blastoma and bone metastases may occur. The exact mode of action of vitamin B₁₂ in this condition is not understood.

Summary

Three cases of neuroblastoma are described in each of which the unusual power of catecholamine secretion gave rise to a clinical picture resembling phaeochromocytoma.

From the evidence presented it appears that tissues other than chromaffin are capable of catecholamine secretion.

We are of the opinion that neuroblastoma with high catecholamine secretion will prove to be not as rare as the literature suggests.

The three cases bring the total number recorded to five.

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In his report for the year 1958 Dr. Robert Aitken, Vice-chancellor and Principal of the University of Birmingham, mentions the work of the university health service. Mass radiography revealed five active cases of tuberculosis. Four of these had developed since the routine check in 1957, a fact which underlines the value of the annual chest examination for students. Dr. Aitken's report continues: "Nevertheless accidents, many on the road, rather than disease, remain the greatest single cause of lost time among students. Every year there are more student motor cars and motor cycles, and experience seems to point to the depressing conclusion that there will therefore be more accidents to students. The multiplication of vaccination campaigns of various kinds is adding yet another sizeable task to the many jobs the health service already does. Polio vaccine is now available to students, and B.C.G. vaccine against tuberculosis will probably need to be offered to larger numbers in the near future. This work is time-consuming, but its protective value is such as to make it well worth while."

RESPIRATORY DIFFICULTIES AT BIRTH*

BY

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"What have we done in resuscitation of the newborn infant in respiratory distress? We have poked, massaged, slapped, probed, struck, dilated sphincters, stimulated by physical and chemical means, jackknifed, rocked, air-locked, heated and now cooled, under- and over-oxygenated the newborn infant with an enthusiasm far beyond our knowledge of the problem." (Abrahamson, 1956.)

Prevention of respiratory distress in the newborn and resuscitation of the asphyxiated infant remain outstanding problems. The literature with its dogmatic and often contradictory opinions, and the numerous drugs, methods, and machines recommended for resuscitation, testify to our ignorance. It is proposed to review the problem of respiratory difficulty immediately after birth in the light of recent research and current opinion so that we may see what progress has been made in our efforts to gain a better understanding of the processes involved. From inability to cover every aspect, the circulatory adaptations associated with birth and the establishment of respiration have been chosen for special consideration.

Respiratory and circulatory functions cannot be separated. In the foetus the circulatory system is designed primarily to support the exchange of blood between placenta and foetus. Blood moves fastest and most abundantly to the umbilical arteries and slowly and in smaller amount to the head and lungs, but an ingenious device ensures the passage of freshly oxygenated blood to the head. The change-over at birth is dramatic, as cineradiography has shown (Barclay *et al.*, 1944; Lind and Wegelius, 1954), with a sudden increase in the speed and volume of blood flowing into the lungs. As the circulation to the lungs speeds up, so does that to the head, whereas the flow to the placenta now falls to zero. In each case it is the organ of respiration which receives the fast and abundant circulation. Clearly, anything which prevents the operation of this principle will militate against the well-being of the baby.

Function of the Ductus Arteriosus

Inspired by the pioneering work of Sir Joseph Barcroft, Dawes and his colleagues in Oxford have carried out a series of brilliantly conceived experiments to establish the course of the foetal circulation in the lamb and the changes occurring at birth. They have shown that the ductus arteriosus will contract in response to either a high arterial oxygen saturation (probably around 90%) or asphyxia, the latter operating by release of sympathetic amines. Contraction occurs within 5 to 15 minutes of birth, when asphyxia is likely to be the initial stimulus, but a satisfactory rise in arterial oxygen saturation is necessary to maintain contraction. As the ductus contracts (usually to half its original diameter), a characteristic Gibson "machinery" murmur is heard in the lamb, suggesting

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the presence of an appreciable aorto-pulmonary shunt (Dawes *et al.*, 1955a). Barclay *et al.* (1944) and Barcroft (1946) had considered such a contracted ductus to be functionally closed, but Dawes and his colleagues find that for some hours after birth a large proportion (sometimes as much as half) of the pulmonary artery blood flow passes through this constricted ductus (Dawes *et al.*, 1955b).

