# American Academy of Pediatrics

## Proceedings

### TENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

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### Round Table Discussion on Anemias of Infancy

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#### Development of the Blood and Changes in the Blood Picture at Birth

**William F. Windle, Ph.D.,* Chicago**

It is proper to commence a symposium on anemias in infancy with a consideration of the developmental physiology of the blood. It is essential to form as clear a picture as possible of the blood at the end of fetal life and the beginning of postnatal life before discussing anemia in the newborn infant. I should like to define certain normal blood standards for you, but I must warn you at the start that I am unable to do so to my own complete satisfaction. I must plead that investigators have yet to uncover all the necessary facts. You are undoubtedly aware that there is no agreement on what are to be considered the true normal values for red corpuscles and hemoglobin at birth, and that until we have such standards, we will be unable to say with certainty what constitutes anemia in the newborn infant.

*The Blood of the Fetus:*

Genesis of red blood cells occurs shortly after the formation of the germ layers. It starts in the wall of the embryonic yolk sac and persists there until the second month. Blood formation begins to shift to the body mesenchyme and blood vessels about the fifth week. The liver starts to produce red blood cells in the sixth week, soon becomes the most active erythropoietic organ, and remains so until midfetal life. Erythropoiesis is initiated in the spleen at the end of the second month, and in the bone marrow during the third month. The activities of the various organs overlap and most foci of erythropoiesis are transient. Even in the liver, formation of blood elements stops at birth. Only the bone marrow normally carries it on into postnatal life.

Although some investigators believe that the various blood elements arise from two or three different types of parent stem cells, many now hold that they have one common ancestor, a generalized mother cell, often called a hemocytoblast or hemoblast. This is a large ameboid element resembling a large lymphocyte. Differentiation of red blood corpuscles proceeds through proerythroblasts, erythroblasts, normoblasts, and reticulocytes. Proerythroblasts show the first traces of hemoglobin in

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their cytoplasm, and are the only "red" cells of the blood during the first six weeks of development. After the third month they are confined to the hematopoietic centers. Some authors use the term megaloblast synonymously with proerythroblast. Normoblasts are small cells with pyknotic nuclei and more hemoglobin than erythroblasts; they first develop from erythroblasts in the fetal liver and are the predominant type of red cell in the blood at two months. Erythroplastids, or true red blood corpuscles, arise from normoblasts by fragmentation and extrusion of their nuclei. They make their appearance as spherical forms in the liver at about two months and become the predominant hemoglobin-containing element of the blood during the third month of fetal life.

At three months approximately 90 per cent of the red corpuscles are reticulocytes. The number of reticulocytes diminishes rapidly to 15 to 30 per cent at six months and to only 4 to 6 per cent at birth. About 0.1 per cent normoblasts are found at birth; other types of nucleated cells are not normally present.

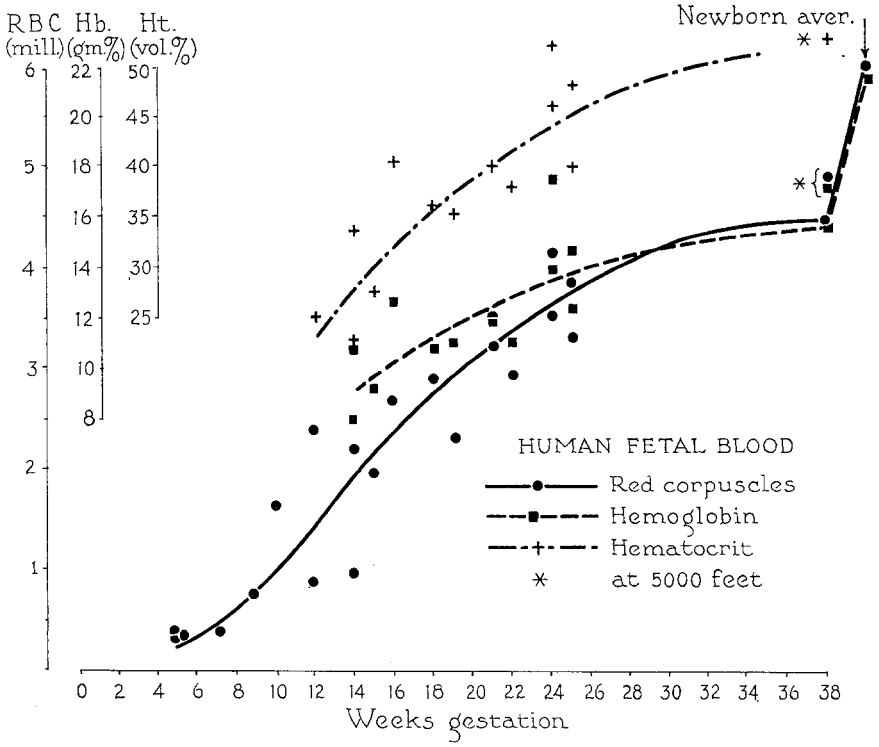


Fig. 1.—The blood picture in the human fetus. (Date from Knoll, 1927; Wintrobe and Shumacker, 1935; Mugrage and Andresen, 1936; DeMarsh, Alt, and Windle, 1940.)

It has been known for many years that the total number of hemoglobin-containing cells, as well as the number per cubic millimeter, increases progressively as the fetus grows; numerical data are limited and no complete systematic study of the blood picture during development has been made in man. All information available for the number of corpuscles and amounts of hemoglobin has been assembled in Fig. 1. The number of red corpuscles in the circulating blood increases from less than 400,000 per cubic millimeter at five weeks to approximately 3.5 million per cubic millimeter at six months. In our laboratory, the average number of red corpuscles in the blood at the end of gestation (from the umbilical cord at the moment of birth) was found to be 4.48 millions per cubic millimeter in thirty-five cases. Mugrage

and Andresen obtained slightly higher values in forty cases, but at an elevation of 5,000 feet. For reasons to be discussed when we speak of changes in the blood picture at birth, the much higher numbers of corpuscles reported in the literature for premature infants as well as for newborn infants cannot be accepted as representative of the true blood picture in the later months of prenatal life.

The amount of hemoglobin in fetal blood is relatively great at a time as early in prenatal life as estimations have been made. In the fourth month it is approximately 10 Gm. per 100 c.c. of blood, increasing gradually to reach 15.7 Gm. at the end of gestation.

Fetal red corpuscles are larger than those of the infant after birth. Great variation among individual corpuscles is encountered. The average diameter of corpuscles at three months' gestation has been reported to be 9.2 $\mu$, and at six months, 8.1 $\mu$ in the dry state (smears). At birth the average diameter in dry preparations has been determined to be 7.99 $\mu$ by Faxén, although other values have been reported.

The increase in the number of corpuscles during development more than offsets the progressive decrease in corpuscular size. Consequently, hematocrit values rise as gestation proceeds toward term. The mean corpuscular hemoglobin available to transport oxygen is a function of the total number and the volume of red corpuscles, and its concentration within individual corpuscles does not vary. A striking similarity has been described between the normal development of the blood picture and the blood in pernicious anemia patients undergoing continuous and effective treatment with a potent antipernicious-anemia factor.

Establishment of these facts has been made possible by a number of studies on development of the blood picture in the common laboratory and domestic animals. Only enough data are available in human fetuses to indicate that the processes are similar to those in the rat, rabbit, cat, dog, pig, and sheep. The most serious deficiency in our knowledge of the prenatal blood picture is lack of total blood volume determinations. Nothing is known in man. Only in the sheep have accurate estimates been made by an improved colorimetric method.

In viewing the problem of total blood volume in prenatal life, one must not lose sight of the fact that the placental circulation contains a large part of the fetal blood. We cannot consider blood volume in terms of surface area, for the fetus has no surface from a physiologic point of view. We must relate the blood volume to weight of all the tissues through which the blood flows, i.e., the weight of fetal body plus that of the placenta. Blood constitutes about 15 per cent of the weight of the sheep fetus at the end of gestation.

In the sheep, the placenta reaches a maximum size about the middle of gestation, when the fetus, the size of a large rat, has attained only about one-sixteenth of its birth weight. Blood forms a much larger proportion of the fetal weight at this time than it does near term. The absolute amount of blood increases greatly with gestation, but the ratio of blood volume to body weight declines. The amount of blood in the placenta remains nearly constant throughout the last third of fetal life, while that in the body increases several fold. The blood is about equally divided between placenta and fetal body at the beginning of the last third of prenatal life; at term, approximately one-fourth of it is in the placenta.

Data on total blood volume and hemoglobin synthesis in the human fetus are badly needed. The blood mass of the sheep fetus at full term (147 days) was found to have a total hemoglobin content of approximately 80 Gm. At eighty days' gestation the fetus had manufactured only 4 Gm. of hemoglobin, and at 100 days', only about 15 Gm. The last third of gestation therefore, was the period of greatest gain by the fetus. The pregnant sheep showed a slight loss of hemoglobin at the end of the first third of pregnancy. This was gradually regained and there was no reduction of the mother's hemoglobin during the time the fetus was synthesizing it so rapidly.

In the human fetus at birth we know that the placenta contains a large portion of the total blood mass. From 50 to more than 200 c.c. of blood have been recovered from placentas for "blood banks." It is natural for the newborn infant to retrieve most of this from its placental circulation if severing of the cord is delayed for a sufficiently long time. It was found that the average amount of blood in the placental vessels in one series of 120 cases was 105 c.c. Fifty-one per cent of this flowed into the infant from the placenta in the first minute after delivery; 79 per cent reached the child in the first five minutes, and 91 per cent in the first ten minutes.

Total blood volume has been estimated in the human newborn infant by the vital dye technique. An average of 531 c.c. of blood was found in twelve infants three to twenty-four hours after birth. This was 15.5 per cent of body weight. However, we do not know that this accurately represents the true total blood volume at the end of gestation, because the investigators failed to say whether or not placental blood had been allowed to return to the child before the umbilical cord was clamped. If 531 c.c. is the total blood volume at the end of gestation, it is evident that the placental circulation in man contains, on the average, approximately one-fifth, and in some individual cases more than one-fourth, of all the fetal blood.

