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Cerebral Palsy

A Clinical and Neuropathological Study

BY

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FOREWORD

Roy Spector

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To Professor Preben Plum

The Cover

The cover photograph shows a monument dedicated by the gate-keeper of the temple in Memphis. Accompanied by his wife and son, the gate-keeper is making a sacrifice, probably to the goddess Ishtar. The inscription below is a prayer to the goddess for a good funeral on the burial ground of Memphis.

It has been generally accepted that this man had had poliomyelitis (Williams 1929, Ghalioungui and Dawakhly 1965), although Slomann (1927) discussed other possibilities such as coxitis. However, from the appearance of the leg a spastic condition also seems a possibility, and the diagnosis of a spastic hemiplegia is supported by the fact that the right arm is thinner than the left. An exact diagnosis is unfortunately impossible without a neuropathological examination.

The photograph was kindly placed at our disposal by Professor Koefoed-Petersen, at the Glyptotek of Ny Carlsberg, Copenhagen, where the sculpture is now exhibited.

Ghalioungui, P., Dawakhly, Z. el (1965) Health and Healing in Ancient Egypt. Dar Al-Maaref: Egyptian Organisation for Authorship and Translation.

Slomann, H. C. (1927) 'Deux cas de paralysie infantile dans l'ancienne Egypte', *Bull. et Mém. de la Soc. d'Anthropologie de Paris*, 75–85.

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Foreword

Research into the prevention of cerebral palsy is hampered by a lack of sufficient information regarding the relative importance of multiple aetiological factors in producing this group of brain disorders, and a lack of correlation between the clinical picture and the anatomical changes in the nervous system. This book is an account of a remarkably detailed study in which obstetrical, neonatal and neurological investigations on a large group of patients are presented with full neuropathological data found at subsequent necropsy.

The work is particularly valuable (and almost unique) in that the study was prospective and a single clinician made the initial diagnosis and, in large measure, followed the progress of each patient. It is against this background that the anatomical changes in the brain and spinal cord are discussed.

The vitally important criterion of good biological research is not that it necessarily enables the truth to become immediately apparent but that it allows the construction of hypothetical models which themselves are fruitful in stimulating further research and discussion. The authors have not only succeeded in discovering new information about the causes and results of brain damage in childhood, but have suggested interpretations of their work which in themselves could lead to profitable lines of research relating to cerebral palsy.

Roy G. Spector

CHAPTER I

Introduction

Cerebral palsy is one of the most important groups of disabling disorders of infancy and childhood as well as of adult life. The purpose of the present report is to compare the clinical and pathological findings and relate these to aetiological and pathogenic factors in an autopsy series of 69 cerebral palsy patients. They were collected between 1948 and 1964 and derived from a clinical group of more than 1,000 patients with cerebral palsy. All patients were seen at the University Clinic of Paediatrics, Copenhagen, and examined by Professor P. Plum. Many of the patients were followed as out-patients in the cerebral palsy clinic over the years by the same clinician. A great number of the patients spent years in different institutions before death, so that in many cases they were observed for virtually their whole lives.

Much work has been done in the past few years to clarify the problems of cerebral palsy, but many problems are unsolved. This is illustrated by the arguments about the actual definition and proposed clinical classification of cerebral palsy. As these problems relate to our own study some illustration of these discussions is pertinent. A good example is the discussions arranged by the Little Club. In 1959 the following clinical definition was proposed: 'Cerebral palsy is a persistent but not unchanging disorder of movement and posture, appearing in the early years of life and due to a non-progressive disorder of the brain, the result of interference during its development.'

Later the same group (1964) proposed this clinical definition: 'It will probably be agreed (with modification as desired) that cerebral paresis is a disorder of movement and posture appearing in the early years of life and due to disorders of the brain present before the development of the brain is completed', and they continue: 'It will be necessary to decide whether cerebral paresis due to progressive disorders of the brain are to be included or not', and that 'It will be necessary to discuss progressive motor disorder, or deterioration of motor function, due, not to progressive brain disorder, but to constitutional maladies, disuse atrophy, prolonged bed rest or splinting operation, contractures, including deterioration sometimes seen at adolescence'.

In September 1964 a further study group suggested the following definition of cerebral palsy: 'Cerebral palsy is a permanent, but not unchanging disorder of movement and posture due to a non-progressive defect or lesion of the brain in early life.'

In this definition they tried to meet the problem that a once-for-all damage — such as a cyst formation — frequently shows clinical progression over the years. This explains why the clinical material of cerebral palsy may include patients with definite progressive encephalopathies with symptoms from early infancy. In many of these cases the correct diagnosis can first be made at autopsy. In the present material such patients, where a clinical diagnosis of cerebral palsy was made, are included in the series even if a progressive encephalopathy such as a leucodystrophy had been suspected,

because of the later clinical course of the condition or because of similar disease in a sibling.

Many different clinical classifications have also been proposed. Some are very detailed, such as that of Phelps (1941) — a system which has been modified and used by others — Andersen (1954), Collis *et al.* (1956), and Henderson *et al.* (1961). A number of difficulties arise in using this classification as much emphasis in some of the sub-groups is placed on the muscle tone, and this is known to vary within the same condition during growth (Ingram 1964). Perlstein (1952) classified cerebral palsy by a number of different parameters including, besides clinical findings, aetiological and other factors. The seven-choice scheme of the American Academy of Cerebral Palsy (Minear 1956) is not easy to handle. Crothers and Paine (1959) produced a simple clinical classification which included cases with spinal cord injuries. Ingram (1955) and Balf and Ingram (1956) use a classification based upon the neurological diagnosis in the typical groups, but with a rather too detailed subgrouping. Some confusion may also arise in their system from the second grouping which relates to the extent of the cerebral palsy. Ingram has recently published a further valuable discussion (1964) of the problem.

The Little Club (1959) has suggested the following classification:

Spastic cerebral palsy
- Hemiplegia
- Diplegia
- Double hemiplegia

Dystonic cerebral palsy

Choreo-athetoid cerebral palsy

Mixed forms of cerebral palsy

Ataxic cerebral palsy

Atonic diplegia.

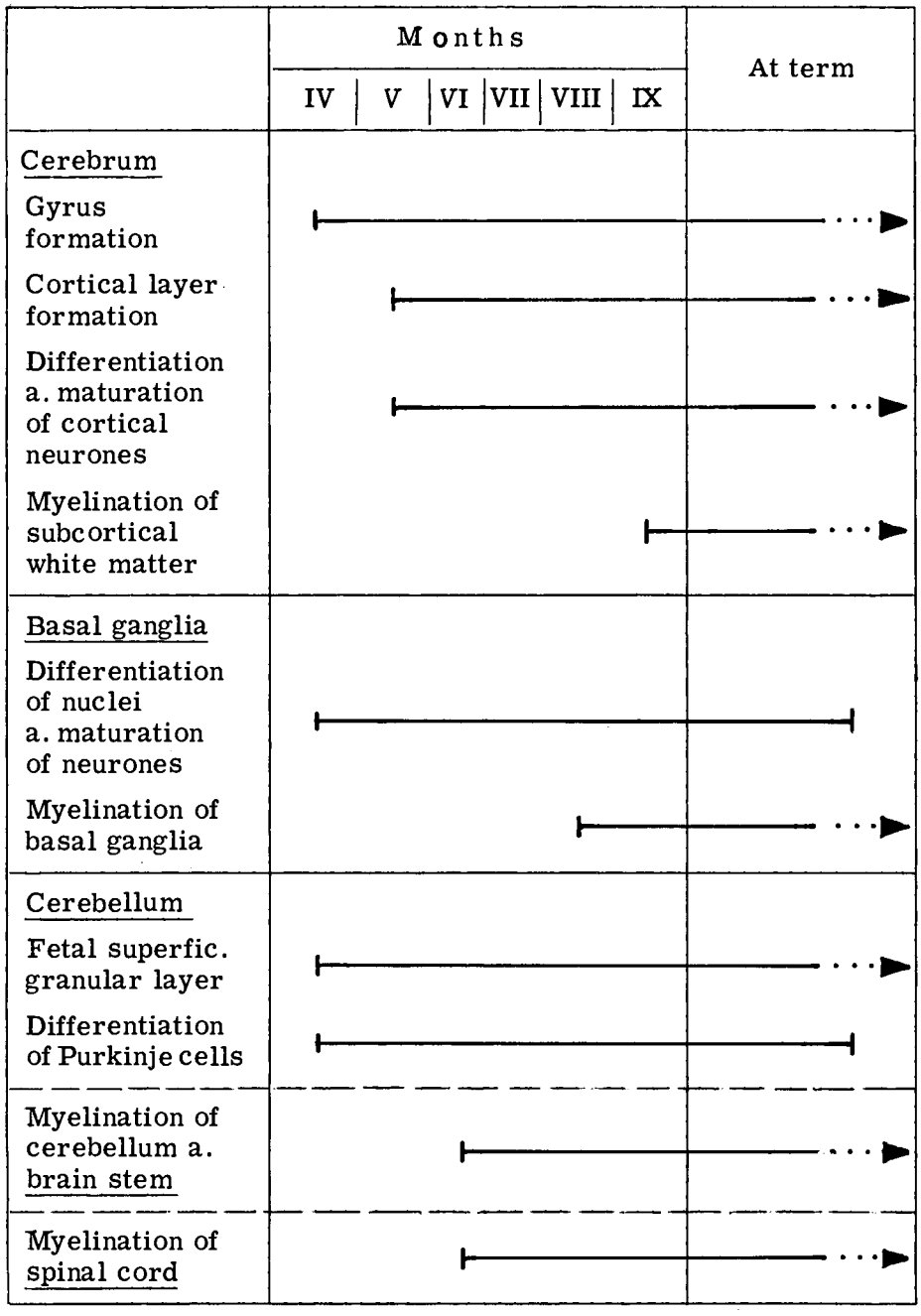
A somewhat similar but more simple clinical classification has been used at the University Clinic of Paediatrics, Rigshospitalet, Copenhagen. The definition and classification used are given in Chapter III.

In spite of intensive collection of aetiological and clinical information in the present study, some of the earlier cases are not as fully documented as later cases. All neuropathological examinations have been carried out by one of us (E.C.), but some of the early neuropathological examinations were carried out as routine examinations and this means that sometimes relevant information is not available. Another difficulty has been that many of the autopsies have been carried out in different institutions without the assistance of trained pathologists. This means that only the brain has been removed and sent for special examination, and even where a full autopsy has been carried out only gross abnormalities have been reported. It also explains why the whole spinal cord has rarely been examined.

The collection of the material over 16 years means that full biochemical examinations have only been carried out on the later cases, but many patients have been extensively examined and, in spite of these intensive studies, only very few cases of

TABLE I

PRENATAL DEVELOPMENT OF CENTRAL NERVOUS SYSTEM



inborn errors of metabolism have been established such as the metachromatic leucodystrophies. Among the earlier cases a few patients resembled patients with known chromosome abnormalities. This cannot of course be proved, as they died before chromosome examinations were possible.

In such an autopsy series it must be expected that the material will consist of the most severe cases of cerebral palsy among the clinical group of more than 1,000 cases. Spastic tetraplegia therefore predominates. For this reason we have chosen — in the clinical grouping — to place tetraplegia with pronounced asymmetries together with hemiplegias, as well as the diplegias together with paraplegias. Each group has then been studied with regard to the neuropathological findings. A neuropathological grouping has been made independently and afterwards compared with the clinical picture. In both the above-mentioned groupings the available aetiological and pathogenic information is taken into consideration.

On the basis of a review of the most relevant literature and our own findings we have tried to sum up possible characteristics of the separate groups as well as to define differences. This has been illustrated from the aetiological, clinical, and pathological aspects.

In order to understand the developmental disorders of the central nervous system one must have at least an acquaintance with the normal prenatal development, which in gross outline can be seen in Table I. (See also Owen (1868), Walker (1942), Hamilton *et al.* (1945), Ostertag (1956), Dodgson (1962) and Richter (1965)).

Normal brain weights at different ages are as follows:

full term	approx.	335g.
age of 6 months	„	660g.
age of 12 months	„	800g.
adult females	„	1,282g.
adult males	„	1,440g.

(Ref: Conel (1939, 1961), Pakkenberg and Voigt (1964)).

CHAPTER II

A Review of the Literature

Great interest in cerebral palsy has existed for more than 100 years, even before Little (1843) published his famous series of lectures. Prior to that Pinel (1822) and Cazauvieilh (1827) reported cases combining clinical with brain autopsy findings of what is now termed cerebral palsy. In 1843 Little first gave a survey of the clinical findings in the spastic diplegic type of cerebral palsy. He stated that the aetiology in most cases was perinatal asphyxia and prematurity. In his later study (1862) 'On the influence of abnormal parturition, difficult labours, premature birth, and asphyxia neonatorum on the mental and physical condition of the child, especially in relation to deformities' he described spastic diplegia and athetosis based on the findings in 47 patients.

Freud (1897) is the first author who proposed a neuropathological classification of cerebral palsy. He examined brains from patients with the clinical diagnosis of hemiplegia and diplegia. He recognised prenatal, perinatal and postnatal injury as of possible aetiological significance; in some instances the injury was of infective origin. Among those the luetic cases were considered as a special group. The neuropathological terms most commonly used to describe findings in cerebral palsy cases at that time were (a) diffuse or partial lobar atrophic sclerosis, (b) hypertrophic nodular sclerosis, and (c) porencephaly.

Freud's Classification

Freud suggested the following new classification:

(a) atrophic sclerosis
(b) porencephaly
(c) hypertrophic sclerosis
(d) meningoencephalitis
(e) encephalitis
(f) cortical agenesis.

He did not discuss the correlation between the aetiological factors he had described and the neuropathological findings.

(*a*) *Atrophic Sclerosis*

Freud's lobar and atrophic cortical sclerosis are common findings in brains from cerebral palsy patients. Several other terms — granular atrophy, ulegyria and microgyria — have been used by later authors (Meyer 1953, Norman 1955, Hallervorden and Meyer 1956, Wolf and Cowen 1956, and Towbin 1960). Meyer and Norman draw attention to the fact that besides degeneration of isolated ganglion cells with secondary satellitosis and diffuse gliosis, there is sometimes laminar necrosis of the cortical grey matter; such changes are localized to the boundary zones between two arterial territories and are believed to be caused by a fall in blood pressure during a perinatal shock.

The asymmetrical cortical atrophy found in other cases is thought to be compression of one or several arteries.

(*b*) *Porencephaly*

This is a common finding in brains from patients with cerebral palsy. The name was employed by Heschl in 1859. He first thought, in accordance with Cruveilhier (1829), that porencephaly which involves more or less of one or both hemispheres was a primary congenital developmental brain abnormality with secondary hydrocephalus. Later he changed his mind as he found absence of pial vessels in a case of porencephaly, and then he considered a vascular anomaly as the primary phenomenon in porencephaly. In brains from some patients with Little's syndrome, Morsier (1932) found abnormalities in the cerebral medial arteries, especially in the sylvian arteries, and symmetrical cysts in these territories. Globus (1921) and Eisenstein and Taylor (1941) found that the most frequent cause of porencephaly was an intrauterine inflammation with subsequent injury of the circulation. Among other authors, De Vos and Divry (1933) said nothing of the origins of porencephaly except that it arises early in life.

Yakovlev and Wadsworth (1946) maintain that the brain lesion in schizencephaly or hydranencephaly takes place early in foetal life, which explains the lack of development of telencephalon. Becker (1949) has produced hydranencephaly in newborn dogs by paraffin injections in the internal carotid artery and he thinks that a carotid thrombosis can be the cause of hydranencephaly in man. He emphasises (as does Hallervorden 1952) the ability of the damaged immature brain tissue to be resorbed without leaving any scar formation. This includes the mesodermal tissue and the vessels.

The term *polyporencephaly* describes multiple cystic degenerations localised to the cortical grey matter and/or to the basal ganglia. In patients who survive a long time the cysts may be traversed by glial trabeculae and when found in the hemispheres they are often covered by more or less atrophic grey matter.

Siegmund (1923) suggested that the most frequent genesis of polyporencephaly was anoxic perinatal brain damage. A relationship with infections and early postnatal injuries is accepted by most authors since then (Christensen and Schondel 1946, Christensen and Bisgaard-Frantzen 1952, Benda 1945, 1954, 1960, Freeman and Gold 1964).

(*c*) *Hypertrophic Sclerosis*

Freud's hypertrophic sclerosis describes brains with a loss of neurones in the cortical grey matter and with a severe reactive gliosis such as seen in brains from patients who have survived an infection. This term has not been used by later authors as it is generally included in the group with cortical degeneration and gliosis.

(*d and e*) *Meningitis and Encephalitis*

Different agents can produce meningo-encephalitis and encephalitis in the pre-, peri-, and early post-natal life (Wolf and Cowen 1959). If such patients survive the acute stage they often develop cerebral palsy. Congenital syphilis is now no longer considered a common cause of cerebral palsy as it was in Freud's day (Benda 1952, Straussler 1958).

Infants with congenital cytomegalic inclusion body disease usually die shortly after birth, for which reason these patients do not develop cerebral palsy. The clinical picture will be characterised by a diffuse cerebral and generalised organ involvement (Eichenwald and Shinefield 1962).

In congenital toxoplasmosis the clinical picture is dominated by mental retardation, epilepsy, and hydrocephalus (Eichenwald 1960), because the localisation of the cerebral lesions produces difficulties in the flow of the cerebrospinal fluid. As the periventricular parts of the basal ganglia and the white matter are very often involved the clinical picture of cerebral palsy may also develop, but such cases have not been found described in the literature.

The most common prenatal and perinatal cerebral infection is caused by E. coli (Haggerty and Ziai 1964). Among early postnatal cerebral infections several other bacterial and viral infections are described (Van Bogaert 1959, Blattner and Heys 1962). Some of these patients may develop cerebral palsy, depending on the localisation of the lesion.

(*f*) *Cortical Agenesis*

Freud collected the different kinds of cerebral maldevelopment causing cerebral palsy under the name cortical agenesis. Other authors have divided these abnormalities according to the stage of foetal life where development has ceased.

In lissencephaly or agyria cerebri the development has stopped before gyri formation has started in the fourth month of foetal life (Owen 1868, Walker 1942). Cerebellar folia formation starts at the same age.

Pachygyria is due to lack of secondary and tertiary gyrus formation taking place from the sixth month of foetal life to the first year of postnatal life (Crome 1956). In such brains the number of neurones is reduced, the ganglion cells are not fully developed and there is deficiency in layer formation.

A real maldevelopment with displacement of the neurones is most often due to genetic damage (Minkowski 1952), but the increased knowledge of experimental and human teratology has shown that more than 400 agents are able to cause such lesions. These agents include viruses, radiation and drugs (Copelman 1963).

From a histological point of view it is therefore impossible to distinguish between a genetic and foetal cerebral damage.

Cerebral palsy will only be present in brains where areas concerned with motor activity are involved. When we are dealing with an abnormality in one special motor area the clinical picture is identical when either degeneration or maldevelopment of genetic or exogenous cause is present.

Basal Ganglia Disease

Freud did not draw attention to abnormalities in the basal ganglia in patients with cerebral palsy, but a great number of later German neuropathologists have published findings from patients with different clinical pictures of cerebral palsy in which abnormalities in the basal ganglia were found at autopsy.

From 1911 to 1924 the famous neuropathologists C. and O. Vogt collected such cases from the literature and to these added their own. They found that the basal ganglia in all cases were more or less atrophic on macroscopical examination. Through precise histological examinations they divided the cases into separate entities, and they correlated each special neuropathological group with a different clinical type of cerebral palsy. The original neuropathological terms given by these authors were for many years wrongly used as clinical diagnoses.

The entities are the following:

Status marmoratus is characterised by a poverty of ganglion cells in relation to the number of myelinated neurofibrils in the basal ganglia. Here the dominant clinical symptom was athetosis.

Status fibrosus covers the histological picture of elective necrosis of ganglion cells and compensating gliosis with secondary compression of the neurofibrils. In these cases different kinds of hyperkinesia in combination with athetosis commonly occurred.

In *status dysmyelinatus* both the number of ganglion cells and the myelinisation of neurofibrils are diminished. Here the Vogts found spasticity as the most common symptom in combination with hyperkinesia.

Status cribosus and *lacunaris* are, as the terms suggest, characterised by spongy degeneration of the basal ganglia. These findings are most often present in patients with Parkinsonism, and not in patients with cerebral palsy.

The Vogts first thought that a developmental abnormality of genetic origin in the corpus striatum was the cause of these lesions. Later they considered that different types of insult could give rise to those histological pictures, but only in combination with genetic factors. These specific neuropathologic patterns which they believed were due to a combination of genetic factors and exogenic factors, they called 'patoclisis' (1921). The term describes the different vulnerability of each neurone system — for instance of the globus pallidus compared to the caudate nucleus and the putamen.

A common exogenous factor in their material was perinatal anoxia. Later authors have considered the above states as sequelae of anoxia alone (Schwartz 1927 and 1965, Norman 1947). Malamud (1950) finds that also pre- and perinatal cerebral inflammation can be followed by status marmoratus. He emphasises that the particular mechanism of the marble patterns of the lesions and their tendency to localise predominantly in the striate and thalamic region are still unsolved problems, but he draws attention to the hypothesis suggested by Norman (1947) that it has to do with the venous drainage from the veins of Galen, as the involved part of the brain corresponds to this area.

Kernicterus

Today kernicterus or nuclear jaundice — beside, or together with perinatal anoxia — is considered a common cause of perinatal damage of the basal ganglia (Claireaux *et al.* 1953, Towbin 1960, Courville 1961). It may be found both in infants with Rhesus-, ABO-, and those with other blood incompatibilities (Forster and McCormack 1944, Zuelzer and Mudgett 1950). The problem about the development of nuclear jaundice and the explanation of the selective vulnerability of the different nuclei in the brain is still under discussion, as well as the importance of anoxia as a basic factor

in kernicterus (Jakob 1948, Meriwether *et al.* 1955, Day 1956, Ernster *et al.* 1957).

We have in fact made little progress since Schmorl (1904) gave an excellent pathological description of the findings in brains from infants with this disease. He established the characteristic localisation of the brain damage to the subthalamic nuclei, Ammon's horn, globus pallidus, inferior olive, cranial nerve nuclei in the floor of the 4th ventricle and in the dentate nuclei, flocculi and cerebellar vermis. Schmorl also named the disorder 'Kernicterus,' and he noticed that the bile pigment in the brain must be a product of decomposition.

In 1964 an experimental nuclear jaundice was produced in monkeys, but only if they were asphyxiated at the same time (Lucey *et al.* 1964). This suggests that oxygen deficit plays an important role also in kernicterus.

In patients who have had kernicterus neonatally, and who die after infancy, all bile pigment has disappeared from the central nervous system, and the findings in these brains are unspecific, consisting of ganglion cell degeneration and gliosis in those nuclei which have been icteric (Lund 1955). Only the localisation of the brain damage to special parts of the basal ganglia suggests that we are dealing with sequelae of kernicterus. Similar localisation of the brain lesion can be found in some cases of perinatal anoxia. Contrary to most other authors, Soeken (1957) finds no differences in the localisation of brain damage following perinatal anoxia and kernicterus. She claims that the oxygen deficit in kernicterus is already present in foetal life, and that this can produce an arrest of the development of the most oxygen-sensitive parts of the brain. This disagrees with the clinical finding following exchange transfusions in cases with nuclear jaundice when the symptoms disappear. The different localisation of the brain damage following kernicterus and most cases of pure perinatal anoxia suggests that some unknown factors must be present producing the different lesions.

Cerebellar Findings

Lyssenkow (1931) and Norman (1958) have stated that both in cases with maldevelopment and degeneration of different parts of the cerebellar cortex, associated nuclear atrophies may occur in the olive and the cerebellar nuclei. It is therefore difficult to distinguish between a primary and secondary degeneration of the cerebellar nuclei.

Norman (1963) divides abnormalities in the cerebellum which most often lead to ataxia and hypotonia into four types:

1. Prenatal hypoplasia, among which three different types are known, the universal hypoplasia, hypoplasia of vermis and Brouwer's ponto-neocerebellar hypoplasia. Histological examination of such cases shows deficiency in myelination, differentiation and maturation of Purkinje cells and granular cells.
2. Prenatal cerebellar atrophy due to prenatal damage. As an example of this he mentions a case of cerebellar microgyria most likely caused by radium treatment of the mother during the 5th - 6th month of pregnancy. Here there was disruption of the arrangement of granular cells, Purkinje and glial cells in the atrophic gyri.
3. Congenital cerebellar atrophy. This may be caused by perinatal anoxia, which in some cases may selectively affect the cerebellar cortex.

Perinatal compression both of superior and inferior posterior cerebellar arteries and their branches may also damage the cerebellum, but Norman emphasises that such isolated cerebellar lesions have not been described. Therefore pure cerebellar ataxia due to birth injury he considers a speculation diagnosis.

In cases of congenital cerebellar atrophy the essential features are an atrophic cerebellum with absence of cells in the granular layer, disordered arrangement of the degenerated Purkinje cells also placed in the molecular layer and dense fibrous gliosis of cortex.

4. Progressive cerebellar ataxias (Friedreich's ataxia and ataxia-telangiectasai (Louis-Bar's syndrome)). These entities do not belong to cerebral palsy and no further comment is given here.

Norman's paper makes it clear that it is possible to distinguish between hypoplasia and degenerative changes in the cerebellum.

Perinatal Haemorrhage

Perinatal intracerebral haemorrhage can also give rise to formation of cysts of varying size with surrounding gliosis. Their origin can only be recognised if blood pigment is still present. The haemorrhages can be either of venous or arterial origin. Venous engorgement with consequent haemorrhages can arise in connection with blood pressure abnormalities (Ylppö 1919), but this phenomenon is most often secondary to severe asphyxia (Gröntoft 1954), and the haemorrhages in such cases are usually localised around the anterior terminal veins in the white matter causing symmetrical paraventricular softenings and cyst-formation (Benda 1945, Schwartz 1965).

Schwartz has studied such birth injuries for many years. In his first paper (1921) he states that Virchow's term 'encephalitis interstitialis' is not an encephalitis sui generis, but a sequela of birth injury, and most recently (1963, 1965) he maintains that intracerebral haemorrhages involve the terminal veins and the choroid veins and occur only in infants injured during birth. He considers them therefore to be of traumatic origin, even if the blood extravasation does not arise from ruptures but from the confluence of innumerable minute diapedetic haemorrhages. Even if he also finds such haemorrhages in other organs where direct birth trauma can be excluded he gives little credence to the possibility of anoxic intracerebral haemorrhages.

Rydberg (1932) summarized the most important pathogenic explanations of intra-cranial haemorrhage in newborn infants and divides them into mechanical and non-mechanical theories.

Mechanical Theories

1. Bleeding may arise through the tearing of certain veins caused by compression effects on the head during the passage through the birth channel.
2. The deformation of the head during parturition sometimes causes ruptures of the cerebellar tentorium; in such cases bleeding may arise from ruptured vessels in the tentorium (Beneke 1910) and these can cause various different brain lesions.
3. Bleeding may arise from an obstruction in the venous flow, notably through kinking or tearing of the vein of Galen (Holland 1920, 1922).

4. During parturition a general stasis occurs in the head, causing venous engorgement and vascular rupture (Schwartz 1927).

2. *Non-Mechanical Theories*

1. Asphyxia is itself sufficient to cause bleeding into the cranial cavity.
2. Intracranial haemorrhages may be caused by a change in the chemistry of the blood.

Rydberg concluded that the most acceptable aetiological explanation of cases of primary brain tissue change associated with intracranial bleeding is that the circulation was inadequate during delivery, the primary pathogenic agent being the compression of the head. He found that the tissue destruction was more severe in cases where most of the blood extravasation was situated supratentorially than in cases where most of the bleeding was infratentorial.

Neuropathological Findings Linked with Clinical Findings

The literature discussed above is predominantly based on the neuropathological findings with some consideration of pathogenesis and some of aetiology, but rarely also of the clinical findings.

Rydberg's work (1932) included a clinical account of 48 patients with major cerebral symptoms in the neonatal period who survived for at least a year. He found a relation between the degree of perinatal symptoms, development of cerebral palsy and other clinical symptoms such as mental retardation and epilepsy. As he has not followed these patients throughout their lives and no autopsy findings were reported, nothing can be said about the kind of brain lesions in these patients presenting the different clinical pictures of cerebral palsy.

Roberts (1939) found during examination of spinal fluid that intracranial haemorrhage occurred in 1-2 per cent of all newborn babies. Among the children who survived the initial shock of birth injury for more than three days he found that 75 per cent would develop normally. He concluded that cerebral palsy in a large number of cases was not due to direct birth injury, but attributable to secondary degeneration or maldevelopment. He does not mention anoxia as an aetiological factor.

Chronic subdural haematoma in infancy may also be a late sequela of birth injury. It has to be taken into consideration in cerebral palsy, as most of the infants with subdural haematoma show diffusely hyperactive reflexes, intermittent or constant rigidity and ankle clonus. If we are dealing with a unilateral subdural haematoma the patients may develop a spastic hemiplegia. If a brain involvement exists together with the subdural haematoma the prognosis is serious, whereas a patient with an uncomplicated subdural haematoma has a good prognosis if the haematoma is removed early (Ingraham and Heyl 1939, Ingraham and Matson 1944 and 1954, Christensen and Husby 1963).

Courville (1961) considers cerebral anoxia the most important cause of cerebral palsy, producing lesions of the cortex, the basal ganglia and the cerebellum. He has for many years studied the problem from both a pathogenic and pathological point of view and collected his experiences in a monograph (1953). Here a survey is given of the mechanisms of anoxia and of the acute, subacute, and chronic structural cerebral

changes both in infancy and in later life. He discusses the possibility of antenat a oxygen deficiency as a pathogenic factor in congenital cerebral malformations. Based on his neuropathological findings he suggested the following clinical classification of cerebral palsy (1954):

A. Cortical syndromes: (1) spastic diplegias — mainly in the lower limbs, (2) hemiplegias, (3) double hemiplegia, (4) monoplegia.

B. Ganglionic syndrome: symptoms referable to the basal ganglia.

C. Cerebellar syndromes.

Hallervorden and Meyer (1956) based their study on aetiological, clinical and pathological observations. The causes of cerebral palsy were considered as sequelae of either a general or localised cerebral disorder from the time of conception through the whole intrauterine development until the full maturation of the central nervous system after birth. They state that cerebral palsy is a *clinical* entity of the final result of diseases involving the central nervous system through development and maturation, and that the symptoms are most often those of hemiplegia, diplegia and numerous other neurological syndromes often combined with mental retardation and epilepsy. Their *pathological* material includes a great variety of disorders: developmental abnormalities, acquired lesions varying from focal loss of neurones, scars, and cavity formations, defects of a whole cerebral lobe and even to the total loss of one or both hemispheres. They consider the unusual dimensions of the damage and the variability in the pathological picture to be due to the special sensibility of the immature nervous tissue.

Their detailed definition covers all aspects of the syndrome. They gave no real classification but a detailed pathological description of the various neuropathological lesions: (1) porencephaly; (2) hydranencephaly; (3) lesions located in the cortex; (4) lesions located in the white matter; (5) lesions located in basal ganglia, brain stem, spinal cord and cerebellum.

Benda in 1952 and later in 1960 suggested an aetiological clinical classification partly based on the neuropathological findings. He divides his material into two groups each with a different aetiology: (1) birth injuries and anoxia, (2) infectious diseases. He emphasises that a clinical distinction between infants with birth injuries and developmental brain disorders is possible, as the last group does not show clinical symptoms until weeks or months after birth, whereas the birth-injured patients have severe clinical symptoms in the neonatal period. Benda excludes the developmental disorders *sui generis* even if these can result in some type of cerebral palsy, as only in rare instances does there occur an error in brain development without effect on the motor system. From this selection he recommends the following classification: (1) Little's spastic rigidity (decerebrate rigidity), (2) the pyramidal type (mono-, hemi-, di-, and paraplegias), (3) the mixed-extrapyramidal types (paraplegia with athetosis), (4) the ataxic-atonic cerebellar type.

Malamud and collaborators (1964) report the preliminary results of 68 autopsied cases of cerebral palsy from a state hospital for the mentally retarded. Based on the neuropathological findings they classified their material in 4 aetiological categories:

(a) malformations, (b) presumable sequelae of perinatal trauma, (c) presumable sequelae of kernicterus, (d) presumable sequelae of postnatal disorders.

The authors claim to find agreement between neuropathological pictures and clinical symptoms, but their present publications do not allow the reader to evaluate the results and a more detailed publication is awaited.

Cerebellar Damage

The relationship between certain clinical states and cerebellar damage in cerebral palsy has been known a long time. Schmorl (1904) drew attention to the degeneration of dentate nuclei, flocculi and vermis following kernicterus. Courville (1954) included cerebellar syndromes in his classification of cerebral palsy. Benda (1960) did the same in his ataxic-atonic group. Crothers and Paine (1959) and Ingram (1964) found ataxia in cerebral palsy patients with cerebellar involvement, whereas Norman (1963) emphasised that abnormalities could be found in the cerebellum in patients without any cerebellar symptoms.

Spinal Cord Lesions

The clinical picture of spinal apoplexy in the newborn was first described by Kennedy (1836). The value of the examination of the spinal cord has been emphasised many times, but only in a very few places has this been performed as a routine examination. Ford (1925) describes 6 cases of perinatal transverse lesions of the spinal cord. Crothers and Putnam (1927) report 28 cases and review the literature from 1870, comprising only 10 autopsied cases. The importance of intraspinal haemorrhages was emphasised by Klaue (1948).

Towbin (1964) has performed a routine examination of the spinal cord in cases of perinatal death and frequently he found the explanation of neonatal respiratory depression in lesions of the spinal cord. He divides these lesions into: (1) epidural haemorrhage, (2) involvement of the spinal skeleton and soft tissue structures, (3) tears in the dura and avulsion of spinal nerve roots, (4) lesions of the spinal cord varying from frank laceration to focal haemorrhage and malacia. He concluded that 10 per cent of neonatal deaths in the U.S.A. are caused by brain stem and spinal cord lesions and that the broad range of neurological sequelae in those who survive predicate a serious need for wider examination of this form of central nervous system injury. Schwartz (1963) has also drawn attention to these findings.

Only a few authors (Greenfield *et al.* 1958 and Benda 1959) have called attention to the fact that maldevelopment of the spinal cord excluding spina bifida with myelomeningocele can lead to neurological symptoms.

Conclusion

It can be seen from this selective review of the literature that it has been and still is a problem to decide what aetiological factors are acceptable as elements in the cerebral palsy syndrome. Benda, for instance, excludes malformations of the central nervous system even if patients with such abnormalities are, from a clinical point of view, often included among cerebral palsy patients.

It also emerges from the literature how varying the neuropathological picture can be both with regard to localisation and to the abnormality of the brain. It must be emphasised, as was done by Hoff *et al.* (1945), that microscopical examination of brains from patients with cerebral palsy who die at different ages will only in some cases give immediate information about the pathogenesis of their condition; the late sequelae of different kinds of perinatal brain lesions vary only in size, localisation, and age, but not in the histological picture itself, as the findings in all cases are characterised by loss of neurones, demyelinisation and gliosis in the surrounding tissue.

Cerebral palsy does not form an entity either from an aetiological, clinical, or neuropathological point of view, even if the dominant clinical picture in autopsy cases has been spastic tetraplegia, which can occur as an isolated symptom or combined with varying extrapyramidal symptoms.

Previous authors have in varying degree paid attention to the differentiation of the clinical pictures of the different types of cerebral palsy. A correlation between aetiology, clinical symptoms, and pathological findings has also been attempted, but a comparison between the long-term prognosis in the different forms of cerebral palsy and the neuropathological findings has not been carried out. The only exceptions are in reports of studies on mentally retarded populations; within these groups special attention has been drawn to the cerebral palsied (Benda 1952, Malamud *et al.* 1964, Christensen *et al.* 1965).

CHAPTER III

The Danish Clinical Material

Previous Studies

Hansen (1960) found an incidence of cerebral palsy in Denmark of between 1·3 and 1·9 per thousand. Of the 2,621 patients he ascertained, 78·5 per cent had spasticity, 9·3 per cent had athetosis, and 7·1 per cent were mixed types. This high incidence of spasticity agrees with many other surveys carried out in other countries on smaller numbers. Andersen in Norway (1957) found 65 per cent patients with spasticity, D'Avignon and Gardeström (1958) in Sweden found 80·3 per cent spastics and Ingram in Scotland (1955) 77·8 per cent. Among Hansen's spastic patients 14·5 per cent had paraplegia, 41·9 per cent had hemiplegia, 21 per cent had diplegia, and 18·3 per cent had tetraplegia.

From 1948 until the first of April 1965 approximately 1070 children with a diagnosis of cerebral palsy have been examined at the University Clinic of Paediatrics in Copenhagen where there has been continued interest in cerebral palsy for more than 20 years.

This group does not of course include all cases of cerebral palsy in Denmark, as there are naturally other centres in the country. There has however been no definite selection of cases, and no case has been turned down even if there was serious brain damage with other clinical symptoms besides motor disturbances.

The definition of cerebral palsy used in the clinic is the following:

'Cerebral palsy is a group of disorders characterised by reduced ability to make voluntary use of the muscles, caused by a non-progressive and non-hereditary brain disorder arising before or at delivery or during the first years of life.'

The classification used has been a rather simple one based on the clinical findings alone. More refined diagnosis may be useful clinically but does not help with classification for research purposes.

Spasticity
- tetraplegia
- hemiplegia → diplegia
- paraplegia → paraplegia with slight involvement of the upper extremities
- paraplegia → pure paraplegia

Athetosis
Ataxia
Other types

A number of studies all based on the same material have been published over the years and some of the findings are summarised in Table II.

