

The third group, characterized by a fall of haemoglobin in the second half-year of life, comprises the results of Drucker, Elvehjem, Merritt and Davidson, Mugrage and Andresen and the present author. The inclusion of some infants of low birth weight may possibly account for the second fall in the haemoglobin level observed by most of these authors as such infants often make a rapid gain in weight, and Mackay found that 'from six to twelve months old the haemoglobin level was correlated with the rate of growth: babies who made the largest percentage increase in weight over their birth weight tend to have the lowest haemoglobin levels.' All these investigators were careful to select full-term, healthy infants for their series and the present author made a minimum birth weight (6 lb.) an additional criterion of normality. (In Faxen's cases the minimum birth weight was 3,000 g. or 6 lb. 9 oz.) In the breast-fed group in the present series infants who at the age of one year had made an excessive gain in weight (i.e. more than three times their birth weight plus 10%) were excluded. Even so it was found in serial blood counts in apparently healthy infants that the evidences of the onset of nutritional anaemia could be found before the fact became apparent clinically and before an isolated blood count could properly be said to indicate anaemia. It is probable therefore that, with the exception of Mackay's and Elvehjem's ideal normal groups, the results of all workers are affected in this way by the unsuspected inclusion of mildly anaemic infants and that such is the explanation of a fall in the mean haemoglobin level in some cases in the second half-year of life.

The difference between the actual haemoglobin value found by different authors in the second six months of life still requires an explanation. Williamson, Merritt and Davidson, and Faxen give values never less than 90% (Faxen's cases show an average of 95%) whereas all other authors show an average of approximately 85% over the same period. Mugrage and Andresen examined venous blood whereas all other authors examined capillary blood. As some of the earliest and latest work on the haemoglobin appears in each of these categories, any refinements in technique or stricter standards of normality used in later work will not account for such differences. In the present series of cases, though results in individual age-groups varied from 82% to 90%, the average for the second half-year was 85%, and in Mackay's cases the giving of iron did not raise the haemoglobin level above 86% in the second half-year of

life. Both these results were obtained in English children, the former in Birmingham and the latter in London. From this it appears that, anaemia excluded, the wide variation in haemoglobin values recorded by workers in different countries (in America by workers in different parts of the country) is probably due to differences in race.

Red Blood Corpuscles. Table 8 shows the mean values, with their standard errors, of the red cell count in breast-fed infants of the present series from birth to 13 months of age. These values are represented graphically in Fig. 6. In each age-group the number of

FIG. 6.—Changes in haemoglobin, red cell count, haematocrit, and colour index in breast-fed infants during the first year of life.

cases was the same as for the haemoglobin. It may be seen that the changes in the red cell count followed a course somewhat similar to that of the haemoglobin, that is, a high level at birth was followed by a steady fall to a minimum at about three months of age; thereafter there was a rise to a second but much lower maximum at about seven to eight months and this second level was maintained throughout the remainder of the year. At birth the mean red cell count was 6.54 millions per c.mm.; at 9 to 12 weeks it was 4.14 millions; at 25 to 28 weeks 5.14 millions and thereafter varied from 4.72 millions at 33 to 36 weeks to 5.41 millions at 53 to 56 weeks.

FIG. 7.—Red cell count in breast-fed and artificially-fed cases.

A statistical analysis of these figures establishes the reality of the fall in the red cell count from birth to approximately three months of age and also of the subsequent rise to a fairly stable level in the second half-year of life. That is to say, the changes shown in the present series

of cases are not due to a chance selection of unusual infants but truly represent the mean red cell count in this particular infant population from birth to 13 months of age.

In Table 8 also are set out the mean red cell counts with their standard errors of artificially fed infants and 'all cases' in the present series.

In Fig. 7 a comparison is made of the red cell counts in breast-fed and artificially fed infants and in Fig. 6 of breast-fed cases and 'all cases.' It may be seen that the curves are extremely close but the initial fall in the red cell count is greatest in the artificially fed, least in the breast-fed, and with the curve for 'all cases' lying between the other two. After the age of four months the positions are reversed, the highest curve being that of artificially fed cases, the lowest of breast-fed cases, with the curve of 'all cases' again lying between the other two. In spite of the parallelism of these curves

from the fourth month onwards statistical analysis does not distinguish any difference between the red cell counts of the three feeding groups.