With normal breathing and gradual constriction of the ductus the pressure in the pulmonary artery falls while that in the aorta rises, thereby increasing the pressure gradient between the two ends of the duct, and, since the vessel is short, ensuring that substantial quantities of blood pass through at high velocity even when the diameter of the duct has become small. This temporary supplementation of the pulmonary flow helps to raise the arterial oxygen saturation while the lungs are not yet fully expanded, and the increased venous return to the left atrium helps to close the foramen ovale. This transitional "neonatal" circulation—with ductus still open—is regarded as an integral part of the smooth change-over from foetal to adult types. These workers have confirmed the presence of a temporary ductus murmur in the newborn of other mammals (Amoroso *et al.*, 1958), and we had not long to wait for confirmation of its presence in the human infant (Burnard, 1958). "Was man weiss man sieht." The striking difference in post-mortem appearance between the dilated ductus in the stillborn and the contracted ductus at neonatal death (Blanco and Nodot, 1957; Wilson, 1958) corresponds closely to the change observed to take place in the lamb. To complete the similarity, the presence of appreciable aorto-pulmonary shunts through the ductus of newborn infants has now been confirmed (Rowe and James, 1957; Adams and Lind, 1957).

In the lamb, Dawes and his colleagues have shown that moderate asphyxia increases this shunt for a time by raising the arterial blood pressure (Born *et al.*, 1954). But prolonged asphyxia leads to circulatory failure, and the benefit of the open ductus is then lost, as the falling systemic pressure cannot maintain an effective pressure gradient across it, and eventually, with the pulmonary artery pressure remaining elevated, it operates disadvantageously by permitting a shunt in the opposite direction away from the lungs. The right atrial pressure rises and blood flows through the foramen ovale to the left atrium. Thus, "foetal" pathways are re-established with a vicious circle of increasing cyanosis, respiratory distress, and circulatory failure, leading to death if the situation cannot be reversed. That this may be the process in respiratory distress in the newborn has been suggested (Lind, 1953; James and Rowe, 1957).

Pulmonary Capillary Erection

Jäykkä (1954 and 1957) has restated an old idea that lung capillaries have an erectile function and, by their distension after birth, help to expand the alveoli. Using the lungs of full-term stillborn infants, he found it was not possible to expand the alveoli uniformly by applying a negative pressure of -20 cm. of water outside the lungs, with a positive pressure of +20 cm. of water within the trachea. But when the pulmonary artery was perfused with fluid under a pressure of 80 mm. Hg the same air-pressure difference resulted in normal uniform expansion of all the alveoli. There are many criticisms of his experiments which will not

be discussed here, but it is pertinent to point out a weakness in his theoretical arguments.

He uses the example of full expansion of the lungs in the presence of congenital atresia of the larynx to suggest that, since the air inlet is sealed off, some other factor must have been responsible for alveolar expansion—namely, pulmonary capillary erection. But it is an error to presume that foetal lungs are atelectatic: the alveoli are expanded to a great extent by fluid. Fluid is produced in the lungs of non-breathing animals with their placental circulation intact (Dawes, 1954b), and this normally finds egress through the trachea. If the trachea is obstructed it is possible that the alveoli are more greatly distended than is normally the case. Dawes *et al.* (1953) have also shown that expansion of the lamb's lung with saline caused an increase in pulmonary vascular resistance and a decrease in pulmonary blood flow, so that distension of the alveoli by fluid might prevent pulmonary capillary erection. There is also the paradox of intense capillary engorgement associated with widespread atelectasis in "hyaline membrane disease."

