Aspects of Applied Physiology of Neonatal Circulation*

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In talking to clinical students and junior resident staff I have frequently heard the remark that "I have never understood the foetal circulation". As an understanding of this circulation and its conversion to the adult form is fundamental to an appreciation of the circulatory and respiratory physiology and pathology of the newborn infant, I must begin this lecture by mentioning the most important points.

FOETAL CIRCULATION

Fig. 1 is a diagram of the adult circulation as Harvey saw it; Fig. 2 is based on this same diagram, but has had added to it the complexities of the foetal state. The conventions in this diagram are as follows: the volume of flow in the various channels is represented by the diameter of the vessels, and the colours indicate the degree of oxygenation of the blood. One sees that the flow through the pulmonary artery is very small (Harvey thought there was no flow through the lung in the foetal state), and circulation is only possible by the provision of two foetal shunts around the lungs: (1) the foramen ovale leading relatively oxygenated blood from the umbilical vein to the left atrium, and (2) the ductus arteriosus carrying blood from the pulmonary trunk to the aorta. The pulmonary trunk conducts blood of poor oxygenation (at 52 per cent saturation as compared with 80 per cent in the umbilical vein in the lamb (Born *et al.*, 1954)).

In the left atrium there is a mixture of the de-oxygenated blood passing through the pulmonary arteries, with more oxygenated blood arriving from the foramen ovale, and hence the blood in the first part of the aorta supplying the heart, the right arm, and the head and neck is slightly more oxygenated

(62%) than the blood supplying the rest of the body for the blood in the descending aorta is further reduced by the addition of the flow through the ductus arteriosus. Thus, the "arterial" blood supplied to the rest of the body of the foetus is 58 per cent saturated, which is the same level of saturation as the blood bypassing the body and going to the placenta for reoxygenation. Two defects of this diagram are that the exchange system in the placenta is incorrectly represented as a simple counter-current system, which it is not, and for the purposes of the diagram, the foramen ovale has had to be dislocated, so that the fact that the inferior venal caval and umbilical venous blood leads directly into the left atrium (as was recognized by Sabatier in 1778) is not well shown.

For the conversion of this circulation to the adult state, the umbilical circulation, the foramen ovale, and the ductus arteriosus must close, while the pulmonary blood flow must increase to equal that of the aorta.

Closure of Umbilical Vessels. In nature these are torn, stretched, or chewed, and in many species the vessels are very reactive to trauma. Bleeding from the cord appears to be a greater problem if it is cut with a sharp instrument.

Closure of Foramen Ovale and Ductus Arteriosus; Opening up the Pulmonary Blood Flow. The changes in this part of the circulation are not sudden, and proximate causes for the changes are now well understood, thanks largely to the work of Dawes and his colleagues. Dawes has advanced our knowledge of the physiology of the foetal and neonatal circulation more than any man now alive, and I refer to some of his summaries (Dawes, 1961, 1964, 1966). The changes in these parts of the circulation are closely interrelated and the key lies in

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FIG. 1.

FIG. 1.—The concept of the circulation of the blood. An “exploded” diagram, establishing the conventions to be used to explain the variations met in the foetal state. (Reproduced by kind permission of the publishers of the *Manual of Obstetrics* (Holland & Brews). 13th edition, in preparation.)

FIG. 2.—The foetal circulation. Conventions: the blood flows (as calculated in the lamb, Born *et al.*, 1954) are in proportion to diameters of vessels. The colours vary with the degree of oxygenation of the blood as found by the same authors. Note the very limited flow through the lungs, and the circulation of blood permitted by the shunts of the foramen ovale and the ductus arteriosus, so that right and left heart are circulating blood to the foetus and to the placenta. The chief errors in this diagram are the absence of the ductus venosus, the countercurrent flow in the placenta, and the fact that the foramen ovale is not shown to lie (as it does) between the inferior vena cava and the left atrium. (Reproduced by kind permission of the publishers of the *Manual of Obstetrics* (Holland & Brews). 13th edition, in preparation.)