FIG. 8.—Red cell count in breast-fed cases and all cases.

TABLE 9

ABSOLUTE VALUES OF RED CELL CHARACTERISTICS IN BREAST-FED INFANTS FROM BIRTH TO 13 MONTHS

Age	Haemoglobin		Red Blood cells (m. per c.mm.)	Haematocrit (%)	Mean Corpuscular Haemoglobin (γγ)	Mean Corpuscular Volume (c.μ.)	Mean Corpuscular Haemoglobin Concentration (%)	Colour Index
	(G. per 100 ml. blood)	(Percentage Haldane)						
0-48 hours	20.5	148.6	6.54	62.65	31.3	95.8	32.7	1.13
3-7 days	19.4	141.3	6.30	58.61	30.8	93.0	33.1	1.12
8-21 "	18.0	130.7	5.85	54.04	30.7	92.3	33.3	1.12
22-35 "	15.2	110.0	5.02	45.51	30.2	90.6	33.4	1.10
6-8 weeks	13.3	96.1	4.53	38.95	29.3	85.9	34.1	1.05
9-12 "	11.8	86.0	4.14	34.25	28.5	82.7	34.4	1.04
13-16 "	12.0	87.4	4.42	34.66	27.1	78.4	34.6	0.99
17-20 "	12.6	91.1	4.91	36.27	25.6	73.8	34.7	0.93
21-24 "	12.4	89.8	5.03	36.09	24.6	71.7	34.3	0.89
25-28 "	12.4	90.0	5.14	36.98	24.1	71.9	33.5	0.87
29-32 "	12.2	88.4	5.07	36.26	24.0	71.5	33.6	0.87
33-36 "	11.8	86.0	4.72	35.61	25.0	75.4	33.1	0.91
37-40 "	11.8	86.1	5.23	36.59	22.5	69.9	32.2	0.82
41-44 "	11.7	85.2	5.17	36.35	22.6	70.3	32.1	0.83
45-48 "	11.3	82.2	4.96	34.87	22.7	70.3	32.4	0.83
49-52 "	12.5	90.8	5.33	38.00	23.4	71.3	32.9	0.85
53-56 "	11.7	84.5	5.41	35.00	21.6	64.6	33.4	0.79

A graphical comparison of the red cell count with the haemoglobin is seen in Fig. 6. The curves of these two characteristics lie roughly parallel until about 10 weeks of age; the curve of the red cell count then rises rapidly until a second steady level is reached at about six months of age; at about 12 months of age the curve again rises slightly. The haemoglobin curve shows a slight rise at about the fifth month followed by a slight fall to a level maintained throughout the remainder of the year. This change in the relationship of the red cells and the haemoglobin is most clearly expressed by the colour index and the mean corpuscular haemoglobin which show a rapid fall from birth to about six months of age followed by a much slower decline (Table 9, Figs. 6 and 9). It is an indication of the change in the red cells

FIG. 9.—Mean corpuscular haemoglobin in breast-fed cases, all cases, and Mugrage and Andresen's cases.

from a hyperchromic state in the newly-born to a state of hypochromia in the year-old baby.

Table 2 shows the red cell counts recorded by various authors. Four workers have counted the red blood cells in infancy, few compared with the number who measured the haemoglobin, but, as with the haemoglobin, the same type of course is seen: an initial high level, a rapid fall to a low level, followed by a slow rise to a second steady maximum. The actual values recorded by the different authors vary considerably. Table 2 and Fig. 2, its graphical counterpart, make this clear. In Fig. 2, two types of curve are seen. One, in which the fall and rise are well defined, is seen in the work of Faxen and that of the present author and the other, in which the curve is much flatter, in that of Merritt and Davidson and Mugrage and Andresen. At birth Mugrage and Andresen's figure, like that for their haemoglobin, is low, 4.86 million cells per c.mm.; Merritt and Davidson's and Faxen's are much higher, 5.95 and 5.78 millions respectively, and the present author's is still higher, 6.54 million cells per c.mm. Except for Merritt and Davidson's value of 4.61 million cells at four to five