The physiology of circulation and respiration in fetal life has been but poorly understood until recently. Most of us have held that the fetus gets along quite well with little oxygen and that the blood reaching it from the placenta has a high degree of unsaturation. Apparently this is far from the true condition.

Perfection of experimental methods has made it possible for Barcroft and his colleagues to withdraw blood samples from umbilical vessels of sheep fetuses without delivering them. The blood of the umbilical vein (going to the fetus) was found to be more than 90 per cent saturated with oxygen in half of the experiments. Saturation was greatest during the middle third of gestation. Upper limits of 90 per cent in the ox and approximately 84 per cent in man have been reported. At the time of parturition the values are somewhat less. What are the mechanisms that account for such a high degree of oxygenation? Gas tensions in the placenta are certainly not so high as in the lungs.

In the first place, it has been demonstrated that certain anatomic arrangements of the blood streams of the placenta favor an efficient transfer of the blood gases. One can picture the placental circulation rather simply: A well-oxygenated stream of the mother's blood enters the placenta and comes into intimate contact with the fetal blood stream, poor in oxygen. The two do not mix, but the degrees of contact differ in various species of mammals. One might think that the two streams should come into equilibrium in respect to the tensions of their blood gases, the umbilical vein blood becoming as saturated or as unsaturated as the uterine vein blood of the mother, and that the umbilical vein blood of the fetus should become progressively darker as gestation proceeds toward its termination. Actually this does not happen. It has been found that the maternal and fetal capillary streams, instead of flowing parallel to one another, flow in opposite directions in the rabbit placenta. A similar arrangement has been found in some other mammals. Thus the fetal blood is able to come into equilibrium, not with the maternal venous blood, but with that at the arterial end of the maternal capillary bed. The mechanism is illustrated in Fig. 2. That a similar mechanism operates in man is unproved.

The placenta reaches its maximum size while the fetus is still growing and building hemoglobin at a rapid rate. The cessation of gain in placental size is compensated by an increase in efficiency of the fetal circulation. In the sheep, the volume of fetal blood traversing the placenta increases in proportion to fetal weight. An increase in fetal blood pressure throughout pregnancy helps regulate the amount of blood passing through the placenta per minute. Near the end of gestation, 284 to 568 c.c. per minute flowed through these vessels. On the maternal side of the placenta, there appeared to be a somewhat less marked increase in volume of blood

flow, except near term, when it was reduced. Oxygen consumption by the fetal tissues is constant throughout the last third of gestation in the sheep. It is estimated to be 0.0043 c.c./g/mm.

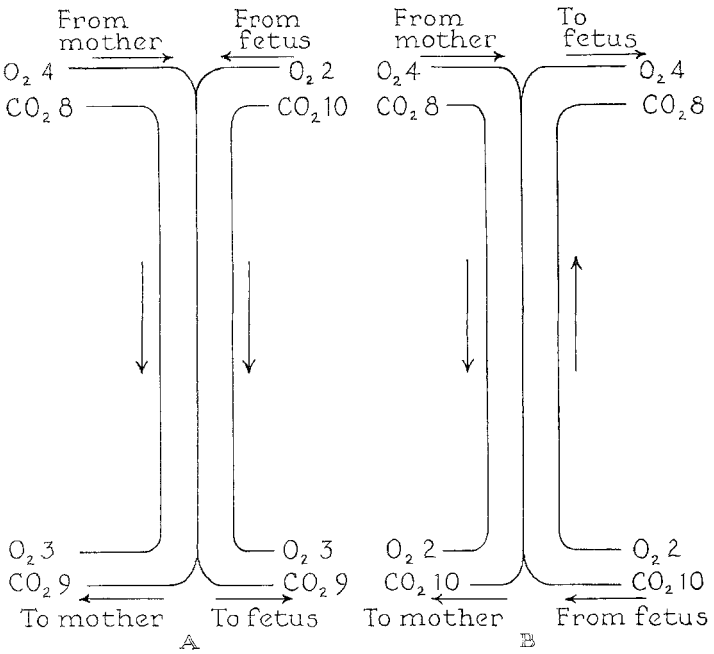


Fig. 2.—The exchange of oxygen and carbon dioxide in the placenta. If the maternal and fetal capillary streams course in the same direction (*A*), blood returning to the fetus will be as venous as that returning to the mother. But if the streams course in opposite directions (*B*), it will come into equilibrium with that of the mother's arterial blood. (From Windle, 1940; redrawn from Mossman, 1926.)

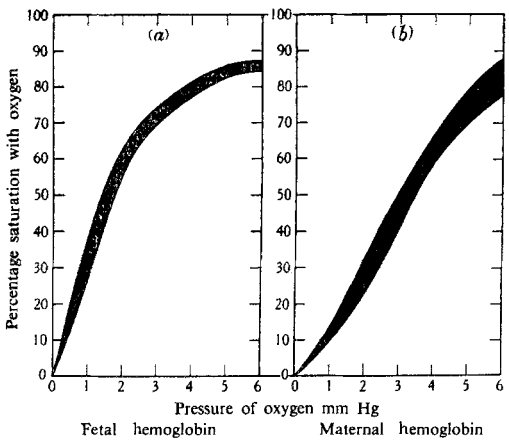


Fig. 3.—Oxygen dissociation curves for fetal (*a*) and maternal (*b*) hemoglobin in the sheep. Limits fall within the dark areas. Approximate temperature was 19° C.; pH, 9.3. (From Windle, 1940; after Hill.)

Another mechanism enables the fetus to obtain oxygen readily in the placenta under the pressure conditions prevailing there. The hemoglobin of the fetal blood differs chemically from that of the adult. The difference is such in the species which

have been studied that oxygen is taken up with greater avidity at low partial pressures by the fetal than by the maternal hemoglobin. The differences can be seen by comparing oxygen dissociation curves for solutions of fetal and maternal hemoglobin, such as those shown in Fig. 3.

In the goat during the last half of gestation fetal hemoglobin becomes 60 per cent saturated with oxygen at a pressure only one-half of that required for the same degree of saturation in the mother, the hydrogen ion concentration of the solutions being the same. Differences become less noticeable as parturition is approached, and by five weeks after birth the kid's hemoglobin attains adult characteristics. Similar differences between fetal and maternal hemoglobin solutions have been reported in rabbits and even in chicks of the domestic fowl. A very pronounced avidity for oxygen at low gas tensions has been demonstrated in whole blood of calves near term. It was shown that dissociation curves of whole blood in relation to those of the mother are inexplainable solely on the basis of greater akalinity of the mother's blood. They are governed by true chemical differences in the hemoglobins.

The human fetus at full term may differ from others, for it has been reported that its hemoglobin in dilute solutions takes up oxygen less than does that of its mother. Nevertheless, buffered (pH 7.4) suspensions of fetal corpuscles, like whole fetal blood, become more highly saturated with oxygen at low partial pressures than similar suspensions of the mother's corpuscles. No data are available for the human fetus prior to full term. Species differences in avidity of the hemoglobin for oxygen may be related to the degree of maturity reached at birth. Other evidence points to a true difference between fetal and maternal hemoglobin.

The significance of the blood picture at the end of fetal life is becoming clear. The full-term fetus does not possess a polycythemia ascribable to a high degree of venocity of its circulating blood. These concepts are wrong. At the end of prenatal life there are actually fewer corpuscles per unit volume of blood than in the adult. The blood received by the fetus from its placenta is essentially arterial blood. It is true that fetal hemoglobin values at term are in excess of those encountered in the normal adult. This is due to the fact that the corpuscles, although decreasing in size progressively throughout gestation, are still larger than adult corpuscles. Special anatomic and chemical mechanisms, already described, enable the fetus to obtain oxygen with great avidity in a placental environment of relatively low oxygen tension and without the necessity for developing an excessive number of red corpuscles. It seems more probable that blood development occurs as it does because hematopoietic centers respond to some intrinsic, perhaps hormonal, growth factors, than that it develops in response to a threat of asphyxiation.

*The Blood Picture in Early Infancy:*

Much has been written concerning the blood in infancy. Nevertheless, our knowledge today is incomplete, and many controversial points remain to be clarified. In reviewing the voluminous literature on the blood picture in the newborn infant, one is impressed by the lack of agreement as to what values for the number of red corpuscles and amount of hemoglobin constitute normal standards. Differences are often too great to be accounted for on the basis of normal race or individual variations. One suspects some other factors. The exact source of blood and the methods of taking samples are often omitted in reports. The methods of estimating hemoglobin vary widely; hemoglobin, frequently reported in per cent, cannot always be transferred into grams per 100 c.c., and what may be even more significant, authors seldom state whether the blood was drawn from infants allowed to retrieve their placental blood or from those deprived of it by immediate clamping of the umbilical cord at birth.

Some investigators have held that a true polycythemia exists at birth, but others have failed to substantiate this. The average figures reported for the number of

red corpuscles and the amount of hemoglobin vary all the way from those encountered in normal adults to average values as high as 6.5 million red corpuscles per cubic millimeter and 23 Gm. of hemoglobin per 100 c.c. Individual counts greater than 7 million red corpuscles per cubic millimeter are not uncommon.

Before we can arrive at a standard, it must be realized that the number of corpuscles in a cubic millimeter of umbilical blood at the end of gestation differs from that in the same quantity of blood drawn from the infant less than an hour after birth. Dr. DeMarsh, Dr. Alt, and I have investigated this subject recently. The average difference amounted to 1 million corpuscles in one group of twenty-five infants whose cords were clamped immediately at birth, and to more than 1.5 million in twenty-five whose cords were not clamped until placental blood had passed into the infants at birth. Corresponding hemoglobin differences were encountered (3 Gm. in immediate clamping and 6 Gm. in the delay group).

