THE CANADIAN MEDICAL ASSOCIATION

LE JOURNAL DE

L'ASSOCIATION MÉDICALE CANADIENNE

NOVEMBER 20, 1965 • VOL. 93, NO. 21

Physiological Adaptation to the Placental Transfusion:

The Eleventh Blackader Lecture

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I CONSIDER it a great honour to have been invited to address this assembly on the present occasion. Too great an honour, in fact, to be carried by one man —and I am therefore happy to be able to share it with several associates. In this particular context it is of course particularly satisfying that so many of these associates of mine are Canadians: Dr. Robert Usher of McGill Univerity and Drs. Wanda Jegier and Leo Stern of the Children's Hospital, Montreal. You might almost think I was addressing the "Association for Swedish-Canadian Collaboration" or the "Society for the Exploitation of Canadian Labour in Sweden". But since this is a lecture for The Canadian Medical Association, the first thing was to select a subject from our research work that might prove of general interest. Such a subject was not difficult to find; something we all have in common, a dramatic event, an exciting process, something we all go through—birth.

Many people, for different reasons, decide to start life afresh. In most cases the new life turns out to be little different from the old. There is, however, one occasion when each of us starts a new life quite different from the old. I refer, of course, to the transition from fetal life to extrauterine life that takes place at birth.

At the moment when a new world-citizen is born and lies there, joined to the mother *via* the umbilical cord, we are dealing with a fetus. A few dramatic seconds, and then comes the first breath, indicating that a fetus has become a child and has started to live an independent life. It also indicates the start of a tremendous readjustment within the organism. The fetus lived in a warm environment, while the child must cope with our chill surroundings. For nine months it has lived in water; now it must live in air. It received all its oxygen and nourishment through the placenta; now the lungs and the gut must take over. The circulation, formerly arranged in parallel, must now run in series.

During these seconds between birth and the first breath, this interval which Professor Clement Smith of Boston has termed "a period of grace", what actually happens? Is it an important period, when a mass of preparatory mechanisms start to function? Mechanisms to prepare the start of respiration and the adjustment of the circulation? We do not know much about this, but we do know that a mass of processes are initiated with the birth of the fetus. Some of these processes promote life, while some *may* be injurious for the child. Until we know more, our attitude must be that of a passive observer.

The field of research involved here is extremely important, in view of the number of children who never manage to adapt to extrauterine life. We need to find out what it is that happens during this "period of grace", what effects the different processes have on the child, and then translate these findings into practical measures for the pediatrician, the obstetrician and the anesthesiologist.

We are now studying *one* problem that represents all of these things that take place in what appears to be an uneventful period. We have studied placental infusion, that is to say, the transfusion of blood from the placenta to the child immediately after birth.

The Umbilical Circulation and Placental Development

Throughout gestation the fetus leads an aquatic existence submerged in the amniotic fluid and totally dependent upon its mother for existence through a special organ of interchange — the placenta. Here gas exchange takes place, food in soluble form enters the fetal circulation and fetal nitrogenous waste material is turned over to the maternal blood for elimination through the mother's kidneys.

In the placenta the fetal and maternal circulations are anatomically and functionally interdependent, and the normal growth of the placenta is essentially a co-ordinated development of the two vascular systems. These two systems are only side channels of their respective systemic circulations and naturally the volume of blood passing through either fetal or maternal circuits is independent of that which goes to the other tissues of the fetus or mother. This arrangement, which is

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Presented at the Ninety-Eighth Annual Meeting of The Canadian Medical Association, Halifax, N.S., June 16, 1965.

reminiscent of the blood supply to the respiratory organs in lower animals, is less advantageous than that present in postnatal life, whereby each time blood circulates through the body, corresponding gas interchange, namely oxygen uptake and carbon dioxide elimination, occurs in the lungs.[1]

The current concept about the human fetal circulation assumes that the most highly oxygenated blood is to be found in the umbilical vein which transmits blood from the placenta into the ductus venosus, inferior vena cava and then to the heart. The major portion proceeds directly into the left heart through the foramen ovale, and goes to the ascending aorta to be distributed mainly to the head, the coronary arteries and the arch of the aorta. The other portion of the inferior caval blood is joined in the right atrium by reduced venous blood coming from the coronary sinus and from the superior vena cava which brings blood back from the head and upper extremities. From the right atrium, the blood goes to the right ventricle and then into the pulmonary trunk. Most of it is shunted through the ductus arteriosus to the descending aorta and returns to the placenta through the two umbilical arteries.[2] Only a small portion — about 12% in sheep fetuses at term[3]—goes to the lungs, which in fetal life are "sleeping", have no respiratory activity and do not contain any air. The resistance to blood flow in the pulmonary circuit is very high, and most of the blood in the pulmonary trunk bypasses the lungs by way of the ductus arteriosus. Both ventricles thus work in parallel and pump blood to the placenta, which behaves as a low resistance circuit placed parallel with the fetal tissues, both systemic and pulmonary. More than 50% of the combined output of both ventricles passes through this route.[3]

The distribution of blood in the feto-placental vascular system is constantly changing throughout pregnancy. From observations made in the sheep and goat during the second trimester, the quantities of blood in the placental and fetal beds are nearly equal. At term, the amount of blood in the fetus is three to four times greater than that in the placenta.[4] It is suggested by these studies that once the cotyledonary structure of the placenta is complete, which should correspond to the end of the sixth month of human gestation, the volume capacity of the placental beds remains fairly constant. It would appear that the later increase in blood volume of the fetal circulation is confined mostly to the enlarging vascular bed of the fetus.

According to Dawes,[3] the mean umbilical blood flow in fetal lambs increases considerably throughout pregnancy. He has calculated the resistance of the placental vascular bed from measurements of umbilical vein flow (using an electromagnetic flowmeter) and of femoral arterial and umbilical venous pressures. It appears from these studies in sheep that the increase in umbilical flow between 90 and 115 days is mainly caused by a fall in vascular resistance, and between 115 and 140 days by a rise in fetal arterial pressure.

