THE ASSOCIATION OF RETROLENTAL FIBROPLASIA WITH CEREBRAL DIPLEGIA

BY

T. T. S. INGRAM and J. D. KERR

From the Department of Child Life and Health, University of Edinburgh, and the Maternity and Child Welfare Department, City of Edinburgh

(RECEIVED FOR PUBLICATION MARCH 15, 1954)

Both retrolental fibroplasia and cerebral diplegia are known to occur more frequently in infants born prematurely than in those born at term, and the chance association of the two conditions might therefore be expected in a small number of premature infants. In the course of two contemporary investigations, the first a survey of the occurrence of retrolental fibroplasia in the City of Edinburgh during the five years 1948-1952 (J.D.K.), the second a survey of the aetiology and incidence of cerebral palsy in the same city (T.T.S.I.), the two conditions were found in association in six instances. From a consideration of the case incidence of the two diseases, it appeared that the association was more frequent than would be expected by chance, and that there were probably aetiological factors other than prematurity common to both retrolental fibroplasia and cerebral diplegia. In the present study the common factors thought to lead to the association of the two diseases are considered.

Scope and Methods of the Survey of Retrolental Fibroplasia

This survey was confined to the study of surviving prematurely born children delivered and resident in the City of Edinburgh, though a number of children born outside the City were also examined.

During 1952 health visitors of the local health authority saw all surviving children with birth weights of 5½ lb. or less. A questionnaire giving details of the ante-natal, natal and post-natal history was completed for each child. Any baby showing visual or other physical defect was routinely examined at a special clinic. In addition, all babies born during 1952 with birth weights of 4 lb. or less were examined routinely at monthly intervals until the age of 6 months. Each examination consisted of weighing, measuring, physical assessment and inspection of the babies' fundi by a consultant ophthalmologist.

If any ocular abnormality was discovered the infant's eyes were re-examined under general anaesthesia and the infant followed up more frequently. The infants who had fully developed retrolental fibroplasia before 1952 were examined in a similar manner on one or more occasions, as indicated.

Twenty-one cases of retrolental fibroplasia were discovered and six of these showed associated cerebral diplegia. One of the six infants was born outside Edinburgh although domiciled in the City.

Scope and Methods of the Cerebral Palsy Survey

The cerebral palsy survey includes all children resident in Edinburgh born between 1938 and 1952 inclusive. Owing to the conditions of the survey the examination of only very limited population samples was possible. For the most part ascertainment was through hospitals, clinics, schools and nurseries to which the children had been referred. Since a number of cases of diplegia are not referred to clinics until they are over 2 years of age, it is probable that a number born since 1950 have been missed. Since the screening of children born prematurely was so thorough during the retrolental fibroplasia survey it is more likely that diplegic cases born at term have been missed than those born prematurely.

All children in whom there was the least suspicion of cerebral palsy were submitted to routine neurological examination. Sixty-two cases of cerebral palsy born in the years 1948-52 and resident in Edinburgh were discovered and of these 29 cases showed cerebral diplegia. Cerebral diplegia is considered as a condition of more or less symmetrical spastic or rigid paralysis dating from birth or shortly after and more marked in the lower than in the upper limbs. It excludes cases in which disorder of movement, dyskinesis, or ataxia are the presenting

features, even if a degree of diplegic paralysis is associated with these disorders. The diplegic cases to be considered comprise children suffering from rigid or spastic paralysis of varying severity and extent, of paraplegic, triplegic or tetraplegic distribution. Such cases were called 'Little's disease' by Freud (1897). Of the 29 cases of cerebral diplegia born in the years 1948-52 and now resident in Edinburgh, 24 were born in the City. Six of the infants showed both diplegia and retrolental fibroplasia; one was born outside Edinburgh.

Description of Cases Showing Retrolental Fibroplasia with Cerebral Diplegia

Clinical details of the six patients showing retrolental fibroplasia and diplegia are summarized in Tables 1 and 2.

It will be seen that all were born prematurely with birth weights of under 4 lb. In three cases there was premature rupture of the membranes and in three ante-partum haemorrhage. In no case was pregnancy normal. In three cases the placenta was abnormal and weighed only 12 oz. in Case 1.