The explanation of these surprising differences is difficult. We thought at first that there might be a discrepancy between capillary (infant's heel) and venous (umbilical vein) blood. This was suggested by several observations in the literature. Waugh and his colleagues reported from 15 to 15.5 Gm. of hemoglobin in blood from umbilical cords as well as from venous sinuses during the first week of life. Osgood found, on the average, 17.2 Gm. of hemoglobin per 100 c.c. of venous sinus blood during the first four days of life. This declined to 16 Gm. by the tenth day. Red corpuscles averaged 4.6 million per cubic millimeter. These values do not differ greatly from our own and others' results on umbilical cord (venous) blood, but they are considerably lower than those we obtained from the heel capillary blood after birth.

Haden and Neff compared capillary and venous sinus blood in newborn infants and found red corpuscles more numerous in capillary blood. Duke and Stoffer discovered a similar discrepancy between capillary and venous blood of adult patients with pernicious anemia. This blood, like that of the newborn infant, contains many large corpuscles. They suggested that these large corpuscles occluded capillaries and led to concentration of corpuscles there. Other investigators have failed to confirm the difference between capillary and venous blood in the newborn infant. Mugrage and Andresen reported that lower values were obtained on cord blood than on venous blood at birth.

We have made comparisons between samples obtained from the superior sagittal sinus (or jugular vein) and form the heel capillaries in six normal infants, as well as from the cubital vein and finger blood of one adult with pernicious anemia. Our results show no significant difference between capillary and venous blood in respect to the number of red corpuscles. Furthermore, the hemoglobin values obtained in venous blood of infants are comparable with the average of those obtained from heel blood.

It is doubtful that the sudden increase in the number of corpuscles in the infant's circulating blood at the time of birth is due to a difference between capillary and venous blood. Postnatal dehydration is an unlikely explanation because the change often takes place in less than half an hour. A possible explanation may be found in the relationship of the spleen to this phenomenon. Polycythemia due to splenic contractions during emotional excitement has been observed in the cat. In prenatal life the smooth musculature of the fetal body is less active than that of the individual after birth. Perhaps initiation of splenic contraction throws a significant reserve of concentrated corpuscles into circulation. This would cause the difference between umbilical cord and heel blood that we have observed. It is interesting to note that Horváth and Hollosi found more red corpuscles and hemoglobin in the infant's umbilical artery blood than in that from the umbilical vein; heel blood drawn at birth showed even higher values.

Granting that the number of corpuscles and amount of hemoglobin per unit volume of blood increase sharply at birth, we are still unable to determine standard

values without accurate knowledge of total blood volume. The height of the rise at birth appears to be related to the amount of blood the infant recovers from its placental circulation. The results of several investigators suggest this, and recent study by DeMarsh, Alt, and myself shows it even more clearly.

The umbilical cords were clamped as soon as possible after normal delivery without anesthesia in one series of twenty-five healthy newborn infants; the time elapsing was thirty seconds or less. In another twenty-five infants the cords were not clamped until the placentas had separated from the uteri. This usually occurred within ten minutes after delivery. It was found that the baby received an additional amount of blood between the time the cord stopped pulsating and the time the uterus contracted firmly, with separation of the placenta. This was measured in ten instances and was found to average 62 c.c. Only a few cubic centimeters of blood at best can be obtained from the umbilical cord after separation of the placenta. In fact, we were unable to draw enough blood from a number of the cords to give adequate determination of hemoglobin and corpuscles.

Red corpuscle counts and hemoglobin determinations were made on cord blood and on blood from the heel of the infant twenty to seventy-five minutes, one day, three to four days, and six to seven days after birth.

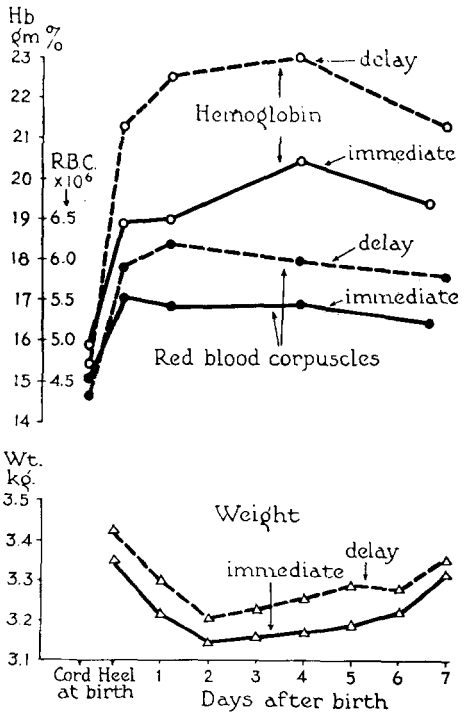


Fig. 4.—Average number of red corpuscles, amount of hemoglobin, and body weights of infants from birth to the seventh day. Solid lines, infants whose cords were clamped immediately; broken lines, infants on whom clamping was delayed. (From DeMarsh, Alt, and Windle.)

Averages of our results are shown graphically in Fig. 4. The average values for cord blood were 4.5 million red corpuscles per cubic millimeter and 15.7 Gm. of hemoglobin per 100 c.c. They were approximately the same whether the cord was clamped early or late. Within twenty to seventy-five minutes after birth, the values in blood from the heel were much higher. Henceforth throughout the week the infants whose cords were clamped immediately had significantly lower corpuscle and

hemoglobin values than those whose cords were clamped late. During the first week the former group averaged 5.45 million red corpuscles per cubic millimeter and 19.5 Gm. of hemoglobin per 100 c.c., whereas the latter group averaged 6.01 million red corpuscles and 22.1 Gm. of hemoglobin. The difference between the two groups at each age period was statistically significant, especially at one, three to four, and six to seven days after birth.

In view of the facts that the placenta contains one-fifth to one-fourth of the total fetal blood at birth and that all this blood does not pass into the infant at birth until after uterine contractions have had a chance to compress the placenta, we believe that the rather common practice of promptly clamping the cord at birth should be condemned. Of course, this will make it impossible to salvage placental blood for "blood banks." However, the collection of usable quantities of placental blood robs the newborn infant of blood which belongs to him and which he retrieves under natural conditions.

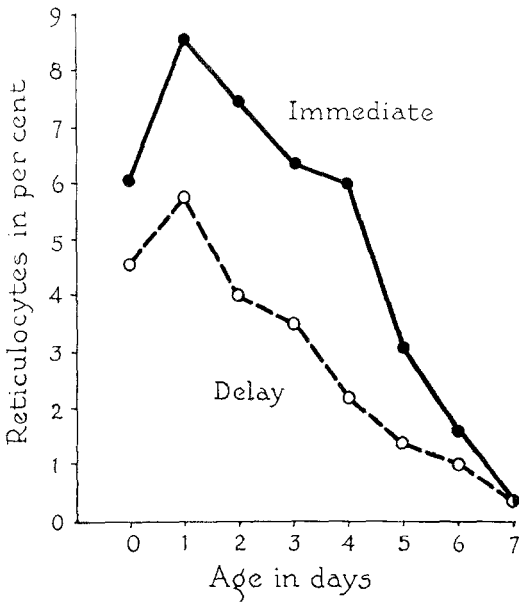


Fig. 5.—Average percentage of reticulocytes in the blood of infants from birth to the seventh day. (From DeMarsh, Alt, and Windle.)

Immediate clamping of the cord is comparable to submitting the infant to a rather severe hemorrhage. It appears to result in increased erythropoiesis which is reflected in an increase in circulating reticulocytes. Most observers have reported the reticulocyte count at birth to average about 4 to 6 per cent, decreasing rapidly to less than 1 per cent at the end of the first week. Some have reported a slight rise on the second day. But no one previously has made comparative studies of the reticulocyte count in the newborn infant after early and late tying of the cord. Our own results in such a study are recorded in Fig. 5. This illustrates average values in six infants whose cords were clamped immediately and in six whose cords were clamped after delay. When the cord was tied immediately, reticulocytes reached an average peak of 8.6 per cent at twenty-four hours and did not fall below 6 per cent until the fifth day. When tying of the cord was delayed, reticulocytes averaged only 5.8 per cent at their peak in twenty-four hours and then fell to 4 per cent in forty-eight hours. A more active blood formation when the cord is clamped early than when it is clamped late is suggested by the higher and more sustained rise in reticulocytes in the former group.

I believe I have reviewed enough data on the blood picture during prenatal and early postnatal life to indicate to you possible relationships between developmental conditions and anemias in infancy. A great need for more accurate standards is evident. When we know something about total red corpuscle and hemoglobin mass at birth and more about the blood picture throughout early life, we will be better able to determine what are departures from normal.

One can easily imagine that loss of nearly one-fourth of the total blood volume in the newborn infant may sometimes be critical. In the latter part of the nineteenth century Engel reported twice as great a mortality in premature infants whose cords were tied early as in those whose cords were tied late. The proportion of fetal blood in the placental circuit is higher in the premature infant than it is at full term.

It is evident from our recent studies that deprivation of the newborn infant of its placental blood may lead to iron deficiency in infancy. Fullerton and Stearns and McKinley have recently called attention to the fact that the principal iron reserve of the newborn infant is in the circulating hemoglobin rather than in the tissues. Iron liberated during blood destruction is stored in the tissues and utilized as needed for hemoglobin formation. The amount of iron lost to the newborn infant in 100 c.c. of placental blood prevented from reaching the child from its placenta is 54 mg. This is enough iron to lower the hemoglobin in a 4-month-old infant from 12 to 9.3 Gm. per 100 c.c. of blood. Therefore, it seems possible that loss of placental blood may be an important factor predisposing infants to anemia during the nursing period.

Another question to which considerable discussion has been given in the literature is the possible relationship between maternal iron deficiency and anemia in the newborn infant. It has been proved that the brief period of rapid hemoglobin synthesis in the sheep fetus has no appreciable effect upon the total hemoglobin of the mother. In fact, the mother's total hemoglobin mass increased slightly during this period. This does not prove that a similar condition prevails in man because placental transmission is different in the two species.

