Changes in the Circulation at Birth

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THE CHANGES in the circulation at birth are abrupt in onset, but are not completed at once. Hence during the past ten years the concept has evolved of a transitional type of circulation, intermediate between that of the fetus and the adult, with its own characteristic properties, lasting usually a few days, sometimes a few weeks.[1] The observations upon animals which led to these conclusions have received ample confirmation from cineangiograms [2] and catheter studies on human infants, but we still rely very largely upon animal experiments for quantitative investigations of the mechanisms which are involved. To understand the changes at birth we must start with the fetal circulation.

The Fetal Circulation

The circulation in the fetus differs from that of the adult in many respects both anatomical and functional. In the fetus the two sides of the heart work in parallel, to pump blood simultaneously from the great veins to the aorta. This is possible because of the presence of the foramen ovale and the ductus arteriosus (fig. 1). The foramen ovale lies between the inferior vena cava and the left atrium (fig. 2); it does *not* join the two atria. Most of the blood flowing up the inferior vena cava enters the left atrium through the foramen ovale; a small proportion passes into the right atrium. All the blood flowing down the superior vena cava normally enters the right atrium. The ductus arteriosus is, in fetal life, a wide channel whose internal diameter is approximately the same as that of the pulmonary trunk or the aorta. Pulmonary arterial blood pressure is higher than aortic pressure, and much of the right heart output passes (right-to-left) through the ductus arteriosus into the aorta. About half the combined output of both sides of the heart goes to the placenta, and the remainder is

fed to the lungs and other tissues of the fetus from the great arteries in parallel (fig. 1).

It is unwise to consider the fetal circulation without reference to the supply and distribution of oxygen to the fetal tissues. Under good physiological conditions many measurements on fetal animals have shown that the umbilical arterial P_{O_2} is 20–30 mm. of mercury, much less than that of the mother. The umbilical arterial P_{CO_2} is about 40 mm. of mercury, a little higher than the maternal. The distribution of oxygen in the blood of the great vessels is variable. The numerals in figure 2 indicate the mean O_2 percentage saturation of blood withdrawn simultaneously and averaged from estimations on 6 normal mature fetal lambs. It is evident that the blood streams entering the heart do not mix thoroughly, so that on average the oxygen content of carotid arterial blood is about 4 per cent greater than that in the descending aorta, and even more than that supplying the fetal lungs via the pulmonary arteries. The O_2 content or tension of the blood in the umbilical arteries (derived from the descending aorta) has been widely used as an index of the blood supply to the fetal tissues generally, and under good physiological conditions this is a reasonable assumption. But when umbilical blood flow is reduced the difference between the carotid and femoral arterial O_2 saturation may increase to more than 20 per cent. And in some circumstances the O_2 content of the umbilical arterial blood can be utterly misleading as a guide to the condition of the fetus. Thus in mature fetal lambs hemorrhage can cause a very substantial (20 per cent) *rise* in the O_2 saturation of umbilical venous, carotid and femoral arterial blood, while the O_2 consumption of the fetus is considerably *reduced.*[3] The explanation of this apparent paradox is that O_2 uptake from the placenta and consumption by the fetal tissues is dependent on blood flow as well as on an adequate gradient in O_2 tension. Consequently, measurement of the O_2 tension alone

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of cord blood on delivery can be an unreliable index of the condition of the fetus.

The arterial blood pressure of the fetus rises progressively during gestation (fig. 3) to reach 50–70 mm. of mercury in the rhesus monkey [4] or human infant at term. In fetal lambs all of the same gestational age (e.g., within a week of term), the arterial pressure is higher in those of greater weight.[5] This has been associated with the greater umbilical blood flow required in larger lambs to maintain adequate O_2 uptake with some margin of safety. Measurements of umbilical blood flow have yielded progressively increasing values over the last 10 years as methods have improved. In some fetal lambs about two-thirds of the way through gestation figures of over 300 ml./kg./minute have been recorded.[3] In mature lambs the flow averages a little less than 200 ml./kg./minute. But the O_2 carrying capacity of the blood rises during gestation, so that there is a fairly considerable safety margin in O_2 supply at term. Oxygen uptake from the placenta does not usually start to fall until umbilical flow is reduced by nearly 50 per cent.

