BLOOD FORMATION IN INFANCY

PART II. NORMAL ERYTHROPOIESIS*

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There is general agreement that the fall in haemoglobin after birth is an expression of the increased oxygen saturation of the blood when lung replaces placenta as a source of oxygen. We have sought to express this idea concretely, to show that the changes which occur in the form and number of red cells after birth are due to variations in the erythropoietic activity of the marrow, and finally to infer that this activity is itself governed by the need to maintain the oxygen content of the blood at a constant level.

Material and Methods

The material was the same as has been described in Part I, consisting of 105 samples of venous blood together with 102 bone marrow samples, taken from 25 infants from birth to 3 months.

Our methods have been described in Part I. They were chosen after considering the following probable causes of the divergent results of previous authors in this field. Differences in haemoglobinometry may cause discrepancies, as may differences in methods of sampling. Skin prick samples of blood are apt to give variable results according to the site and depth of puncture, and tend to give higher values than venous samples, this effect being large in the first week of life (Vahlquist, 1941; DeMarsh, Alt and Windle, 1948; Oettinger and Mills, 1949). Consistent and reproducible results are most surely obtained by venous sampling, which was used exclusively in the present study. Differences in delay before clamping the cord may also affect results. Although DeMarsh, Alt and Windle (1941) list authors as far back as 1877 who have investigated the influence of this factor upon the post-natal blood picture, many subsequent studies have ignored it. Early clamping of the cord was the rule in this series. Differences in infants' growth rates, as Washburn (1941) has clearly shown, are the main factor influencing the rate of decrease in red cell level during the first two months of life. In this context it will often be convenient to consider the total mass of circulating haemoglobin or total red cells as well as their concentrations; the method for calculating these

has been described in Part I. Reticulocyte levels have been commonly used as a measure of erythropoiesis in infants, although it is well known that during a period of sustained red cell production it is only initially that the reticulocytes are numerous. We have measured erythropoiesis by enumerating the erythroid cells in the bone marrow (see Part I).

Results

Fig. 1 shows the changes in the red cell picture from birth to 3 months. The main trends follow those established by others: after birth the haemoglobin level rises abruptly and then falls until the eighth week, thereafter remaining at a level of 11 to 12 g. The red cell level falls proportionately less steeply, due to the coincident decrease in cell size as measured by the mean cell volume (M.C.V.).
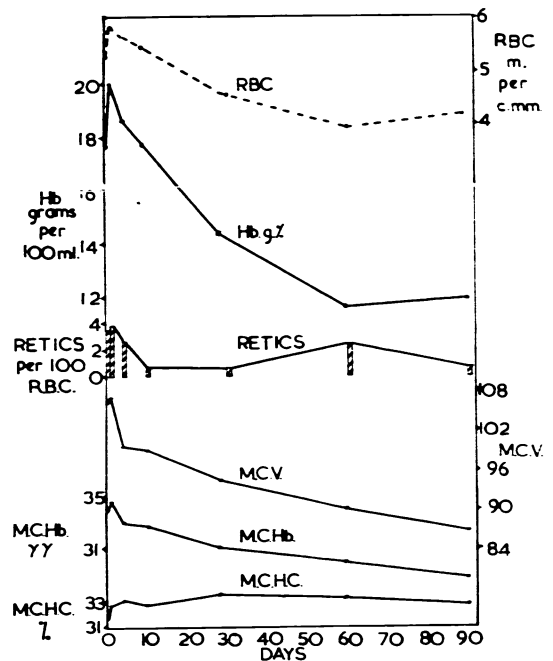

FIG. 1.—Changes in the red blood cells from birth to 3 months.

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The mean corpuscular haemoglobin concentration (M.C.H.C.) remains practically constant throughout. In describing these changes in detail it will be convenient to mention at this stage one conclusion to which the results point—that the erythropoietic system of the infant is ' set ' to maintain a constant oxygen content in arterial blood, equivalent, under normal conditions of blood oxygenation, to a haemoglobin concentration of 11 to 12 g. per 100 ml. With this principle in mind the first three months of life fall into three phases: (1) the first week of life, when the haemoglobin level remains above the level at birth; (2) from the second to about the eighth week, when the haemoglobin level steadily falls to the level of 11 to 12 g.; (3) from the eighth week onwards, when the haemoglobin level is maintained at 11 to 12 g.

