PREMATURITY AND "CEREBRAL PALSY"

BY

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That there is an association between prematurity and "cerebral palsy"* impressed the earliest students of this neurological condition (Little, 1862; Freud, 1897). Its nature has puzzled many; for some, like Brissaud (1894), the effect of prematurity is to cause a developmental anomaly of the pyramidal tracts; for others, like Collier (1924), the two conditions are parallel manifestations of an intrauterine abnormality causing both prematurity and primary antenatal degeneration of cerebral neurones.

Although data on prematurity are available in the collection of cases published by Little, it is largely in recent times that the association between prematurity and cerebral palsy has been put on a quantitative basis. Evans (1948), in 76 cases, and Asher and Schonell (1950), in 400 cases, found an incidence of prematurity of 39%, about eight times that in the normal population, while Lilienfeld and Parkhurst (1951), for 505 cases, give a figure of 22.2% with an incidence of prematurity in their control population (115,281) of 4.8%. It is to be noted that the controls used by Lilienfeld and Parkhurst were survivors at the end of the first month of life, those of Asher and Schonell were survivors at the end of the first year, and those of Evans were matched for age with his cerebral palsy cases. So that in these studies an attempt was made to overcome the error that would result from using figures referring to incidence of prematurity at birth due to the high mortality of premature infants (mainly in the neonatal period), particularly those of lower birth weight (Alm, 1953; Dunham, 1955).

A further idea of the importance of prematurity in cerebral palsy can be obtained from Evans's (1948) data, by considering the proportion of premature infants weighing 4½ lb. (2,040 g.) or less at birth. The relevant figures are: 21 such premature infants among 76 cerebral palsy cases and 1 among 50 controls (28% and 2% respectively). The figures given by Knobloch *et al.* (1956) further support this point. They found an incidence of "overt neurological defect" at 40 weeks of 12.3% in 57 premature babies weighing 1,500 g. or less, of 1.6% in 443 larger prematures, and of 0.6% in 492 full-term controls matched for race, season of birth, parity, hospital of birth, and socio-economic status.

Cerebral palsy is an aggregate of clinical syndromes with various origins, and so is prematurity. The causes of prematurity act on the foetus with varied intensity and at different developmental stages. Furthermore, the foetus prematurely delivered is exposed to extra risks during labour, and the premature newborn baby also faces numerous hazards.

Incidence of Prematurity in Cerebral Palsy

One might expect some types of cerebral palsy to be more strongly associated with prematurity than others. Freud (1897) and Brissaud (1894) correlated prematurity particularly with diplegia. The combined figures of Evans (1948) and Asher and Schonell (1950) show a significant difference in the incidence of prematurity between "non-rhesus athetoids" (29% of 74 cases) and "paraplegias and tetraplegias" (44% of 223 patients). The proportion of prematures among 104 cases of congenital hemiplegia was reported by Asher and Schonell as 30% and by Perlstein and Hood (1953) in their 222 cases as 12%.

A series of 93 cases of dystonic and choreo-athetoid cerebral palsy† was analysed (Polani, 1957, unpublished data). Of 28 cases with severe neonatal jaundice due to blood-group iso-immunization three were premature (11%); of 20 patients with a history of severe neonatal jaundice not associated with blood-group incompatibility 14 were premature (70%); and of 45 patients who did not have severe neonatal jaundice 16 were premature (35.5%). By contrast, in a group of 42 patients with cerebral spastic paraplegia/diplegia,‡ 59.9% were premature (Polani, 1957, unpublished data). Thus the association with prematurity seems high in cerebral palsy due to non-rhesus jaundice and in cerebral spastic paraplegia/diplegia.

The figures given by Ingram and Kerr (1954) confirm the striking association between cerebral spastic paraplegia/diplegia and prematurity (see Table). These figures suggest

Survivors, by Birth Weight, Edinburgh, 1948–52 (Ingram and Kerr, 1954)

Birth Weights	No. of Survivors	Diplegics/ Paraplegics Total No.	Incidence per 1,000
All weights	36,400	36*	1
Over 5½ lb. (2,500 g.)	35,143	23*	0·65
4–5½ lb. (1,800–2,500 g.)	1,017	2	1·96
Under 4 lb. (1,800 g.)	240	11	45·83

* Estimated on the basis of the period 1943–7 (33 cases in 35,866 children).

that, compared with full-term children, premature babies of high birth weight show a threefold increase in the incidence of cerebral spastic paraplegia/diplegia and those of lower birthweights a seventyfold increase. Thus among premature infants weighing under 4 lb. (1,800 g.) at birth the chance of cerebral spastic paraplegia or diplegia is apparently about 1 in 20.