The effect on fetal rats of iron-deficient diets fed to the mother has been reported. The first pregnancy brought on marked depletion of maternal liver iron, but there was no anemia. With the advent of a second pregnancy, an anemia did appear. The first litter of rat pups had normal hemoglobin values, but a reduction in total iron of the entire body by about one-half the normal was evident. The second litter exhibited a reduction of the hemoglobin of the blood, and the total iron content was only one-fourth normal. This work seems highly significant.

Some investigators have reported that anemia in pregnant women is associated with iron deficiency in the human fetus. Infants born of anemic mothers may exhibit hypochromic anemia in the first year of life. However, one suspects that this may have been related to deprivation of the placental blood at birth, a factor which was not controlled in the studies. We will have to obtain more information concerning the normal blood picture, and be certain that the infant starts life with all his available blood, before we can prove that anemia in the mother is related to iron deficiency in the child. Furthermore, it will be necessary to have adequate clinical histories of all infants used in studies of this kind, because between birth and the time an anemia manifests itself there are many factors which can influence the infant's iron and copper metabolism.

## DISCUSSION

The average values for red corpuscles and hemoglobin from cord blood were approximately the same whether the cord was clamped early or late. Within twenty to seventy-five minutes after birth, the values in blood from the heel were much

higher. Subsequently throughout the first week the infants whose cords were clamped immediately had significantly lower corpuscle and hemoglobin values than those whose cords were clamped late.

QUESTION.—How long should clamping of the cord be delayed?

DR. WINDLE.—Until the pulsation has ceased, and until the placenta has separated from the uterus. It is not sufficient to wait only until pulsations have ceased, for then there is still more than half of the placental blood in the placental circulation. Milking of the cord is, in most cases, probably unnecessary; we delayed oftentimes five, six, or ten minutes, rarely more than ten minutes. That seems to be sufficient time for all, or the greater part, of the blood to flow naturally back to the child.

DR. R. N. ANDREWS, MANKATO, MINN.—How do you account for blood's being transferred to the fetus after the cord has stopped pulsating?

DR. WINDLE.—Pressure by the contracting uterus forces the blood out of the placenta.

DR. L. W. DIGGS, MEMPHIS.—What is the effect on the prothrombin time?

DR. WINDLE.—We did no prothrombin time and no bleeding time on these infants.

QUESTION.—Is there any objection by the obstetrician to delay in clamping of the cord?

DR. WINDLE.—I have not heard any objection directly from obstetricians. It is not too much to expect them to wait a short period of time, ten or fifteen minutes under ordinary conditions, and especially when they have adequate help in the operating room.

The matter of early and late tying of the cord has been a forgotten question. In the latter part of the last century it provoked a great deal of discussion in continental Europe, especially in Germany and Austria. In turning back to the old literature, we find many reports on the question of the benefit of early and late tying, although there was nothing in those reports that gave us any great help on this immediate question of comparison of hemoglobin and red blood cell groups.

QUESTION.—What difference is there in the blood picture in the premature and the full-term infant?

DR. WINDLE.—We haven't been able to compare the blood pictures in viable premature infants with those in the full-term infants. The reason is that we have no values taken from the umbilical circuit in the premature infant. All the values have been taken from the infants in the first, second, and third days of life. The same factor operates in viable premature infants to raise the hemoglobin and red blood cell level that operates in the full-term infant.

Splenic contraction, and perhaps the pouring out of concentrated corpuscles from other organs, must take place in the viable premature infant as well as in the full-term infant. It is important to emphasize again that the premature infant has more of its total blood in the placenta, that is, a larger proportion of it in the placental circuit, than does the infant at full term. Perhaps that was the reason that Engel, ten years ago, found that the premature infants whose cords were tied promptly at birth had a 50 per cent greater mortality than the premature infants whose cords were tied late.

DR. H. J. MORRISON, SAVANNAH, GA.—What is the comparative degree of jaundice in infants with cords tied early and those with cords tied late?

DR. WINDLE.—We anticipated that we would see a difference in the degree of jaundice in the two series of infants. We did not do chemical determinations, but we did observe all the infants carefully, looking at the sclera and general skin color. We were surprised to see no significant difference in the two groups, although we did observe jaundice in a number of individuals. In the ones whose cords were tied late, we found three with rather marked jaundice. If I remember correctly, in the ones whose cords were tied immediately, we found five with jaundice. In the series of fifty-three cases which we had, this is not a significant difference.

QUESTION.—Is this directly opposite from that which you expected?

DR. WINDLE.—We would have expected to find more of the infants who got all of their placental blood showing jaundice, but we did not find a significant difference. The jaundice we did see was probably a physiologic jaundice.

DR. M. I. PIERCE, EVANSTON, ILL.—Was a physiologic anemia noted when there had been delayed clamping of the cord?

DR. WINDLE.—The cases were not under observation long enough for this to be determined.

DR. H. G. PONCHER, EVANSTON, ILL.—Do you feel that the analgesic given to the mother has any relationship to the arterial dissociation in the newborn infant?

DR. WINDLE.—Only two of our patients received any analgesic, and each of these received only 2 grains of nembutal.

DR. C. A. SMITH, BOSTON.—What is the relation of the infant's hemoglobin to that of the mother?

DR. WINDLE.—There is no definite relation between the hemoglobin value in the mother and her newborn infant except that the infant's hemoglobin is more often higher than the mother's. Infants born of anemic mothers and exhibiting hypochromic anemia later in the nursing period may be suffering from iron deficiency due to deprivation of placental blood at the time of birth, caused by too early clamping of the cord. Anemia of the mother does not necessarily mean that the infant will be anemic.

DR. H. F. GARRISON, JACKSON, MISS.—If there is very little relationship between the diet and care of the mother and the red blood cell count and hemoglobin of the infant, what is the relation of the blood picture of the infant to that of the mother?

DR. WINDLE.—The evidence does not indicate that anemia of the mother determines the red cell and hemoglobin values in the infant. The loss of placental blood would seem a more important factor relative to anemia in the infant.

CHAIRMAN ABT.—What is the difference in the chemical nature of the hemoglobin of the mother and the infant at birth?

DR. WINDLE.—The hemoglobin of the fetus has a greater avidity for oxygen and reaches a higher degree of saturation under the same oxygen tension than does that of the mother or of the infant after birth. This is also true of fetal corpuscles. The evidence points to a true chemical difference between the fetal and maternal hemoglobin.

QUESTION.—What is the explanation of the greater avidity for oxygen shown by the fetal hemoglobin?

DR. WINDLE.—The further the fetus is from term, the greater is the avidity of its hemoglobin for oxygen and the less readily does it give up its oxygen to the

tissues. There is a spectroscopic as well as chemical difference in the hemoglobin of the fetus, although it is not known exactly what this difference is.

DR. W. R. PHILLIPS, ELMIRA, N. Y.—Why worry about placental blood if it is destroyed early in the neonatal period?

CHAIRMAN ABT.—Iron content of the cell is not lost to the extent that pigment is, so that there is a reserve storage of this material in the body.

DR. PHILLIPS.—Is iron all that is lacking in infants who develop anemia?

CHAIRMAN ABT.—Iron is stored, and possibly other products of cell hemolysis. Needed material other than iron is fairly well supplied in the milk.

DR. PHILLIPS.—Some don't respond to iron.

DR. WINDLE.—If the anemia were due solely to an iron deficiency, it would probably respond to iron therapy.

CHAIRMAN ABT.—There might be an interference with the function of the blood-forming organs.

DR. WINDLE.—If the baby does have difficulty in utilizing iron given in its diet in the early period in postnatal life, then that is all the more reason that the obstetrician should see that it goes into this period with all the iron possible available. The baby, in extreme cases, may lose as much as 200 or more cubic centimeters of blood if the cord is clamped immediately at birth. That would be over 100 mg. of iron. We must think of that iron as retained in the baby's body, as suggested, because it does not excrete it. I think everybody will admit that it would be very difficult to replace that iron in the baby by feeding it during the nursing period. There's a moral there, to see that the child doesn't lose the iron.

DR. M. C. PEASE, NEW YORK CITY.—Does he really throw away his plasma too?

DR. WINDLE.—I wonder how much he really throws away—whether he really throws away anything. I have a feeling that he utilizes a good deal of this hemolyzed blood, not only the iron, but perhaps some other things, copper and other factors in the blood that he hemolyzes. I don't think of that as waste material at all. I think that it enters definitely into the economy of the individual in the weeks that follow. In regard to the comment, there is a certain amount he does lose because of bile pigments in the urine.

DR. STRONG.—Anemia means a deficiency in red blood cells as well as hemoglobin, and may result from various factors. Blood destruction is going on all the time, and if there is not adequate replacement, anemia results. Anything interferring with the balance between blood destruction and regeneration will lead to anemia. Early in neonatal life there is a drop because the blood factory is not functioning 100 per cent. As soon as hematopoiesis is well established, there is a rise in red cells and hemoglobin, to approach normal.

## Anemias of the Newborn Infant

**Robert A. Strong, M.D.,* New Orleans**

It has long been realized that a sequence of anatomic and physiologic changes is initiated as soon as the newborn baby begins its independent existence. In so far as the blood is concerned a study of the evolution of neonatal circulation and hematopoiesis indicates that in the blood certain changes take place immediately after the interruption in placental circulation, while others require several weeks or even

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months. The physiologic changes usually proceed in an orderly manner, without any detectable effects on the infant. They are initiated at the time that the antenatal centers of erythrogenic activity cease to function and hematopoiesis is established in the bone marrow. However, when interruptions in this normal sequence occur at or shortly after birth, there follows in the blood of the infant alterations which cease to be physiologic and become pathologic. The consequences of these alterations are referred to as the *anemias of the newborn infant*, and Dr. Abt has requested me to discuss this phase of the subject.