FIG. 2.

unlocking the pulmonary vascular resistance. The pulmonary arterioles of the foetus have a far higher proportion of smooth muscle than do those of the adult (Naeve, 1961), and are incredibly reactive to stimuli. Falls in pulmonary vascular resistance occur with: (1) expansion of the lungs with a gas, even if that gas is in equilibrium with the foetal blood supply to them (approximately 7% CO₂ and 3% O₂); (2) ventilation of the lungs with nitrogen, which will wash out CO₂; (3) ventilation of the lungs with air or with oxygen. Ventilation of the lungs with air may cause a tenfold fall in pulmonary vascular resistance which allows a great increase in pulmonary blood flow. Under these circumstances the left atrial pressure begins to exceed the right atrial pressure so that the valve of the foramen ovale will become shut for an increasing proportion of the cardiac cycle. One of the most potent stimuli causing relaxation of the smooth muscle of the pulmonary arterioles—the increasing oxygen content of the alveoli and the blood—is also potent in causing the smooth muscle of the ductus arteriosus to contract (Born *et al.*, 1956; Kovalčík, 1963). The ductus arteriosus of the lamb contracts both with high oxygen and with catecholamines which are excreted into the blood in asphyxia (Comline and Silver, 1966). Thus, when the lungs are ventilated with air the pulmonary vascular resistance falls, the systemic arterial pressure exceeds the pulmonary arterial pressure, and the ductus contracts. We now have the conditions for a left-to-right shunt through the ductus and turbulent flow causing a murmur which is heard regularly in the lamb (Dawes, Mott, and Widdicombe, 1955) and calves and foals (Amoroso, Dawes, and Mott, 1958), and less frequently in the human baby (Burnard, 1958). When Dr. Dawes gave this lecture in 1963 he emphasized unexplained “spontaneous” vasodilatations in the pulmonary vessels. Many of these he has now shown to be due to the liberation of kinins, due to contact between foetal blood and glass (Colebatch *et al.*, 1965; Campbell *et al.*, 1966b). The pulmonary vasculature has a sensitivity to these kinins which is about a thousand times greater than that of the adult.

SOME CONSEQUENCES OF TRANSITIONAL NEONATAL CIRCULATION

Respiratory Physiology. In 1951–52 I reported with Warner and Oppé (Cross and Warner, 1951; Cross and Oppé, 1952) that inhalation of 100 per cent oxygen caused the full-term or the premature infant temporarily to underventilate. A reasonable explanation of this phenomenon, which was

widely accepted, was that the normal newborn infant had a chemoreceptor drive which was cut off by giving a high oxygen mixture. However, Pierre Dejours, at the Oxygen Symposium in 1963, pointed out that while infants of 3 days to 6 months showed a transient fall in ventilation when given a single breath of oxygen, this was not true in babies who were 1 to 19 hours of age (Girard, Lacaille, and Dejours, 1960), and he wished to know what explanation I could offer for this. Given time for thought I suggested that just after birth there might still be a sufficient right-to-left shunt (Nelson *et al.*, 1963) to prevent a single breath of oxygen raising the arterial PO₂ to any significant degree, whereas later, when shunts were fully closed, a single breath of oxygen would change the blood PO₂ considerably (Cross, 1964). This has now been illustrated very nicely in the lamb by Purves (1966) (see Fig. 3). I tell this story not only because one has a childish wish to be proved right, but also because it illustrates the fact that one needs considerable familiarity

FIG. 3.—Upper trace: Tidal volume of infant in successive minutes breathing first air then 100 per cent oxygen. Note the distinct diminution of tidal volume when breathing oxygen. (From Fig. 4 of Cross and Warner, 1951.) Lower traces: Change in arterial P_aO₂ of lamb at 2 days and 8 days when breathing 100 per cent oxygen for 1–2 breaths. (From Fig. 2 and 3 of Purves, 1966.)

with the transitional state of circulation if one is to understand the physiology of respiration at this stage of life.