months, all authors show lowest values of approximately 4 million cells at two to three months of age. (Mugrage and Andresen's and Faxen's lowest counts were 3.9 million, the present author's 4.14 million). All four workers find that at about the fifth month a fairly stable value is reached, the highest value at this age, 5 million cells per c.mm., being recorded by the present author, the next, 4.7 million, by Merritt and Davidson, the third, 4.45 million, by Faxen, and the lowest value at this age, approximately 4.23 million cells per c.mm. by Mugrage and Andresen.

Examination of Fig. 2 shows that the curves of Merritt and Davidson's figures and those of Mugrage and Andresen, though roughly parallel, are widely separated. Their separation represents a difference of approximately 500,000 cells per c.mm., Merritt and Davidson's figures being the higher. American children were examined in both cases, but whereas Merritt and Davidson used capillary blood from children of mixed racial origin, Mugrage and Andresen used venous blood mostly from children of white parents. It is unlikely that the personal element could account for the difference of approximately half a million cells at each age-group and, except possibly at birth, it is also unlikely that such differences are due to the use of capillary blood on the one hand and venous blood on the other. One possible explanation is that early cases of anaemia have unwittingly been included in some of the groups. As an increase in the red cell count is the earliest expression of anaemia it is possible that the group with the highest red cell counts contains a disproportionate number of such cases. A second explanation is that such differences are racial, Mugrage and Andresen having examined children of white parents and Merritt and Davidson children of mixed race.

Fig. 2 shows that the curve of Faxen's cases lies parallel to that in the present series but at a much lower level, representing a difference of at least half a million cells per c.mm. from the fourth month onwards. Personal differences in technique could not account for such a great difference in the red cell counts in these two series. It is possible that in the present series, where the minimum birth weight was 9 oz. less than Faxen's minimum, the higher red cell count was due to the inclusion of a disproportionate number of unsuspected early cases of anaemia. Racial differences may also have been a contributing cause.

No satisfactory explanation can be advanced for the differences in the two types of curve, flat after the initial fall in the case of Merritt and Davidson and Mugrage and Andresen, and with a greater fall and rise in the case of Faxen and the present author.

After the age of four months the highest red cell counts were found in the present series of English infants, the second highest in Merritt and Davidson's series of American children of white parentage, the next in Faxen's series of Swedish children, and the lowest in Mugrage and Andresen's series of American children of mixed race.

Haematocrit. Table 10 shows the mean values, with their standard errors, of the packed cell volume in the present series of breast-fed infants at ages ranging from birth to 13 months. For the first three weeks the number

of cases in each age-group was at least 70; from three weeks onward the number was less than 20, and from five months onwards less than 10. In the statistical

TABLE 10
HAEMATOCRIT VALUES IN BREAST-FED INFANTS

Age	Number of Cases	Haematocrit	
		Mean (%)	Standard Error
0-48 hours	70	62.65	0.57
3-7 days	79	58.61	0.53
8-21 "	72	54.04	0.54
22-35 "	16	45.51	0.93
6-8 weeks	11	38.95	1.02
9-12 "	15	34.25	0.94
13-16 "	14	34.66	1.08
17-20 "	11	36.27	1.42
21-24 "	8	36.09	1.77
25-28 "	9	36.98	1.60
29-32 "	10	36.26	1.60
33-36 "	8	35.61	1.77
37-40 "	9	36.59	1.77
41-44 "	5	36.35	2.17
45-48 "	7	34.87	2.01
49-52 "	5	38.00	2.38
53-56 "	4	35.00	2.66

analysis of these results corrections were made for the use of such small numbers. The results are expressed as a percentage and the findings follow approximately the same course as the haemoglobin and the red cell count, that is to say, an initial high value is followed by a fall and this fall is followed by a slight rise to a level that remains practically unaltered for the rest of the year. At birth the packed cell volume was 62.65%, at

two to three months 34.25% and thereafter rose slightly and remained at an average of 36% for the rest of the year. Analysis showed that there was a statistical difference between the results in succeeding age groups from birth to 9 to 12 weeks of age whereas from that time onwards any differences were too slight to be significant.