In the complete readjustment which the newborn baby makes to its change in environment, it is most important that an equilibrium between blood destruction and blood formation be established. The surplus of erythrocytes, which are carried over from intrauterine life, is no longer necessary for the maintenance of adequate tissue respiration following the change from the environment of low oxygen tension in utero to a higher oxygen tension after birth. Therefore, a reduction in the number of erythrocytes and a consequent reduction in the hemoglobin which they contain is an important phase of the establishment of normal levels. The reduction in the number of circulating erythrocytes is brought about by hemolysis. This hemolytic dissolution of the erythrocytes releases hemoglobin, which is then taken from the blood stream by phagocytic cells contained within the liver, spleen, and bone marrow, and is split within these cells into bilirubin and a colorless iron-containing residue. The greater part of the bilirubin thus formed passes into the intestines, where it is reduced to urobilinogen, but a small quantity of it is thought to enter the blood stream directly. Most of the urobilinogen is believed to be reabsorbed from the intestinal tract and is returned to the liver through the portal circulation. The hemolytic process, which occurs at birth, causes such a marked overproduction of bilirubin in some instances that the liver is unable to excrete the excessive amount. The bilirubin content of the blood then increases and may be deposited in the tissues, with the result that an icteric tint of the skin appears on the third or fourth day after birth, but gradually subsides within eight to ten days. This, we call *simple icterus neonatorum*. It is rarely accompanied by any detectable effects on the infant and requires no treatment. It apparently is not possible, however, to exclude definitely some sort of functional incapacity of the liver as an additional causative factor of this condition. In support of this belief, its exaggeration and persistence in premature infants have been frequently cited. In these infants, it is reasonable to assume that the liver function is even more decreased than it is in the normal infant.

In addition to simple icterus neonatorum which is fundamentally caused by a reduction of erythrocytes, a certain amount of anemia may be present when the erythrocytes and the hemoglobin descend to the lowest level after birth. This level is reached about the end of the second or third month. It may remain for a short time before the erythrocytes, following the establishment of medullary blood regeneration, begin to increase. Such anemia is spoken of as *physiologic anemia of the newborn infant*. It is likewise inconsequential in its effect on the infant and cannot be influenced by any administration of iron or copper. Simple icterus neonatorum and physiologic anemia of the newborn infant may both be regarded as benign conditions.

In contrast to these two physiologic conditions, certain pathologic states may occur at or shortly after birth, and the resulting anemias provide a fascinating study. I have been interested in them because it has been our fortune, in common with many of you, to see a number of infants presenting variable symptoms. There is much to be learned about these conditions, and consequently I am pleased to have an opportunity to open a discussion of them in order that we all may broaden our knowledge with the observations which some of you may have made.

Many theories have been advanced concerning the etiology of the anemias of the newborn infant, and varying classifications have been suggested. I am going to

resist the temptation further to complicate the situation by refraining from suggesting any other classification. At the same time, I am going to hope that by our exchange of views, we will leave this meeting more enlightened than when we came here. It is difficult to draw a line between the anemias of the newborn infant and what might be spoken of as the anemias of infancy and childhood. I shall, therefore, confine myself to my conception of what should be regarded as the anemias which have their origin at or shortly after birth.

I believe that we are all in accord that most of these anemias occurring in the earliest days of the neonatal period may be grouped under the symptom complex called *erythroblastosis fetalis*. This term has been widely accepted to include icterus gravis neonatorum, hydrops fetalis or universal edema of the fetus, and congenital anemia of the newborn infant. I am aware that there are some variations in these terms, but they are of a minor nature only. It has been difficult at times to separate the three conditions, because clinical, pathologic, and hematologic studies have established many symptoms which they have in common. The first and most important is the presence of considerable numbers of erythroblasts in the blood. These immature red blood cells remain in the peripheral circulation much beyond the time when they should normally disappear. This is referred to as *erythroblastemia*. Moreover, there is evidence of a very active bone marrow and marked extramedullary hematopoiesis, which is chiefly erythropoietic in character. This is referred to as *erythroblastosis*. Jaundice, which is characteristic of icterus gravis, has been found at birth in hydrops fetalis, while edema, which is an outstanding feature of hydrops fetalis, has likewise been noted in icterus gravis, although it is usually localized and of a slight degree. In both, there are splenomegaly and hepatomegaly, a marked anemia, and the characteristic immature red blood cells in the peripheral circulation.

Stransky is of the opinion that there are two rather distinct types of congenital anemia of the newborn infant. One type is characterized by a nonregenerative blood picture and presents but few, if any, features in common with icterus gravis. The other type, however, which is characterized by an embryonal blood picture, is strikingly similar to icterus gravis in that there is often jaundice, hepatomegaly and splenomegaly, erythroblastosis, and erythroblastemia. Diamond, Blackfan, and Baty have clearly shown that in those few instances after the jaundice has disappeared in infants recovering from icterus gravis, the clinical and hematologic characteristics fulfill the diagnostic criteria of what is generally spoken of as congenital anemia of the newborn infant. This, in my opinion, is enough evidence to justify the conclusion that the three closely related clinical disorders—icterus gravis neonatorum, hydrops fetalis, and congenital anemia of the newborn infant—will continue to be grouped under the heading of erythroblastosis fetalis for some time to come.

This assumption is based on the fact that from time to time certain observations have been made which add to the perplexity of their individual indentity, because the similarities in these disorders, based on the clinical, pathologic, and hematologic findings, are subject to wide variations. For example, in each of the three conditions, cases have been reported in which there was little or no evidence of erythroblastosis. The occurrence of both hydrops fetalis and icterus gravis has been noted without the presence of nucleated red blood cells in the peripheral blood. Further, a marked erythroblastemia in icterus gravis has been found even when the red cells have not dropped below 4 million per cubic millimeter. Finally, it is to be remembered, as pointed out by Pasachoff and Wilson, that erythroblastosis is not confined to these conditions alone, as it sometimes occurs in congenital syphilis and sepsis of the newborn infant.

Perhaps the most convincing evidence of etiological relationship is to be found in the familial association of these three conditions. This familial tendency has been observed repeatedly, and it is not uncommon to find in the same family one child born with icterus gravis, another with hydrops fetalis, and still another exhibiting congenital anemia of the newborn. Macklin, Lamont, and Macklin, in tabulating

the incidence of erythroblastosis fetalis in twins, cite a case in which one of the twins was icteric and the other was hydropic. Maharik has recently cited an instance in which one of uniovular twins was affected while the other was normal. It would be most difficult to explain this on a basis other than a common etiology. No single theory has explained adequately the basic hematopoietic disturbances responsible for erythroblastosis fetalis. There are some facts, however, which are quite significant. One is that the majority of these cases which have been reported in otherwise normal families may be nothing other than the onset of a familial occurrence. The plausible explanation was suggested by Josephs a few years ago. The first-born is nearly always spared and less frequently the second-born, but once the disease occurs in a family, subsequent pregnancies almost invariably result in one of the clinical types of erythroblastosis fetalis. Adams and Cochrane have just reported an exception to this in that the third infant in a family, following two affected infants, was normal. They administered liver extract to the mother during her third pregnancy and suggested that this may have been the reason for the unaffected child.

As a rule, a normal pregnancy precedes the birth of an affected infant, but a few observers, particularly Rolleston, have reported the presence of various forms of toxemias of pregnancy. Similarly, with the notable exception of Parsons, who believes that a maternal anemia due to a deficient diet may, at times, cause an anemia in the offspring, most observers have found that anemia and nutritional disturbances did not exist in the mothers. Further evidence that the primary factor does not arise from the mother is to be found in those instances in which a pregnancy resulted in twins, one of whom was affected with erythroblastosis fetalis and the other was normal. Apparently the disease exhibits no racial tendency. Statistical studies, although few in number, offer evidence that icterus is not so common as was once believed. Clifford and Hertig give an incidence of 1 in 340 newborn infants, and Andrew and Miller, 1 in 490.

*Sepsis of the Newborn Infant:*

Almost any bacteria may cause infection. Those which concern us most frequently are streptococcus, staphylococcus, colon bacillus, and tetanus. The portal of entry to the blood stream is usually the umbilical area, but bacteria may gain entrance through the skin. The symptoms are temperature, jaundice, bleeding, and, of course, some anemia. The blood picture observed in infection in the neonatal period depends upon the severity of the infection as well as the organism. Anemia is more frequent with streptococcus and *B. coli* septicemia than it is with staphylococcus. Infection occurs most often during the latter part of the first week of life and may impede the progress of hematopoiesis during the transition from the antenatal centers of blood production to bone marrow hematopoiesis. Consequently, a fetal type of blood picture with an outpouring of nucleated red cells and immature white cells may characterize the anemia. The newborn infant with congenital syphilis may show this picture, together with jaundice, more marked anemia, enlargement of the liver and spleen, and a tendency to hemorrhage. Winkle's disease should be mentioned at this point, as it is a form of hemolytic anemia which is probably due to infection and is associated with cyanosis, icterus, and hemoglobinuria. There is a widespread tendency at the present time to drop this disease as a clinical entity, because it is apparently indistinguishable from the group of symptoms which follow any sepsis in the newborn infant.

*Erythroblastic-Hemolytic Anemia of the Newborn Infant:*

There are some anemias which make their appearance in the latter part of the newborn period, when hemolysis is in full progress. Among these are the anemias which accompany congenital acholuric jaundice and what has been spoken of as congenital nutritional anemia. There are still others who believe that erythroblastic

anemia or thalassanemia (Cooley's anemia) may make its initial appearance during this period. It is not an easy task to recognize these anemias in the early stages because they occur at a time of rapidly falling blood levels. Dwyer and Neff consider erythroblastic hemolytic anemias of the newborn infant as being the result of a rapid hemolysis of red cells at this period. They add that it is accompanied by icterus, erythroblastemia, macrocytosis, and a color index of 1.0 or above. They contend that there is often leucocytosis with many immature forms, thrombocytopenia with increased bleeding time, and petechial hemorrhages. They believe that the icterus is not the result of the hemolysis alone, because it is not related to the rapidity in the fall of red cells. Furthermore, they advance the belief that bile "thrombi" plugging the capillaries of the liver cause an obstructive type of jaundice with a prompt, direct, or biphasic van den Bergh reaction.