Placental "Transfusion"

Jäykkä's theory has been invoked by Bonham Carter (1957) in a hypothesis to explain the so-called "pulmonary syndrome of the newborn" of Bound *et al.* (1956). He suggests that the infant rendered asphyxial at birth suffers from the presence of an ever-increasing peripheral vascular resistance in the lungs, so that his cardiac output cannot overcome it and his alveoli are never properly expanded. He thought that this situation might arise from or be aggravated by a blood volume diminished by failure to secure the added volume from the placenta or by siphonage out of the baby when gravity is permitted to operate in the wrong direction (Gunther, 1957). In this connexion early ligation of the cord might be an important factor. On the contrary, he believed that an increased blood volume might increase the cardiac output by augmenting the venous return, and this contention was supported by finding high venous pressures in infants with the "pulmonary syndrome" who recovered (Bonham Carter *et al.*, 1956). In favour of this idea it should be mentioned that Dawes *et al.* (1955a) were able to raise the aortic pressure in lambs by intravenous infusions of dextran and thereby increase the flow through the ductus arteriosus, and two veterinary surgeons have claimed that atelectasis in the lungs of foals born by assisted delivery may be due to a loss of placental blood volume (Mahaffey and Rosedale, 1957).

With regard to the venous pressures recorded by Bonham Carter *et al.* (1956), it is not certain that umbilical vein pressures are necessarily a measure of the systemic venous pressure. The patency of the ductus venosus cannot be assumed unless the catheter is advanced into the inferior vena cava. Moreover, it also possesses a sphincter which has been observed to contract (Lind and Wegelius, 1954; Reynolds, 1955). Sometimes the reading obtained may be more nearly a reflection of the pressure in the portal vein, which would rise along with the systemic arterial pressure as an asphyxiated infant begins to recover. Reynolds (1955) believes the sphincter in the ductus venosus contracts in the presence of excessive venous return from the placenta to prevent overload of the foetal heart: the excess volume of blood is accommodated in the liver.

The horse is one of the animals in which a ductus

venous is not present in the full-term foetus (Barcroft, 1946), and there is a ring of muscle in the umbilical cord close to the abdominal wall which constricts tightly when there is sudden traction, as when delivery takes place in the standing position, thus preventing haemorrhage as the cord ruptures. These anatomical features should prevent any large volume of placental blood from augmenting the venous return to the heart in the newborn foal. Indeed, the whole question of "placental transfusion" is highly debatable, and there is a great deal of evidence to suggest that its occurrence is extremely uncertain even when assisted by gravity (Sisson and Lund, 1957). Active "stripping" of the cord is the only certain method of achieving it. It is perhaps significant that during radiographic studies in the newborn Mayer (1953) was unable to correlate persistent atelectasis with either early or delayed ligation of the cord.

Pulmonary Hyaline Membrane

There is a special form of respiratory difficulty which is responsible for a great many neonatal deaths—in some centres as many as 30% of all neonatal deaths. It is commonly seen in premature babies and the infants born of diabetic mothers, especially if they are delivered by caesarean section. It is very rarely seen in full-term infants unless they are caesarean births. Some of these babies appear to breathe well for a time, but very soon exhibit signs of respiratory distress, with increasing cyanosis, intercostal and sternal insuction, chin tug, and grunting respirations. Others have respiratory difficulty from the moment of birth which increases steadily. Death most often occurs in the first 24 hours, but if the infants survive for three days their chances of recovery are good. Radiological findings are regarded by some as diagnostic (Donald and Steiner, 1953), but they have no prognostic value (Bauman and Nadelhaft, 1957). The necropsy findings in the lungs are very striking. The lungs are voluminous, being the size of fully expanded lungs yet having the consistency of liver. Resorption atelectasis and intense congestion are present, and many alveolar ducts and alveoli are lined by a hyaline membrane. Sometimes there is pulmonary oedema.

