THE PATHOLOGY OF ACUTE INFANTILE CEREBRAL DIPLEGIA

By

A. L. WOOLF, M.D.*

From the Department of Pathology, Midland Centre for Neurosurgery, Smethwick

IN this paper, the term Acute Infantile Cerebral Diplegia has been used to denote a group of cases in which a spastic paralysis, affecting principally the lower limbs, develops suddenly in infancy or childhood. The course of the disease is remarkably uniform in the majority of cases, thereby suggesting a common pathogenesis.

The malady characteristically supervenes in the course of a febrile illness, especially when accompanied by dehydration, or associated with suppuration in the head or neck. The onset is usually dramatic, with convulsions which may remain unilateral, or occur simultaneously or successively on the two sides and may be preceded or followed by coma. When these acute manifestations have subsided, the patient is found to be paralysed, the legs being predominantly affected, though the arms may be involved to a less extent. In the weeks that follow this initial phase, the legs become progressively more spastic and the patient is often found to be demented. There may be blindness, without loss of the reaction of the pupil to light. From the clinical description of Acute Infantile Quadriplegia by Schlesinger and Welch (1952)—which is probably the same illness as that discussed here—it would appear that the paralysis may occur, on occasion, without preliminary convulsions. The patients may survive for many years, often in hospitals for the mentally defective. During the passage of time, the early brief period of normality comes to be discounted and a diagnostic label of Little's disease is given. It must be emphasized, that the cases under discussion are all normal for several months after birth, a feature which compels their removal from the group of Little's disease. In the latter group, the disease originates in the pre- or para-natal period. The analysis of the pathogenesis in Little's disease is much more difficult than in Acute Infantile Cerebral Diplegia, owing to the complexity of the noxious factors acting on the brain during foetal life and at birth.

Apart from the bilaterality of the paralysis in Acute Infantile Cerebral Diplegia, there is much in common between this disease and Ford's (1952) Acute Infantile Hemiplegia of Obscure Aetiology. The name given to the bilateral condition in this paper has been chosen to stress this similarity. The term Cerebral Diplegia has been used in preference to Bilateral Hemiplegia as it indicates the resemblance of the patient in the chronic phase to patients in the Little's Congenital Cerebral Diplegia group. Bilateral Hemiplegia is usually considered to imply a bilateral, upper motor neurone paralysis affecting upper and lower limbs to an approximately equal extent, while Cerebral Diplegia indicates the predominant involvement of the lower extremities. The term Acute Infantile Quadriplegia, as used by Schlesinger and Welch, describes the state of the patient accurately, but fails to draw attention to its similarity to that of patients with Little's Congenital Cerebral Diplegia.

* Part of this work was done while holding a Travelling Fellowship from the British Postgraduate Medical Federation.

Although patients with Acute Infantile Cerebral Diplegia differ from those with Ford's Acute Infantile Hemiplegia in rarely being in excellent health at the time of the initial attack, the two diseases resemble one another in the acuteness of the onset, often with convulsions and loss of consciousness, the residual paralysis and frequently associated dementia and the long period of survival with consequent rarity of post-mortem examination. Owing to the lack of post-mortem reports, the pathogenesis of neither condition is completely clear, though Ford suggests that Acute Infantile Hemiplegia is due, in some cases, to vascular lesions and describes a personally observed case with softening of the motor cortex associated with a thrombosis of the superficial branches of the middle cerebral artery.

The object of this paper is to describe the changes in the brains from three cases of Acute Infantile Cerebral Diplegia surviving for many years after the acute stage and to discuss the pathogenesis in the light of these changes. A fourth adult case will be described to illustrate certain points arising from the discussion.

Case 1

Clinical History

The patient was a girl born on 23 November, 1928. On 5 June, 1934, she was admitted to Guy's Hospital. I am indebted to the Medical Superintendent of this hospital for the following extract of notes made during the patient's stay there.

The child had been attending out-patients for the previous three years for a variety of complaints, viz. worms, urticaria, bronchitis and tonsillitis.