In the fetal lamb at term, flow through the intra-abdominal portion of the umbilical vein averages 132 ml./kg./min. These values (about two-thirds of the fetal cardiac output) correlate well with those previously reported in human fetuses[5] and lend support to the supposition that the umbilical flow may be a relatively constant function of the cardiac output throughout the latter half of gestation.

THE PASSAGE OF THE FETUS THROUGH THE BIRTH CANAL

When the full-term pregnant human uterus has a normal volume, i.e. between 4 and 5 litres, the tonus, or lowest pressure between the contractions, is of the order of 10 mm. Hg and the rise in pressure caused by the contractions is about 50 mm. Hg. During its passage through the birth canal the fetus is compressed and stretched. Recording of the intraesophageal pressure in newborn infants during the delivery of the body has shown considerable positive pressure in the thorax, 22 to 95 cm. H_2O.[6]

PHYSIOLOGICAL EVENTS AFTER DELIVERY AND BEFORE THE ONSET OF BREATHING

When the body is delivered, the thorax recoils towards its former shape and in so doing the volume lost during the squeeze tends to be replaced. Air is sucked into the upper airways,[7] and it is conceivable that there may be also sucking of blood into the thoracic cavity from the placental pool. The intraesophageal pressure drops to almost zero immediately after delivery, i.e. equal to the atmospheric pressure.

When the pregnant human uterus has delivered the fetus and expelled the amniotic fluid so that only the placenta remains inside the uterus, the intrauterine volume becomes greatly reduced to about 0.5 litre.[8]

The intrauterine pressure can now be recorded in the umbilical vein, and the placenta behaves like an intrauterine balloon with the umbilical vein in continuity with this balloon and enabling pressures to be obtained with a recording manometer if the cord is clamped. The pregnant uterus has a greater capacity to reduce its volume considerably following delivery, which enables it to exert enough pressure upon the placenta. After the fetus is delivered, the uterus thus continues to produce strong rhythmical contractions. Each contraction causes a rise of about 60-70 mm. Hg in the intraplacental pressure, which forces the fetal blood from the placenta to the newborn at the same time as it prevents blood from the umbilical arteries from entering the placenta. The frequency of these contractions diminishes progressively. The tonus between the contractions is only slight-

ly lower than that existing before delivery of the fetus.[8]

The pressure in the umbilical vein, if not clamped, is a non-pulsative one which decreases progressively after birth. Values obtained at about 10 seconds after the first breath ranged from 15 to 50 mm. Hg and at around 100 seconds from 10 to 20 mm. Hg.[9] There is thus a high pressure gradient between placenta and the child, which will favour transfer of blood to the child. To this gradient must be added the hydrostatic pressure in the umbilical vein, depending on the difference in level between the placenta and the child after delivery.

INITIATION OF BREATHING

When the newborn infant starts to breathe, the aeration of the lungs is effected by the forceful contraction of the inspiratory muscles, mainly the diaphragm. During inspiration there is a negative intrathoracic pressure of 20 to 70 cm. H_2O.[10] Obviously the effect of a sudden negative pressure in the thorax will be a "sucking" of blood as well as of air into the thoracic cavity. Another factor of probable importance is the establishment of surface tension in the alveoli. As surface tension forces would tend to collapse alveolar walls, they may also be expected to have an opposite mechanical effect on the interjacent capillaries. With the aeration of the lungs the resistance in the pulmonary circuit drops, the pulmonary flow increases and the pressure in the pulmonary artery falls. In newborn lambs, the blood content of the lung, derived from the blood hemoglobin concentration and the total iron content of the lungs, increases two-fold after the onset of respiration.[11] This result is comparable to the increase previously found in guinea pigs using the same method and using radioactive iron as a tracer.[12]

SEPARATION OF THE NEWBORN BABY FROM THE PLACENTA

Under natural conditions of mammalian birth, the expulsion of the placenta follows a short time after that of the fetus. The continuity of the cord between the fetus and the placenta is uninterrupted, unless it is torn during the act of expulsion or is bitten off by the mother. No one ligates the umbilical cord. The newborn rests at the feet of the mother if the latter is standing, or below the vulva if the mother is lying down, and probably a portion of blood comes over by gravity from the placenta to the newborn. When ultimately severed, the cord is unligated. According to veterinary obstetrics no important hemorrhage follows the division of the cord.[13]

In the early history of human reproduction, as evidenced in the customs of primitive tribes, the cord was severed by rubbing it between rough stones.

Following a natural birth, many factors combine to ensure an effective closure of the umbilical vessels. The vessels of the cord are devoid of innervation but are relatively quickly closed by the contraction of their muscular walls. The umbilical arteries usually cease to pulsate within five to 10 minutes after birth. The umbilical vein tends to remain distended for a variable period of time depending on the amount of blood that enters from the placenta. The vascular musculature, especially that of the arteries, contracts from exposure to mechanical, chemical and thermal stimuli. These vessels contract when perfused with blood of high oxygen tension and relax when the carbon dioxide content of the perfusate is increased. With the onset of breathing the oxygen content of blood flowing through these vessels rises, which would also tend to promote their closure. Backflow in the umbilical vein is prevented, presumably by the natural constriction of the vessels near the umbilicus and the functional closure of the ductus venosus. Tying of the umbilical cord was not employed until ligation techniques became common practice in surgery. The umbilical cord presented an inviting site for surgical procedure, and the currently common custom of immediate severance and immediate ligation of the cord followed. Ligation of the cord contributed to more rapid care. Whether it has added to the ultimate welfare of the newborn infant is a question.[14] It effectively eliminates the dangers of bleeding, but when should the ligation be carried out? In actual practice, the timing of ligation of the cord is a matter of great variation, and it has been a common opinion that there is no proof that the infant may be harmed by any procedures of clamping the cord. Lately the management of the cord has become a matter of lively controversy. Some obstetricians now insist upon waiting until the pulsation has ceased, 15 to 20 minutes after delivery, stating that immediate clamping has several ill effects: it interrupts the chain of physiologic events and it interferes with the return to the fetal circulation of a substantial amount of blood which would otherwise naturally find its way into the fetal circulation.[14] Stripping of the cord in the direction of the baby has been advocated in order to increase the baby's blood volume and his iron stores.[29] This method has, however, been considered dangerous by others. Each stroke is said to bring about 10 to 15 ml. of blood into the fetal circulation, which might have difficulties in accommodating this blood so abruptly.

