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THE EFFECTS OF LABOUR ON THE FOETUS AND THE NEWBORN

Report of a WHO Scientific Group

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WHO SCIENTIFIC GROUP ON THE EFFECTS OF LABOUR ON THE FOETUS AND THE NEWBORN

Geneva, 12-18 May 1964

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THE EFFECTS OF LABOUR ON THE FOETUS AND THE NEWBORN

Report of a WHO Scientific Group

1. INTRODUCTION

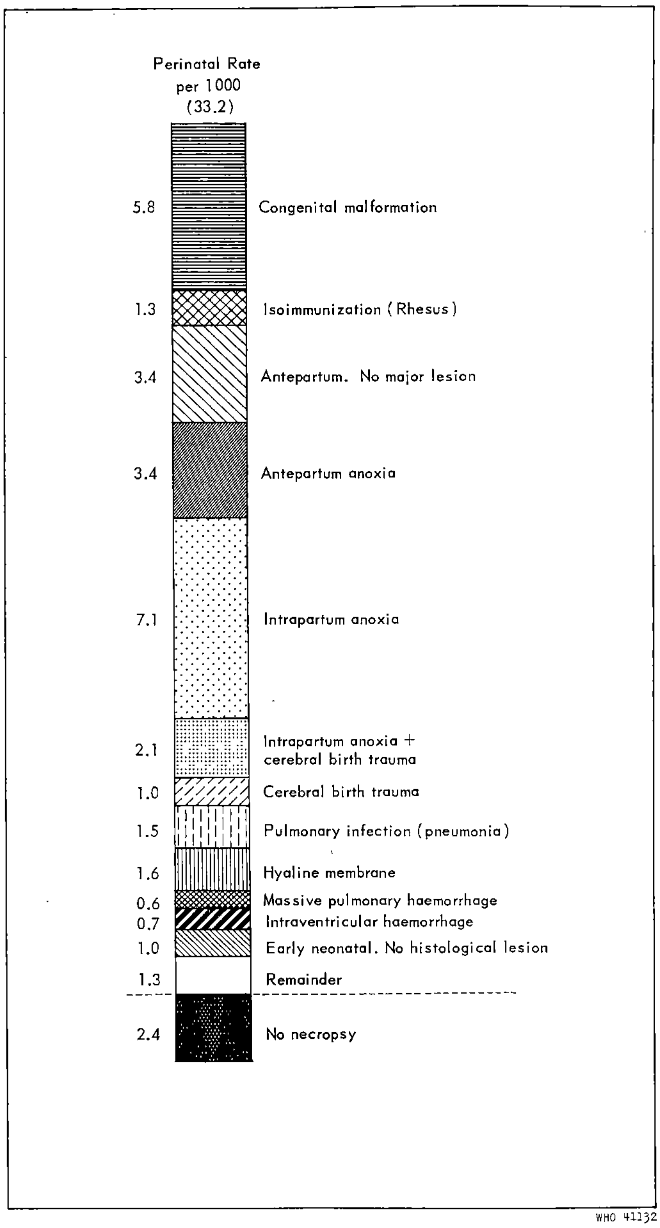
A WHO Scientific Group was convened in Geneva from 12 to 18 May 1964 to advise the Director-General on current research into the effects of labour on the foetus and the newborn. The meeting was opened by Dr F. Grundy, Assistant Director-General. Professor D. H. Barron was elected Chairman, Professor M. A. Petrov-Maslakov, Vice-Chairman, and Dr G. S. Dawes and Dr L. S. James, Rapporteurs.

The effects of labour on the foetus and newborn infant are ultimately to be judged by perinatal mortality and by the long-term sequelae in the child. There is much useful information available about perinatal mortality. The rate has dropped in many countries to around 30 per 1000 births, but during the past ten years this figure has remained almost stationary. That is to say, the improvement, which was noticeable from the beginning of the century and which was accelerated by the introduction of methods for treating bacterial infections, has practically ceased. Yet one recent investigation (the British Perinatal Mortality Survey) has indicated that further improvement is still possible. It states, for instance, that: " intrapartum anoxia was the most common cause of perinatal death at 22.9%. Most of these infants were otherwise normal and born after 38 weeks gestation ; clearly they constitute the group with the greatest potential for salvage " and " ...of those with intrapartum anoxia, one in eight was born alive but failed to respond to resuscitation ".[1] Some of the data from this survey are shown in Fig. 1. Experience in other countries, while differing in detail, also suggests that many infants could be saved with better deployment of medical resources and application of existing knowledge.

We have much less factual information on the effects of the long-term sequelae of labour on the infant. Certainly, some children suffer brain damage at birth that permanently cripples them and leaves them as a charge on the community for the rest of their lives. But how many of the spastic or mentally subnormal children have suffered injury during the perinatal

[1] Butler, N. R. & Bonham, D. G. (1963) *Perinatal mortality. The first report of the 1958 British Perinatal Mortality Survey*, Edinburgh and London, Livingstone, p. 293.

FIG. 1. PRIMARY NECROPSY FINDING (1958 BRITISH PERINATAL MORTALITY SURVEY)



SOURCE: Butler, N. R. & Bonham, D. G. (1963) *Perinatal mortality. The first report of the 1958 British Perinatal Mortality Survey*, Edinburgh and London, Livingstone. (Reproduced by kind permission of the publishers and of The National Birthday Trust Fund.)

period is not known. The suspicion that there may be a proportion of such children whose condition is entirely preventable is one of the greatest spurs to future investigations of this subject.

2. THE INITIATION OF LABOUR AND THE LIFE EFFICIENCY OF THE INFANT

The actual causes of the initiation of labour are still undetermined. The fitness of the mother to undergo labour and to preserve the child and the ability of the foetus to withstand the stress of labour and the transition to extra-uterine life both affect the final outcome. Indeed, the health and well-being of the mother before and during pregnancy determine to a great extent the physiological reserves with which the infant faces the future. From this point of view the mother and her baby *in utero* must be regarded as a whole.

The size and development of the infant at birth, its metabolic reserves, and its capacity for homeostatic regulation are significant factors in survival. But it is not only the infant's survival that must be ensured; of major importance is the safeguarding of its capacity for a full life and its reproductive efficiency, which can be compromised by inadequate care of the mother and child before, during, and after delivery.

3. PLACENTAL FUNCTION AND THE NORMAL INTRA-UTERINE ENVIRONMENT

In addition to acting as the organ of gaseous exchange, the placenta performs many other functions vital for the maintenance of pregnancy and for normal foetal growth. It also acts as a barrier separating the foetus from its mother, who is genetically distinct. The complex interaction of immunological endocrine factors in the foetus, placenta, and mother is incompletely understood.

Regarding gaseous exchange, several pertinent questions can be asked. Does the foetus have to make do with its placenta, or does the functional capacity of the placenta become adapted to its needs? Observations at high altitudes suggest that adaptation can occur in both mother and placenta, but more detailed quantitative information is needed. Studies of human placental development have shown a much higher incidence of abnormal features in monochorionic twin pregnancies, such as velamentous insertion of the cord and unusual umbilical vascularization. These studies provide an indication of some of the factors that may influence early placental growth.

In considering the transport function of the placenta, particular attention should be given to gas transfer, since this is directly related to the immediate effects of labour on the foetus. Other substances such as hormones, proteins and fats are likely to be of significance over a long term, and on this point more information is required. The blood-glucose of the foetus is closely related to that of the mother, and the maintenance of an adequate supply of glucose to the mother and foetus during labour is of considerable importance.

Direct measurements on human foetuses *in utero* are as yet insufficient to give a clear picture of the normal internal environment. It is only during the last few years that information has become available from animal experiments with long-term implantation of catheters. These have shown that the partial pressure of arterial oxygen (pO_2) of the foetus is very stable during the last half of gestation. Although it is low by adult standards it does not fail, nor does the O_2-carrying capacity of the blood rise, until shortly before or during delivery. Contrary to what was once thought, there is no direct evidence to support the view that in a normal pregnancy the foetus outgrows the capacity of the placenta to supply it with its basic needs. It does not appear to suffer from O_2 lack, probably because of a reasonable O_2 saturation and high umbilical and foetal systemic blood flow. The maternal arterial pCO_2 is reduced during pregnancy and the foetal arterial pCO_2 is normally at approximately the same level.