In Table 11 are set out the mean haematocrit values, with their standard errors, of breast-fed infants, artificially fed infants, and 'all cases' in the present series from birth to 13 months. The number of cases in the artificially fed group was less than 10 in the first three months, between 20 and 26 from three to ten months, and thereafter was approximately 11. The numbers were much greater in the group of 'all cases' averaging 100 in the first three weeks, never falling below 40 from the third to the tenth month and thereafter ranging from 19 to 26 in each age-group. Fig. 10, showing the haemato-

FIG. 10.—Haematocrit percentage in breast-fed and artificially-fed cases.

crit values in breast-fed and artificially fed infants, is a graphical representation of Table 11 with the curve for

TABLE 11
HAEMATOCRIT VALUES IN INFANCY (VOLUME OF PACKED RED CELLS PER CENT.)

Age	Breast-Fed Infants			Artificially Fed Infants			All Cases		
	No. of Cases	Mean (%)	Standard Error	No. of Cases	Mean (%)	Standard Error	No. of Cases	Mean (%)	Standard Error
0-48 hours	70	62.65	0.57	7	63.71	1.77	98	63.25	0.47
3-7 days	79	58.61	0.53	6	61.03	1.88	103	59.76	0.45
8-21 "	72	54.04	0.54	8	55.56	1.68	100	54.51	0.46
22-35 "	16	45.51	0.93	3	47.83	2.66	30	44.26	0.71
6-8 weeks	11	38.95	1.02	2	33.75	2.38	22	36.95	0.74
9-12 "	15	34.25	0.94	3	31.43	2.17	39	33.90	0.63
13-16 "	14	34.66	1.08	21	34.91	0.94	40	35.04	0.66
17-20 "	11	36.27	1.42	22	35.56	0.94	43	36.00	0.70
21-24 "	8	36.09	1.77	26	36.87	0.99	48	36.79	0.73
25-28 "	9	36.98	1.60	22	35.64	1.00	41	36.51	0.76
29-32 "	10	36.26	1.60	26	36.02	1.00	58	36.32	0.70
33-36 "	8	35.61	1.77	23	36.41	1.08	43	36.35	0.78
37-40 "	9	36.59	1.77	20	36.77	1.19	41	36.72	0.84
41-44 "	5	36.35	2.17	13	36.12	1.42	26	36.43	1.00
45-48 "	7	34.87	2.01	13	35.79	1.47	27	35.48	1.02
49-52 "	5	38.00	2.38	9	36.62	1.77	19	36.83	1.19
53-56 "	4	35.00	2.66	11	36.06	1.60	19	35.58	1.22

'all infants' omitted for the sake of clarity. From approximately three weeks to four months there is a slight divergence of the curves but thereafter they are indistinguishable. The curve for 'all infants' lies between the artificially fed and breast-fed curves until the curves merge at about the fourth month. An examination of the table shows that in each group the results are extremely close. By statistical analysis it was found that in the present series of cases the three types of feeding did not differ in their effects on the packed cell volume in the first 13 months of life.

Two sets of figures for packed cell volume, those of Drucker and those of Mugrage and Andresen, are available for comparison with the present series. In Table 3 and Fig. 3 are set out the mean values in the breast-fed group of infants and the values in Drucker's and Mugrage and Andresen's cases. As with the haemoglobin and red cell count there is a wide difference between the haematocrit values at birth as recorded by