Saling[15] has recently recommended the clamping of both umbilical arteries at birth and then waiting one and a half to two minutes before cutting the cord in order that no blood may be transported from the baby back to the placenta. This method should guarantee the baby a large placental transfusion and at the same time avoid unnecessary cooling of the infant.

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THE BLOOD VOLUME OF THE NEWBORN INFANT AND PLACENTAL TRANSFUSION

Discussions pertaining to the question of when to clamp the cord suffer from lack of knowledge of the blood volume of the newborn infant, the size of the placental transfusion and its consequences for the adaptation of the newborn infant to extrauterine life.

Thus previous studies of neonatal blood volume have shown an exceedingly wide range of individual values, from 55 to 150 ml./kg.[16, 20]

The role of placental transfusion in the size of the blood volume of the newborn is disputed. Numerous studies[21-23] have shown that there is an increase in weight of about 100 g. during the first five minutes of life when the cord is left unclamped. Measurements of blood volume by DeMarsh, Windle and Alt[16] demonstrated the red cell volume to be 40% greater when the cord was clamped late rather than early. More recent studies,[24] however, found no difference in red cell volume when the cord was clamped early or late, although higher values were obtained when the cord was stripped.

There is disagreement also about the change in blood volume following birth. Gairdner *et al.*[25] have reported that the hematocrit rises immediately after birth. They concluded that this rise in hematocrit is evidence of a decrease in blood volume due to plasma transudation. Sisson and Whalen,[26] on the other hand, have found an increase in both blood volume and hematocrit during the first hours of life, suggesting an influx of concentrated blood from a storage reservoir such as the liver. More recently, Steele[20] has reported that blood volume decreases proportional to the level of the hematocrit. In none of these reports was consideration given to the possible effect of placental transfusion on the change in blood volume after birth.

Our first investigation was designed to measure the blood volume of the normal full-term infant at intervals after birth, and to changes in blood volume after birth.

The subjects of this study, as well as of all others discussed in this paper, were full-term normal newborn infants born to healthy mothers after an uncomplicated gestation, labour and vaginal delivery with cephalic presentation. The infants were delivered between the 38th and 42nd week of gestation, and weighed 2600 to 4600 g. at birth. The mothers received no analgesia or anesthesia, except in about 10% of cases, in which the mothers received short periods of intermittent nitrous oxide inhalation. The infants were delivered on to the bed on which the mother was lying and the infants lay about 10 cm. below the level of the introitus until the cord was clamped. All were breast-fed after a 12-hour fast. The infants were admitted to one of three study groups depending on how the umbilical cord was clamped. *Immediate*: In nine infants the cord was clamped early, within 10 seconds of delivery. *Delayed*: Eleven infants were clamped after pulsation ceased, about five minutes after delivery. *Delayed clamping and stripping*: In seven infants the cord was stripped firmly towards the infant once every 30 seconds for five minutes and was then clamped.

Measurements of blood volume were made four times on each infant, at the ages of approximately one-half, four, 24 and 72 hours. A dilution technique was employed, using I^{131}-tagged human albumin in a dose of 0.2-0.5 microcuries per determination.

The Volemetron counter[27] was used to measure radioactivitiy. The final reading is mechanically calculated and expressed as ml. blood volumes by a simple dilution formula.

The total error of the method, including sampling, dose administration and counting, was determined by duplicate measurements of blood volume made at one-half hour intervals in 24 infants. The error of the method, $\sqrt{\Sigma(d^2)/2N}$, was found to be 4.1%.

BLOOD VOLUME AND ITS ACCOMMODATION AFTER BIRTH

The blood volume of infants with delayed cord-clamping was measured as 100 ml./kg. at one-half hour, 90 ml./kg. at four and 24 hours, and 90-95 ml./kg. at 72 hours (Fig. 1). Ten of the 11 infants

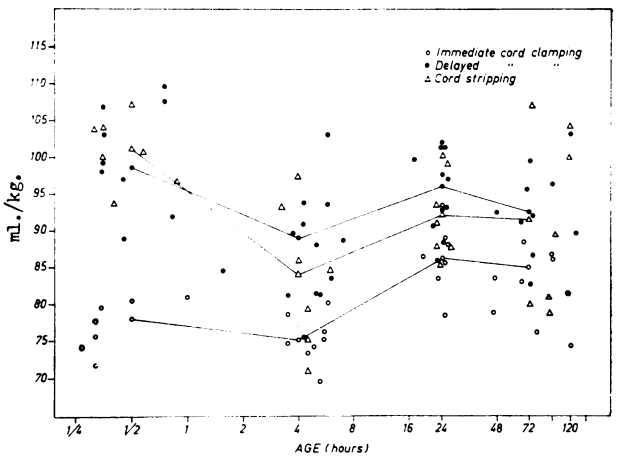

Fig. 1.—Scattergram of serial measurements of blood volume in nine infants with immediate cord clamping, 11 infants with delayed cord clamping, and seven infants with delayed clamping and stripping, including mean values and standard error of the mean.[33]

had a decrease in blood volume between one-half hour and four hours, and an increase between four and 24 hours. Cord stripping did not significantly augment this transfer of blood.