In four cases the presentation was vertex and spontaneous delivery took place under trilene or chloroform analgesia. In two cases the child was delivered by assisted breech extraction, in one following prolapse of the cord.

Five of the six cases were stated to be in poor condition at birth while the sixth was said to be in fair condition. All required incubation and prolonged continuous oxygen therapy for more than one week after birth. In three cases the lung expansion was specifically stated to be very poor for as long as seven days after the birth.

Two cases had congenital inguinal herniae at the time of birth. One case had a valgus deformity of the foot and one a congenital haemangioma. Cases 3 and 5 had persistent respiratory infections throughout infancy and both were admitted to hospital suffering from pneumonia within the first four months of life.

On discharge from the maternity hospitals the first abnormality relating to retrolental fibroplasia or cerebral diplegia observed by the mothers was the child's apparent inability to see in four cases. The ages at which medical help was sought were 10, 12, 17 and 24 weeks in Cases 1, 2, 3 and 6 respectively.

TABLE 1
ANTE-NATAL AND NATAL HISTORY IN SIX CASES SHOWING CEREBRAL DIPLEGIA AND RETROLENTAL FIBROPLASIA

Case	Sex	Year of Birth	Birth Weight (lb. oz.)	Gestation (Weeks)	Age of Mother at Time of Birth (Years)	Social Class (Father)	Family History	Ante-natal History	Natal History
1	Male	1949	3 9½	30	27	IV	One previous child alive and well; miscarriage at 3 months in 1945	Premature rupture of membranes at 28 weeks	Vertex presentation spontaneous delivery, labour 18 hr. 40 min., trilene anaesthesia, placenta 12oz., no infarcts
2	Female	1949	3 0	30	27	III	One previous child alive and well; miscarriage in 1947	Rupture of membranes at 5 months; admitted to hospital and kept till delivery	Breech extraction, labour 18 hr. 30 min., chloroform anaesthesia
3	Male	1951	3 3	29	30	III	One previous child alive and well; miscarriage at 2 months in 1950	Haemorrhage 3 days before delivery; leg cramps for 2 months before delivery	3 days poor pains—8 days good pains, vertex presentation, trilene anaesthesia, placenta pale and abnormal
4	Male	1951	3 5	29	32	IV	One previous child alive and well; father alcoholic	Haemorrhage 1 week before delivery and profuse the day before delivery	Prolapse of cord, breech extraction, labour 3 hr. 40 min., trilene anaesthesia, hole in membranes at placental edge
5	Male	1951	3 8	30	22	IV	One previous child alive and well; mother and two aunts tuberculous, ovariectomy in 1949	Profuse haemorrhage two days before delivery	Vertex presentation, labour 5 hr. 45 min., chloroform anaesthesia, placenta 15 oz., no infarcts
6	Male	1949	3 0	28	22	II	First pregnancy	Severe influenza at 3rd month of pregnancy, premature rupture of membranes	Vertex presentation, spontaneous delivery, labour 5 hr. 30 min., Minnitts anaesthesia