Mugrage and Andresen and the author. Mugrage and Andresen's figure, estimated on blood from the umbilical cord, was 53.18% compared with the present author's 62.65%, obtained on blood from the peripheral circulation. (Drucker did not examine any infants under three weeks of age.) At two to three months of age Drucker's value was 35.7% while Mugrage and Andresen's and the author's values were a little lower and almost identical, being 34.18% and 34.25% respectively. In Mugrage and Andresen's cases a slight rise to 37.4% at four to seven months of age was followed by a slight fall to 36.8% at 9 to 12 months. The value in Drucker's cases rose slightly after the third month to an average of 38.2% from the seventh to the twelfth month. In the present work an average of 36% remained practically constant from the fourth month onwards (Table 3 and Fig. 6). Mugrage and Andresen's haematocrit readings and those of the present series are extremely close except for the values at birth, and the great difference at this

TABLE 12
ABSOLUTE VALUES OF RED CELL CHARACTERISTICS IN ALL CASES FROM BIRTH TO 13 MONTHS

Age	Haemoglobin		Red Blood cells (m.per c.mm.)	Haematocrit (%)	Mean Corpuscular Haemoglobin (γγ.)	Mean Corpuscular Volume (Cμ.)	Mean Corpuscular Haemoglobin Concentration (%)	Colour Index
	(G. per 100 ml. blood)	(Percentage Haldane)						
0-48 hours	20.7	149.6	6.60	63.25	31.4	95.8	32.7	1.13
3-7 days	19.8	143.8	6.39	59.76	31.0	93.5	33.1	1.12
8-21 "	18.2	131.7	5.85	54.51	31.1	93.2	33.4	1.13
22-35 "	15.2	110.5	5.02	44.26	30.3	88.2	34.3	1.10
6-8 weeks	13.1	95.2	4.47	36.95	29.3	82.6	35.4	1.06
9-12 "	11.7	85.5	4.14	33.90	28.3	81.9	34.5	1.03
13-16 "	12.0	87.4	4.56	35.04	26.3	76.8	34.2	0.96
17-20 "	12.3	89.2	4.93	36.00	24.9	73.0	34.1	0.90
21-24 "	12.4	89.7	5.12	36.79	24.2	71.8	33.7	0.87
25-28 "	12.2	88.7	5.19	36.51	23.5	70.3	33.4	0.85
29-32 "	11.9	86.4	5.11	36.32	23.3	71.1	32.8	0.84
33-36 "	11.8	85.6	5.12	36.35	23.0	70.9	32.5	0.83
37-40 "	11.9	86.5	5.29	36.72	22.5	69.4	32.4	0.82
41-44 "	11.7	85.0	5.20	36.43	22.5	70.0	32.1	0.82
45-48 "	11.5	83.4	5.14	35.48	22.4	69.0	32.4	0.81
49-52 "	12.0	86.9	5.33	36.83	22.5	69.1	32.6	0.82
53-56 "	11.4	82.3	5.30	35.58	21.5	67.1	32.0	0.78

age may be due to the fact that blood from the umbilical cord was examined by Mugrage and Andresen whereas capillary blood was examined by the present author. Stasis of blood in the capillaries in the newborn is of common occurrence and may have contributed to the higher findings in the present series.

Mean Corpuscular Haemoglobin, Mean Corpuscular Volume, Haemoglobin Concentration, and Colour Index. Table 9 shows the absolute values and their derivatives of the red cell characteristics in breast-fed infants from birth to 13 months of age. Similarly, Table 12 shows the values in 'all cases.' Figs. 11, 9, and 12 are graphs of the

shows a steady fall from 31.3 $\gamma\gamma$ (colour index 1.13) at birth to 25.6 $\gamma\gamma$ (colour index 0.93) at 17 to 20 weeks followed by a much slower fall to 21.6 $\gamma\gamma$ (colour index 0.79) at 53 to 56 weeks. This fall coincides with the change from the hyperchromia seen at birth to the relative hypochromia of the year-old infant (Guest and Brown, 1936; Faxen, 1937).

The figures for the mean corpuscular haemoglobin concentration varied very little during the first year. They were 32.7% at birth, rose a little to 34.7% at 17 to 20 weeks, fell slightly to 32.1% at 41 to 44 weeks, and rose again to 33.4% at 53 to 56 weeks. Except for

FIG. 11.—Mean corpuscular volume of breast-fed cases, all cases, and Mugrage and Andresen's cases.