The blood volume did not change during the first hours of life following immediate cord clamping, but in infants with delayed cord clamping there was a decrease during the first four hours, presumably due to transudation of fluid. Between four and 24 hours of age there was an increase in plasma volume in all but two infants, averaging 20 ml. per infant, which was not related to the method of cord-clamping. Infants with immediate cord clamping had a measured volume significantly lower than those with delayed cord clamping

for all but the 24-hour determination. There was no tendency for blood volume to decrease between one-half and four hours of age with immediate clamping, although all nine infants had an increase in blood volume between four and 24 hours.

VENOUS HEMATOCRIT

The venous hematocrit rose in infants with delayed cord clamping from 59% by one-half hour to 64% by four hours. It then fell to 61.5% and 60% at 24 and 72 hours. Hematocrit values were similar in infants whose cords were stripped.

Infants with immediate cord clamping showed no rise in hematocrit after birth; the estimated cord-blood hematocrit and the one-half hour and four-hour measurements were all about 48%. The hematocrit then fell to 44% at 24 and 72 hours.

PLASMA VOLUME

Infants with delayed cord clamping had plasma volumes of 50 ml./kg. at one-half hour which then decreased to 40 ml./kg. at four hours. Following this, it increased to 45 ml./kg. at 24 and 72 hours. Plasma volumes obtained after cord stripping were essentially similar.

With immediate cord clamping the plasma volume at birth was estimated at 45 ml./kg. and did not change.

RED CELL VOLUME

Delayed cord clamping resulted in a red cell volume of 50 ml./kg. at one-half hour of age (Fig. 2). This was 60% larger than the 32 ml./kg. red cell volume found after immediate cord clamping (P — 0.001). Infants whose cords were stripped had red cell volumes similar to those with delayed clamping.

There was no appreciable change in red cell volume per kg. body weight during the first 72

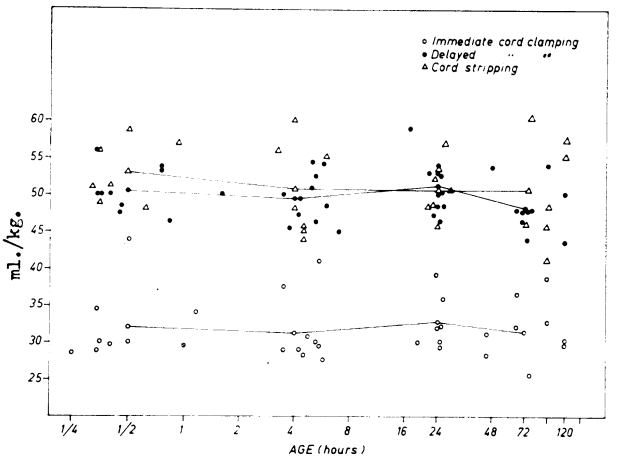

Fig. 2.—Scattergram of serial measurements of red blood cell volume in nine infants with immediate cord clamping, 11 infants with delayed cord clamping, and seven infants with delayed clamping and stripping, including mean values and standard error of the mean.[33]

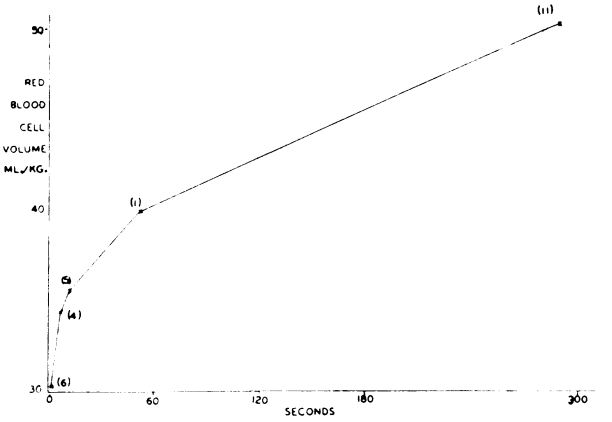

Fig. 3.—Rate of placental transfusion as indicated by average red blood cell volume at one-half hour of age following cord clamping at different intervals after birth. These include the 20 infants who comprised the immediate and delayed cord clamping groups, with the addition of seven more infants whose cords were clamped at varying times during the first minutes of life. The figures in parentheses indicate the number of infants studied during each time interval.[33]

hours of life in any of the 27 infants. There was a correlation between hematocrit and red cell volume (P — 0.001) which could be approximately expressed as follows: red cell volume (ml./kg.) = hematocrit (%) — 12.

Analysis of red cell volumes obtained when the umbilical cord was clamped at different intervals after birth suggests that *the rate of the placental transfusion* is exceedingly rapid during the first seconds of life and then becomes progressively slower (Fig. 3). One-quarter of the placental transfusion, or about 40 ml. of blood, enters the infant within 15 seconds, and one-half (80 ml.) within 60 seconds after birth.

These findings indicate that it is difficult to prevent an infant who is delivered normally from receiving a placental transfusion unless the cord is clamped the moment the umbilicus is delivered. Perhaps such terms as "early" and "late" clamping had better be avoided unless they are specified with respect to the timing. The findings also indicate that objective documentation of the presence or absence of a placental transfusion should be an integral part of every clinical study of the effect of placental transfusion.

This investigation demonstrated the wide individual variation which was found in the previous studies of blood volume in time of cord clamping and therefore in the amount of placental transfusion.

THE RESPIRATORY ADAPTATION TO EARLY AND LATE CORD CLAMPING

The results of this study demonstrate that there is a significantly large placental transfusion at birth. To explore the significance of the increase in blood volume during the first minutes of life and to investigate the effects of its deprivation we instituted studies of the respiratory adaptation to early and late cord clamping.[28]

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Sixty-two full-term newborn infants were studied, of whom 32 were clamped early (mean time of clamping was 7.6 seconds after birth [range: 1-36 seconds]) and 30 infants were clamped late (mean time 3 minutes 34 seconds [range: 2½-5 minutes]).