TABLE 2

NEONATAL AND POST-NATAL HISTORY IN SIX CASES SHOWING CEREBRAL DIPLEGIA AND RETROLENTAL FIBROPLASIA

Case	Condition at Birth	Neonatal History	Post-natal History	Eye Examination	Central Nervous System Examination
1	Asphyxiated, responded slowly to oxygen	Poor lung expansion for one week, inguinal hernia noted	Legs stiff and extensor spasms from age of 3 mth., milestones delayed, general health good, walking at 4 yr.	Defective vision noted at 10 weeks of age, bilateral retrolental membranes, no vision	Some sparing of right arm, Severe spastic diplegia, intelligence probably subnormal
2	Very limp, 1 ml. coramine given into cord	Oxygen given for 10 weeks; valgus deformity of foot; jaundice at end of first week	Using left hand at 6 mth., not using right hand, milestones delayed, grand mal fits from age of 3 years	Defective vision noted at 12 weeks of age, bilateral retrolental membranes, no vision	Severe spastic diplegia, associated extensor reactions, overactive behaviour disturbance, subnormal mentally
3	Asphyxiated infant	Oxygen given for 3 weeks, very feeble, tube fed for 10 days	Milestones normal, pneumonia at 4 months. otitis media at 8 months	Looked to one side at age of 4 mth., retinal fold in left eye, pale areas surrounded by pigmentary changes at periphery of both fundi	Moderately severe spastic diplegia, speech defect, abducent muscle weakness, intelligence probably normal
4	Poor condition, cyanosed and feeble, intermittent CO_2 and O_2 given	Persistent poor lung, expansion for one week, inguinal hernia	Milestones normal save not walking at 2½ yr. of age, grand mal fits from 23 wks., hernia repair at 4 months	Given 6 wk. course of cortisone at 4 mth., right eye became normal, left eye deteriorated with fibrous mass in anterior vitreous with scattered pigmentary change temporally	Moderately severe spastic diplegia, arms slightly affected, some athetosis in hands especially the right, left abducent paresis, intelligence normal
5	Shocked, cyanosed, responded to oxygen	Poor lung expansion for one week, repeated respiratory infections, anaemia required transfusion, small haemangioma	Milestones delayed, recurrent respiratory infections, pneumonia at 15 wk. of age, recurrent otitis media	Bilateral retrolental membranes, no vision	Very severe spastic diplegia and amentia
6	Condition fair	Slow to feed, 2 mth. in incubator	Milestones normal, general health good	Defective vision noted at 6 mth., nystagmus, visual activity mainly by right eye, left fundus shows retinal fold running laterally from the disc	Severe spastic diplegia affecting left arm rather more than right, bilateral abducent paresis, intelligence on test probably lower than normal

In Case 5 lethargy and extreme backwardness were the presenting symptoms. In this patient the mother suspected blindness only at the age of 6 months.

Only in Case 1 was specific complaint made by the mother of any abnormality in the limbs. In all the others they complained of backwardness, blindness or both. In Cases 1 and 5 the mothers had noted that the child became stiff on handling. In each case the onset of stiffness was sudden and resulted in transient opisthotonic attitudes being assumed for a few seconds, without impairment of consciousness. The attacks occurred for a period of three months in Case 1 and persisted until after the age of 2 years in Case 5.

Two of the children with partial vision had been observed by their mothers to look sideways at objects from the age of a few months. On examination useful vision was considered to be present in three of the six cases. Two of these (Cases 3 and 4) appeared to have intelligence within the normal limits, but in the remaining cases intelligence was thought to be impaired. The degree of impairment was assessed as moderate in Case 6, considerable in Cases 1 and 2 and very severe in Case 5.

It is interesting to observe that the severity of the diplegia, the extent of the retrolental fibroplasia and the degree of impairment of mentality are roughly parallel in the six cases. Thus Case 5, with contractures of all four limbs and great rigidity, was classified as a severe diplegic. He was completely blind and grossly mentally defective. Cases 1 and 2 showed tetraplegic involvement with early contractures, but there was much less severe involvement in the arms than in the legs and in each case some sparing of one arm was evident. In Cases 3, 4 and 6 both arms were considered to be functionally useful. In Cases 3 and 6 the legs were only moderately affected and both walked before the age of 2 years.

Two cases had epilepsy. Case 2 had her first fit at the age of 35 months and in spite of anti-epileptic drugs, generalized convulsions with loss of consciousness have occurred, on an average, twice every three months. Case 4 had three generalized fits, with loss of consciousness, between the age of 23 and 26 weeks, but these ceased with the administration of phenobarbitone.