In contrast to the great increase in basic knowledge of pulmonary physiology in recent years, advances in our understanding of gas and solute transfer across the placenta have lagged behind. Although the blood supply to the uterus can be modified by administration of catecholamines and oestrogens, the proportion flowing to the placenta, as opposed to that flowing to the myometrium, is not known. The physiological control of blood flow through the foetal side of the placenta (the umbilical circulation) has been studied in more detail, but the dynamic and mutual adjustment of the two blood-streams within the area of gas and solute exchange has not been investigated. Interpretation of measurements of the diffusion capacity of O_2 and urea is hindered by lack of precise information on the nature of the barriers to diffusion and O_2 consumption within the placenta itself. Nevertheless, there is evidence that, in the lamb, the diffusion capacity of urea increases during the last half of gestation, although the placenta has already reached its maximum weight, and histological investigations show that the placenta continues to develop in this as in other species. There are no adequate tests of placental sufficiency, and in their absence we have to rely on human studies of such criteria as weight, morphological appearance, and foetal survival.

4. THE EFFECT OF LABOUR ON THE INFANT

Delivery is accomplished by uterine contractions that dilate the cervix and, aided by the contractions of the abdominal muscles and diaphragm during the second stage, bring about the birth of the infant. A normally developed, healthy foetus withstands without harm the stress of normal labour, the compression of the head and body, and the transient diminution of placental blood flow accompanying uterine contractions, and is born in a healthy condition. There are even some indications that normal labour facilitates the infant's adaptation to extra-uterine life. But the foetus may not withstand the stress of labour when this is greater than usual, and when its physiological reserves are reduced by disease or other abnormal circumstances. Labour may then cause intrapartum death or result in the delivery of a depressed infant that does not survive or is liable to subsequent complications. The British Perinatal Mortality Survey noted that " intrapartum anoxia and/or birth trauma were ... responsible for almost one in three of all perinatal deaths ".[1] Irreversible brain damage may also result from intrapartum or neonatal asphyxia when the foetal reserves are insufficient.

The immediate effect of labour on the infant has been assessed by changes in the foetal heart rate and in movements. The usefulness of these methods of assessment has been much increased during the last few years, firstly by the more extensive use of automatic recording methods, and secondly by observing the effect of stimuli applied to the mother—stimuli that have included hot and cold applications, the injection of insulin, and the temporary arrest of breathing. These changes often give warning of impending disaster and their recognition is useful as a guide to therapeutic measures. Accuracy of observation has been improved (for research purposes) by making direct records from the foetus *in utero*, both in animals and in man. Nevertheless, additional objective methods of assessing the physiological condition and the reserves of the human infant *in utero* are badly needed. In looking for new methods both the empirical approach and the application of known physiological principles derived from animal experiments should be employed. There is too much dependence on changes in heart rate, which are apparent only when the physiological reserves of the infant are almost exhausted and which represent changes in the cardiovascular system alone.

A brief, rapid decrease in heart rate, occurring within a few seconds of the peak of a uterine contraction (Type I dip; Fig. 2), is usually caused by

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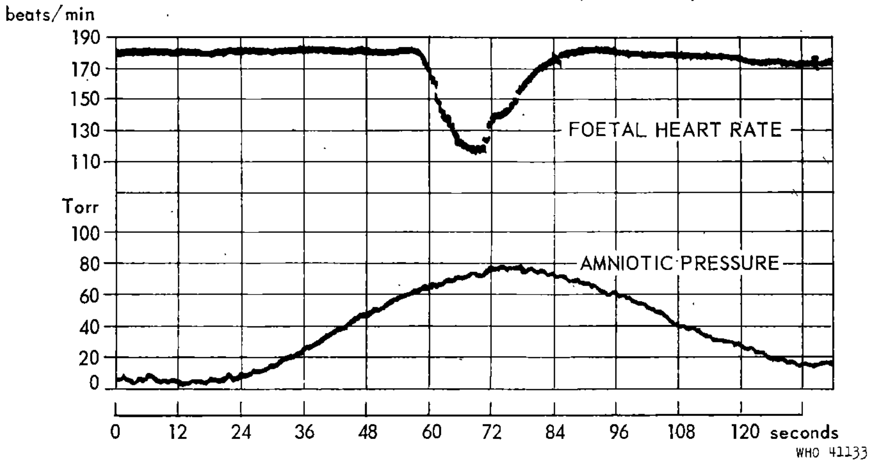
[1] Butler, N. R. & Bonham, D. G. (1963) *Perinatal mortality. The first report of the 1958 British Perinatal Mortality Survey*, Edinburgh and London, Livingstone, p. 293.

FIG. 2. CHRONOLOGICAL RELATIONSHIP BETWEEN UTERINE CONTRACTIONS AND DECREASE IN FOETAL HEART RATE (TYPE I DIP) *

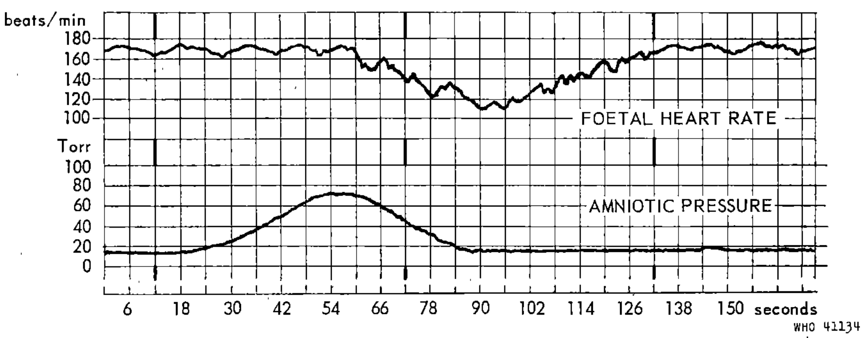


SOURCE: Caldeyro-Barcia, R., unpublished data.

* Cf. Fig. 3.

compression of the foetal head. This effect is usually recorded after rupture of the membranes and when cervical dilatation has progressed beyond 5 cm. Manual compression of the head has the same effect, which is attributed wholly to excitation of the cardiac branches of the vagus nerve, since it is abolished by injection of atropine into the foetus. Of more sinister significance is a longer-lasting decrease in heart rate, the rate reaching its minimum about 45 seconds after the peak of a uterine contraction (Type II dip; Fig. 3). This bradycardia of slow onset is not wholly abolished by atropine and has

FIG. 3. CHRONOLOGICAL RELATIONSHIP BETWEEN UTERINE CONTRACTIONS AND DECREASE IN FOETAL HEART RATE (TYPE II DIP) *



SOURCE: Caldeyro-Barcia, R., unpublished data.

* Cf. Fig. 2.

been shown to be due to partial foetal asphyxia. It is of particularly bad prognostic significance when superimposed on a heart rate already elevated above the normal level (e.g., over 160 beats per minute) and when associated with rapid fluctuations in rate. The hypoxaemia that gives rise to it may be due to compression of the umbilical cord or, more often, to a decrease in the maternal placental blood flow due to compression of the vessels as they pass through the myometrium or (as shown by angiography, in about one-sixth of the women studied) to compression of the descending aorta by the contracting uterus when the patient is in the supine position.

The position adopted by the mother in labour varies in different countries, and even in different communities within the same country. Adoption of the supine position during labour is now believed to be unfavourable to the foetus, since it leads to partial obstruction of the inferior vena cava and predisposes to compression of the aorta during uterine contractions. The signs of foetal distress (as instanced by prolonged bradycardia of slow onset) have been decreased or abolished in a number of women by changing them from a supine to a lateral position.