This fall in O_2 consumption is a most interesting phenomenon. In adult man or adult animals the basal O_2 consumption is maintained during increasing hypoxia until a certain critical point is reached at which the circulation collapses, blood pressure falls catastrophically, O_2 uptake *ceases* abruptly and death is imminent unless immediate action is taken. But in the fetus subjected to progressive asphyxia or hypoxemia the circulation can be maintained for a long time in spite of a very substantial decrease of O_2 uptake. There are two factors which contribute to this end.

Fig. 2. The figures indicate the mean O_2 percentage saturation of blood withdrawn simultaneously and averaged from estimations on 6 lambs. I.V.C., inferior vena cava; S.V.C., superior vena cava; R.V., right ventricle; L.V., left ventricle; D.V. ductus venosus; D.A., ductus arteriosus; F.O., foramen ovale; B.C.A., brachiocephalic artery. (Reprinted with permission from Born *et al.*, Cold Spr. Harb. Symp. Quant. Biol., 1954.)

Firstly the course of the fetal circulation is such that even when arterial pressure is much reduced some umbilical blood flow is still maintained, and uptake of O_2 from the placenta and distribution to the fetal tissues continues. *In vivo* measurements of the vascular resistance of the umbilical circulation show that it is remarkably insensitive to the direct effect of changes in blood gas tensions.[5] And secondly the fetal ventricular muscle contains very high concentrations of carbohydrate [6] (fig. 4) and can therefore continue to derive some energy by glycolysis in the absence of oxygen. Repeated episodes of asphyxia gradually reduce this reserve of energy, which is only rebuilt during a period of an hour or more after recovery.[7]
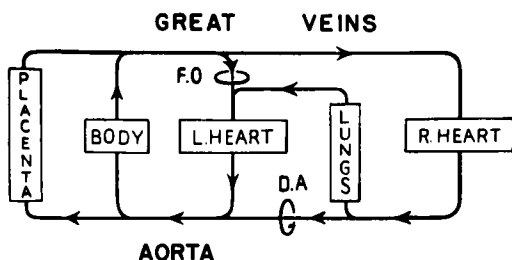

Fig. 1. Schematic view of the fetal circulation, to show that both sides of the heart work in parallel to pump blood from the great veins to the aorta, by way of the foramen ovale (F.O.) and ductus arteriosus (D.A.).
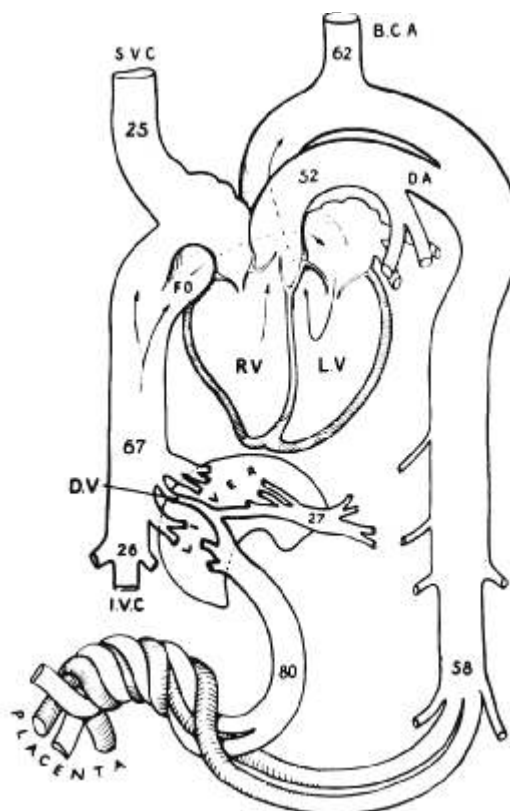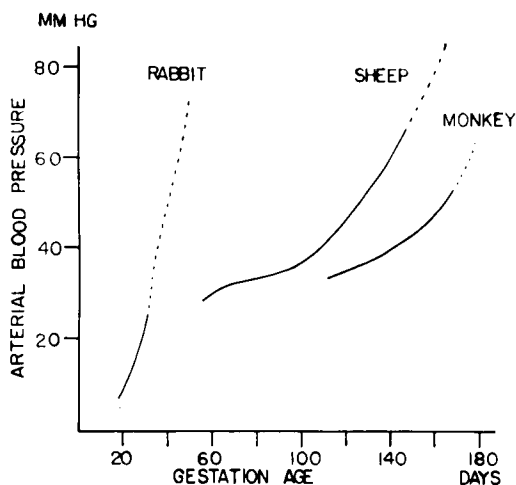
Fig. 3. The figure shows the rise of blood pressure with increasing age, before birth (continuous line) and after birth (broken line) in three species. (Reprinted with permission from Dawes.[4])