Three of the six children (Cases 1, 2 and 5) had

TABLE 3

AETIOLOGICAL FACTORS IN CEREBRAL DIPLEGIA AND RETROLENTAL FIBROPLASIA

	Cerebral Diplegia		Retrolental Fibroplasia	Both Disorders	Normals
	Over 5½ lb.	5½ lb. and under	5½ lb. and under	5½ lb. and under	4 lb. and under
Number of cases					
Males	11	8	15	5	224
Females	7	3	8	4	95
Pregnancy					
Normal	5	3	3	0	89
Hyperemesis	2	2	1	0 }	
Pre-eclamptic toxaemia	5	1	6	0 }	89
Premature rupture of membranes	0	2	0	2	—
Ante-partum haemorrhage	0	2	4	3	56
Twin pregnancy	0	0	5	2	32
Other abnormalities	0	2	3	1	—
Delivery					
Normal	4	4	7	2	167
Abnormal	7	4	8	3	50
Foetal distress	2	1	0	1	—
Placenta					
Abnormal	5	4	3	4	25
No record	3	2	0	1	—
State of child					
Good	8	2	3	0	155
Poor	3	6	12	5	69
Neonatal course					
Normal	7	3	4	2	132
Respiratory abnormalities	1	4	8	3 }	
Nervous system abnormalities	3	0	1	0 }	92
Infections	0	1	9	1 }	
Oxygen therapy					
Less than 1 week	2	6	0	0	134
More than 1 week	0	0	15	5	16
No record	0	0	0	0	57

no useful vision due to the presence of bilateral retrolental membranes. Cases 3 and 6 showed unilateral retinal folds which were not considered to be congenital in origin, and Case 4 showed a unilateral membrane although in each case the opposite eye appeared normal. All three cases were thought to have vision adequate for education by visual means.

Study of the Aetiological Factors

In Table 3 the possible aetiological factors in groups of cases of diplegia, retrolental fibroplasia and of cases showing both disorders are compared with groups of infants showing neither disorder but born prematurely. Table 3 includes only those children born in Edinburgh.

Maternal Age and General Health

Maternal ages were not dissimilar in the groups of prematurely born abnormal cases, but there was a larger proportion of mothers over the age of 35 years in the cases of full-term diplegic patients. In this latter group, two mothers had failing periods for some months before the conception of the affected child. Two mothers, one in the full-term diplegic group and the other in the group of prematurely born diplegic cases, had ovariectomies performed before conception occurred.

Abnormalities of Pregnancy and Delivery

With the small numbers of cases in each group it is impossible to draw statistical conclusions regarding the relative importance of the various abnormalities of pregnancy and delivery.

The incidence of abnormal pregnancy was high in all groups. In the cases showing retrolental fibroplasia associated with diplegia no normal pregnancies occurred. The commonest single abnormality of pregnancy in the prematurely born cases of diplegia and retrolental fibroplasia, as with those showing both disorders, was ante-partum haemorrhage. There was no obvious association between a particular type of labour and the occurrence of the two conditions. The state of the child immediately after birth was poor in all five of the cases showing both disorders and in approximately one-third of the group of normal premature infants.

Whereas all five of the infants showing cerebral diplegia and retrolental fibroplasia required oxygen for prolonged periods, as did those with retrolental fibroplasia alone, the necessity for oxygen was less marked in the normal premature group and in the infants suffering from diplegia only.

In a large proportion of the group with retrolental fibroplasia, and in three of the five showing both disorders, lung expansion was very poor for at least one week after delivery.

TABLE 4
NUMBERS OF CASES OF CEREBRAL DIPLEGIA AND RETROLENTAL FIBROPLASIA IN EDINBURGH 1948-52

Year of Birth	Corrected Population	Cerebral Diplegia	Retrolental Fibroplasia	Cerebral Diplegia and Retrolental Fibroplasia
1948	7,700	4	2	0
1949	7,500	10	2	3
1950	7,200	3	4	0
1951	7,100	3	5	3
1952	6,900	3	2	0
Total	36,400	23	15	6

It is apparent that in many cases of all groups more than one abnormality existed. In some, pregnancy, delivery and the state of the child at birth were abnormal and an unsatisfactory neonatal period frequently ensued. This adds to the difficulty of assessing the importance of any one aetiological factor.

Incidence of Diplegia and Retrolental Fibroplasia in Edinburgh

In Table 4 are shown the ascertained figures for the incidence of retrolental fibroplasia and cerebral diplegia in Edinburgh for the years 1948-52. As has been noted there is probably some failure of ascertainment of diplegic cases. On the basis of the figures for the period 1943-47, in which 33 cases of diplegia were discovered in a population of 35,866 children, it is likely that the true incidence of diplegia is about one per 1,000 surviving children of all birth weights in both periods. Thus in a population of 36,400 it would be expected that there would be approximately 36 cases of diplegia. Of these approximately 40%, or 14-15 cases, would be born prematurely. Since 14 prematurely born cases were ascertained it is probable that few cases of diplegia born prematurely in the years 1948-52 have been missed.