Raising the pO_2 of the maternal blood by giving the mother 100% O_2 to breathe causes an increase in foetal arterial pO_2 in experimental animals and can sometimes reduce the signs of foetal distress during human labour. Conversely, the administration to the mother of mixtures low in O_2 (e.g., 10.5% O_2 in nitrogen or in nitrous-oxide-air mixtures) invariably causes a fall of foetal arterial pO_2 in experimental animals and may induce signs of foetal distress in human labour. *The use of apparatus for anaesthesia or analgesia that allows the mother to inhale gas mixtures containing less than 21% O_2, even for short periods of time, is potentially dangerous and should be abandoned.*

5. ABNORMAL PREGNANCY AND LABOUR

A very high proportion of pregnancies are to some degree abnormal. In general, disease processes in the mother or disorders of the pregnancy itself (e.g., bleeding) interfere with the growth and development of the foetus. The foetus thus approaches labour less able to withstand stress and to face the adaptations needed in the neonatal period. Sometimes a disorder of pregnancy is also responsible for the premature onset of labour. A poorly grown child born prematurely, and depressed (i.e., unresponsive), may have great difficulty in surviving the neonatal period.

Many of the syndromes of abnormal pregnancy—e.g., pre-eclampsia and premature separation of the placenta—are of unknown etiology. While the worst effects of these and other abnormal conditions can be prevented by skilled ante-natal, intrapartum and neonatal care, such care calls for the deployment of considerable medical resources. *A concerted* *effort is needed to study afresh these and other syndromes of abnormal pregnancy by engaging the interest and co-operation of obstetricians, physicians, and other specialists in related disciplines.*

Diabetes, which is associated with a high incidence of pre-eclampsia and polyhydramnios and has unusual effects on the growth and development of the foetus, offers the opportunity for a particularly valuable natural experiment. *In institutions where large numbers of mothers suffering from various forms of diabetes mellitus can be collected, intensive multidisciplinary team studies are likely to provide rapid results.*

Abnormal labour may endanger the infant in several ways. Inadequate uterine contractions lead to mechanical difficulties in labour and delivery. By prolonging labour they increase the risk of intrapartum infection. They are an indication for the use of oxytocic drugs, with the possible risks that this entails.

Excessive contractions (arising without obvious cause or in association with, for example, premature placental separation, severe pre-eclampsia, or the injudicious use of oxytocic drugs) may produce hypoxaemia of the foetus.

Hypoxaemia may also result in labour, from deficient uterine blood flow secondary to an abnormal condition of pregnancy in the mother. Maternal hypotension leading to inadequate uterine blood flow may follow on maternal blood loss, or the use of such drugs as chlorpromazine, or spinal or epidural analgesia.

Several of these problems may occur in the same individual, and their effect on the foetus is cumulative.

6. ORGAN AND ENZYME MATURITY

The condition of the foetus at birth is important in determining its ability to survive the stresses of labour and the change to an extra-uterine existence. It should be recognized that the various organs of the body do not develop and mature at the same rate during gestation. For instance, the late development of the lung is one of the principal obstacles to survival at birth after premature delivery, and the capacity for renal excretion is also limited in the newborn infant. Similarly, within any one organ the concentrations of enzymes are not always at the adult level : two particularly striking examples are hepatic glucuronyl transferase and glucose-6-phosphatase. These are of special interest because of their importance in bilirubin excretion and in hepatic glycogen mobilization respectively.

After birth the concentration of these enzymes rises rapidly. That of glucose-6-phosphatase may come to exceed the adult level very greatly. Among the mechanisms that may be responsible for the rise are all those resulting from the separation of the foetus from its mother, including asphyxia and neonatal hypoglycaemia. In the case of glucose-6-phosphatase the rise in enzyme concentration may be due to the cessation of " product repression ", since it can be prevented by glucose administration. *Further work is certainly needed to improve understanding of these interesting and sometimes critical changes.*

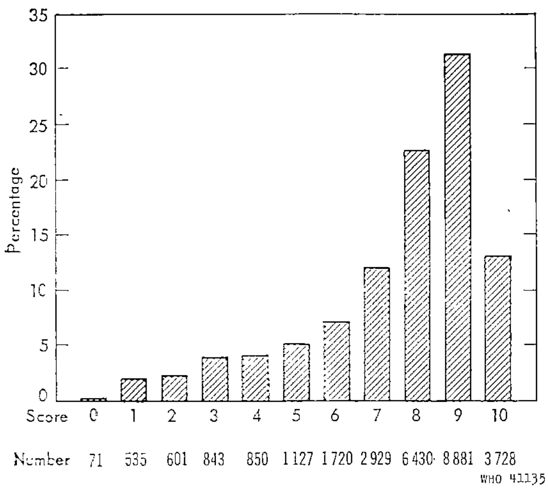
7. THE NORMAL INFANT AT BIRTH

After an uneventful labour and delivery in which few or no sedatives or analgesic drugs have been given to the mother, the healthy newborn infant begins to breathe promptly, and within a few seconds is crying lustily.

The Apgar scoring system has proved to be a useful aid for clinically evaluating the condition of the baby during the first few minutes of life and is being widely used in children from different ethnic groups. It is given one minute after the complete birth of the infant and is based on five signs : heart rate, respiratory effort, muscle tone, reflex irritability, and colour. A score of zero is given for each of the following conditions : no heart beat ; no respiratory effort ; no muscle tone ; no response to a glancing slap on the soles of the feet ; and a blue or pale colour. A score of one is given for a slow heart beat (under 100) ; slow or irregular respiratory effort ; some flexion of the extremities ; a grimace in response to a glancing slap on the soles of the feet ; and a pink body with blue extremities. A score of two is given for a heart rate over 100 ; a good respiratory effort accompanied by crying ; good flexion ; a cry in response to the slap on the feet ; and a body pink all over.

The distribution of the score at one minute for 27 715 newborn infants delivered at one institution over an eight-year period is presented in Fig. 4

FIG. 4. DISTRIBUTION OF APGAR SCORE IN 27 715 LIVEBORN INFANTS WEIGHING OVER 500 GRAMS AT BIRTH



SOURCE : Based on data from : Apgar, V. & James, L. S. (1962) *Amer. J. Dis. Child.*, **104**, 419.

and the 28-day mortality in Fig. 5. This method of evaluation and graphic presentation might prove a useful index for comparison of the conditions of newborn infants in different institutions and countries in which obstetric and anaesthetic practice varies widely (see Fig. 6). The score at five minutes appears to give a better correlation with the long-term prognosis.