The incidence of spasticity has remained the same at approximately 75 per cent, with 18 per cent athetoids and 1-2 per cent ataxias.

TABLE II

Clinical studies by Plum based on the cerebral palsy patients from the University Clinic of Paediatrics, Rigshospitalet, Copenhagen

Date of article	*No. of cases in study*	*Aim of Study*	*No. cases studied*	*Results (see also Text)*
1956	543	clinical survey	543	spastic tetraplegia 223 (41%) spastic hemiplegia 106 (19.5%) spastic paraplegia 96 (17.7%) athetosis 92 (16.9%) ataxia 19 (1.7%) other types 7
1957	478	aetiology of athetosis	80 (17%)	high incidence of neonatal jaundice and of severe asphyxia, but most often separately
1958	590	follow-up more than 3 years	203	82% marked or severe motor handicap. 37% moderate or great mental retardation. motor progress rare in cases with severe motor handicap. seizures, below normal head circumference associated with a poor prognosis.
	—	mortality	55	44 under 5 years of age. spastic tetraplegia 43 athetosis 8 ataxia 2 hemiplegia 1 paraplegia 1
1962	c. 800	early diagnosis of spastic paraplegia	121	pure paraplegia 53 paraplegia with slight affection of upper extremities 32 diplegia 36
1965	c. 1000	aetiology of athetosis	173 (c. 17%)	+ neonatal jaundice 134 + neonatal asphyxia 68 + neonatal asphyxia without jaundice 31

In his early studies there were few familial cases, but later, particularly in paraplegia, Plum (1962) showed that a family history of neurological disorders was an important factor with regard to the intellectual development. Glenting (1963) found the same when he studied the course and prognosis of spastic hemiplegia in patients from our clinic and from the Orthopaedic Hospital. The occurrence of seizures, retarded intelligence and mental disorders in the family suggested the presence of a genetic factor together with non-genetic factors, corresponding to Vogt's old theory of pathoclisis.

A number of other problems have been examined in the different papers. Low birth weight (Plum 1956) was found more frequently than normal, most commonly in the group with paraplegia. A history of complicated deliveries was also found more frequently than normal, particularly in the groups with hemiplegia, tetraplegia, and athetosis. Evidence of mental deficiency was more than twice as common in the group with tetraplegia than in the groups with hemiplegia, paraplegia, and athetosis. There was a positive correlation between the degree of mental deficiency, the presence of seizures, small head circumference and squint.

In a follow-up study of over 3 years (Plum 1958) the importance of the degree of motor handicap was emphasised. The motor handicap was marked or severe in 82 per cent. The intelligence was moderately or greatly reduced in 37 per cent. In cases with a slight motor handicap, motor ability was nearly always improved. In cases with marked motor handicap the improvement was clearly related to intelligence. In patients with severe motor handicap satisfactory motor progress was rarely seen, and only when the intelligence was normal.

The aetiology of athetosis has been discussed (Plum 1957, 1965) particularly with regard to neonatal asphyxia, idiopathic and physiological jaundice, A-B-O- and Rh-sensitisation and prematurity. Thirty-one of the 1,000 patients had a history of asphyxia without neonatal jaundice, and in this group there were more cases with signs of spasticity, but hearing loss was only present in the post-icteric group. More cases of athetosis developed after idiopathic icterus than after icterus due to immunization, presumably as a result of fewer exchange transfusions in this group. As one might guess, significant differences were found between the sensitised and non-sensitised groups; prematurity and neonatal asphyxia are commoner in the non-sensitised group, but signs of kernicterus and of impaired hearing are commoner in the sensitised group. There were no differences in the degree of motor handicap, intelligence, epilepsy, and neurological signs indicating spasticity. The susceptibility of premature infants to kernicterus was estimated to be about 5 times that of normal full-term infants.

As part of a prospective study of 10,000 newborn children, Plum *et al.* (1964) and Zachau-Christiansen and Vollmond (1964) showed that children with neonatal jaundice were in general delayed in their motor development during the first year of life and the higher the bilirubin level the greater had been the delay (Vollmond and Zachau-Christiansen 1966).

Nielsen (1966) has studied the psychological aspects of a small group of cerebral palsy children from the University Clinic, and particularly investigated the different kinds of psychological tests being used for studying children with motor handicap and brain damage. In a group of hemiplegic children matched with paraplegics she found that the hemiplegics were the most severely affected mentally.

Comparison of Danish material can be made with other surveys. In Boston Crothers and Paine (1959) were dealing with a much higher proportion of hemiplegias among their 467 cases of cerebral palsy — 40·5 per cent against 19·5 per cent, whereas tetraplegia was present in 19 per cent as opposed to the Danish figure 41·1 per cent. Ingram (1964) studied 200 patients, of whom approximately 160 had congenital forms, and of these 50 per cent were tetraplegic, but if the acquired forms were added the proportion of hemiplegics was almost 40 per cent. His figure for athetosis is small, less than 10 per cent as against the Danish figure of 17 per cent.

The clinical material from Plum's clinic seems therefore to include a high proportion of cases of tetraplegia and athetosis and rather severely affected cerebral palsy patients compared with the other clinical surveys. This may be due to the wide-ranging facilities provided in this clinic, which attract the more severely handicapped patient. Some changes in the incidence of cerebral palsy as a consequence of the prophylactic procedures (obstetric management, exchange transfusions etc.) have been noted recently (Brandt *et al.* 1964).

TABLE III

Clinical Diagnosis

	alone	*Combined with*		
		tetra-plegia	*tetraplegia + rigidity*	*tetraplegia + athetosis*
spastic tetraplegia	15			
spastic tetraplegia with rigidity	16			
spastic hemiplegia	6			
spastic hemiplegia		2		2
spastic paraplegia	1			
spastic paraplegia		2	1	1
spastic monoplegia	1			
athetosis	3			
athetosis with rigidity	3			
athetosis		11		
ataxia		3	2	

Clinical Findings in the Present Series of Autopsy Material

We have performed brain autopsies on as many as possible of the patients in the Danish series who died. The general autopsies were frequently done in other hospitals and institutions and material forwarded to our neuropathological laboratory. Sixty-nine neuropathological examinations of the central nervous system have been made on patients born between 1928 and 1964 who died between 1948 and 1964.

Some detailed case reports have already been published (Brandt *et al.* 1952, Christensen *et al.* 1956, 1960, 1961, 1963, Christensen and Hojgaard 1964, Christensen and Melchior 1960, Lund 1955, Melchior 1961, Melchior and Tygstrup 1963).

The clinical diagnoses in these 69 cases are listed in Table III. Our diagnoses were based on classical methods of clinical examination which we do not propose to detail here. We are aware that different examiners may reach different conclusions about the same child but we feel this is particularly likely to occur with less severely afflicted children. All the children in the sample had been seen on more than one occasion and the diagnosis reached after consultation with other physicians experienced in cerebral palsy. Further discussion of the clinical findings follows in later chapters (page 26 *et seq.*). Pure clinical cases of hemiplegia, paraplegia, monoplegia and athetosis only occur 14 times among the 69 patients, whereas the number of patients with spastic tetraplegia either alone or combined with other forms of cerebral palsy is very high, 55 of the 69 cases (80 per cent). In 21 of the 55 tetraplegias the clinical picture was

mixed, but even if tetraplegia was the most obvious diagnosis the patient is grouped under a heading such as hemiplegia or paraplegia for the purpose of the pathological-anatomical study.

The high frequency of spastic tetraplegia (80 per cent) is to be expected in an autopsy series. In the clinical material Plum (1956) found 40 per cent of cases of spastic tetraplegia, and Hansen (1960) among 2,621 living cerebral palsy patients found 40 per cent with tetraplegia and diplegia, but among 199 deceased patients the same figure was 52 per cent. The same high incidence of tetraplegia was also found in an autopsy series from an institution for the mentally retarded (Christensen *et al.* 1965). Among the 175 consecutive brain autopsies there were 66 clinical cases of cerebral palsy; 48 (73 per cent) of these were tetraplegia — as high a figure as in the present material.

TABLE IV

Possible Aetiological Factors in 69 Autopsied Cases

Total number		*family history of CNS disorders*	*prenatal*	*prematurity*	*perinatal*	*postnatal*
23	Family history of central nervous system disorders	*7*	6	2	8	1
17	Prenatal factors	6	*2*	4	11	0
7	Prematurity	2	4	*1*	4	0
36	Perinatal factors	8	11	4	*12*	0
10	Postnatal factors	1	0	0	0	*9*
5	Unknown					

Figures in italics indicate cases with only one aetiological factor.

Aetiological Factors

Possible aetiological factors are listed in Table IV. The information was collected as described by Plum (1965), but as the present study covers a long period some of the earlier data is not complete. Thirty-three patients had multiple aetiological factors (47 per cent), which compares with other studies of brain damaged patients (Fuglsang-Frederiksen 1958, Melchior 1961). The most common factor is a perinatal history of some possible brain lesion.

The incidence of prematurity, 10 per cent, is somewhat higher than in the Danish population generally, where Nørregaard (1953) found an incidence of 6·5 per cent. On the other hand the figure is smaller than in the overall cerebral palsy population. Hansen found an incidence of 29·7 per cent in cerebral palsy patients born between 1949 and 1953; Asher and Schonell (1950) had a figure as high as 39·4 per cent prematures. Skatvedt (1958) in her Norwegian material found 28·2 per cent with birth weights below 2500 g. Both Andersen (1957) in Norway and Crothers and Paine (1959) in Boston also report a high incidence of prematurity in their material. Spastic paraplegia is a common diagnosis in patients with cerebral palsy following prematurity and this may explain our somewhat low figure, as the number of paraplegics is small in the autopsy sample.

Prematurity was defined as birth weight below 2500 g. We are aware that sometimes we are dealing with children with a birth weight below 2500 g. and a normal gestation and these dysmature babies may be the result of an abnormal pregnancy. Gruenwald (1965) and others have suggested using the term 'infants of low birth weight' for all these patients, but we support Gellis' (1966) retention of the term 'prematurity' and use, if indicated, some other description for special conditions.

McDonald (1962, 1963) has studied the risk of developing cerebral palsy when a child is born with a birth weight below 2500 g., and found that 6·5 per cent of 1,081 children with a birth weight below 1,800 g. became cerebral palsy patients, mostly spastic diplegics. Plum (1966) has calculated the total risk of developing spastic tetra- or diplegia among all prematures to be 0·47 per cent, against a risk in mature children of 0·013 per cent. If only infants with a birth weight below 1500 g. are considered, he found that 2·8 per cent would develop spastic paraplegia based on the calculations. This seems to agree roughly with McDonald's findings.

The number of boys in this sample is much higher than that of girls (60 per cent boys and 40 per cent girls), and this figure is the same as in many clinical studies dealing with neurological disorders in childhood (Stutte 1941, Andersen 1954, Vigouroux *et al.* 1954, Skatvedt 1958, Bertelsen 1958, Melchior 1961).

Degree of Motor Handicap

In estimating the motor handicap the following classification has been used:

Slight motor handicap describes a handicap which does not prevent the patient from carrying out the movements necessary in daily life.

In *marked motor handicap* the defect of movement makes it impossible for the patient to carry out the ordinary movements in a normal manner, or the carrying out of these movements demands considerable exertion.

Severe motor handicap describes a handicap which, practically speaking, completely prevents the patient from carrying out voluntary movements with the parts of the body involved.

As one would expect the degree of motor handicap in this autopsy series was dominated by the finding of severe motor handicap. 63 cases (91 per cent) were severe, 5 were marked and only one slightly handicapped. This high incidence of severely handicapped children makes it meaningless to try and correlate the degree of motor handicap with the neuropathology.

Head Circumference

The head circumference was routinely recorded, and 15 patients had a circumference more than 2 cm. below that expected for their age. A deviation of 2 cm. is a good indication of abnormality. The standardisation we used was a Scandinavian one (Sundal 1949), where the standard deviation was between 1·3 and 1·5 cm. In similar studies of older children, Watson and Lowrey (1948) reported a standard deviation 1·4 to 1·8 cm. (see also Silver and Deamer 1948). Paine and Oppé (1966) show that the 10 percentile is similar to a deficit of 2 cm. with very little change at different ages.

We have also taken into account the birth weight as indicated by Justesen (1962), who showed that with a birth weight below 2500 g. the head circumference could be from 0·5 to 1·5 cm. below the average until the age of 12 years.

In contrast to the rather high proportion of small heads, only five patients had a head circumference 2 cm. or more above the average. Crothers and Paine (1959) reported that, out of 85 spastic tetraplegias, 47 were microcephalic, which is the term they use for a small head. (We prefer not to use this term, as it is needed for the neuropathological description, where its meaning is a precise one.) Plum (1958) has shown that a small head is associated with a poor prognosis, and this is confirmed in the present material. Ingram uses the terms microcephaly and small head circumference synonymously, and he found that, in his 8 patients with bilateral hemiplegia, 6 had small heads. He also found a high incidence of small heads in his group of diplegics and was not able to confirm Yannet's (1944) hypothesis that a small head circumference indicates a prenatal lesion rather than a peri- or post-natal lesion. Among our 15 patients with small heads there were equal numbers of dysplasias and degenerations.

Intelligence

It has been difficult to determine the intelligence in many cases, both because of the young age groups we are often dealing with, and because of the well known difficulties in obtaining a reliable I.Q. in a child with a severe motor handicap. Of the 69 patients 18 were considered to have a normal intelligence and 51 (74 per cent) to be retarded in different degrees (Table V). The incidence of mental retardation is much higher than in the clinical material, where Plum found 37 per cent with marked or severe mental retardation. In his survey Hansen (1960) found the incidence of retardation among living patients was 27 per cent, as against 60 per cent among the 199 dead patients. The high incidence again points to the fact that in the present material we are dealing with severely damaged brains.

TABLE V

The Intelligence among the 69 Cases

Normal intelligence	18	
I.Q. between 55 and 80	0	51
I.Q. between 35 and 55	4	
I.Q. below 35	22	
Retarded, but undetermined	25	

TABLE VI

Age of Death in 69 Cases of Cerebral Palsy

	boys	girls	total	
< 1 year:	10	1	11	45
1—2 years:	8	2	10	
2—5 — :	14	10	24	
5—15 — :	6	13	19	
>15 — :	3	2	5	
	41	28	69	

Sixty-four of the 69 patients died before the age of 15 years (Table VI) and 45 died before the age of 5 years. Plum (1958) found that out of 55 who died, 44 were under 5 years of age. This finding again suggests we are dealing with severely damaged brains.

Eye disorders were found in 21 patients out of the 69 (30 per cent). Eighteen had squints and 18 had nystagmus. This figure is smaller than Plum's (1956). He found 54 per cent in spastic tetraplegia and 72 per cent in athetosis not due to immunization. The presence of squint and/or nystagmus may be a bad prognostic sign with regard to mental development in cerebral palsy (Plum 1958), but not with regard to vital processes. Our figure is somewhat higher than Hansen's (21·2 per cent) or Andersen's (17 per cent). Crothers and Paine found 35 per cent squint among their hemiplegic patients, but other examiners who have especially looked for eye disorder have found higher percentages (e.g. Guibor (1953) 75 per cent, and Frandsen (1954) 41 per cent).

Epilepsy

Epilepsy was present in 42 of our 69 patients (60 per cent). Thirty had grand mal epilepsy, 8 infantile spasms and two focal seizures. In two the seizures were not classifiable. A further 6 had petit mal, but all of these also had grand mal. Hansen found 22·2 per cent with epilepsy among his 2621 patients, and Ingram (1964), in a group of 208 cerebral palsied patients, found 28·4 per cent with grand mal and 10·5 per cent with petit mal and myoclonic seizures. Perlstein *et al.* (1955) studied 1217 cerebral palsy cases and found 47 per cent had convulsions, while Crothers and Paine (1959) found an incidence of 66 per cent among their spastics and 34 per cent in athetoids. Gibbs *et al.* (1963), following up their earlier work, found that hemiplegics had the highest incidence of seizures (67 per cent), tetraplegics had 56 per cent, paraplegics 31 per cent, and athetoids 27 per cent.

Our high figure must be considered against the background of the high incidence of tetraplegia and also the clinical observation that the occurrence of seizures makes the prognosis worse (Plum 1958).

EEG Studies

EEG was performed in 58 patients and was considered normal in 23 of these. Diffuse abnormalities were found in 32 cases, including hypsarrhythmia. One patient had a definite focus as the only abnormality and 3 had minor atypical alterations of activity and distribution. The importance of EEG in cerebral palsy is discussed by Gibbs *et al.* (1963), and by Trojaborg (1965), but it might be worthwhile to note that this examination may offer more help in patients where the injury has damaged but not killed the neurones. Trojaborg (1965) found, in 21 autopsied patients with spike foci, that there was no evidence of focal pathology localized to the region of the spike focus. Recently Trojaborg (1966) has studied the focal spike discharges in many other cerebral palsied children longitudinally.

Pneumoencephalography (PEG)

This had been carried out on 48 patients of the present series. It is a valuable method of estimating the degree of brain damage. For some years we have emphasised

the prognostic value of the PEG findings not only in relation to dilatation of the lateral ventricles but also according to the size of the third ventricle (Melchior 1961).

It has been possible to measure Evans' ratio (largest width of the anterior horns divided by the largest internal cranial diameter) on 44 patients. Two of these revealed a ratio below 0·30 and were considered normal. In thirty cases we found a diffuse symmetrical dilatation with ratios from 0·30 to 0·90:

Ratio	*Number*
0·30—0·34	7
0·35—0·39	13
0·40—0·49	6
0·50—0·90	4

An asymmetrical dilatation was found in 12 cases. In two of these only one lateral ventricle was measurable, but among the other 10 patients the left lateral ventricle was larger in 6 cases. A displacement of the midline of the ventricular system was found in 3 cases, two of whom had spastic hemiplegia.

Among the 12 patients with asymmetry 4 had spastic hemiplegia, one had rigidity and paraplegia, and 7 had pure tetraplegias.

Of special interest is the finding in case No. 13, where the right lateral ventricle appeared rather indistinct and small compared with the left, which had a ratio of 0·35. The clinical finding was a left-sided spastic hemiplegia. At autopsy a fibrillary astrocytoma was found in the right hemisphere, emphasising the fact that a discrepancy between a clinical finding and PEG and/or EEG finding must raise suspicion of a space-occupying lesion. In another case (33) a hypoplastic callosal body and absence of the septum pellucidum were found both at PEG and autopsy.

The third ventricle could be measured in 27 cases.

As can be seen from Fig. 1 the width of the third ventricle is always greater than the normal value for the age. In two cases where the third ventricle measured 22 and 28 mm. the examination was performed in relation to an acute purulent meningitis and is thus considered a mere accidental finding not included in the figure. The normal values (dotted line in Fig. 1) are based on the findings of Durand and Scagliotti (1951), Göllnitz (1954) and Engeset and Lønnum (1958).

Abnormalities over the surface have been of little value as many of the patients have had their PEGs in the first year or two of life, when it has been shown that cortical air is unreliable (Brandt *et al.* 1952, Melchior 1961).

The PEG findings in cerebral palsy have been reported by many authors, and the examination has been considered of value (Guttman 1929, Brenner 1941, 1942, Andersen 1954, 1957, Eek 1955, Denhoff *et al.* 1956, Skatvedt 1958). PEG is thought to be most useful in cases of hemiplegia and among patients with seizures. Crothers and Paine (1959) stated that they used it less and less.

In the Paediatric Clinic, Rigshospitalet, PEG has been performed on 20-25 per cent of all our cerebral palsy patients. In a review of these studies (unpublished) it is shown that the decision to perform a PEG in itself indicates that we are dealing with a more serious case. The examination is only rarely performed in patients with

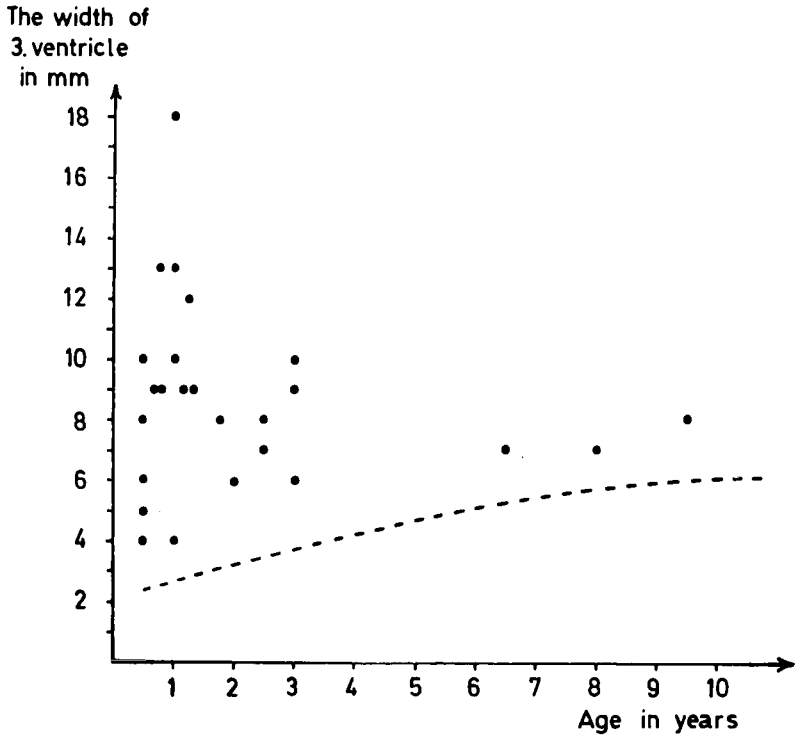


Fig. 1. The width of the third ventricle in relation to age. The dotted line indicates normal values (see text).

slight motor handicap and without epilepsy or mental deficiency or more specific signs which eventually could lead to an air study. This finding agrees with the figure of nearly 70 per cent PEG studies among this autopsy series, as against 20-25 per cent in the whole clinical material.

Comparing the figures from our present autopsy series with both the clinical Danish material and with other series of either general or special studies from other centres, it can be seen that we are dealing with a severely affected group of patients not representative of the average cerebral palsy material. There is a high incidence of tetraplegia, small heads, seizures, mental retardation, epilepsy, and of severe abnormalities in the high number of PEGs performed in these patients. There is an early age of death.

CHAPTER IV

General Autopsy Findings and Neuropathological Techniques

Danish law forbids autopsies until twelve hours after death, and the body is not allowed to be transferred to the mortuary for six hours after death. These provisions allow post-mortem changes to develop which have to be taken into consideration by the pathologist. The law also prohibits postmortem intracranial formalin injection for 6 hours after death, and this is the reason why this has not been performed.

Of the 69 patients in the present material 7 had only their central nervous system examined. In 3 no detailed information of the general autopsy findings are available. No abnormalities were found outside the central nervous system in 16 of the remaining 59 cases, and therefore the cerebral disorder is considered the cause of death. In 41 patients the general autopsy revealed respiratory infections (bronchopneumonia, tracheobronchitis and bronchitis). Gastric malaciae was found in two children and colitis in one case. In the present material we had no cases of congenital heart disease, whereas Melchior and Terslev (1964) found 24 cases of cerebral palsy among 615 children with congenital heart disease.

Another point of interest is the small number of changes in the urinary system; pyelonephritis was present in only one case, a stone in the pelvis in another, and uraemia in a third. This is astonishing when one considers the high frequency of urinary malformations among mentally retarded patients, and the fact that many of these patients had been confined to their beds for a long time and stood a greater chance of becoming infected. Neither in the present series nor in Ingram's material did kidney malformations occur.

The autopsy showed no other malformations outside the central nervous system than the 7 cases (10 per cent) found by the clinical examination (see Table VII).

TABLE VII

Congenital malformations outside the central nervous system	
Congenital dislocation of the hip	2 (24, 66)
Haemangioma of the skin	2 (59, 16)
Hiatus hernia	1 (35)
Dermoid cyst	1 (40)
Adenti and syndactyly	1 (47)

(*Case no. in brackets*)

Ingram (1964) found that 38 (24 per cent) of 160 patients with congenital cerebral palsy had malformations. Most of these were syndactyly and hypertelorism. Hydrocephalus was present in 2 cases. Congenital heart disease was found in 3 patients. Patients with hemiplegia and dyskinesia of perinatal origin had the lowest incidence of malformation.

CHAPTER V

Neuropathological Findings In The Different Clinical Entities

Clinical Classification and Definitions

In this chapter the neuropathological findings for each different clinical picture are presented. In each section a summary of the aetiological, clinical and neuropathological findings is given. Case reports have been chosen to demonstrate that a multiplicity of different aetiological factors can give the same clinical picture, e.g. pure spastic tetraplegia. They illustrate further that dysplastic changes, most likely both of unknown genetic and of metabolic genetic origin, may give clinical symptoms which are similar to the symptoms in cases with pure degenerative changes of the central nervous system. The localization of the lesion is therefore probably more important than the pathology of the lesion.

The following clinical groups are discussed:

spastic tetraplegia, pure and with rigidity
spastic hemiplegia
spastic paraplegia and diplegia
athetosis, pure and with rigidity
athetosis and spastic tetraplegia
ataxia, combined with other forms of cerebral palsy

By *spasticity* we mean a condition where the muscles react to passive stretching by the examiner with an abnormally strong increase of resistance — increased tone. It is likely that the proprioceptive afferent impulses are normal, but excite too strong efferent impulses from the spinal cord because the regulating influence from higher centres is lacking. The spastic muscle is weak, but when the examiner tries to bend the patient's knee there will be a strong initial resistance which suddenly disappears (the claspknife phenomenon). Because of these abnormalities in the tone control, contractures of the joints (hips, knees and feet) are very frequent findings when the spasticity has lasted for some time without treatment.

The terms *tetra-, hemi- and paraplegia* are used to describe the topographical extent of the handicap. Tetraplegia includes cases in which all four limbs are involved more or less equally or the upper limbs more than the lower; hemiplegia means the involvement of the limbs on one side of the body; paraplegia means the involvement of the lower limbs and, rarely, of the arms only. In diplegia all four limbs are involved but the upper limbs less than the lower limbs.

Where there has been a marked clinical asymmetry we have placed the case in the hemiplegia group in order to obtain enough material in this group. Similarly with regard to paraplegia, where the cases of diplegia are included.

We also use the term *rigidity*, and use it to subdivide the groups further. By rigidity we mean a resistance to passive movement which lasts throughout the whole

movement, but which can vary from time to time. The patient with both tetraplegia and rigidity has a very characteristic posture with extreme extension of the whole body so that the child takes up an opisthotonic position (see Figure 12). When these findings are coupled with the typical findings of spasticity — reflex changes such as extremely increased patellar reflexes, ankle and perhaps patellar clonus and a positive Babinski sign — we describe the child as having spasticity with rigidity to see if the pathology differs from that of children with spasticity. There are patients where the condition can change, one pattern can dominate at a certain time, another pattern at another time (Plum 1958).

In *athetosis*, which means without a fixed position, the most characteristic finding is the presence of involuntary movements which in the severe cases make all voluntary movements practically impossible. Frequently the movements are circular but in mild cases only minor, almost myoclonic movements of single muscle groups are seen. In pure cases contractures are rare. The muscle tone varies very much and not infrequently rigidity is seen in combination with athetosis. In some cases it is difficult to distinguish between the athetoid movements and the spastic movements of a symmetrical muscle group when a certain movement is carried out. In cases of athetosis and athetosis combined with rigidity there are no reflex disturbances as in cases of athetosis combined with spasticity. Our group of 'athetosis and spastic tetraplegia' does not indicate that athetosis is a more important element than the spasticity, only that the two occur together.

Ataxia, meaning lack of order, is characterised by marked decrease of muscle coordination, whereas the tone and strength of the muscles are normal. The patient finds it impossible to make rapid movements, and this is particularly so when the child tries to walk, but voluntary hand and finger movements are also difficult. These difficulties are demonstrated by the finger-nose test and other similar tests. It is a diagnosis which is usually made rather late as many of the disabilities which suggest the diagnosis are not apparent in the immature child. In combination with other clinical forms of cerebral palsy it is often a tentative diagnosis, as the presence of spasticity or hyperkinetic movements can make it extremely difficult to diagnose ataxia. In the present material (where we had no single case of pure ataxia) we must stress that the ataxic diagnosis has in all the cases been only a suggestion based on the clinical examination supported by the case history. In all cases the other diagnosis has been the most important feature of the child's condition.

SPASTIC TETRAPLEGIA

A clinical diagnosis of spastic tetraplegia was made in 55 out of the 69 cases. This high proportion is due to the fact that we are dealing with an autopsy series which must include a majority of the clinically most affected group. Of the 55 patients with tetraplegia 15 had no other clinical manifestations of cerebral palsy. They form the 'pure tetraplegia' group. Sixteen patients had tetraplegia combined with rigidity. This is not usually considered a separate entity within the cerebral palsies, but we find rigidity of such importance that we have studied this group separately.

In the remaining 24 patients, tetraplegia was combined with one or two other types of cerebral palsy which dominated the clinical picture. They will be discussed

TABLE VIII

24 Cases of Spastic Tetraplegia Combined with Other Forms of Cerebral Palsy

	Athetosis	*Athetosis+ hemiplegia*	*Athetosis+ paraplegia*	*Athetosis+ ataxia*	*Hemi-plegia*	*Para-plegia*	*Ataxia*
Tetraplegia (12 cases)	2 (51,62)	1 (7)	1 (26)	2 (18,55)	1 (6)	2 (31,46)	3 (5, 29, 34)
Tetraplegia with rigidity (12 cases)	9 (9,11,17, 22,32,42, 43,54,60)	1 (47)	0	0	1 (16)	1 (49)	0

The figures in brackets are the case numbers.

together with these special types but the different combinations are listed in Table VIII. Athetosis occurs in 16 cases (in 10 of these combined with rigidity), hemiplegia was found in 4 cases, paraplegia, properly classified as diplegia, in 4, and ataxia in 5 cases. In 5 patients the clinical picture was a complexity of different types of cerebral palsy, and these patients had more than one diagnosis.

PURE TETRAPLEGIA

Fifteen cases had spastic tetraplegia without any other clinical cerebral palsy symptoms (Case No. 1, 2, 4, 8, 10, 15, 27, 33, 36, 37, 45, 52, 56, 59, 63).

There were 7 girls and 8 boys.

Age at Death

< 1 year	1
1—2 years	2
2—5 years	9
5—15 years	2
> 15 years	1

(N.B. 12 died before the age of 5 years)

Family History

There was a history of neurological disease in the family in 3 cases: 2 had siblings dying of the same kind of progressive encephalopathy — one of metachromatic leucodystrophy (36), one of an unknown type of severe dysplasia (63). Case 63 also had perinatal jaundice. The third patient (56), who was premature, had a younger brother who had had an exchange transfusion, possibly for A-O-immunization disorder.

Other Causation

Possible prenatal aetiology was present in 3 cases. The twin of No. 52 died at delivery and had hydrocephalus. There was no information about the placenta. In case No. 59 there was a threatened abortion in the third month of pregnancy and a maternal viral infection in the eighth month. Here marked dysplasia corresponding to a lesion late in foetal life was found on examination of the brain. In the third case (45) the mother had influenza during the sixth month of pregnancy.

Besides case 56, only one other case was premature (2). This is a low incidence of prematurity compared with the Danish clinical material.

There was a history of difficult delivery in 8 cases: 3 were forceps deliveries, and one a caesarian section. All 8 infants were asphyxiated for a shorter or longer time. It is noteworthy that the 4 cases with dysplasia (developmental abnormality) all had neonatal difficulties. This might be due to a general weak condition at the time of delivery consequent to the prenatal dysplasia. One case had some neonatal symptoms but these had disappeared by the age of 10 days, and cerebral palsy was first diagnosed later during the first year of life. The three other patients had no symptoms during the first months of life.

In 2 cases a definite postnatal aetiology was found. One (8) had a colimeningitis at the age of 5 days and the other (4) had a severe febrile illness believed to be a meningo-encephalitis at the age of 6 months, 2 weeks after vaccination against diphtheria and tetanus.

The aetiology was unknown in 1 patient (No. 27), who had clinical symptoms from the age of 5 months which showed slow progression until death at 2 years and 8 months of age. Histological examination of the brain revealed spongy degeneration of the cortical grey matter similar to that seen in cases of poliodystrophy.

Clinical Findings

Besides the pronounced spastic tetraplegia, mental retardation was present in all the cases. The I.Q. was below 35 in 7 cases and definitely reduced but not determined in the remaining 8 cases. A small head circumference (more than 2 cm. below average) was present in 4 cases, enlarged head circumference (more than 2 cm. above average) in 3 cases (1, 8, 36).

Different forms of epileptic seizures were diagnosed in 13 of the 15 patients; 7 had grand mal, one of these also had petit mal. Three children had infantile spasms, 2 had focal seizures, and one had undefined convulsions. Of the 2 patients without epilepsy, one (No. 36) had metachromatic leucodystrophy, and No. 59 had a very pronounced cortical dysplasia with an EEG revealing reduced activity. There were 9 patients with diffuse abnormalities of the EEG and 3 patients with focal abnormalities. Only one patient (56) had a normal EEG, although this patient had pyramidal tract degeneration due to damage of the motor cortex. In one case EEG was not performed.

PEG showed diffuse dilatation in all 13 cases in which it was performed. No case of cerebral hyperpyrexia was found in this group.

Clinically 3 patients (27, 36, 63) showed some deterioration. Autopsy in these cases revealed one case of poliodystrophy, one of metachromatic leucodystrophy and one of severe cerebral dysplasia. In this last case no definite proof of an inborn error of metabolism or a chromosomal abnormality could be established at the time of death, but increased knowledge and more refined diagnostic methods might possibly later clarify similar cases. These three patients have been included in this series although the definition of cerebral palsy excludes progressive disorders. The distinction between clinical deterioration and changes in the pattern of the disease during development is not always easy. All had symptoms during the first years of life and at

that time the diagnosis of cerebral palsy alone was entertained. Although changes in their condition put the clinical diagnosis in doubt their diagnosis remained cerebral palsy until autopsy.

Neuropathological Findings

The dominant neuropathological findings in this group of 15 pure spastic tetraplegic patients with marked mental retardation were abnormalities in the cortical grey matter. Ten of the brains were microcephalic.

Cortical degenerative changes due to peri- and post-natal damage were present in 8 cases.

In 4 of the 8 cases (4, 8, 27, 33) there were degenerative changes of the cortical grey matter without any cavity formation. In 2, the lesions were sequelae of postnatal meningo-encephalitis. One case (33) was considered to have sequelae of perinatal brain damage with degeneration of the motor cortex and subsequent degeneration of the pyramidal tracts. This localised type of cortical lesion corresponds with the fact that this patient was not severely mentally retarded. The fourth patient (27) had a special kind of lesion, a spongy cortical degeneration with gliosis and nearly complete destruction of all ganglion cells, which is called poliodystrophy (see chapter on progressive encephalopathies).

In the other 4 brains (Nos. 10, 15, 37, 45) of the 8 with degeneration, cortical and subcortical polyporencephalic processes — due to perinatal damage — were present. Here atrophy or complete loss of neurones and gliosis were present in the cortical grey matter surrounding the porencephalic processes. In the subcortical white matter different degrees of myelin sheath degeneration and gliosis occurred, whereas only minor changes were present in the deeper parts of the white matter and the basal ganglia.

Case No. 56 (cf. p. 35) had degenerative cortical changes without polyporencephaly, suggesting perinatal damage. But in addition there was a malformation of the spinal cord indicating a real dysplasia. Case 52, on the other hand, had marked microcephaly with distinct dysplasia of the cortical grey matter, but in addition to these malformations, polyporencephalic processes and gliosis of the basal ganglia were present.

Four brains in this series (1, 2, 59, 63) showed cortical dysplasia indicating a prenatal maldevelopment of the brain without any histological signs of perinatal degeneration. The incidents leading to the maldevelopment must have occurred in the last part of the pregnancy (between months 6 to 9), during the formation of gyri, and before the layer formation was completed. These 4 brains are all included in the 10 microcephalic brains in this series. They showed no changes in the basal ganglia, which is in conformity with the suggestion that the damage occurred late in pregnancy after the development of the ganglion cells of the basal ganglia was complete.

The findings in the brain from the last patient, No. 36, are entirely different from the others as the pathological findings were confined to the white matter, showing a metachromatic leucodystrophy. However, the changes here were so severe that the function of the cortical ganglion cells, which appeared normal, must have been

blocked or otherwise disturbed to the point where the clinical picture was the same as in a primary cortical damage.

Degeneration or maldevelopment of the pyramidal tracts was only found in 4 cases, but routine examination of the spinal cord was not performed.

As one would expect from the clinical findings, cerebellar changes were an unusual finding among these patients, and present in only 3 cases. In one case (No. 8) there was a true degeneration following E. coli meningitis. Another patient (No. 33) had a very pronounced spastic tetraplegia and this may have masked cerebellar symptoms, which must have been present as the histological examination revealed a severe degeneration of both the granular cell layer and the Purkinje cells. The third patient (No. 63) showed a severe dysplasia of the cerebellum but his clinical condition too was so bad that no diagnosis of a cerebellar disorder could be established.

Histological examination revealed intra- and extra-cellular calcification in the cortex of two patients who had both had severe perinatal anoxia (see Fig. 6, p. 33).

As has been stated, the most striking changes were found in the cortical grey matter, but moderate changes were found in the basal ganglia in 11 of the 15 cases. The changes consist most often of periventricular gliosis.

Case Reports

Case No. 10. Female, born April 1954, died aged 2 years and 5 months.

Clinical summary: Birth weight 3250 g., uncomplicated delivery, but she did not cry until four hours after delivery. Convulsions from 36 hours, straw-coloured spinal fluid with elevated protein content, progressing hypertonicity and mental retardation. EEG revealed severe diffuse abnormalities. PEG at the age of one year showed a ratio of 0·46/0·66. The spasticity was most pronounced on the left side. The head circumference at 13 months was 40 cm.