Among the infants who were clamped early the *mean time of onset of the first breath* was 6.3 seconds (standard error of mean: 0.60 second). The infants who were clamped late had a mean onset of their first breath at 9.2 seconds with a standard error of the mean of 1.3 seconds. The difference was statistically significant. The earlier onset of respiration in the infants clamped early may be due to an earlier fall in blood oxygen saturation and corresponding elevation of carbon dioxide content resulting from the early interruption of placental circulation.

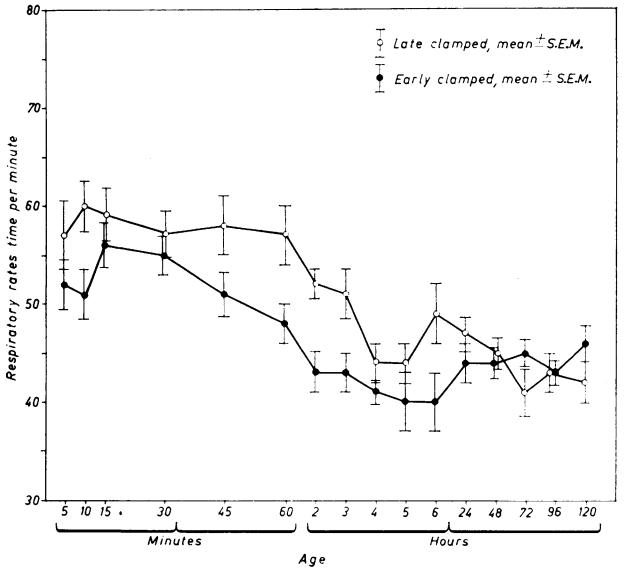

Fig. 4.—Respiratory rates of 25 late clamped and 25 early clamped infants during the first five days of life.[28]

Both groups of infants had *respiratory rates* of 51-60 per minute during the first hour of life (Fig. 4). However, in contrast to the infants who were clamped early, amongst whom the respiratory rate decreased to 48, 43 and 43 per minute at one, two and three hours of life, the group of infants who were clamped late continued to breathe at rates of 59, 52 and 51 per minute at one, two and three hours of life, respectively. The differences in respective rates at these ages between the two groups were significant ($p < 0.05$). Thereafter, the respiratory rates of the two groups of infants were similar. The differences in respiratory rates between the two groups from one to three hours of age occurred at the time when capillary fluid transudation is presumably maximal, as shown by the simultaneous venous and capillary hematocrit measurements in the infants who were clamped late. We suggest that infants allowed maximal placental transfusion at birth adjust to the vascular distension by a process of fluid transudation from the capillary bed. It is possible that such a process may occur in the pulmonary capillary bed, resulting in some degree of pulmonary edema and thus a faster respiratory rate. It should be pointed out, however, that respiratory rate alone, without supplementary data concerning tidal volume, is not adequate to permit valid conclusions. Differences in some of the physical properties of the lungs of newborn infants subjected to late and early cord clamping may be elucidated by further studies of pulmonary compliance and resistance.

THE CIRCULATORY ADAPTATION TO THE PLACENTAL TRANSFUSION

The influence of changes in blood volume upon circulation has been studied to some extent in man. Although most investigations on the hemodynamic consequence of changes in the blood volume have been concerned with hypovolemic states, there are some reports on the effects of hypervolemia.

From the literature it seems clear that the circulatory system of a healthy man in supine position is capable of adapting easily to a change of ±20% of the blood volume. In most instances, the systemic pressures are only moderately affected and cardiac output is maintained, whereas the pulmonary circuit is more sensitive to these changes.[29]

Wallgren, Barr and Rudhe (29), working with us, studied the effect of acutely induced hypovolemia and hypervolemia in 16 erythrcblastotic infants prior to exchange transfusion. Blood volume changes were induced by the stepwise withdrawal or addition of approximately 25% of the estimated blood volume. The withdrawal was followed by an average decrease in heart size of 30% and a pulse acceleration of 40 beats per minute. The average drop in the right filling pressure was 5 mm. Hg. Pulmonary as well as systemic pressures fell to approximately half of the initially observed value. Restitution of initial blood volume immediately normalized all values. Hypervolemia was accompanied by an average increase in heart size of 18%. Systemic pressures rose on an average by 20-25% while the two observations on pulmonary artery pressure revealed an increase of approximately 100% during hypervolemia.

The marked effect on systemic blood pressure, in contrast to the cited findings in adult man, suggests that the circulatory system of the newborn infant is less adaptive. The relative inability of the cardiovascular apparatus to cope with hypervolemic and hypovolemic conditions reported here is also reflected in the marked changes in the right heart filling pressure which, together with the impressive changes in heart size and pressures of the systemic as well as pulmonary arteries, indicate an effect on the altered blood volume.

These observations on adults and on babies subjected to exchange transfusion do not permit

any direct conclusions concerning the infant's adaptation to the placental transfusion at birth. Immediately after birth the newborn baby reacts differently than he does some hours later. Furthermore, the placental transfusion is a unique experience in life, which to my knowledge has not been reproduced experimentally. During the first minute of life about 80 ml. blood is transfused into the baby. If this amount were magnified to adult dimensions, the corresponding volume for a 60-kg. adult would be 1600 ml. in a minute!

How does the newborn baby react to this transfusion? Does the placental transfusion represent a massive overexpansion of the infant's circulation involving the risk of heart failure? What happens when the baby is deprived of this transfusion? As the central hemodynamic event at birth is the opening up of new vascular beds in the lungs at the initiation of breathing, clamping of the cord might obviously lead to hypovolemia with the potential danger of hypovolemic shock.