(1) From Birth to 9 Days. Fig. 2 shows the essential facts covering this period. The haemoglobin level rises abruptly after birth, so that on Day 1 (2-24 hours) it is 12% above the cord blood level; thereafter it declines, returning to the level in cord blood by Day 9. The calculated value for the total haemoglobin also appears much higher on Day 1 than at birth, but by Day 4 has already returned to the value at birth, and remains at the same value on Day 9. The red cell count (Fig. 1) shows similar changes. Erythropoiesis diminishes

rapidly after birth; at birth the marrow erythroid count (see Part I) is high, 41,000 per c.mm., but by Day 4 this figure has fallen to 7,000, and by
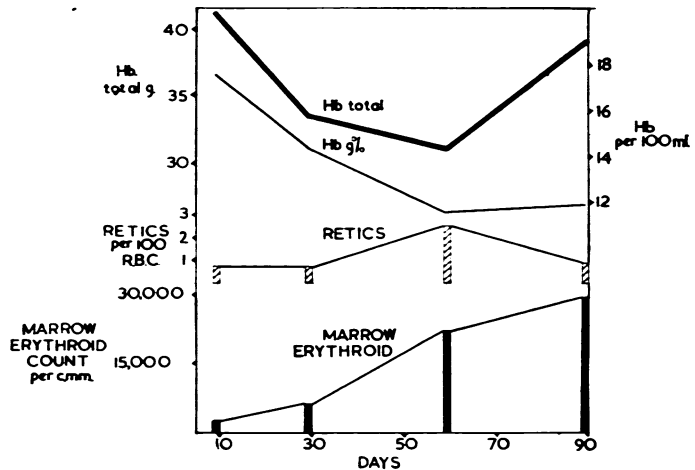
FIG. 3.—Changes in haemoglobin concentration, total haemoglobin, reticulocytes and marrow erythroid count from nine to 89 days.

Day 9 to 2,800. Reticulocytes, from high levels at 3·5% at birth and 3·9% on Day 1, likewise fall steadily.

(2) Days 9 to 59. During this period the haemoglobin level falls (Fig. 3) until by the end of the second month it has reached a level of 11 to 12 g. per 100 ml. The total haemoglobin falls also at first rapidly (Days 9 to 29), then more slowly (Days 29 to 59). Fig. 4 shows the rate of disappearance of total haemoglobin in 14 individual subjects in the phase of rapid fall; the fact that the majority of the lines show much the same slope points to the existence of some single factor which controls the rate of disappearance of haemoglobin. The average rate of disappearance of haemoglobin from Days 9 to 29 is 0·90% per day. The corresponding figure for total red cells is calculated as 0·70% per day. The significance of these figures will be discussed presently. Erythropoiesis is at a low level at the beginning of this period, the marrow erythroid count being 2,800 per c.mm. on Day 9. As the haemoglobin level falls the marrow erythroid count tends to rise, so that by Day 29 when the haemoglobin level has fallen to 14·4 g. the marrow erythroid count has risen to 6,300 per c.mm. As the haemoglobin approaches the level of 11 to 12 g. erythropoiesis rises sharply, so that by Day 59 when the haemoglobin has fallen to 11·4 g. the marrow erythroid count has risen to 22,000, and the reticulocytes to 2·5% from previous values during this period of under 1%.
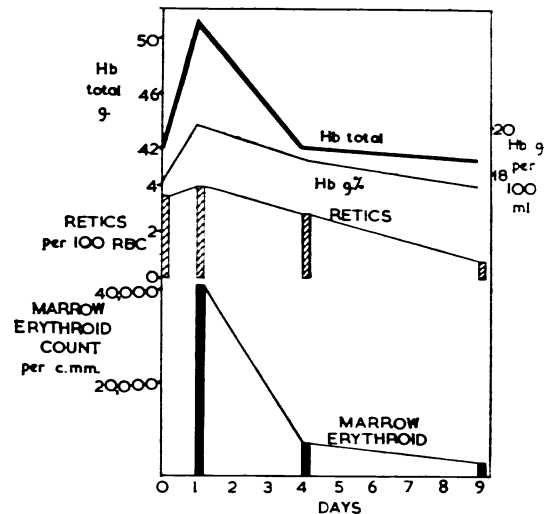
FIG. 2.—Changes in haemoglobin concentration, total haemoglobin, reticulocytes and marrow erythroid count, from birth to 3 months.