With the exception of Parsons and his co-workers and Neale and Hawksley, the consensus is that infants born of mothers who have suffered from iron deficiency during pregnancy show a normal blood picture at birth and the influence of inadequate storage does not become manifest until later in the first year. Nutritional anemia or anemia due to iron starvation will be taken up subsequently by Dr. Abt. In the state of confusion which characterizes the blood picture during the latter part of the newborn period, it is difficult for me to understand how a sufficient amount of evidence can be obtained to diagnose an early erythroblastic anemia or thalassanemia. If the infant is of Mediterranean parents, we could suspect the diagnosis, with the idea of proving it later. However, since Foster has reported a definite case of erythroblastic anemia in a Chinese girl, we can no longer consider erythroblastic anemia as being a disease found exclusively in Mediterranean races.

*Anemia of Prematurity:*

Last year, at a round table discussion on the therapeutics of anemia, Dr. Josephs raised the question as to what is to be considered the anemia of prematurity. I am going to go one step further and suggest that it no longer can be regarded as a clinical entity. I have gained the impression, as doubtless many of you have, that we have too many types of anemia which have so much in common with other types and that the time has arrived when we should at least attempt to reduce the number of designations.

It seems to be very well established that normally a low level of hemoglobin and red cells occurs between the eighth and the twelfth weeks after birth. This is physiologic, and without therapy the hemoglobin and the erythrocyte levels slowly rise during the following four to five months until the normal levels of about 4.5 million red cells per cubic millimeter and 13 to 14 Gm., or 80 per cent or better, of hemoglobin are reached. In the premature baby, hematopoietic activity is generally delayed longer than it is in the full-term baby, so that the resulting anemia is likely to be more severe and to last longer. Josephs suggested this explanation last year and it certainly is plausible. I think that iron is not a factor. A number of years ago, Helen Mackay established the fact that iron administration failed to influence the fall in hemoglobin or erythrocytes and demonstrated that nothing could be done to initiate a rise until normal hematopoiesis is established. We should not be surprised if it is delayed in the premature infant, because every other physiologic function is delayed in this type of infant, who is poorly prepared for independent extrauterine existence. I believe, therefore, that the so-called anemia of prematurity should be regarded as a physiologic anemia of an infant with an impaired anatomic and physiologic development.

## DISCUSSION

DR. PHILLIPS.—Does a young infant show at times an ideopathic congenital anemia which does not belong to any of the groups that have been described?

DR. STRONG.—Yes, that would be the third of the group, which I didn't make perfectly clear. Following an icterus gravis, when the icterus clears up, the baby looks very pale underneath the yellow tint. And a mild anemia can follow an infection sepsis of the newborn infant.

CHAIRMAN ABT.—There has been an interesting report in which one man and his wife had several babies born with erythroblastosis fetalis. For some reason or other they separated; after remarriage, normal children were born to the husband's second wife, but the first wife by the second husband gave birth to a baby with erythroblastosis fetalis. The same author reported another family where the same condition occurred, but when husband and wife remarried, abnormal children appeared on the paternal side of the second marriage.

QUESTION.—What about the white blood cell count in erythroblastosis fetalis?

DR. STRONG.—It is not much higher than 20,000; we have had four cases, and that's been about the average figure. The platelets are about 200,000. There is apparently no effect on them.

CHAIRMAN ABT.—In this group of cases are found many nucleated red cells, and the older authors appear to have confused these with white cells. As a result, some of the cases of erythroblastosis fetalis were diagnosed as leucemias.

DR. ANDREWS.—Will Dr. Strong enlarge on his discussion of congenital anemia?

DR. STRONG.—It is one of the group of erythroblastic anemias, less severe than icterus gravis neonatorum or hydrops fetalis. It is due to a delay in the development of the normal postnatal hematopoietic function.

DR. HEARN BRADLEY, NASHVILLE.—Does erythroblastosis underly hydrops fetalis and icterus gravis?

DR. STRONG.—Erythroblastosis fetalis is a symptom complex occurring in congenital anemia of the newborn infant, icterus gravis neonatorum, and hydrops fetalis, all of which are due to the same underlying cause.

DR. BRADLEY.—Does iron help anemia in the first four months of life?

DR. STRONG.—Physiologic anemia of the newborn infant cannot be influenced by any administration of iron or copper. Likewise in those pathologic anemias in which the condition is due to a delay in the development of normal postnatal hematopoiesis, it is unlikely that administration of iron would have any effect until normal hematopoiesis is established. If the "blood factory" is not functioning, no amount of building material will result in increased blood formation.

DR. PIERCE.—It is possible that allergy may be a factor in anemia of the newborn infant.

CHAIRMAN ABT.—The products of blood destruction due to hemolysis in the neonatal period may be stored in the body for subsequent use in the manufacture of new blood when needed.

DR. GARRISON.—Does the condition of the infant's blood bear any relation to that of the mother? Does the mother's diet have any effect on the baby's blood?

DR. WINDLE.—It is doubtful whether there is any correlation between anemia in the mother and in the baby. In rat experiments there is a suggestion of some connection, but there are no facts to prove this correlation in human beings.

DR. T. B. COOLEY, DETROIT.—There is no definite evidence that erythroblastosis fetalis is hereditary, in the sense that it is passed on from one generation to an-

other, although the familial tendency has been repeatedly observed. Anemia of the mother, in my opinion, does influence the development of anemia in the baby.

DR. U. J. BUSIEK, SPRINGFIELD, MO.—The statement was made that the cord should be tied late to allow the infant to obtain more blood. Then it was said that icterus simplex was due to hemolysis of surplus red cells. If surplus cells are being destroyed, why is it advisable to allow the child to obtain even more blood by waiting to clamp the cord?

DR. WINDLE.—Although the surplus cells are not needed at the time they are destroyed, the products of their destruction are, for the most part, stored in the infant's body, and are used later to make new blood cells as need for these arises. Availability of this material for use later in the nursing period is believed to prevent the development of anemia that would otherwise occur if the placental blood were lost by early clamping of the cord.

## Anemia of Late Infancy

**Arthur F. Abt, M.D., Chicago**

*I. Hemolytic Disease:*

When seen in early infancy, hemolytic disease displays certain differences from the manifestations presented when the first occurrence is noted in later childhood. In early infancy, anemia is often a more pronounced symptom than icterus and is generally quite severe. The onset in the young infant may occur as a severe hemolytic crisis and may terminate fatally. The blood changes are usually exaggerated, both as to size and shape of the red cells. The number of nucleated and reticulated erythrocytes may consist of a very high percentage of the total red cells. Splenomegaly is usually of a considerable degree.

*Onset.*—The onset, contrary to popular conception, may be noted in the newborn period. I have recently reported a case in which the jaundice was noted at birth. The onset may be insidious, or the condition may develop suddenly and terminate fatally. The earlier in infancy the symptoms appear, the more severe they are likely to be.

*Clinical Findings.*—The following clinical observations have been noted when the disease occurs in early infancy:

1. Familial Occurrence: The occurrence of this condition in cousins, as mentioned by Parsons, is the only instance in which a familial history is noted when the disease occurs in infancy. Debré has recently reviewed the familial occurrence in fourteen families and believes that the condition is transmitted as a dominant characteristic according to Mendel's law.

2. Jaundice: When the condition is first manifested in early infancy, jaundice may be entirely absent, even though there be indisputable evidence of a considerable increase in blood destruction. The jaundice varies considerably from time to time and is most marked in the remission after the crisis.

3. Anemia: Anemia is always one of the most striking features of the disease in young infants and may be quite severe. In one of my cases, the red cell count fell to 790,000, and the hemoglobin similarly diminished. The color index is usually over 1.

4. Blood Findings: (a) Size and Shape of Erythrocytes: It has been generally believed that one of the diagnostic criteria is the spherocytosis and microcytosis so commonly noted in the condition. Until recently microspherocytosis was indeed a criterion without which the diagnosis could hardly be made. However, it has now been recognized in the older patients suffering from the condition, and particularly in the infants, that neither microcytosis nor spherocytosis is a prerequisite to this condition. Occasionally, as pointed out by Hill, macrospherocytosis may be noted.

The occurrence of macrocytosis surely cannot rule against the diagnosis. The tendency for macrocytosis to be more or less physiologic in the young infant probably accounts for the frequency here noted.

(b) Reticulocytosis: This is a most characteristic finding in this condition. The increase is considerable in young infants. Baty has recorded a case with 92 per cent reticulocytosis in the peripheral blood.

(c) Erythrocyte Fragility: Since the days of Chauffard, increased fragility of the erythrocytes has been one of the outstanding criteria for the diagnosis of this condition. However, the fragility may be normal, or the resistance of the erythrocytes may be even somewhat increased. Debré notes this fact, and E. Schiff has recently reported a typical case with normal fragility of the red blood cells. A normal or even an increased resistance does not rule out the diagnosis.

(d) Other Blood Findings: The white blood count generally ranges from normal to somewhat increased. The number of platelets is usually within normal limits. Occasionally, a considerable rise in the number of platelets have been noted following splenectomy. A certain increase in the number of normoblasts is generally noted. Bilirubinemia is always present. The icterus index is increased, and the indirect van den Bergh test gives a positive reaction.

5. Bone Marrow: Smears of the bone marrow obtained by sternal puncture reveal an increased number of nucleated erythrocytes. Instead of the normal 15 per cent, 50 per cent or over have been noted in this condition. This hyperactivity of the bone marrow is characteristic of hemolytic disease.

6. Splenohepatomegaly: In all cases of this condition the spleen is enlarged. When the disease appears in early infancy, this is particularly true, and the enlargement may extend below the umbilicus and completely fill the left flank. The liver may also show considerable enlargement. Both spleen and liver are firm to the touch.

7. Miscellaneous Physical Findings: Occasionally there may be general glandular enlargement in the older group of patients suffering from hemolytic anemia. This is usually not noted in early infancy.

Cardiac murmurs have been heard. These are probably so-called hemic murmurs due to the anemia.