Between the ages of three and three and a half years, she had many curious attacks, in which she was unable to see, her pupils were dilated and she appeared pale. Her tonsils were removed on 2 May, 1934, following repeated sore throats. On the evening of 4 June, she felt ill and on waking up on the 5 June, her mother noticed a lump on the left side of the neck. She was admitted to Guy's Hospital. On examination, she was very pale and in poor condition. P. 140/min., T. 103° F., R. 30/min. A mass of glands the size of a walnut was visible and palpable in the upper part of the left anterior triangle in the neck. The mass was in part superficial to the sternomastoid, but was not adherent. The throat was inflamed. There was no abnormality in the chest, abdomen or nervous system. On the next day her condition was a little worse. Râles and rhonchi were diffusely present in the chest. The blood urea was 27 mgm. per 100 ml. On the 7 June, the urine contained a trace of albumin, red blood cells, leucocytes, epithelial, hyaline and granular casts. Albumin and blood were observed daily in the urine until the 17 June, after which no further observations are recorded. On the 9 June, the patient's face was pale and puffy, but no oedema was apparent on the legs or back. She had been running an intermittent pyrexia between 97° and 105° F. since admission. Her pulse rate had varied between 100 and 130/min. On the 13 June, the cervical adenitis was subsiding. On the 17 June, a papular rash appeared on the trunk and by the next day, the exposed parts had a blotchy appearance.

In the evening, convulsions occurred on the right side. They were relieved after a few minutes by lumbar puncture, which yielded cerebrospinal fluid under pressure. The fluid contained 2 r.b.c. and 1 lymphocyte per cub. mm. and 15 mgm. per 100 ml. of protein. Chloroform was administered and large quantities of chloral given rectally, after which the convulsions of the limbs ceased. The facial convulsions ceased after about 2½ hours. The next morning, aphasia and extensor plantar responses were observed. By the 21 June, the pulse rate had fallen from 160/min. to 70/min., aphasia was still present and there was a right facial weakness. There was no papilloedema. The cerebrospinal fluid showed 56 r.b.c., 6 lymphocytes and 4 polymorphonuclear leucocytes per cub. mm. There was 45 mgm. per 100 ml. of protein, the Lange curve and Pandy test were normal. An area of tenderness and oedema was present behind the right mastoid process. This is the only reference to the laterality of the oedema, and there is no indication as to the side upon which craniotomy was subsequently performed. These events took place over twenty years ago and it has proved impossible to contact anyone with a clear memory of the case. In view of the right sided nature of the convulsions and the left sided predominance of the cerebral lesions later to be described, it may well be that this note by a medical student was incorrect and that the oedema was in fact on the left side. On the 22 June, Mr. W. J. Ferguson opened up the mastoid air cells (presumably on the left side), explored the middle fossa and made a trephine hole above and posterior to the meatus. The dura was observed to be bulging slightly but there was no extradural abscess. A cannula was passed through the dura towards the motor area. By the 23 June, the pulse was 120/min. but the patient was still febrile and aphasic. Hypertonic saline was administered by rectum. On the 24 June, the temperature fell to normal. On the 2 July, the patient was still aphasic and

unable to understand the spoken word. She was incontinent of urine and faeces. On the 13 July, the cerebrospinal fluid showed 4 lymphocytes per cub. mm., 50 mgm. per 100 ml. of protein and 700 mgm. per 100 ml. of chlorides. The patient was discharged to the Fountain Hospital on the 2 August, 1934.

The aphasia and right sided facial weakness persisted and the child altered greatly in personality, becoming dirty in her habits, speaking only in grunts and putting everything into her mouth.

On examination on the 17 August at the Maudsley Hospital (Dr. Mildred Creak), she was seen to be pale and ill, behaved like an idiot and showed an aphasia thought to be predominantly receptive; she did not appear to be deaf and showed no papilloedema or optic atrophy. She was returned to the Fountain Hospital where she was restless and destructive but less faulty in her habits. After two years she developed minor epileptic seizures, in which she gave a jerk and almost fell to the ground. Her mental age remained under one year. She was transferred to St. Lawrence's Hospital, Caterham, where she was described as a low grade imbecile with epilepsy and spastic diplegia, walking with difficulty on her toes. She died of bronchopneumonia, following status epilepticus, sixteen years after the onset of the acute illness.

The post-mortem examination was carried out by Dr. M. K. Beattie on the 22 December, 1950, and I am indebted to her for the following extract from the post-mortem report and for the opportunity to examine the brain and spinal cord.

External Appearances

The body was that of a rather obese young female. The obesity was general and did not show any abnormal distribution. There was marked cyanosis of the fingers, lips and ears.

Internal Examination

Head and neck: The skull was extremely thick. The thickening was irregular, measuring up to ¾ in. There was marked hyperostosis of the anterior and middle fossae of the skull, forming rather smooth, nodular projections and reducing considerably the internal capacity of the cranium. This was most marked on the left side and affected the anterior and middle fossae but not the posterior. The brain which weighed 1,005 gm., was small, corresponding to the reduced capacity of the skull. The olfactory bulbs were removed from narrow recesses in the bone, but were not adherent to the skull. The optic nerve was obscured by the overlapping bone. The brain and spinal cord were fixed uncut. The quantity of cerebrospinal fluid appeared to be excessive. The pituitary was compressed antero-posteriorly. Hypertrophied lymphoid tissue was noted at the back of the tongue and the tonsils were also enlarged. The thyroid was unusually small.