Respiratory Distress Syndrome. In respiratory distress syndrome a more bizarre phenomenon may be seen. Chu *et al.* (1967) sampled simultaneously from the temporal artery and the umbilical artery in infants breathing 100 per cent oxygen. They found in sick infants that the temporal arterial blood may have a Po_2 well in excess of 200 mm. Hg (thus endangering the eyes with retrolental fibroplasia), while the umbilical arterial blood may have a Po_2 of only 53 mm. Hg, which must surely provide an environment which is less than ideal for the liver. This differential would be brought about by a reversion to the foetal state with a high pulmonary vascular resistance, a small pulmonary blood flow, and a right-to-left shunt through the ductus arteriosus.

In normal adult man the only occasion when raising the ambient oxygen above 21 per cent will increase the metabolic rate is in heavy muscular work (Christensen, Krogh, and Lindhard, 1934), but in respiratory distress June Hill and I have found (Hill, 1966) that oxygen consumption may be raised significantly by increasing the inspired oxygen from 40 to 100 per cent. One assumes that the oxygen has lowered the pulmonary vascular resistance somewhat and allowed an increase of pulmonary blood flow, for an increase in diffusion alone would be insufficient to account for the increase in oxygen consumed, i.e. in respiratory distress syndrome the oxygen consumption is presumably limited by diminished pulmonary blood flow. This certainly fits with findings reported by Chu *et al.* (1965) who demonstrated a very low pulmonary blood flow in respiratory distress syndrome, which could be increased by infusion of acetyl choline which is a pulmonary vasodilator. Thus, in considering the distribution of the cardiac output in asphyxia, the physician to the newborn has to bear in mind a much more complicated problem than the physician to the adult. The adult physician may measure an increase and redeployment of cardiac output, wondering what percentage is going to the brain, the muscles, the heart, the skin, etc. and by implication he is happy that all of the right cardiac output is going through the lungs, but in the newborn an anoxic episode may include a limitation in the lung blood flow and hence the limitation of oxygen supply to the body. Further distributions within the systemic circulation have to be considered against this background.

EFFECTS OF ASPHYXIA

In adult man or in the adult animal asphyxia has a well-recognized pattern of responses. One expects hyperventilation, tachycardia, hypertension, increased cardiac output, and redistribution of this cardiac output. Most of these responses will not occur after chemoreceptor denervation. In the later stages asphyxia will lead to bradycardia, hypotension, and respiratory failure. The newborn animal survives asphyxia for much longer than the adult (Boyle, 1970; Mott, 1961), and there is a very close relation between the length of survival and the amount of glycogen in the cardiac muscle. This relationship holds if the cardiac glycogen is varied experimentally (Stafford and Weatherall, 1960) and is also found in the human infant. If the human infant suffers a catastrophic death without asphyxia the cardiac glycogen may be as high as 47 mg./g. wet weight, while it may be as low as 2.5 mg./g. after prolonged asphyxia (Shelley, 1964).

Chemoreceptor Reflex. I have just said that the responses to asphyxia in the adult include tachycardia and hyperventilation. In 1958 Professor Michael de Burgh Daly started to report a series of analyses of chemoreceptor reflexes, which showed quite clearly that the *primary* effect of carotid chemoreceptor stimulation in the dog was to slow the heart, but that tachycardia occurred in the intact animal as a secondary consequence of hyperventilation (Daly and Scott, 1958). At first sight this seems of academic interest only, until one remembers that diving mammals and fetuses do not hyperventilate in response to hypoxia.

Professor Daly cannot be so dogmatic about the primary effect of stimulation of the aortic bodies on the heart rate. As he explained to me, most of the work in experimental animals which is designed to examine aortic chemoreceptor reflexes is less clear cut than one would wish, for even if the ascending aorta is separately perfused with asphyxial blood, he has not yet succeeded in preventing this blood from also perfusing the heart and in particular the sinoatrial node (Daly and Ungar, 1966). Daly feels that this criticism of his own work applies with even greater force when aortic body chemoreceptor responses are tested with drugs such as cyanide and lobeline. Left atrial or aortic injections will again perfuse the local nerve ganglia of the heart as well as the aortic bodies, and there is no proven pure chemoreceptor stimulant.