Since all of the 1,257 surviving children prematurely born in Edinburgh in the years 1948-52 were followed up during the retrolental fibroplasia survey, it seems improbable that any cases of this condition have been missed.

Table 5 shows the incidence of both conditions by birth weight in surviving premature infants born in Edinburgh. It will be observed that the incidence of both retrolental fibroplasia and cerebral diplegia increases as birth weight decreases. In the 240 surviving children born and resident in Edinburgh, whose birth weights were 4 lb. or less, there were 11 cases of diplegia and 17 of retrolental fibroplasia. That there were, in fact, five cases showing both disorders strongly suggests that there may be other aetiological factors in addition to prematurity common to diplegia and retrolental fibroplasia.

Discussion

Discussion will be confined to a consideration of the importance of the various aetiological factors which are common to cerebral diplegia and retrolental fibroplasia.

Prematurity. Most observers are agreed that retrolental fibroplasia is confined almost exclusively to premature infants of low birth weight and that its incidence increases as the birth weight decreases. No evidence of retrolental fibroplasia has been found by the examination of large numbers of full-term infants (Griffiths, 1951; Chace, Merritt and Bellows, 1950) though occasional cases have been encountered (King, 1950; Cole, 1950). In a series of 238 cases of retrolental fibroplasia all weighed less than 5 lb. and 84% weighed less than 4 lb. and 10% had a birth weight between 3 and 4 lb. (King, 1950; Unsworth, 1951). It has been suggested that, irrespective of birth weight, the crucial time for the development of retrolental fibroplasia is when the infant weighs between 3 and 4 lb.

TABLE 5
INCIDENCE OF CEREBRAL DIPLEGIA AND RETROLENTAL FIBROPLASIA AMONG SURVIVING PREMATURE CHILDREN BORN AND RESIDENT IN THE CITY OF EDINBURGH (1948-1952)

Birth Weight	Number of Survivors	Cerebral Diplegia		Retrolental Fibroplasia		Cerebral Diplegia and Retrolental Fibroplasia	
		Number of Cases	Incidence per 1,000	Number of Cases	Incidence per 1,000	Number of Cases	Incidence per 1,000
Over 4 and under 5½ lb. ..	1,017	2	1·96	3	2·95	0	0
4 lb. and under ..	240	11	45·83	17	70·82	5	20·83
Total ..	1,257	13	10·34	20	15·91	5	3·97

The connexion between diplegia and prematurity is generally agreed to be less close than that between prematurity and retrolental fibroplasia. That premature birth is important in the aetiology of diplegia has been recognized for many years and at one time was considered the most important known cause of the condition (Little, 1862; Brissaud, 1894). Little appears to have been the first author to have recognized the significance of prematurity in the aetiology of diplegia. He did not regard it as the only cause of the condition and noted the importance of other forms of abnormal parturition. He thought the occurrence of abnormal positions of the child, difficult delivery of the child on account of rigidity of the maternal soft parts, versions, and torsions of the cord were also important in the aetiology of his cases. He believed that they caused damage to the nervous system because they resulted in neonatal asphyxia and consequent intracranial haemorrhages.

A number of surveys of large series of cases of diplegia were published towards the end of the last century and the aetiology of the condition was more systematically studied. It became increasingly apparent that the causes of diplegia were multiple in many cases, and that prematurity itself could not be regarded as directly causal.

Great efforts were made to assess the relative importance of hereditary taints, Little's factors and maternal and extra-uterine abnormalities in the aetiology of the various types of diplegia (Freud, 1893, 1897; Ganghofner, 1895). Recent surveys have continued to show a high incidence of prematurity in patients with diplegia (Evans, 1948; Asher and Schonell, 1950; Pohl, 1950; Hellebrandt, 1951). Nevertheless the recent trend has been to consider prematurity of importance chiefly in predisposing to asphyxial states in the newborn (Cole, Kimball and Daniels, 1939; Macgregor, 1943; Evans and Smith, 1946). In general more stress is now laid on the importance of anoxic states in the premature infant than on prematurity itself as a cause of diplegia (Wilson, 1940; Ford, 1952).

