

and its frequency is unknown. The circulatory dysfunction resulting from alveolar hypoventilation may go undetected clinically for many years. Accurate recognition is dependent on analysis of arterial blood gases; hypercapnia is invariable,⁴ though hypoxia is the main factor causing pulmonary vasoconstriction.¹⁴ Whether or not the pulmonary vascular resistance can be restored to normal depends on the extent of secondary changes in the pulmonary vessels and the degree to which the cause of the vasoconstriction can be relieved. When the vasoconstricting stimulus is hypoxia secondary changes are uncommon. Pulmonary hypertension in subjects born at high altitudes has been shown to disappear after residence at sea level,¹⁵ and pulmonary hypertension resulting from alveolar hypoventilation in hyaline membrane disease may prove temporarily reversible by treatment.¹⁶ Pulmonary hypertension resulting from obstructive lesions in the upper respiratory tract can almost always be cured by surgery.

Alveolar hypoventilation has many causes in children.³ Lower respiratory tract infections,^{17, 18} asthma,¹⁹ and other respiratory disorders²⁰ can all cause hypoxia and hypercapnia. Airways obstruction with respiratory acidosis develops in the majority of infants in heart failure,²¹ and wheezy respirations are still insufficiently appreciated as one of the features of left ventricular failure in infancy.²² Stridor with recurrent tracheitis and bronchitis from birth are common features of constrictive vascular rings. It is therefore surprising that there is no documentary evidence of pulmonary hypertension in infants and children in whom the trachea is constricted by anomalies of the aorta,^{23, 24} or by the less common anomalous origin of the left pulmonary artery from the right pulmonary artery.^{25, 26}

Some of these factors may have been partially responsible for the pulmonary hypertension in Levy's patient.⁵ His findings emphasize the need for more information on the frequency with which airways obstruction is responsible for haemodynamic changes in children. The clinical signs of stridor or wheezing should suggest the possibility of this syndrome. More widespread use of arterial blood gas analysis and cardiac catheterization may show that alveolar hypoventilation is a factor in pulmonary hypertension and heart

failure in childhood more often than has been appreciated. Recognition is important, because treatment may be simple and effective.

Outlook in Rh-haemolytic Disease

The use of anti-D gammaglobulin in the prevention of Rh-haemolytic disease is one of the most remarkable advances in the history of preventive medicine. Professor C. A. Clarke in his Lumleian Lecture,¹ which described the co-operative studies in Britain, Germany, and the United States, showed that anti-D gammaglobulin injected within 48 hours of delivery will almost always prevent the development of immunization. Rhesus immunization had not occurred in more than 600 mothers given anti-D gammaglobulin when tested six months after their first pregnancy, and no evidence of immunization had been found in several women after a second pregnancy. Nevertheless, Clarke pointed out that more experience with serial pregnancies was necessary before prophylaxis could be shown to be completely effective.

It might be tempting to conclude that Rh-haemolytic disease will rapidly vanish as a problem, and that techniques such as exchange transfusion will no longer be necessary. This situation will not occur immediately, however, for two main reasons. The first is that women already immunized cannot be treated with anti-D globulin. Secondly, an adequate supply of the globulin will be necessary. How much is needed will depend on the titre of the antiserum produced and on the quantity required to clear the maternal circulation of foetal cells at delivery. The amount that needs to be injected is now the subject of several controlled trials in Britain, Europe, and the United States. Antiserum will have to be produced from human sources until it can be made synthetically. The ideal human source would seem to be mothers who have already been immunized, although in time effective prophylaxis will reduce the number of these donors. Unfortunately, in both Holland² and Britain³ attempts to establish panels of donors have met with little success. Young mothers are not willing to make regular journeys, and older women are more subject to illness, so that the number of donors of suitably high titre plasma soon falls. The policy of deliberate immunization of rhesus-negative male volunteers has been used by the Liverpool group. By the use of plasmapheresis it is estimated that 15 donors providing a litre of plasma a month can serve the needs of a population of one million.

Even if an adequate supply of anti-D gammaglobulin was available at present it would not affect the future of those women who have already become immunized. Thus rhesus haemolytic disease and the use of early induction of labour and exchange and intrauterine transfusions will be familiar for at least twenty years. In addition, though it is rare, Rh-haemolytic disease does occur during the first pregnancy.⁴ In a careful study O. Hartmann and O. Brendemoen⁵ showed that 23 of 520 Rh-negative women developed antibodies who had no previous history of trans-

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¹⁰ Murray, S., *ibid.*, 1967, 4, 296.

¹¹ — *ibid.*, 1967, 4, 682.

fusion, injection of blood, or abortion. Three mothers had stillbirths and three gave birth to babies requiring exchange transfusion.