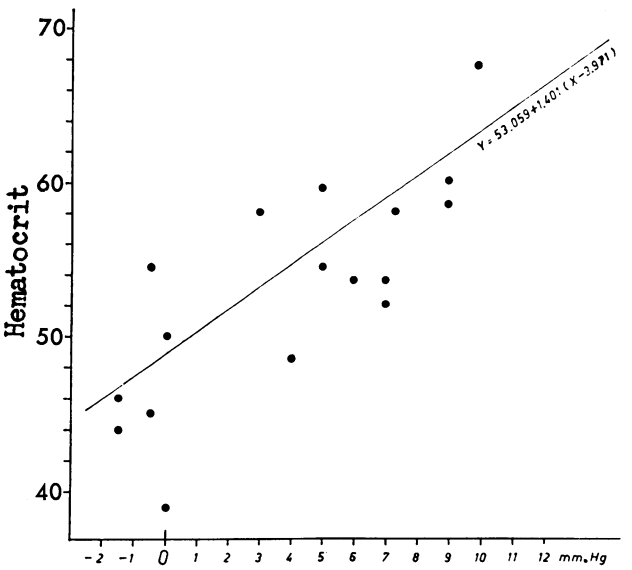

Fig. 5.—Central venous pressure in mm. Hg on the abscissa and corresponding hematocrit values on the ordinate. Correlation coefficient r = 0.76.

We began our circulatory studies by determining the central venous pressure in the first hour of life and investigating its relationship to placental transfusion[30] (Fig. 5). Later, right and left atrial pressures were obtained on newborn infants up to the age of 14 hours. The pressure in the inferior vena cava was studied in the first hour of life, in 24 normal, full-term, newborn infants with varying amounts of placental transfusion. During the first hour, the pressure in the central venous system varied with the amount of placental transfusion. The central pressure observed in infants who received a large amount of placental transfusion (10 infants) ranged between 0 mm. Hg and 10 mm. Hg, with a mean of 5.7 mm. Hg. The pressure in the group receiving a lesser amount of placental transfusion (seven infants) ranged between 1.5 mm. Hg and 5 mm. Hg, with a mean of 1.7 mm. Hg. According to Bonham-Carter *et al.*,[31] the mean venous pressure in normal newborn babies during the first 18 hours is 2.0 ± 0.9 mm. Hg. This pressure difference between the two groups of subjects was also observed in the left atrium. However, by the second hour and thereafter, these differences were no longer observed.

Ashworth and Neligan[32] measured the blood pressure changes almost immediately after birth and demonstrated a decline in systolic blood pressure during the first 24 hours of life. They also showed that the blood pressure level of the infants whose cords were clamped early declined more rapidly than did that of infants who were clamped late, although the magnitude of fall was the same.

We made similar observations on 25 infants from the group who were clamped early and on 25 infants from the group who were clamped late.[28] Systolic blood pressure and pulse rates were measured at five, 10, 15, 30, 45 and 60 minutes of age, and then hourly for the first six hours. These determinations were repeated at 24, 48, 72, 96 and 120 hours of age. The systolic blood pressure was measured by a two-cuff xylol indicator with one-inch cuff technique, described by Ashworth and Neligan,[32] with a slight modification.[33] All determinations were done five times in succession on the extended right upper extremity, with the infants in supine position and kept in a quiet state. Pulse rates were determined by directly counting the movement of the xylol columns on the sphygomanometer.

Our observation of a high systolic blood pressure at five minutes of life followed by a rapid decline during the first six hours and subsequent rise in the second day in the infants whose cords were clamped late is in conformity with the observations of other workers[32, 33] (Fig. 6). In the group who were clamped early, however, our results demonstrated that the systolic blood pressure starts at a much lower level than in the infants clamped late, and is followed by a slight rise during the first 15 minutes of life. Thereafter it remains at a slightly lower level than that of the infants who were clamped late (Fig. 6). Differences in blood volumes and red cell volumes constitute the basic effect of early and late cord clamping.[34] It is likely that the systolic blood pressure differences found between the infants whose cords are clamped early and those who are clamped late, are in large part due to the differences in their blood volumes.[29, 35, 36] The positive correlation between systolic blood pressures and simultaneously determined venous hematocrits during the first four hours of life further supports this assumption, since venous hematocrit has been shown to correlate well with blood volume.[34]

We were also interested to find out to what extent the hemodynamic effects of early and late clamping of the cord were reflected clinically in

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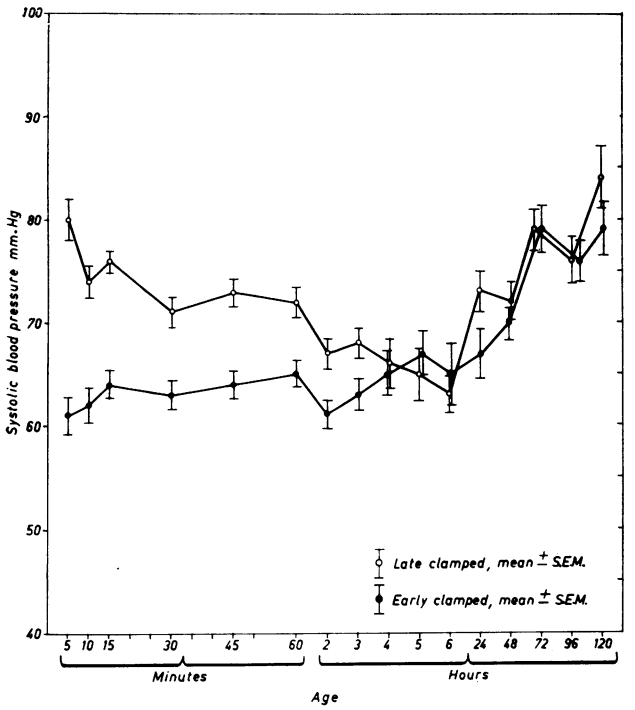

Fig. 6.—Systolic blood pressure of 25 infants whose cords were clamped late and 25 infants who were clamped early, during the first five days of life.[28]

the form of cardiac auscultatory findings during the early neonatal period.[38]

Phonocardiograms were obtained serially from 59 normal full-term newborn infants commencing immediately after birth and repeated at frequent intervals during the first hour, during six to 12 hours, and daily thereafter until their discharge four to seven days later. Clamping of the cord was performed immediately (within a few seconds) in 13 infants, whereas in the other 46 cases it was done after three to five minutes following delivery.