There is also the question of what may be called cardiovascular competence. To what extent is the fetal circulation under the control of the autonomic nervous system, and how well is its faculty for homeostasis developed? The myth that the newborn infant is physiologically incompetent still survives. Of course it is small and unable to perform certain functions or to fend for itself, but its cardiovascular system is remarkably well developed. For example, a newborn rabbit, weighing only 50 g. and with a mean arterial blood pressure of 35 mm. of mercury can increase its oxygen consumption from 20 up to 60 ml./kg./minute on exposure to cold, and calculation shows that it must then have a cardiac output of nearly 500 ml./kg./minute (equivalent to 35 liters/minute for a 70-kg. man). Its chemoreceptor [8] and baroreceptor [9] reflexes are well developed at birth; indeed its aortic baroreceptors are as sensitive to pressure changes as those of an adult rabbit.[10] And recent investigations by Joan Mott (unpublished) have shown that it is just as well able to withstand hemorrhage. The heart of a mature fetal lamb is clearly under autonomic nervous control, since thoracic sympathectomy causes a large fall in rate; and calculations of the cardiac output suggest that it also is high, up to 250 ml./kg./minute for each ventricle. Many observations suggest that some degree of autonomic nervous control

is established early in gestation, before the fetus becomes viable.

Finally the architecture and functional physiology of the fetal circulation makes clear how it comes about that fetuses with gross anomalies of the cardiovascular system can survive until term. Since both ventricles work in parallel, transposition of the great vessels, absence or malfunction of one ventricle are quite compatible with survival.

The Onset of Breathing

It is easy to understand why a fetus starts to breathe on delivery. It is not quite so simple to explain why it continues to breathe! It starts to breathe because its umbilical cord is tied, it is asphyxiated, it has well-developed chemoreceptor reflexes, and the afferent impulses from the aortic and carotid bodies together with the cutaneous stimuli it receives during delivery, are quite sufficient to initiate strong respiratory efforts. These efforts produce very large falls of intrapleural pressure, to less than -50 mm. of mercury, which is sufficient to overcome the surface tension forces at the air-fluid interfaces within the lung, and so to expand the alveoli with air for the first time.