If we accept Lilienfeld and Parkhurst's (1951) idea of a "continuum of reproductive wastage," with cerebral palsy as one link in a chain of unfavourable reactions, other elements of which are mental defect (Pasamanick and Lilienfeld, 1955b; Lilienfeld and Pasamanick, 1956), epilepsy (Lilienfeld and Pasamanick, 1954; Pasamanick and Lilienfeld, 1955a), behaviour disorder (Pasamanick, 1954; Rogers *et al.*, 1955, Pasamanick *et al.*, 1956), and foetal and neonatal death, we may observe even more subtle cerebral effects associated with prematurity. For example, the lowered intelligence quotient found by Douglas (1956) in his group of premature children, and confirmed by Dann *et al.* (1956), may represent more limited (or different) results of a harmful association between prematurity and brain function.

Causal Connexion

What could be the causal connexion in the association between prematurity and cerebral palsy? As stated, this association may manifest itself in different effects, depending on the different causes of prematurity, the different times in foetal development when they act, their different intensities, and the various stresses to which prematurity itself subjects

*This term is used here to mean a persisting qualitative motor disorder due to non-progressive damage of the encephalon occurring before the growth of the central nervous system is complete.

†In dystonic cerebral palsy abnormalities of muscle tone predominate, and the hypertonus, when present, is plastic in character (Denny-Brown, 1946). In choreo-athetoid cerebral palsy the outstanding motor abnormality is the presence of unwanted movements—dyskinesia of Perlstein (1952) and Balf and Ingram (1955).

‡Cerebral spastic paraplegia denotes a condition of lower-limb paralysis of cerebral origin, without notable functional involvement of the upper limbs. Patients with spastic diplegia have predominantly lower-limb and trunk involvement, and also upper-limb involvement, which, however, is less marked than that of the lower limbs. The difference between the two conditions may be essentially one of degree.

the developing organism. To deal with one example, prematurity may cause cerebral palsy (generally dystonic or choreo-athetoid cerebral palsy) through the mechanism of neonatal jaundice. Premature babies have a greater tendency to a rise in the serum-bilirubin level, presumably because of an inability of their livers to conjugate the liposoluble bilirubin (indirect-reacting bilirubin) with glucuronic acid and transform it into the water-soluble pigments I and II (direct bilirubin, bilirubin mono- and di-glucuronide) (see Cole and Lathe, 1953; Billing *et al.*, 1957; Gray, 1957). For this reason, in a proportion of premature infants, even in the absence of increased haemolysis due to blood-group iso-immunization, the serum bilirubin will rise to dangerous levels and the liposoluble pigment cross the blood–brain barrier and produce kernicterus*.

If the breakdown of red cells is increased, as, for instance, when certain vitamin-K analogues are given in excess (Laurance, 1955; Crosse *et al.*, 1955; Allison, 1955), the extra production of bilirubin will increase the proportion of premature babies who get kernicteric damage. It has furthermore been shown by Diamond (1956) that the administration of sulphafurazole ("gantrisin") to premature babies may favour kernicteric damage without an excessive rise in serum bilirubin; Lathe (1957) has suggested that this is due to a lowering of the threshold of the blood–brain barrier. Kernicterus in a rabbit has been produced by this mechanism (Ernster *et al.*, 1957).

Anoxic and Mechanical Trauma

But prematurity may be responsible for cerebral palsy through other mechanisms. The premature baby is generally frail and his respiratory efficiency is often less than that of the full-term infant, with consequent possibilities of "anoxia." Furthermore, the lower the birthweight of premature infants (Calkins, 1955) the higher the incidence of breech delivery, which exposes the foetus and the newborn to added risks from mechanical or asphyxial injury, with consequent possibility of brain damage and so of cerebral palsy. Such mechanical or "anoxic" trauma would explain reasonably well some forms of cerebral palsy, such as double hemiplegia and "post-anoxic" choreo-athetoid and dystonic forms of the disorder.