Brain autopsy showed microcephaly (brain weight 660 g.) and cortical atrophy with unequal microgyria (Fig. 2). Frontal sections revealed polyporencephaly in the anterior two-thirds of the brain (Fig. 3) predominantly located in the cortical and subcortical tissue, but also involving the basal ganglia (Fig. 3). The ventricular system showed dilatation of both lateral and third ventricles, whereas no abnormalities were found in the brain stem and cerebellum.

Histological examination verified the macroscopical diagnosis of microcephaly, microgyria and severe polyporencephaly.

Comment: In this case of severe spastic tetraplegia there is agreement between the symptoms lasting from the perinatal period, the clinical picture of organic brain injury and the neuropathological findings pointing to diffuse sequelae of perinatal anoxia. There was no history of difficult delivery and we have no explanation for the prolonged perinatal respiratory difficulties. Athetosis was not apparent even though severe damage of the basal ganglia was present. The explanation may be that the severe spastic tetraplegia had 'covered' the presence of athetosis.

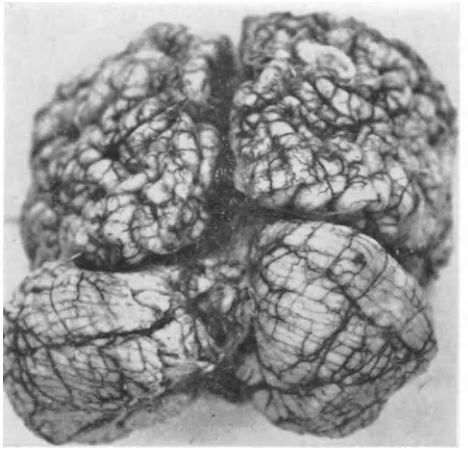


Fig. 2.* Case 10; female 2 years 5 months old. Clinical diagnosis: oligophrenia and spastic tetraplegia (sequelae of cerebral anoxia). Microgyria of occipital lobes. Reduction: 5/8. By courtesy of the Editor, *Acta paediat. (Uppsala)*.

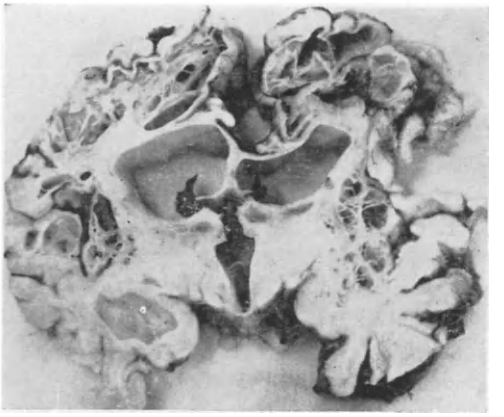


Fig. 3. Case 10 (see caption to Fig. 2). Frontal section showing severe polyporencephaly of both hemispheres and basal ganglia. Reduction: 5/8. By courtesy of the Editor, *Acta paediat. (Uppsala)*.

Case No. 37. Male, born March 1953, died aged 2 years.

Clinical summary: Birth weight 3250 g. Pregnancy was normal, but there was a forceps delivery, and partial asphyxia was present during the neonatal period. At 6 weeks of age he was admitted to a paediatric department, and a diagnosis of atrophic encephalopathy and spastic tetraplegia was made. After discharge he had infantile spasms several times a day. When readmitted aged one he was still having seizures several times each day, and now showing a severe degree of mental retardation. PEG revealed a dilatation of the ventricular system. He was admitted to a state institution for the mentally retarded where he died.

Brain autopsy showed a severe microcephaly (brain weight 250 g.), and microgyria most marked in the neighbourhood of both central sulci of Roland (Fig. 4). Considerable ventricular dilatation was present due to the presence of numerous polyporencephalic cortical and subcortical areas and also caused by an atrophy of the brain tissue, which in many places only measured 3-4 mm. in thickness (Fig. 5). Both temporal lobes, brain stem, and cerebellum as well as the Sylvian aqueduct and fourth ventricle were normal at macroscopical examination. Macroscopically the basal ganglia appeared normal except for some slight atrophy.

Histological examination: The walls of the numerous cysts and the trabeculae traversing the cysts consisted of fibrillary astrocytes. In the cyst walls small perivascular encephalomalacic regions of different age were present. On the ventricular walls small astrocyte granulomas could be seen. In the remaining part of the cerebral grey matter various alterations occurred, especially in the left hemisphere. The ganglion

*Standards of clinical photography have improved in the past ten years and many of the older pictures are not as good as we would like. In particular, a scale is missing from many photographs and the reduction has therefore been measured on preparations or estimated. In all instances, actual brain weights are available.

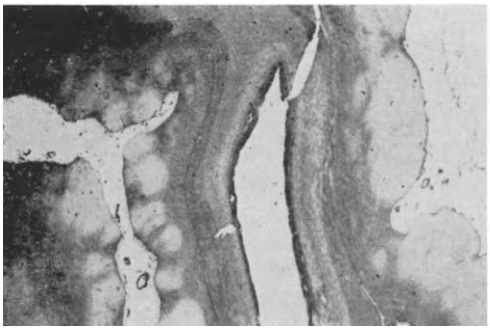


Fig. 4. Case 37; male 2 years old. Clinical diagnosis: hydrocephalus and spastic tetraplegia (sequelae of asphyxia). Brain section from right sulcus of Roland with severe microgyria and gliosis. Holzer's stain x 4·5.

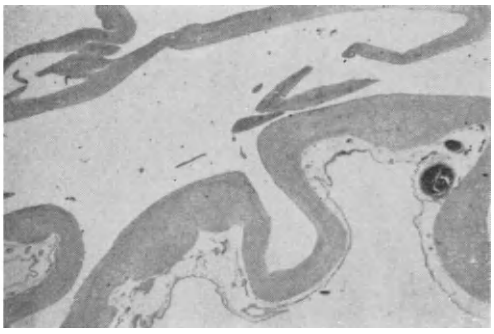


Fig. 5. Case 37 (see caption to Fig. 4). Brain section from occipital lobe showing severe atrophy and hydrocephalus. Van Gieson stain x 4·5.

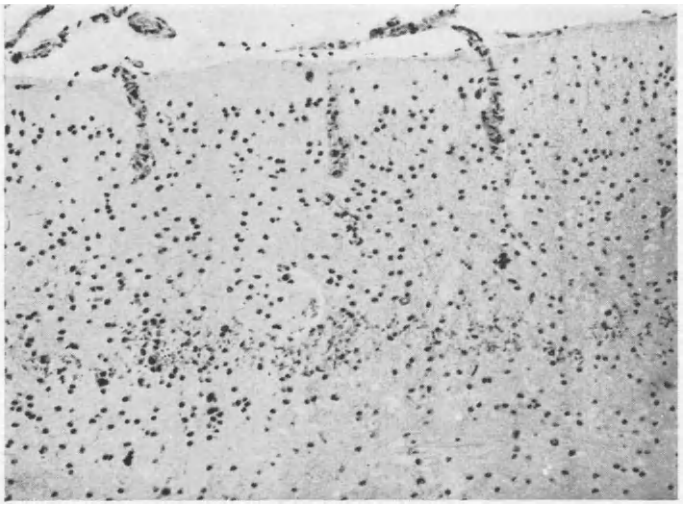


Fig. 6. Case 37 (see caption to Fig. 4). Cerebral cortex, motor region with delayed development, atrophy of ganglion cells and calcification of the inner layers of the cortex. H-E stain x 160. By courtesy of the Editor, *Dan. med. Bull.*

cells were immature, and besides this, there was atrophy of the ganglion cells, proliferation of astrocytes and numerous calcified granules (Fig. 6). In the corpus striatum calcifications and several degenerated foci of varying age could be seen. Examination of the brain stem and cerebellum did not reveal any abnormalities.

Histological diagnosis: Microcephaly, internal hydrocephalus. Polyporencephaly with atrophy predominantly of the cortical grey matter, but involving the basal ganglia.

Comment: In this case there is agreement between the aetiology (perinatal anoxia), the clinical picture of 'organic brain syndrome', and the neuropathological findings of polyporencephaly and microcephaly.

The presence of periventricular calcification suggested toxoplasmosis, cytomegalic inclusion body disease or similar infections, but no further evidence of any infection was found. The histological examination did not support an infection and the serological studies for toxoplasmosis were negative. (Published in detail by Christensen and Melchior 1960).

Case No. 45. Male, born March 1954, died aged 2 years and 6 months.

Clinical summary: Birth weight 3300 g. The mother had influenza during 6th month of pregnancy. Delivery normal. No neonatal symptoms. He had infantile spasms from the age of 4 months, and at the age of 5 months it was evident that he had a spastic tetraplegia and presumably was mentally retarded. At that time EEG revealed hypsarrhythmia. An air study showed diffuse dilatation of the ventricular system. The spasticity was symmetrical and very severe. He continued to develop very slowly. Frequent febrile episodes of unknown origin occurred, but he died of pneumonia.

Brain autopsy: Brain weight after fixation 855 g. Macroscopic examination showed nothing abnormal in the right hemisphere, brain stem, or cerebellum, but the left hemisphere was partially transformed into a large cyst containing clear, thin fluid. The cyst extended from the back part of the left frontal lobe down into the temporal lobe and into the premotor and postmotor gyri as well as into the supramarginal and angular gyri.

Coronal sections revealed that the whole left corpus striatum and the left hemisphere, apart from the frontal and occipital pole and thalamus were involved. The lateral cyst wall was 2-3 mm. thick and consisted of atrophic brain tissue. The cyst was transversed by numerous trabeculae, and did not communicate with the ventricles. On the right side cystic degeneration occurred only in the caudate nucleus and the putamen, and the tissue was sclerotic especially around the cyst in the corpus striatum (Fig. 7). There was a marked diffuse ventricular dilatation and the whole ventricular system was displaced to the left. In the cerebellum the white substance was sclerotic, otherwise no macroscopic abnormalities could be found here or in the fourth ventricle and the brain stem.

Histological examination: The cyst walls and trabeculae of the cyst consisted of fibrillary astrocytes, and in the periphery of the cyst walls small perivascular encephalomalaciae, with lipid-containing macrophages and the first stages of astrocyte proliferation could be seen. On the ventricular wall neighbouring the cyst wall granular ependymitis occurred. No inflammation or haemorrhages were present. In the remaining parts of the cortical grey matter there was normal layer formation, but both the nuclei in the ganglion cells and glial cells seemed to be pycnotic, and the cells showed varying degrees of atrophy. Several cerebellar gyri contained atrophic Purkinje cells and in the corresponding subcortical tissue myelin degeneration and astrocyte proliferation occurred. In the brain stem the right pyramidal tract appeared atrophic.

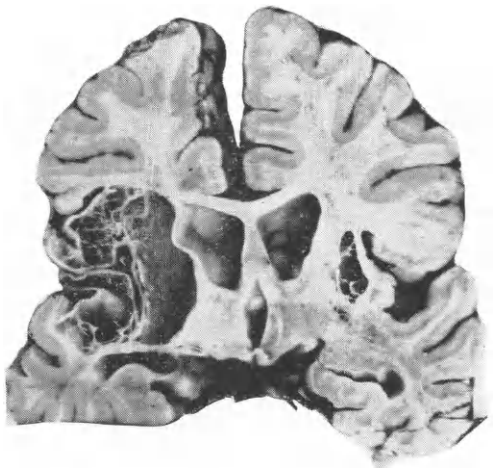


Fig. 7. Case 45; male 2 years 6 months old. Clinical diagnosis: spastic tetraplegia, mental retardation and infantile spasms. Coronal section of the brain showing polyporencephaly, especially of the left hemisphere. Reduction:
By courtesy of the Editor, *Dan. med. Bull.*

Histological diagnosis: Polyporencephaly, especially of the left hemisphere. Cortical atrophy of the brain and cerebellum. Internal hydrocephalus.

Comment: In this case of severe symmetrical spastic tetraplegia the only known aetiological possibility is a viral infection in the 6th month of pregnancy, but this is in disagreement with the neuropathological findings of polyporencephaly which suggest a perinatal damage. (Published in detail by Christensen and Melchior 1960).

Case No. 56. Female, born June 1951, died aged 6 years.

Clinical summary: Birth weight 1750 g. A younger brother was born with hare lip and had an exchange transfusion owing to A-O-immunization. Before the relevant pregnancy there were two abortions, and during this one the mother had severe vomiting in the fourth month. Delivery took place four weeks before term. Mild jaundice was present for two weeks. Her development was very slow. At the age of 4 months she had febrile convulsions. An EEG at the age of 10 months showed diffuse abnormalities. When eighteen months old she could not sit unsupported and could not use her hands. She had grand mal epilepsy. Neurological examination showed spastic tetraplegia involving the arms more than the legs. The spasticity progressed until death. PEG revealed a ratio of 0·38 and an increased amount of surface air. EEG was normal when she was 19 months old. She was placed in a home for the physically disabled. At the age of 6 years she died from a possible virus infection.

Brain autopsy: Brain weight 1200 g. Macroscopical examination showed no abnormalities but the spinal cord appeared narrower than normal.

Histological examination showed slight, acute leptomeningitis and brain oedema. Atrophic ganglion cells with satellitosis could only be demonstrated in the cortex of the island of Reil and the motor region, but in the whole cortical grey matter the total

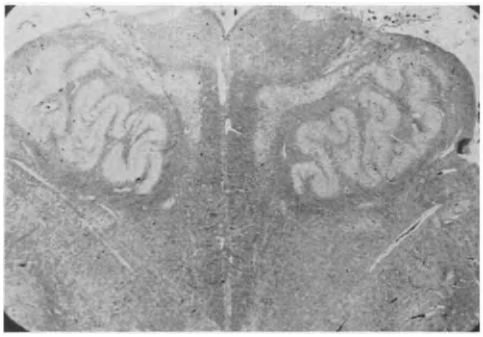


Fig. 8. Case 56; female 6 years old. Clinical diagnosis: spastic tetraplegia, oligophrenia, epilepsy. Myelin-degeneration of both pyramids in medulla. Weil stain x 4.5.

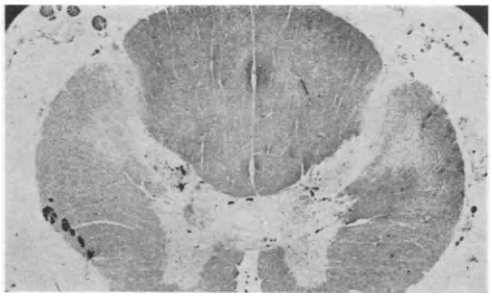


Fig. 9. Case 56 (see caption to Fig. 8). Cervical part of spinal cord with myelin-degeneration of pyramidal tracts. Weil stain x 4.5.

number of ganglion cells, especially of the pyramidal cells, were reduced and the layer formation was incomplete in places. In the white matter there was no degeneration of myelin sheaths and no gliosis. In the mesencephalon and the pons the pyramidal tracts showed severe diminution in intensity of myelin staining. Cerebellum was normal. Both pyramids in the medulla were diminished in size and showed marked lack of myelination, (Fig. 8) but the axis cylinders were preserved. All other tracts in the medulla showed normal myelination, and the ganglion cells were normal except for slight swelling and chromophobia. Sections from all parts of the spinal cord showed lack of myelin in the pyramidal tracts in the lateral columns (Fig. 9). The number of anterior horn cells was diminished but the cells present were of normal development and well preserved. The other parts of the grey matter in the spinal cord were normal. There was a slight hydromyelia in the thoracic part of the spinal cord and a reduplication of the central canal in the lumbar part of the cord.

Comment: The history of abortions, vomiting in pregnancy, and possible A-O-immunization points to familial, prenatal and perinatal lesions of the central nervous system. The neuro-pathological findings support both perinatal damage and prenatal damage. The slight deficiency in layer formation in the cortical grey matter might be caused by prematurity. The histological picture of the spinal cord is in accordance with the findings in amyotrophic lateral sclerosis and may be explained by the damage to ganglion cells of the motor cortex, e.g. a lesion of the upper motor neuron. The hydromyelia and reduplication of the central canal in the lumbar part of the spinal cord are independent malformations and not secondary to the atrophic pyramidal tracts. The clinical and histological findings do not support a possible disorder due to vascular incompatibility, even if mild perinatal jaundice was present. Multiple aetiological factors are present and in this case the present examination has not clearly differentiated between the various possibilities. We may be dealing with a combination of a congenital abnormality and changes due to prematurity combined with perinatal damage.

Case No. 27. Male, born June 1951, died aged 2 years and 9 months.

Clinical summary: Birth weight 3500 g. Pregnancy and delivery were normal. He had slight jaundice for the first two weeks of life. At the age of five months he had generalised convulsions and his EEG was diffusely abnormal. PEG showed at six months a ratio of 0·50/0·43, third ventricle 10 mm. He had a spastic tetraplegia of a moderate intensity. At the age of two and a half years he was admitted to a State Institution and his condition deteriorated. There were frequent convulsions, his spastic tetraplegia was now severe and he was completely helpless. His head circumference was 43 cm. Three months after admission he died of pneumonia.

Brain autopsy: Marked microcephaly. Brain weight 400 g. Leptomeninges showed some fibrosis, especially over the frontal lobes. Collections of subarachnoid fluid were found. There was diffuse dilatation of the ventricular system including the aqueduct and fourth ventricle. Atrophy of the cortical grey matter and the basal ganglia as well as the corona radiata was present and no clear demarcation between the grey and white matter in the basal ganglia could be seen. Pons, cerebellum and medulla were smaller than usual but otherwise macroscopically normal.

Histological examination: A marked deficiency of cortical layer formation could be seen. Only a few cortical ganglion cells were present, and most of these were atrophic. A pronounced cortical glial proliferation could be seen. In the deeper part of the cortex the tissue was spongy and laminar necrosis was found corresponding to the the atrophic third and fifth layers. The basal ganglia showed status marmoratus with incomplete myelination and gliosis. The cerebellum was normal. In the mesencephalon, pons and medulla some glial proliferation was present around the Sylvian aqueduct and fourth ventricle.

Comment: The aetiology is unknown except for the history of slight jaundice. The histological findings in this markedly microcephalic brain showed both cortical dysplasia and degeneration of such a severe degree that the cytoarchitecture had been completely destroyed. In the cortical grey matter the findings are similar to those of poliodystrophy where the aetiology is unknown, but in most of the published cases there seems to be both a genetic and an exogenous factor. In this condition there is no involvement of the basal ganglia. The finding of status marmoratus in the present case suggests anoxic damage. Lesions of the basal ganglia characteristic of kernicterus were not found in this case. The clinical picture was a spastic tetraplegia which grew steadily worse. (Published in detail by Christensen and Højgaard 1964).

Case No. 63. Male, born August 1957, died aged 2 years and 5 months.

Clinical summary: Birth weight 3600 g. The father had a mild left-sided spastic hemiplegia. A younger brother (case no. 66) died of a similar disease to this patient. The pregnancy and delivery were uneventful. Neonatally the child developed mild jaundice lasting for 3 weeks, and blood tests at the age of one year revealed the possibility of A-O-immunization, as the mother was type O with immune anti-A agglutinins and the child was A. He started to have infantile spasms at 6 months and a diagnosis of spastic tetraplegia was made (Fig. 10). An air study done when he was 9 months old showed dilatation of the ventricular system and an increased amount of air on the

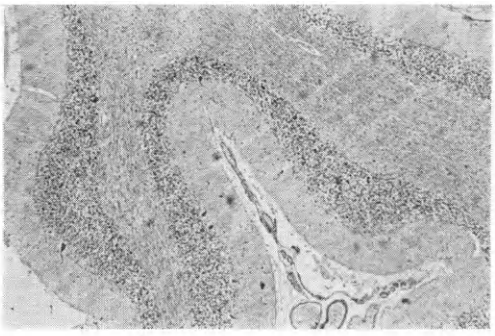
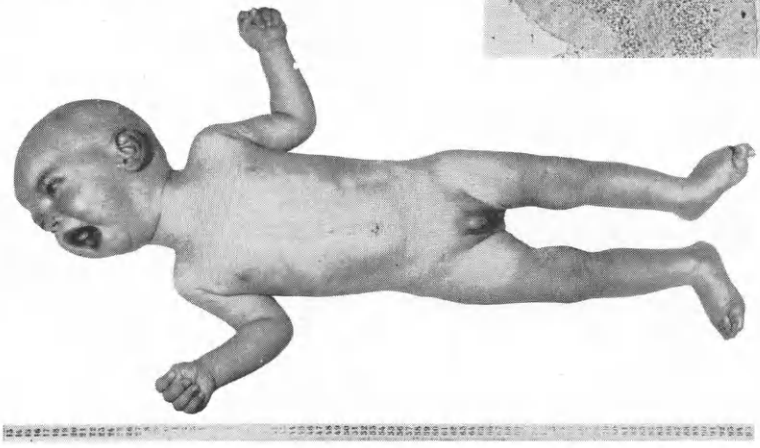


Fig. 11 (right). Case 63 (see caption to Fig. 10). Dysplasia of the cerebellar folia with reduced number of Purkinje cells and granular cells. Mallory stain x 4·5

Fig. 10. (below). Case 63; male 2 years 5 months old. Clinical diagnosis: spastic tetraplegia, infantile spasms and mental retardation.



surface of the brain. Treatment was started with ACTH and 'prednisone' when he was one year old. There was no effect from this or from treatment with anti-epileptic drugs. There was no evident intellectual development and the course was downhill. He had very few spontaneous movements and, despite spasticity, his muscular strength was very weak. He died at an age of 2 years and 5 months from pneumonia.

Brain autopsy: Brain weight 960 g. Macroscopical examination showed irregular microgyri. The cerebellum was small but the brain stem was macroscopically normal. Coronal sections revealed moderate dilatation of both lateral ventricles and 3rd ventricle. The fourth ventricle was only slightly dilated. The consistency of the white matter was very solid, especially in the cerebellum. The whole cerebellar cortex was atrophic both in the paleo- and neo-cerebellum.

Histological examination: The cortical ganglion cells were immature with incomplete layer formation. Myelination was delayed both in the central white matter and the basal ganglia. The pyramidal tracts appeared thinner than normal but no myelin abnormalities could be seen, and the ganglion cells in the basal ganglia showed no degeneration. Glial proliferation could only be seen in the subpial and periventricular regions, where the ependymal cells were lacking in some of the ventricular walls. The number of Purkinje cells and ganglion cells in the granular layer was diminished, but the cells present were normally developed (Fig. 11). The basal ganglia and brain stem did not show any abnormalities.

Histological diagnosis: Dysplasia of the cortical grey matter both in the cerebrum and cerebellum. Internal hydrocephalus with periventricular gliosis.

Comment: No cause is known but a familial metabolic disorder is suggested by the brother's similar disorder. The possibility of sequelae of A-O-immunization can be excluded both by the clinical examination and by the neuropathological findings. From the histological picture no other diagnosis can be made but a cerebral and cerebellar dysplasia of unknown type. (Published in detail by Christensen and Melchior 1960).

Case No. 52. Female, born December 1950, died aged 9 years and 5 months.

Clinical summary: Birth weight 2600 g. The mother had oedema during pregnancy, and the child was the first of twins. The second twin was stillborn and severely macerated.

When she was 6 months old the mother had her examined as she was considered to be developing abnormally. She was unable to sit upright and could not grasp objects. On admission to hospital at that age the EEG revealed severe focal dysrhythmia. She did not follow light. Later bilateral optic atrophy was found, and at the age of 1 year she had grand mal convulsions. She became more and more retarded and from the age of 1 year she had a marked tetraplegia with contractures of the ankle joints and severe adduction tendency of the hips. All the reflexes at that time were hyperactive and there was a bilateral Babinski sign. She was placed in an institution for the mentally retarded at the age of one year and made no progress over the years. She had more frequent seizures until she died at the age of 9 years.

Brain autopsy: Brain weight after fixation 600 g. Leptomeninges were slightly thickened. The brain was deformed owing to marked hydrocephalus of the parieto-occipital regions, where the brain tissue consisted of a membrane measuring 1 to 4 mm. in thickness. In the frontal and central regions the brain substance measured between 20 and 50 mm. In these parts gyrus formation could be recognized, but pronounced microgyria was present. Leptomeninges appeared normal. The brain stem was small, otherwise normal. No macroscopical abnormalities could be seen in the cerebellum.

Coronal sections of the brain revealed ventricular dilatation of the frontal horns, which in transverse diameter measured 45 mm. and were 40 mm. high. The transverse diameter of the third ventricle was 13 mm. The temporal and occipital lobes were large thin-walled 'cysts'. The aqueduct measured 4 mm. in transverse sections but the fourth ventricle appeared to be of normal size. The corpus callosum was atrophic because of the hydrocephalus. A porencephalic area was present in the central white matter of the right frontal lobe and extended into the lateral part of the right lentiform nucleus. Otherwise the basal ganglia appeared macroscopically normal, and the impression was that the hydrocephalus was mainly due to atrophy of the white matter. The brain stem appeared atrophic, but the cerebellum showed no gross abnormalities.

Histological examination: In all parts of the cortical grey matter both pronounced dysplastic and degenerative changes were present. Nowhere could layer formation be seen, and the few remaining immature ganglion cells were collected in clusters. This could also be seen in the thin rim of brain tissue in both parietal and occipital lobes. The scanty white matter showed a diffuse deficiency in myelin.

The degenerative changes appeared as diffuse cortical gliosis and satellitosis. The gliosis was most pronounced around the porencephalic area in the right hemisphere. The cyst was traversed by glial trabeculae. In all parts of both lentiform nuclei severe ganglion cell degeneration was present, and the ependymal cells on the ventricular walls were in many places replaced by granular astrocyte proliferation. Both in the brain stem and cervical part of the spinal cord deficiency in myelination of the pyramidal tracts was present. Otherwise no abnormalities could be seen.

Comment: Clinically this twin was a severe case of tetraplegia.

From a neuropathological point of view both perinatal and prenatal damage is present in this brain. The astrocyte proliferation in the surrounding tissue and glial trabeculae traversing the porencephalic cysts were considered a degeneration of perinatal origin, as no scar formation (glial proliferation) occurs in prenatal degenerative cysts (Hallervorden 1952). In addition to this, subependymal and subpial gliosis was present, together with ganglion cell atrophy and satellitosis in the cortex and basal ganglia. The hydrocephalus was of the schizencephalic type (Yakovlev and Wadsworth 1946) most likely due to congenital abnormalities of the pial vessels and secondary malformation of the hemispheres.

Discussion

A summary of the most important aetiological and neuropathological findings in this group of 15 cases of pure spastic tetraplegia can be seen in Table IX. We are clearly dealing with a group of patients with severe brain damage as the age of death is below 3 years in 10 of the 15 cases. The high incidence of epilepsy and the low I.Q. in association with the frequent severe dilatation of the ventricular system also point to an extensive lesion. These findings are in agreement with those in the literature (Benda 1952, Malamud 1961, Melchior 1961, Christensen *et al.* 1964). Plum (1958) and Hansen (1960) have drawn attention to the fact that the survival of cerebral palsy patients is prolonged once they have passed the 5th year of life.

The neuropathological findings are strictly degenerative in 8 cases, and this corresponds closely with the aetiology of perinatal anoxia or post-natal meningitis in 7 of the cases. All of these patients had symptoms from the first weeks of life, except case 45 where the disease was first noticed at the age of 3 months. In this case a history of viral infection in the 6th month of pregnancy does not appear to be related to the finding of polyporencephaly, which indicates peri- or postnatal anoxia.

Neither macroscopical nor histological examination of the central nervous system provides evidence of a cerebral haemorrhage as the cause of the porencephaly (Rydberg 1932, Schwartz 1961, 1965). Both the cortical gliosis and polyporencephaly are most likely due to perinatal anoxia (Norman 1947, Gröntoft 1952). This is also in agreement with the findings of Becker (1949) and Hallervorden (1952), that immature brain tissue — following brain lesions — has a more marked tendency to absorption than mature brain tissue.

Dysplastic changes occurred in 7 cases. In five of these they were predominantly localized to the cortical grey matter and seemed to have arisen late in foetal life (Minkowski 1952, Crome 1956). In one of these 5 cases there was a marked develop-

TABLE IX
Pure Tetraplegia

Case No.	*Sex*	*Age at death (years)*	*Aetiology*	*Symptoms observed from*	*Epilepsy*	*I.Q.*	*PEG*	*Brain weight g.*	*Pathological-anatomical findings*
4	f.	2	? meningitis	6/12	right-sided	<35	0·85/0·65	750	Degeneration due to meningo-encephalitis
8	m.	10/12	coli meningitis	5/365	grand mal	low	0·90	500	Degeneration due to meningo-encephalitis
10	f.	2 5/12	perinatal anoxia	2/365	grand mal	<35	0·46/0·66	600	Polyporencephaly due to anoxia
15	m.	2 3/12	perinatal anoxia	0/365	grand mal	low	0·43	500	Polyporencephaly due to anoxia
37	m.	2	perinatal anoxia	0/365	inf. spasms	low	0·68	250	Polyporencephaly due to anoxia
45	m.	2 6/12	prenatal infection	3/12	inf. spasms	low	0·34/0·44	855	Polyporencephaly – unknown origin
56	f.	6	pre- and perinatal (premature with jaundice)	0/365	grand mal	?	0·38	1200	Degeneration due to anoxia
33	f.	4 3/12	perinatal anoxia	0/365	grand mal	<35	0·45	560	Degeneration due to anoxia
27	m.	2 9/12	unknown	3/12	grand mal	?	0·46	400	Degeneration (poliodystrophy)
52	f.	9 5/12	prenatal (twin)	0/365	grand mal + petit mal	<35	0·52	600	Degeneration and dysplasia
1	f.	1 2/12	perinatal anoxia	0/365	atypical	low	—	1150	Dysplasia
2	m.	20	perinatal (premature)	<1 y.	grand mal	<35	—	560	Dysplasia
59	f.	1 6/12	prenatal-perinatal anoxia	2/12	no epilepsy reported	<35	0·33	800	Dysplasia
63	m.	2 5/12	prenatal-perinatal (jaundice)	7/12	inf. spasms	low	0·36	960	Dysplasia
36	m.	4 10/12	prenatal-perinatal	2 y.	no epilepsy reported	<35	0·38	unknown	Metachromatic leucodystrophy

mental abnormality in the folia of the cerebellum which was probably a familial disorder.

Of the remaining two cases, one had a special cortical abnormality — Alper's disease or poliodystrophy. The origin of this disease is still obscure, but it is probably a metabolic disorder combined with an exogenous factor (Christensen and Højgaard 1964). In the other case a primary abnormality of the white matter was present and the metachromatic type of leucodystrophy was diagnosed (Hagberg *et al.* 1962).

In four of the above 7 cases with cerebral dysplasia, there was a history of temporary perinatal respiratory difficulties. This finding accords with Benda's (1960) view that such difficulties are a consequence of prenatal brain anomaly and not of perinatal brain damage.

Only one patient had a specific lesion of the basal ganglia (status marmoratus) and here a history of perinatal jaundice was present, but there was no question of any blood group incompatibility.

Intracerebral calcification was present in one case and was secondary to degeneration and not to toxoplasmosis or other inflammatory processes (Melchior *et al.* 1960).

The brain was microcephalic in 10 of these 15 cases with pure tetraplegia. The brain weight was unknown in one case.

Conclusions

In pure spastic tetraplegia the main lesion is an abnormality of the cortical grey matter.

Clinically there is no difference between degenerative and dysplastic cases except that on looking at the case histories one has the impression that cases with perinatal damage have persistent symptoms from birth, while patients with dysplasia first develop symptoms several weeks or months after birth.

TETRAPLEGIA WITH RIGIDITY

Sixteen patients had tetraplegia and rigidity: case nos. 12, 14, 21, 23, 24, 30, 35, 38, 40, 41, 44, 48, 50, 58, 61, and 66. There were 11 girls and 5 boys.

Age at Death	< 1 year	4
	1 — 2 years	2
	2 — 5 years	6
	5 — 15 years	2
	> 15 years	2

(12 were dead by five years of age).

Family History

There was a history of familial disorders in three cases (Nos. 21, 40 and 66); each of them had a sibling with a similar disorder to their own.

The clinical diagnosis of No. 21 was postnatal cerebral palsy but at autopsy both he and a younger brother who developed a similar clinical picture proved to have globoid cell leucodystrophy (Krabbe's disease).

No. 66 was the brother of No. 63 (cf.p. 37). Clinically both had tetraplegia, but only the present case, No. 66, had rigidity. This is in agreement with the fact that only this patient had lesions in the basal ganglia.

The third patient (No. 40) had a family history of epilepsy and mental disorders.

Other Causation

Possible *prenatal aetiology* is present in 4 cases. One mother had 'asiatic flu' in the fourth month (No. 12) and the child was a twin. Two mothers had serious attacks of pain in the fourth and fifth months respectively (Nos. 38 and 50), and in one case (61) the parents were first cousins. Besides this the mother had severe vomiting during the first three months of pregnancy.

Neuropathological examination confirmed a prenatal aetiology in case 61 (revealing the presence of a metachromatic leucodystrophy) and also in case 66. Both in this case and in No. 14 there was a history of neonatal jaundice but not of immunization or of clinical signs of kernicterus. Microscopy showed severe cerebral dysplasia, but degenerative changes in the basal ganglia and brain stem, as seen as sequelae of kernicterus, only in case 66.

Two children (23 and 50) were premature with a birth weight of 2200 g. One of these (23) had a difficult delivery (caesarean section) and at the age of 4 months severe gastroenteritis, but brain autopsy revealed degeneration most likely due to perinatal anoxia. In case 50 the neuropathological changes were also degenerative.

Perinatal aetiology was suspected in 10 patients. The mother of one of these (No. 48) also had a history of vaginal bleeding from the eighth month. In three cases there was forceps delivery and in one a caesarian section. Four had perinatal asphyxia and one was a precipitate delivery. While there was no history of difficult delivery or of asphyxia in case 58, the mother had a very narrow pelvis. The infant had bilateral subdural haematomas and microcephaly probably due to a perinatal lesion. The aetiology is consequently classified as perinatal.

Postnatal aetiology. Case 41 had a meningoencephalitis at the age of 5 months.

The aetiology was unknown in 2 patients (24, 44): case 24 was said to have developed normally until the age of 8 months, from which time it was evident that he had cerebral palsy. The other patient (44) had a normal delivery. When he was a few days old, the mother noticed trembling of the extremities and at 4 weeks old he had a grand mal seizure. Autopsy findings suggested the severe sequelae of anoxia.

Clinical Findings

A small head circumference was recorded in 5 cases (14, 24, 30, 40, 58). The I.Q. was below 35 in 7 patients, 2 (48, 61) were definitely retarded, but I.Q. was not determined in these patients.

Epilepsy was present in 9 out of the 16 cases. Six patients had grand mal attacks and two of these also had petit mal. Three patients (12, 23, 66) had infantile spasms — two of these had degeneration and one a severe dysplasia of the cortex.

A normal EEG was found in the two cases of leucodystrophy (21, 61), and in two cases with degeneration of the basal ganglia (30, 44). Case 48 had a normal EEG

performed at the age of 4 months, which is astonishing as severe cortical degeneration was present at death at the age of 7 months. Diffuse abnormalities in the EEG were found in 6 patients, all with severe cortical changes (14, 23, 35, 41, 58 and 66). Focal abnormalities were found in two cases (12, 38), one with infantile spasms, the other without seizures, both with degenerative changes due to anoxia. An EEG was not performed in 3 cases (24, 40, 50).

PEG showed diffuse dilatation in all 11 cases in which it was performed.

The seven cases without convulsions had the following changes. Cases 21 and 61 had leucodystrophies; cases 30, 38 and 48 had pure degenerative processes, two of of these primarily in the basal ganglia. Cases 14 and 40 belonged to the dysplasic group.

Cerebral hyperpyrexia occurred in 4 cases (14, 30, 58, 61); all of these had marked damage of the basal ganglia. It is of interest that no case of cerebral hyperpyrexia was found in the group of pure tetraplegia.

Neuropathological Findings

A normal brain weight was found in 9 cases. Microcephaly was found in 7 cases. Only one patient with a small head circumference (40) did not belong to this group, as the brain weighed 1100 g., but in this case the actual weight must be regarded with reservation as there was oedema and hyperaemia of the brain.

Degenerative changes in the cortical grey matter were present in 10 cases. Three of these brains also had polyporencephaly involving the basal ganglia. In two cases the changes were considered secondary to anoxia and in the third case there was a possibility of a sinus thrombosis secondary to infection. The degenerative changes of the cortical grey matter in the remaining seven cases without porencephaly were due to perinatal anoxia in 6 cases. In case 23 a combination of aetiological factors was present, as perinatal damage due to caesarean section, prematurity, and postnatal lesions following a severe gastroenteritis at the age of 4 months were possibilities, but the sequelae of perinatal anoxia seemed most likely.

Cortical dysplasia was found in four cases. In three of these the formation of secondary gyri was incomplete indicating that the maldevelopment occurred after the 6th month of pregnancy.

In the fourth case the arrest of development must have occurred before the fourth month as the malformation was a hydrocephalus of the schizencephalic type (Yakovlev and Wadsworth 1946).

In two cases no primary dysplasia of the cortical grey matter was present; these showed leucodystrophy, one of the Krabbe's type and one metachromatic. These two were classified as dysplasias probably due to an error of metabolism.

Pyramidal tract degeneration was found in 6 patients and, as in the group of pure tetraplegia, these patients were among the older of the series. The age of death was between 3 and 6 years, but not younger than this. However the two oldest of the present group both had dysplasia and had no pyramidal tract degeneration. In the two cases of leucodystrophy pyramidal tract changes were found as a part of changes of the white matter.