Now we have to consider the problem of why the newborn infant continues to breathe. Before delivery a fetal lamb may have an arterial P_{O_2} of 25 mm. of mercury and a P_{CO_2} of 40 mm. of mercury. On delivery by cesarean section under local anesthesia, but still attached to its mother with an intact umbilical cord, it remains quiet and without any respiratory movements. An hour or so after the cord is tied the same lamb may be sitting quietly on the ground, breathing, rhythmically and with little effort, with an arterial P_{O_2} of more than 70 mm. of mercury and a P_{CO_2} of 35 mm. of mercury. Clearly the continuation of rhythmical breathing is not dependent on an increased activity of the systemic arterial chemoreceptors. Some other factor or factors must be involved, and it is possible that this may include a general increase in sensory afferent excitation. Thus when a fetal lamb, still connected to its mother by the umbilical cord, with lungs unexpanded and with its trachea attached to a saline-filled tube, is cooled by application of ice-cold packs to its
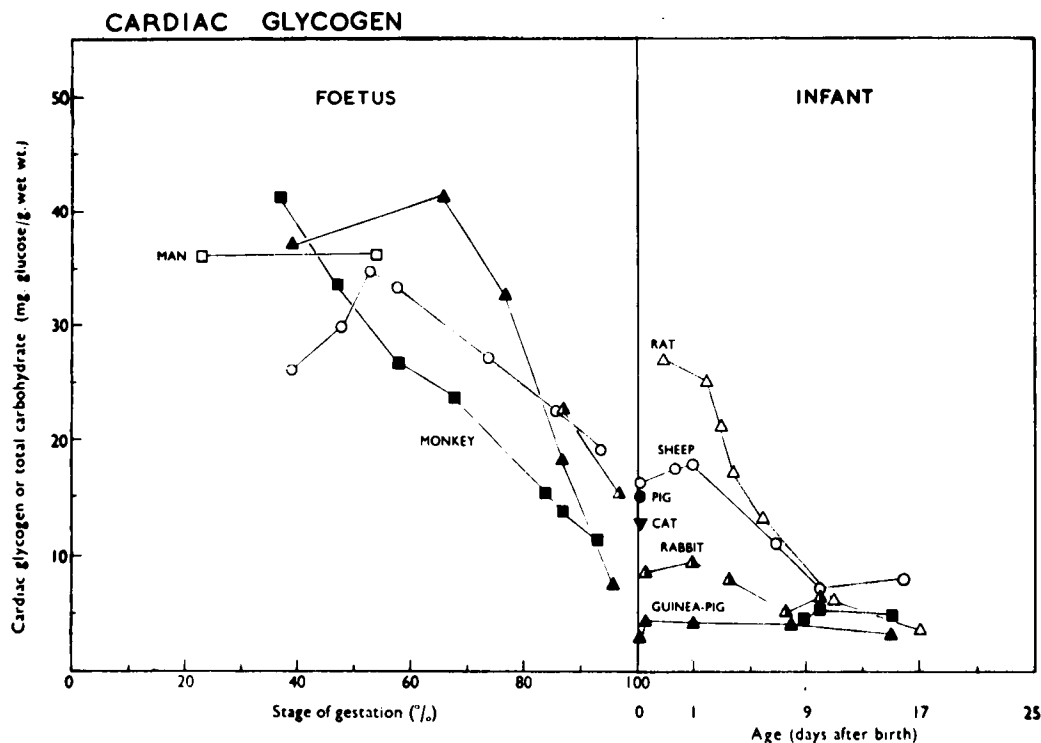
FIG. 4. Cardiac glycogen in different species before and after birth.
(Reprinted with permission from Shelley.[6])

skin, it begins to make respiratory movements (Dawes and Mott, unpublished data). These are not the deep convulsive gasps of asphyxia, but gentle rhythmical movements, each causing a fall of intrapleural pressure to −12 mm. of mercury or so, sufficient only to wash a few ml. of fluid in and out of the lungs. When cooling ceases, these movements also cease. Hence it is possible by appropriate stimuli to arouse the respiratory centers to rhythmical activity in the fetus.

Thus the onset of breathing at birth consists of two components. Firstly, the dramatic deep inspiratory efforts which lead to gaseous expansion of the alveoli, and secondly the changes which result in the establishment of quiet rhythmic respiration and a very large rise in arterial P_{O_2}. The changes in the circulation at birth are directly attributable to the severance of the umbilical cord, the expansion of the lungs and the rise in arterial P_{O_2}.

The Pulmonary Circulation

It has been assumed since the time of Harvey that the volume of blood flow through

the lungs in the fetus is necessarily low, because the lungs are not expanded. And the first direct observations on the pulmonary circulation in the fetus supported this conclusion.[11] But recent observations have shown that the pulmonary blood flow in the fetus may undergo remarkable spontaneous changes, increasing to as much as 50–80 ml./kg./minute through the left lung alone.[12] We now know that the tone of the pulmonary blood vessels is remarkably labile, that it is under the control of the autonomic nervous system, that injection of small doses of acetylcholine causes vasodilatation [13, 14] and of noradrenaline causes vasoconstriction,[15] and that asphyxia causes an extreme degree of pulmonary vasoconstriction both in the innervated or denervated fetal or neonatal lung. Hence before the baby is born asphyxia will tend to maintain umbilical blood flow (to the placenta, the organ of gaseous exchange) by diverting some of the cardiac output from the lungs (fig. 1). It is probable that pulmonary blood flow is usually low after delivery, and before the first breath is taken, because the terminal stages of delivery often
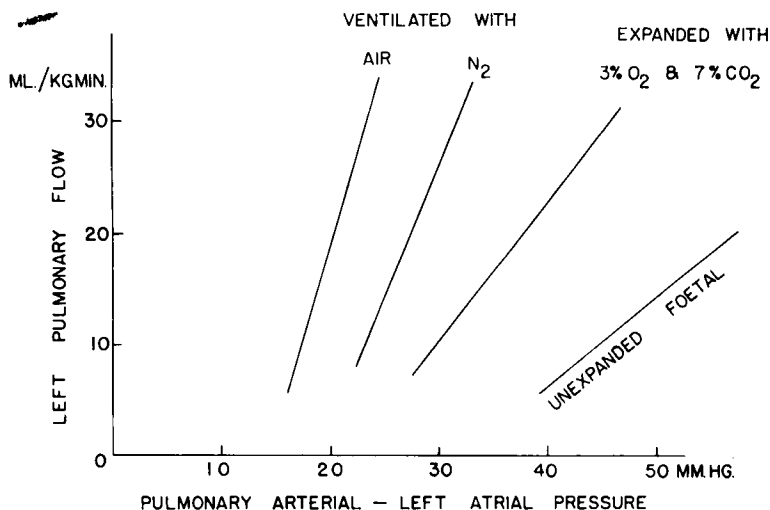
Fig. 5. Mean left pulmonary arterial pressure-flow curves from mature fetal lambs before expansion of the lungs, after a single brief inflation with 3 per cent O_2 and 7 per cent CO_2 in nitrogen, and during rhythmical positive pressure ventilation with N_2 and with air.[16, 17]