(3) Days 59 to 89. Throughout this period the high level of erythropoiesis (Fig. 3), as measured by the marrow erythroid count, is sustained
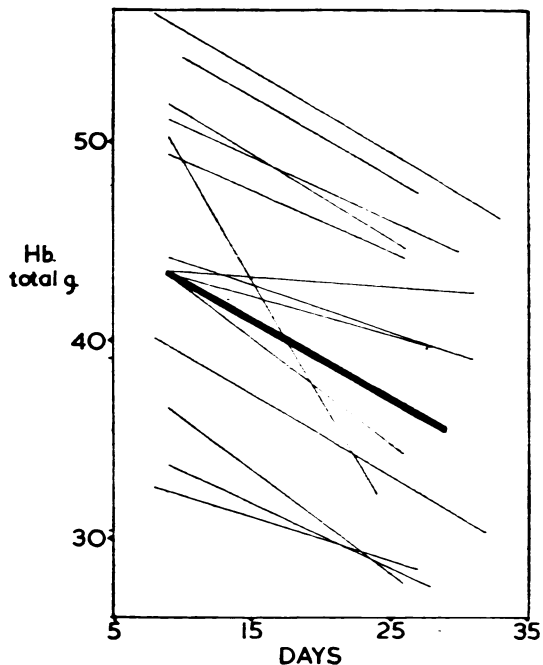

FIG. 4.—Rate of decline of total haemoglobin between Days 8 and 32 in 14 infants. The slope of the majority lies near the mean, shown by the thick line. (The graph with the exceptionally large slope almost certainly resulted from an experimental error.)

(22,000 per c.mm. on Day 59, 30,000 on Day 89). Consequently the total haemoglobin now rises steeply with a gain of 10 g. in 30 days. Nevertheless, as this rate of gain is matched by the rate of body growth, the haemoglobin concentration changes only insignificantly from 11·6 to 11·9 g. %.

Discussion

The facts so far elicited fall into place if we suppose that the erythropoietic tissue is sensitive to variations in the oxygen content of arterial blood, and that it is 'set' to maintain the oxygen content at a level which is constant for a given age. It will be shown that throughout the first 18 months this level corresponds to a concentration of oxy-haemoglobin of about 11 g. per 100 ml., and that a similar level obtains in late foetal life.

Changes in Haemoglobin Level Immediately after Birth. In the foregoing section the general shape of the haemoglobin curve over the first three months has been explained on the assumption that the level of erythropoiesis is determined by the

divergence of the haemoglobin from the level of 11 to 12 g. At birth the haemoglobin lies far above this level, hence erythropoiesis soon falls to a very low level and the haemoglobin consequently declines. As the haemoglobin approaches a level of 11 and 12 g. erythropoiesis increases so that the decline in haemoglobin is first slowed and then arrested, erythropoiesis being finally adjusted to maintain the haemoglobin level constant at 11 to 12 g.

Additional factors are responsible for the changes in the red cell picture immediately after birth. Our results (Fig. 2) show that whereas the haemoglobin in cord blood averaged 17·6 g., the haemoglobin at two to 24 hours averaged 20·0 g., that is 12% higher. A difference of the same order was noted in each of three individual subjects where blood samples taken two and a half, three and seven hours after birth could be compared with cord blood. The fact that within a few hours of birth the concentration of haemoglobin is considerably higher than in cord blood is apparent also in the figures given by Vahlquist (1941) and Mollison and Cutbush (1949), although no such difference was found by Waugh, Merchant and Maughan (1940). (In considering the effect it is
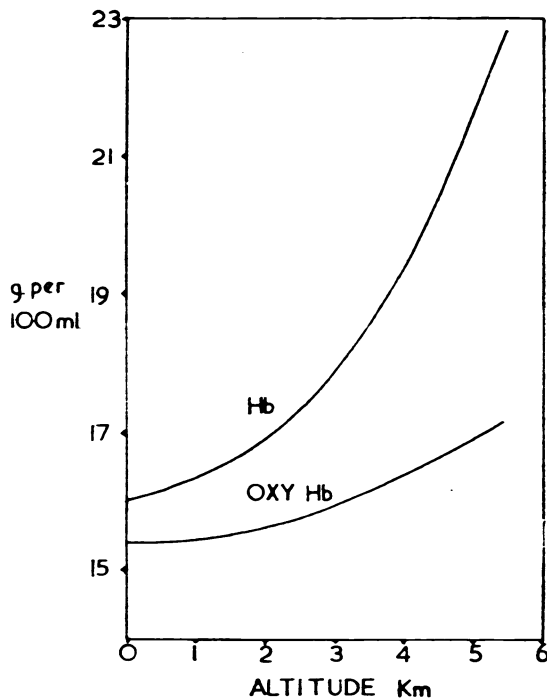