If the cord of the foetal lamb is tied there is a bradycardia (Dawes, Mott, and Shelley, 1959), but of course this is not necessarily an asphyxial effect, for tying the cord increases the peripheral resistance,

and the bradycardia may be a consequence of the hypertension acting through the baroreceptor reflex. The same phenomenon of bradycardia is seen when the cord is obstructed in the human foetus (Caldeyro-Barcia, 1963). Caldeyro-Barcia has also shown that when the maternal Rhesus monkey is given nitrogen to breathe for 40 seconds she shows tachycardia and hypertension while the foetus shows bradycardia. It is attractive to suggest that the bradycardia observed in the asphyxiated foetus is a direct chemoreceptor reflex, mediated on the afferent side through the chemoreceptors and on the efferent side through the vagus. Certainly the human foetus normally has some vagal tone, for Mendez-Bauer *et al.* (1963) have shown that direct injections of atropine into the foetal buttock cause quickening of the heart rate and a diminished response to rises in amniotic pressure.

A real difficulty in comparative work on the chemoreceptor reflexes is that different species (and different specimens within one species) seem to have more dominant responses either from carotid or aortic areas. As far as the adult cat, dog, and rabbit are concerned, the conspicuous respiratory responses to hypoxia arise from the carotid bodies. One needs to inquire of the situation in man, and here the evidence is scanty. Holton and Wood (1965) have shown in two adult human subjects that carotid body removal causes lack of response to hypoxia with a persistent response to hypercapnia. Thus, it appears possible that the response to oxygen lack in the human may be mediated largely through the carotid chemoreceptors.

Bradycardia of Asphyxia. In this lecture I am only considering a very limited aspect of heart rate changes in asphyxia. There is a much more complete account of these changes by Caldeyro-Barcia *et al.* (1966). While I would accept the descriptions and many of the conclusions in their work, I do not find that there is convincing evidence concerning the quantities of catecholamine release in the human infant (Comline and Silver, 1966), and therefore some of the inferences on "sympathetic tone" should, in my view, remain *sub judice*.

There are two aspects of this bradycardia which is a consequence of asphyxia in the experimental animal. Dr. Godfrey (working at The London Hospital) has shown that when nitrogen is given to the newborn rabbit, there is a precipitate fall in heart rate from 300 to about 80 beats a minute, which gradually rises back to about 100 beats a minute while gasping lasts (Godfrey, 1966a). In the vagotomized newborn animal there is a higher resting heart rate which does not fall so rapidly with nitro-

gen (Fig. 4). The heart rates of both groups are similar during the latter part of asphyxia when we are seeing the direct effect of asphyxia on the heart uncomplicated by vagal efferent effects. Thus, the two effects are: early abrupt slowing which is vagally mediated and long-lasting slowing which is a direct effect on the heart.

FIG. 4.—Effect of N₂ on heart rate of newborn rabbits (lightly anaesthetized with ether). Mean heart rate of 12 normal newborn rabbits and 13 vagotomized newborn rabbits. Vertical lines are the standard errors of the means. (From Godfrey, 1966a.)

I would like now to say a word about the newborn, or foetal rabbit as an experimental model for studying asphyxia and its treatment. First of all, I have committed the sin of speaking of asphyxia when newborn animals are being given nitrogen to breathe. The truth is that though newborn animals do gasp in nitrogen they do not maintain their PCO₂ or their hydrogen ion concentrations constant, for the PCO₂ is doubled and the hydrogen ion concentration is increased out of proportion to the CO₂ retention by the time they come to their last spontaneous gasp. I shall concentrate here particularly on the foetal and neonatal rabbit, for the situation has been examined extensively in the lamb and the Rhesus monkey (Dawes *et al.*, 1959, 1963a, b; Adamsons *et al.*, 1963). Dr. Godfrey has now examined the pleural pressure swing, the heart rate, the blood pressure, and selected reflexes of the asphyxiated foetal and neonatal rabbit. He has added some quite new knowledge in showing that this animal has lost all reflex responses examined before it comes to its last gasp, and these reflexes