Although, admittedly, anoxia can be selective in its action, the frequency of the association between cerebral spastic paraplegia and prematurity is more difficult to explain adequately on the grounds of a relatively indiscriminate and diffuse cerebral damage. The post-prematurity spastic paraplegia type of cerebral palsy is a striking clinical entity, striking for the symmetry of the neurological signs, for their distribution, for the relatively good intelligence of the patients, and for their comparative freedom from seizures; and all these features tend to militate against the idea of brain injury being responsible.

Possibility of a Development Mechanism

A developmental origin (Brissaud, 1894) seems a more logical explanation for the syndrome, and it might be reasonable to accept Collier's (1924) idea that the same factors which are responsible for the disturbed mother/foetus relationship, and so for prematurity, are also responsible for the disorder of brain development and so for cerebral spastic paraplegia. If this were so, the incidence of cerebral spastic paraplegia (and diplegia) might be expected to vary in groups of premature infants when the prematurity is due to different causes. If the disordered development were related to the cause of prematurity it would follow that the cerebral abnormality would be of prenatal origin. Prevention would be possible only if the causative factors were avoidable.

It should be made clear that when cerebral palsy cases are compared with a control population to assess the importance of obstetric factors in the aetiology of cerebral palsy (toxaemia of pregnancy, ante-partum haemorrhage, breech delivery, forceps delivery, breathing "difficulty," etc.) the control population generally contains a much lower proportion of premature children, so that what such comparisons reveal in the cerebral palsy population is the excess of obstetrical factors responsible for the prematurity though not necessarily for the cerebral palsy. Such comparisons would be more valid if the control population were matched for incidence of prematurity.

Few studies have separated prematurity into aetiological groups and correlated them with the frequency of cerebral palsy, thus trying to link *causes* of prematurity and cerebral palsy. Douglas's (1956) findings are worth noting in this context, though they do not refer to cerebral palsy but to mental ability of premature children. He examined a prospectively studied national sample of premature children aged 8 years and found a small group of them who made ". . . outstandingly poor scores in all tests—namely, those whose prematurity is unexplained either by obstetric abnormality" or by their genetic background. Lilienfeld and Parkhurst (1951) found a higher incidence of prematurity among those cases of cerebral palsy where complications of pregnancy and labour had not been present than among those where they had. They tried to explain this finding by suggesting a higher mortality rate among cerebral palsy premature infants with complications of pregnancy. Eastman and DeLeon (1955) have shown that in only one-third of their cerebral palsy cases associated with prematurity was there a complication of pregnancy that could have been responsible for the cerebral palsy through the mechanism of foetal anoxia. In two-thirds they concluded that the origin of cerebral palsy was in some way attributable to the prematurity itself.

It is possible to suggest mechanisms by which prematurity, by itself, is at times the operative factor in determining the paraplegia/diplegia type of cerebral palsy. The condition might be of post-natal origin, from failure of final structural and functional maturation of the brain, and it would then be the *degree* of prematurity rather than its cause that would be linked with the frequency of the condition. The figures of Ingram and Kerr (1954), given in the Table, stress the association between a greater degree of prematurity and a greater frequency of cerebral spastic paraplegia/diplegia.

A Matter for Conjecture

How this particular type of cerebral palsy could be produced by prematurity itself is a matter for conjecture. A possible explanation would be one that took into consideration the relatively anaerobic metabolism of the foetal nervous system, and its maturation, centre by centre, to the adult aerobic metabolism, apparently essential for the quick release of high energy presumably required for brain function. This has been demonstrated in the experimental animal by Himwich (1951) and his collaborators, and has been suggested in the human by the work of Racker (1942). It is a plausible conjecture that, possibly through interference with enzymic maturation or adaptation, premature birth deprives those parts of the nervous system which are at a crucial stage of anatomical development or functional maturation of the environment favourable to this development or maturation. The damaging factor may well not be anoxic, but rather hyperoxic, though even a hyperoxic insult may ultimately result in anoxic damage through interference with oxidative enzymes (Himwich, 1953; Dickens, 1946a, 1946b). Alternatively, brain structure and function may be damaged by a prolonged condition of absolute or relative hyperoxia, through alteration of the blood vessels of the differentiating cortex, much as can happen in the eyes of premature babies, with consequent retrolental fibroplasia.