Abnormalities of the cerebellum were a rare finding in this group, only occurring in two cases of dysplasia (40, 66), and in the two cases of leucodystrophy.

In four cases the histological examination revealed both intra- and extracellular calcification located in the basal ganglia. Only in one of these cases was there also calcification in the cortex.

Case Reports

Case No. 30. Male, born August 1954, died aged 2 years and 9 months.

Clinical summary: Birth weight 3250 g. The pregnancy and delivery were normal. The child was apnoeic for more than 5 minutes. There was slight jaundice from 2nd to 5th day of life. From the age of 5 weeks he started to assume opisthotonic postures and was admitted to hospital several times because of encephalopathy. He had frequent episodes of high fever of unknown origin. On admission to the paediatric clinic, he was found to have a very severe spastic tetraplegia with pronounced rigidity so that he lay in an opisthotonic position (Fig. 12). His head circumference was 40 cm. PEG gave a ratio of 0·34. EEG was normal at 11 months but, repeated at 17 and 20 months, it showed excess of fast activity. He died aged 2 years 9 months from respiratory disease.

Brain autopsy: Brain weight after fixation 675 g. Macroscopical examination of the brain showed microcephaly and microgyria, especially on the convexity. In coronal section the cortical grey matter was considered normal, but the white matter was atrophic although no ventricular dilatation occurred. The corpus striatum was also atrophic and sclerotic and encephalomalacia was present in the cortex of the insula, the putamen, and the caudate nucleus on the right side. No macroscopical abnormalities could be seen in the brain stem or cerebellum.

Histological examination: Part of the ganglion cells of the cortical grey matter was immature but the layer formation was present. A mild degree of gliosis, particularly of the subpial glial membrane, could be seen. In the basal ganglia there was diffuse gliosis, with deposits of iron pigment and calcifications, degeneration of ganglion cells and especially marked degeneration of the myelin sheaths. There was adventitial hypertrophy around many vessels (Fig. 13). The degeneration occurred in the putamen, globus pallidus, caudate nucleus and thalamus on both sides, the periventricular areas were most affected, and on the right side an old area of encephalomalacia was present. In the brain stem degeneration of both pyramidal tracts could be seen—more on the right than on the left side. Examination of the cerebellum did not reveal any abnormalities.

Histological diagnosis: Microcephaly, sequelae of cerebral anoxia with degeneration most pronounced in the basal ganglia and pyramidal tracts.

Comment: The history of perinatal asphyxia together with the severe clinical symptoms of spastic tetraplegia and pronounced generalized rigidity from early infancy correspond with the neuropathological findings both in the cortex and basal ganglia. No specific sequelae of kernicterus were found.

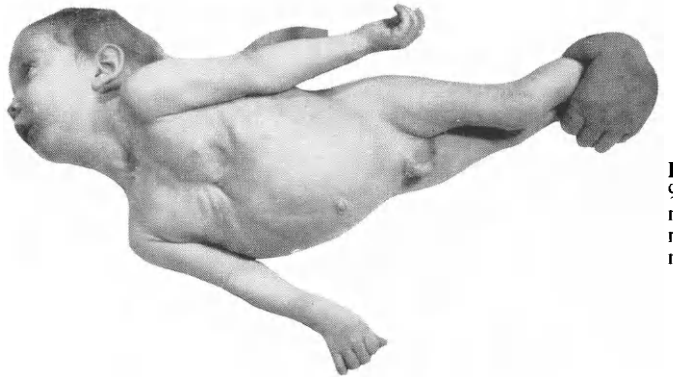


Fig. 12. Case 30; male 2 years 9 months old. Clinical diagnosis: spastic tetraplegia with rigidity, microcephaly and mental retardation.

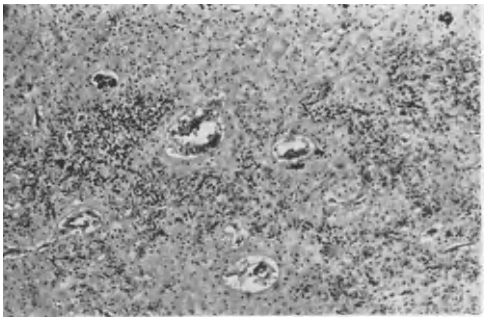


Fig. 13. Case 30 (see caption to Fig. 12). Degeneration of putamen with gliosis, fibrosis of the vessels and deposits of iron pigment and calcification. Mallory stain x 60.

Case No. 12. Male, born March 1958, died aged one year.

Clinical summary: Birth weight was 2500 g. The mother had 'asiatic flu' during the fourth month of pregnancy. The patient was twin A, the delivery was difficult and forceps were used. There was no asphyxia. The twin sister was normal. At the age of 5 months he was found to have a spastic tetraplegia, and he started to have infantile spasms at the age of 6 months. PEG showed a severe diffuse dilatation of the ventricular system. He was admitted to the paediatric clinic, and became increasingly rigid and spastic. He was unable to perform voluntary movements. In the weeks before he died from pneumonia, he was treated with ACTH without effect.

Brain autopsy: Brain weight 760 g. The brain surface was normal, but there was a slight degree of microcephaly. Coronal sections revealed a moderate dilatation of the ventricular system. The periventricular tissue was yellowish and solid with calcifications. The brain stem and cerebellum were macroscopically normal.

Histological examination: In the cortical grey matter subpial gliosis and atrophy of the nerve cells occurred. The layer formation and myelination were normal. Around the dilated ventricular system gliosis, calcification and regions of perivascular encephalomalacia of varying age could be seen, more pronounced in the white matter, the caudate nuclei, and the internal capsules, less pronounced in the thalami. In some of the encephalomalacic areas a great deal of lipid-containing

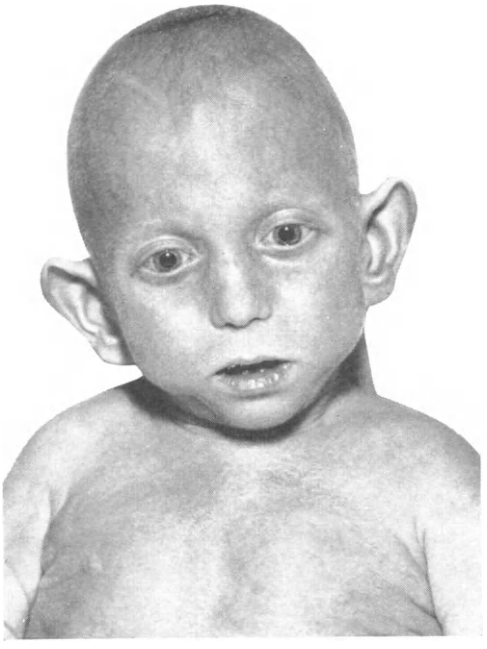


Fig. 14. Case 38; male 9 months old. Clinical diagnosis: spastic tetraplegia with rigidity, microcephaly, sequelae of bilateral subdural haematomas, ichthyosis.

macrophages were present. Other affected regions were older with gliosis and development of connective tissue and vessels. No abnormalities could be seen in the brain stem and the cerebellum.

Comment: In spite of the history of a prenatal infection the neuropathological findings of cortical and periventricular gliosis, periventricular calcifications, and old encephalomalacic processes in both striated bodies suggest that we are dealing with perinatal damage in association with the difficult delivery, although there is no history of perinatal asphyxia. (Published in detail by Christensen and Melchior 1960).

Case No. 38. Male, born June 1956, died aged 9 months.

Clinical summary: Birth weight was 2900 g. During the fourth month of pregnancy the mother had pains in the right side of her abdomen for a few days. Delivery was complicated and forceps were needed. There was no asphyxia or jaundice, but shortly after delivery it was noticed that the extremities were flexed and the infant became increasingly rigid and cyanotic. A diagnosis of spastic tetraplegia was considered. He was discharged from the local hospital at the age of 6 weeks but did not develop satisfactorily. He was admitted to the paediatric clinic at 6 months, where he was found to have a severe spastic tetraplegia with rigidity. He had ichthyosis and his head circumference was slightly below average. His appearance, which included webbing of the neck, suggested some distinct syndrome, not of the Sjögren-Larsson's type but more likely a trisomy 17-18 (Fig. 14). Subdural taps revealed bilateral haematomas and he had immediate surgery. After operation there was liquor leakage, and he developed a meningoencephalitis and died.

Brain autopsy: Brain weight after fixation 700 g. The convexities of both hemispheres were covered with large subdural flabby membranes with purulent accumulations between the two membranes. On the right side adhesions between the subdural membranes, leptomeninges and brain were present. The basal part of the dura of the anterior and medial cranial fossae was thickened and flabby, but without membranes. Horizontal sections through the brain revealed diffuse atrophy and sclerosis of the whole brain substance, including the basal ganglia, and there were purulent accumulations in the dilated ventricular system. The leptomeninges around the cerebellum and the brain stem were slightly thickened and blurred.

Histological examination showed pronounced inflammatory changes in the dura with marked proliferation of the inner capillary layer and formation of subdural connective tissue membranes in which inflammation was also present. This could also be seen in the leptomeninges which in some areas adhered to the subdural membranes. The cell infiltration consisted of lymphocytes, plasma cells, granulocytes and macrophages. Quite a few pial arteries were thrombosed, some with recanalisation.

The whole brain tissue was the seat of inflammation, encephalomalacia, gliosis, and spongy degeneration. Varying degrees of calcification were also present. The ventricles were filled with fibrin and granulocytes. Around the periventricular vessels cuffings of round cell infiltration were present. The severe inflammatory processes made it impossible to distinguish clearly the developmental abnormalities of the cortical grey matter and basal ganglia. Around the brain stem and cerebellum moderate leptomeningitis could be seen, and the aqueduct and fourth ventricle were filled with fibrin and granulocytes, but there were here no abnormalities in the parenchyma, except for oedema and stasis.

Comment: The subdural abscess was considered a complication of the subdural haematoma. This masked the primary lesion in the brain. It is impossible to decide whether we are dealing with prenatal and/or perinatal damage. The history and the child's appearance suggest both possibilities.

Case No. 58. Female, born August 1953, died aged 6 years and 2 months.

Clinical summary: Birth weight 3000 g. The mother had a narrow pelvis though delivery itself was uncomplicated. No neonatal asphyxia or jaundice was noted. Development was said to be normal until the age of seven months when the child developed a cold and otitis media, and following this had convulsions. The clinical diagnosis of encephalitis was made, but lumbar puncture was normal. She developed spastic tetraplegia which became progressively more pronounced, particularly in the arms. There was also widespread rigidity. PEG was performed and the ratio was 0·39/0·34. There was an abnormal amount of cortical air in the frontal area. At the age of eighteen months bilateral craniotomy was performed, and this revealed an old subdural haematoma. The subsequent course was characterised by lack of development, increasing rigidity and a small head circumference (at 3 years: 44 cm.). She died from pneumonia.

Brain autopsy: Brain weight 300 g. Diffuse atrophy and microgyri. The cerebellum and brain stem were normal (Fig. 15). On the cerebrum and at the base of the brain

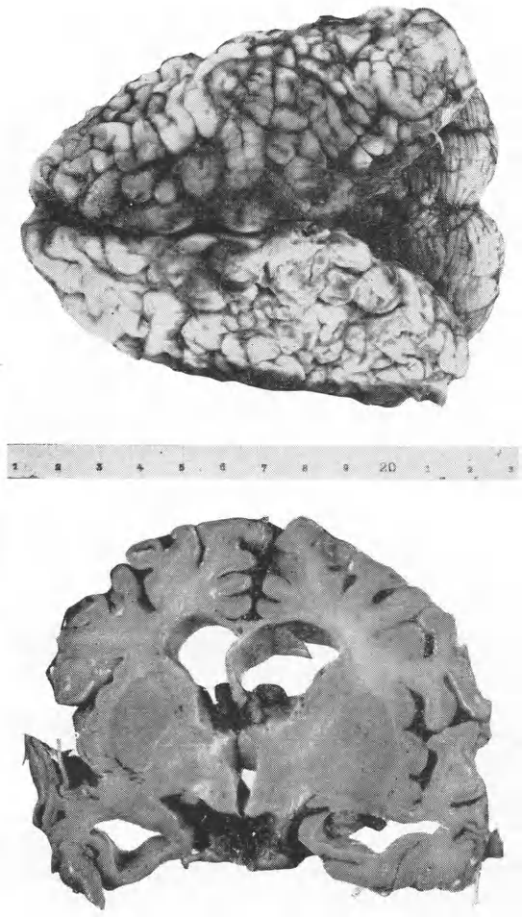


Fig. 15. Case 58; female 6 years 2 months old. Clinical diagnosis: spastic tetraplegia with rigidity, microcephaly, epilepsy and mental retardation—sequelae of bilateral subdural haematoma. Microcephaly and diffuse microgyria.

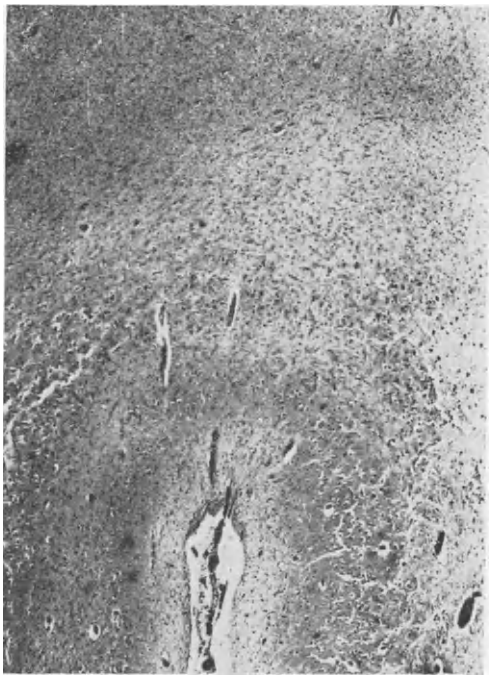


Fig. 16. Case 58 (see caption to Fig. 15). Coronal section of the brain showing microgyria and ventricular dilatation. Size approx 2:3.

Fig. 17. Case 58 (see caption to Fig. 15). Spongy degeneration and gliosis of the cortical grey matter. Mallory stain x 10.

there were reddish-grey subdural membranes and the dura was fibrosed and thickened. No pronounced thickening of the leptomeninges. Frontal section of the brain showed diffuse ventricular dilatation. The anterior horns measured 16 mm. diagonally and 13 mm. transversely. The third ventricle was 7 mm. at its widest point. The gyri were small and atrophic, and the sulci broad and deep. No cyst formation or haemorrhages were present (Fig. 16).

Histological examination: All around the cerebrum, outer and inner membranes from the subdural haematoma were present. The outer membrane was thicker than the dura and consisted of cellular connective tissue with proliferating tortuous capillaries and small perivascular haemorrhages with blood containing macrophages and fibroblasts. The inner membrane consisted of loose connective tissues and a few

vessels. In several places small islands of bone formation were present in the outer membranes. There were no signs of inflammation. Severe degenerative changes with ganglion cell degeneration and gliosis were present in the cortex (Fig. 17), but in the best preserved areas normal layer differentiation could be found, together with normally developed and preserved ganglion cells. Myelination was incomplete in the white matter and there was marked widespread glial proliferation. In the corpus striatum the ganglion cells were relatively well-preserved, and myelination was fairly good. No inflammatory changes were present. Normal myelination was present in the brain stem except in the area corresponding to the pyramidal tracts.

Comment: The neuropathological finding of a subdural haematoma without signs of inflammation supports a perinatal aetiology associated with a narrow pelvis. However, while no active signs of encephalitis were present at brain autopsy, the severe changes in the cortical grey matter suggest the sequelae of encephalitis, and as the patient first had symptoms from the age of seven months the subdural haematoma may be secondary to the cerebral inflammation.

Case No. 14. Female, born February 1951, died aged 3 years and 10 months.

Clinical summary: Birth weight 3650 g. Pregnancy and delivery uncomplicated. She had respiratory difficulties in the first hours of life. There was moderate jaundice lasting 3 weeks, but no signs of nervous disorder were noticed until the age of 7 months when she was found to be somewhat retarded in her motor development. On admission to the paediatric clinic at 15 months there was a marked spastic tetraplegia and rigidity with her legs in the scissor position. The head circumference was 42 cm. PEG revealed dilatation, ratio 0·42. She was severely mentally retarded and was transferred to an institution for the mentally retarded, where she died nearly 4 years old.

Brain autopsy: Brain weight after fixation 320 g. The brain was hydrocephalic. Both hemispheres consisted of thin membranes in the posterior half where no gyrus formation could be recognised. The frontal lobes, the precentral region and both temporal poles looked nearly normal. Neither the brain stem nor cerebellum showed any other gross abnormalities except for a moderately dilated aqueduct and fourth ventricle. Coronal sections revealed agenesis of the corpus callosum, partial absence of the septum pellucidum, and atrophy and sclerosis of the basal ganglia. However, it was possible to identify the internal capsules. The middle and occipital part of the lateral ventricles measured 50 mm. in transverse diameter, and here the brain tissue was only 1 to 3 mm. thick. The atrophy was most marked near the calcarinal fissures. The transverse diameter of the third ventricle was 15 mm. at the level of the massa intermedia. The brain stem appeared narrow, but the gross appearance of the cerebellum was normal.

Histological examination revealed slight infiltration with lymphocytes and macrophages in the oedematous leptomeninges. Otherwise no signs of inflammation could be seen. In the whole cortical grey matter there was a varying degree of deficiency of ganglion cells and reduction of the white matter. In the most atrophic parts practically no ganglion cells were found. Here the tissue consisted mainly of astrocytes.

The structure of the basal ganglia was also abnormal both with regard to the number of ganglion cells and to myelination, but marked gliosis was also present. The ventricular ependymal lining was normal. The myelination of the brain stem especially in the pyramidal tracts showed marked deficiency, and satellitosis occurred around many ganglion cells. The number of Purkinje cells in the cerebellar cortex was also clearly diminished. Otherwise no abnormalities could be found here, and there was no occlusion of the foraminae of Magendie and Luschka.

Comment: Both the macroscopical and microscopical examination of the brain pointed to a dysplasia occurring within the first half of foetal life (schizencephaly and agenesis of the callosal body). The gliosis was considered a secondary phenomenon due both to compression of the brain tissue and to anoxia caused by her poor physical state. Her poor perinatal condition was therefore considered a sequela of the maldeveloped brain and not of a primary perinatal anoxia.

Case No. 66. Male, born May 1961, died aged 3 years and 2 months.

Clinical summary: An older brother (63) died aged 2 years of a disease similar to this patient's. The only difference in the case history is that this patient developed both spastic tetraplegia and marked rigidity (Fig. 18), and in spite of the brother's history no neurological abnormalities were found until the age of 6 months.

Histological examination showed cortical cerebral and cerebellar dysplasia, but the number of ganglion cells was also reduced in the basal ganglia, in contrast to what was found in the brother's brain.

Comment: As in the case of his brother (63) no known aetiology except a familial disorder was found. In both cases the neuropathological findings showed a severe dysplasia of unknown type, explaining the severe tetraplegia and infantile spasms (Fig. 19). In this case involvement of the basal ganglia led to rigidity.

Case No. 21. Male, born September 1950, died aged 3 years and 7 months.

Clinical summary: Birth weight 3800 g. A younger brother developed the same disorder as the patient. There were no neonatal symptoms of neurological disorders. The development was normal. When two years old he developed an acute illness with general weakness and pain in his legs and left arm. He became sluggish and four days later was admitted to an infectious disease unit with a diagnosis of non-paralytic poliomyelitis. On admission the spinal fluid was normal. At the time of discharge three weeks later he was unable to sit or walk, but there was no evidence of paresis. A few days later he was admitted to the paediatric clinic, where he remained for 13 months and was there considered a case of postnatal cerebral palsy. On admission he had a spastic tetraplegia and later rigidity developed, and he showed an increasing tendency to an opisthotonic position. His vision decreased and at three years he was blind and had deteriorated mentally. He had frequent episodes of unexplained high temperature. EEG was normal on three occasions. PEG showed a dilated ventricular system. At three years and 7 months he died during a hyperthermic episode, at a hospital for mentally retarded children.

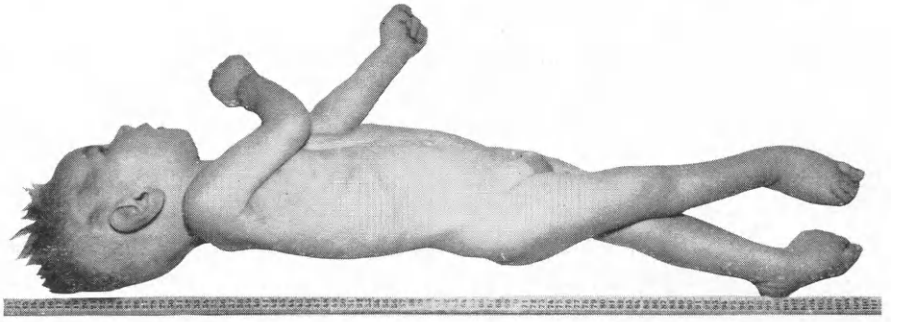


Fig. 18. Case 66; male 3 years 2 months old. Clinical diagnosis: spastic tetraplegia with rigidity, infantile spasms, mental retardation.

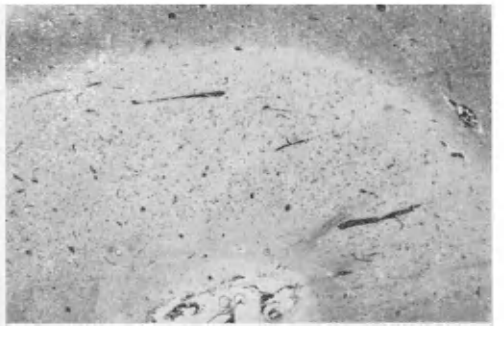


Fig. 19. Case 66 (see caption to Fig. 18). Narrowed cortical grey matter without visible layer formation. Mallory stain x 4·5.

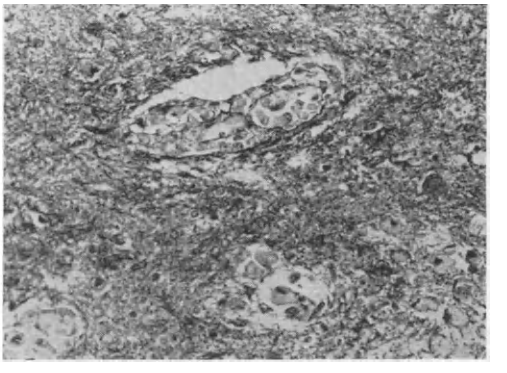


Fig. 20. Case 21; male 3 years 7 months old. Clinical diagnosis: spastic tetraplegia with rigidity, possibly sequelae of encephalitis, mental retardation. White matter from the corona radiata with myelin-degeneration and globoid cells diffusely spread and in perivascular clusters. H-E stain x 160. By courtesy of the Editor, *Acta neurol. Scand.*

Brain autopsy: Brain weight after fixation 950 g. Macroscopical examination showed irregular microgyria over the right occipital-temporal region. There were petechial subarachnoid haemorrhages, but otherwise no abnormalities on the surface of the brain. Coronal sections showed cortical atrophy corresponding to the areas of microgyria. Otherwise the cortical grey matter and basal ganglia were macroscopically normal. The white matter was granular and solid. There was an asymmetrical diffuse dilatation of the ventricular system, most pronounced in the right occipital horn. The brain stem was normal, but the white matter of the cerebellum was firmer than normal.

Histological examination of the brain showed that the cortical grey matter was normally developed, but the nerve cells were more or less atrophic with pycnotic nuclei. Almost total degeneration of the myelin sheaths was found in all parts of the white

matter including the basal ganglia and cerebellum except in the subcortical U-fibres. The neurofibrils were partly degenerated and marked proliferation of the astrocytes occurred, many of them being gemistocytic. Globoid cells were present especially around the vessels (Fig. 20). A number of lipid-containing macrophages could be seen. The oligodendroglial cells were degenerated, but showed no tendency to proliferation. Special stains of the white matter did not reveal extracellular lipid, but a small amount of neutral fat was present in the glial cells and a larger amount in the macrophages.

Comment: The acute and late onset of his disease in a period of an epidemic of poliomyelitis was the reason why this clinical diagnosis was suggested. The diagnosis of cerebral palsy was consequently made but the later course, as well as the similar disease in a younger brother, made a familial progressive encephalopathy more likely, and at autopsy the diagnosis of leucodystrophy of globoid cell type (Krabbe's disease) was made. (Published in detail by Christensen *et al.* 1960).

Discussion

In this group of 16 cases of spastic tetraplegia with rigidity (Table X) both degenerative and dysplastic involvement of the cortical grey matter were present as in the group of pure tetraplegia, but besides this, more pronounced lesions were found in the corpus striatum (porencephaly, gliosis and calcification). One would expect that the patients in this group with more diffuse alteration of the brain would die at an earlier age than the presumably less damaged group of pure tetraplegias, but the opposite is the case. A possible explanation might be that the autopsy findings do not necessarily represent the position at the time of birth. Gliosis and calcification of the ganglion cells can be considered as secondary changes which might lead to clinical progression over the years and by their localization to rigidity and cerebral hyperpyrexia.

Mental retardation was present in all cases, with I.Q. below 35 in seven. Only 9 of 16 patients had epilepsy. Familial incidence was present in 3 cases. Prenatal causes were possible in 4 cases, but only proved in two cases.

The finding of schizencephaly (hydranencephaly) in case 14 suggests early prenatal damage (Yakovlev and Wadsworth 1946) but here also there is a history of perinatal anoxia. The perinatal symptoms may be secondary to the prenatal existing brain damage or we may be dealing with two independent brain lesions (Minkowski 1952).

Two cases in this group were premature (Nos. 23 and 50). Cases 12 and 50 were twins. Case 12 also had a low birth weight (2500 g.). In none of these cases is there evidence of a prenatal lesion of the central nervous system.

The main causative factor is perinatal anoxia (Table X) which is in agreement with other authors (Rydberg 1932, Courville 1953, Gröntoft 1953). There is agreement between the peri- and postnatal aetiology and the finding of *pure degenerative changes* in 10 cases.

As lumbar puncture had not been carried out in the neonatal period it cannot be stated how many patients had subarachnoid haemorrhage or other forms of intracranial haemorrhage. This had been reported as a common phenomenon (Roberts

TABLE X

Tetraplegia with Rigidity

Case No.	*Sex*	*Age at death (years)*	*Aetiology*	*Symptoms observed from*	*Epilepsy*	*I.Q.*	*PEG*	*Brain weight g.*	*Pathological-anatomical findings*
23	f.	2 9/12	premature, perinatal? postnatal	4/12	infantile spasms	retarded	0·38	1150	Degeneration due to possible intoxication
41	m.	3 5/12	postnatal	5/12	grand+petit mal	<35	—	500	Polyporencephaly due to possible sinus thrombosis
30	m.	2 9/12	perinatal anoxia	0/365	not present	low	0·34	675	Polyporencephaly due to anoxia
35	m.	1	perinatal anoxia	0/365	grand+petit mal	low	0·76	340	Polyporencephaly due to anoxia
12	m.	1	prenatal infect. + perinatal anoxia, twin A	0/365	infantile spasms	low	0·42	760	Degeneration due to anoxia
38	m.	9/12	perinatal anoxia	0/365	not present	low	—	700	Degeneration due to anoxia (subdural haematomas)
44	m.	1 7/12	unknown	0/365	grand mal	<35	0·41	400	Degeneration due to anoxia
48	m.	7/12	perinatal anoxia	0/365	not present	retarded	—	750	Degeneration due to anoxia
50	f.	12	perinatal anoxia premature, twin	0/365	grand mal	<35	—	1200	Degeneration due to anoxia
58	f.	6	birth trauma	7/12	grand mal	<35	0·37	300	Degeneration due to subdural haematomas
14	f.	3 10/12	perinatal anoxia	0/365	not present	<35	0·42	320	Dysplasia, early
24	m.	19	unknown	8/12	grand mal	<35	—	1050	Dysplasia
40	f.	15	precipitated delivery	3/12	not present	low	0·33	1100	Dysplasia
66	m.	3	familial disp.	6/12	infantile spasms	retarded	0·39	1025	Dysplasia
21	m.	3 7/12	familial disp.	24/12	not present	<35	0·32	950	Leucodystrophy, globoid type
61	m.	8/12	prenatal hyperemesis	5/12	not present	retarded	0·39	1000	Leucodystrophy, metachromatic type

1939). In our case histories, however, perinatal anoxia rather than intracranial haemorrhage is the common finding. This corresponds to Rydberg's conclusions (1932), that it is more compression of the head and secondary anoxia than a primary brain lesion (including primary intracerebral haemorrhage) which gives rise to cerebral palsy. Perinatal birth trauma is the most likely explanation of the origin of the subdural haematoma in case No. 38. As this patient had severe anoxic changes in the brain these circumstances explain the fact that the prognosis in patients with chronic subdural haematoma depends on the state of the brain (Ingraham and Heyl 1939, Ingraham and Matson 1944, Christensen and Husby 1963).

Dysplastic changes were found in six cases, two of them leucodystrophies.

In one case (14) there is a history of perinatal anoxia but the neuropathological examination revealed only dysplastic changes. In 2 further cases of dysplasia there was a late onset of the clinical symptoms after 3 but before 24 months and no history of perinatal anoxia. The same was found in the two cases of leucodystrophy. Only one case of cerebral dysplasia with a marked microcephaly had permanent symptoms dating from birth. This observation of a symptom-free period after birth in most patients with dysplasia corresponds to the finding of Benda (1960).

It is an interesting observation that a severe post-natal infection of unknown origin (case No. 41) has given similar clinical symptoms of cerebral palsy and neuropathological changes as perinatal anoxia. The explanation must be that the brain reacts in the same way until development of the central nervous system is complete. This is in agreement with Hallervorden (1952) who stressed that maturation of the nervous system is of major importance and that the brain is peculiarly vulnerable before that time.

The abnormalities of the basal ganglia are limited to the corpus striatum without involvement of the subthalamic nucleus or other nuclear masses such as the olives or dentate nucleus. This corresponds with the fact that no case of kernicterus exists in this group. The findings in the basal ganglia do not correspond to any of the entities described by C. and O. Vogt (1911, 1924), but must be considered as more uncharacteristic degenerations (Malamud 1950).

Conclusions

In cases of tetraplegia with rigidity the neuropathological findings in the cortical grey matter are similar to the cases with pure tetraplegia, but the findings in the basal ganglia are distinct. The corpus striatum is involved in all cases where rigidity is found.

SPASTIC HEMIPLEGIA

The spastic hemiplegia group consists of 10 patients, of whom 6 had a 'pure' hemiplegia and 4 were mixed but, as explained earlier, presented largely with asymmetry.

Age at Death	*girls*	*boys*
< 1 year	1	1
1 - 2 years	0	2
2 - 5 years	0	2
5 - 15 years	3	0
> 15 years	1	0

With this group we discuss our one case of spastic monoplegia. This is a rare condition (Crothers and Paine 1959, 0·4 per cent: Ingram 1964, no cases) and it is often and probably correctly regarded as being an example of a mild case of hemiplegia.

Our patient (19) had a history of prolonged labour and jaundice. At the age of one year he had febrile convulsions and later afebrile seizures. Before the age of 3 years weakness of the right leg was noticed and on admission a spastic monoplegia was found. PEG showed diffuse dilatation of the ventricular system. When 7 years and 9 months old he had mumps and his condition deteriorated. A cortical biopsy showed subacute meningitis. As he showed signs of increased intracranial pressure a ventriculostomy was performed on two occasions. At necropsy the acute widespread damage done by a purulent meningoencephalitis unfortunately made it impossible to elucidate the basic neuropathological changes in this single case of monoplegia.

Family History

There was only one case in this group with a positive family history (No. 28).

Other Causation

A possible pre-natal cause for the condition was present in two cases where the mothers had both had pyelonephritis during pregnancy.

There was a history of possible perinatal damage in 5 cases.

A postnatal infection was thought to be the cause of the condition in one case. In three cases the aetiology was unknown until shortly before death or at autopsy.

Clinical Findings

There were six cases with *pure hemiplegia* (No. 13, 20, 28, 57, 65, 68). All had normal head circumferences. Intelligence was normal in 3 cases, undetermined in 2 and below 35 in case 68. Only cases 57 and 68 had epilepsy. The EEG was initially abnormal in three cases but in two others it altered and became severely abnormal. In one case it was always normal. PEG was carried out in all six cases and in one there was no filling of the ventricular system (this patient later proved to have a tumour). There was dilatation in 5 cases and in 3 there was marked asymmetry.

There were four cases with a *mixed clinical picture* (No. 6, 7, 16, 47). They all had a combination of spastic tetraplegia and hemiplegia and in cases 7 and 47 there were also signs of athetosis. They are placed in this hemiplegic group because of the marked asymmetry in their clinical signs. This gave the impression that they were predominantly cases of hemiplegia.

Only one case had a small head circumference (No. 7). The I.Q. was below 35 in two cases. In the other two it had not been determined but there was definitely retardation in one of these cases. All four cases had grand mal epilepsy, and the EEG was abnormal with focal changes in the three patients in which it was performed. PEG showed diffuse dilatation in the two cases in which it was performed.

Neuropathological Findings

Pure Hemiplegia

The six patients with pure hemiplegia showed very definite neuropathological changes which had not been accurately diagnosed during life. In three of these cases (Nos. 13, 20, 65) a benign glioma was present involving part of one hemisphere and the basal ganglia on the same side.

Case no. 28 had a cyst involving the subcortical white matter and cortex in the middle third of the left hemisphere (Fig. 22) with severe atrophy of the basal ganglia on that side (cf. p. 58).

The last two cases (57, 68) of pure hemiplegia both showed an atrophy of one hemisphere including the motor cortex and the corpus striatum on the same side, associated with degeneration of the ipsilateral pyramidal tract. One of these, No. 68, had a history of postnatal purulent meningitis and apparently a septic thrombosis in the right carotid artery.

Mixed Group

In these four cases neuropathological examination revealed, as would be expected from the clinical findings, widespread but asymmetrical abnormalities.

In case 16 a marked microcephaly was present as the only gross abnormality. Histological examination revealed diffuse severe ganglion cell degeneration and gliosis in all regions of the basal ganglia and the dentate nuclei and olives. In the cortical grey matter, including the motor region, only a moderate degeneration of ganglion cells was found. The lesions were not clearly asymmetrical.

In case No. 6 macroscopical examination of the brain showed only a slight ventricular dilatation. Histological examination revealed both a cortical dysplasia of the brain and cerebellum and secondary gliosis. No abnormalities were found in the basal ganglia in this case.

The last two cases of the mixed hemiplegic group (Nos. 7, 47), who clinically also had athetosis, had an asymmetrical cortical pachygyria, regarded as a maldevelopment, and diffuse gliosis of the basal ganglia (in case 47 predominantly of the globus pallidus). This last finding, in combination with the degenerative changes in the dentate nuclei in both of these cases, supports the view that we are here dealing with lesions following kernicterus.

In case 16 cerebellar abnormalities were also present but only as a deficiency in the formation of secondary cortical folia.

From this survey it can be seen that all cases both in the pure and mixed group, except one (No. 6), showed involvement of the basal ganglia which was worse on the relevant side.

Case Reports

Case No. 28. Male, born October 1958, died aged one year and 3 months.

Clinical summary: Birth weight 3000 g. A brother who was 2 years older had an asymmetric spastic tetraplegia. In the brother's case PEG had shown that the median

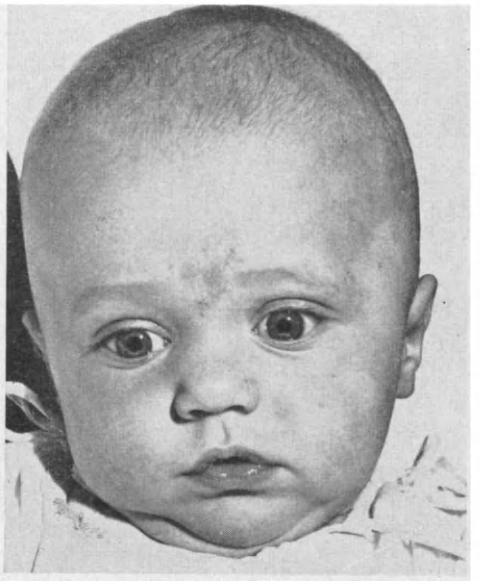


Fig. 21. Case 28; male one year 3 months old. Clinical diagnosis: right-sided spastic hemiplegia. Aplasia of the left hemisphere.

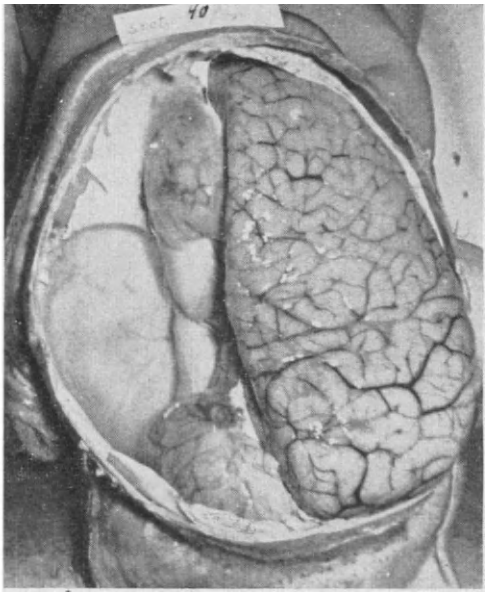


Fig. 22. Case 28 (see caption to Fig. 21). Brain *in situ* with subtotal aplasia of the left hemisphere due to anomaly of the circle of Willis. Size approx. 1:2.

third of one hemisphere was lacking. In both children pregnancy and delivery were uncomplicated. The patient was slightly jaundiced from birth until 6 to 8 weeks of age. No immunization was present. It was noticed from birth that he did not use the right hand and it was always closed. He was examined in the paediatric clinic at 6 months old, and a spastic hemiplegia was diagnosed. EEG showed severe abnormalities on the left side and he was transferred to the neurosurgical department where a craniotomy revealed total aplasia of the left hemisphere. During the following 9 months he made some progress in spite of the hemiplegia. He had no seizures. There was only slight asymmetry of the face and the head circumference was normal (Fig. 21). Six days after the last clinic visit he became suddenly ill with episodes of paleness, screaming and flexion of the legs. On admission he was semiconscious and shortly afterwards he died.