Genetic and Developmental Abnormalities. The idea, first discussed by Freud, that underlying disturbances of the relationship between mother and foetus might result in disturbances of pregnancy and delivery and abnormalities in the foetus has received more recent support. It has been suggested that most cases of diplegia are due to primary neuronal degeneration occurring during pre-natal or post-natal life. Abnormalities of pregnancy or delivery or the presence of asphyxia are regarded as merely coincidental manifestations of the underlying disturbances of the relationship between mother and foetus. They are not thought to be of direct importance as causes of diplegia (Collier, 1899, 1924).

Recent pathological studies have tended to confirm that primary neuronal degeneration is important as a cause of diplegia in a proportion of cases. But it has been pointed out that the types of cerebral lesions are too diverse to be due to any single cause and that multiple aetiological factors must be postulated. The significance of the finding of neuronal degeneration and to what extent it may be accepted as being primary are also matters for discussion (Patten, 1931; Stewart, 1942).

The theory that genetic factors might be important in the aetiology of diplegia in some patients receives support from the results of a study of 66 mentally defective diplegic patients. It has been suggested that there might be some relationship between genetic factors producing diplegia and some types of mental deficiency (Penrose, 1938).

A syndrome of congenital encephalo-ophthalmic dysplasia has been described. In its fully developed form it consists of various abnormalities of the eye, including retrolental fibroplasia, malformation of the cerebrum and single or multiple cutaneous haemangiomas. Isolated manifestations of the syndrome are commoner than the fully developed form. Thus abnormality of the cerebrum or haemangiomas may be lacking in cases showing ocular lesions, or ocular lesions absent in those showing cerebral damage. The cause of the condition is considered to be foetal anoxia and the resulting manifestations depend on the state of foetal development when the anoxic insult occurred. In fact, the descriptions of the condition appears to imply only that foetal anoxia is capable of producing cutaneous haemangiomas, cerebral disorder and ocular abnormalities, either alone or in combination (Krause, 1946; Ingalls, 1948).

Some observers think that retrolental fibroplasia is a form of retinopathy resulting from anoxia. Changes in other tissues, similar to those occurring in the eyes, have been observed. These affect the brain most frequently, and, depending on the stage of cerebral development at the time of the anoxic insult, the infant may or may not show cerebral palsy and mental retardation (Szewczyk, 1952).

Birth Injury. There has been no serious attempt to incriminate birth injury as a cause of retrolental fibroplasia, except in so far as abnormal birth is a cause of asphyxia. The position is very different when diplegia is considered. It is generally conceded that the causes of diplegia are diverse and that it is frequently due to multiple aetiological factors.

On the other hand, Collier's claim that abnormal birth is practically never the cause of diplegia has been rejected by most workers since his time. It appears to be generally agreed that difficult birth is important in the aetiology of diplegia, but that it usually causes cerebral damage by producing anoxia. A smaller number of cases probably do receive direct cerebral injury at the time of birth. Little's factors therefore remain important.

Anoxia. In the survey of retrolental fibroplasia it was found that the presence of anoxia was prominent in the pre-natal and neonatal periods of the cases that developed the condition. After analysing all the factors which might have produced an anoxic state in the foetus or newborn, it was found that the affected babies had received, on an average, almost twice the number of anoxic insults as had the infants who showed no signs of the condition. If anoxia was a factor in the production of retrolental fibroplasia, it would be expected that the affected infants might show features other than the eye condition (Szewczyk, 1952). Apart from the cases showing cerebral diplegia four infants suffering from retrolental fibroplasia were considered to be subnormal mentally compared with 16 of the 224 infants born prematurely and showing no ocular abnormality.