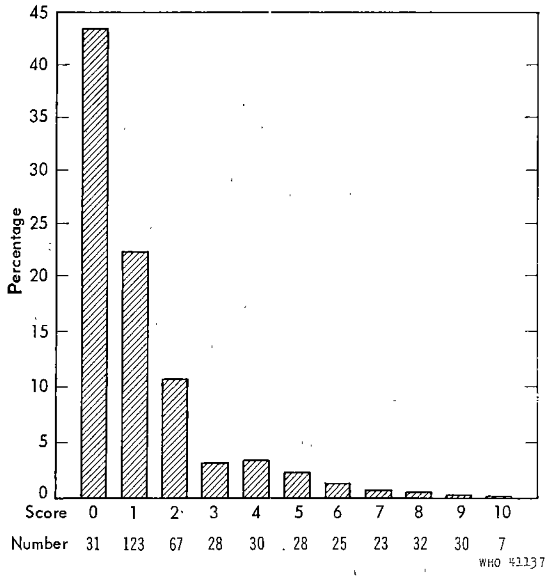


FIG. 5. MORTALITY (28-DAY) ACCORDING TO APGAR SCORE IN 27 715 LIVEBORN INFANTS WEIGHING OVER 500 GRAMS AT BIRTH

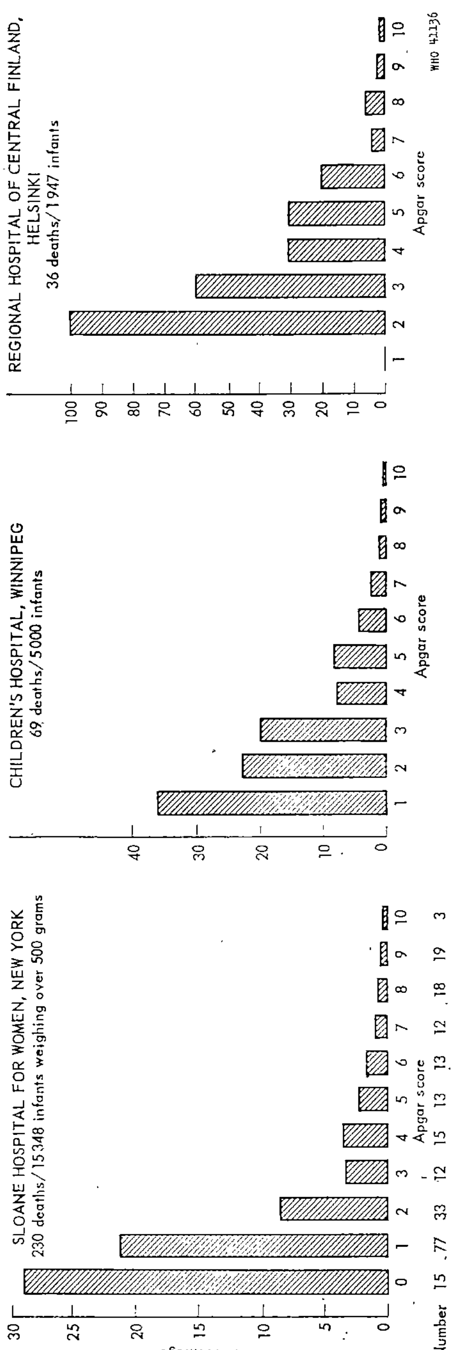
SOURCE: James, L. S. (1960) *Anesthesiology*, **21**, 405. (Reproduced by kind permission of the publishers.)

The majority of infants are vigorous, have a score of 7-10 and cough or cry within seconds of delivery. No special procedures are necessary for them. Mildly to moderately depressed infants score 4, 5, or 6. Although they are blue and have not established sustained respiration, their heart rate and reflex irritability are good. The severely depressed infants score 0, 1, or 2, points being given for heart beat and occasionally a feeble reflex response. This third group requires prompt and careful resuscitation.

Asphyxia and maternal medication can both cause depression at birth. Other factors such as precipitous or traumatic delivery, pre-natal infection, congenital defects, and prematurity are additional causes. At delivery it is difficult to separate these factors, although some can be anticipated. Because of the possibility that one factor interacts with or potentiates another, additional means for differential diagnosis are needed.

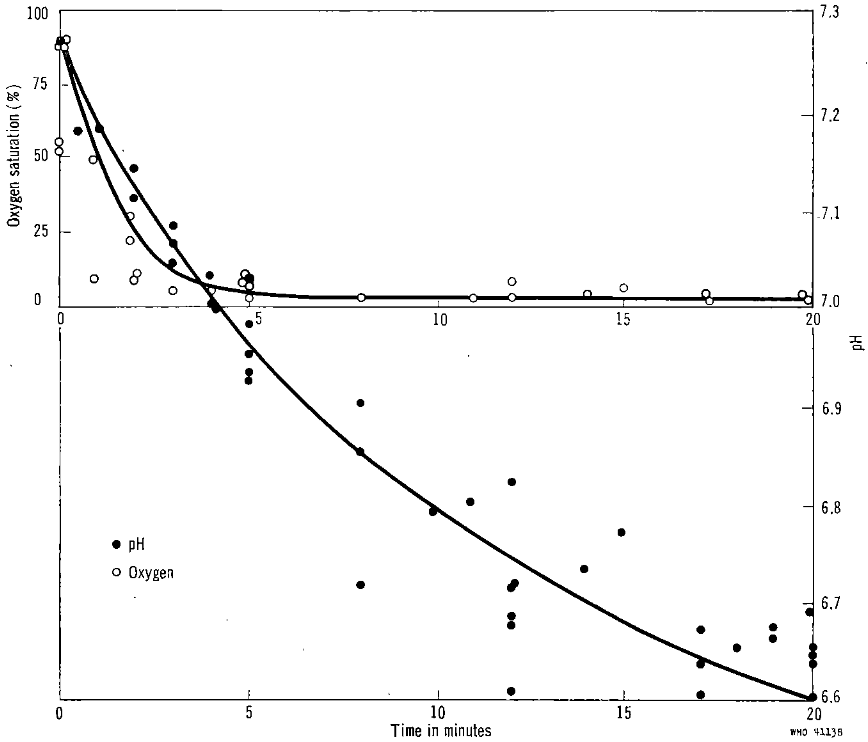
In the most vigorous infants, oxygen levels in the umbilical arterial blood at birth range from zero to nearly 70% saturation. This wide range and, in particular, the presence of zero levels in completely healthy infants indicate that during the final stages of delivery there has been an interference

FIG. 6. DISTRIBUTION OF DEATHS BY APGAR SCORE IN THREE DIFFERENT CENTRES



SOURCE: Based on data from: Apgar, V. & James, L. S. (1962) *Amer. J. Dis. Child.*, **104**, 419.

FIG. 7. CHANGES IN OXYGEN SATURATION AND pH IN APNOEIC NEWBORN PUPPIES



SOURCE: James, L. S. (1960) *Acta Paediat.*, **49**, Suppl. 122, 17. (Reproduced by kind permission of the publishers.)

in the gaseous exchange between mother and infant. These varying degrees of hypoxia are accompanied by varying degrees of hypercapnia and acidosis. Immediately following birth there is an increase in acidosis, which continues for several minutes despite good lung expansion and rapid reoxygenation. The relationship of acidosis to hypoxia and the brief increase in acidosis following delivery support the concept that the healthy infant becomes mildly asphyxiated [1] during the course of delivery. Oxygen saturation in normal infants averages 22%; in nearly one-quarter of such infants it is 10% or less. This indicates that the oxygen supplies are low or exhausted immediately after birth even in the most healthy, vigorous newborn.

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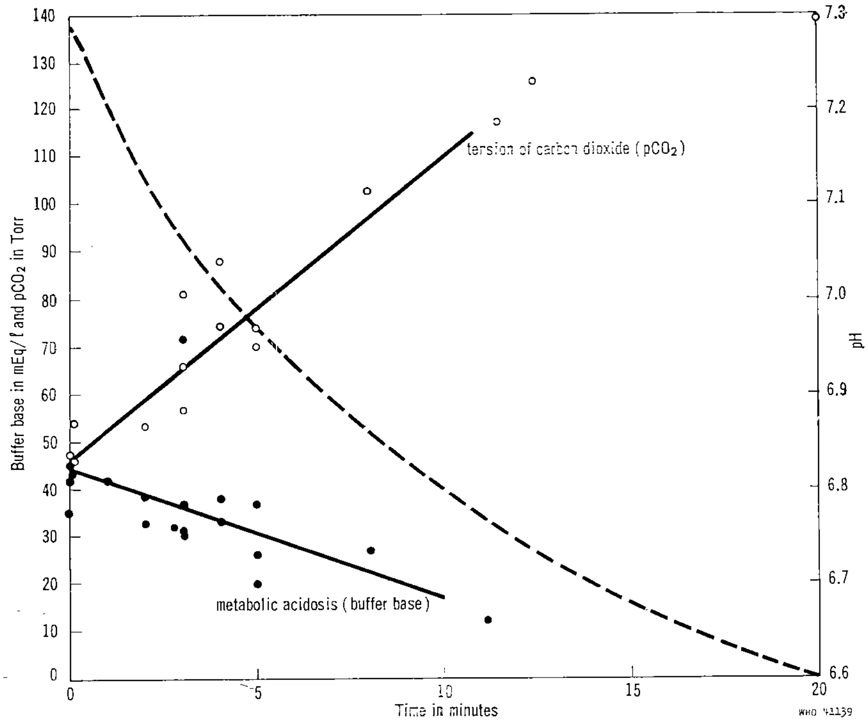
[1] Asphyxia as used here describes the condition of the infants' arterial blood and connotes hypoxaemia plus hypercapnia and acidosis. Unresponsive infants are described in this report as *depressed* rather than asphyxiated.