The idea that the hyaline membrane results from aspiration of amniotic fluid or its contents is now out of favour, as the evidence for an endogenous vascular origin has become incontrovertible (Gitlin and Craig, 1956). The membrane has been identified as fibrin (Gitlin and Craig, 1956), possibly with extravasated red cells (Lynch, 1956; Lynch *et al.*, 1956). It is very likely that this condition also results from some disturbance of the pulmonary haemodynamics at birth. During the circulatory adjustments already discussed it is possible that exudation of fluid from the capillaries in the lung normally occurs to a slight extent (Hadders and Dirken, 1955), and, as the pulmonary flow is established and peripheral vascular resistance diminishes, intracapillary pressure falls below the oncotic pressure and this fluid is reabsorbed. Indeed, it is surprising that exudation does not occur normally in the adult lung. As Lilienthal and Riley (1954) have said: "The entire cardiac output hurtles through this delicate system, yet even when the minute blood flow approaches that of the contents of a five-gallon gasoline can, the delicate balance between oncotic and hydraulic pressures is regulated so exquisitely that gaseous exchange is accomplished without appreciable exudation of fluid."

Gruenwald (1953) regards atelectasis as the important finding in these lungs and facetiously referred to the membranes as "eosinophilic herrings." However, they are not present in normal lungs, and Craig *et al.* (1957) have demonstrated that they are truly obstructive. There is some reason, too, for suspecting an iatrogenic origin, else it is difficult to understand why only one example of pulmonary hyaline membrane was found in a recent survey of 215 stillbirths and neonatal deaths from Vellore, in South India, where obstetric practice was adjudged to be rather primitive (Hadley *et al.*, 1958).

Because of the peculiar characteristics of the lesser circulation and of the difficulty in obtaining direct measurements, and most of all in interpreting them, there is much imaginative speculation, which is apt to assume the guise of established fact. We do know that in the newborn lamb (Born *et al.*, 1954) and in the newborn infant (Rowe and James, 1957; Adams and Lind, 1957) initial pressure in the pulmonary artery is high, denoting a very considerable peripheral vascular resistance. This is a primary effect of unexpanded lung together with a secondary effect from the small calibre of the vessels in the periphery. It is probably a justifiable assumption that under these circumstances the peripheral resistance is maximal and will not increase further with asphyxia (Dawes, 1957). Therefore, if forward distension of pulmonary alveolar capillaries is to occur in unexpanded or partially expanded lungs in which the critical opening pressure of the vessels is high, especially in the immature foetus (Born *et al.*, 1955), very high pressures must be attained in the pulmonary artery, and capillary pressures above the oncotic pressure of the plasma are likely to result. A moderately increased flow through the ductus arteriosus at a time when the capacity of the pulmonary bed is relatively small may help to achieve such pressures.

Dawes (1954a) and Born *et al.* (1956) have observed in lambs a transient rise in systemic blood pressure following ligation of the cord *before* ventilation, enough to cause a significant flow through the ductus until the aortic pressure falls again. We have recently heard a typical "machinery" murmur in an asphyxiated infant within minutes of birth and before he took a breath. Thus I have postulated that early ligation of the cord in the presence of delayed onset of breathing might be a significant factor in the aetiology of hyaline membrane (Brown, 1957). Silverman and Nishihara (1957) argued that if early ligation of the cord was a factor, then hyaline membrane should be commoner in the firstborn of twin deliveries, but they were unable to confirm this from a retrospective survey of necropsy material. Their argument was really based on the question of "placental transfusion," and their survey does not tell us whether ligation of the cord was performed early *relative to onset of respiration* in each twin. On the contrary, in another series (Rogers and Gruenwald, 1956), out of five twin gestations terminating prematurely, one pair showed hyaline membrane in both twins, while in the other four pairs it was present only in the firstborn.

Factors in Hyaline Membrane Formation

There can be very little doubt that delayed onset of respiration is a most important factor in its aetiology. This may result from depression of the respiratory centre by anoxia from foetal distress or asphyxia at

delivery, or by the effect of anaesthesia. The latter is a big factor, especially in caesarean sections (Apgar *et al.*, 1957). Indeed, if regional analgesia is used the "Apgar score" (Apgar, 1953) for infants born by caesarean section is very little worse than for those born per vaginam.