The tracings of the infants whose cords were clamped late differed in some respects from those of the group who were clamped early. During the first 24 hours a comparatively wider splitting was observed in the group who were clamped early

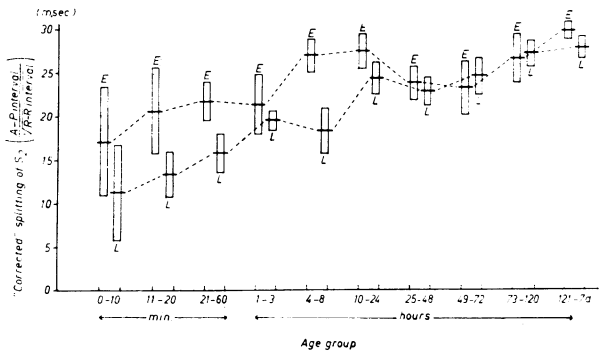

Fig 7.—Comparative splitting of the second heart sound in newborn infants whose cords were clamped early and in those who were clamped late. The graph shows the mean values joined by the dotted lines (and the range of 1 SEM) after "correction" for heart rate in the various age groups. (E = early-clamped group; L = late-clamped group.) (Corrected for heart rate.)[38]

(Fig. 7). The incidence of murmurs in this group was also higher. These differences appear to be related to an earlier drop in the pulmonary artery pressure in the group who were clamped early, as has been already shown.

PERIPHERAL RESISTANCE

The response of the vascular bed to changes in blood volume has been studied in man,[38] and it has been found that through a compensatory increase in peripheral resistance the systemic blood pressure is maintained, provided that blood loss does not exceed 700-1000 ml. The increase in peripheral resistance results chiefly in a redistribution of blood away from skin, kidneys and the gastrointestinal system.

The fact that the newborn infant is able to withstand the dramatic stress and circulatory changes at birth strongly suggests that he possesses effective mechanisms for controlling the vascular bed. Quantitative measurements of blood flow rates in parts of the systemic circulation during the immediate postnatal period have shown markedly slow flow rates in the extremities.[39] Measurements in a baby recovering from severe asphyxia illustrated, however, a very wide range of possible flow rates. The rate of blood flow when the baby was in normal condition at the age of two days was around 8 ml./min./100 ml. of tissue. During the first few hours of life it was as low as 0.4 ml./min./100 ml. When the maximal flow capacity was explored by promoting reactive hyperemia in a limb following a 10-minute arrest of circulation, the dilated blood vessels of the limb permitted flow rates up to 70 ml./min./100 ml.

No measurements of the peripheral blood flow have been made specifically on infants with known amounts of placental transfusion.

Visual observations of the infants studied in the present investigation revealed that the vascular compartments of the skin participate in the redistribution of blood flow following birth, and there appears to be less blood in the cutaneous vessels after early clamping than after late clamping. It is generally agreed that, with some limitations, peripheral blood flow correlates well with cutaneous temperatures.[35, 41] In order to demonstrate indirectly some differential features of peripheral blood flow in infants whose cords were clamped early and in those who were clamped late, we carried out serial measurements of temperatures of the rectum, cutaneous areas of the heels, palms, ear lobes and epigastrium, in 30 normal-term newborn infants from birth through the fifth day of life.[36] The umbilical cords of 14 infants were clamped immediately after birth, while in 22 infants the cords were occluded after their arterial pulsation stopped. At birth the mean skin temperatures of the heel and palms dropped precipitously from 35.4 to 29.8° C. during the first 10 minutes of life.

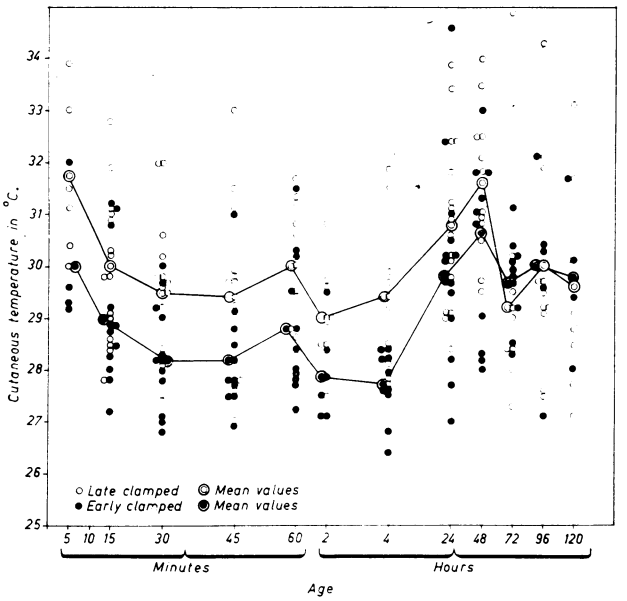

Fig. 8.—Heel cutaneous temperature in 16 infants whose cords were clamped late, and in 14 who were clamped early, recorded from birth through the fifth day of life.[36]

The infants clamped early had a significantly lower cutaneous temperature in the palms and heels and to a lesser extent in the ear lobes (Fig. 8). No difference was observed in the cutaneous epigastric and rectal temperatures between the two groups. The lower cutaneous temperature of the peripheral areas in the infants who were clamped early may also be taken to reflect the comparatively smaller skin flow in these subjects.

CIRCULATORY ADAPTATION TO CLAMPING OF THE CORD

The time of clamping the cord has hitherto been considered to be a question only of the amount of blood received from the placenta by the newborn baby. Apparently this is not so. During fetal life the placental circulation is a low-resistance circuit through which more than 50% of the total cardiac output passes. Early clamping of the cord must be expected to have significant consequences for the circulation in the newborn baby. If the cord is tied immediately in a lamb which has been delivered by Cesarean section, there is an abrupt and shortlived rise of arterial pressure due to the increase in peripheral vascular resistance on exclusion of the umbilical circulation.