result in partial asphyxia of the infant, but we cannot be sure that this is always so. However, let us assume that it is so and see what happens when respiration is established.

A single full expansion of the lungs with a gas, even a gas mixture (3 per cent O_2 and 7 per cent CO_2 in N_2) which causes little or no alteration in fetal arterial gas tension,[16] causes a large shift in the position of the pulmonary arterial pressure-flow curve, due to vasodilatation (fig. 5). When the lungs are rythmically ventilated with the same gas mixture, no further change occurs. But when CO_2 is removed from the gas mixture there is a further vasodilatation,[18] and when the O_2 concentration is increased to 21 per cent there is a yet further vasodilatation (fig. 5). Thus the large decrease in pulmonary vascular resistance which is observed when the fetal lungs are for the first time rhythmically ventilated with air is partly due to gaseous expansion of itself, and partly to the change in the alveolar and arterial gas tensions. Quantitatively similar changes are seen whether the lung is innervated or denervated.[16] Consequently whether or not pulmonary vascular tone is low on delivery, it will become low as soon as the lungs have been expanded with air. If the vascular tone was high before ventilation was begun, the changes can be very dramatic as shown in figure 6. There is then a striking increase in pulmonary blood flow and a fall in pulmonary arterial pressure.[11]

To digress a moment from this description of what normally happens at birth, the facts described above and illustrated in figure 5 are of particular importance in considering various methods of resuscitating asphyxiated infants. As already mentioned asphyxia causes intense pulmonary vasoconstriction. Positive pressure ventilation with air will expand the lungs, raise the alveolar and arterial P_{O_2} and lower the P_{CO_2} and hence cause a profound pulmonary vasodilatation. Administration of O_2 without ventilation, whether at 1 or more atmospheres' pressure, will only raise the ambient P_{O_2} and will have a much smaller effect on the pulmonary circulation. This, together with the reduction in P_{CO_2}, goes far to explain the greater efficacy of positive pressure ventilation as compared with the administration of hyperbaric oxygen in controlled trials of resuscitation in newly delivered rabbits.[19]

The Ductus Arteriosus

When the umbilical cord is tied systemic vascular resistance rises, and when the lungs are ventilated pulmonary vascular resistance falls.[11] Therefore, in the normal lamb or human infant a situation is created soon after birth in which a left-to-right shunt may take place through the ductus arteriosus so long as it is patent (fig. 6). Right-to-left and left-to-right shunts can also occur at different parts of the same cardiac cycle. In the lamb,

calf and foal the direction of blood flow through the ductus arteriosus reverses from the normal fetal (right-to-left) to the neonatal (left-to-right) within a few minutes of establishing normal breathing. In the human infant pulmonary arterial pressure appears to fall relatively more slowly, and some degree of right-to-left shunt can detected by analysis of simultaneous pulmonary arterial and descending aortic blood samples for up to an hour after normal birth.[20] If the lungs are not yet functioning perfectly and left atrial blood is not fully saturated, a left-to-right shunt can have the advantage of permitting the recirculation of partly saturated blood through the lungs where more O_2 can be taken up, but at the expense of a greater left heart output. Hence in the first few days after birth the circulation is in a stage of transition, and complex shunts are present and change volume and direction with changes in the physiological condition of the infant.