FIG. 5.—Blood pressure and heart rate changes in a single newborn rabbit when given pure nitrogen (lightly anaesthetized with ether). L.S.G. = last spontaneous gasp. (From Godfrey, 1966a.)

do not return until several minutes after successful resuscitation (Godfrey, 1966b). This reflex loss is presumably central in origin, for the afferent fibres carrying stretch receptors are still “firing” when the lungs are stretched and in some phases the diaphragm is still contracting. I would like to emphasize that as the newborn rabbit is only some 50 g. in weight it requires considerable technical skill to perform these investigations in the limited periods available.

Blood Pressure in Asphyxia of Newborn. If the asphyxia is caused by occlusion of the cord there is a temporary hypertension, because when the foetal-placental circulation, which is a low resistance area, is cut off it will considerably raise the peripheral vascular resistance (Dawes *et al.*, 1959, 1963b). When, in the newborn rabbit, asphyxia is caused by nitrogen then the blood pressure falls precipitately to recover a little with the heart rate and then to fall again to very low levels (Fig. 5). Each gasp causes a small recovery of the blood pressure, and after the last spontaneous gasp heart rate and blood pressure continue to fall. At a variable stage the electrocardiographic pattern begins to change within the QRST complex and AV block develops. As in the human infant, electrical activity of the heart continues long after there is any measureable arterial pressure. Godfrey (1966a) has shown quite clearly that the chances of resuscitation of a foetal rabbit are dependent upon the mean arterial blood pressure. Blood pressures below 6 mm. Hg make recovery with intermittent positive pressure ventilation unlikely.

The pattern in the rabbit has been emphasized, for it is a convenient and cheap experimental animal which advertises the fact that it is coming to its last gasp by having a terminal acceleration of gasping (Fig. 6).

RESUSCITATION FROM ASPHYXIA

Criteria for Testing Treatments. If one considers the drugs, mainly chemoreceptor stimulants, that have been used to resuscitate animals, they can be tested at three obvious periods. (1) In the normoxic newborn animal the effect of the true chemoreceptor stimulant would show whether chemoreceptors could be stimulated in this species and whether such stimulation affected respiration. (2) During early or primary apnoea, occurring in asphyxia: here the drug would be expected to excite gasping to return earlier in an animal which will in any case gasp again (Daniel *et al.*, 1966). (3) The crucial test is to find out what the drug will do to an animal which is beyond its last spontaneous gasp—an animal that will not in fact recover unless some effective therapy is undertaken. Barrie, Cottom, and Wilson (1962) have tested vanillic acid diethylamide (ethamivan) by sublingual administration in normal newborn babies. They found that this stimulated respiration, and they recommended its use in “less severe degrees of asphyxia”, and argued that it could reduce the need for intubation and inflation. Unfortunately the accurate diagnosis of the severity of asphyxia is a very difficult one in the human baby, and generally the most likely diagnosis can only be arrived at retrospectively after the effects of proper treatment have been

FIG. 6.—Mean heart rate (clear circles) and number of gasps (solid circles) in 123 newborn rabbits exposed to N_2 . The number of gasps was measured for each rabbit in each fifth of the intermediate period between the end of primary apnoea and the onset of terminal acceleration of gasping. The vertical lines indicate the standard errors of the means. (From Campbell *et al.*, *J. Pediatr.*, **68**, 153–163, 1966, The C. V. Mosby Company, St. Louis, Missouri.)