Another group at risk from haemolytic disease which will not be amenable to prophylaxis will be the group of ABO and rare blood-group incompatibilities. As D. Macaulay and Z. Qureshi⁶ have noted, these represent a not inconsiderable proportion of those requiring exchange transfusion. Rarely, it is even possible that prophylaxis of Rh immunization will be ineffective. Clarke has described a case, and seven others were recently reported in the *B.M.J.*⁷⁻⁹

Hence the problem of neonatal haemolytic disease seems likely to be present for some time, though on a gradually reducing scale. It is also possible that widespread introduction of prophylaxis may bring some further problems. The use of gammaglobulin prepared by the present method eliminates the risk of homologous serum jaundice. Clarke records local reactions to injections, but these are rare and comparatively trivial. Immunization to gammaglobulin does occur; though its incidence is difficult to assess at present, it may be as high as 5%. Shelagh Murray^{10, 11} has emphasized that little is known about the effect of antibodies developed against gammaglobulin on the mother or her subsequent children. The fruitful research of Clarke and his many colleagues has made it possible to prevent the distress caused by rhesus-haemolytic disease. This work now requires support on a national scale to ensure that prophylaxis should be absolutely safe.

Anencephalus and Spina Bifida

During the past 20 years knowledge of anencephalus and spina bifida has steadily grown. Anencephalus is a common condition in the British Isles, its incidence varying from about one in a thousand births in the south-east to two or three times that figure in north-west England, Wales, and most of Scotland, and reaching four or more per thousand in Ireland. International studies have shown even greater variation, the incidence in Belfast being 40 times that of Bogota or Ljubljana.¹ Among some Asiatic communities it is as common as here, but it is a rare malformation among Negroes. It affects females about three times as frequently as males, and first-born infants more often than second- or third-born. Usually it is most frequent among children conceived in the early summer,²⁻⁴ but there have been some years when this pattern was interrupted.⁵ The offspring of poor parents are affected much more frequently than those of the well-to-do, and women of short stature are more likely than others to have affected children.⁶

Spina bifida cystica is almost as common as anencephalus and has similar but less pronounced epidemiological features. For example, the sex ratio does not deviate from the normal so much, and the seasonal variation in incidence is less conspicuous. A close association between the two conditions is evident from statistics for their annual incidence⁷ and from the relative frequency with which both types of malformation occur within the same fraternity.^{8, 9}

This association is perhaps hardly surprising, since both conditions are the result of defects in development of the neural tube. Whether the basic fault is a failure of fusion of the neural folds¹⁰ or a breakdown of the tube after closure is not decided. We are even more ignorant of the agent or

agents which could bring this about in the human embryo. Attempts to incriminate virus infections in pregnancy have not been convincing, and drugs, with the possible exception of aminopterin,¹¹ seem to be equally blameless. No consistent chromosomal abnormalities have been detected.

It is often stated that these conditions must be genetically determined, but a simple genetic explanation is hardly acceptable for conditions which occur so frequently and are so lethal. The frequency of discordance in monozygous twins also provides strong evidence against such a view. It has been suggested, however, that a more subtle genetic mechanism may be involved, some maternal gene modifying the intra-uterine environment to favour the development of these malformations.^{12, 13} But recent work by L. Naggan and B. MacMahon¹⁴ makes this hypothesis seem unlikely. Their survey, based on hospital records in Boston, Massachusetts, contained 305 anencephalics and 393 infants with spina bifida, and a control group of 1,041 births. When the series was divided according to religion it was found that Roman Catholics had the highest incidence of both malformations (a combined rate of 2.8 per 1,000 births), Protestants came next (2.0 per 1,000), and Jews last (0.7 per 1,000). The high figure for the Catholics could be accounted for by the fact that a substantial proportion of these families had their origins in Ireland, though the rate in these families was not so high as the rates usually reported from the present inhabitants of Ireland. Further analysis showed that the rate among offspring of Irish mothers married to non-Irish fathers was exactly the same as that for Irish fathers married to non-Irish mothers (3.30 per 1,000), and the rate was very similar when both parents were Irish.

Other interesting points shown by this survey are that the rate among Boston Jews was very similar to that reported for Jews of European origin living in Israel. The Jews were the only ethnic group which did not show an increasing frequency of malformation with descent in social class. Though there is some evidence that these malformations are rare in France,¹⁵ a high incidence was noted in this American series among persons with French names (mostly French Canadians from Quebec). The survey adds to a growing literature one more instance of an authentic monozygous twin pair with one member malformed and the other normal. Anencephaly in both of dizygous twins of opposite sex has also been reported.¹⁶

Naggan and MacMahon conclude that the ethnic variations which they have reported probably stem from environmental rather than genetic differences. There will no doubt be some disagreement with this view, but on the whole it seems to be consistent with the evidence so far available.

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