FIG. 7. Observations on a fetal lamb. The pressure difference between the ends of the ductus arteriosus, and the volume and velocity of flow through it have been plotted against its calculated internal diameter and cross-sectional area. In the upper part of the diagram is shown the term $V\rho d/\eta$ (above) and the comparative intensity of the murmur in the pulmonary trunk, estimated from phonocardiograph records (below). When $V\rho d/\eta$ exceeded about 750 (where V is velocity of flow, ρ the density and η the viscosity of blood, and d the internal diameter of the ductus), a murmur appeared, but not otherwise. (Reprinted by permission from Dawes et al.[21])
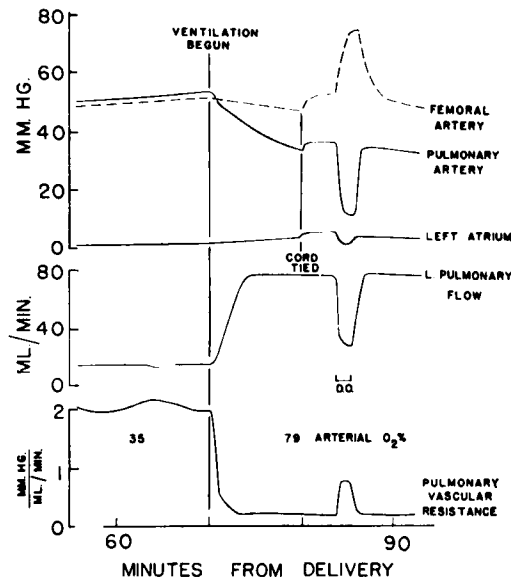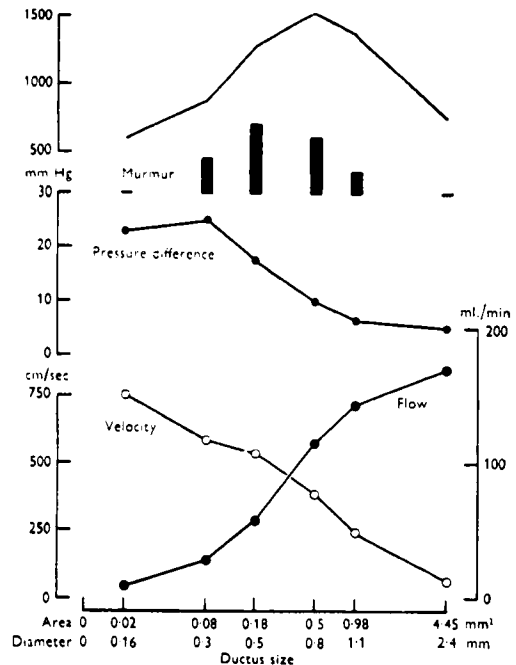

FIG. 6. Mature fetal lamb. Artificial positive pressure ventilation of the lungs caused a large fall of pulmonary vascular resistance, an increase in pulmonary flow and a fall in pulmonary arterial pressure. Temporary occlusion of the ductus arteriosus (D.O.) caused a rise in femoral pressure and a fall in pulmonary arterial pressure and flow, showing that blood had been flowing from the aorta into the pulmonary trunk. The figures 35 and 79 indicate the carotid arterial O_2 percentage saturation. (Modified from Dawes et al.[11])

So long as the ductus arteriosus is widely patent no turbulence or murmur can be detected. When it begins to constrict, the velocity of blood flow through it increases, and at a certain critical point (dependent on the velocity of flow and the diameter of the vessel among other things) turbulence appears, the walls of the blood vessels begin to vibrate and a murmur becomes audible. With further constriction of the vessel, even though the velocity of flow increases still more, the conditions for turbulence disappear and the murmur is no longer heard (fig. 7). Hence the presence of a ductus murmur indicates that flow is proceeding through a partly constricted vessel, but the absence of a murmur provides no evidence as to flow. In the larger farm animals
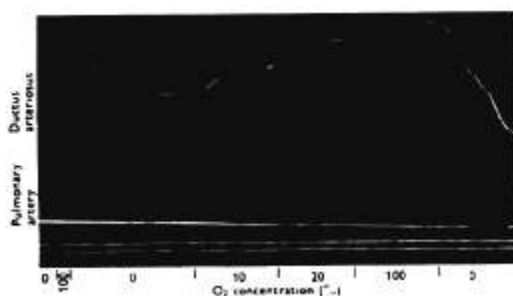
FIG. 8. Isolated strips of sheep fetus ductus arteriosus and pulmonary artery suspended in warm Tyrode solution. Increasing concentrations of O_2 in the gas mixture bubbled through the solution caused contraction of the ductus only. Time marker, 1 minute. (Reprinted by permission from Kovalčik.[24])

