PROGRESS IN PEDIATRICS

Recent Advances in the Field of Prematurity *

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During the past few years, the 3 most interesting advances in this field have been the discoveries of:

(1) the cause and prevention of blindness due to retrolental fibroplasia;

(2) the cause and prevention of kernicterus or prematurity, not associated with haemolytic disease;

(3) hyaline membrane found in association with atelectasis in premature babies dying during the first few days after birth.

Retrolental Fibroplasia.

Although the final stages of this disease were described by Terry [1] in 1942, and the early signs by Owens and Owens [2] in 1949, the cause was not finally established and generally recognised until 1953.

The disease has an acute phase followed by a cicatricial phase; both eyes are affected, although different stages may be present in the two eyes; and spontaneous arrest may occur at any stage. The acute phase usually begins between the ages of 3 weeks and two months; the smaller the birth weight, the later the onset. The first sign is dilatation and tortuosity of the blood vessels, the fundus then becomes pale and haemorrhages appear alongside the blood vessels; these haemorrhages spread into the vitreous either in the periphery or near the optic disc, and this is followed by separation of the retina which usually commences at the periphery and is most marked at the sites of the haemorrhages. New vessel formation and vitreous opacities may be seen at the junction of the attached with the separated retina.

After several weeks the acute phase passes gradually into the cicatricial phase, this being characterised by organisation of the vitreous and formation of a retrolental membrane. The anterior

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chamber becomes shallow and impairment of vision may be accompanied by squint, nystagmus and photophobia. Microphthalmia is a common sequel and secondary glaucoma may occur. The damage done during the cicatricial phase depends on the severity of the acute phase and the stage at which the disease is arrested. Mild or abortive cases may be followed by little or no abnormality. The exact stage at which the condition becomes irreversible is not known.

It is now well established (Reece et al.,[3] 1952; Ashton et al[4]., 1953) that the earliest stage of retrolental fibroplasia (R.L.F.) consists of an irregular localised proliferation of capillary endothelial cells associated with a more diffuse proliferation of "glial" cells, confined initially to the nerve fibre layer of the retina. If this vasoformative tissue becomes too exuberant, it bursts through the limiting membrane into the vitreous. Protein transudate then seeps through the new vessels growing into the vitreous and this becomes organised into fibrous strands which distort or detach the retina. Detachment of the retina is followed by absorption of the vitreous and pulling together of the retina behind the lens, leaving only a stalk of rolled-up retinal tissue connected posteriorly with the optic disc. New vessels may appear on the iris and glaucoma may develop as a sequel to shallowing of the anterior chamber and angle block, and late atrophic changes cause a shrunken eye.

Cause: The occurence of R.L.F. has coincided with the increase in the use of oxygen, and the incidence of the condition is now known to depend on

(1) the concentration of oxygen given,

(2) the length of time of administration of oxygen,

(3) the degree of immaturity of the eyes at the time when oxygen is given, (the fundus is not mature until about 34 weeks'gestation, i. e. 2000 g. weight).

The safe concentration of oxygen is not yet known; it is certainly below 40 % (Report of sixteenth M. and R. Pediatric Research Conference [5] 1955), and probably even lower, because a few cases are still being reported from clinics using concentrations between 30% and 40%. In three Birmingham Units where a concentration of 30% is rarely exceeded there has only been one case of R.L.F. since 1950 (2,000 babies weighing less than 2000 g. at birth). During the previous 18 months oxygen had been given freely and 8 cases had occured among 500 babies weighing less than 2000 g. at birth.

The incidence of R.L.F. increases with the duration of exposure to high concentration of oxygen (Medical Research Council Report, 1955) [6], and the risk of developing R.L.F. from exposure to oxygen

diminishes as the birth weight increases, i.e. as the retina becomes more mature. R.L.F. rarely occurs in infants weighing more than 2000 g. at birth.

Animal experiments by Ashton et al [4]., (1953) and Patz et al [7]., (1953) show that exposure of suitable animals to oxygen results in immediate obliteration of the developing retinal vessels, (proportional to the duration of exposure and concentration of the oxygen) and that this is followed later by neovascularisation, haemorrhage and retinal detachment as in R.L.F.

The age at onset of the disease is inversely related to the birth weight (or maturity) of the infant and is not related to the date of cessation of administration of oxygen, (Medical Research Council Report, 1955) [6]. It varies from the age of 5 weeks in the larger infants (1,750-2,000 g.) to 9 weeks in the smallest (under 1,000 g), so it occurs, on an average, 26 days after maturation of the fundus among the larger babies and 12 days after maturation among the smallest babies (M. and R. Report 1955) [5].