When the lungs take over the gaseous exchange from the placenta, they at the same time establish a low-pressure circuit within the circulation. As the ventricles now work in series the pulmonary vascular bed can, like the vasculature of the placenta, function as a safety-valve for the systemic circulation, owing to the presence of the patent ductus arteriosus which permits shunts between the systemic and pulmonary circulation.

After clamping of the cord and until the newborn has established good aeration of the lungs, he has no safety-valve; his circulation is neither of fetal nor of adult type. In cases in which it is doubtful whether the baby can immediately establish good air-filling of his lungs (e.g. in cases of asphyxia or in Cesarean section babies) it might therefore be an advantage not to shut this safety-valve by clamping the cord or by holding the placenta high above the child.

WHEN SHOULD THE CLAMPING OF THE UMBILICAL CORD BE PERFORMED?

In our studies we have not observed any harmful clinical effects of either immediate or late cord clamping in healthy, unanesthetized full-term newborns. Our studies have shown, however, a significantly different mode of respiratory and hemodynamic adjustment during the first hours of life. The infants clamped early were found to have lower blood volume, red cell volume and hematocrits. They also had lower central venous and atrial pressures, as well as lower pulmonary and aortic pressures, and probably lower peripheral blood flow. These differences, which are compensated for and tolerated in full-term newborn infants, might be harmful in premature infants, in Cesarean section babies and in babies following complicated deliveries.

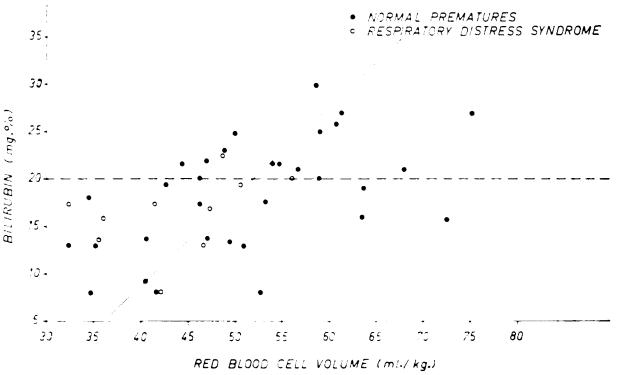

Fig. 9.—Correlation between red cell volume (x) and peak bilirubin concentration (y) during the first six days of life in 32 healthy premature infants from the present study, and in 10 premature infants with respiratory distress syndrome from another study.[16] The correlation is statistically significant ($P - 0.001$), the regression line being expressed by the formula, $y = -28.87 + 0.943x$.

To consider one example: From physiological considerations alone it would seem that red cell volume should have a greater effect on bilirubin concentration in premature infants than in full-term infants. In fact such an association between placental transfusion and hyperbilirubinemia has been convincingly shown[42, 43] (Fig. 9).

Differences in the time of cord clamping in different hospitals may therefore account for variations in the incidence of hyperbilirubinemia among their premature infants. If delayed cord clamping becomes more generally adopted in an attempt to reduce the incidence of respiratory distress in premature babies, severe hyperbilirubinemia may become more common.

So when should the cord be clamped in cases of prematurity? in Cesarean-section babies? in asphyxiated babies? A wide field of urgently needed clinical research opens up here.

Life is dangerous, and birth certainly gives us realistic practice. But, as we know, it is always darkest before the dawn and this is particularly true of the first dawn of a human being. It follows that all of us who are active in child welfare must redouble our efforts to help as many children as possible to pass from the shadowy world of the fetus into the daylight of their individual lives. Just as the sun with great precision dispels the darkness, so should it be possible for us to determine exactly the ideal time for severing the umbilical cord.

When we know this, the charter of human rights should be amended to include the right to have one's umbilical cord severed on time.

CONCLUSION

The time of cord clamping modifies placental transfusion and the blood volume of the newly born infant. Transient but significant physiologic changes occurring in the immediate newborn period are attributable to the magnitude of this placental transfer.

The studies carried out in our laboratory have been generously supported by the Association for the Aid of Crippled Children, New York, U.S.A., and National föreningen mot Hjärt- och Lungsjukdomar, Stockholm, Sweden.

I wish to express my gratitude to Drs. René Arcilla, Willard Blankenship, Wanda Jegier, William Oh, Leo Stern and Robert Usher for their stimulating co-operation.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

THIS SERIOUS PROFESSION

Littré, in his prefatory remarks upon the oath, has well said "the profession of medicine is one of the most difficult that may fall to the lot of a man; with its grave responsibility, limited power, obscurity in many cases, fugitive opportunities and the impossibility of retracing one's steps. Certainly one may not trifle with the dangerous serpent of Epidaurus. Add to this the personal dangers of the study and practice, the perpetual contact with suffering and death, the scientific training that strengthens and aggrandizes the soul; the feelings of humanity which dominate in the exercise of an art essentially benevolent, and one will not be astonished that even in remote antiquity this serious profession should have inspired a work of so elevated a character as that known as the Hippocratic Oath."

Thus in the treatise *de medico* one finds the following: "It is essential for the physician that his complexion be of good colour and that he have that degree of rotundity which may be naturally suitable to him."

You may not all satisfactorily meet this requirement. The exigencies of student life do not encourage the development of embonpoint. But do not be discouraged, the day will come for many of you, I trust, when your anxiety will be roused lest you may overdo, rather than fail in this requirement. The next items are, however, more under your control. "Further," it is said, "all things about him must be clean, his raiment appropriate and his perfumes agreeable, having an odour beyond all suspicion." Cleanliness is next to godliness, nay, from the surgical standpoint it is of even greater importance. Nowadays with our greater knowledge of the cause and dissemination of disease, lack of cleanliness is criminal for a medical man; "all about him must be clean" and the sooner the habit of scrupulous cleanliness be formed, the better it will be for you and for your future patients.—J. Playfair McMurrich, *Canad. Med. Ass. J.*, 5: 955, 1915.