FIG. 5.—Effect of altitude upon haemoglobin and (arterial) oxy-haemoglobin levels, from data collected by Hurtado *et al.* (1945). Note relative constancy of oxyhaemoglobin.

important to confine attention to data relating to venous samples.) None of these authors made any special attempt to clamp the cord early. DeMarsh, Windle and Alt (1942) compared the haematocrit of cord blood with that of venous blood taken one quarter to three hours after birth and found that a rise in haematocrit occurred only when the cord was clamped late. When it was clamped early there was no such rise.

If a transfer of placental blood is the cause of the immediate post-natal rise in haemoglobin, a gain by the infant of at least 40 ml. of placental blood would be necessary to account for the rise observed in our series. Although the cord was clamped as early as conveniently possible, 10-15 seconds usually elapsed after the birth of the infant, and it is conceivable that a transfer of as much as 40 ml. of blood could take place in this period, since Haselhorst and Allmeling (1930) showed that the average amount of blood in the placental circuit was 104 ml. and that 51% of this was transferred to the infant in the first minute after birth. Possibly also some placental blood transfer may take place in the terminal phases of delivery.

However, we do not regard it as yet settled that placental blood transfer is the sole factor causing the post-natal rise in haemoglobin. It seems not impossible that other factors may play some part, such as, for instance, a temporary redistribution of body fluids causing haemoconcentration. We are making a closer study of the changes in the blood picture immediately after birth, which will be the subject of a further communication. Meanwhile we regard with reserve the values we have calculated for total haemoglobin and red cells at birth and on Day 1.

From Day 4 to Day 9 the picture is clearer. Fig. 2 shows that the total haemoglobin remains unchanged over this period, so that red cell destruction is now balanced by formation. Although the erythroid cells in the marrow fall to a low level during the first nine days after birth, those cells present in the marrow at birth must continue to mature, so that it is only when the momentum of foetal erythropoiesis has spent itself, some time during the second week, that the total haemoglobin begins to fall.

Constancy of Oxyhaemoglobin Level in Foetus and Infant. Although it is generally accepted that the decline in haemoglobin level after birth is related to the different degree of oxygen saturation of blood in intra-uterine and extra-uterine life, it is useful to put this idea into concrete terms. We have shown that once the haemoglobin concentration has fallen to 11 to 12 g. erythropoiesis is adjusted to maintain this level. Our own studies

have followed this process only as far as the third month, but there is general agreement from the work of others that from the third month to 18 months the haemoglobin remains substantially unchanged at about 11 to 12 g. per 100 ml. (Mackay, 1933; Josephs, 1936; Magnusson, 1935; Mugrage and Andresen, 1936; Guest, Brown and Wing, 1938; Vahlquist, 1941; Selander, 1944; Findlay, 1946; Horan, 1950). Only Merritt and Davidson (1934) and Faxen (1937) give a rather higher figure of 12 to 13 g. Since arterial blood is 95% saturated with oxygen we can conclude that the oxyhaemoglobin level from the third month to 18 months is maintained at about 11 g. per 100 ml.