Difficulties in development and infantilism have been reported, as well as skeletal deformities. However, these are due to the chronicity of the disease, and would not be expected in infants suffering from hemolytic anemia. The association of gallstones with this condition has been reported occasionally.

In older patients ocular lesions may occur, but have been in infancy.

8. Febrile and Hemolytic Crises: The crises which characterize the course of this disease may show different degrees of severity and different manifestations. Generally, the infant manifests prodromal symptoms, such as lassitude, lack of appetite, and fretfulness. This is followed by a deepened jaundice and an increase of anemia. Usually during these periods of crisis the spleen enlarges and the urine becomes dark. Abdominal pain and colic have not been characteristic of the condition in infancy.

Occasionally crises are initiated by febrile attacks and all the symptoms are magnified, and the infant may be extremely prostrated. When fever accompanies the crisis, the anemia is most severe. Periodicity in the occurrence of these hemolytic crises is the rule. The interval between crises varies considerably.

The extent of jaundice and anemia produced by single crises in the same individual will vary considerably from attack to attack.

9. Urine and Stool: The urine contains increased amounts of urobilin, which is especially noted following a crisis. Occasionally hemoglobinuria may be noted. The stools are normal but occasionally of a dark color. Acholia is never present.

*Treatment.*—The best temporary treatment following a crisis is a transfusion. In an acute crisis, where anemia is so severe that there is danger of anoxemia and

insufficient blood volume, frequent small transfusions must be resorted to, although the transfused blood seems to be much more rapidly hemolyzed when given during the crisis than when given during the interval.

Blood serum has been recommended, and one case here reported, in addition to transfusions during the crisis, also received 200 c.c. of human serum in 20-c.c. doses over a period of several weeks.

The only permanent and successful type of therapy is splenectomy. This operation was inaugurated by Banti in 1903 for this condition. Although the operation carries with it a certain risk, it seems wise to urge that it be performed, even in early infancy. The normal growth and development of the infant following operation, as well as the prevention of certain skeletal and developmental complications which occur during the chronic course of the disease, seem to more than counterbalance the operative risk.

It would seem well to advise the operating surgeon to search for any possible accessory splenic tissue at the time the spleen itself is removed. It has been reported occasionally following splenectomy that improvement resulted for a time and then symptoms returned. Upon second operation, a greatly hypertrophied accessory spleen has been removed. Permanent success, therefore, depends upon the removal not only of the spleen, but also of any accessory splenic tissue.

Following operation, certain changes occur, some of which have already been noted. The crises ceases. Jaundice lessens and usually disappears entirely. Occasionally a subicteric tinge remains, which is especially noted in the sclerae. The anemia rapidly improves, and the blood generally returns to normal. Rarely, following splenectomy, the platelet count rises, sometimes to a marked degree, but usually it subsides to normal range after a period of time. The reticulocyte count gradually drops to normal. Occasionally the microcytosis persists and the fragility of the red cells remains somewhat increased following operation. The increased signs of hemolysis quickly disappear following operation.

*Differential Diagnosis.*—In the newborn infant, hemolytic anemia must be differentiated from physiologic icterus, anemia of the newborn infant, and erythroblastosis fetalis, sepsis, and congenital syphilis. Congenital obstruction of the bile ducts and congenital hepatic cirrhosis will cause jaundice but not anemia of the hemolytic type. In the neonatal period an early-manifesting case of sickle-cell anemia or Cooley's disease might cause some difficulty in differentiation. When the progress of such an infant is followed and the recurring crises are noted, the differentiation is not too difficult for this condition. The only other condition in which increased fragility of the red blood cells has been noted is toluendiamine poisoning.

In those cases ushered in by an acute hemolytic crisis, one may first be in doubt whether he is dealing with the first attack of hemolytic anemia or whether he is confronted with a type of acute hemolytic anemia described by Lederer. Parsons recently stated that he has observed this latter condition in the neonatal period, although he states that the age incidence is usually above 6 months.

Debré notes that, in his opinion, conditions diagnosed as acute hemolytic anemia of the Lederer type turn out, after careful study, to be hemolytic crises in patients suffering from congenital hemolytic disease. He stressed the fact that final diagnosis of the Lederer type of anemia should be made only if, in the subsequent course, no further attack occurs.

*II. Erythroblastic Anemia of Cooley (or Mediterranean Anemia):*

This disease has been confined chiefly to infants whose parents have been born in Mediterranean countries. Bywaters, in 1938, reported a case of Cooley's syndrome in an English child, none of whose ancestors came from the Mediterranean countries. It is a familiar disease and may be suspected in the neonatal period when a definite diagnosis has been made in a preceding sibling.

The anemia develops insidiously and is usually not of any considerable degree until the latter half of the first year of life. The characteristic lemon yellow pigmentation of the skin, the mongoloid facies, and the characteristic bone changes revealed by roentgenologic examination do not manifest themselves until the anemia has progressed for some time.

In addition to the gradually developing anemia, the following blood changes are characteristic in a typical case of Cooley's anemia. There is usually a marked erythroblastosis accompanied by polychromatophilia, poikilocytosis, and anisocytosis. While there may be an occasional microcyte present, the macrocytic erythrocytes are the most abundant and typical of the condition. Most of these red cells are characterized by their abnormal thinness. Cooley has pointed out that the most characteristic type of red cell in this condition is a large, pale erythrocyte which is extremely thin and leaflike. He has shown that in wet preparations the edges may fold over and ridges may be formed, and the hemoglobin is distributed in clumps.

In Cooley's type of anemia, the resistance of the red cells to hemolysis is often of a considerable degree. As in hemolytic anemia, sternal puncture reveals an increase far above normal of the number of nucleated erythrocytes.

As the disease develops and the symptoms of anemia progress, the spleen enlarges and may reach great size, as may the liver. The skin assumes a subicteric tint, and occasionally a definite jaundice with yellowing of the sclerae may be manifested. The facies develop a mongoloid appearance which is produced by changes in the skull bones. The changes in the skull also do not appear until some time after the development of the anemia.

In the later stages the roentgenologic changes reflect the extreme marrow hyperplasia. The shafts of the long bones are widened and the cortex is thin. In late cases, the characteristic spicules, appearing as bristly hairs, are noted in a lateral x-ray of the skull. While these x-ray findings are characteristic of Cooley's anemia, it must not be forgotten that they may also be present in other anemias of long duration.

*Diagnosis.*—The following should be considered in the diagnosis: This is a disease of familial occurrence in infants and children of Mediterranean origin. There is progressive anemia, splenomegaly, Mongoloid facies, yellowing of the skin, and typical roentgenologic changes in the bones.

The blood picture is the chief diagnostic aid. In early cases erythroblastosis may not be as marked as later in the disease. Progressive changes in the blood, which include an increasing erythroblastosis, anisocytosis and poikilocytosis, and the peculiar thinness of the red blood cells, with the unequal distribution of hemoglobin, will confirm the diagnosis in a case which is followed for a long time.

Sickle-cell anemia has been observed in Greek and Italian children and must be differentiated from Mediterranean anemia.

*Treatment.*—No known treatment is recognized in this country as helpful to erythroblastic anemia. In reports from Greece of cases described as erythroblastic anemia in malaria-infested areas, the authors have been able to demonstrate malarial parasites in the blood; according to their accounts, the disease was cured by intensive antimalarial treatment (quinine, plasmochin, and atebrin).

One can only note that, while malaria may have been the causal factor of these cases reported in Greece, it does not apply to this country, for patients carefully studied in our clinics have never revealed malarial infestation.

*III. Congenital Aplastic (Aregenerative) Anemia:*

An increasing number of case reports on this apparently rare condition occurring in early infancy gives the impression that possibly the condition has been overlooked and that more cases will be recognized in the future. Apparently, the condi-

tion is of congenital or constitutional origin. The anemia usually manifests itself early in the newborn period and is characterized by its chronicity and the failure of all therapeutic attempts, except frequent blood transfusions, to relieve it.

In 1911, Benjamin described several cases of aregenerative anemia associated with other malformations in young children. He believed the anemia was on a purely functional basis. Finkelstein also noted in 1911 that there is a constitutional type of anemia in the newborn period. Stransky (1925) reported several cases of aregenerative anemia in early infancy. Hugh Josephs, in 1936, reported the cases of two infants suffering with a constitutional type of anemia. He noted an aplastic anemia which was apparently due to a failure of erythropoiesis which was so marked that the patient could be kept alive only by transfusions.

Recent interest in this condition was stimulated by the report of Diamond and Blackfan, who used the term "hypoplastic anemia" to describe the disease. They reported four cases of this type of anemia, beginning early in infancy, with no hemorrhagic tendency, moderate leucopenia, and the production of a small and inadequate number of reticulocytes from the bone marrow. The bone marrow smears revealed a reduction in the number of nucleated red cells, as recently shown in the case reported by Margrit Esser. Apparently, the aplasia is confined to erythropoiesis; the other cellular elements seen to be normal.

According to Diamond and Blackfan, two theories as to the etiology of this condition may be considered. One is that there may be a congenital insufficiency of the red bone marrow which fails to produce mature erythrocytes when needed; life can be sustained only by repeated transfusions of mature erythrocytes. The second theory has to do with an error in the metabolism of some blood building substances, which results in a deficiency state.

As has been noted, every form of therapy, with the exception of transfusion, has failed in the cases reported. No therapy stimulates hematopoiesis, and these infants are kept alive by substitute transfusions. Growth and development may proceed fairly normally in such an infant, if the transfusions are repeated. Some of these infants have made astonishingly good progress, even when fairly low levels of red cells and hemoglobin values were maintained, and these patients apparently adjust themselves to these lower levels without showing diminution in activity or in appetite, or other symptoms of anoxemia. I have seen one such case through the courtesy of Dr. Irwin Rubell of Chicago, and this child (as in one of the cases reported by Diamond) is now able to regenerate sufficient erythrocytes and hemoglobin to go without transfusions. The ultimate prognosis in this condition is extremely uncertain, and the only treatment is repeated transfusion.