It is important to realise that a restricted use of oxygen has reduced the incidence of R.L.F. without reducing the survival rates (Crosse and Evans 1952 [8], Medical Research Council Report [6] 1955).

Preventive treatment: The use of oxygen must be restricted to babies who become cyanosed without it, and this is particularly important for babies weighing less than 2,000 gm. at birth, i.e. less than 34 weeks maturity. If oxygen is necessary, the minimum concentration which will keep the baby pink should be used, and it should be given for the minimum period of time.

The concentration of oxygen must be controlled by the use of reliable flow meters and by regular estimations of the concentration by some simple oxygen analyser. The concentration of oxygen should only exceed 30% in exceptional cases and it should never exceed 40%. Obviously, higher concentrations can be given by face-mask for short periods for the purpose of resuscitating a cyanosed infant (e.g. after aspiration or during a cyanotic attack) but high concentrations must never be given for more than very short periods. Nurses must be taught to record the percentage of oxygen given to each individual infant, and not the flow in litres per minute; and they should never use more than 30% oxygen continuously without medical advice.

Positive-pressure resuscitators should be used with an oxygen and air mixture, e.g. 10% oxygen in air=28% oxygen. Air, or 10% oxygen in air (never pure oxygen) should be used in nebulisers, and also in incubators or boxes used for transport.

Curative treatment: There is no cure, therefore preventive treatment is very important.

Follow-up: The eyes of all babies who weigh 2000 g. or less, and of larger babies who have required oxygen during the first two weeks of life, should be examined before discharge in order to keep a check on the results of preventive therapy.

Kernicterus of Prematurity.

Formerly kernicterus was most commonly associated with haemolytic disease of the newborn, but with the introduction of adequate exchange transfusions this complication of haemolytic disease has been virtually eliminated. Among babies suffering from haemolytic disease, it has always been recognized that premature babies were more liable to develop kernicterus than full term babies; and in 1950 two groups of workers (Aidin et al., [9] 1950, Zuelzer and Mudgett [10] 1950) independently drew attention to the fact that kernicterus could occur in premature babies who were not suffering from haemolytic disease.

Kernicterus of prematurity gives the same clinical picture as that of kernicterus associated with haemolytic disease except that the onset is usually later; the neuropathology of the two conditions appears to be the same (Aidin et al; [9] 1950, Govan and Scott [11] 1953). Gerrard [12] (1952) has shown that the subsequent development of the survivors is the same in both groups.

Affected infants develop a well-marked physiological jaundice but appear to make fairly good progress until the second half of the first week. Signs of kernicterus usually develop between the 4th and 8th day of life, with the maximum incidence on the 6th day; the onset tends to be later as the birth weight increases (Crosse et al.,[13] 1955). The early signs of kernicterus include lethargy, a disinclination for food, vomiting, cyanotic attacks, a high-pitched cry, restlessness, an expressionless face, eye-rolling, head retraction and alterations in muscle tone. Mild cases may easily be overlooked, especially if the signs are transitory. Because of the plethoric colour of some prematures even a marked icterus may be missed unless it is carefully looked for, in daylight, by stretching the skin.

There is a high mortality rate, death usually occurring 12-48 hours after the onset of signs.

Infants who survive get less stiff and many become hypotonic for a while; they may continue to have spasms of opisthotonos on handling, but after a few weeks they appear to be quite normal.

Subsequent development is, however, very disappointing. The most severely affected babies soon develop spasticity, and these babies usually die during the first year of life. The subsequent development of less severely affected cases varies tremendously; some tend to be irritable and jumpy, to cry a great deal, to feed and sleep badly, and to continue having spells of opisthotonos and eye-rolling. These babies are usually late in reaching their mile-stones and tend to retain infantile reflexes longer than usual. Residual damage to the central nervous system includes varying degrees of one or more of the following: rigidity, choreo-athetosis, deafness, emotional instability and mental retardation. Some cases appear to be developing reasonably normally until they begin to walk, and athetoid movements are not as a rule fully developed before the age of 3-5 years (Gerrard [12] 1952). Evans and Polani [14] (1950) state that 80% of their older survivors showed athetosis, choreo-athetosis, or chorea, and that the majority had mental impairment. Gerrard [12] (1952) found perceptive deafness in 80% of his older survivors.

Cause: The cause of kernicterus of prematurity is now believed to be immaturity of the liver which allows bilirubin to accumulate in the blood. Among 60 cases occurring in three Birmingham premature baby units 1951—1954, the incidence of kernicterus increased as the birth weight and maturity decreased; of the babies at risk (those who had survived 48 hours) the incidence of kernicterus was more than 12 times greater for babies delivered before the 30th week than for those delivered after the 36th week. The babies who developed kernicterus showed more signs of immaturity (atelectasis, cyanotic attacks, haemorrhagic diathesis and hypothermia) than their controls, i.e. babies of similar birth weight and maturity.