In comparing this with the level in intra-uterine life one finds that the few available measurements of the oxygen saturation of foetal umbilical vein blood vary widely, but the majority lie between 45% and 80%, with an average of about 65% saturation. (The matter is reviewed by Barcroft (1946) and by Smith (1945): the former also found that in the sheep foetus at term the oxygen saturation of umbilical vein blood is 65%.) If we take the figure of 65% saturation and apply it to the average cord blood haemoglobin in our series, 17·6 g. per 100 ml., we arrive at a value of 11·4 g. per 100 ml. for the concentration of oxyhaemoglobin in the arterial blood of the foetus at the end of gestation. In view of the doubt as to the data from which this figure is derived, it is not of great significance that the calculated oxyhaemoglobin level in the arterial blood of the foetus corresponds so closely to that found in the infant after post-natal adjustment of the haemoglobin level has had time to take place. Nor have we taken into account the fact that in the foetus arterial blood is partly mixed with venous blood and so is less oxygenated than umbilical vein blood. The figures nevertheless illustrate the general principle that under widely different conditions of oxygenation the haemoglobin level is adjusted to give an oxyhaemoglobin level which changes relatively little.

That this principle is of wide application can be illustrated from two further sources. Barcroft (1946), working with the sheep foetus, has shown that owing to differences in the rates of growth of placenta and foetus, the oxygen saturation of umbilical vein blood fluctuates throughout gestation: nevertheless the oxygen content of umbilical vein blood is maintained at a roughly constant level, since when its oxygen saturation is low, this is balanced by an increased oxygen capacity. This is equivalent to saying that the haemoglobin level varies in such a way that the oxyhaemoglobin level is maintained constant.

Fig. 5 is based on figures collected by Hurtado,

Merino and Delgado (1945) for the haemoglobin level and oxygen saturation of dwellers at high altitude. It shows that as altitude and the resulting anoxia increase, so the haemoglobin level rises steeply, while the oxyhaemoglobin is maintained at a level differing only slightly from that obtaining at sea level.

Erythropoietic Response to Variations in Oxyhaemoglobin Level. Within three hours of birth the infant achieves an adult level of 95% arterial oxygen saturation (Smith, 1946), so that, assuming that erythropoiesis is dependent upon the level of oxyhaemoglobin, when dealing with normal subjects we can conveniently use the haemoglobin level as a measure of the stimulus to erythropoiesis. The changes shown by the marrow erythroid count—its rapid fall after birth, its persistence at a low level until the haemoglobin begins to approach 11 to 12 g. per 100 ml., and its gradual rise at this stage—have already been shown to accord with the simple principle that erythropoiesis depends upon the stimulus of a haemoglobin level lying near to, or below, the optimal level. Fig. 6 shows that erythropoiesis is in general active only when the

haemoglobin level falls below 15 g., and that there is then a fairly close correlation between the amount of erythropoietic activity, as measured by the marrow erythroid count and the haemoglobin level.

Fig. 7.—Course of erythropoiesis in an infant with rapid growth. Compare with average infant in Fig. 3.

The principle that erythropoiesis depends upon the stimulus of an optimal or sub-optimal level of oxyhaemoglobin is further illustrated by two individual subjects. The first (Fig. 7) shows the blood and marrow changes in an infant with a rapid weight gain, the low birth weight (5¼ lb.) being doubled in 12 weeks. Although the rate of decline of the total haemoglobin is normal, 0·90% per day, the rapid weight gain brings about an abnormally rapid decline in haemoglobin concentration, so that at Day 29 this has already fallen to 10·5 g. per 100 ml. At this stage erythropoietic activity increases, as shown by the rise in marrow erythroid count, the total haemoglobin starts to rise, while the haemoglobin concentration remains at 11 to 12 g. These are the changes seen normally, except that in this case they occur a month earlier than usual on account of the earlier decline of haemoglobin to the critical level of 11 g. per 100 ml.