Of necessity, the place of anoxia in the aetiology has been mentioned repeatedly in discussing other possible causal factors. The relative frequency with which prematurely born infants develop diplegia has been explained as being a result of the greater incidence of pre-natal or neonatal anoxia in this group than amongst those born at term. Moreover, the premature infant, though probably less likely to die, is more likely to suffer cerebral injury from a given anoxic insult than an infant born at term. It might be expected, therefore, that a larger proportion of premature infants than of infants born at term might survive to show cerebral lesions which were the results of anoxia (Gruenwalk, 1953).

In view of the above it is interesting to observe the much higher incidence of anoxic insults in the retrolental fibroplasia and premature diplegic groups than in the full-term diplegic infants or those prematurely born showing neither disorder.

Oxygen. It is not proposed to discuss fully the part played by oxygen therapy in the production of retrolental fibroplasia, a subject recently reviewed by Ashton, Ward and Serpell (1953).

One possible explanation of the relationship between retrolental fibroplasia and oxygen therapy may be related to certain similarities between the adult with cor pulmonale, the result of long-continued pulmonary disease, and the premature infant with much pulmonary atelectasis. In both cases there is inadequate respiratory exchange, a relatively high blood carbon dioxide content, a raised alkali reserve and a tendency for respiratory activity to be stimulated to a greater extent by oxygen lack than by carbon dioxide excess (Meakins and Davies, 1925; Windle, 1940; Smith, 1951).

The accumulation of carbon dioxide in the blood and tissues, well above physiological levels, which may be precipitated by oxygen therapy in adult patients with cor pulmonale may result in drowsiness, cerebral vasodilatation, an increase of cerebrospinal fluid pressure and papilloedema (Beaumont and Hearn, 1948; Davies and Mackinnon, 1949). Having been greatly interested in these manifestations which were observed in detail in seven patients with cor pulmonale it seemed possible to us that a somewhat similar series of events occurred in premature infants with much pulmonary atelectasis when treated with oxygen. Marked drowsiness, dilatation of the retinal vessels, most markedly the veins, and apparently moist, glistening fundi were frequently observed in such infants within 24 hours of their receiving continuous oxygen, and persisted for a week or longer in a number of cases. In these circumstances failure to absorb the retinal exudate, if this is the cause of the glistening retina, might be expected to result in its organization and invasion by fibrous tissue. To find if such a series of events actually occurs obviously requires much more research, and clearly does not rule out of consideration the possibility of other infective or congenital factors being present.

The six infants under review received oxygen for an average of seven to 10 days longer than the premature infants not affected by retrolental fibroplasia. No convincing evidence has been discovered, however, to suggest that oxygen therapy is an aetiological factor in the causation of cerebral diplegia, and for this reason oxygen therapy *per se* (as distinct from the anoxia or atelectasis rendering its use necessary) is not stressed as a common factor in the association of retrolental fibroplasia and cerebral diplegia.

Summary and Conclusions

Six cases have been described in which retrolental fibroplasia and cerebral diplegia occurred in association.

While both conditions are liable to occur in premature infants, it appeared probable that the frequency of the association was greater than was

accounted for by chance, and that in addition to prematurity other common aetiological factors were operative.

Possible aetiological factors have been discussed. These factors, which were frequently multiple, included abnormal pregnancy, abnormal delivery, and post-natal asphyxia.

Prolonged oxygen therapy had been given to each of the six cases under review, but whereas there is clinical and experimental evidence that oxygen therapy may be closely related to the incidence of retrolental fibroplasia, the same does not apply to cerebral diplegia.

It is suggested that anoxia in the pre-natal, natal and post-natal periods, resulting from the abnormalities described, is important in determining the association of retrolental fibroplasia and cerebral diplegia in a proportion of prematurely born infants.

We wish to thank Drs. H. E. Seiler and H. P. Tait for providing facilities for the surveying of premature infants in Edinburgh, Dr. John Thomson for help with their examination, and Dr. G. I. Scott for his reports of the ophthalmological findings. The surveys would have been impossible without the ready cooperation of the many physicians and surgeons who reported and granted access to their cases.

We are most grateful to Professor R. W. B. Ellis for much encouragement and assistance during the surveys and also in the preparation of this paper.