observed. Bolton, Godfrey, and I have tested ethamivan by intravenous injection of 5 mg./kg. in newborn rabbits in the three circumstances listed above. (1) When given to the normoxic rabbit it caused hyperventilation (Fig. 7A). (2) When given to the newborn rabbit which had received nitrogen and was in primary apnoea it caused violent gasping when the animal would normally have been quiescent. It was noticeable that the total period of gasping in this animal was reduced to 7.5 minutes, while 33 normal controls, lightly anaesthetized with ether, gasped for 19.9 minutes, with a standard error of 1.1 (Fig. 7B). (3) When ethamivan was given to the newborn rabbit, which was beyond the last spontaneous gasp in nitrogen, ethamivan further lowered the heart rate and reduced the blood pressure. It did not excite any respiratory activity (Fig. 7C). Sublingual ethamivan would probably not have this effect in the severely asphyxiated infant for the perfusion of tissues at this time is so reduced that the drug would probably not be absorbed. Unfortunately, the makers of ethamivan advise that treatment should be “neonatal asphyxia . . . intravenous injection of 0.1 ml. 5% solution diluted to 1 ml. injected into the umbilical or other suitable vein”. I suggest that if ethamivan is given sublingually to a seriously asphyxiated baby it merely wastes precious seconds, while if given intravenously it would do active harm, for it would lower the blood pressure at a time when maintenance of even a minimum blood pressure seems to be quite vital. Unfortunately, just because the stage of asphyxia cannot be judged in the baby, ethamivan even when

given intravenously will seem to be effective if it has in fact been given in test period 2. It will very naturally be rated a success when given in good faith and thus will persuade the doctor to continue to use a treatment which is potentially dangerous when it is most needed.

Effective Resuscitation. When one considers the physiology of the foetal circulation outlined above it is not surprising to find that effective treatment consists of ventilating the lungs with air or with an oxygen-rich mixture. This will cause the vital re-routing of the circulation already described. Tests have been done by Cross *et al.* (1964) showing that foetal rabbits can normally be resuscitated after the last spontaneous gasp with intermittent positive pressure inflation of the lungs but cannot be resuscitated with hyperbaric oxygen. A further trial on newborn rabbits that had gas in their lungs when they were taken to the last gasp in nitrogen was undertaken by Campbell *et al.* (1966a). This showed that 34 per cent could be resuscitated in pure oxygen, 59 per cent could be resuscitated with hyperbaric oxygen, and 85 per cent could be resuscitated with intermittent positive pressure ventilation, with or without cardiac massage (these results differ significantly from one another). *The most striking fact in resuscitation is that circulatory recovery always precedes the onset of respiration.* The increase in heart rate, the rise in blood pressure, and the improvement in colour may precede by many minutes the first gasp of recovery. Whether recovery will occur or not is independent

FIG. 7A.—The effect of ethamivan (Vandid) 4.2 mg./kg. i.v. on the respiration (oesophageal pressure, OP), the blood pressure (BP), and the heart rate from electrocardiogram of a newborn rabbit (aged 1 hour), lightly anaesthetized with ether and breathing air. Two inflations were performed (tracheal pressure, TP) showing a paradoxical reflex followed by a Hering Breuer reflex before the i.v. ethamivan. Ethamivan caused vigorous overbreathing.

FIG. 7C.—The effect of ethamivan (Vandid) 5.0 mg./kg. i.v. on the blood pressure of a rabbit in secondary apnoea (see Fig. 6). Note fall of blood pressure. There was no stimulation of respiration. (Unpublished data of Bolton, D. P. G., Cross, K. W., and Godfrey, S.)

FIG. 7B.—The effect of ethamivan (Vandid) 4.2 mg./kg. i.v. on the gasping frequency of a rabbit in primary apnoea (see Fig. 6), as compared with 33 controls of Godfrey (1966a).