Animal experiments indicate that under conditions of asphyxia the blood gases change rapidly, the oxygen content of arterial blood falls to near zero in 2½ minutes, the carbon dioxide content rises at a rate of approximately 10 Torr per minute and the pH initially falls at a rate of approximately 0.1 pH units per minute (Fig. 7 and 8). The rapidity with which the blood gases change indicates that in the healthy newborn the period of asphyxia is quite brief and probably acts as one of the major stimuli to respiration.

The return of the blood gases to normal is rapid, but it takes up to 2-3 hours to achieve a relatively normal acid-base balance—primarily by pulmonary excretion of CO_2. Within 24 hours the healthy newborn has reached the same acid-base state as the mother's before labour started. Knowledge of the way in which healthy, vigorous infants recover from the asphyxial effect of delivery and achieve a normal acid-base balance puts one in a better position to evaluate the depressed or premature infant in whom the ability to make such an adjustment is impaired.

FIG. 8. DEVELOPMENT OF A RESPIRATORY AND METABOLIC ACIDOSIS WITH ASPHYXIA IN NEWBORN PUPPIES



SOURCE: James, L. S., unpublished data.

8. CARDIOPULMONARY ADJUSTMENTS AFTER BIRTH

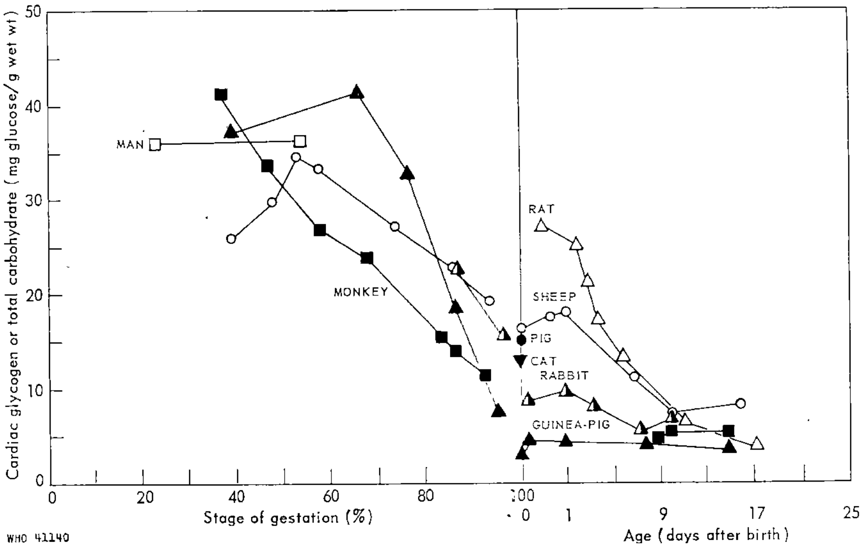
From observations on man and on animals much is now known about the establishment of normal breathing and of the circulatory adjustments that occur after birth. The initiation of breathing is due to a combination of asphyxia and sensory stimuli. Its maintenance, at an arterial pO_2 substantially above that which obtains during foetal life, is attributed to a continued inflow of sensory stimuli to the respiratory centres, but the mechanisms that initiate and sustain the activity of the respiratory centres need further investigation. So also does the quantitative interaction of pCO_2, pO_2, pH and temperature in the regulation of respiration in the newborn. The other parameters of respiratory function—e.g., the subdivisions of lung volume—have been investigated much more thoroughly. In the mature, healthy, vigorous infant the lung is capable of ample gas exchange within a few minutes of birth.

Adjustment of the circulation after birth depends primarily on the establishment of an adequate pulmonary blood flow. The pulmonary vascular resistance of the foetus and newborn is extremely labile and considerable changes have been observed even before expansion of the lungs. The physiological regulation of pulmonary flow before and after birth deserves further investigation, since large blood-flows through underventilated areas of lung after birth result in hypoxaemia. The natural history of, and reasons for, the closure of the foetal vascular channels have been studied in some detail. The studies indicate that there is an intermediate condition of the circulation that may last for some days, in which large shunts of blood may take place between different parts of the circulation. Much less is known about the regulation of the systemic circulation in the foetus and newborn ; in them, for instance, the skin is a much larger organ relative to the whole than in the adult. More detailed quantitative information is needed on cardiac output (both in normal and sick infants) and on its distribution to the coronary vessels, brain, liver, and kidney, to take only a few examples. The few investigations available, on blood flow to the foot and skin, demonstrate that the newborn infant can adjust these regional circulations with considerable efficiency. The circulation to the brain in the foetus and newborn should be of particular interest, since the brain comprises so large a fraction of the infant's weight. And it is worth remarking that no direct measurements are yet available of cerebral O_2 consumption, which even in the five-year-old child is one half of the total O_2 consumption at rest.

9. THE METABOLIC RESERVES OF THE FOETUS AND NEWBORN INFANT AND THEIR CONTROL

During foetal life large metabolic reserves are normally accumulated. The concentration of glycogen in the liver, skeletal muscle and heart rises during gestation and fat is laid down, to a different extent in different species (Fig. 9 and 10). We do not know in detail the mechanisms that

FIG. 9. CARDIAC GLYCOGEN IN DIFFERENT SPECIES BEFORE AND AFTER BIRTH



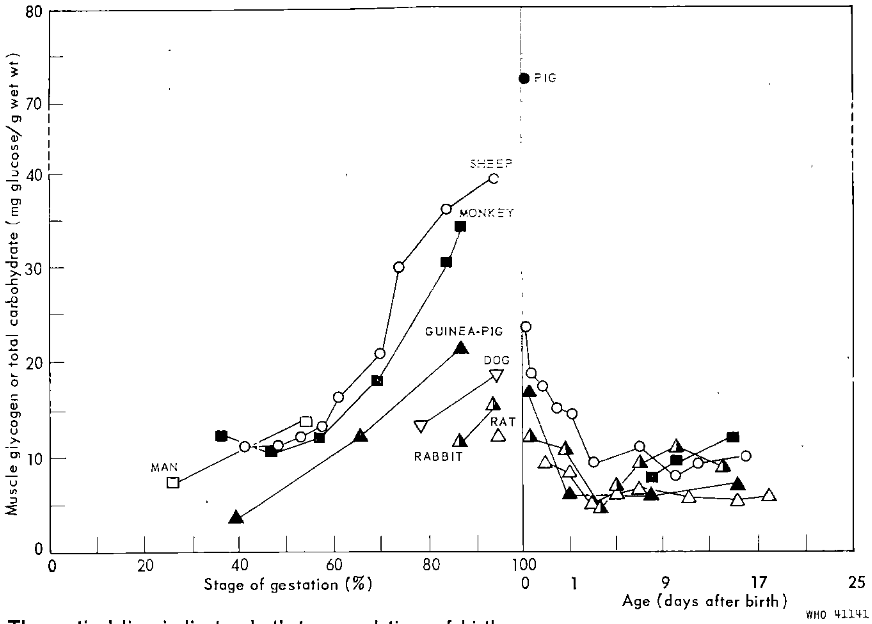
The vertical line indicates both term and time of birth.

- □ Man (Villee, C. A. (1954) *Cld Spr. Harb. Symp. quant. Biol.*, **19**, 186)
- ■ Rhesus monkey (Shelley, H. J. (1960) *J. Physiol.*, **153**, 527; and unpublished data)
- ○ Sheep (Shelley, H. J. (1960) *J. Physiol.*, **153**, 527)
- ● Pig (McCance, R. A. & Widdowson, E. M. (1959) *J. Physiol.*, **147**, 124)
- ▼ Cat (H. J. Shelley, unpublished data)
- △ Rat (Dawes, G. S., Mott, J. C. & Shelley, H. J. (1959) *J. Physiol.*, **146**, 516)
- ◭ Rabbit (Dawes, G. S., Mott, J. C. & Shelley, H. J. (1959) *J. Physiol.*, **146**, 516; Shelley, H. J., unpublished data)
- ▲ Guinea-pig (Dawes, G. S., Mott, J. C. & Shelley, H. J. (1959) *J. Physiol.*, **146**, 516; Shelley, H. J., unpublished data)

SOURCE: Shelley, H. J. (1961) *Brit. med. Bull.*, **17**, 137. (Reproduced by kind permission of the publishers.)

control these processes. The glycogen reserves of the heart fall, even before delivery, in animals such as the lamb and calf, which are born in a very mature condition. But there are large quantities left in the young of species born in a less mature condition that enable the circulation to be maintained during asphyxia, in the course of which they are reduced and may be exhausted.