Brain autopsy: Brain weight after fixation 850 g. The right hemisphere was normal; in the left hemisphere the paramedian portion of the parieto-occipital lobe was normal, but in the frontal pole micropolygyria was present. The whole middle part of the hemisphere including the island of Reil consisted of a one mm. thick membrane (Fig. 22). The circle of Willis revealed gross abnormalities on the left side as only one short hypo-plastic artery replaced the middle cerebral artery. The posterior cerebral artery was absent. Coronal sections showed severe atrophy of the basal ganglia, the corpus callosum and the septum pellucidum on both sides. The right hemisphere and cerebellum showed no gross abnormalities, but the left half of the brain stem exhibited aplasia of the pyramidal tract.

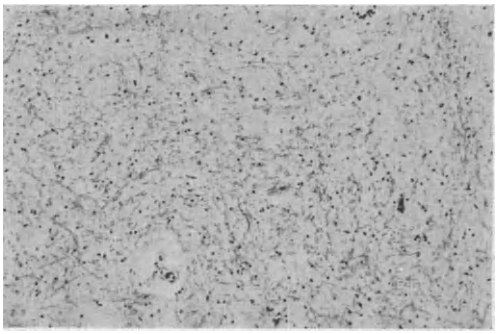


Fig. 23. Case 57; male 8 months old. Clinical diagnosis: left-sided spastic hemiplegia. Hypoglycaemia. Globus pallidus with status dysmyelinatus. Weil myelin stain x 40.

Histological examination showed, in accordance with the macroscopical findings, hypoplastic and aplastic areas in the left hemisphere and basal ganglia, but no signs of inflammation or tumour.

Comment: The right-sided spastic hemiplegia and the neuropathological findings, with maldevelopment of the circle of Willis and secondary subtotal aplasia of the left hemisphere, are in close agreement. But no explanation can be given of the occurrence of a familial vascular malformation. He had no seizures.

Case No. 57. Male, born May 1950, died aged 8 months.

Clinical summary: Birth weight 4150 g. The mother had pyuria during pregnancy. The delivery was normal. He suffered from convulsions from the age of three months. PEG at the age of five months showed a ratio of 0·36/0·33. As the seizures were thought to be of hypoglycaemic origin an exploratory laparotomy was performed, but no islet cell tumour was found. From the age of 7 months a moderate spastic hemiplegia on the left side was noticed, most pronounced in the arm. Head circumference was 45 cm. He died 8 months old and autopsy revealed bronchopneumonia and empyema.

Brain autopsy: Brain weight after fixation 650 g. In the right precentral region there was shrinking of the medial and inferior gyrus and also atrophy of the right central gyrus. In the pituitary fossa a bulging of the third ventricle could be seen behind the optic chiasma. Otherwise the cerebrum, brain stem and cerebellum were macroscopically normal. The leptomeninges only appeared a little thickened. Coronal sections revealed moderate dilatation of the ventricular system, more of the right than of the left anterior horn. The third ventricle and aqueduct appeared dilated. No macroscopical abnormalities could be seen in the basal ganglia.

Histological examination showed incomplete layer formation and immature ganglion cells of the cortical grey matter, and focal cortical gliosis and atrophy of the ganglion cells, most pronounced in the motor region and cortex of the insula on the right side. The basal ganglia revealed degeneration with gliosis and atrophy of the ganglion cells in the caudate nuclei, and status dysmyelinatus, which means a

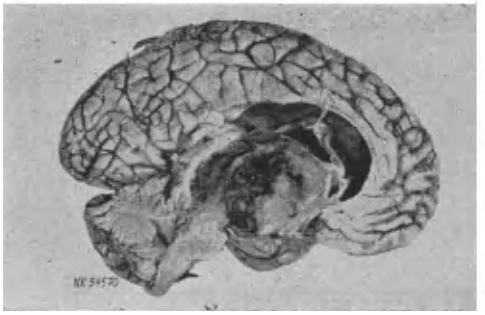


Fig. 24. Case 65; female 17 years 6 months old. Clinical diagnosis: right-sided spastic hemiplegia. Ventriculocisternostomy performed. Sagittal section through the brain showing an encapsulated tumour filling the third ventricle. Size approx. 1:3.

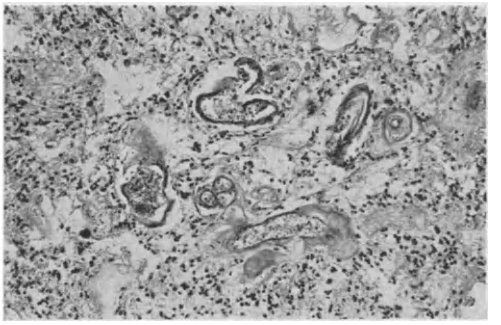


Fig. 25. Case 65 (see caption to Fig. 24). Ependymoma of third ventricle. Van Gieson stain x 60.

diminished number of ganglion cells, and poor myelination of the putamen and globus pallidus on both sides (Fig. 23).

Comment: The aetiology is unknown. There is no history of perinatal asphyxia. His spastic hemiplegia was first noticed from the age of 7 months. We consider both the hypoglycaemic seizures and the spasticity as related to brain damage of unknown origin. Histological examination points both to maldevelopment and anoxic changes — most likely a subclinical anoxia due to hypoglycaemia. Most of the neuropathological findings with ganglion cell atrophy and gliosis are of degenerative character both in the cortical grey matter and basal ganglia, whereas the incomplete layer formation in the cortex points to maldevelopment (Etheridge and Millichap 1964, Melchior *et al.* 1967. This case is published in detail by Brandt *et al.* 1952).

Case No. 65. Female, born July 1946, died aged 17 years and 11 months.

Clinical summary: Birth weight 3350 g. Pregnancy and delivery were normal. She developed normally until the age of 2 years when she had a spell of pallor lasting 30 minutes. After that it was noticed that she did not use her right hand as much as previously. At the age of 3 years it was noticed that the right foot was not functioning as well as before. She was treated as a spastic hemiplegic from that time. At the age of 6 years she was admitted to the paediatric clinic after several periods of vomiting. Besides spastic hemiplegia, papilloedema was found, and the question of a space-occupying lesion was raised. In the neurosurgical department a severe dilatation of the ventricular system was found on ventriculography, and as an intermittent block of the aqueduct, possibly due to a tumour of the pons, could not be excluded, a Thorkildsen's operation with ventriculocisternostomy was performed. This diagnosis was withdrawn as during the next 10 years her condition was good and there was improvement of the spastic hemiplegia. She left normal school at the age of 16 years and spent the next year at a high school. Her condition was satisfactory until 2 months before death, when she had vomiting and headache. She was re-admitted to the neurosurgical department with the suspicion of a tumour, and operation revealed an ependymoma of

the third ventricle invading the left corpus striatum and mesencephalon. She died in the postoperative period.

Brain autopsy: Brain weight after fixation 1900 g. The brain was oedematous with flattened gyri on the convexity and with a drain in both the left postcentral region and the left side of the vermis. On the basal side tumour nodules bulged out on the floor of the third ventricle, more on the left than on the right side. The brain stem was displaced to the right. Sagittal sections revealed an encapsulated tumour filling the whole third ventricle compressing the left corpus striatum (Fig. 24). Invasion into brain tissue could only be verified in the left side of the mesencephalon. Both lateral ventricles showed marked dilatation. No macroscopical abnormalities could be seen in the cerebellum or fourth ventricle.

Histological examination showed a normal picture in the cortical grey matter, right basal ganglia and cerebellum. The left corpus striatum was compressed but without ingrowth of tumour. Tumour tissue from the third ventricle was moderately vascularized and contained cells of ependymal origin radiating from the vessel walls with fibrils attached to the walls. The tumour cells were small and contained round nuclei (Fig. 25). No mitosis could be seen, but in places multinucleated cells and small necrotic areas were present. These last findings were considered as sequelae of the X-ray treatment. In the periphery of the tumour some proliferation of astrocytes was present, especially in the mesencephalon.

Histological diagnosis: Ependymoma of the third ventricle compressing the left corpus striatum.

Comment: In this case the tumour must have been present from early childhood, although it was impossible to prove it, but the ventriculocisternostomy and the location of the tumour, together with its benign character and slow growth, made the clinical course particularly prolonged.

Discussion

The six patients with pure hemiplegia differ from all other patients in this series, as they had changes localised to one hemisphere (Table XI). Three of these patients had benign tumours, one a post-infectious brain disorder, one a vascular malformation, and one (No. 57) a developmental abnormality and degeneration. The history of this case was complicated. He had hypoglycaemic attacks of unknown origin, and his seizures were thought to be due to hypoglycaemia.

In the four cases where hemiplegia was present with a general picture of spastic tetraplegia, there was perinatal damage which could have led to the diffuse degenerative changes and to the tetraplegia. The hemiplegic component can be explained as due to asymmetry in the changes in the two hemispheres, and the dysplastic changes (pachygyria) which were also present were much more pronounced in the hemisphere corresponding to the hemiplegia.

The incidence of hemiplegia is much higher in clinical material of cerebral palsy than in this autopsy series. In Hansen's Danish material 41·9 per cent of the spastic group had hemiplegia, and in Ingram's (1964) Scottish material, around 40 per cent. In the present autopsy series the hemiplegic group only amounts to 14 per

TABLE XI

Hemiplegia

Clinical picture	*Sex*	*Case No.*	*Age at death (years)*	*Aetiology*	*Symptoms from*	*Epilepsy*	*I.Q.*	*PEG*	*Brain weight g.*	*Pathological-anatomical findings*
Pure hemiplegia	f.	13	8	unknown	4 years?	—	normal	left: 0·35	1600	Astrocytoma in right hemisphere
Pure hemiplegia	m.	20	3 4/12	unknown	6/12	—	normal	no filling	unknown	Polar spongioblastoma in right hemisphere*
Pure hemiplegia	f.	65	17 11/12	unknown	2 years	—	normal	0·90	1900	Ependymoma of third ventricle
Pure hemiplegia	m.	28	1 3/12	familial perinatal	birth	—	undetermined	0·50/1·00	850	Aplasia of the left hemisphere
Pure hemiplegia	m.	57	8/12	unknown	3/12	grand mal	"	0·35	650	Dysplasia and degeneration especially of right hemisphere
Pure hemiplegia	m.	68	3 6/12	meningitis	5/12	infantile spasms	<35	0·50/0·41	890	Polyporencephaly of the right hemisphere
Hemi+tetraplegia +athetosis	f.	7	14 6/12	perinatal	birth	grand mal	<35	0·33	1300	Dysplasia and degeneration
"	m.	47	1 8/12	perinatal	birth	grand mal	retarded	0·36	1080	Dysplasia and degeneration
Hemi+tetraplegia	f.	16	7/12	perinatal	birth	grand mal	undetermined	—	500	Degeneration
"	f.	6	14 10/12	perinatal premature	birth	grand mal	<35	—	1150	Dysplasia and degeneration

*According to Zülch and Christensen (1956), Russell and Rubinstein (1959), Bailey and Cushing (1926) the polar spongioblastoma is a relatively benign tumour of young subjects arising in brain stem, third ventricle and cerebellum. It is composed of well-fibrillated uni-bipolar cells which form intersecting bundles.

cent. The reason for this is of course that hemiplegic patients survive for a long time (Glenting 1963). A large autopsy series of hemiplegic patients does not exist.

It is striking that three patients had gliomas. From a critical point of view it could be claimed that these three patients should have been excluded from the cerebral palsy material but it has to be emphasized that the progression of the symptoms was so slow that the tumour diagnosis was first verified shortly before death or at autopsy.

Hansen (1960) mentions that 6 patients in his material of cerebral palsy patients had gliomas and that he therefore excluded them from his material. The fact that gliomas are not usually mentioned in discussion of the aetiology of cerebral palsy is of course because most authors' definition of cerebral palsy excludes tumours (Little Club 1962). As Ingraham and Matson (1954) state, spastic hemiplegia is not an uncommon finding in patients who have cerebral gliomas (see also Low *et al.* 1965) and most clinical series of spastic hemiplegia probably contain cases of tumour. It would seem to us wrong to exclude these cases from a clinical series *retrospectively* because of autopsy findings and it is for this reason they are included in this series.

In our series one patient only (No. 68) had a venous thrombosis following meningitis at the age of 5 months, although Mitchell (1952) finds it commonly in association with hemiplegia. He states that it occurs (1) following acute infections, (2) with local infection such as mastoiditis or sinusitis and (3) in apparently healthy children. There is only one brain autopsy in his series of 11 patients, but he concludes both from his clinical findings and from a study of the literature that venous thrombosis is a common cause of acute hemiplegia in children. The course may be fatal in cases of thrombosis of the longitudinal sinus. He also mentions syphilitic endarteritis as a cause of hemiplegia. Syphilitic infections did not occur in our series. Intracranial vascular malformations were present in one case (No. 28.) In a previous paper Christensen and Brandt (1959) have reported a case of spastic hemiplegia caused by a ruptured intracerebral angioma.

Conclusion

Any post-mortem series of hemiplegics is bound to be unrepresentative as most of these patients survive for a long time.

We have included in this series the 3 cases where tumours were found. These cases emphasize the importance of considering this diagnosis in any case of pure hemiplegia, however long the clinical history might be. This is particularly so when there is no history to suggest another aetiology.

In 'pure' hemiplegias the lesions are localized to one hemisphere whereas in the mixed cases the lesions are widespread, but asymmetrical.

SPASTIC PARAPLEGIA AND DIPLEGIA

Five patients had paraplegia (26, 31, 46, 49, 64), two boys and three girls.

Age at Death	*girls*	*boys*
< 1 year	0	1
1 - 2 years	0	0
2 - 5 years	2	0
5 - 15 years	1	1

Of considerable diagnostic interest was a child who for a long time showed weakness and neurological signs in the lower extremities which suggested mild cerebral palsy. For a time he formed part of this clinical series. However, the paresis progressed in the legs and the dominant symptoms became weakness and pseudohypertrophy. A muscular biopsy confirmed the diagnosis of progressive muscular dystrophy. He died aged 12 years and 9 months and the brain autopsy showed a diminished number of pyramidal cells, but otherwise only minor changes. This patient will be reported in detail in a later publication and contributes to the present discussion of central nervous system involvement in progressive muscular dystrophy (Dubowitz 1965, Zellweger and Niedermeyer 1965).

Possible Causation

A family history was positive in three cases. In case 46 the mother's sister had spina bifida and hydrocephalus. Case 49 had a younger sister who was mentally retarded with congenital malformation of the eyes. Case 64 had a sister with a mild spastic tetraplegia. Two of these patients had also had difficult deliveries. One (46) was delivered by forceps due to foetal distress. The other (64) was a breech presentation. Case No. 26 had a precipitate delivery without any professional assistance. No case of perinatal disease was found. Surprisingly only one patient (46) had a birth weight below 2500 g. (2400 g.) The aetiology was unknown in one case (31) where the symptoms were first noticed at one year of age.

Clinical Findings

The head circumference was normal in all cases. I.Q. was below 35 in one case, between 35-55 in three cases and apparently normal in one case. Epilepsy was present in two cases (26, 31), who both had grand mal and petit mal. The EEG showed diffuse abnormalities in these two cases. Normal EEG was found in the other three patients.

PEG was performed in four cases — it was normal in one patient (64) and diffuse dilatation of the ventricular system was found in the other three.

Only in one case (64) was the clinical picture pure paraplegia. In the remaining four cases there was a spastic tetraplegia of the diplegic type with most marked findings in the lower extremities. In one case there was also athetosis.

Neuropathological Findings

Microcephaly was found in two cases, one with polyporencephaly (26) and one with severe cortical dysplasia (46), and normal brain weight in the remaining 3 cases. Cortical abnormalities, especially in the motor region, were found in all 5 cases. Three (31, 46, 49) were dysplasias with micropolygyria (Fig. 26).

In the other cases (26, 64) the findings were of a degenerative character. No. 26 had polyporencephaly (Fig. 27), and case 64 had degenerative lesions with laminar necrosis of the motor cortex on both sides, but in addition severe post-traumatic myelopathy was found due to a lesion in the cervico-thoracic spine with ascending tract degeneration. Two patients had lesions of the basal ganglia. Of these one (No. 26), who had clinical signs of athetosis, had porencephaly and No. 31 had periventricular

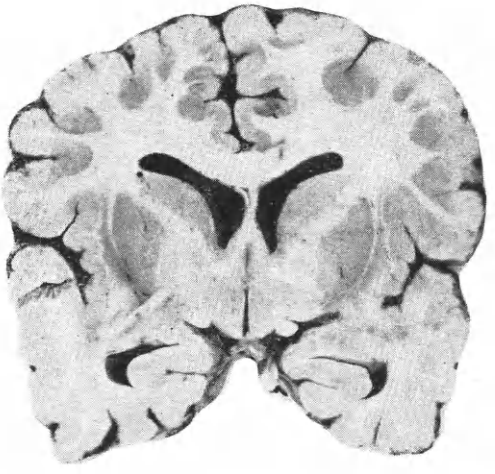


Fig. 26. Case 46; female 9 years old. Clinical diagnosis: spastic tetraplegia with predominant involvement of the legs, microcephaly and mental retardation. Coronal section through the brain showing pachy- and microgyria with deficiency of secondary gyri formation. Size approx. 3:5.

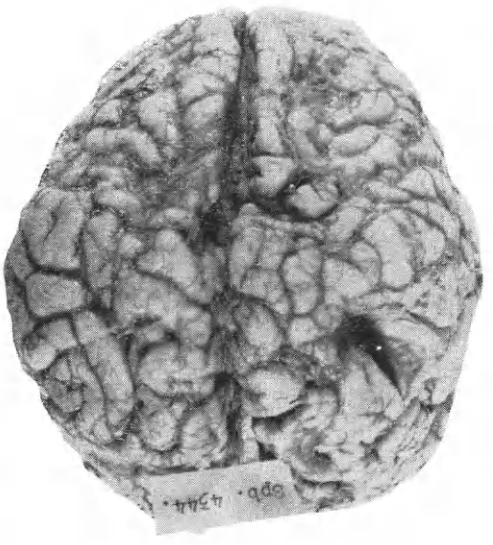


Fig. 27. Case 26; female 3 years 9 months old. Clinical diagnosis: spastic tetraplegia with predominant involvement of the legs, microcephaly and mental retardation. Brain seen from above, with cortical atrophy corresponding to the porencephalic areas. Size approx. 1:2.

gliosis of the caudate nuclei only. Dysplastic changes were present in the cerebellum in cases 49 and 31.

Degeneration of the pyramidal tracts was seen in two cases (26, 64), as a consequence of a lesion of the motor cortex.

Case Reports

Case No. 64. Male, born October 1960, died aged 7 months.

Clinical summary: Birth weight 3100 g. The sister had mild spastic tetraplegia. Pregnancy was normal. The delivery was a breech presentation without complications. For the first two days the infant was apathetic and generalised oedema developed. He became increasingly lethargic and had abdominal respiration only. On the fifth day he was referred to the paediatric clinic. On admission generalised hypertonia was present. Within a few days the arms were almost rigid. In less than two weeks Moro's reflex and the grasping reflex disappeared but sucking reflexes and primary walking reflexes persisted. Paradoxical respiration was present and continued for 2 weeks. Less than a month after birth mobility of the legs improved and the hypertonia diminished. Later hypotonia of the legs developed. He often assumed an opisthotonic position. Throughout hospitalisation his respiration remained inadequate, and generally of an abdominal character. The thoracic respiratory muscles seemed to be paralysed. Episodes of oedema, cyanosis, and fever of unknown origin occurred intermittently. PEG was normal. EEG was slightly abnormal. He died aged seven months.

Autopsy of spinal cord and brain: Incision of the spinal dura mater exposed a 15-20 mm. long narrowed area of spinal cord in the lower cervical and upper thoracic region. The leptomeninges were greyish, hypertrophic and adhered both to the dura and the atrophic spinal cord.

The cut surface of the spinal cord at this level revealed soft tissue without the normal patterning. No vascular changes were found. Examination of the brain showed no other abnormalities than focal superficial degeneration in the pre-central cortical areas on both sides. These consisted of about 4 areas of brown-stained softened brain tissue.

Histological examination of the motor cortex revealed small areas of a reticular structure with a few accumulations of macrophages rich in lipid, and blood pigment. Here the nerve cells had disappeared and astrocyte proliferation, occasionally diffuse, was seen (Fig. 28). At the site of these processes isolated macrophages containing blood pigment were present in the leptomeninges. The spinal cord was completely demyelinated and normal nerve cells were absent (Fig. 29) in the macroscopically abnormal part. The tissue contained numerous small cysts and consisted of astrocytes and connective tissue forming islands of dense cicatricial tissue. The hypertrophic leptomeninges extended as fine strands into the posterior and lateral funiculi. Rostral to the lesion the spinal cord showed demyelination both in the posterior and the lateral funiculi (Fig. 30), and the lower thoracic and lumbar segments showed demyelination in the lateral and anterior pyramidal tracts.

Comment: The neuropathological findings indicate that this is not a congenital malformation but a perinatal lesion of the brain and spinal cord. The lesion of the motor cortex has caused the pyramidal tract degeneration rostral to the involvement of the spinal cord. All other findings were pathognomic of a transverse lesion of the spinal cord produced by the breech delivery. (Reported by Melchior and Tygstrup 1963).

Case No. 49. Male, born June 1953, died aged 9 years 4 months.

Clinical summary: Birth weight 3400 g. He was the fifth of six pregnancies. The second was aborted in the second month, and the fourth was stillborn following prolapse of the umbilical cord. The sixth child is blind and mentally retarded. The pregnancy and delivery were uncomplicated. From the age of one month it was noticed that the eye movements were abnormal, and later it was found that he only saw very near objects. When he was admitted to the paediatric clinic at one year and 10 months of age, he could not speak and could only sit very poorly with support. The legs were spastic. PEG showed cerebral atrophy, ratio 0·45. EEG was normal. He was placed in a home for mentally retarded children and lived in an institution from the age of 6 years until he died. Latterly he was unable to use his hands normally. In the arms the muscle tone was decreased whereas the spasticity of the legs was severe and there were contractures. He developed a left-sided cataract, which was treated surgically. Tests for galactosaemia were negative. He died when he was being prepared for a second operation on his cataract.

Brain autopsy: Brain weight after fixation 1325 g. Macroscopical examination revealed diffuse micropolygyria. Only the upper parts of vermis cerebelli were present (Fig. 31). Coronal sections showed a failure of secondary gyrus formation (Fig. 32).

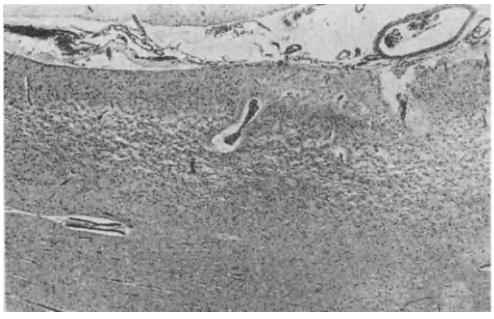


Fig. 28. Case 64; male 7 months old. Clinical diagnosis: myelodysplasia. Motor cortex with marked subpial gliosis, atrophy of the ganglion cells and spongy degeneration. Van Gieson stain x 16.

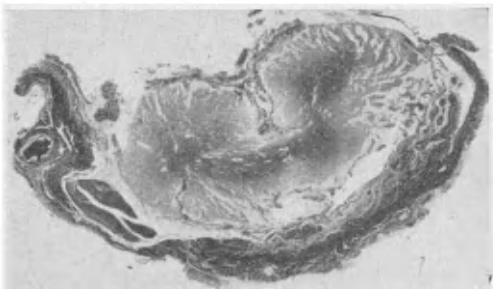


Fig. 29. Case 64 (see caption to Fig. 28). Horizontal section through the tapering area of the spinal cord showing very pronounced degeneration and fibrosis of the leptomeninges. Weil's stain x 8.

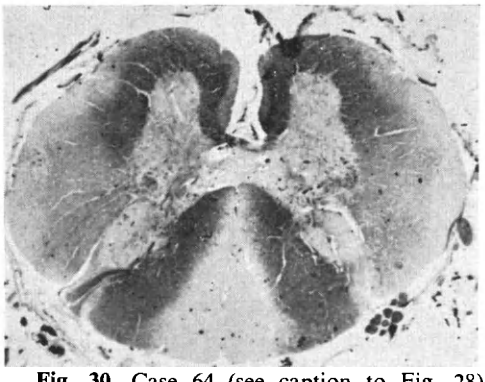


Fig. 30. Case 64 (see caption to Fig. 28). Cervical part of the spinal cord rostral to the tapering area. Degeneration of the pyramidal tracts and of the medial part of the posterior funiculi. Weil's stain x 8.

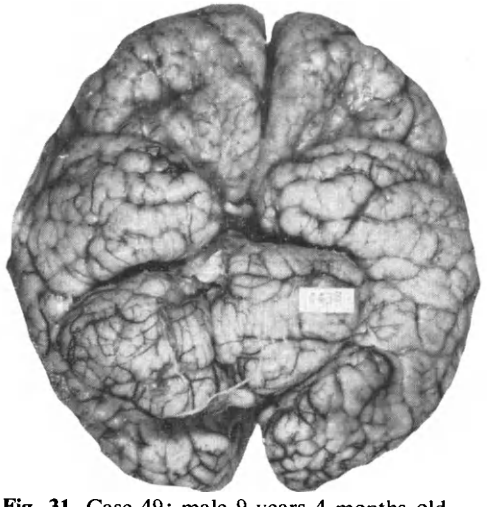


Fig. 31. Case 49; male 9 years 4 months old. Clinical diagnosis: spastic tetraplegia with predominant involvement of the legs. Mental retardation, cataract. Brain seen from below with pronounced micropolygyria and deficiency of cerebellar vermis. Size approx. 3:5.

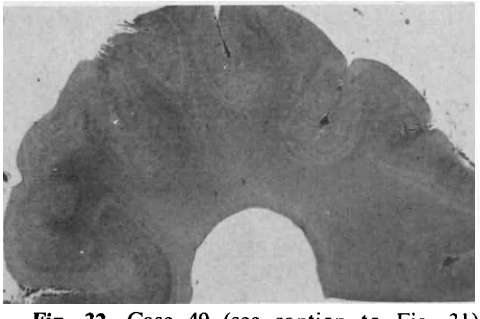


Fig. 32. Case 49 (see caption to Fig. 31). Maldevelopment of gyri from frontal and occipital region with micropolygyria. Mallory's stain x 4·5.

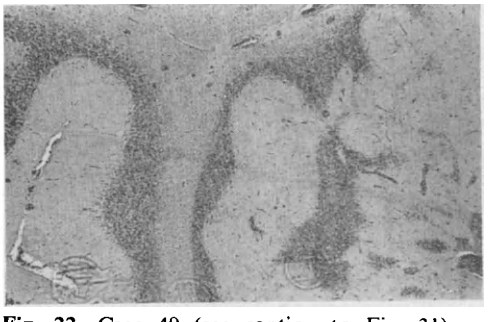


Fig. 33. Case 49 (see caption to Fig. 31). Maldevelopment of cerebellum with deficiency of secondary folia formation, Purkinje cells and granular layer. Einarsson's stain x 4·5.

Histological examination: Cortical lamination was incomplete and most of the nerve cells in the cortical grey matter were not fully developed. The abnormalities of the cerebellar folia were of the same character, as both the Purkinje cells and the granular layer were poorly developed in the hypoplastic secondary folia (Fig. 33). Besides these developmental abnormalities subpial gliosis was present in the brain. No histological abnormalities could be found in the basal ganglia, brain stem and dentate nuclei.

Comment: The mother had a poor reproductive history. A sibling was blind and mentally retarded. This case had no symptoms of perinatal asphyxia but he first showed neurological symptoms at one month. The neuropathological findings of a dysplastic brain character are in accordance with a prenatal lesion, but we are unable to state the exact nature of this.

Case No. 46. Female, born March 1947, died aged 9 years.

Clinical summary: Birth weight 2400 g. A maternal aunt had myelomeningocele and hydrocephalus. The pregnancy was uncomplicated, but delivery was difficult and forceps were used. By the age of 3 months development was noticed to be slow, and at the age of 8 months she was admitted to the University Clinic of Paediatrics. At that time she could not sit alone or keep her head upright. The neurological examination suggested paraplegia, but tone was at that time not increased. Later spasticity of the lower extremities was obvious, and when she was examined at the age of 6 years spasticity of the arms was also definite. Her mental development was much retarded, and she was placed in a state institution when she was just under 8 years old, where she stayed until her death one year later.

Brain autopsy: Brain weight after fixation 800 g. The brain appeared small with pronounced microgyria especially on both parieto-occipital lobes. No thickening of leptomeninges could be seen. Coronal sections showed macroscopically visible deficiency of gyrus formation with such pronounced pachygyria that the sulci only appeared as narrow grooves on the surface, except in the frontal and temporal lobes and in the regions of both calcarine fissures. The structure of the basal ganglia was macroscopically abnormal with no clear separation of white and grey matter. The ventricular system was normal. Brain stem and cerebellum were small but normal.

Histological examination revealed marked deficiency both in layer formation and in the maturation of ganglion cells. The neurofibrils present showed normal myelination. In a few parts of the cortex some gliosis could be seen. Otherwise no signs of degeneration were present. The basal ganglia contained ganglion cells which were for the most part mature but the nuclei were difficult to differentiate. In the brain stem and cerebellum all ganglion cells appeared mature and the white substance present showed normal myelination.

Comment: In this case there is the possibility of a familially-determined disorder. The neuropathological findings suggest prenatal maldevelopment from the fifth month of foetal life. From the histological examination a differentiation between an exogenous and genetic defect cannot be made. The slight cortical gliosis was considered as a sign of perinatal damage.

TABLE XII

Paraplegia.

Clinical picture	*Sex*	*Case No.*	*Age at death (years)*	*Aetiology*	*Symptoms from*	*Epilepsy*	*I.Q.*	*PEG*	*Brain weight g.*	*Pathological-anatomical findings*
Pure paraplegia	m.	64	7/12	familial, perinatal (breech presentation)	birth	—	normal? undetermined	0·28	800	Degeneration of motor cortex and spinal cord
Para+tetraplegia +athetosis	f.	26	3 9/12	precipitate delivery	birth	grand+ petit mal	<35	no dilatation	400	Polyporencephaly
Para+tetraplegia	f.	31	2 1/12	unknown	1 year	grandmal	35-55	0·35	1040	Severe cortical and cerebellar dysplasia
Para+tetraplegia	f.	46	9	familial, premature perinatal (forceps)	3/12	—	35-55	—	800	Severe cortical dysplasia
Para+tetraplegia +rigidity	m.	49	9 4/12	familial	1/12	—	35-55	0·46	1325	Severe cortical, cerebral and cerebellar dysplasia

Discussion

Only 5 cases (7·3%) of paraplegia and diplegia (Table XII) are found in the present autopsy series as against 35·5% in Hansen's Danish clinical material (1960).

Causative factors appeared to vary and were complicated. Three had familial disease; one of these was premature and delivered by forceps and another a breech delivery. In one case there was a history of perinatal damage, and no cause was found in the last case.

A common feature in the neuropathological findings was cortical abnormalities, with cortical dysplasia in three cases and cortical degeneration in the other 2 brains. The pure paraplegic patient had localised lesions of the motor cortex and the spinal cord. This was considered a sequel of birth trauma due to compression (Rydberg 1932) and not following primary intracranial and intraspinal haemorrhage. In 2 brains a slight to moderate degree of gliosis of basal ganglia was noticed.

The clinical pictures were similar in the two different groups and there was no distinction between dysplasia and degeneration. PEG showed slight ventricular dilatation in 3 cases and was normal in one, and this is consistent with the microscopically practically normal basal ganglia.

No conclusion can be drawn about the correlation between prematurity and neuropathological findings from case 46 or from the other 6 premature children in the series (2, 6, 22, 23, 50 and 56.) There were 3 cases of cortical dysplasia, one case of cortical gliosis and two cases of combined gliosis and dysplasia, and one case without any cortical changes (cf. Table XVIII).

Conclusions

The discrepancy between the number of paraplegic diplegic patients in this autopsy series and in clinical material indicates that the survival time in paraplegic and diplegic patients is long. The brain lesion is predominantly cortical. Both dysplastic and degenerative cortical changes occur.

ATHETOSIS

The clinical diagnosis of athetosis was made in 22 cases. Athetosis was the sole diagnosis or combined with rigidity alone in 6 patients (3, 25, 39, 53, 67, 69). Athetosis was present in combination with tetraplegia in 11 cases (9, 11, 17, 22, 32, 42, 43, 51, 54, 60, and 62). Two patients (7, 47) had hemiplegia and athetosis, one paraplegia (26), and two a combination of tetraplegia, ataxia, and athetosis (18, 55). (Table XIII).

TABLE XIII

Pure athetosis and athetosis combined with other forms of cerebral palsy

	pure	*tetraplegia*	*tetraplegia and ataxia*	*tetraplegia and hemiplegia*	*tetraplegia and paraplegia*
Athetosis	3 (3, 25, 53)	2 (51. 62)	2 (18, 55)	1 (7)	1 (26)
Athetosis with rigidity	3 (39, 67, 69)	9 (9, 11, 17, 22. 32, 42, 43, 54, 60)	0	1 (47)	0

PURE ATHETOSIS

Pure athetosis was present in two boys and one girl (3, 25, 53). In three boys rigidity was also present (39, 67, 69).

Age at Death	< 1 year	2
	1 — 2 years	2
	2 — 5 years	2

Possible Causation

A family history was present in 3 cases. In case 3 the mother had epilepsy, while a younger sister had died from a similar disorder to our patient (no autopsy). Nos. 67 and 69 were first cousins and both had severe neonatal jaundice.

In case 53 the mother had hypertension during pregnancy. There was no case of prematurity in this group.

A perinatal origin was a possibility in all six cases: No. 3 was asphyxiated for a short time, and No. 53 had neonatal convulsions. The remaining 4 all had severe jaundice. In one patient (39) an A-O immunization was found and the maximal bilirubin level before repeated exchange-transfusion was 32·5 mg.%. The two first cousins revealed no immunization disorder. In no case were there any suggested postnatal aetiological factors.

Clinical Findings

One case (3) had a small head circumference. The I.Q. was undetermined in all these cases, but considered normal in two, while two appeared moderately retarded, and two severely retarded.

Convulsions characterised as infantile spasms with hypsarrhythmia were present in one case (53). There were no other cases of convulsions.

EEG was performed in four cases and in two patients (3 and 6) slight abnormalities with spike formation occurred. PEG was carried out in two cases, and in both patients diffuse dilatation of lateral and third ventricles was found.

Neuropathological Findings

The brain was microcephalic in case 3, all the others had normal brain weights.

Cortical abnormalities were present in case 3 as a part of a severe generalized cerebral dysplasia. In case 53 porencephaly was found in both occipital lobes.

The dominant pathological abnormalities were found in the basal ganglia with diffuse involvement in three cases (3, 25, 53), whereas 3 other cases (39, 67 and 69) had major abnormalities not only in the globus pallidus but also in the olivary and dentate nuclei. These last three were clinically classified as kernicterus, one due to A-O immunization, the others of unknown type despite extensive serological studies.

The nature of the lesions was degenerative except in case No. 3, where the changes are part of a severe dysplasia. It must be emphasized that this is the only case in the whole material where clear-cut dysplastic changes are present in the basal ganglia.

Case No. 3. Female, born October 1953, died aged 3 years and one month.

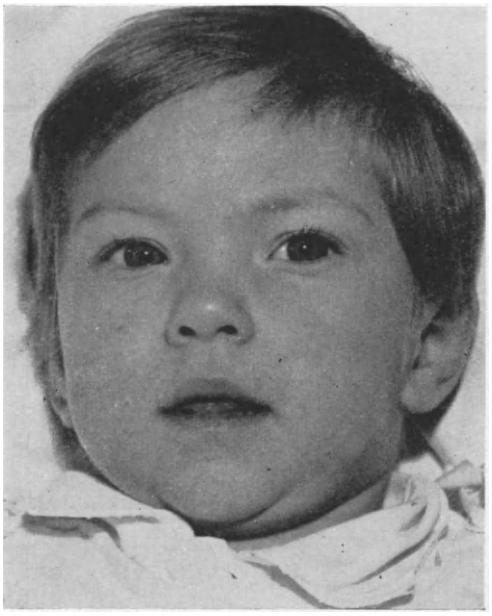
Clinical summary: Birth weight 3500 g. Family history: The mother had convulsions and was treated with antiepileptic drugs until 3 years before pregnancy. A younger brother was healthy, but the only younger sister died at the age of 13 months from a disease similar to our patient's, but no autopsy was performed.