By contrast Fig. 8 shows the blood and marrow changes in an infant with congenital heart disease causing severe cyanosis, that is, a low oxygen saturation. There is an absence of the fall in erythropoiesis normally seen after birth, the marrow erythroid count remaining constantly at 8,000
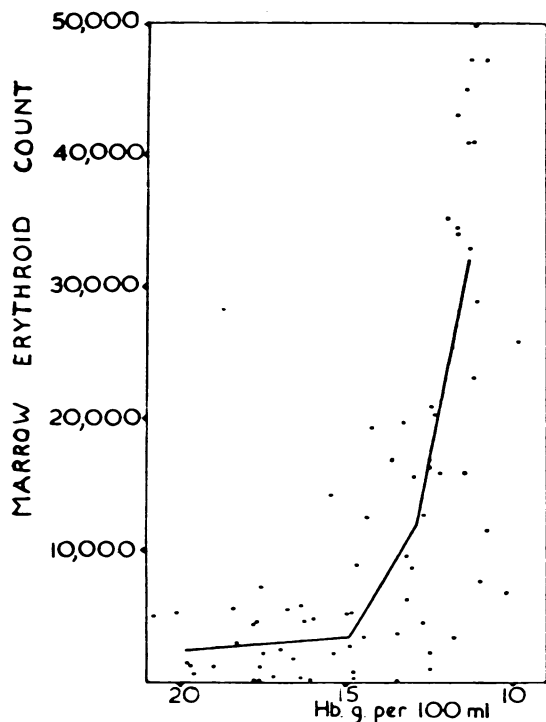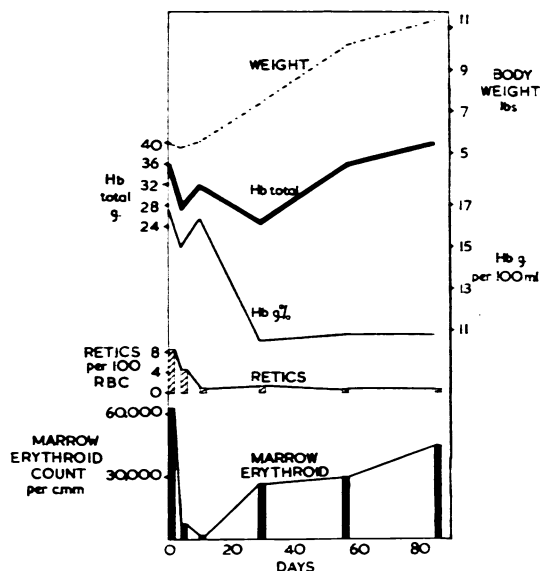

Fig. 6.—Relationship between erythropoietic activity of marrow and haemoglobin level of blood in normal infants aged from 8 to 84 days. The line roughly indicates the trend, which shows that erythropoiesis is at a low level when the haemoglobin lies above 15 g.%, and rises steeply as the haemoglobin falls below this level.

to 10,000 per c.mm., and the reticulocytes tending to remain above 2%. In this case instead of the haemoglobin showing the usual fall over the first two months, it rises to a level of 15·6 g. per 100 ml.
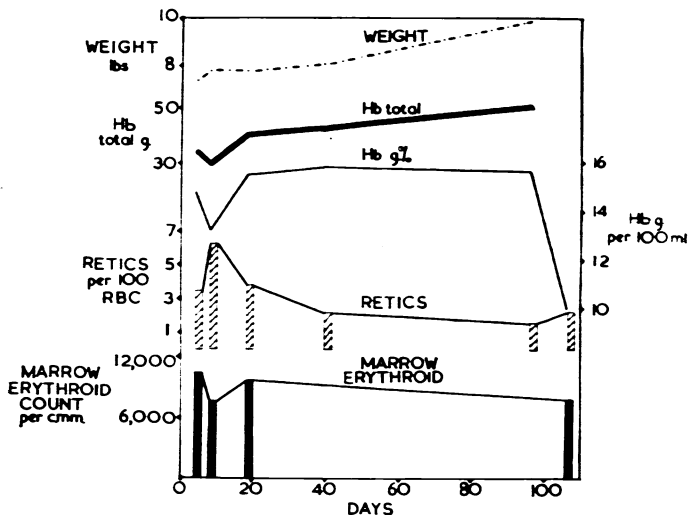

FIG. 8.—Course of erythropoiesis in an infant with cyanotic heart disease. The reticulocyte and marrow erythroid counts show no post-natal fall, and the haemoglobin level is maintained at about 16 g.% until terminal circulatory failure at 106th day.

at 19 days and remains about this level until death from heart failure at 15 weeks.