FIG. 10. SKELETAL MUSCLE GLYCOGEN IN DIFFERENT SPECIES BEFORE AND AFTER BIRTH



The vertical line indicates both term and time of birth.

- □ Man (Villee, C. A. (1954) *Cld Spr. Harb. Symp. quant. Biol.*, **19**, 186)
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- ● Pig (McCance, R. A. & Widdowson, E. M. (1959) *J. Physiol.*, **147**, 124)
- ▽ Dog (Schlossmann, H. (1938) *J. Physiol.*, **92**, 219)
- △ Rat (Martínek, J. & Mikuláš, I. (1954) *Physiol. bohemoslov.*, **3**, 53; Stafford, A. & Weatherall, J. A. C., personal communication)
- ◭ Rabbit (Shelley, H. J., unpublished data)
- ▲ Guinea-pig (Shelley, H. J., unpublished data)

SOURCE: Shelley, H. J. (1961) *Brit. med. Bull.*, **17**, 137. (Reproduced by kind permission of the publishers.)

The very large glycogen reserves of the liver can be mobilized by asphyxia during foetal life, but the blood-glucose concentration is altered little by intravenous infusions of adrenaline or glucagon. The reason for this is still unknown. However, in the hours after birth the liver glycogen falls to very low levels, because the supply of glucose from the placenta has ceased. In normal infants the liver glycogen at birth is sufficient to tide the infants over the first 24 hours before feeding is established. But in many infants the blood-glucose drops to dangerously low levels—20 mg/100 ml or less. Clinical experience has shown that prolonged hypoglycaemia, particularly when associated with neurological manifestations, leads to permanent cerebral damage. It has been argued that since low blood-glucose levels have been seen in normal infants with no neurological signs, the glucose concentration is of little importance. Recent experiments on newborn animals have shown that hypoglycaemic fits are not observed when the blood-lactate concentration is high, but appear when it is lowered. These observations may explain the clinical findings. They emphasize the importance of a better understanding of carbohydrate metabolism in this critical period of life.

The glycogen reserves of skeletal muscle are also much higher at normal birth than in the adult. These reserves, unlike those of the liver, are not available generally but are consumed locally. In infants dying of respiratory distress there is no carbohydrate left in the respiratory muscles.

The fat reserves of the body may be considerable at birth, though there are large species variations. Recently attention has been concentrated on the stores of brown adipose tissue, which are of particular significance for temperature control after birth. Some species, such as the rabbit, have large reserves of brown fat (5% of body-weight) and the human infant also has considerable quantities. On exposure to cold the O_2 consumption is raised and the temperature of the brown fat rises higher than that elsewhere in the body. Removal of brown fat almost wholly destroys the ability of an animal to raise its O_2 consumption on exposure to cold and grossly impairs its thermal stability. Some animals, such as the rat, are born with comparatively little fat, and their ability to maintain their body temperature is especially dependent on early feeding.

The importance of these metabolic reserves is clearly established. They are relatively less in infants that are underweight for their gestational age at birth, and they may be decreased by asphyxia. The effects of some forms of abnormal pregnancy and placentation and of abnormal labour are therefore to reduce the metabolic reserves possessed by the infant at birth. Hypoxaemia after birth also reduces the ability of the infant to increase its O_2 consumption on exposure to cold. These considerations emphasize the need to maintain the infant in a warm environment. The desirability of feeding within the first few hours after birth should be explored further, along with the question of maintaining an adequate supply of glucose, water, and salts. Continued experimental investigation of the accumulation and dissipation of these metabolic reserves is also required.

10. OXYGEN CONSUMPTION AND THERMAL ENVIRONMENT IN THE NEWBORN INFANT

In the period immediately after birth, deep body and skin temperatures fall rapidly, at a rate of approximately 0.1°C and 0.3°C per minute respectively in an average delivery-room temperature of 25°C. This gives a calculated heat loss of approximately 200 cal/kg/min. These losses exceed maximum observed heat production threefold and indicate that, irrespective of the infant's metabolic rate, there will always be a fall in body temperature when environmental conditions are unfavourable (e.g., low room temperature).

Recovery from birth asphyxia is influenced by the stress imposed by this loss of heat. Under these conditions vigorous infants are able to achieve and maintain a relatively normal pH. This is accomplished by increasing CO_2 elimination to compensate for the persistent metabolic acidosis. Infants depressed for even a brief period at birth are unable to maintain their pH and develop a larger metabolic acidosis in a cold environment.

Oxygen consumption is regulated predominantly by the thermal gradient *across the body surface*—i.e., the thermal gradient between subcutaneous heat and the environment—and not by the absolute values of either skin or core temperature. In order to reduce the metabolic rate to basal levels, therefore, abolition of this gradient alone is sufficient. Thus, the mere placing of a cold infant in an environment in which both the air temperature and that of radiating surfaces are equal to or greater than the skin temperature will reduce its O_2 consumption to basal levels. For the maintenance of basal metabolism, conditions for heat dissipation must also be present once normal body temperature has been reached. If no allowance is made for heat dissipation, body temperature will rise, leading to restlessness and a marked increase in metabolic rate.

These new data have several practical implications. They indicate the conditions under which the metabolic demands of the newborn infant may be reduced to a minimum and enable it to conserve its energy stores. The placing of an infant in warm air only (as in standard incubators) will not provide basal conditions if the radiating surfaces (the walls of the room, etc.) are cold.

11. RESUSCITATION AND BRAIN DAMAGE

In severely depressed infants resuscitation may be necessary. The initial object of resuscitation is to restore the uptake of oxygen and the elimination of carbon dioxide as rapidly as possible. In apnoeic infants the most effective method is by inflation of the lungs with O_2-enriched gas mixtures. If the heart rate does not increase rapidly within half a minute of ventilation, this indicates that the pulmonary blood flow is inadequate (even though the heart is still beating). It is then necessary to apply external cardiac massage repeatedly until the heart accelerates considerably, if continuing asphyxia is to be avoided. In a severely asphyxiated infant an interval of some minutes may elapse after recovery of the circulation and restoration of normal O_2 uptake before gasping begins, and an even longer period of time before rhythmic breathing is established.

In rhesus monkeys asphyxia after delivery at term causes a brief period of respiratory efforts followed within a minute by *primary apnoea*. In unanaesthetized animals primary apnoea may last only 1-2 minutes, but administration of anaesthetics or analgesics greatly increases its duration. There then follows a sequence of gasps. Asphyxia after the last gasp (i.e., *secondary apnoea*) causes permanent brain damage of rapidly increasing severity. The lesions are bilaterally symmetrical and widely distributed in the brain stem, but certain nuclei (e.g., those of the inferior colliculi and corpora quadrigemina) are most susceptible to asphyxial damage. Rapid intravenous infusions of alkali (e.g., tris(hydroxymethyl)aminomethane) with glucose solution can reduce the incidence and severity of permanent brain damage, and restore the arterial pressure and breathing during secondary apnoea. This form of therapy might now be investigated as an adjunct to artificial ventilation in human infants in a few selected clinical centres.

The use of analeptics, such as lobeline, has proved ineffective and even dangerous in secondary apnoea, since they may cause the arterial pressure to fall more rapidly. Although application of cold may act as a respiratory stimulant in primary apnoea, animal experiments indicate that rapid cooling does not initiate respiratory efforts in secondary apnoea.

Further investigation is needed to establish why, in monkeys, certain areas of the brain are more susceptible to asphyxia than others, and to determine whether the same areas are damaged in human infants that have suffered asphyxia at birth or shown signs of neurological damage or cerebral palsy in infancy. More information is needed on the physiological and biochemical changes leading to the death or survival of neurones subjected to asphyxial or other trauma. The association of spastic diplegia with cyanotic attacks in premature infants suggests that the effects of brief periods of post-natal asphyxia warrant further detailed study. The relation between maturity and susceptibility to brain damage after birth also requires investigation. In cases in which there is depression of the newborn by pethidine or morphine, this may be treated by administration of morphine antagonists after resuscitation has been begun. Further studies of such drug antagonists are needed.