a loud ductus murmur can be heard for many hours after birth. Cardiac murmurs have been reported in normal newborn human infants but their origin is still uncertain. They may arise from the ductus arteriosus or, perhaps, from mitral regurgitation.[22]

The mechanisms responsible for the closure of the ductus arteriosus have been analyzed in some detail. The changes in transmural pressure which occur after birth are less important than the rise in arterial P_{O_2}, which causes the large mass of smooth muscle in the vessel wall to contract by a direct action. This has been demonstrated *in vivo*, and in isolated heart-ductus arteriosus—artificial lung preparations,[23] and in isolated muscle strips suspended in saline solution.[24] A progressive increase in the O_2 content of the gas bubbling through the saline solution causes a progressive contraction of the isolated ductus arteriosus (fig. 8). The ducture arteriosus is also caused to constrict by sympathomimetic amines, and it is probable that this may explain why it can constrict for a short while during asphyxia on delivery. In the normal newborn infant it may remain partly open for several days after birth, particularly if birth has been premature. This can throw an excessive load on the left heart, with development of progressive failure. This uncommon complication has been successfully treated by ligation of the vessel within two weeks of birth. But usually the ductus closes of its own accord before this happens. It is interesting that the smooth muscle of the ductus arteriosus alone is particu-

larly susceptible to changes in ambient P_{O_2}. The muscle of the adjacent aorta and main pulmonary artery, and of the umbilical arteries, prepared in the same way are insensitive.

The Foramen Ovale and Ductus Venosus

In the fetus the valve of the foramen ovale, which lies on the left atrial side of the foramen, is held open by blood entering from the inferior vena cava. The valve itself is composed of cardiac muscle, which contracts during atrial systole. When the umbilical cord is tied the volume of blood returning from the placenta is reduced and this, with an increase in pulmonary venous return to the left atrium, causes the mean pressure in the left atrium to rise above that in the vena cava.[25] So long as there is a left-to-right shunt through a patent ductus arteriosus, this will tend to exaggerate the rise in left atrial pressure over that in the vena cava (fig. 9). The valve then tends to close though it may not remain closed at all phases of the cardiac cycle. Anatomical closure is not complete for a week or more, and during the first few days after birth a small right-to-left shunt through the foramen ovale is usual. But the relatively high arterial O_2 saturations of most newborn infants suggests that such shunts are small.

The ductus venosus constitutes a bypass between the abdominal part of the umbilical vein and the hepatic vein, short circuiting the fetal liver (fig. 2). The volume of blood flow through it at term is still a matter of guesswork; it has been estimated at about one-sixth of umbilical blood flow. In some species (horse, pig) it closes a long time before birth, but in most species including man it closes after birth. The mechanism of closure is uncertain. A sphincter controlled by smooth muscle has been described at its junction with the umbilical vein, but there is some doubt as to whether this exists in man (Aherne, personal communication). It is possible that closure is effected by the elastic tissue in its wall when the pressure in the umbilical vein falls after the cord has been tied. The ductus venosus is not easily accessible to experimental investigation, and it lies on the under surface of the liver and is usually covered by a thin layer of tissue.

Other Changes After Birth

The closure of the main fetal blood channels does not conclude the changes in the circulation after birth. Pulmonary arterial pressure falls abruptly when the cord is tied and the lungs are expanded, but it does not reach adult levels at once (fig. 6). It continues to fall, more slowly, over a period of 2 weeks or more after birth. During this time the smooth muscle of the smaller pulmonary arterioles, which is well developed at birth, partly atrophies. Similarly, while the left ventricle continues to grow, the wall of the right ventricle (which at birth is as thick as the left) also suffers some atrophy.[26] Mean left atrial pressure gradually rises over the same period of time to become about double that of the right atrium, probably as a result of a change in the elasticity of the walls of the two ventricles. The eventual rise in left atrial pressure ensures that there is no right-to-left shunt through the foramen ovale even if the valve is incompetent.