References

Asher, P. and Schonell, F. E. (1950). *Archives of Disease in Childhood*, **25**, 360.
Ashton, N., Ward, B. and Serpell, G. (1953). *Brit. J. Ophthal.*, **37**, 513.
Beaumont, G. E. and Hearn, J. B. (1948). *Brit. med. J.*, **1**, 50.
Brissaud, E. (1894). *Sem. méd., Paris*, **14**, 89.
Chace, R. R., Merritt, K. K. and Bellows, M. (1950). *Arch. Ophthal., Chicago*, **44**, 236.
Cole, P. (1950). *Proc. roy. Soc. Med.*, **43**, 834.
Cole, W. C. C., Kimball, D. C. and Daniels, L. E. and Discussion (1939). *J. Amer. med. Ass.*, **113**, 2038.
Collier, J. S. (1899). *Brain*, **22**, 373.
—— (1924). *Ibid.*, **47**, 1.
Davies, C. E. and Mackinnon, J. (1949). *Lancet*, **2**, 883.
Evans, M. and Smith, G. S. (1946). *J. Obstet. Gynaec. Brit. Emp.*, **53**, 440.
Evans, P. R. (1948). *Archives of Disease in Childhood*, **23**, 213.
Ford, F. R. (1952). *Diseases of the Nervous System in Infancy, Childhood and Adolescence*, 3rd ed. Oxford.
Freud, S. (1893). *Zur Kenntniss der cerebralen Diplegien des Kindesalters*. Vienna.
—— (1897). *Die Infantile Cerebrallähmung* in *Specielle Pathologie und Therapie*, ed. Nothnagel, H. bd., 9, t. 3, 2, abt. 2.
Ganghofner (1895). *Jb. Kinderheilk.*, **40**, 219 (1895). Quoted by Freud (1897).
Griffiths, S. P. (1951). *M. and R. 2nd Pediat. Res. Conf. Rep. quoted by Zacharias, L.* (1952). *Amer. J. Ophthal.*, **35**, 1426.
Gruenwald, P. (1953). *Prematurity, Congenital Malformation and Birth Injury*, Section III. Proc. Conference New York Academy of Medicine, 1952. Association for the Aid of Crippled Children, New York.
Hellebrandt, F. A. (1951). *Trends in the Management of Cerebral Palsy*. Lectures delivered 1950-51 in Medical College. Virginia. (Unpublished.)
Ingalls, T. H. (1948). *Pediatrics*, **1**, 315.
King, M. J. (1950). *Arch. Ophthal., Chicago*, **43**, 694
Kinsey, V E. (1950). *Ibid.*, **44**, 749.
Krause, A. C. (1946). *Ibid.*, **36**, 387.
Little, W. J. (1862). *Trans. obstet. Soc. Lond.*, **3**, 293.
Macgregor, A. R. (1943). *Edinb. med. J.*, **50**, 332.
Meakins, J. C. and Davies, H. W. (1925). *Respiratory Function in Disease*. Edinburgh.
Patten, C. A. (1931). *Arch. Neurol. Psychiat., Chicago*, **25**, 453.
Penrose, L. S. (1938). *A Clinical and Genetic Study of 1,280 Cases of Mental Defect*. Spec. Rep. Ser. med. Res. Counc. London. No. 229.
Pohl, J. F. (1950). *Cerebral Palsy*. St. Paul, Minnesota.
Sachs, B. and Hausman, L. (1926). *Nervous and Mental Disorders from Birth through Adolescence*. New York.
Smith, C. A. (1951). *The Physiology of the Newborn Infant*, 2nd ed. Oxford.
Stewart, R. M. (1942). *Proc. roy. Soc. Med.*, **36**, 25.
Szewczyk, T. S. (1952). *Amer. J. Ophthal.*, **35**, 301.
Unsworth, A. C. (1951). M. & R. Pediat. Res. Conf. Rep. Quoted by Zacharias, L. (1952). *Ibid.*, **35**, 1426.
Wilson, S. A. Kinnier (1940). *Neurology*. London.
Windle, W. F. (1940). *Physiology of the Fetus*. Philadelphia.
Wyllie, W. G. (1951). In *Modern Trends in Neurology*, ed. Feiling, A., pp 125-148. London.