12. IDIOPATHIC RESPIRATORY DISTRESS SYNDROME (IRDS) OR HYALINE MEMBRANE DISEASE

This condition is related to prematurity, abnormal pregnancy, abnormal and operative delivery, and birth asphyxia. The precise etiology is unknown, and it remains to be determined whether the syndrome results from the interaction of several variables or has a single cause, and whether it is initiated solely by ante-natal events.

Hyaline membranes can be produced experimentally in a variety of ways, most of which are associated with the production of pulmonary oedema. Recently a full clinical syndrome that appears to be identical with the idiopathic respiratory disease syndrome (IRDS) has been produced in newborn lambs by rendering the mother hypotensive several hours before delivery, in newborn rabbits by giving the mother 10% oxygen to breathe before delivery, and in newborn monkeys and lambs by acute asphyxiation at birth. Thus several techniques are available for the design of precise experiments to test the various etiological possibilities. Such an approach is likely to provide an answer more readily and rapidly than is possible in the human. Furthermore, controlled clinical trials in animals would be a cheaper and safer way to explore therapeutic measures.

Although in this syndrome the signs of illness become more severe during the first hour or two of life, careful observation of the foetus during labour and of the infant immediately after birth by experienced personnel has drawn attention to the fact that many of these infants are not normal at birth. There is, however, a need for more detailed observations, particularly in the early phases of illness, to define more clearly the clinical signs and pathogenic mechanism. Until then treatment can only remain symptomatic and supportive.

13. PERINATAL INFECTION AND ITS RELATION TO LABOUR

Infection of the foetus during pregnancy or labour is of some importance in perinatal mortality and morbidity and in relation to long-term damage to the child.

In the recent British Perinatal Mortality Survey, pulmonary infection was the primary necropsy finding in 13% of early neonatal deaths. This type of infection is usually an ascending bacterial infection, associated with a primary infection of the membranes, amniotic sac, and placenta. The incidence varies very much from institution to institution, but the condition is positively correlated with prolongation of the period from rupture of the membranes to delivery and with prolonged labour itself.

Bacterial infections (*Escherichia coli*, coagulase-positive staphylococci, *Pseudomonas aeruginosa*) are to some extent preventable and are also amenable to chemotherapy during labour. Unfortunately, however, the organisms are frequently insensitive to the less toxic antibiotics and there may be some danger to the child in the use before labour and after birth of those antibiotics to which the organisms are sensitive—e.g., tetracycline and chloramphenicol.

The risk of such infections is insufficiently appreciated in clinical practice and there is still much to be learnt about their pathology. The following questions arise :

(1) Can such infections precede rupture of the membranes ?

(2) Are maternal pyrexia and a raised foetal heart rate adequate and consistent indices of such infection ?

(3) How can the infecting organism best be identified ?

(4) How should such infections best be treated ?

In addition to overt clinical infection of the amniotic sac or foetus, some 10%-15% of delivered placentae show histological evidence of inflammation. It is not known whether this placental inflammation can be attributed in all instances to infection.

Other forms of infection of the mother and foetus are known. Viral infection probably has its greatest effect on the early developing foetus, but if the infection (e.g., with Coxsackie B virus) should coincide with labour the effect on the child can be serious. Listeriosis seems to have a very variable incidence, being relatively frequent in some areas and absent in others. Its effects are very serious but easily preventable.

More emphasis should be placed on the study of all forms of uterine and foetal infection.

14. DRUGS AND OTHER THERAPEUTIC MEASURES

Many drugs are commonly given to women before and during labour and may reach the foetus in substantial quantities. They include drugs used for the treatment of maternal disease, anaesthetics, analgesics, hypnotics, and sedatives, as well as the common household medicaments that vary so much and change so frequently in different parts of the world. While public opinion has compelled a detailed inquiry into the effects of drugs on the foetus in early pregnancy, much less attention has been given to the effects of drugs on the placenta, the foetus, and the relation between foetus and mother in late pregnancy and in labour. The effects are particularly important in the newborn infant, whose enzyme systems and detoxication and excretion mechanisms may be very different from those of the adult. For instance, newborn infants are much more susceptible to non-volatile anaesthetics than are adults, and comparatively little is known about the effects of drugs on the placenta.

New drugs recommended for use during late pregnancy, in labour, and in the newborn should be tested in animals in circumstances as close as practicable to those contemplated for their use in man. And controlled clinical trials of new drugs, or of drugs whose action is established in adults, should be undertaken and critically assessed before general release of the drugs for use in pregnant women or newborn infants. In addition, there is a strong case for controlled clinical trials of some drugs that are at present in general use.

The same principles as govern the testing of new drugs should also apply to the introduction of other new methods of treatment e.g., apparatus for resuscitation, changes in the environment such as heat or cold, and variations in gas tension.

The Group was not unmindful of the effects of smoking, exhaust fumes of various origin, etc., on pregnancy and labour, but it was not in a position to make any recommendation beyond suggesting that the question deserved serious consideration.

15. FOLLOW-UP STUDIES

It is evident that unfavourable events during the perinatal period may cause irreversible damage to the foetus or the newborn that will lead to clinical manifestations later in life. Short-term intensive studies give valuable information, but in the long run follow-up studies with particular emphasis on the central nervous system are required. The effects of neuromuscular and psychological factors, as well as morbidity, *after* the perinatal period must be taken into consideration. The planning and design of such follow-up studies entail many special methods of examination and data collection.

Follow-up studies can be applied to particular groups of patients selected according to their perinatal history. But information about the course of the intra-uterine period is also necessary. This means that in institutions where perinatal studies are carried out, the ante-natal and perinatal data must be carefully recorded and filed in such a way that they can be used for later analyses. Since untoward events during the perinatal period cannot be foreseen, all the data from all patients must be collected. This would also enable the incidence of various conditions in the specially selected groups to be recorded and facilitate the selection of control groups. It would also then be possible to compare the experiences of different institutions in different countries.

Prospective studies of the influence of pregnancy, labour, and perinatal events on the subsequent life efficiency of the child are required. Small-scale studies in areas in which it is easy to keep track of patients might yield rapid and useful results.

Follow-up studies of infants with adequate records of their obstetrical and post-natal history should be instituted along the following lines:

(1) Objective assessments should be made of the relation between psychological and neurological tests on the infants and histological evidence of brain damage.

(2) Specific studies of particular value would be:

(*a*) on twins;

(*b*) on infants of low birth-weight ; and

(*c*) on infants asphyxiated and subjected to birth trauma.

(3) An attempt should be made to study the relation between the events that occur at birth and emotional and mental development and minimal degrees of brain disorder.

16. DEFINITION OF TERMS

International agreement is essential on the meaning of certain terms applied to the foetus and on the criteria to be met before certain terms are applied to clinical syndromes in infant or mother. An agreed nomenclature would be of particular importance in the event of international comparisons of, for example, the causes of perinatal death, low birth-weight, or the long-term effects of pregnancy and labour on the child.

It is impossible to give an exhaustive list, but some of the terms discussed during the meeting on which agreement is needed are as follows :

anaemia
anoxia
asphyxia
dysmature
full term
hypoxia
hyaline membrane disease
idiopathic respiratory distress
intra-uterine pneumonia
low birth-weight
perinatal death
post-mature
pre-eclampsia
premature
premature separation of the placenta
pyelonephritis
toxaemia

The Group recommended that WHO take any necessary and possible action to obtain international agreement on the definition of these terms.