The pregnancy was normal. There was a face presentation and she was asphyxiated for a few minutes. No jaundice. Except for some slight difficulty with sucking, no abnormalities were noticed until the child was 6 months old when the mother reported she was flaccid and uninterested in her surroundings. She was first admitted to the paediatric clinic when she was 16 months old. The head circumference was 44 cm. The muscle tone was generally increased and there were marked athetoid movements. She was unable to sit unsupported, but she showed interest in her surroundings and had no sight or hearing loss and gave no impression of noticeable mental retardation (Fig. 34). From that time she was treated with exercises and made some progress, but she never managed to sit or stand alone and her athetoid movements increased. She had repeated episodes of high fever without any explanation. EEG was normal at her first admission, diffuse abnormalities were present later. PEG was not performed. She died following a stay in a treatment home, where once more she ran a high fever and had to be admitted to a local hospital.

Brain autopsy: Brain weight after fixation 750 g. Frontal sections of the brain revealed a severe malformation. The frontal part of the brain was not separated into two hemispheres and both frontal horns were missing (Fig. 35). In the white matter heterotopic islands of grey matter could be seen. The anterior part of the corpus striatum also showed a macroscopically abnormal structure forming one continuing mass around the abnormal small third ventricle. It was impossible to identify the internal capsules. The septum pellucidum was missing and of the corpus callosum only a small posterior part existed. The temporal lobes and posterior half of both hemispheres were macroscopically normal, and it was possible to identify the mammillary bodies and the thalamus on both sides. The brain stem and cerebellum, including the fourth ventricle, did not show any gross abnormalities.

Histological examination showed — in accordance with the macroscopical findings — severe dysplasia of the cortical grey matter, especially in the anterior part of the brain where the ganglion cells were immature and reduced in number. Cortical layering was absent. Also in the macroscopically abnormal part of the basal ganglia the maturation of ganglion cells and myelination were deficient, and numerous heterotopic areas of grey matter were found scattered in the white matter. In the thalamus, mesencephalon, pons, medulla and cerebellum the histological picture was normal both with regard to myelination, and development of ganglion cells. No degenerative changes could be demonstrated.

Comment: In this case we have a history of similar disorder in a younger sister, and despite the difficult delivery the clinical manifestations were of late onset. She made some progress under treatment. Besides a somewhat small head circumference no malformations were found on clinical examination and only moderate mental



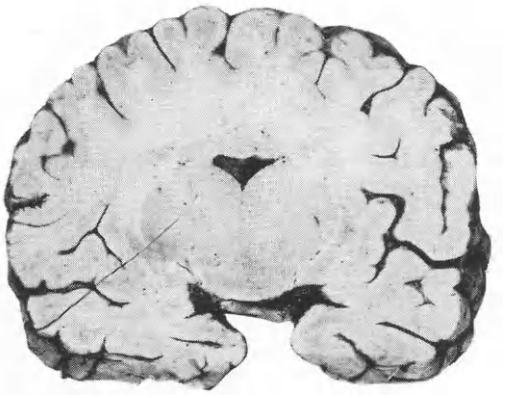


Fig. 35. Case 3 (see caption to Fig. 34). Frontal section through the frontal lobes and former parts of temporal lobes showing severe malformation.

Fig. 34. Case 3; female 3 years 1 month old. Clinical diagnosis: athetosis, microcephaly.

retardation was diagnosed. The severely abnormal brain with holoprosencephaly (Bishop *et al.* 1964) suggests a genetic disorder (no chromosome studies were performed at the time of her death). There is no evidence of perinatal damage.

Case No. 67. Male, born October 1962, died aged 1 year and 11 months.

Clinical summary: Birth weight 3300 g. Besides his first cousin (69), who had an identical history to this patient's, no known case of nervous disorder exists in the family. The mother had a threatened abortion in the third month and was put to bed for two weeks. Delivery was uncomplicated. When he was 6 days old jaundice was noticed, and as it became more pronounced he was admitted to the paediatric clinic for possible exchange transfusion. Lumbar puncture showed a yellow fluid but a normal number of cells. Bilirubin just before transfer was 37 mg.%, but after admission it was 27 mg.%. At that time he was 8 days old, and had definite clinical signs of kernicterus with an opisthotonic position and hyperkinetic athetoid movements of all extremities. It was considered too late for exchange transfusion as the damage was already pronounced. The mother and the child had identical blood groups, and there was no incompatibility between the maternal serum and the child's erythrocytes. EEG at 24 days of age showed a few sharp waves bifrontally. Protein bound iodine was normal. When he was discharged at 6 weeks of age he had definite athetosis. It was not possible to provoke an acoustic blink reflex. In spite of physical treatment he developed a pronounced opisthotonic posture and rigidity. PEG showed diffuse dilatation of the ventricular system when he was 9 months old. A thorough biochemical study revealed

no specific abnormalities with regard to liver function or copper-metabolism. He died at the age of 23 months from an infection.

The clinical history of his first cousin (Case No. 69) is exactly similar. He died when he was 17 months old.

Brain autopsy (Case Nos. 67 and 69). Both brains were of normal size and macroscopical examination did not show any abnormalities.

Histological examination showed normal layer formation in the cortical grey matter, but in the ganglion cells both acute and chronic degeneration with satellitosis occurred. The myelination of the white substance appeared normal. The corpus striatum showed isolated and severe degeneration of the globus pallidus with marked gliosis, demyelination, disappearance of most of the ganglion cells and calcification in some of the remaining ones. Around some of the vessels macrophages were present, but otherwise no cell infiltration was seen. In the red nuclei, substantia nigra, superior olives, and dentate nuclei severe chronic ganglion cell degeneration and satellitosis were seen in association with demyelination. In case 69 degeneration of the ganglion cells of the vestibular nuclei was also found. It has to be emphasized that both the Purkinje cells and the granular layer in the cerebellum appeared normal. Histological examination did not reveal abnormal pigmentation in any part of the brain substance.

Comment: The neuropathological findings are characteristic of the sequelae of kernicterus with selective degeneration of globus pallidus, red nucleus, substantia nigra, superior olivary, and dentate nucleus (and in case 69 also of the vestibular nucleus). The clinical picture of severe jaundice and neurological symptoms in the neonatal period is also typical of kernicterus. Nevertheless it has been impossible in these two first cousins to find any cause of the jaundice.

Discussion

These six patients are grouped as pure athetosis although three also had rigidity.

Only one of the patients died before one year of age (Table XIV). Neonatal jaundice was present in four cases but only in one of these could A-O immunization be established. These four patients presented symptoms from birth, as did the only patient in this group with a history of perinatal anoxia.

The last case (No. 3) presented transient neonatal symptoms, but definite symptoms first developed at the age of six months. This is in accordance with the neuropathological findings of severe cerebral dysplasia (holoprosencephaly). Both according to Benda (1960) and to the findings in this material the symptoms in patients with cerebral dysplasia develop later than in patients with perinatal damage.

Conclusion

The athetotic patients all had severe damage of the basal ganglia and this is in accordance with the findings of previous authors (among others, C. and O. Vogt 1911-1924.) The presence of nuclear jaundice without blood incompatibility in such patients has also been found by other authors (Foerster and McCormack 1944, Zuelzer and Mudgett 1950). Both the selective vulnerability of the different nuclei in the brain (in three cases predominant lesions of globus pallidus. olivary, and dentate nuceli, and

TABLE XIV

Pure athetosis

Case No.	*Sex*	*Age at death (years)*	*Aetiology*	*Symptoms from*	*Epilepsy*	*I.Q.*	*PEG*	*Brain weight g.*	*Neuropathological findings*	*Basal ganglia* caud.	put.	pal.
3	f	3	familial perinatal	6 months	—	undetermined	—	750	generalized dysplasia	+	+	+
25	m	2 1/12	perinatal (jaundice)	birth	—	undetermined	—	1750	degeneration	+	+	+
53	m	1	perinatal	birth	infantile spasms	retarded	0·43	700	polyporencephaly	+	+	+
39*	m	10/12	perinatal (A-O immunization)	birth	—	undetermined	—	unknown	degeneration	(+)	(+)	+
67*	m	1 11/12	familial perinatal (jaundice)	birth	—	undetermined	dilatation	1400	degeneration	—	—	+
69*	m	1 5/12	familial perinatal (jaundice)	birth	—	undetermined	—	unknown	degeneration	—	—	+

* with rigidity

in three other cases diffuse lesions in the basal ganglia) and the importance of coexisting anoxia are unsolved questions (Jakob 1948, Meriwether *et al.* 1955, Day 1956, Ernster *et al.* 1957, Lucey *et al.* 1964). Again we emphasize that identical clinical pictures develop when we are dealing with maldevelopment and with degeneration. The clinical symptoms depend on the site of the lesions and not on the type. This is illustrated by the fact that rigidity was present in cases with major lesions in the globus pallidus.

ATHETOSIS AND SPASTIC TETRAPLEGIA

In 6 males and 5 females the diagnosis of athetosis was made in combination with spastic tetraplegia.

Age at Death	*boys*	*girls*
< 1 year	0	0
1 — 2 years	1	0
2 — 5 years	2	2
5 — 15 years	2	3
> 15 years	1	0

Possible Causation

In no case was a family history considered relevant but in case 22 a prenatal aetiology is likely. The mother had carbon monoxide poisoning in the second month of pregnancy and had 'asiatic flu' in the fourth month, but a prenatal disorder could not be confirmed at autopsy. There was a history of difficult and prolonged delivery in 3 cases and 5 children had severe jaundice. In two of these (43, 60) immunization was proven (one due to Rhesus-factor and one to A-O incompatibility). Exchange transfusion was performed in the Rhesus case.

There were two premature children, with birth weights of 1850 g. (No. 17), and 2100 g. (No. 22).

Case 11 had a postnatal aetiology. The disorder started after a serious burn at the age of one year. The patient was not admitted to any hospital, but developed high fever (39·5°) and later the wounds became infected. Ten days after the burn she had an acute respiratory disease diagnosed as laryngitis. There was no information of loss of consciousness or asphyxia at the time of the burn.

The origin was unknown in two cases (9, 42); both appeared clinically and pathologically to be chronic necrotizing encephalopathy.

Clinical Findings

Only one (60) had a small head circumference (3 cm. below average) but the brain weight was normal.

The I.Q. was below 35 in 3 cases, 5 were retarded but with the I.Q. undetermined, and 3 patients had normal intelligence.

Grand mal occurred in five patients (17, 32, 42, 54 and 62). Two of these (42 and 62) also had petit mal epilepsy. One patient (22) had left-sided epileptic seizures, and Case 9 had atypical seizures.

Fig. 36. Case 51; male 35 years old. Clinical diagnosis: athetosis and spastic tetraplegia, mental retardation. Isolated degeneration of globus pallidus with gliosis and fibrosis of the vessels. Mallory stain x 4·5.

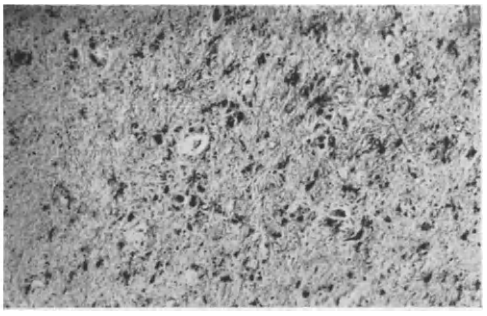


Fig. 37. Case 51 (see caption to Fig. 36). Atrophic ganglion cells, myelin degeneration and gliosis of globus pallidus. Mallory stain x 40.

EEG was normal in six cases (9, 17, 22, 43, 54 and 60), although four of these patients had epileptic seizures. It was diffusely abnormal in two cases (42 and 62).

PEG showed diffuse ventricular dilatation in six cases (9, 11, 17, 42, 60, 62).

Neuropathological Findings

Degenerative changes of the basal ganglia were found in all 11 cases. Eight showed degeneration of the globus pallidus as the most dominant feature with only minor abnormalities in the other basal ganglia (Cases 11, 17, 22, 32, 43, 51, 54, 60) (Figs. 36 and 37). Five of these had perinatal jaundice, two perinatal anoxia, and one symptoms following a postnatal burn and infection.

The last three cases had their most striking abnormalities in the caudate nuclei and putamina. One had chronic degenerative changes with gliosis whereas the last two cases, 9 (Figs. 38, 39 and 40) and 42, showed residua of necrotizing lesions with cyst formation.

No real cortical dysplasia was seen, although some of the cortical ganglion cells were not fully mature in four brains (17, 54, 60, 62), except in case 54 where the cortical dysplasia was more marked.

The brain weight was normal in seven cases (9, 11, 22, 42, 43, 54, 60) and unknown in two (17, 32). Microcephaly was present in two cases (51, 62). These patients had perinatal disease but no history of familial or prenatal disorder.

Case Reports

Case No. 43. Male, born February 1957, died aged one year and 11 months.

Clinical summary: Birth weight 2800 g. There were a number of males with epilepsy in the paternal family. The index patient was the product of the fifth of six pregnancies. All six children were jaundiced. The third child died aged 10 hours. The sixth child required an exchange transfusion. During her fifth pregnancy the mother suffered from nausea and vomiting but the delivery was uncomplicated. Jaundice was present from the eighth day, was very intense and lasted two weeks. No blood tests were performed. The infant was floppy and did not eat well. He was admitted to the paediatric clinic aged 3 months after several attacks of cyanosis and opisthotonic posturing. He

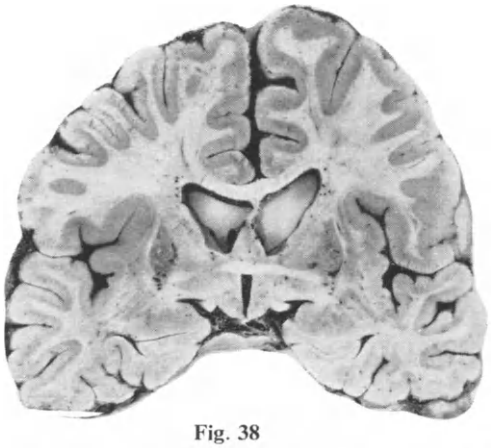


Fig. 38

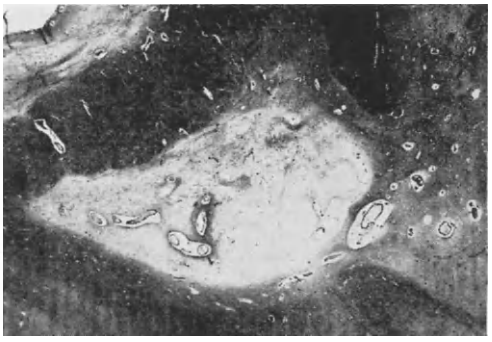


Fig. 39

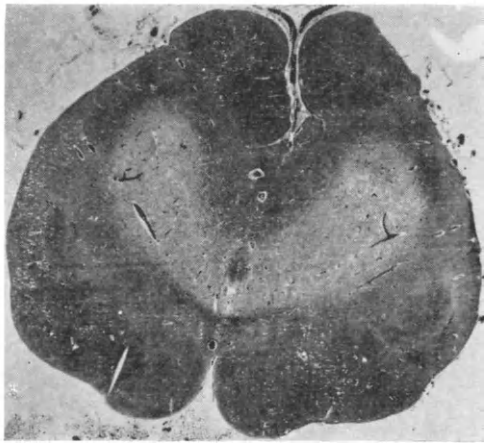


Fig. 40

Fig. 38. Case 9; male 10 years 8 months old. Clinical diagnosis: athetosis. Frontal section of the brain with isolated atrophy of caudate nuclei and putamina and moderate dilatation of both lateral ventricles. Histological diagnosis: chronic necrotizing encephalopathy. Size approx. 1:2. By courtesy of the Editor, *Acta paediat.* (*Uppsala*).

Fig. 39. Case 9 (see caption to Fig. 38). Cystic degeneration, gliosis and fibrosis of the vessels in the caudate nuclei and putamina. Weil's stain x 4·5. By courtesy of the editor, *Acta paediat.* (*Uppsala*).

Fig. 40. Case 9 (see caption to Fig. 38). Medulla with recent degeneration of reticular formation. Van Gieson stain x 4·5.

was mentally retarded. The tone of the muscles varied but extensor postures predominated. Serological studies revealed a definite A-O immunization. From the age of three months he had several episodes of high temperature of unknown origin. His movements became progressively more athetoid and he was unable to sit unsupported. There was an increasing opisthotonic tendency. Phenobarbital and mysoline only made him drowsy, and chlorpromazine had no effect. Repeated EEGs were normal. He died in hyperpyrexia.

Brain autopsy: Brain weight after fixation 950 g. Macroscopical examination did not show any abnormalities.

Histological examination revealed diffuse chronic degeneration of the ganglion cells in the cortical grey matter. In the globus pallidus there was severe gliosis and shrinking of the ganglion cells. Some of these were calcified. No degenerative changes were present in the putamen and caudate nuclei. In both hypothalamic nuclei, superior olivary, and dentate nuclei gliosis and chronic ganglion cell degeneration were found, but of more moderate degree than in the globus pallidus.

Comment: The A-O immunization, the clinical and the neuropathological findings with predominant degeneration of the globus pallidus, moderate degeneration of subthalamic nuclei, superior olives, and dentate nuclei all accord with kernicterus and its sequelae.

Case No. 42. Female, born December 1947, died aged 14 years.

Clinical summary: Birth weight 4375g. Two older siblings are normal. A third child was stillborn with the umbilical cord around its neck. Pregnancy and delivery in this case were normal. Except for some abnormal movements of the eyes there were no neonatal symptoms. Her motor development was slightly retarded. On admission to the paediatric clinic at the age of 3 years she could speak only a few words but understood most of what was said to her. She had to be supported in both sitting and standing positions. There was a slight left-sided paresis with considerable hypertonicity in all four extremities, the tendon reflexes were brisk and the plantar reflexes normal. Ventriculography showed only a moderate symmetrical dilatation of the lateral ventricles (ratio 0·34), the width of the 3rd ventricle being 10 mm. Her condition improved during the following years, and it was noted that she talked fluently at 5. When she was 6 years old her pyramidal signs with general spasticity had increased, rigidity and bilateral Babinski reflexes were now present. Her speech became difficult to understand. Nystagmus and alternating convergent squint were noticed. From the age of 10 she had petit mal seizures, later grand mal convulsions. Episodes of fever of unknown cause lasting up to two weeks occurred. When she was $11\frac{1}{2}$ years old, she was unable to talk and was more rigid and inactive than before. Occasionally she had athetoid rhythmic movements, mainly of the shoulder muscles on the left side. During the succeeding years her condition got worse. She developed contractures at the knees, but the intellectual development was considered nearly normal. In the three months prior to her death she developed increasing respiratory difficulties. A tracheostomy was performed, but she died 2 weeks later in hyperpyrexia at the age of 13 years and 10 months.

During her long illness a great number of laboratory studies had been performed but very few abnormalities were found. The sedimentation rate was increased at the start of her disease, but was later normal. Serum proteins, serum lipids and liver function were normal. EEG was severely abnormal with the exception of her first one. The spinal fluid was examined several times and each time was normal with regard to content of cells, electrolytes, and proteins.

Brain autopsy: Brain weight after fixation 1500 g. Macroscopical examination showed oedema. Coronal sections revealed a moderate symmetrical dilatation of the ventricular system and symmetrical sharply outlined necrotic areas occupying both putamina. The caudate nuclei were atrophic, whereas the internal capsules, the hypothalamus and the globus pallidus were macroscopically normal on both sides (Fig. 41). In the brain stem the tissue appeared grey, yellow and soft in the periventricular parts of the pons and medulla. The cerebellum was normal.

Histological examination revealed a slight degree of infiltration with lymphocytes and macrophages in the leptomeninges, but there were no other lesions in the cortical grey matter apart from acute anoxic changes with shrinkage of the nerve cells and their

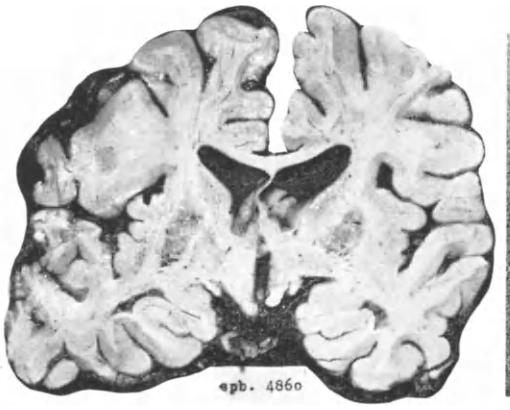


Fig. 41. Case 42; female 14 years old. Clinical diagnosis: athetosis and spastic tetraplegia, epilepsy. Histological diagnosis: chronic necrotizing encephalopathy. Size approx. 1:2. By courtesy of the Editor, *Acta paediat.* (*Uppsala*).

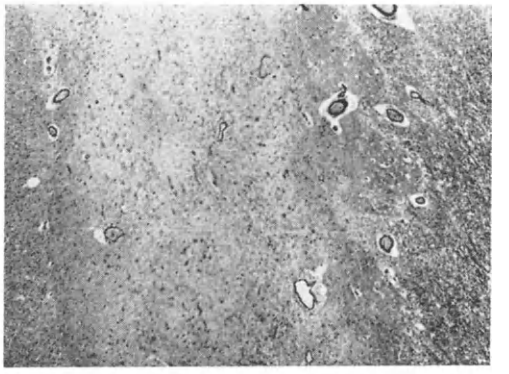


Fig. 42. Case 42 (see caption to Fig. 41). Spongy degeneration with gliosis of putamen. Van Gieson stain x 10. By courtesy of the Editor, *Acta paediat.* (*Uppsala*).

nuclei. There was no myelin degeneration in the white matter. In the caudate nuclei a few nerve cells were preserved in the periventricular areas, but the ependymal cells were normal. Otherwise there was complete degeneration of the nerve cells both here and in the putamina. The remaining tissue consisted of fibrillary astrocytes and vessels with thickening of the walls, but without obliteration of the lumen (Fig. 42). There was an irregular extension of the process into the internal capsules on both sides, but only minimal involvement of the globus pallidus on one side. Thalamus, substantia nigra, hypothalamic nuclei and the red nuclei appeared normal. The examination of the brain stem showed subacute and acute degeneration in the periaqueductal tissue and in the periventricular parts of the pons and medulla with preserved ependymal cells. The reticular formations were involved, but in the nuclei ambigui and the hypoglossal nuclei only some of the nerve cells were destroyed. No abnormalities were found in other parts of the medulla or cerebellum. From the spinal cord only the two upper cervical segments had been removed and showed acute degenerative changes in the grey matter.

Comment: The clinical course is characterized by a late onset and a slow but constant progression of the symptoms, but without any serious mental deterioration. The neuropathological findings are characterized by chronic degeneration in the caudate nuclei and putamina, and subacute and acute degeneration of the brain stem and upper spinal cord, described as a separate entity by Christensen *et al.* (1956 and 1963) under the term infantile chronic necrotizing encephalopathy. The isolated lesion of the caudate nuclei and putamina does not occur in any other disease, but is similar to the acute necrotizing encephalopathy described by Feigin and Wolf (1954). A recent survey of both types of such necrotizing lesions has been made by Ebels *et al.* (1965). The acute type is most often familial whereas the chronic type is isolated. A metabolic disorder has been considered but the aetiology is still unknown. Throughout the course of her condition the diagnosis of cerebral palsy had not been questioned.

Discussion

In this group of 11 patients (Table XV), the age at death is high — six were more than 5 years old. The I.Q. was below 35 in 3 cases (in 2 children with perinatal damage and 1 with a postnatal lesion). Six patients had seizures, and where PEG had been performed it showed only slight dilatation. There was slight microcephaly in two cases only.

Dysplastic changes were not found in this group. The predominant lesion was in the globus pallidus in 8 cases and in the caudate nucleus and putamen in 3 cases. In 5 cases with lesions of the globus pallidus there had been jaundice in the neonatal period, and in 2 perinatal asphyxia. The patient who had a severe burn also fell into this group. The 3 cases with predominant lesions in the caudate nuclei and putamina had chronic necrotizing encephalopathy (2 cases) and perinatal anoxia.

There is little to distinguish the two groups of athetoids. In both groups the main lesions were in the basal ganglia — localised in the globus pallidus in 14 cases (6 from the pure athetosis group and 8 from the combined group). In the pure group there was diffuse involvement of the basal ganglia in 3 cases, whereas the other three cases in the mixed group show predominant abnormalities of caudate nuclei and putamina.

Conclusions

These findings show that nuclear jaundice in the newborn period is clearly a possible cause of lesions of the globus pallidus. The occurrence of athetosis combined with spastic tetraplegia is most often present when a history of neonatal jaundice exists. Athetosis can be produced by lesions either in the globus pallidus or in the caudate nuclei and putamen. This corresponds to the conclusions of Courville (1961), who had the same difficulties in locating a uniform mechanism in choreoathetosis.

ATHETOSIS COMBINED WITH OTHER TYPES OF CEREBRAL PALSY THAN TETRAPLEGIA

Besides the 17 cases described as two separate varieties of athetosis 5 more patients had athetosis combined with another type of cerebral palsy. They are dealt with under one of these other types. Two were hemiplegic (7 and 47 cf. p. 57), two were ataxic (18 and 55) (cf. p. 83), and one paraplegic (26) (cf. p. 64). All of these 5 patients also had spastic tetraplegia.

Two of these patients had neonatal jaundice and one of them (47) was immunized.

The neuropathological findings in the basal ganglia of these patients can be summarised as follows:

Three had uniform involvement of all the ganglia (7, 26 and 55), but presented three different clinical pictures.

The last two patients (18, 47) had predominant lesions of the globus pallidus. Case 18 had a history of perinatal anoxia and case 47 of kernicterus.

TABLE XV

Athetosis and spastic tetraplegia

Case No.	*Sex*	*Age at death (years)*	*Aetiology*	*Symptoms from*	*Epilepsy*	*I.Q.*	*PEG*	*Brain weight g.*	*Neuropathological findings*	*Basal ganglia* caud.	put.	pal.
51	m	35	perinatal	birth		<35	—	890	degeneration	—	—	+
62	f	14	perinatal	birth	grand mal + petit mal	<35	0·39	900	degeneration	+	+	—
9	m	10 6/12	unknown	2 6/12	atypical	normal	0·32	1475	chronic necrotizing encephalopathy	+	+	—
42	f	14 10/12	unknown	8/12	grand mal + petit mal	retarded	0·36	1500	chronic necrotizing encephalopathy	+	+	—
11	f	10	postnatal	1		<35	0·36	1000	degeneration	(+)	(+)	+
17	m	2 1/12	premature perinatal (jaundice)	birth	grand mal	retarded	0·31	?	degeneration	—	—	+
22	f	2	Prenatal (CO-intoxication, A-flu) premature perinatal (jaundice)	5/12	focal	normal?	—	1250	degeneration	—	—	+
32	m	5 6/12	perinatal (jaundice)	4/365	grand mal	normal?	—	?	degeneration	—	—	+
43	m	1 11/12	perinatal (A-O-immunization)	2/12	—	retarded undetermined	—	950	degeneration	—	—	+
54	m	2 1/12	perinatal	birth	grand mal	retarded undetermined	—	1050	degeneration	(+)	(+)	+
60	f	2 2/12	perinatal (Rh.-immunization)	birth	—	retarded undetermined	0·39	1000	degeneration	—	—	+

Conclusion

No real difference seems to exists between the group of pure athetosis, athetosis combined with spastic tetraplegia, and these last five patients represcnting a mixed group. The constant occurrence of lesions in the basal ganglia, including the globus pallidus, is of major importance in the development of athetosis.

ATAXIA

Five cases of ataxia occur in the present material (Case nos. 5, 18, 29, 34, 55). This symptom was combined with spastic tetraplegia in all five patients. Two also had athetosis (Table XVI).

There were 3 boys and 2 girls.

Age at Death

	girls	*boys*
2 — 5 years	1	1
5 — 15 years	1	2

Possible Causation

Positive family history was present in 3 cases. Two patients with leucodystrophy (5, 34) had siblings with the same kind of progressive neurological disease. In a third case there were both affected siblings suggesting a familial disorder and a history of a difficult delivery with asphyxia. Prenatal origin was possible in one case (18) as the mother had hypertension and eclampsia during pregnancy. In one case (no. 55) pure perinatal origin was present with difficult forceps delivery and a long period of asphyxia. The origin was unknown in one case (29).

Clinical Findings

A small head circumference was found in 3 patients, but only one (29) had microcephaly. The two cases with leucodystrophy had normal head circumferences.

The I.Q. was below 35 in one case (29), between 35 and 55 in one (55), and undetermined in the remaining three cases, but these patients were also considered mentally retarded.

Epilepsy of grand mal type was present in 4 patients (5, 29, 34, 55), all with family history of a similar disorder.

The EEG was abnormal in two cases (34, 55), normal in cases 18 and 29, and not performed in case 5.

PEG performed in 3 patients showed dilatation in two cases (34, 55), and was normal in one case (29).

Neuropathological Findings

Microcephaly was only present in one case of dysplasia (29); the other four patients had normal brain weight.

Degeneration of the cortical grey matter was seen in case no. 5, whereas case 34 (a leucodystrophy) had a normal cortex. Cerebral cortical dysplasia was present in

TABLE XVI

Ataxia

Ataxia combined with	*Sex*	*Case No.*	*Age at death (years)*	*Aetiology*	*Symptoms from*	*Epilepsy*	*I.Q.*	*PEG*	*Brain weight g.*	*Pathological-anatomical findings*
Tetraplegia	m.	5	5	familial	2 years	grand mal	retarded undetermined	—	1200	leucodystrophy, metachromatic type; cerebellar degeneration
Tetraplegia	f.	34	3	familial	1 3/12	grand mal	retarded undetermined	0·33	1000	leucodystrophy, metachromatic type
Tetraplegia	f.	29	8	?	1 year	grand mal	<35	normal	900	dysplasia of cerebrum and cerebellum
Tetraplegia + athetosis	m.	18	5 6/12	prenatal-perinatal	birth	—	retarded undetermined	—	1250	dysplasia of cerebrum and degeneration of basal ganglia
Tetraplegia + athetosis	m.	55	14	familial perinatal	birth	grand mal	35-55	0·37	1000	dysplasia of cerebrum, basal ganglia, and cerebellum

three cases (18, 29 and 55). In no case were macroscopical changes found in the cerebellum.

Cerebellum was only available for histological examination in three cases and among these dysplasia was found in 2 cases (55 and 29) and degeneration in one (5). The dysplasia was characterised by lack of secondary folia formation in case 55, and both here and in case 29 the granular layer was thinner than normal, with a marked deficiency of the number of Purkinje cells.

The basal ganglia were involved in three patients, two showing a diminished number of ganglion cells but no signs of degeneration (29, 55). In one case (18) degenerative changes of the type of status dysmyelinatus with a diminished number of ganglion cells and abnormal myelination were found. The two patients with leucodystrophy also showed changes in the white substance of the basal ganglia.

The white matter was severely involved in the two cases of metachromatic leucodystrophy (5, 34). In both these cases the diagnosis was first established at autopsy.

Pyramidal tract abnormalities were present in two cases (18, 55), the changes being in conformity with the severe cortical dysplasia.

Case Reports

Case No. 29. Female, born August 1951, died aged 8 years and 3 months.

Clinical summary: Birth weight 3000 g. Pregnancy and delivery were normal. She was sitting unsupported at the age of 8 months. At one year old she had a febrile illness and after that time her development was very much delayed. On examination on admission to the paediatric clinic aged 2 years and 4 months her EEG and PEG were normal. Her walk was slow and unstable with widespread legs. Two years later her walk was still ataxic and there was also a definite spastic tetraplegia. She was severely mentally retarded with poor speech development and reduced hearing. From the age of 6 years she had grand mal epilepsy. She died from bronchopneumonia.

Brain autopsy: Brain weight after fixation 900 g. Macroscopical examination showed microgyria especially of both occipital lobes. Frontal sections of the brain and horizontal sections through the brain stem and cerebellum revealed no abnormalities.

Histological examination: The layer formation of the cortical grey matter was incomplete, and could only be seen in some areas. The number of ganglion cells, especially of the pyramidal cells, was smaller than normal. Also in the basal ganglia a lack of large ganglion cells could be demonstrated. In the cerebellum the granular layer contained a smaller number of ganglion cells than normal, whereas only a slight reduction in number of the Purkinje cells could be seen. The development of the white matter was normal and no signs of degeneration could be found in the whole brain other than a moderate subpial gliosis.

Comment: The fact that the clinical symptoms appeared rather late is in agreement with the finding of a generalized cerebral dysplasia, with microcephaly, microgyria and dysplasia of the basal ganglia and cerebellum. Despite the history of a febrile illness at the age of one year, no signs of encephalitis were seen.

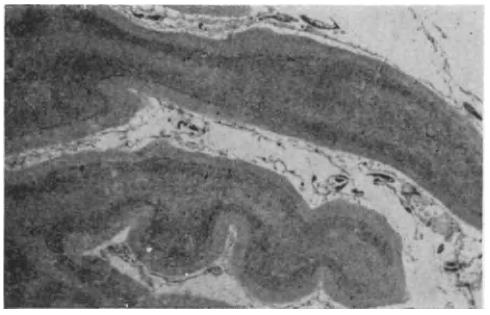


Fig. 43. Case 55: male 14 years 3 months old. Clinical diagnosis: ataxia, spastic tetraplegia and athetosis, epilepsy, mental retardation. Severe dysplasia of the cerebellum with deficient development of the secondary folia. H-E stain x 40.

Case No. 55. Male, born October 1946, died aged 14 years.

Clinical summary: Birth weight 4000 g. The eighth of eight pregnancies. The two oldest siblings died at three days from convulsions. Two pregnancies ended in abortions. Three siblings are healthy. The relevant pregnancy was normal, the delivery was at term but difficult. He was asphyxiated for 45 minutes and had convulsions from the first day of life. His motor development was always slow, as was his intellectual development. He was treated for spastic diplegia from the age of three years, and was first seen in the University Clinic of Paediatrics at the age of five years. The clinical picture was dominated by spasticity, most pronounced in the legs, but there were also ataxic and athetotic movements principally in the arms. Over the years he developed contractures and dislocations of the hips in spite of intensive treatment. EEG was severely abnormal on several occasions, and PEG at the age of 5 years showed a ratio of 0·37. He was mentally retarded and for this reason he spent his last three years in an institution, where he died of bronchopneumonia.

Brain autopsy: Brain weight after fixation 1000 g. Macroscopical examination of the brain and brain stem revealed no other gross abnormalities except for a mild degree of microcephaly and slight diffuse dilatation of the ventricular system, and atrophy of the corpus striatum. The cerebellar folia appeared small and maldeveloped, otherwise no abnormalities could be seen in the cerebellum.

Histological examination: The cerebral cortex showed deficiency in layer formation but the ganglion cells were mature. There was a varying degree of subpial gliosis. In the temporal lobes there was satellitosis. In the caudate nuclei and the putamina the number of ganglion cells was diminished but no myelin degeneration could be seen. In the brain stem and part of the spinal cord, deficiency in myelination of the spinal tracts could be seen, but here no signs of degeneration were present. The cerebellar cortex showed severe abnormalities. Both the molecular and granular layers were thinner than normal, and only a few Purkinje cells could be found. Besides these dysplastic changes, marked proliferation of Bergmann's glial cells together with ganglion degeneration and satellitosis of the dentate nuclei were present (Fig. 43).

Comment: From a clinical point of view the cerebral disorder was due to perinatal anoxia, but neuropathological examination showed both dysplasia and degeneration. These were compatible with sequelae of perinatal anoxia.

Discussion

There are only five patients in this group and all had other types of cerebral palsy as well (Table XVI).

The earliest death was at three years. Grand mal epilepsy occurred in 4 cases and only one had an I.Q. below 35. In three of the cases a familial history of neurological disorders was present.

Two patients with perinatal anoxia had symptoms from birth, whereas the clinical symptoms first developed after the age of one year in the other 3 cases. Autopsy revealed that two of these had leucodystrophy and one had cerebral and cerebellar dysplasia.

The brain weight was normal in four of the five patients. Involvement of the cerebellum was found in the three cases where it was available for examination. Two had dysplasia of the cerebellum, combined in one case (55) with degeneration. In the case of leucodystrophy the white matter of the cerebellum was also involved.

Conclusion

The cerebellar abnormalities in the ataxic group demonstrate again that it is the localization and not the type of the lesion which is of importance in relation to the clinical symptoms. Different sorts of degenerative disease and dysplastic change give identical clinical pictures. The constant finding of cerebellar abnormalities in combination with more widespread abnormalities of the central nervous system in cases with ataxia is in agreement with Batten's (1905) observations.

CHAPTER VI

The Neuropathological Findings and Classification

The previous chapter has surveyed the present material from a clinical point of view, but in each clinical entity the neuropathological findings have been considered. In this chapter the present series has been rearranged and divided into groups according to the neuropathological picture. It was hoped that the neuropathological findings could be linked with the aetiological and the clinical pictures.

The same case can be found under different headings as changes are found in different parts of one single brain.

The neuropathological studies are grouped as follows:

1. Lesions in the cortical grey matter.
2. Lesions in the white matter.
3. Lesions in the basal ganglia.
4. Lesions in the cerebellum.
5. Lesions in the brain stem and spinal cord.
6. Calcification.

1. The Cortical Grey Matter

The findings in the cortex are further sub-divided as follows:

(i) Cortex with predominance of chronic degenerative changes: (a) gliosis and infections, (b) porencephaly.

(ii) Cortex with predominance of dysplastic changes.

(iii) Cortex with a mixture of chronic degenerative and dysplastic changes.

(iv) Cortex without any chronic changes.

(i) *Cortical Degeneration*

(*a*) *Gliosis.* Chronic cortical ganglion cell degeneration with gliosis was a common finding in brains with many different types of lesions.

The degree of ganglion cell degeneration varied from a slight shrinking to marked atrophy or finally to complete disappearance of areas of cells. Satellitosis and diffuse astrocyte proliferation were present in association with this degeneration. Subpial gliosis was most pronounced. Gliosis of the cortical grey matter is therefore a constant finding when ganglion cell degeneration is taking place whatever the aetiology.