In haemolytic disease, the incidence of kernicterus was shown to be related to the level of serum bilirubin as early as 1952 (Hsia et al.,[15] 1952), and this is also the case with kernicterus associated with prematurity only (Crosse et al [13]., 1955, Meyer [16] 1956).

Hsia et al.,[17] (1953) observed that the post-natal bilirubin levels of premature babies reached higher levels than those of full-term babies, and since then other workers have shown that the rise in the level of serum bilirubin increases as the birth weight decreases (Billing et al.,[18] 1954, Crosse et al [13]., 1954, Meyer [16] 1956).

It is likely that any condition which increases haemolysis or interferes with liver function may be a contributory factor in the development of kernicterus. Anoxia has been suggested as a factor by several workers, the anoxia possibly being due to anaemia (Claireaux [19] 1950), atelectasis (Aidin et al.,[9] 1950), or birth asphyxia

(Govan and Scott[11] 1953). A high incidence of anoxia (due to antepartum haemorrhage, birth injury or atelectasis) was found among the Birmingham cases, but anoxia was not invariable.

Laurence[20] (1955) reported a remarkable increase in the incidence of kernicterus in premature babies following an increase in the routine dosage of Vitamin K. In three Birmingham units there was a steadily increasing incidence of kernicterus which could be related to an increasing dosage of Vitamin K (Crosse et al[13]., 1955). Meyer and Angus[21] (1956) working in these units found that intramuscular doses of 10 mg. or more of Synkavit raised the postnatal serum bilirubin level in babies of all weights, thus increasing the risk of the development of kernicterus in the premature baby with its already high level of bilirubin. Kernicterus occurs, however, in infants to whom no Vitamin K has been given. Silverman et al[22] (1956) reported cases of kernicterus following early prophylactic administration of Gantrisin to premature babies.

Preventive treatment: The incidence and degree of prematurity should be reduced by good antenatal care. Birth asphyxia should be avoided if possible and good facilities must be available for resuscitation. It is preferable to give Vitamin K to the mother during labour, but if this has not been done one single intramuscular dose of 0.5 mg. may be given to the infant at birth.

For the first week of life the infant must be carefully watched and if more than a slight degree of jaundice develops regular serum bilirubin estimations must be made (daily or more frequently if necessary) and an exchange transfusion undertaken if dangerous levels (18-20 mg. 100 ml.) are likely to be reached before the end of the first week of life. In some cases several exchanges will be necessary to keep the bilirubin below a dangerous level.

In July 1955, the above treatment became a routine in three Birmingham units and up to the end of 1956 only two cases of kernicterus had occurred. One infant was admitted on the 6th day of life suffering from kernicterus. A second was exchanged for a high bilirubin level on the 6th day of life, the level rose again on the 8th day and unfortunately all efforts to repeat the exchange failed. This number can be compared with 30 cases in 18 months when high doses of Vitamin K were being given and 13 cases for a similar number of admissions (900) before 1949 when only 1 dose of Vitamin K (1 or 2 mg.) was being given.

Curative treatment : There is no curative treatment, therefore preventive treatment is very important.

Follow-up: All cases in which marked jaundice have occurred should be followed up, whether signs of kernicterus have developed or not. In the Birmingham Units, a few jaundiced babies who showed only minimal signs of kernicterus during the first 10 days of life later developed cerebral palsy, mental retardation, or deafness; and Gerver and Day [23] (1950) have reported cases of mental retardation following deep jaundice without signs of kernicterus. It is therefore unwise to give a definite prognosis until at least the age of 1 year, and the hearing should be tested in all babies who have been severely jaundiced.

Hyaline Membrane.

Atelectasis has long been recognised as the chief cause of death among premature babies during the first 48 hours of life, but only recently has hyaline membrane been recognised as the principal cause of secondary atelectasis.

Pathology: In this condition the alveolar ducts and bronchioles become irregularly lined with a homogeneous eosinophilic membrane which obstructs the air passages and causes widespread resorption of air and collapse of the alveoli.

Incidence: From autopsy studies of neonatal deaths, Miller and Jennison [24] (1950) found hyaline membrane in at least 15 per-cent of all live-born premature babies weighing between 1,000 and 2,000 g. at birth; the incidence decreased as the birth weight increased and was practically non-existent in infants over 3,000 g. at birth. Potter [25] (1950) found this membrane in 4 per cent of premature babies and in only 0.1 per cent of infants weighing more than 2500 g. at birth: among these larger infants it occured most commonly in those delivered by Caesarean section. Hyaline membrane also occurs in infants of diabetic mothers and infants of mothers with placenta praevia. It is not found in stillborn babies nor in babies dying under the age of one hour.