17. CONCLUSIONS AND RECOMMENDATIONS

17.1 Training needs

The human mother is selected for reproduction by chance and not by any measure of her genetic, physical, emotional, or other abilities to reproduce well. She is, moreover, liable to be exposed in pregnancy and labour to external influences and environmental conditions that may be gravely to her disadvantage. *The Group considered it essential that the mother and infant should be cared for by qualified personnel, adequately trained to detect and deal with any abnormal condition and, as far as possible, provided with the facilities and equipment required.*

(1) *Clinicians and workers in the basic sciences*

There are grave shortages in the supply of clinical staff who have had a grounding in one or more of the basic or paraclinical sciences. This is particularly true in obstetrics. In many countries the excess of clinical work in training and the career structure are such as to make it practically impossible for a young physician to obtain experience of research in disciplines other than his own.

Specialists-in-training, early in their career, should be enabled and encouraged to spend a year or more in a department of anatomy, physiology, pharmacology, biochemistry, or pathology.

Members of scientific departments are also largely unaware of the real problems of human reproduction. It would be greatly to their advantage to carry out studies with human material, not isolated in their laboratories but as part of the clinical team. Secondment of these workers to clinical departments should be actively encouraged.

Young research workers should be encouraged to make national or international visits of some duration to obtain extended research experience. Well-established physicians and scientists should make shorter visits to exchange information and to learn new methods.

It is particularly important to interest a wider range of medical scientists in the fundamental problems that lie behind the practical problems discussed. For instance, it would be valuable if neurophysiologists and biochemists would study the ability of different kinds of nerve cells to survive asphyxia at birth. Similar co-operation is required to obtain a better understanding of the processes leading to the initiation of labour and the control of myometrial activity.

(2) *Practising obstetricians and midwives*

It is essential that all physicians, midwives and nurses who care for pregnant women and newborn infants should be encouraged and given the opportunity to continue their education. They should also be kept abreast of advances in knowledge. The greatest single problem at present is the development of methods by which the standards and techniques now possible with existing knowledge can be employed to the advantage of the individual mother and her child.

(3) *Action by WHO*

It is recommended that WHO bring these training needs to the notice of those national bodies that can best help in meeting them—i.e., universities, research councils, health ministries and professional organizations.

17.2 Areas for research

The Group wished to stress that the following list of recommended investigations is not exhaustive and that it amplifies some recommendations made in the text of this report. Some of the studies recommended will need to be approached both from a " basic science " and a " clinical " point of view; they have been marked with an asterisk.

(1) *General recommendations*

(*a*) Attention should be given to the factors determining the degree to which " stores " or " reservoirs " are developed in the mammalian foetus, since their level frequently determines the foetus's capacity to survive at birth.

(*b*) Attention should also be directed to the means whereby control mechanisms for internal homeostatic regulation are developed within the foetus.

(2) *The placenta*

(*a*) Tests of placental function in respect of gas and solute transfer.

(*b*) The distribution of uterine blood flow between myometrium and placenta.

(*c*) Homeostatic adaptation in the placenta (e.g., in foetuses of different sizes or at high altitudes).

(*d*) The relation and mutual adjustment of maternal and foetal blood within the placenta.

(*e*) The development of the placenta in primates.

(3) *The cardiovascular system*

* (*a*) Foetal and neonatal cardiac output and blood distribution to the organs before and after birth.

(*b*) The source, volume, and composition of fluid accumulating in the foetal lung.

(*c*) The rate and regulation of foetal pulmonary blood flow *in utero*.

(*d*) The importance of the transfer of placental blood at birth for immediate survival and subsequent health.

(*e*) The influence of the position of the mother in labour and during delivery on her cardiovascular system.

(*f*) Cardiovascular adjustments in the foetus during normal and abnormal labour.

(*g*) Regulatory mechanisms causing foetal heart changes during labour, and their significance.

(4) *The respiratory system*

(*a*) The mechanisms whereby the basal oxygen consumption of the foetus *in utero* is determined.

(*b*) The oxygen consumption of the brain and of its different parts *in utero*.

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* Studies that need to be approached both from a " basic science " and a " clinical " point of view.

* (*c*) The factors determining the levels at which the arterial pO_2 and pCO_2 lead to the rousing of the foetus and the onset of breathing; and the levels set by respiration in the newborn.

(*d*) The factors determining the appearance of surface-active material in the alveoli.

(*e*) The change in lung size and diaphragmatic tone after birth.

(*f*) The circumstances leading to the development of respiratory distress after asphyxia at birth.

(*g*) The breathing movements of the foetus *in utero* under normal and asphyxiated conditions.

(*h*) Effects of uterine contractions on the placental circulation and on foetal pO_2, pCO_2, and pH.

(*i*) Maternal pO_2, pCO_2, and pH during labour; influence of analgesia, anaesthesia and position of the mother.

(*j*) Causes of respiratory depression in the infant at birth.

(5) *The nervous system*

* (*a*) The reason for the greater susceptibility of some areas of the brain of the newborn to asphyxial damage and the factors that influence neurone recovery from such damage.

* (*b*) The distribution and character of the cerebral lesions in infants after asphyxia at birth and in older children with brain damage and cerebral palsy.

* (*c*) Electro-encephalographic changes as an index of abnormal brain function in the foetus and in newborn infants and animals.

(*d*) The correlation of brain damage with pressure on the foetal head during labour and delivery.

(6) *Metabolism*

* (*a*) Quantitative methods of assessing the condition of the foetus and its reserves *in utero*.

* (*b*) The effects of steroid hormones on uterine blood flow, the sexual development of the foetus, and the respiratory and circulatory systems of the foetus and newborn.

(*c*) The mechanisms involved in the rapid change in concentration of certain enzymes at birth.

(*d*) The factors determining the accumulation of metabolic reserves, and particularly of brown adipose tissue, before birth.

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* Studies that need to be approached both from a "basic science" and a "clinical" point of view.

(*e*) Quantitative measures of placental reserves in all placental functions.

(7) *Uterus*

The mechanisms leading to the onset of labour and the control of uterine muscle action in labour.

(8) *Treatment of the foetus* in utero

The techniques and dangers of treating the foetus *in utero* by means of drugs given to the mother or directly to the foetus.

(9) *Epidemiological studies*

(*a*) Perinatal mortality in different environmental circumstances and ethnic groups.

(*b*) The influence of pre-natal and intrapartum infection on labour and on the foetus.

(10) *Follow-up studies*

The effects of pregnancy and labour in closely defined populations, e.g.:

twins;
infants of low birth-weight; and
mature babies asphyxiated at birth.

(11) *Action by WHO*

It is recommended that WHO distribute this list of recommended areas for investigation as widely as possible among workers in the appropriate fields, so as to encourage research on these subjects.

17.3 Practical recommendations

The Group considered the following recommendations to be of immediate and practical importance.

(1) *Analgesia apparatus*

Apparatus for giving analgesic gas mixtures in labour should not deliver less than 21% oxygen to the mother.

(2) *Incubators*

Incubators for newborn infants should be so designed as to produce a wall temperature and an air temperature within 2°C of one another and capable of being regulated within 2°C. The airflow should be sufficient to ensure that CO_2 does not accumulate. The interior should be free from crevices and easy to clean and disinfect.

(3) *Resuscitation*

In newborn infants that have not breathed for one minute resuscitation is best undertaken by endotracheal intubation and positive pressure ventilation. If a slow heart beat does not accelerate within one minute after positive pressure ventilation is established, external cardiac massage should be given.

Analeptics such as lobeline should not be used, since they cannot be relied on as active respiratory stimulants and may be dangerous.

(4) *Drugs*

New drugs, or drugs already in use for adults, and other methods of treatment (including equipment) contemplated for women in pregnancy and labour and for newborn infants should be carefully scrutinized before use. Their performance may need to be examined before use and this can be achieved only by animal tests and controlled clinical trials in selected centres. Such tests should be designed to study the possibility of deleterious effects on the placenta and on the infant as well as on the mother.

(5) *Action by WHO*

It is recommended that WHO bring the above recommendations to the notice of all national bodies concerned.

17.4 Subjects for further discussion

Other scientific groups convened to examine this subject, or related subjects, should consider discussion of:

(*a*) The etiology and treatment of idiopathic respiratory syndrome in infants after birth.

(*b*) Maturation of enzymes in foetal and newborn development.

(*c*) Mechanisms of accumulation of metabolic reserves in the developing foetus.