An additional factor may be the increased extracellular fluid volume which is present in premature infants (McCance and Widdowson, 1954), the babies of diabetic mothers, and infants born by caesarean section, especially when this takes place before the onset of labour pains (Furuhjelm, 1954). Sutherland, in Boston (Curtis, 1957), has found evidence of a shift of fluid into tissue spaces in "hyaline membrane disease," and this change of fluid volume is reversed as the child begins to improve clinically. He also found that urine output seemed greater in these infants than in unaffected premature infants of similar weight. During a personal investigation of serum protein levels in premature infants suggestive evidence of initial hydraemia followed by a shift in the extracellular fluid compartment was found.

The idea that the congestion in these lungs results from sudden left ventricular failure and backward distension of the capillaries (Lendrum, 1955) is less attractive, since other examples of sudden left ventricular failure produce pulmonary oedema without much congestion. The suggestion that it results from excessive flow through bronchial arteries (Baggot, 1957) is unlikely in view of the absence of pulmonary congestion in infants with congenital pulmonary atresia. However, Lendrum (1955) quotes an attractive theory which attributes exudation of plasma and possibly blood from bronchopulmonary anastomoses to pulmonary hypertension in the presence of left ventricular failure, leading to unbalanced flow from the pulmonary artery into these anastomoses (Lendrum *et al.*, 1950). This theory could also account for hyaline membrane formation in other conditions such as acute glomerulonephritis and rheumatic carditis. The exudate in these conditions is seen as a fibrinous cast of the alveolar duct and its related alveoli. In the experimental production of hyaline membranes in animals made to breathe high oxygen tensions, it would be instructive to create an artificial pulmonary stenosis and then see if it was still possible to produce membranes. Certainly, in infants with prolonged asphyxia there exists a high pressure in the pulmonary artery together with a falling systemic pressure. Low blood pressures are also noted in premature infants and caesarean births (Holland and Young, 1956).

The clinical picture in these infants is very like that of infants with congenital heart lesions characterized by large left-to-right shunts, such as those with persistent patency of the ductus arteriosus (Taussig, 1947). Reminiscent of the "pulmonary syndrome of the newborn" is the description by Sheila Mitchell (1957) of a 13-day-old infant with persistent ductus arteriosus dying in respiratory distress. Congestion of the lungs and low flat diaphragms, which are features of hyaline membrane disease (Hardy, 1953), must interfere seriously with respiratory exchange quite apart from any interference caused by membranes.

Whatever the primary cause of this condition there seems no doubt that if normal pulmonary blood flow, systemic pressure, and cardiac output can be maintained there is hope that the infant may recover.

Role of Pressor Amines in Asphyxia

Since the importance of maintaining the systemic blood pressure has been stressed it now seems logical to review the possible role of pressor amines in the infant at birth. It has long been known that chromaffin tissue is present in the paraganglia and suprarenal medulla at an early stage of development in the mammalian foetus. Similar chromaffin bodies are present in the sympathetic plexuses, the largest of which are the two organs of Zuckerkandl. These lie close to the root of the inferior mesenteric artery, and at birth attain their greatest length (approximately 1 cm.). After birth they degenerate, but they do not disappear completely until about the third year. Correspondingly, West *et al.* (1953) have shown that these organs and the suprarenal medulla contain noradrenaline only at 15–20 weeks, the concentration of which increases in the organs of Zuckerkandl until birth, when it declines and finally disappears at 3 years. The suprarenal medulla contains less noradrenaline and negligible amounts of adrenaline. Furthermore, the blood supply to these organs is well developed at birth.