*IV. Letterer-Siwe's Disease:*

This condition, occurring in early life, is characterized by anemia, generalized lymphadenopathy, splenohepatomegaly, hemorrhagic cutaneous manifestations, and osseous changes. The pathologic picture is characterized by widespread hyperplasia of the macrophages, without lipoid storage in the various organs. The condition is neither hereditary nor familial. All reported cases have occurred in infants or young children. The disease is of unknown etiology, with fatal prognosis, and duration varies from a few weeks to several years. It is a disease which involves the reticuloendothelial system and may be termed a reticuloendotheliosis.

Each author who attempts an analysis of this intriguing condition gives it a new name. E. Glanzmann, in April, 1940, reported the condition under the title of "Infectious Reticuloendotheliosis (Abt-Letterer-Siwe's Disease) and Its Relation to Schüller-Christian Disease." In September, 1940, Arvid Wallgren reported it as "Systemic Reticuloendothelial Granuloma (Nonlipoid Reticuloendotheliosis) and Schüller-Christian Disease."

The anemia is of a progressive, secondary type and usually manifests itself with a white blood cell count varying from a moderate leucocytosis to definite leucopenia.

The localized skeletal changes, as well as the cutaneous manifestations, have been shown pathologically to be due to proliferation of reticuloendothelial cells in the affected areas.

Wallgren's recent review seems to agree with our conclusions that infection does not play a causative role in this condition. The younger the patient at the onset of the condition, the more malignant the course will probably be. Both Glanzmann and Wallgren feel that Letterer-Siwe's disease and Schüller-Christian disease are different types of the same malady. The malignant type of the disease, with the short course, appearing in infants, is a nonlipoid reticuloendothelial hyperplasia. According to these authors, when the condition occurs in adults and older children, it runs a more protracted course; reticulum cells have time to ingest large amounts of cholesterol, and the foam cells typical of this type of the disease (Schüller-Christian type) predominate. In the malignant type occurring in infancy, where the anemia is rather severe and the disease is rapidly fatal, there is no treatment.

*V. Anemia Accompanying Infection:*

The anemias that are caused by and accompany the acute infections, especially the upper respiratory diseases, are probably the most common encountered in young infants. The anemia due to infection is not an entity, however, but merely a symptom, and will vary according to the direct or indirect effect the infection may have on the blood-forming organs. The infection may cause a diminished production of erythrocytes by a so-called toxic suppression of the bone marrow, or a diminution of erythrocytes by increased hemolysis, which would be termed a hemolytic anemia. There may, of course, be a combination of both mechanisms in any given case.

The anemia in these mild infections is usually of a slight and secondary nature, and will yield quickly as soon as the infection is cleared up. However, a succession of colds or upper respiratory infections may produce a more severe anemia; the anemia in turn aggravates the infection through lowered resistance of the infant, rendering him more susceptible and the infection more difficult to clear up. Thus, the more infection, the more anemia, and the more anemia, the more susceptible the infant is to infection.

It should be noted in this connection that as long as the active infection is in progress, it is extremely difficult to affect the anemia permanently by any form of therapy. It is only after the baby is afebrile and on the way to recovery from his infection that therapy will be at all effective.

*VI. Anemias of Nutritional Deficiency:*

The anemias of purely alimentary or nutritional origin have been long considered in etiological discussions as having an important place in the classifications of the anemias of infants.

We may recall that following the early hemolysis of red blood cells in the newborn period, a certain supply of available iron is present to meet the demands of rapidly increasing blood volume which corresponds to the general rapid growth in the infant in the first half year. We then realize that the building stones for new blood formation may be used up if new materials are not furnished in the diet. Two facts should be here noted. Mackay has observed that those infants with lower birth weights tend to have lower hemoglobin values as they develop. In other words, the baby with the lower birth weight is growing more rapidly and will therefore exhibit a greater demand for new blood formation than the heavier, more slowly growing infant.

Further, milk, both human and cow's, is low in iron content. As cow's milk contains less iron, it follows that artificially-fed infants tended to show lower hemoglobin curves than wholly breast-fed infants. Krasnogorski, in metabolism experiments, showed that the iron retention of infants on human milk was greater

than that of infants on cow's or goat's milk. It was formerly held that goat's milk anemia was caused by the same essential etiological factors as cow's milk anemia. Recently it was thought that a deficiency of the "extrinsic factor" present in liver and yeast might be responsible for the production of goat's milk anemia. This factor is a component of the vitamin B complex. While goat's milk is not entirely lacking in this "extrinsic factor," the fact that this anemia can be cured by liver and not by iron points to a deficiency of this component of the vitamin B complex as the causative factor in producing goat's milk anemia.

There is good evidence to believe that alimentary or nutritional anemia is caused by a simple insufficiency or lack of blood-building material, especially iron, in the diet. The older theories proposed, such as hereditary predisposition, injurious products in cow's milk (fat injury of Czerny), lack of fresh air and sunlight, and functional weakness of blood-forming organs, need no longer be considered.

Just as other imbalances in infant nutrition may produce disturbances, it can be said that alimentary anemia is not directly due to an injurious effect of cow's milk or any of its constituents. The same anemia may develop in an exclusively breast-fed infant.

The whole nature of the process depends on the proper supply of the necessary blood-building materials, which the infant on an exclusive, long-continued milk diet lacks. The error is not one of commission, but rather one of omission. It is not what we are giving the infant, but what we are failing to give him, that is causing the anemia.

The early addition to and the balancing of infant diets, which is becoming more and more of common usage and knowledge, is greatly reducing the incidence of pure alimentary anemia.

*VII. Anemia of Scurvy:*

In reports of adults suffering with scurvy, anemia is a common complication, and the vitamin C deficiency is supposedly responsible for this anemia. However, in reports of scurvy in the infant, anemia is not constantly associated with scurvy. According to Hans Aron, it is often difficult to determine whether one is dealing with a scurvy accompanied by an anemia or with an alimentary anemia complicated by scurvy. In recent experiments with guinea pigs, Aron was able to show that anemia did not develop in young guinea pigs weighing approximately 250 Gm., on a scorbutic diet. On the other hand, when adult pigs weighing approximately 400 Gm. were made scorbutic, anemia regularly developed. We may conclude, therefore, that when anemia accompanies infantile scurvy, the anemia is not due to a deficiency of vitamin C per se, but that other elements as iron and protein are probably also lacking in the infant's diet. In adult scurvy, however, a lack of vitamin C probably has some direct connection with the production of the accompanying anemia.

*VIII. Anemia Due to Drugs:*

A severe aplastic anemia may accompany the administration of certain drugs such as arsphenamine, nirvanol and other coal-tar products, and sulfanilamide. Poisoning with lead and benzol may cause severe aplastic anemia. Exposure to x-ray and radium may also produce an aplastic anemia.

These anemias due to drug poisoning may clear up rapidly if the drug is withdrawn. On the other hand, the anemia may persist with great stubbornness if serious damage has been done to the bone marrow. The blood changes following administration of sulfanilamide and related compounds are of special interest at present. A slight rise in the reticulocyte count level has been reported following the administration of sulfanilamide. Severe hemolytic anemia may follow administration of even small doses of sulfanilamide. Leucopenia may develop, and agranulocytosis and granulocytopenia have also been reported.

It should be emphasized that frequent blood counts should accompany the administration of these drugs, and the drug should be immediately discontinued when unfavorable response of the bone marrow is noted from the blood count.

One should also remember that if a patient has once had a leucopenia with an acute hemolytic anemia or a purpura hemorrhagica in the course of therapy with sulfanilamide or its derivatives, it is quite likely that, if the drug is administered a second time, the patient may have another earlier and probably more severe toxic reaction. Patients who have had a toxic reaction with one of the sulfanilamide derivatives may have a similar reaction with another member of the group. A careful history as to previous toxic manifestations due to sulfanilamide and its derivatives should always be elicited before the drug is started, and care should be used when changing from one derivative to another if toxic manifestations have followed the use of one derivative of the sulfanilamide group.

Time does not permit a separate discussion of the specific anemias associated with malaria, hookworm, and *Bothriocephalus latus* infections, and those accompanying rheumatic fever, syphilis, and other infections and diseases.

DISCUSSION

DR. COOLEY.—In certain families there is a hemolytic constitution. This occurs as a dominant characteristic, and if either parent has it, the children will. In recent years Cooley's disease has been found not to be confined to the Mediterranean races, although formerly it had been so reported.

DR. H. W. DARGEON, NEW YORK CITY.—Is there any evidence that a deficiency in vitamins other than the "extrinsic factor" might be a cause of goat's milk anemia?

CHAIRMAN ABT.—There might be a vitamin B deficiency.

DR. BRADLEY.—How important is it when giving sulfanilamide and allied drugs to check up on the infant's blood for evidence of anemia?

CHAIRMAN ABT.—One should be on the lookout for clinical signs of anemia, and the blood should be examined if the drug is given over any length of time.

DR. COOLEY.—Results with sulfanilamide should be obtained rather quickly if at all, so the drug should not be continued too long if no benefit is noted.

# Academy News

Dr. Henry L. K. Shaw, of Albany, N. Y., died March 26 of heart disease, after a brief illness. Dr. Shaw initiated and organized the division of child hygiene of the New York State Department of Health, the first state department of its kind. He has been interested in all pediatric organizations in this country, particularly the American Child Hygiene Association. He was president of the American Pediatric Society in 1929, at its St. Louis meeting.

Region II of the Academy will meet at the Hotel John Marshall, Richmond, Va., on April 24 and 25, 1941. There will be round table discussions on Mental Health of the Child, Nutrition of the Child, and Communicable Diseases and Their Relation to the Child, all as related to national defense.

Region IV of the Academy will meet at the Fairmont Hotel, San Francisco, on May 1-3, 1941. There will be four scientific sessions consisting of papers, case reports, and panel discussions during the mornings and afternoons of May 2 and 3. In addition, two other features have been added to the program: first, a pre-session