The Size of the Red Cell. Our figures (Fig. 1), in common with those of others, show that at birth the mean cell volume is high (M.C.V.=107 c.μ), thereafter decreasing until at three months it has reached adult values (87 c.μ). It is known (Wintrobe, 1946) that there is a progressive decrease in red cell size throughout foetal life, whence it follows that the high M.C.V. present at birth is due to a proportion of the red cell population being made up of large cells laid down some time before the end of gestation. Thus if we suppose that the average life of the red cell in the foetus is 120 days as in the adult, some of the red cells at birth will have been laid down at a foetal age of 160 days when, according to Wintrobe, the M.C.V. is 130 c.μ. Those red cells coming to the end of their span would thus have a larger size than the average, and in this way a progressive decrease in M.C.V. would occur, as has been suggested by Mollison (1948).

It is interesting to note that anoxaemia is capable of partially reversing the normal disappearance of the macrocytosis of foetal life, for the red cells both of dwellers at high altitudes and of children with cyanotic heart disease show an increased

M.C.V. (Hurtado *et al.*, 1945; Prader, Rossi and Holländer, 1950).

The Rate of Red Cell Destruction. In the older literature it was taken for granted that the post-natal fall in haemoglobin and red cells was due to rapid haemolysis: for instance, Josephs, reviewing the subject in 1936, concluded that this factor was of comparable importance to the reduced level of erythropoiesis. Although we have made no direct measurements of the rate of red cell destruction, it is possible from our data to show that variations in erythropoiesis alone are adequate to account for changes in haemoglobin and red cell levels, assuming that in infants the life span of a red cell is about the same as that accepted for adults, evidence for which will be discussed.

Over the first nine days of life we have shown (Fig. 2) that there is no fall in total haemoglobin. Other studies which have employed venous samples have also shown that compared with cord blood, the haemoglobin concentration at the tenth to the fourteenth day is either rather higher (Guest *et al.*, 1938; Vahlquist, 1941) or only slightly lower (Waugh, Merchant and Maughan, 1940). This significant fact has been obscured when capillary samples have been used, since the haemoglobin value of capillary blood, which at birth is markedly higher than that of venous blood, progressively approaches the latter during the first one or two weeks (Vahlquist, 1941; Oettinger and Mills, 1949). We conclude that there is nothing pointing to unusually rapid blood destruction during the first nine days after birth.

The succeeding period from nine to 29 days corresponds to the period of maximum rate of fall in haemoglobin (Figs. 3 and 4). During this period the rate of disappearance of total haemoglobin is 0·90% per day, and of the total red cells 0·70% per day. (The difference between the two is due to the fact that the red cells which disappear are larger than normal and have a higher haemoglobin content.) The figure for the decline of red cells differs by only 16% from the rate of 0·83% per day which would be anticipated if no new red cells were being added, and the existing red cells had a span of 120 days. This difference would be accounted for if red cells were being formed at the rate of one to every six cells destroyed. Such a low rate of erythropoiesis is in keeping with the low marrow erythroid count obtaining throughout

this period (Fig. 3). Thus during the first four weeks of life the changes in red cells and haemoglobin can be simply accounted for on the basis of a normal rate of red cell breakdown.

We must now consider other evidence bearing on this conclusion. The rate of disappearance of distinguishable cells is the most direct method of investigating the matter, and easily shows up the fate of different types of red cells in infants with haemolytic disease, Rh-positive cells disappearing usually within 10 days, Rh-negative cells surviving about 90 days (Mollison, 1943); the latter figure agrees well with the survival of red cells transfused into adults (Wintrobe, 1946). Hedenstedt and Vahlquist (1948) have measured the survival of elliptocytes transfused into newborn infants and find this to be the same as in older children. Such experiments indicate that transfused adult red cells are destroyed by young infants at the normal rate. The question remains whether the newborn infant's own red cells are destroyed more rapidly. Mollison (1951) compared the survival of placental and adult blood transfused simultaneously into anaemic infants and concluded that the mean cell life of the ' placental ' red cells was a little shorter than that of the ' adult ' red cells. However, the difference was small and, without the observations on the control population of adult red cells, would have been difficult to demonstrate. (Earlier, the same author had reported a distinctly greater rate of fall in the concentration of placental red cells during the first 10 days after transfusion (Mollison, 1948); however this was probably due to the initial values having been falsely high as a result of using skin-prick samples (Mollison, 1951). An explanation of this effect would probably be forthcoming if we knew how cells of different ages were distributed amongst the cell population at birth. If, for example, we supposed that about 110 days before birth erythropoiesis is particularly active, then an infant at birth would possess a large complement of cells nearing the end of their span of 120 days, so that an undue proportion of red cells would disappear during the first 10 days after birth. An explanation along some such lines may account for Mollison's (1951) finding.