As Maureen Young (1956) says, it is attractive to consider that hypoxia and sensory stresses during birth and in the neonatal period will stimulate the liberation of noradrenaline from the organs of Zuckerkandl, which will enhance the tone of the cardiovascular system and assist in the readjustments taking place. Noradrenaline is better suited for this than adrenaline as it increases the peripheral resistance without accelerating the heart and does not exhaust the infant's oxygen stores by increasing the metabolic rate. Thus the organs of Zuckerkandl may have teleological significance. Dawes *et al.* (1956) found that pressor amines caused a larger change of heart rate when injected into the femoral vein of a mature lamb than into the jugular vein, in spite of the fourfold greater dilution in the inferior vena caval stream. This is because none of the superior vena caval blood enters the left atrium. Now the suprarenals and organs of Zuckerkandl are so placed that their secretions must also enter the inferior vena cava and likewise produce a maximal effect. The amines which pass to the placenta produce no direct effect and are possibly destroyed there by enzyme action, so that the increase in heart rate, blood pressure, umbilical blood flow, and oxygen-carrying capacity of the blood which can be produced in the lamb by anoxaemia, or by injection of pressor amines, must result from increased peripheral vascular resistance in the foetus, causing an alteration in the partition of blood to the placenta and foetus.

In the foetal circulation the ductus arteriosus is, so to speak, out of the noradrenaline stream, which might explain why it fails to contract in the asphyxiated stillbirth. In the depressed infant cord pulsations may continue for many minutes, but as soon as the arterial oxygen saturation rises sufficiently the vessels constrict (another reason for reluctance to ligate the cord immediately when respiration is delayed). Once the cord is ligated injections of noradrenaline produce a larger rise of blood pressure, probably because the low peripheral resistance of the placenta is cut off, but constriction of the ductus arteriosus (which can now occur) is an added factor.

Maureen Young (1956) has suggested the use of a continuous intravenous infusion of noradrenaline in

resuscitation of the newborn, for in addition to its other effects it apparently stimulates respiration (Whelan and Young, 1953). We have recently used this treatment in a severely distressed premature infant in an attempt to maintain the systemic blood pressure at a level sufficient to prevent reversed flow through the ductus. Noradrenaline was administered in 5% dextrose water through a catheter inserted in the umbilical vein. From an initial level of 45 mm. Hg the blood pressure rose immediately to 80 mm. Hg, and then, with the rate of noradrenaline administration fixed at 0.4 μ g./kg./minute, was maintained between 60 and 75 mm. Hg for 14 hours. A definite improvement was noted, and the infant made a complete recovery. We believe that this form of therapy may be of real value in the management of "hyaline membrane disease."

Neonatal "Shock"

This review would not be complete without some reference to the idea that severe respiratory distress may be a manifestation of "shock" in the newborn infant. Gruenwald (1955) is one of the chief protagonists of this idea, and in his paper on perinatal distress he describes what he calls "shock lesions" in many organs. He gives a comprehensive review of the literature and quotes articles in which the process of birth is compared to an alarming stimulus (in the sense of Selye). There is room for further investigation along these lines, for the development of the foetal adrenal cortex at birth and its subsequent involution seem to be "equally as mysterious as its undetected function" (Jones, 1957). Writing on the use of the pump oxygenator to sustain life during neonatal asphyxia in lambs, Harned *et al.* (1957) referred to a pattern of biochemical changes and circulatory degeneration similar to that of irreversible shock. They found that unless the perfusion was started soon after interruption of the umbilical arterial flow when the lamb's aortic blood pressure was only moderately depressed, recovery of the circulation did not occur in spite of arterialization of aortic blood to over 85% saturation. If perfusion was started early almost immediate improvement in cardiac function was observed.

Conclusion

It is emphasized that although newborn infants have a relative tolerance to anoxaemia, so that healthy normal infants have resulted from caesarean births as long as 20 minutes after sudden death of the mother, yet their tolerance to ischaemia is no better than in the adult. Therefore, establishment and maintenance of the correct circulatory "pathways" after birth is essential for their survival. This is the important principle in considering methods of resuscitation in the newborn.

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In a paper presented to the Australian Citizenship Convention at Canberra recently, Sir MACFARLANE BURNETT, F.R.S., said: "From the genetic angle, there is much to be said for allowing into the country as much non-European genetic material as the community can safely assimilate. . . . Experience everywhere indicates that it would be disastrous to open the doors to a large dissimilar minority introduced to provide cheap low-grade labour. Experience, however, equally points to the acceptability of upper class cross-racial marriage, and where this is accepted clearly no general contempt for the half-breed can develop" (*The Times*, January 22).