Gliosis and chronic ganglion cell degeneration of the cortical grey matter were present in 26 cases in the present series (no. 4, 8, 11, 12, 17, 18, 23, 27, 33, 38, 39, 41, 43, 44, 48, 50, 51, 56, 57, 58, 60, 62, 64, 67, 68, 69).

Six brains (Cases 12, 33, 44, 51, 57, 62) revealed different degrees of diffuse cortical ganglion cell degeneration, satellitosis, and subpial glial cell proliferation.

Moderate deficiency of the cortical layer formation and slight immaturity of the ganglion cells was a feature of all 6 brains. Four of the brains were microcephalic and had predominant lesions of caudate nuclei and putamen or diffuse lesions of the basal ganglia. One (12) with normal brain weight had calcification of the basal ganglia and one (57) had generalised involvement of the basal ganglia. The abnormalities were considered to be of perinatal origin and in all 6 cases there was a history suggestive of perinatal anoxia.

In nine other brains (nos. 17, 18, 39, 43, 48, 50, 60, 67, 69) the cortical changes were similar to the changes described above but the brain weights were normal. In addition the lesions in the basal ganglia were predominantly localised to the globus pallidus, subthalamic nucleus and vestibular nucleus.

There is no acceptable explanation of the difference in brain weight between the majority of the first group and all 9 in the other group, except that the perinatal damage in the microcephalic group was more severe than in this other group of nine patients.

According to Schmorl (1904) and Lucey *et al.* (1964) both pure perinatal anoxia and nuclear jaundice can give rise to arrest in development of the cortical grey matter combined with chronic degenerative changes both here and in the basal ganglia. In nuclear jaundice there is localization to the globus pallidus, subthalamic and vestibular nucleus. The aetiological information in our 9 cases is that six of them had a history of kernicterus and three of severe perinatal anoxia. The present authors disagree with Soeken's view (1959) that the oxygen deficit in such cases is already present in foetal life and may cause an arrest of development and degeneration of ganglion cells. Otherwise her opinion corresponds with that of Lucey *et al.* and the present authors that there is an interaction between the cerebral oxygen deficiency leading to a breakdown of the blood-brain barrier, and the nuclear jaundice.

Three cases (23, 56, 64) presented isolated or severe degeneration of the motor cortex combined with pyramidal tract degeneration, and in cases 23 and 56 there was also degeneration of the basal ganglia. These two were premature and no. 56 had neonatal jaundice without blood incompatibility. Here the possibility of increased vulnerability in immature brains has to be considered (Towbin 1960). In case 64 the lesion is probably due to birth trauma (Rydberg 1932, Schwartz 1963-65) (p. 66).

Two other brains (27, 58) showed pronounced microcephaly with atrophy of gyri at macroscopical examination. In case 58, a girl who died at the age of 6 years, a chronic subdural haematoma of obscure origin had been evacuated four years before death. Histological examination revealed in both these cases the typical picture of poliodystrophy with spongy degeneration of the cortical grey matter. (Case 58 is reported in detail by Christensen and Højgaard 1963). The severe damage of the cortical grey matter explains the poor clinical state of this patient better than the presence of the subdural haematoma, and the findings correspond to Ingraham and Matson's conclusions (1944) that the most important element determining the clinical course in a patient with subdural haematoma is the condition of the underlying brain.

TABLE XVII

Clinical Findings in 26 Cases of Cortical Gliosis

Case no.	*Clinical diagnosis*	*Sex*	*Age at death*	*IQ*
4	T	f	2 years	< 35
8	T	m	10/12	low
27	T	m	2 9/12	?
33	T	f	4 3/12	< 35
56	T	f	6 years	?
12	TR	m	1 year	low
23	TR	f	2 9/12	low
38	TR	m	9/12	low
41	TR	m	3 5/12	< 35
44	TR	m	1 7/12	< 35
48	TR	m	7/12	retarded
50	TR	f	12 years	< 35
58	TR	f	6 years	< 35
57	H	m	8/12	?
68	H	m	3 6/12	< 35
64	P	m	7/12	retarded
39	AR	m	10/12	retarded
67	AR	m	1 11/12	?
69	AR	m	1 5/12	?
51	AT	m	35 years	< 35
62	AT	f	14 years	< 35
11	ATR	f	10 years	< 35
17	ATR	m	2 1/12	retarded
43	ATR	m	1 11/12	retarded
60	ATR	f	2 2/12	retarded
18	AtAT	m	5 6/12	< 35

Abbreviations used in Tables XVII-XXV:

T: tetraplegia. H: hemiplegia. R: rigidity. P: paraplegia. A: athetosis. At: ataxia.

In case no. 11, the brain showed no gross abnormalities but histological examination revealed precipitates of iron pigment both in the leptomeninges and the globus pallidus, and severe diffuse atrophy of the ganglion cells in the cortex and globus pallidus combined with marked glial proliferation. This patient, who died 10 years old, first developed symptoms of cerebral palsy after a severe burn at one year of age, followed by an infection. The abnormalities in the brain were probably caused by cerebral anoxia and the iron pigment was the result of intracranial anoxic haemorrhages occurring at the same time.

In five patients (4, 8, 38, 41, 68) the degenerative changes in the brains were due to the sequelae of chronic meningo-encephalitis starting in the perinatal period or early in post-natal life. Case 38, who died aged six months, had a bilateral subdural haematoma which was evacuated and then developed meningo-encephalitis. The cortical changes were mostly secondary to the infection.

Case 8 had a perinatal coli-meningitis with secondary hydrocephalus due to granular ependymitis of the Sylvian aqueduct and fourth ventricle. A shunt operation had been carried out at the age of five months. He died aged ten months and brain autopsy revealed persistent non-bacterial chronic purulent meningo-encephalitis, diffuse ganglion cell degeneration and gliosis and granular ependymitis.

The most obvious explanation of the degenerative changes in the two brains from cases 41 and 68 is that the former had developed thrombophlebitis in the sagittal sinus in association with meningitis under one year of age, and that the abnormalities in the brain from case 68 were due to a septic thrombosis in the internal carotid artery developing after a purulent meningitis at the age of 6 months.

The negligible role which intracranial infections play in the origin of cerebral palsy in the present series corresponds to the finding of Wolf and Cowen (1957). They emphasize that perinatal infections of the central nervous system can be caused by a great number of different agents, but they conclude that, in spite of this possibility, infection must still be considered one of the less common causes of pathological changes in the brain in the perinatal period.

The clinical diagnosis in the 26 patients with gliosis, as well as their age at death, intelligence and sex, can be seen from Table XVII.

Five patients had pure tetraplegia (8 with rigidity), 2 had hemiplegia and one paraplegia. In 3 cases the clinical diagnosis was athetosis and rigidity, and in 6 athetosis and tetraplegia. One case had the combined picture of ataxia, athetosis and tetraplegia. Altogether 20 out of the 25 had tetraplegias.

Seventeen were males and 9 females. The intelligence was low in all cases. The age of death varied from 6 months to 35 years. Six died before one year of age, and a further 13 before the age of 5 years.

(*b*) *Porencephaly.* Porencephaly occurred in 14 cases. The encephaloclastic or degenerative form of porencephaly is the commonest finding presenting as polyporencephaly. It was found in 11 cases (4, 10, 15, 26, 30, 35, 37, 41, 45, 53, 68). The cyst formations varied in size and localisation, but in all cases the subcortical white matter was involved, and in all but two (15, 68) porencephalic processes could be found in the basal ganglia.

Macroscopical examination of these 11 brains showed in all cases marked microcephaly with varying degrees of polymicrogyria. The brain weight varied between 250 and 855 g., with an average of 590 g. This is a severe degree of microcephaly as it is well below brain weight for a six-month-old infant, which is 660 g. and the normal brain weight for a full term baby is 335 g. (Conel 1939 and 1951).

In case 68 the encephaloclastic cyst formation was strictly localised to the cerebral white matter of the right hemisphere. This patient, who was hemiplegic, died at the age of 3 years and 5 months. The cerebral involvement was caused by a septic thrombosis in the right carotid artery in connexion with a purulent meningitis.

The common histological picture in these cases is as follows: around the encephaloclastic processes astrocyte proliferation takes place; the degree of this varies according to the age of the process, and in old cases the cysts are traversed by glial trabeculae. If degeneration is still going on at the time of histological examination macrophages are present, predominantly containing lipid, and in lesser degree blood pigment. In the surrounding white substance there is myelin degeneration which is total in the cyst walls and diminishes in accordance with the glial proliferation. If an encephaloclastic process involves grey matter, there is loss and atrophy of ganglion

TABLE XVIII

Clinical Findings in 14 cases of Porencephaly

Case no.	*Clinical diagnosis*	*Sex*	*Age at death*	*IQ*
4	T	f	2 years	< 35
10	T	f	2 5/12	< 35
15	T	m	2 3/12	retarded
26	PTA	f	3 9/12	< 35
30	TR	m	2 9/12	retarded
35	TR	m	12 months	retarded
37	T	m	2 years	retarded
41	TR	m	3 5/12	< 35
45	T	m	2 6/12	retarded
53	A	m	12 months	retarded
68	H	m	3 6/12	< 35
14	TR	f	3 10/12	< 35
28	H	m	3 4/12	retarded
52	T	f	9 5/12	< 35

cells parallel to the glial proliferation. Around superficial cysts, fibrous thickening and infiltration with macrophages and lymphocytes may be seen. Also the vessel walls in the involved parts of the brain may show fibrous thickening, and along this a proliferation of connective tissue may take place. If periventricular tissue is involved a granular ependymitis with proliferation of astrocytes and appearance of ependymal cells may be found on the ventricular walls. However, it must be remembered that prenatal damage particularly may give rise to cyst formation without leaving any scar formation (Becker 1949, Hallervorden 1952).

Regarding the aetiology, there was a history of prenatal difficulties and perinatal anoxia in one case (15). In 6 patients (10, 26, 30, 35, 37, 53) severe perinatal anoxia occurred and in 3 cases (4, 41, 68) the polyporencephalic processes are considered of early postnatal origin caused by various forms of cerebral infections. In case 45 the aetiology is unknown. The findings do not fit with prenatal infection.

Mental retardation was very pronounced in all cases; the patients in whom determination of intelligence was possible had I.Q.s of below 35 (cf. Table XVIII). The age of death in 10 of the 11 patients varied between 6 months and 3 years 6 months, indicating that these patients all had severe brain damage.

The clinical diagnosis was pure tetraplegia in 5 cases (4, 10, 15, 37, 45) and tetraplegia with rigidity in 3 cases (30, 35, 41). Case 26 had paraplegia, case 53 pure athetosis and case 68 hemiplegia.

In schizencephaly the brains are more or less hydrocephalic around the sylvian fissure and the brain tissue may only consist of a narrow rim about 1 mm. in thickness. The schizencephalic form of porencephaly (Yakovlev and Wadsworth 1946) was present in 2 cases (14, 28), and a third case (52) presented a transitional type as both schizencephaly and polyporencephaly were present in the right frontal lobe and insular region.

In case 28 the right hemisphere was transformed into a thin-walled cyst, which corresponds with the presence of abnormalities in the arteries of the circle of Willis

(see p. 58) on the same side. Case 14 presented symmetrical hydrocephalus in the middle part of both hemispheres with corresponding deficiency in layer formation. Here no gross abnormalities of the vessels could be established.

These 3 patients died between the ages of 6 months and 4 years. The clinical diagnosis was, in case 52, pure tetraplegia, in case 14, tetraplegia and rigidity, and in case 28, hemiplegia. All three were mentally retarded (see Table XVIII).

It is interesting that Nos. 28 and 52 were the only cases among the porencephalic patients with a positive familial history.

In the present series no brains presented the picture of symmetrical cyst formations around the venae terminales. This is considered by several authors (Gröntoft 1953, Courville 1953) as anoxic change due to stagnant anoxia, but by others as a sequel of post-traumatic perinatal bleeding from the venae terminales (Rydberg 1932 and Schwartz 1961). Whatever the cause of this characteristic symmetrical cyst formation, the absence of this special type of lesion in the present material may be because we are dealing with severely damaged brains. It must be supposed that patients with damage strictly localised to the tissue surrounding the venae terminales will survive to an older age and present milder symptoms of cerebral palsy.

(ii) *Cortex with Predominance of Dysplastic Changes*

Sixteen patients (1, 2, 3, 14, 24, 28, 29, 31, 40, 46, 49, 54, 55, 59, 63, 66) had dysplasia of the cortical grey matter characterised by different degrees of deficiency in gyrus and layer formation, lack of maturation and diminished numbers of ganglion cells. In some cases — particularly in case 3 with holoprosencephaly (see p. 72) — maldevelopment of the whole brain could be seen at macroscopical examination. In two cases (Nos. 14, 28) schizencephaly occurred. Otherwise the gross abnormalities consisted of varying pachy- and microgyria. Six of these 16 cases were microcephalic. The microcephaly was of moderate degree in 5 of the patients. Case 14 showed marked microcephaly, as the brain weight at death at 14 years of age was 320 g. — well below the average for a normal full term baby (Conel).

Histological examination revealed a great variety in the severity of dysplastic changes, from complete lack of layer formation, with immature ganglion cells in the cortical grey matter collected in clusters, to slight deficiency in layer formation and maturation. In 7 of the cases (3, 29, 31, 40, 49, 63, 66) the dysplastic changes were also present in the cerebellar folia with deficiency either in the formation of secondary folia and/or in the number of Purkinje and granular cells. Marked deficiency in myelination of the pyramidal tracts was present in 4 cases (2, 14, 28, 55).

In most of these 16 cases with predominant cortical dysplastic changes, slight cortical degeneration evidenced by subpial gliosis could be seen. In 11 of the 16 cases degenerative changes were present in the basal ganglia. In 8 brains (14, 24, 29, 40, 49, 55, 63, 66) there was diffuse basal ganglia degeneration as part of another pathology. In cases 31 and 46 the lesions were localised to the caudate nucleus and putamen. Only one case (54) showed predominant lesions of the globus pallidus.

In case 28 a maldevelopment was seen on one side of the basal ganglia relating to the hemiaplasia of one hemisphere. This patient was hemiplegic. Only case 3, with

holoprosencephaly, had a real and marked maldevelopment of all basal ganglia. She was also the only case with the clinical diagnosis of pure athetosis. Cases 1 and 2 were the only ones in this series where no abnormalities were found in the basal ganglia. The clinical diagnosis in these two cases was pure tetraplegia.

A familial causation is present in 7 of the 16 cases (3, 28, 46, 49, 55, 63, 66). In case 59 there is a possible prenatal origin. Case 2 was premature.

A history of perinatal asphyxia is present in a total number of 7 cases (1, 3, 14, 46, 54, 55, 59), and case 40 had a precipitate delivery. The sequelae of this type of damage do not explain the occurrence of dysplastic abnormalities within these brains. A postnatal origin is suggested for case 29. The causation is in reality unknown in 7 cases (1, 14, 24, 29, 31, 40, 54) as a perinatal and postnatal causation cannot be accepted from the evidence of the neuropathology. The histological picture in the familial cases did not differ from the non-familial cases.

TABLE XIX

Clinical Findings in 16 Cases with Predominance of Cortical Dysplastic Changes

Case no.	*Clinical diagnosis*	*Sex*	*Age at death*	*IQ*
1	T	f	1 2/12	low
2	T	m	20 years	< 35
59	T	f	1 6/12	< 35
63	T	m	2 5/12	< 35
14	TR	f	3 10/12	< 35
24	TR	m	19 years	< 35
40	TR	f	15 years	low
66	TR	m	3 years	retarded
28	H	m	1 3/12	undetermined
31	PT	f	2 1/12	35—55
46	PT	f	9 years	35—55
49	PTR	m	9 4/12	35—55
3	A	f	3 years	undetermined
54	ATR	m	2 1/12	retarded
29	AtT	f	8 years	< 35
55	AtAT	m	14 years	35—55

The clinical findings are given in Table XIX. Four cases had pure tetraplegia and 4 rigidity as well. Tetraplegia combined with other types of cerebral palsy was found in 6 patients. One case had pure hemiplegia, and one pure athetosis.

The I.Q. was undetermined in two patients, and retarded in the remaining 14 cases. The age of death varied from 14 months to 20 years.

(iii) *Cortex with a Mixture of Chronic Degenerative and Dysplastic Changes*

The third group of cortical abnormalities is the mixed group, consisting of four patients (6, 7, 47, 52) where both the degenerative and dysplastic changes were so pronounced that it was impossible from a neuropathological point of view to determine which was of major importance.

TABLE XX

Clinical Findings in 4 Cases with a Mixture of Cortical Degeneration and Dysplasia

Case no.	*Clinical diagnosis*	*Sex*	*Age at death*	*IQ*
6	HT	f	14 10/12	< 35
7	HTA	f	14 6/12	< 35
47	HTA	m	1 8/12	retarded
52	T	f	9 6/12	< 35

The three brains from cases 6, 7 and 47 had normal weight, although macroscopical examination showed varying degrees of pachy- and microgyria, and in two cases atrophy of the cerebellum.

Histological examination revealed dysplastic changes both as a deficiency in secondary gyri formation and cortical layer formation and as deficiency in maturation of ganglion cells. In the two cases with a macroscopically atrophic cerebellum both the number of Purkinje cells and of ganglion cells in the granular layer were markedly decreased.

The degenerative changes visible in all three cases were atrophy of a great number of the cortical ganglion cells, with accompanying satellitosis and subpial gliosis. In the basal ganglia chronic ganglion cell degeneration was present with deficiency and degeneration of myelination accompanied by astrocyte proliferation.

In case 47 the sites of changes included the subthalamic olivary and dentate nuclei. The mixture of dysplastic and degenerative changes in case 7 may be explained by the fact that this patient was premature. It is known that the brains of premature infants are more vulnerable than the brains of full term babies (Towbin 1960, Gruenwald 1965).

Case no. 7 had a difficult delivery which accounts for the degenerative changes. In No. 47 there was A - O immunisation, and here the localisation of the degenerative processes, especially in the basal ganglia, were similar to the changes following kernicterus (Schmorl 1904). All three patients were severely mentally retarded.

No. 52 also had both schizencephaly and polyclastic porencephaly in the right hemisphere (see p. 39).

Table XX shows the clinical diagnosis. All had tetraplegia and in 3 there was a marked difference between the two sides.

(iv) *Cortex Without any Chronic Changes*

In 14 of the 69 patients there was a normal cortex. From a neuropathological point of view these 14 brains could be divided into four well-defined groups (Table XXI).

a. Five cases of leucodystrophy (5, 21, 34, 36, 61).
b. Three cases of benign gliomas, one (65) located in the third ventricle, and two (13, 20) in the white matter of the hemisphere.
c. Two cases of chronic necrotizing infantile encephalopathy (9, 42).
d. Four cases with chronic degeneration in the basal ganglia predominantly in the globus pallidus (16, 22, 25, 32).

TABLE XXI

Clinical Findings in 14 Cases without Cortical Changes

Neuropathological group	*Case no.*	*Clinical diagnosis*	*Sex*	*Age at death*	*IQ*
leucodystrophy	5	AtT	m	5 years	undetermined
	21	TR	m	3 7/12	< 35
	34	AtT	f	3 years	undetermined
	36	T	m	4 10/12	< 35
	61	TR	m	8/12	retarded
tumours	65	H	f	17 11/12	normal
	13	H	f	8 years	normal
	20	H	m	3 4/12	normal
infantile chronic necrotizing encephalopathy	9	ATR	m	10 6/12	normal
	42	ATR	f	14 10/12	retarded
predominant degeneration in globus pallidus	16	HT	f	7/12	undetermined
	22	ATR	f	2 years	normal
	25	A	m	2 1/12	undetermined
	32	ATR	m	5 6/12	normal

In relation to these negative findings in the cortex, only the 5 patients with leucodystrophy showed any significant intellectual reduction.

Only the 4 patients in group (d) fit into the strict definition of cerebral palsy and, as the case reports show, all have a history of perinatal anoxia, kernicterus or neonatal jaundice. The different disorders in the other 10 patients are progressive, but they have been placed among these cerebral palsy patients because the early onset of the disease and the slow progression led to a clinical diagnosis of cerebral palsy being made.

Discussion

A comparison between the degenerative and the dysplastic group shows the following marked aetiological and clinical differences:

(1) There was a high incidence of affected siblings in the dysplastic group and not in the degenerative group.

(2) In 10 of the 14 dysplastic cases the onset of symptoms was stated to be after the age of one month — in some cases first after the age of six months — whereas in the degenerative group symptoms were seen from birth. This observation corresponds to Benda's findings (1960).

(3) In the dysplastic group transient perinatal symptoms were present in 6 patients. These symptoms are probably caused by a weakened foetus having a prolonged delivery and accompanying transient respiratory difficulties after birth. These perinatal difficulties must be the explanation of the findings of both severe dysplastic and degenerative changes in four brains in the present material.

(4) A surprising finding is that a history of a possible prenatal aetiology was only present in one case (59) of cortical dysplasia. This fact, in association with the pronounced familial picture in the dysplastic group, suggests that we are dealing with a *genetically determined* group of disorders.

(5) The age of death among the patients with cerebral dysplasia is higher than in the degenerative group. Only 2 in the dysplastic group died before the age of

2 years, and 3 were over 15 years at death. On the other hand 34 of 41 patients with cortical degeneration died before the age of 5 years.

(6) Only 4 patients with spastic diplegia had a real cortical syndrome (Courville 1954) deriving from birth trauma (Rydberg 1932) with selective degeneration of the motor cortex, but even in the most clear-cut case (64) the clinical picture was complicated by trauma of the spinal cord. Courville classes hemiplegia in the cortical syndrome, but as can be seen from Table XXI, 3 of the 10 patients in our hemiplegic group had tumours localised in the ventricular system or basal part of the brain. Hemiplegia, therefore, cannot necessarily be regarded as part of the cortical syndrome.

2. The White Matter

Different problems arise about the white matter as the myelination is not complete at the time of lesion in cerebral palsy patients. Therefore both deficiency in myelination and myelin degeneration may be found. Degenerative myelin products are, however, rarely seen, as we are dealing with a process which, except in the cases of leucodystrophy, is not active at the time of examination. Glial proliferation is present in the white matter both when delay in and degeneration of myelination have taken place.

Abnormalities in the white matter may be found as isolated phenomena, but more often they are a part of the brain disorder as a whole. When we are dealing with cortical dysplasia the number of ganglion cells is diminished and consequently the number of axons is also smaller than in a normal brain. In such cases no degeneration occurs. The presence of microcephaly with a diminished amount of white matter as a whole indicates a diminished number of axons even if a count cannot be carried out.

A certain degree of cortical degeneration will lead to degeneration of the tracts corresponding to the degenerated cortical area. The most striking example of this is the pyramidal tract degeneration occurring in cases with degeneration of the motor cortex.

All the above-mentioned types are represented in the present material, as follows:

(a)	leucodystrophies (see p. 95)	5 cases
(b)	polyporencephalies (see p. 91)	11 "
(c)	tumours invading or compressing the white matter	2 "
(d)	abnormal white matter due to cortical dysplasia	7 "
(e)	abnormal white matter due to cortical degeneration	10 "

It is not possible to draw any conclusions about the correlation between the abnormalities of the white matter and the clinical symptoms.

3. The Basal Ganglia

The basal ganglia — predominantly the corpus striatum — were affected in 58 out of the 69 cases.

As a result of neuropathological examination the whole series can be divided into 4 groups:

(i) Predominant involvement of the globus pallidus (17 cases: 11, 16, 17, 18, 22, 23, 32, 39, 43, 47, 48, 50, 51, 54, 60, 67, 69).

(ii) Predominant involvement of the caudate nuclei and/or putamen, without involvement of the globus pallidus (10 cases: 9, 12, 27, 28, 30, 31, 42, 58, 62, 65).

(iii) Generalized involvement of the basal ganglia as part of another pathology (31 cases: 3, 4, 5, 6, 7, 8 10, 14, 15, 21, 25, 26, 29, 33, 34, 35, 36, 37, 38, 40, 41, 44, 45, 52, 53, 55, 56, 57, 63, 66, 68).

(iv) No involvement of the basal ganglia (11 cases: 1, 2, 13, 19, 20, 24, 46, 49, 59, 61, 64).

(i) *Predominant Involvement of the Globus Pallidus*

Seventeen patients (11 males and 6 females) showed this pathology (Table XXII).

TABLE XXII
Involvement of Basal Ganglia:
Predominant involvement of the globus pallidus

No.	*Clinical type*	*Caudate nucleus*	*Putamen*	*Globus pallidus*	*Cerebellum, other basal ganglia*	*Aetiology*
11	TAR	+	+	+++		Co-intoxication
16	THR			+++	+++	anoxia
17	TAR			++		prem. jaundice
18	TAAt		++	+++		anoxia
22	TAR			+++	+	prem. jaundice
23	TR	+	+	++		prem. infection?
32	TAR			++	+	jaundice
39	AR	+	+	++	++	kernicterus
43	TAR			+++	+++	kernicterus
47	TAR	+	+	+++	++	anoxia
48	TR	+		+++		anoxia
50	TR			++		prem. anoxia
51	TA			+++		anoxia
54	TAR	(+)	(+)	+++	+++	anoxia
60	TAR			+++	+++	kernicterus
67	AR			+++	+++	kernicterus
69	AR			++	++	kernicterus

The macroscopical findings in the basal ganglia were characterized by atrophy and corresponding ventricular dilatation of varying degree. Only in one case (11) was a brown discolouration in the globus pallidus visible on both sides. This is a sequela of red infarction leading to deposits of iron-containing pigment, deriving from possible anoxic changes after a serious burn at the age of one year.

The histological changes in the basal ganglia were uniform in all 17 cases, only the degree of alteration varied. The predominant abnormalities were seen in the globus pallidus, where disappearance or atrophy of ganglion cells occurred in all cases and in some accompanied by intracellular calcifications. The ganglion cell degeneration was combined with satellitosis and more diffuse gliosis. The myelination was diminished or

lacking according to the degree of degeneration of the ganglion cells. In no case were porencephalic areas found, nor were lipid-containing macrophages seen, so degeneration of myelin was not occurring at the time of death. Signs of inflammation were not found in any case, and the vessels revealed only secondary fibrosis.

Eight patients in this group had a history of kernicterus or neonatal jaundice, and in 7 of these brains the changes in the globus pallidus were accompanied by chronic ganglion cell degeneration in the subthalamic nucleus, dentate nucleus and olive. This occurred among only 3 of the 7 cases with a history of perinatal anoxia, and the 2 patients with another aetiology. This observation suggests that kernicterus on the one hand leads to more diffuse changes in the basal ganglia, while anoxia is more selective, causing predominant degeneration of the globus pallidus (Table XXII).

Turning to the clinical picture, all 17 patients except No. 11 had symptoms from birth, 14 patients had tetraplegia, combined with rigidity in 13 and athetosis in 11. Three patients with a history of kernicterus (39, 67, 69) presented no signs of tetraplegia but a marked athetosis, combined with rigidity. Only in one case (18) with a history of perinatal anoxia was there ataxia, and, unfortunately, neuropathological examination in this case was inadequate, as the cerebellum and medulla were not examined.

The frequent occurrence of kernicterus in these cases with predominant lesions of the globus pallidus, in some cases combined with degeneration of the subthalamic nucleus, olive, and dentate nucleus, corresponds to Schmorl's description (1904), and Lund's (1955) and Tygstrup's (1964) of neuropathological findings in patients with kernicterus. They contradict Soeken's opinion, as she concludes that the localisation of the brain damage in kernicterus corresponds to the brain lesions following pure perinatal anoxia. However, the problems of the topographical lesions in C. and O. Vogt's terms have not yet been solved, nor has the problem of the significance of the associated cerebral anoxia in experimentally-produced kernicterus in monkeys (Lucey *et al.* 1964) been elucidated.

The cortical grey matter in 9 of the 17 cases in this series showed a varying degree of chronic ganglion cell degeneration with satellitosis and subpial gliosis. Delayed maturation of the cortical ganglion cells occurred in 5 cases (39, 43, 60, 62, 69) of the 9 cases where there was a history of kernicterus and in 3 cases with a history of perinatal anoxia. This last change was considered due to the sequelae of perinatal damage and not a true dysplasia.

In case 11, with postnatal development of cerebral palsy at the age of one year, atrophic cortical ganglion cells with satellitosis and marked diffuse gliosis only were seen.

Prenatal dysplastic cortical changes were present in 4 of the 17 cases (17, 47, 50, 51) in the form of deficiency of layer formation, and in Nos. 17 and 51 combined with micro- and pachygyria. Two of these patients (Nos. 17 and 50) were premature with birth weights of 1800 g. and 2200 g. respectively. In these cases maldevelopment of the basal ganglia could not be established. Nevertheless this last finding indicates the significance of prematurity in cerebral palsy patients. A possible explanation of this is a great vulnerability of the immature brain tissue (Churchill 1958).

Histological examination revealed no cortical changes in 4 brains (16, 22, 23, 32) of the 17 cases. Two of these were considered normally mentally developed and the 2 others only slightly retarded. The remaining 13 patients were definitely retarded; 3 had an I.Q. below 35.

The age of death (Table XXII) was below 5 years in 12 of the 17 cases, which suggests these patients had severe brain damage. Three of the 4 patients without any cortical changes died before the age of 2 years, and only one (No. 32) reached the age of 7 years.

(ii) *Predominant Involvement of the Caudate Nucleus and/or Putamen, and Not Involving the Globus Pallidus*

Five males and 5 females belong to this group (Table XXIII).

TABLE XXIII

Involvement of Basal Ganglia:

Predominant involvement of the caudate nucleus and/or putamen, and not involving the globus pallidus

No.	*Clinical type*	*Caudate nucleus*	*Putamen*	*Globus pallidus*	*Cerebellum, other basal ganglia*	*Aetiology*
9	TAR	++	++			?
12	TR	+++	(+)	(+)		prenatal + anoxia
27	T	++	++			?
28	H	+ left > right			+	malformation
30	TR	++	++			anoxia
31	TP	++			++	?
42	TAR	++	+++		++	?
58	TR	++	++	+		subdural haematoma
62	TA	++	++			anoxia
65	H	+ left > right			++	tumour

Macroscopical Examination. In 4 of the cases (27, 30, 58, 62) marked microcephaly was present, and one (no. 58) had a bilateral chronic subdural haematoma. In these 4 brains there was moderate ventricular dilatation, but no macroscopically visible abnormalities in the basal ganglia.

Six cases (9, 12, 28, 42, 62, 65) had a normal brain weight. In 2 of these macroscopic examination revealed polycystic degeneration of both putamina and atrophy of the caudate nuclei. The brain from No. 28 (see p. 58) had subtotal aplasia of the left hemisphere and of the left basal ganglia. In one brain (No. 65) a tumour occupying the third ventricle with invasion of the left caudate nucleus was found. The localization of the tumour and secondary hydrocephalus had caused diffuse atrophy of the basal ganglia. The last 2 (12, 31) of these 4 brains with normal brain weight had macroscopic symmetrical atrophy of the caudate nuclei. In case 12 periventricular calcification was visible.

Histological examination confirmed the various changes found macroscopically. All 4 cases with microcephaly and microgyria revealed pure degenerative changes both in the basal ganglia and in the cortical grey matter. The bilateral subdural haematoma in case 58 had led to laminar necrosis of the cortex, delayed myelination of the white matter and pyramidal tract degeneration, besides atrophy of the basal ganglia, especially the caudate nuclei. Cases 27, 30 and 62 showed no other abnormalities than the degenerative changes in the caudate nuclei and putamina.

Histological examination of the brains from the 6 patients with normal brain weight showed that 2 cases (Nos. 9, 42) had chronic infantile necrotizing encephalopathy (see p. 76). In case 12 (see p. 46) the macroscopically visible periventricular calcifications were related to the caudate nuclei, and placed both intra- and extracellularly. Both here and in the putamina marked gliosis was found.

The intraventricular tumour in case 65 was a benign ependymoma with some ingrowth into the left caudate nucleus. Atrophy of ganglion cells and gliosis were seen in the right caudate nucleus. The atrophy was due to pressure from the tumour and possibly also to increased ventricular pressure.

In case 28 with the subtotal left-sided hemiaplasia, marked maldevelopment of the ganglion cells, atrophy, gliosis, and intra and extracellular deposits of calcification were found both in the aplastic left hemisphere and the left basal ganglia.

In the last of these 6 cases with normal brain weight, marked atrophy of the ganglion cells in both caudate nuclei was present, combined with gliosis, especially in the periventricular areas. This case was the only one in the series of 10 patients with a predominant lesion of the corpus striatum showing diffuse cortical dysplastic changes in the form of pachygyria and immature ganglion cells, and the only one where diffuse deficiency in myelination of the white matter occurred.

It can be concluded that neither a specific cause nor a specific clinical picture exists in patients with a predominant lesion of the caudate nuclei and putamina.

Conclusions. This group with predominant lesions of the caudate nuclei and putamina differs from the group with lesions of the globus pallidus (see Table XXII) in the neuropathological findings, aetiology, and clinical picture, including the time of onset of symptoms.

The aetiology in this group of 10 patients is variable (Table XXIII). It is unknown in 5 cases except for a possible enzymatic deficiency in the thiamine metabolism in the 2 cases of chronic necrotizing encephalopathy (Ebels *et al.* 1965). One patient (65) had a tumour.

Only 2 cases (27, 30) with widespread chronic degenerative changes both in the cortex and caudate nuclei and putamina had neonatal jaundice. Kernicterus did not occur. Two others (58, 62) had symptoms from the neonatal period following a difficult delivery. (In the former group with predominant lesions of the globus pallidus 15 of 17 patients had neonatal jaundice, kernicterus and/or perinatal anoxia.)

Clinically, in this group with involvement of the caudate nuclei and putamina all types of cerebral palsy except ataxia occurred. The onset of symptoms was after 6 months of age in 6 patients. (Compare with the globus pallidus cases).

The age of death was high in this group. Only 4 of 10 died before the age of 5 years (see below). (Twelve of 17 patients in the group with involvement of the globus pallidus died before they were 5 years old.)

Age at death in 10 *patients with involvement of caudate nuclei and putamina*

	boys	*girls*
< 1 year	1	0
1— 2	1	0
2— 5	2	0
5—15	1	3
> 15	0	2
	5	5

(iii) *Generalised Involvement of the Basal Ganglia as Part of Another Pathology*

Thirty-one cases showed generalised involvement of the basal ganglia as part of another pathology (Table XXIV).

Group 1. In 12 brains (4, 8, 10, 15, 26, 35, 37, 41, 45, 53, 57, 68), including 4 cases of sequelae of meningo-encephalitis, degenerative changes occurred.

Group 2. In 6 brains (3, 29, 40, 55, 63, 66) diffuse degenerative processes in the basal ganglia occurred, associated with dysplastic changes in the cortical grey matter.

Group 3. Seven brains (6, 7, 14, 25, 33, 52, 56) differed from the first groups by having both degenerative and dysplastic changes in the cortex.

Group 4. In 4 cases (5, 21, 34, 36) a diagnosis of metachromatic or globoid cell leuco-dystrophy was made at autopsy.

Group 5. Two cases (38, 44) have to be considered as odd cases.

Group 1. In 7 of the brains (10, 15, 26, 35, 37, 45, 53) with diffuse degenerative changes there was a degree of microcephaly due to atrophy. Case 37 (a two-year-old boy) had a brain weighing only 250 g. Polymicrogyria and polyporencephalic areas of different size involving both white matter and basal ganglia were found in all these 7 cases. There was irregular, marked dilatation of the ventricular system associated with the atrophy and polyporencephaly.

Histological examination showed pronounced atrophy and disappearance of ganglion cells both in the cortical grey matter and basal ganglia. Diffuse astrocyte proliferation was present, being most pronounced around the porencephalic cysts, which in most cases were traversed by glial trabeculae. The white matter showed complete loss of myelin around the porencephalic areas, but only in a few cases were lipid-containing macrophages found, indicating that active myelin degeneration was occurring at the time of examination. No signs of inflammation could be seen in any of these 7 brains, but in one (15) deposits of intra- and extracellular calcifications were found in the putamen on both sides. Pyramidal tract degeneration secondary to the degenerative processes was present in nearly all cases.

The aetiology was perinatal anoxia in 5 cases. In case 53 there was a possible

TABLE XXIV

Involvement of Basal Ganglia:
Generalized involvement of the basal ganglia as part of another pathology

No.	*Clinical type*	*Caudate nucleus*	*Putamen*	*Globus pallidus*	*Cerebellum, other basal ganglia*	*Aetiology*
3	A	+	+	+		familial, anoxia
4	T	+ left > right	+ left > right	+ left > right		meningitis
5	TAt	+	+	+		familial
6	TH	+	+	+		prem. anoxia
7	TAH	++	+	+		anoxia
8	T	+	+	+		meningitis
10	T	++	++	++		anoxia
14	TR	++	++	++		anoxia
15	T	++	++	++		anoxia
21	TR	+	+	+		familial
25	A	+	+	+	+	jaundice
26	TAP	++	++	++	++	perinatal
29	TAt	(+)	(+)	(+)		?
33	T	++	++	++	++	anoxia
34	TAt	++	++	++	++	familial
35	TR	++	++	++		anoxia
36	T	++	++	++	++	leucodystrophy
37	T	++	++	++		anoxia
38	TR	++	++	++		subdural haematoma, prenatal
40	TR	(+)	(+)	(+)	++	perinatal?
41	TR	++	++	++		meningitis
44	TR	+++	++	++		anoxia
45	T	+++ left > right	+++ left > right	+++ left > right		prenatal infection
52	T	+	+	+		prenatal
53	A	+	+	+		prenatal, anoxia
55	TAAt	+	+	+		familial, anoxia
56	T	(+)	(+)	(+)		prem. jaundice
57	H	++	++	(+)		?
63	T	+	+	+		prenatal, jaundice
66	TR	+	+	+	++	familial
68	H	++ left > right	++ left > right	++ left > right		meningitis

history of prenatal anoxia and in case 45 a prenatal infection could not be excluded.