Diagnosis: Infants suffering from hyaline membrane may cry well at birth and appear pink and vigorous, but after a very short period respiration becomes irregular and laboured with marked sternal recession and grunting expiration. Attacks of apnoea and cyanosis (or greyness) develop and these tend to increase in frequency and degree, and death usually occurs within the first 48 hours of life. In many cases respiratory difficulties are present from birth. The air entry is poor in spite of the great respiratory efforts and the cry is weak. Mucus production is usually excessive and

moist sounds are often heard in the lungs. Subcutaneous oedema is generally present.

It is often impossible to distinguish between primary atelectasis, secondary atelectasis, atelectasis due to persistent effects of narcotics given to the mother during labour, and atelectasis associated with intracranial haemorrhage, as any of these conditions may occur. Lung infections, lung haemorrhages and congenital heart disease may also cause difficulties in diagnosis.

Prognosis: Infants with these signs may survive if they can be carried over the first 48 hours of life, after which time the condition tends to improve.

Cause: It was originally suggested that hyaline membrane might be derived from inhaled amniotic sac contents (Johnson and Meyer[26] 1925), but Gitlin and Craig [27] (1956) have shown that the membranes consist mainly of fibrin and it is now believed that they are derived from pulmonary oedema fluid. Various causes have been suggested for the pulmonary oedema, e.g. vagal disturbance (Miller, Behrle and Gibson [28] 1952), the administration of high concentrations of oxygen or the presence of high steroid levels (Bruns and Shields [29], heart failure with pulmonary congestion (Lendrum [30]), overloading of the poorly developed pulmonary circuit in premature babies following postnatal closure of foetal circulatory channels (Polacek [31]), and Polacek wondered if the practice of late clamping of the cord was entirely harmless in the premature baby. It is still believed that aspiration of liquor amnii may play a part by conversion of the fibrinogen of the oedema fluid into fibrin by the thromboplastin in the liquor (Lauffe and Stevenson [32]). It is also possible that the breathing of dry air or oxygen may help in the formation of membranes (Gellis [33]).

Investigation of 923 premature babies admitted to Sorrento Premature Baby Unit during the three years 1953—1955 (Crosse [34]) showed that the incidence of hyaline membrane (proved by autopsy and histological examination) decreased as the birth weight increased. The signs shown by babies proved to have hyaline membrane (cyanosis, sternal and rib recession, grunting expiration, excessive mucus secretion, and subcutaneous oedema), and the frequent association of certain autopsy findings with hyaline membrane (excessive fluid in the trachea and bronchi, subcutaneous oedema, and oedema of the leptomeninges) led to the conclusion that hyaline membrane was due to:

(1) A generalised increased permeability of the capillaries in the premature baby (accounting for the subcutaneous oedema

and oedema of the leptomeninges as well as the pulmonary oedema).

(2) Overloading of the immature pulmonary vascular system at birth.

(3) Compression of the pulmonary oedema fluid against the walls of the air spaces by respiration.

The increased incidence of hyaline membrane found among premature babies born after complications of pregnancy and labour, and among babies showing asphyxia at birth, suggested that asphyxia increased the risk of hyaline membrane by increasing pulmonary congestion and perhaps also increasing the capillary permeability, or by leading to aspiration of liquor which hastened the conversion of fibrinogen to fibrin.

Prevention: Good antenatal care can reduce the incidence and degree of prematurity, and also the incidence of birth asphyxia. Good care during delivery can further reduce the likelihood of birth asphyxia. Unnecessary Caeserean section should be avoided.

The following post-natal treatment might help to reduce membrane formation.

(1) Careful resuscitation at birth. This should include aspiration of the stomach as well as the air passages, to reduce the risk of later aspiration of vomitus.

(2) Good drainage of the air passages for the first 48 hours of life, preferably by nursing the baby in the prone position.

(3) Delayed feeding to reduce the risk of regurgitation and inhalation.

(4) Avoidance of oxygen unless the baby is cyanosed. If oxygen is given the concentration should be kept below 30%. (Experiments at Sorrento have shown that the oxygenation of the blood is just as complete with 30% oxygen as with pure oxygen).

(5) Humidification of air and oxygen for at least the first 2-3 days of life. It can do no harm and could help the drainage of the air passages if the infant is in a suitable position.

Treatment: This consists of good nursing care, careful administration of oxygen when indicated, re-establishment of respiration during periods of apnoea, and the administration of antibiotics.

Research: Research into this problem should be continued.

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