FIG. 12.—Mean corpuscular haemoglobin concentration in breast-fed cases and all cases.

changes in these derivatives in breast-fed cases and in 'all cases,' that is, in the mean corpuscular volume (Fig. 11), the mean corpuscular haemoglobin (Fig. 9), and the mean corpuscular haemoglobin concentration (Fig. 12).

In the breast-fed group the mean corpuscular volume is high, 95.8 c. μ ., at birth, falls rapidly to about 73.8 c. μ . at 17 to 20 weeks, and then falls more slowly to 64.6 c. μ . at 53 to 56 weeks. The figures for 'all cases' are slightly but consistently lower over the same period. The steep fall from birth to five months coincides with the change from the macrocytosis seen at birth to normocytosis. The continued fall after the fifth month runs parallel with the tendency to microcytosis seen towards the end of the first year (Guest and Brown, 1936; Faxen, 1937). The figures for the mean corpuscular haemoglobin of breast-fed cases and of 'all cases' are a great deal lower than those recorded by Mugrage and Andresen, that is, 108.9 c. μ . in cord blood and 85.3 c. μ . from 12 to 18 months.

The values for the mean corpuscular haemoglobin of breast-fed cases and of 'all cases' show a similar but less abrupt fall to the mean corpuscular volume. The graph of the mean corpuscular haemoglobin of breast-fed cases is the same as that of the colour index (Fig. 6) and

the value of 34.7% at 17 to 20 weeks these figures lie within Mugrage and Andresen's range of 32 to 33.8% and are all within the normal limits for adults. The mean corpuscular haemoglobin concentration in 'all cases' did not show as great a variation as in breast-fed cases. It reached its maximum at about eight weeks, started to decline sooner and thereafter remained at a slightly lower level.

Summary

An investigation is described which attempted to establish normal values in the blood picture for infants, to account for the disparity between the findings of different workers, and to determine whether all infants should receive prophylactic doses of iron in their first year of life.

The sample consisted of 249 infants drawn from Birmingham and its suburbs. The sample racially was as purely English as could be obtained. Twins and infants weighing less than 6 lb. at birth were excluded, as also were those who had suffered any serious illness and those failing to make the expected weight gain. No infant was included whose mother had proved to be anaemic during pregnancy.

The technique used is described, and the results of approximately 1,200 blood counts analysed.

It was found that the haemoglobin curve of breast-fed infants ran parallel and close to that of other workers, and after the age of six months was practically identical with Mackay's, also working with English material. In no one age-group, however, was there any statistical difference between the haemoglobin values in breast-fed infants, artificially fed infants, or infants fed on a mixture of breast and cow's milk, but on averaging the results of all age groups it was found that the means of three methods of feeding were significantly different, the highest in breast-fed, and intermediate in cases only partly breast-fed. At 12 months of age the difference between the haemoglobin levels of artificially fed infants and those receiving iron were statistically significant, the iron-fed group having the higher figure. The differences in haemoglobin values recorded by various workers appear to be fundamentally racial.

The red cell values in the first year of life of breast-fed infants lay roughly parallel to those of Faxen, although the actual values were much higher, as also they were after the age of four months compared with those of the other workers cited. There was no statistical difference between the red cell counts in breast-fed infants, artificially fed infants, or infants fed on a mixture of breast and cow's milk.

The curve of the haematocrit values of breast-fed infants ran roughly parallel to those of the haemoglobin and red cell count.

Mean values for the haemoglobin, red cell count,

and haematocrit were established at ages ranging from birth to 13 months.

Thanks are due to the medical officers of the Maternity and Child Welfare Service of the City of Birmingham Health Service for their co-operation, as, without access to children under their care at the maternity homes and child welfare clinics, this work could not have been undertaken. Thanks are also due to the Medical Research Council for defraying the expenses of this investigation; to Mr. E. A. Cornish of the Australian Council for Scientific and Industrial Research, who made a statistical analysis of the results, and to Miss N. R. McArthur, of the Walter and Eliza Hall Institute, Melbourne, for her help and advice in preparing the tables and graphs.

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