of whether the animal has been vagotomized (Godfrey, 1965), so one assumes that the improvement of the circulation is primarily dependent on perfusion of the heart with blood containing some oxygen. With this knowledge in mind and as the facts have been confirmed in the lamb, the Rhesus monkey, and the rabbit, we decided to examine the effects of intermittent positive pressure ventilation in babies who required resuscitation, who were in the labour wards at The London Hospital. Not surprisingly, in view of our experience, we felt that a proper monitoring of the heart rate was fundamental; therefore, on any baby in need of resuscitation, we attach the electrocardiograph and the R wave is converted to a sound pulse which is played on a loud speaker. The rest of the apparatus we

have constructed consists of a closed circuit system (Ditchburn, Hull, and Segall, 1966; Adamsons *et al.*, 1964), around which air is pumped and from which CO_2 is removed. Tidal volume is recorded quite accurately on a spirometer, and intermittent positive pressure is given at will to any desired volume or pressure. All the data obtained and any comments made by the operators are stored on a tape-recorder so that the details can be analysed at leisure. This work will be reported by my colleagues Hey and Kelly (1968), but I would like to report briefly one case and make one generalization.

My colleagues recently attended a mother whose infant had 10 minutes of proven total asphyxia before it could be intubated. The heart rate was

15 a minute at birth, as measured by the electrocardiogram. There was no palpable pulse and no heart sounds could be heard. Whether the baby should receive an Apgar score of 1 for this electrical activity of the heart is debatable. There was also evidence of anoxic damage of the heart with various types of block. Three periods of cardiac massage and intermittent positive pressure ventilation were necessary for 22 minutes; the first spontaneous gasp was given by the baby at 13 minutes after birth and 21 minutes after the start of asphyxia. The points of great interest about this baby were that the pattern of recovery was identical to that seen in our most severely asphyxiated experimental animal, and the march of recovery was as previously seen, with cardiac acceleration *preceding* gasping and also preceding adequate oxygen uptake. So far the follow-up reveals a perfectly normal baby with a normal thermogenic response to a slightly cool environment (Hill and Rahimtulla, 1965). We find (unpublished work) that an absent thermogenic response can be an early sign of asphyxial brain damage.

The generalization which we find of great interest is this: that in babies where resuscitation is necessary the oxygen consumption of the baby rises up to the basal level for the baby over a matter of one or two minutes or several minutes. This pattern is quite different from that seen when one resuscitates asphyxiated adult animals such as the rabbit. Here, when resuscitation is successful, oxygen uptake is at first very much above normal, perhaps being double that of the basal rate, and over a matter of minutes it comes down to the normal level. It seems to me likely that this contrasting pattern should take us back once more to a reconsideration of the foetal circulation. I would suggest that in the severely asphyxiated baby there is a very low pulmonary blood flow, that the increasing oxygen consumption which we see is really an index of an increasing pulmonary blood flow, and that in fact oxygen consumption is at this time limited by the high resistance of the pulmonary arteriolar vasculature. We have been fortunate in obtaining a special grant from the Medical Research Council to test this hypothesis in suitable experimental animals.

In conclusion, unless we who are working in the field of British paediatrics equip ourselves to make precise and detailed investigations when dealing with the newborn then this field of applied physiology stands in real danger of being developed in countries other than this one. If this happens, it seems to me that we shall be relinquishing our birthright, for so much of the fundamental foetal physiology has been pioneered in this country.

SUMMARY

The changes in the foetal circulation at birth normally progress steadily towards the adult pattern with an intermediate period when the shunts are partially shut and still reversible. These changes must be understood by all who treat the newborn if the treatment is to be rational. The *mechanisms* of these changes show quite clearly that the logical treatment for severe asphyxia in the newborn is to ventilate the lungs with air or oxygen (for this is the prime mover in obtaining the adult pattern of blood flow), and to raise arterial pressure by cardiac massage if necessary. Drugs, which are advertised for resuscitation, lower the blood pressure in the grossly asphyxiated experimental animal.

My thanks are due first to my research colleagues, both academic and non-academic, who have done most of the work which I have described. I would also like to acknowledge the remarkable co-operation I have received from my clinical colleagues and the nursing staff of The London Hospital. At different stages the work has been supported by The Spastics Society, the Nuffield Foundation, the Wellcome Trust, and the Sir Halley Stewart Trust.

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