It is perhaps relevant in this connexion to mention the work of Ashton *et al.* (1957), who poisoned the eyes of kittens with fluoride and iodoacetate and observed changes

*The present evidence is in favour of the cerebral damage being due to a direct action (Claireaux *et al.*, 1953; Ernster *et al.*, 1957).

similar to those resulting from exposure to high oxygen concentrations. They tentatively suggested that the mechanism at work was one of inhibition of glycolysis resulting in swelling of retinal tissue and subsequent vascular compression and obliteration (see also Graymore, 1958). By this technique they were able to produce a biochemical lesion owing to a particular vulnerability linked to a definite stage of functional development and maturation, and it is worth noting that similar changes could not be produced by them in the eyes of more adult cats. If the incidence of cerebral palsy (particularly cerebral spastic paraplegia/diplegia) were greater in babies stressed by high oxygen concentrations, the hyperoxic hypothesis would perhaps be more acceptable. Fuldner (1955) found an association between cerebral spastic paraplegia and retrolental fibroplasia. That the incidence of cerebral spastic paraplegia/diplegia in babies with retrolental fibroplasia is greater than would be expected has been shown by Ingram and Kerr (1954). However, they suggested that the cause of cerebral damage in their patients was abnormality of pregnancy and of labour, leading to post-natal asphyxia which necessitated oxygen therapy and in turn caused retrolental fibroplasia.

The above suggestion that premature birth may at times cause post-natal interference in development and maturation of critically maturing neurones is entirely hypothetical. It can be put to the test by experiments with high oxygen pressures in immature animals. The understanding of the delicate metabolic mechanisms involved can be furthered by detailed studies of the vascular, enzymic, histological, and functional maturation of the human brain, in continuation of the work done by Racker (1942) and Villee (1953). The main use of such a hypothesis is that it directs attention to possibilities of prevention.

Summary

The incidence of prematurity in various clinical types of cerebral palsy is reviewed. A particularly strong association is found with two neurological syndromes: dystonic/choreo-athetoid cerebral palsy following severe neonatal jaundice not due to blood-group incompatibility, and cerebral spastic paraplegia/diplegia. The possible mechanisms of this latter relationship are considered and a selective developmental origin for the neurological troubles is favoured tentatively. Because of the association between retrolental fibroplasia and cerebral spastic paraplegia/diplegia, and because of the clinical features of the cerebral spastic paraplegia syndrome without history of perinatal or postnatal troubles, a postnatal interference with development is the mechanism postulated for this clinical type of cerebral palsy.

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CORTICOTROPHIN AND STEROIDS IN THE DIAGNOSIS AND MANAGEMENT OF "OBSTRUCTIVE" JAUNDICE

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Jaundice due to hepatitis with prolonged bile retention (Eppinger, 1937; Watson and Hoffbauer, 1946) or occurring as a complication of therapy with chlorpromazine and other drugs (Hanger and Gutman, 1940; Hollister, 1957) may have clinical and biochemical features indistinguishable from that associated with extrahepatic biliary obstruction. Solem and Olsen (1953), aware that jaundice in patients with hepatitis often clears rapidly with steroid therapy (Ducci and Motlis, 1951), reported that the effect of a four to seven-day trial of corticotrophin (A.C.T.H.) therapy on the icteric index permitted a clear-cut distinction between extrahepatic obstructive jaundice, which was not significantly influenced, and hepatitis. However, later observations showed that the effect of corticotrophin or steroids in hepatitis was very variable (Sborov *et al.*, 1954) and that considerable reduction in serum bilirubin concentrations could follow use of the drugs in extrahepatic biliary obstruction, thus invalidating their application as a diagnostic test (Chalmers *et al.*, 1956; Katz *et al.*, 1957).

The subject has received only passing mention in this country (Shaldon and Sherlock, 1957; Summerskill, 1958), although the laparotomy indicated in extrahepatic obstruction may be unnecessary and hazardous in hepatitis. We therefore report the effect of corticotrophin and steroid drugs on serum bilirubin and alkaline