As already described the pulmonary blood vessels of the fetus are intensely reactive, contracting to small doses of noradenaline and dilating on injection of acetylcholine and histamine to a degree quite unknown in the adult. Presumably this intense reactivity to excitation of the autonomic nerves to the lung, to changes in arterial or alveolar P_{O_2} or P_{CO_2} and even to alterations in transmural pressure, may subside soon after birth. But precise quantitative measurements have not been undertaken at different ages after birth. We can only guess that the reactivity of the pulmonary vascular bed decreases *pari passu* with the fall of pulmonary arterial pressure and the relative decrease in size of the muscular wall of the pulmonary vessels after birth.

Summary and Conclusions

The changes in the circulation at birth are qualitatively similar in man and animals. They result from the tying of the umbilical cord, the expansion of the lungs and the rise
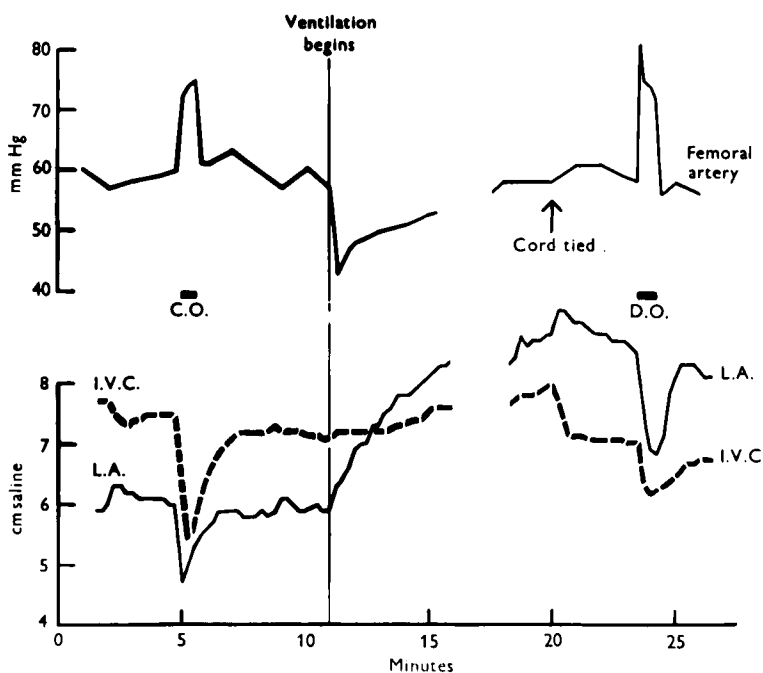

FIG. 9. Ventilation of the lungs of a mature fetal lamb caused a rise in mean left atrial pressure. When the umbilical cord was occluded (C.O.) or tied the inferior vena cava (I.V.C.) pressure fell. Occlusion of the ductus arteriosus (D.O.) reduced the pressure difference across the foramen ovale after ventilation, because there was then a left-to-right shunt through the ductus. Hence ventilation of the lungs, tying the cord and continued patency of the ductus all contribute to the rapid reversal of the pressure gradient across the foramen ovale after birth. (Modified from Dawes *et al.*[25])

in arterial P_{O_2}, but they are not completed for several days. During this period of time, which can be extended to a week or more after premature delivery, blood may continue to flow through the ductus arteriosus and foramen ovale. The multi-directional shunts which can thus develop make measurement of cardiac output in the newborn particularly difficult. The systemic arterial baroreceptors and chemoreceptors are well developed at birth, and the competence of the cardiovascular system, as judged by its ability to withstand hemorrhage or to provide for a large increase in O_2 consumption on exposure to cold in some species, is good. The pulmonary circulation is very labile in the fetus and newborn, asphyxia causing intense vasoconstriction. The possibility thus arises that pulmonary blood flow can be reduced under certain conditions after birth, to such an extent as to limit O_2 uptake. This may be the explanation for the progressive deterioration in infants dying of the respiratory distress syndrome.[17] It is evident that the mechanisms which regulate pulmonary flow in the fetus and newborn require more intensive study.

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