Less direct methods of investigating the matter have also been employed. Using bile pigment excretion as a measure of red cell breakdown, Josephs (1934) and more recently Künzer (1951) reached the conclusion that excessive red cell breakdown is a factor in the decline of haemoglobin after birth: however, the questionable assumptions implicit in the method must render this conclusion open to doubt. Finally, Vahlquist (1941) from an elaborate study of serum iron in infancy, has provided evidence against the view that there is increased haemolysis after birth.

The fact that if the cord is tied late the chance of an infant developing jaundice is increased (Book, 1935) has been quoted as proof that neonatal jaundice is at least partly haematogenous (Smith, 1946). Since, however, the infant whose cord is tied late receives an addition of about 100 ml. of blood to its existing blood volume of about 300 ml., thereby increasing its total red cells by one third, the normal breakdown of red cells will also increase by one third. Such an increase in the amount of bilirubin liberated would, in the presence of the low excretory capacity of the newborn infant's liver (Mollison and Cutbush, 1949; Yudkin, Gellis and Lappen, 1949), be doubtless enough to account for an increased incidence of jaundice. If this factor is kept in mind the known facts about neonatal jaundice seem to be adequately accounted for on the basis of hepatic immaturity alone.

Thus from a consideration of our own results, together with those of others mentioned, we conclude that there is no important increase in the rate of red cell breakdown in the neonatal period. The effect of plethora in adults is, we know from the recent study of Birkhill, Maloney and Levenson (1951), to cause a virtual cessation of erythropoiesis until the normal blood level has been restored, while red cell breakdown continues at a normal rate. A precisely similar picture emerges when the plethora of the newborn infant is studied.

Summary

The course of erythropoiesis in a series of infants from birth to 3 months has been defined, using the marrow erythroid count as a measure of erythropoiesis.

The factors responsible for the changing red cell picture after birth are two, changes in erythropoietic activity and the effect of body growth. There is no evidence that increased haemolysis is a significant factor.

Erythropoietic activity is governed principally by the arterial oxyhaemoglobin level. From the age of 2 months to 18 months the oxyhaemoglobin is maintained constant at about 11 g. per 100 ml.

In the foetus it is probable that erythropoiesis is also adjusted to maintain a similar level of about 11 g. of oxyhaemoglobin per 100 ml.

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HAEMATOLOGICAL DATA

TABLE 1

MEAN VALUES FOR RED CELLS IN VENOUS BLOOD AND FOR ERYTHROID CELLS IN MARROW IN NORMAL INFANTS FROM BIRTH TO 3 MONTHS

Age mean	Birth	Day 1	Day 4	Day 9	Day 29	Day 59	Day 89
Age limits	Cord blood	2–24 hours	3–5 days	8–10 days	26–33 days	55–62 days	82–99 days
Number of cases	12	10	24	22	19	7	11
Haemoglobin (g. per 100 mL.)	17·6	20·0	18·6	17·6	14·4	11·6	11·9
Haemoglobin (total g.)	42·2	51·4	41·9	41·4	33·7	31·1	39·2
Haematocrit	56	63	57	50	44	35	37
R.B.C. (m. per c.mm.)	5·25	5·81	5·67	5·41	4·61	3·91	4·22
R.B.C. (total × 10-9)	1,276	1,502	1,296	1,270	1,093	1,045	1,403
M.C.Hb. ($\gamma\gamma$)	33·7	34·5	32·9	32·7	31·2	29·9	28·7
M.C.V. (c.μ)	107	108	99·3	99·2	94·3	90·0	86·8
M.C.H.C. (%)	31·8	32·6	33·0	32·8	33·5	33·2	32·8
Reticulocytes (per 100 R.B.C.)	3·5	3·9	2·75	0·79	0·76	2·5	0·88
Marrow erythroid count per c.mm.	—	40,632	6,995	2,813	6,316	22,300	29,500