The clinical picture of cerebral palsy varied according to the localization and degree of the degenerative processes. One brain (case 57) showed degenerative changes in the basal ganglia with unknown aetiology, possibly hypoglycaemia.

The last 4 brains (4, 8, 41, 68) in this group of 12 cases with degenerative changes differed from the above cases in all having different forms of inflammation.

Macroscopically the brains were moderately atrophic with fibrous thickening of the leptomeninges. Polymicrogyria and mantle sclerosis were present in case 41 with a possible history of thrombophlebitis in the sagittal sinus. As the dura was not available for examination this could not be proved. In case 68 the atrophy was much more

pronounced on the right than on the left side. This might have been the sequel of a right-sided carotid thrombosis.

Three of the brains were hydrocephalic with granular ependymitis on the ventricular walls causing stenosis of the Sylvian aqueduct.

Microscopy showed fibrous thickening and infiltration with macrophages and lymphocytes in the leptomeninges. The vessel walls were fibrous and thickened. No inclusion bodies or bacteria could be found at the time of death. In cases 4 and 8 perivascular infiltration with lymphocytes and macrophages was present in the brain tissue, and in case 4, who had had a tuberculous meningitis 6 months before death, calcifications were present in and around some of the vessels in the basal ganglia.

Otherwise histological examination showed changes in the cortical grey matter, basal ganglia, and around the porencephalic cysts as in the previous 7 cases.

Group 2. Examination of 6 brains (3, 29, 40, 55, 63, 66) with generalised involvement of the basal ganglia showed a picture distinct from the first group.

In all 6 brains a varying degree of dysplasia was present in the cortical grey matter with deficiency in layer formation and maturation of ganglion cells. Case 3, with holoprosencephaly (see p. 72), was the only patient in the present series showing marked dysplastic changes in the basal ganglia.

In the brains from cases 40 and 66 the number of ganglion cells in the basal ganglia was slightly and diffusely diminished, but there were patches of atrophic ganglion cells with proliferation of astrocytes as in the other cases, except case 3. In all 6 cases maldevelopment of the cerebellar folia was seen, as the granular layer was thinner than normal and the number of Purkinje cells was diminished in different degrees.

Myelination was deficient in the pyramidal tracts and in the brain stem, and in the cervical part of the spinal cord where it was examined, in all cases.

Polyporencephaly or microgyria did not occur in any of these cases.

The aetiology was either familial or unknown (Table XXIV). Case 52 was premature and had neonatal jaundice, but without blood incompatibility.

In none of these cases was there a history of severe anoxia, and the onset of clinical symptoms was after the neonatal period in 5 of the 6 cases.

Case 55 was the only one in this group who presented degeneration of the dentate nuclei of the cerebellum, and the only patient with symptoms from birth. The clinical picture varied in these cases (Table XXIV).

Group 3. Examination of the 7 brains from cases 6, 7, 14, 25, 33, 52, 56, showed marked dysplastic changes, as well as chronic degenerative changes in the cortex and basal ganglia, with ganglion cell atrophy and proliferation of astrocytes. The brain weight and macroscopical appearance of the brains were normal in 4 cases (6, 7, 25, 56). But in 3 (14, 33, 52) some degree of microcephaly was present. In case 14 with schizencephaly the brain weight at death at 4 years of age was only 320 g. (corresponding to a normal brain weight for a six-month-old infant (Conel 1951)).

Case 52 also had schizencephaly and microcephaly (brain weight 600 g. at death at the age of 9 years and 6 months). In this case polyclastic porencephaly was present in the right hemisphere, as well as the diffuse degenerative and dysplastic changes.

Case 33 had a brain weight of 560 g. at death aged 4 years. Here also irregular macro- and microgyria over both hemispheres and deficiency in development of secondary folia in the cerebellar cortex could be seen. Histological examination showed pronounced deficiency in layer formation and maturation of ganglion cells, both in the cerebrum and cerebellum. The number of ganglion cells was also diminished.

In cases 6 and 25 moderate dysplastic cortical changes were found both in the cerebrum and cerebellum at histological examination, whereas cerebellar dysplasia alone was present in case 7, with a diminished number of Purkinje cells and ganglion cells in the granular layer.

Histological examination of the central nervous system from case 56 showed, as well as a subacute lymphocytic meningitis, chronic degenerative changes both in the cortex and basal ganglia, with ganglion cell atrophy and astrocyte proliferation. Besides this, marked myelin deficiency or degeneration was present in the pyramidal tracts of the brain stem and the whole spinal cord. The picture was identical with amyotrophic lateral sclerosis. The dysplastic changes in the spinal cord were confined to the lumbar part where there was a duplication and dilatation of the central canal. The aetiology in these 5 cases differs from the aetiology in the other two groups. Cases 6, 33 and 56 were premature. Case 33 was severely asphyxiated with the cord around the neck. This corresponds to the severe degenerative changes in this brain. Cases 25 and 56 had neonatal jaundice without blood incompatibility. Case 7 was severely asphyxiated at birth. In case 6 with the severe dysplastic changes the infant may have been born prematurely because of the severe cerebral and cerebellar dysplasia.

Group 4. Brain autopsy revealed leucodystrophy of the metachromatic or globoid cell type in 4 cases (5, 21, 34, 36). As the abnormalities in the myelin sheaths were diffuse the basal ganglia were also involved.

Group 5. *Odd Cases.* Case 38 had been operated on for a bilateral chronic subdural haematoma and this had been followed by a purulent meningo-encephalitis and ependymitis. The resultant secondary changes partly covered the original abnormalities in this brain. The primary lesion was probably a chronic subdural haematoma, but it was impossible to say if the atrophy in the brain alone was due to compression by the haematoma or whether primary anoxic changes were present. Marked gliosis and atrophy of the ganglion cells was found both in the cortex and basal ganglia together with intra- and extracellular calcification.

The brain from case 44 was microcephalic and sclerotic (brain weight 400 g. at death at 4 years of age). The ventricular system was dilated. Histological examination revealed severe astrocyte proliferation in the cortical grey matter, white matter, and basal ganglia. Most ganglion cells were atrophic, and laminar necrosis was present in large areas of the cortical grey matter. These pronounced lesions in this brain were most likely due to perinatal anoxia, which agrees with the history.

Conclusions. All 31 cases were severely mentally retarded, most with an I.Q. below 35, and this accords with the widespread cortical abnormalities. Abnormalities in the basal ganglia occurred in association with rigidity and/or athetosis. Otherwise the clinical picture varied.

The age of death was under 5 years in 26 of the 31 cases, and most of these died before 3 years of age. Case 29 died aged 6 years, and only 4 cases (6, 7, 40, 55) survived to the age of 14 or 15 years. The early death of most of these patients accords with the severe, diffuse abnormalities in their brains. (See Table XXIV).

(iv) *No Proven Involvement of the Basal Ganglia*

In 11 cases no abnormalities of the basal ganglia could be demonstrated by the neuropathological examination. In most instances this corresponds to the clinical picture; three (1, 2, 59) had pure tetraplegia, one (19) monoplegia, two (13, 20) hemiplegia, and two (46, 64) paraplegia, which in one case (46) was combined with tetraplegia.

In 3 patients (24, 49, 61) both rigidity and tetraplegia were found. One would, therefore, expect involvement of the basal ganglia as well. Case 61 had a leucodystrophy of the metachromatic type, but post mortem changes in this brain made it impossible to say anything definite about the basal ganglia. Cases 24 and 49 both had severe dysplasia of the cortical grey matter, and case 49 also of the cerebellum. It is probable that dysplastic changes were also present in the basal ganglia, although this was not proved.

Conclusions. In 6 of this group without changes in the basal ganglia, the cortical abnormalities were classified as dysplastic changes, whereas dysplasia of the cortical grey matter only occurred in 8 cases among the 58 patients with abnormalities of the basal ganglia. Dysplasia only very rarely involves the basal ganglia; in the whole material only one case (case 3) revealed a severe dysplasia of the basal ganglia. On the other hand, quite a few patients had degenerative changes in the basal ganglia associated with cortical dysplasia.

Conclusion

We have not tried to divide the neuropathological lesions described into the entities given by C. and O. Vogt (1911-1924) as we feel that status marmoratus, fibrosus and dysmyelinatus represent different degrees of the same type of lesion rather than separate entities, and that all are due to degeneration and not to true developmental abnormalities. This view is shared by several later authors (Schwartz 1927, 1965, Norman 1947, Malamud 1950, Courville 1953, 1961). The main findings from the present series are the following:

All but 2 of 17 patients with predominant lesions of the globus pallidus had kernicterus or neonatal jaundice and/or severe perinatal anoxia; most of these patients had spastic tetraplegia combined with rigidity and/or athetosis (Table XXII).

No specific clinical picture can be seen in cases with predominant lesions of the caudate nuclei and putamen (Table XXIII); only 3 of these 10 patients had athetosis. Of the other 7 patients 5 had tetraplegia with or without rigidity and 2 had hemiplegia.

In the group with diffuse involvement of the basal ganglia as a part of another pathology (Table XXIV), the aetiological factors are much more varied. Both familial and prenatal factors occur as well as cerebral infection, progressive degenerative

disease and, in some cases, anoxia. Neonatal jaundice was present, but there were no cases of kernicterus. The clinical picture did not include athetosis.

Only in one case (3) with holoprosencephaly was there real maldevelopment in the basal ganglia as part of a maldevelopment of the whole brain.

4. Cerebellum

Abnormalities were found in the cerebellum in 24 patients.

We suspected involvement in 4 more cases, but unfortunately the cerebellum was not available for study.

The Neuropathological Findings

Macroscopical examination revealed abnormalities in only 4 cases. In 2 cases the cerebellum was atrophic — in case 8 following meningo-encephalitis and in case 33 as a result of severe anoxia. In case 63 the cerebellum was small with maldevelopment of the vermis and in case 49 deficient formation of secondary folia could be seen.

The histological findings allow the division of the group into two:

(a) *Cortical cerebellar dysplasia* was the predominant finding in 10 cases (7, 14, 29, 31, 40, 47, 49, 55, 63, 66). In two of these cases (49, 63) with macroscopically visible abnormalities, very pronounced microscopical changes with marked deficiency of folia formation were seen. There were very few Purkinje cells and granular cells in all 10 cases and consequently the granular layer was invariably thinner than normal.

In 5 of these cases (7, 47, 49, 63, 66) degenerative changes characterized by proliferation of the Bergmann glial cell layer and/or gliosis and degeneration of the ganglion cells in the dentate nuclei were present. In all of these 5 cases the case reports showed that perinatal anoxia had been present.

(b) *Degenerative changes of the ganglion cells* were found in 11 cases (8, 16, 22, 25, 33, 39, 43, 54, 60, 67 and 69); in 9 of these the degeneration — predominantly atrophy and satellitosis — was located in the neurones of the dentate nuclei alone.

Of the other 2 cases, case 8 with sequelae of neonatal B. coli meningo-encephalitis showed pronounced ganglion cell degeneration of the cerebellar cortex with diffuse gliosis and satellitosis and marked granular ependymitis. In the other case (33) degeneration of the Purkinje cells and ganglion cells in the granular layer and in the dentate nuclei occurred and here there was a history of perinatal anoxia.

In the remaining 3 of the 24 cases (5, 21, 61) the cerebellar abnormalities were part of a pronounced leucodystrophy with diffuse involvement of the white matter both in the cerebellum and cerebrum.

Abnormalities of the cerebellar white matter apart from these cases of leucodystrophy were found only in one case (66), in the form of deficient myelination of the spino-cerebellar tract. This negative finding may be explained by the early age at which most of our patients died — before the completion of myelination.

Among the 5 patients with clinically verified ataxia, the cerebellum was not available for examination in 2 cases (34, 18). In the other 3 cases (5, 29, 55) different

TABLE XXV

Clinical Findings in 24 Patients with Cerebellar Involvement

Case no.	*Clinical diagnosis*	*Sex*	*Age at death*	*IQ*
7	HTA	f	14 6/12	< 35
14	TR	f	4 years	< 35
29	AtT	f	8 years	< 35
31	PT	f	2 1/12	35—55
40	TR	f	15 years	low
47	HTA	m	1 8/12	retarded
49	TRP	m	9 4/12	35—55
55	At AT	m	14 years	35—55
63	T	m	2 4/12	< 35
66	TR	m	2 years	retarded
8	T	m	10/12	low
16	HT	f	7/12	undetermined
22	ATR	f	2 years	< 35
25	A	m	2 1/12	retarded
33	T	f	4 3/12	< 35
39	AR	m	10/12	retarded
43	ATR	m	1 11/12	retarded
54	ATR	m	2 1/12	retarded
60	ATR	f	2 2/12	retarded
67	AR	m	1 11/12	undetermined
69	AR	m	1 5/12	undetermined
5	At T	m	5 years	undetermined
21	TR	m	3 7/12	< 35
61	TR	m	8/12	retarded

degrees of dysplasia of the cerebellar folia were present, and in case 55 the dysplastic changes were combined with degeneration.

It is important to note that ataxia was only present in 5 cases although cerebellar abnormalities were found in 24 patients.

Among the 11 cases with proved degenerative changes in the dentate nuclei there was proven evidence of kernicterus in 6 cases and of neonatal jaundice without blood incompatibility in one case. A summary of clinical findings is given in Table XXV.

Conclusion

Both degenerative changes and maldevelopment are visible in the cerebellar cortex, whereas degenerative changes only have been found in the dentate nuclei. In the cases with a history of kernicterus the changes are confined to the dentate nuclei.

It is a well known fact that patients with ataxia have involvement of the cerebellum (Courville 1954, Crothers and Paine 1959, Benda 1960, Norman 1963, Ingram 1964). Few of our patients had ataxia, even when the neuropathological examination demonstrated severe cerebellar lesions, but it may be that the involvement of the central nervous system in these patients was so severe that clinical ataxia was masked by other symptoms, such as spasticity, rigidity, and athetosis. The early age at which most of these patients died may also play a role.

5. The Brain Stem, Medulla and Spinal Cord

In view of the severity of the disease it is not surprising that changes were found in the brain stem, medulla and spinal cord.

The brain stem, including the mesencephalon, pons and medulla, and in most cases the upper part of the cervical spinal cord, were examined.

The abnormalities in the brain stem can be divided into two groups:

(1) Primary lesions, which were found in the 2 cases of glioma with direct involvement of the brain stem and in one case of operated hydrocephalus where there were post-infectious changes.

(2) Changes caused by lesions of the upper motor neurone. These can be divided into two subgroups:

(a) pre- and neonatal disorders leading to deficiency of the centrifugal tract formation.

(b) postnatal lesions after partial completion of myelination, leading to a tract degeneration with more or less marked demyelination, as seen in the patients with cerebral tumours. The five cases of leucodystrophy belong to this group.

In this series neuropathological examination of the spinal cord was often impossible, because many of the brains were sent to us from different institutions and hospitals. For this reason we were able to examine the whole spinal cord in only 5 cases (9, 47, 56, 64 and 66).

In one case of chronic necrotizing encephalopathy (9) there was recent degeneration of the anterioı horn cells, especially in the cervical part of the spinal cord. The remaining patients showed varying patterns. Examination of the spinal cord from case 47 revealed maldevelopment of ganglion cells both in the anterior horns and in Clark's columns, as well as partial degeneration in the pyramidal tracts and spinocerebellar tracts, indicating abnormalities in the upper and lower motor neurones. This patient also had a cerebral dysplasia and probably the sequelae of kernicterus.

Case 56 was a pure spastic tetraplegia due to perinatal anoxia. Here primary degeneration of the cortical grey matter, especially the motor cortex, had led to severe pyramidal tract degeneration. The histological picture in the spinal cord was identical with the findings in amyotrophic lateral sclerosis, where the upper motor neurones are damaged.

In case 64 (see p. 66) a traumatic lesion was found in the cervico-thoracic part of the spinal cord (Melchior and Tygstrup 1963) which explained the clinical picture.

If the spinal cord had been available in a larger number of spastic tetraplegias similar changes would certainly have been found.

One case of dysplasia of the whole central nervous system (66) (see p. 51) showed deficient myelination of the pyramidal tract, secondary to aplasia of the upper motor neurone.

Our examination of the five whole spinal cords provided much valuable information and we believe that this examination will continue to be of great importance in the future, as it has been in the past (Litzmann 1880).

6. Calcification

Intracerebral calcification is found in diseases such as hyper-parathyroidism, tuberous sclerosis, Sturge-Weber disease and in some slow-growing gliomas (ependymoma and oligodendroglioma). Idiopathic familial intracerebral calcification also exists as an entity. It can also be seen following cerebral infections, such as congenital toxoplasmosis, and often in brains from patients with sequelae of perinatal anoxia and kernicterus. Calcification can be so extensive that it is macroscopically visible, but more often it is first recognized at histological examination. The localization varies with the cerebral involvement.

Histologically the deposits are present as small granules, both intra- and extracellular. In extracellular calcification clusters of varying size may be seen, frequently bearing no relationship to the blood vessels and indeed without there being any calcification in the vessel walls themselves.

Intracellular calcification is seen as granules in the nuclei and cytoplasm of atrophic ganglion cells without any surrounding satellitosis. The ganglion cells may be incrusted with deposits of calcium granules.

There is no explanation of why intracerebral calcification occurs in some but not in other cases of the same disorder. The occurrence often seems to be related to prolonged cerebral hypoxia.

In the present series, intracerebral calcification was found in 9 cases (12, 15, 16, 28, 38, 48, 51, 68, 69). In all but 3 (28, 38 and 68) they were located in the ganglion cells of the basal ganglia. In 3 cases (16, 48 and 69) the incrusted ganglion cells were limited to the globus pallidus and in 3 others (12, 15 and 51) to the caudate nucleus and putamen. All these patients had a history of perinatal anoxia, and in 2 of them where the incrustation was in the globus pallidus (16 and 69) there had been kernicterus as well. The brain from case 12 was the only one in which calcification was macroscopically visible.

Case 38 had purulent meningitis and encephalitis after an operation for a bilateral subdural haematoma. Intracellular calcification was present in the ganglion cells of the cortical grey matter and in the basal ganglia.

Cases 28 and 68 both had subtotal hemiaplasia of the brain. In case 28, with maldevelopment of the circle of Willis, the deposits were seen extra-cellularly and predominantly in the subarachnoid space of the atrophic hemisphere. In the last case (68) with hemiaplasia (probably following a septic carotid thrombosis), both extra- and intracellular calcifications were present in the ganglion cells of the cortical grey matter as well as in the basal ganglia of the atrophic hemisphere.

CHAPTER VII

Progressive Encephalopathies

Some cases which proved to have a progressing lesion at autopsy are included in the present series. As has been emphasized, the cases were selected on the basis of clinical diagnosis of cerebral palsy and not retrospectively when the autopsy findings were known.

The Little Club (1959) suggested the clinical definition of cerebral palsy as a persistent but not unchanging disorder of movement and posture, appearing in the early years of life and due to a non-progressive disorder of the brain, the result of interference during its development. According to this definition the autopsy findings in a total number of 12 cases (5, 9, 13, 20, 21, 34, 36, 42, 61, 63, 65, 66) of the present series of cerebral palsy revealed that they did not have cerebral palsy in the strict sense.

Three of the patients (13, 20, 65) proved to have benign gliomas (astrocytoma, ependymoma and spongioblastoma), which in all cases had a very slow progression, so that the diagnosis could not be established during life in spite of intensive examination (see p. 63).

Among the other 9 cases, 5 had familial leucodystrophies, one case (21) of the globoid type (Krabbe's disease) and 4 (5, 34, 36, 61) of the sulphatide type (Greenfield's disease). Detailed reports of these have been published by Christensen *et al.* (1960, 1961). Two cases (9 and 42) proved to have chronic necrotizing encephalopathy (Christensen *et al.* 1956, 1963).

The two last patients (63 and 66) were siblings; neuropathological examination showed identical dysplastic changes of cerebrum and cerebellum in both cases, and this must probably be considered as a familial progressive disorder of unknown type, possibly due to an inborn error of metabolism, although intensive metabolic studies did not reveal any known metabolic defect in these cases. The main reason why these cases have been retained in this series is that the diagnoses given above were first established at autopsy or shortly before. They demonstrate the difficulties the clinician has in distinguishing cerebral palsy in a strict sense from slowly progressing disorders in infancy and childhood.

The clinical finding of tumours in three cases with hemiplegia (13, 20, 65), indicates that even if it is present from infancy, but without a definite aetiology, the presence of hemiplegia ought always to arouse suspicion of another disease apart from cerebral palsy in a strict sense. In the section on hemiplegia (cf. p. 57) it is shown that this small group of 6 pure hemiplegic patients had the most varying aetiology of the whole series.

In the five cases of leucodystrophy the clinical findings were tetraplegia in case 36, tetraplegia and rigidity in cases 21 and 61, and ataxia with tetraplegia in 2 cases (5, 34). The relatively frequent occurrence of ataxia among leucodystrophic patients again

suggests that an alternative diagnosis should be considered when this symptom is found. Diffuse involvement of the cerebellum is necessary for the development of ataxia.

The two patients (9, 42) who both had chronic necrotizing encephalopathies showed a clinical picture of athetosis, tetraplegia and rigidity. In these cases the lesions were localized in the caudate nucleus, putamen and brain stem.

Two patients (63 and 66) had tetraplegia, which in case 66 was combined with rigidity. They were brothers, both had marked cortical dysplasia, and in case 66 pronounced degeneration of the basal ganglia was also established.

Conclusion

The clinical findings in these 12 patients who proved to have a progressive cerebral disorder at autopsy emphasize that the presence of hemiplegia and ataxia in patients with a tentative diagnosis of cerebral palsy must lead to suspicion of another disorder. Three of 6 hemiplegic patients and 2 of 5 patients with ataxia proved to have a progressive disorder of the central nervous system. On the other hand, the clinical picture in the 6 patients with progressive cerebral disorders with tetraplegia, in some cases combined with athetosis and rigidity, could not be distinguished from cerebral palsy clinically. This is in accordance with the findings of Benda and Melchior (1958).

CHAPTER VIII

Epilepsy

It has become increasingly common to discuss central nervous system disorders in infancy under the term of the brain damage triad, which includes mental retardation, epilepsy and cerebral palsy.

Regarding the relationship between epilepsy and brain damage, there has been and still is disagreement between the German school of neuropathologists (including Norman) and the neurophysiological school of Penfield. Scholz's monograph (1951) surveys the findings of the German school of neuropathology in particular. Scholz puts forward the concept that all the lesions in brains from epileptic patients must be due to cerebral damage following convulsions. The changes he identifies are primarily the ischaemic nerve cell changes described by Spielmeyer (1922) and are due to disturbances in blood circulation during a seizure. These changes could, if very pronounced, lead to ischaemic necrosis with loss of nerve cells and later glial proliferation. Scholz states, in agreement with previous German authors (Spielmeyer 1927, Bodechtel 1930, Uchimura 1928, Hiller 1936), that the selective tissue damage seen in certain areas of the brain (Ammon's horn, especially the Sommer sector, and the Purkinje cells of the cerebellum) was caused by the special architecture of the vessels in these areas. In the basal ganglia nerve cell loss and gliosis were most frequently seen in the thalamus, but in the cerebral cortex, laminar or diffuse lesions were seen. He also considered status marmoratus and dysmyelinatus (Vogt) as lesions produced by seizures. It is likely that in Scholz's opinion the macroscopically visible lobar sclerosis of the cerebral and cerebellar cortex, as well as the cortical polyporencephalic processes, were due to the same cause.

As seen from the report of the Little Club study group (1961) on acute hemiplegia in childhood there still exist two different views about the pathogenesis of brain lesions found in brains of epileptic patients. Norman maintains in accordance with Scholz that epileptic seizures, besides producing the well known small foci of ganglion cell degeneration, especially in the region of the hippocampal gyrus, can cause large asymmetrical lesions of the brain, sometimes leading to hemiatrophy. The hypothesis that hemiatrophy of the brain can arise as a sequel of grand mal seizures has never been verified. He does not pay much attention to the double pathology of brain lesions which is suggested by (among others) Gastaut (1957, 1960). According to this theory primary brain oedema can give rise to lesions of the hippocampal gyrus due to compression, and later on be the focus of origin of epileptic seizures, during which further oedema arises, and a vicious circle is built up.

Another factor which has to be taken into consideration is the difference in the findings in brains from patients dying in or having had status epilepticus many times, and the lesions in brains where the patients never had had status epilepticus. In the first group the lesions are due to diffuse brain oedema and consequent long-standing

anoxia, whereas the localized lesion in the second group can partly be explained on the basis of localized vascular compression.

Penfield (1941) expressed another view of the relationship between brain damage and epileptic seizures. He emphasized that an epileptogenic focus could either consist of abnormal grey matter resulting from periodic closure of minute blood vessels, or could arise as a consequence of grey matter not obviously abnormal in itself but influenced in an abnormal manner by an adjacent lesion in another part of the brain. This view is supported by the well known fact that epileptic foci can move from one area to another in the same hemisphere, and cross to the other hemisphere. This has been verified by EEG. A detailed neurophysiological study of children with cerebral palsy and abnormal EEG's has recently been published by Trojaborg (1966). His series includes part of the present material.

One of us (E.C.) has examined a series of 96 brains from patients with genuine epilepsy living for many years at Filadelfia, the Danish hospital for chronic epileptics. In all these brains diffuse and/or more or less localized unspecific chronic ganglion cell degeneration, satellitosis, and subpial gliosis were found, but there was no hemiatrophy or porencephaly. These abnormalities were of the same kind and localization as the histological findings of Scholz's genuine epilepsy material. However, from a histological point of view it is impossible to distinguish between an original epileptic focus and a lesion following oxygen deprivation during a prolonged epileptic seizure.

If Scholz's and Norman's theory were correct we would have expected, among this group of patients with prolonged severe convulsions all finally leading to institutionalization, that some of them would have had changes such as hemiatrophy, porencephaly, or lobar sclerosis.

The neuropathological findings in the present material from 30 patients with grand mal epilepsy in a total number of 42 patients with epileptic seizures support our point of view, that the major brain damage is primary to the seizures. Of the 27 patients without epileptic seizures, 16 had predominant lesions of the basal ganglia, 4 were pure hemiplegic and 4 para- and diplegic.

Three patients with progressive encephalopathies developed grand mal epilepsy in the course of their disease (2 cases of metachromatic leucodystrophy (5 and 34), and one case of infantile chronic necrotizing encephalopathy (42)).

As the aetiology of chronic necrotizing encephalopathy is unknown it could be claimed that the pathological finding in this case was secondary to a so-called genuine epilepsy, but we have another case of chronic necrotizing encephalopathy (case 9) in our material without epileptic seizures. Therefore the epileptic seizures are considered secondary to the original brain lesion in the case of necrotizing encephalopathy.

Petit mal occurred in six cases but only in association with grand mal seizures.

Infantile spasms occurred in 8 cases. In 4 of these (12, 23, 45, 53) the seizures were considered secondary to perinatal anoxia, in 2 (63, 66) there was severe cortical dysplasia and in one case (68) cerebral inflammation was present. In one case (20) a spongioblastoma was found. This observation of the variable aetiology and neuropathological findings in infantile spasms is in complete agreement with our conclusions

in the previous paper (1960). Here six autopsy reports were presented from children with infantile spasms and 'hypsarrhythmia'. The pathological-anatomical findings represent endogenous as well as exogenous changes and transitional cases. The typical findings in all cases were changes in the cortex, either degenerative or dysplastic alterations. The theory was presented that infantile spasms and hypsarrhythmia depend on two factors: (1) the degree of maturation of the nervous system, especially the ganglion cells, and (2) the age of the patients, so that the syndrome can only be seen when there is a certain discrepancy between (1) and (2). This could explain the many aetiological theories and the effect of various therapeutic agents including ACTH. Similar findings are reported from Japan by Okuyama (1965).

These findings indicate that a primary brain damage very often leads secondarily to epileptic seizures, and that cyst-formation, hemiatrophy, and other large focal degenerative changes in brains from patients with epilepsy are primary to and not sequelae of the seizures.

CHAPTER IX

Summary and Final Conclusions

We have presented data on 69 patients with cerebral palsy who died between the years 1948 and 1964 and in whom a neuropathological autopsy examination has been carried out. The 69 patients are collected from a clinical material of more than 1,000 patients with cerebral palsy all of whom have been examined at the University Clinic of Paediatrics, Rigshospitalet, Copenhagen.

Fifty-five of the patients had either pure tetraplegia or tetraplegia combined with other forms of cerebral palsy. There is only one case of pure paraplegia, which corresponds with the clinical experience that these patients often survive until adult life, and die outside hospitals. Pure hemiplegia was present in 6 patients, and monoplegia in one. Athetosis with or without rigidity occurred in 6 patients, and occurred in combination with other forms of cerebral palsy in another 16 patients.

Ataxia is considered to be a relatively rare symptom in cerebral palsy, particularly in severely involved patients like those in the present series. Here this symptom was present only in 5 patients, and no case of pure ataxia occurred. Furthermore autopsy revealed that two of these patients had leucodystrophy and therefore did not belong to the cerebral palsy group *sui generis*.

All the cases of cerebral palsy *sui generis* except 4 had damage of the cerebral cortex. In 10 further cases where the cortex was not involved the brain autopsy revealed that the cases did not really belong to the cerebral palsy group.

Only 11 cases had no involvement of the basal ganglia. Six of these belonged to the cortical dysplasias, and they represent about half of the dysplastic cases (in all 14). This indicates that cortical dysplasia in cerebral palsy patients is likely to occur together with normal basal ganglia. Only one patient (case 3) in the whole material had a true dysplasia of the basal ganglia. The explanation of this might be that patients with severe general dysplasia of the brain, including the basal ganglia, die in foetal life or early in neonatal life, and therefore will not be included in a group of cerebral palsy patients.

The following conclusions can be drawn by comparing the aetiology, the clinical picture, and the neuropathological findings in the present material:

1. In pure tetraplegia the lesions predominantly involve the cortex, but when tetraplegia is combined with rigidity the basal ganglia are also severely damaged. It therefore seems to us useful to distinguish clinically between these two types of tetraplegia. In nearly all cases of tetraplegia, both in its pure forms and when it is combined with rigidity, the lesion was acquired, most often following perinatal anoxia. The lesions in the brains are severe and widespread. Most of the patients have epileptic seizures, mental retardation and microcephaly.

2. The pure spastic hemiplegic patients had either a tumour in, or a maldevelopment of one hemisphere. In the cases of spastic hemiplegia combined with other signs and symptoms, both hemispheres are invariably involved but one more than the other.

3. The 5 patients in the paraplegic and diplegic group show a varying aetiology. In 3 cases there was a family history of neurological disease; one of these was also premature and forceps-delivered, and in another there had been breech presentation. One had a history of precipitate delivery and in the last case the aetiology was unknown. Here and in two of the cases with a positive family history cortical dysplasia was found, whereas the third patient with familial disorder and breech delivery was the case with pure paraplegia and with lesions limited to motor cortex and spinal cord.

These facts suggest we are dealing with a group which differs from clinical groups of paraplegic and diplegic patients, as most of these are premature and have a longer survival.

4. Most patients with pure athetosis had had kernicterus, and only a few had severe anoxia. In all these cases the brain damage was localized to particular parts of the basal ganglia including the amygdaloid and dentate nuclei. On the other hand almost half of the cases who had had kernicterus did not have athetosis alone, but also had spastic tetraplegia, usually combined with rigidity, and in addition had more widespread brain lesions.

5. Ataxia was found in 5 patients combined with other types of cerebral palsy, but pure ataxia did not occur in the present series. This relates to the fact that isolated cerebellar abnormalities were not proved in any case. The reason why ataxia was only diagnosed in 5 patients, although neuropathological examination revealed cerebellar abnormalities in 24 cases is discussed on page 108.

6. *Associated Findings.* Epilepsy occurred in 60 per cent of our patients, which could be expected as it is common in organic brain damage. We consider it secondary to the brain lesion. In the present series where we are dealing with severely damaged cerebral palsy patients, it has been impossible to prove any connection between the occurrence of eye symptoms and particular neuropathological findings.

7. When perinatal damage has occurred the symptoms will start at birth and continue throughout life. In contrast to this, patients with maldevelopment may only present some minor transient neonatal disturbances and frequently they appear to develop normally during the first months of life.

8. Patients with perinatal damage die within the first 5 years or usually survive into adulthood. In contrast, patients with dysplasia may die at any time in childhood.

A neuropathological classification has been attempted (Table XXVI) in order to see if this could improve the classification and understanding of cerebral palsy. This simple classification tentatively links the lesion both with the clinical findings and with the presumed aetiology.

A number of questions arise which future research must solve.

Brain autopsy revealed that 3 of 6 patients with pure hemiplegia in the present series had benign, slow-growing tumours. It is clearly of interest, especially from a clinical point of view, to confirm or disprove that patients with pure hemiplegia have a definite one-sided lesion not belonging to cerebral palsy *sui generis*.

The finding that there is a comparatively symptom-free period in children who develop cerebral palsy because of a dysplasia, in contrast to patients with severe perinatal lesions of degerative type, needs to be followed up in a larger series.

TABLE XXVI

A Neuropathological Classification

Neuropathology	*Possible Aetiology*	*Clinical Picture*
Cortical degeneration	anoxia	tetraplegia
Cortical dysplasia	? genetic	tetraplegia
Cortical degeneration linked with damage to any basal ganglia	anoxia	tetraplegia + rigidity
Globus pallidus damage	kernicterus or severe anoxia	athetosis
Globus pallidus + other basal ganglia	kernicterus	athetosis + tetraplegia
Cortical degeneration or dysplasia of only one hemisphere	vascular lesions ? genetic	hemiplegia
Cortical degeneration or dysplasia predominantly of one hemisphere with involvement of the other	anoxia and varying	hemiplegia + tetraplegia

One of the major prospects for future neuropathological studies in cerebral palsy is to enlarge the autopsy material to include clinical cases where the cerebral palsy is of a minor degree. Hopefully valuable neuropathological information will thus be obtained as more localized lesions will be present than in the present material. Brains from these cases are difficult to obtain, as these patients most often die outside hospitals and institutions. Such studies, therefore, depend on a close collaboration between a large group of people. The laws of different countries have also to be taken into consideration.

The spinal cord in the present series and in many other series has only been available for neuropathological examination in a few instances. The study of the spinal cord is invaluable both with regard to primary lesions in the cord and to secondary changes caused by the brain lesion. This examination ought to be a routine in cerebral palsy autopsies.

Further study of isolated lesions of the basal ganglia is needed to find out the exact role of the ganglia which, except for the globus pallidus, has not been determined.

Close co-operation is necessary between biochemists, geneticists, gerontologists, clinicians, and neuropathologists if progress is to be made. The neuropathological examination itself must now be extended, as more histochemical and electron-microscopical techniques are available to help solve the many problems of cerebral palsy.

APPENDIX

Pathological Material and Staining Methods

All brains were placed in 10 per cent saline-formaldehyde solution hanging from a string around the basilar artery for at least 14 days.

All brains were weighed after fixation.

Macroscopic examination included description of leptomeninges, basal arteries and the appearance of the convolutions. Most brains were cut in coronal sections and both the ventricular system and the structure of the surface were carefully examined macroscopically. Brain stem and cerebellum were cut in horizontal sections.

Routine specimens for histological examination were taken from frontal, temporal, and motor cortical regions, from several parts of the basal ganglia including the cortex of insula Reilii, from different levels of the brain stem and from the cerebellum. The number of specimens taken varied according to the lesions present in the individual brain.

Paraffin embedding was the routine method used. The basal staining methods used were haematoxylin-eosin, van Gieson-Hansen's stain, Weil's myelin stain and Einarson's gallocyanin stain for nucleoprotein. Mallory's aniline-blue orange-G was useful for looking for gliosis and myelin degeneration; for fibrillary gliosis Holzer's stain was used. Frozen sections were used for Cajal's astrocyte stain and Penfield's oligodendroglia and Hortega's microglia staining methods.

In certain cases cresylecht-violet and toluidin blue stains were used to examine for metachromasia, both on paraffin and frozen sections. Frozen sections were further used for Sudan III stain for lipid, whereas Sudan B staining was performed on paraffin sections. Walther's, Davenport's, and Bielchowsky's endofibril staining methods were carried out on both paraffin and frozen sections in special cases. PAS stain, Gram's bacterial stain and Turnbull's iron stain were also included in the staining methods and used in special cases.

Celloidin embedding was not carried out.

All paraffin sections had been through xylol, 99%, 96% alcohol, distilled water for removing paraffin before staining.

Staining Methods Used

1. Bielchowsky's stain for endofibrils.
2. Cajal's stain for astrocytes.
3. Stain for metachromasia (a) Cresylecht-violet
   (b) Toluidin-blue.
4. Davenport's stain for endofibrils.
5. Einarson's stain for nucleoproteins.
6. Gram's stain for bacteria.
7. Haematoxylin-eosin stain.

8. Holzer's stain for fibrillary astrocytes.
9. Van-Gieson-Hansen's stain.
10. Mallory's aniline-blue orange-G stain.
11. PAS (periodic acid Schiff) stain.
12. Hortega's microglial stain.
13. Penfield's oligodendroglial stain.
14. Sudan B stain for lipoprotein.
15. Sudan III stain for lipid.
16. Thionine stain for Nissl substance.
17. Turnbull's iron staining.
18. Walther's neurofibril stain.
19. Weil's myelin stain.

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Index