Thorax: The thymus was persistent. The aorta was narrower than normal, but otherwise normal. There was creamy pus in the bronchi, bronchopneumonia in both lungs and a mucocele of the gall-bladder associated with a stone in its neck.

Examination of the Brain

The convolutions of both frontal lobes were narrower than normal. On coronal section, the brain showed marked hydrocephalus of the left lateral ventricle including its inferior horn. The right lateral ventricle was also a little enlarged. The third ventricle was dilated and distended posteriorly so as to form a diverticulum lying dorsal to the pineal gland. There was slight enlargement of the fourth ventricle. The left superior temporal and the superior half of the middle temporal convolutions were markedly atrophic. The white matter of the whole of the left temporal lobe, with the exception of the hippocampal gyrus, was extremely hard and whiter than that of the rest of the brain. The pulvinar of the left side was so foreshortened as to appear absent on coronal section. In a similar way, the left lateral geniculate body did not appear in sections in which the body on the right side was large and prominent. The spinal cord appeared normal. The dural sinuses were not available for examination.

Histology

Frozen sections from the right frontal lobe were stained with scharlach R, Holzer and Gros-Bielschowsky. Frozen sections from each temporal lobe were also stained with Holzer. Blocks were taken for celloidin embedding from the following regions: left and right temporal lobes at two different levels, from the right and left parietal lobes, the left lateral lobe of the cerebellum, the brain stem at all levels and the cervical cord. Sections were stained with cresyl violet, haematoxylin and van Gieson, Loyez, phosphotungstic acid-haematoxylin and Holzer.

Findings

There was dense fibrous gliosis of the white matter of both *frontal lobes* and the *left temporal lobe* (Figs. 1 and 2). The gliosis was least marked around the ventricle. Less severe gliosis was present in the *right temporal lobe*—including sclerosis of the *Ammon's horn*—and the *right parietal lobe*. In the latter, the gliosis was only marked on approaching the Sylvian fissure. In the occipital lobes, gliosis was slight and confined to the digitate white matter. There was severe pallor of myelin staining in the *superior* and *middle temporal convolutions* on the left side and in the dorsal part of the *left frontal lobe* (Fig. 3). There was slight pallor of

FIG. 1.—Case 1. Right frontal lobe, showing dense fibrous gliosis of the white matter, sparing the periventricular tissue. Frozen section stained with Holzer.

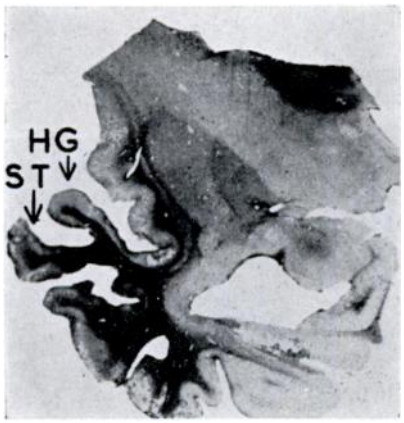

FIG. 2.—Case 1. Left temporal lobe, showing sclerosis and shrinkage of the white matter with ulegyria of the superior temporal convolution and gliosis of the dorso-medial nucleus of the thalamus. Frozen section stained with Holzer.
HG = Heschl's gyrus. ST = Superior temporal gyrus.

myelin staining in the dorsal part of the *right frontal lobe*. The pallor of myelin staining was due to a reduction in myelinated fibres which was paralleled fairly exactly by the loss of axis cylinders. The remaining myelin sheaths were more slender than normal and often showed globular swellings. The axis cylinders appeared normal. Throughout the rest of the brain the myelin was well preserved. Only a very occasional compound granular corpuscle was seen in the Virchow-Robin space in *the frontal lobes*.

Considerable areas of the cortex of the *left temporal and both frontal lobes* showed a laminar sclerosis with status spongiosus of the third layer. The most severe degeneration was found at the depths of the sulci, where complete loss of the normal cortical architecture was encountered. In the anterior part of the *superior temporal gyrus*, there was complete loss of nerve cells from all layers of the cortex, with marked narrowing of the underlying digitate white matter, resulting in ulegyria. Ulegyria was also seen in the *left frontal lobe*, on either side of the sulcus between the *middle* and *inferior frontal gyri*. The gliosis severely affected the capsulae externa and extrema on the left side, but only to a slight extent on the right. There was severe gliosis of the *dorsomedial nuclei of the thalamus* on both sides, with almost total loss

https://doi.org/10.1192/bjp.101.424.610 Published online by Cambridge University Press

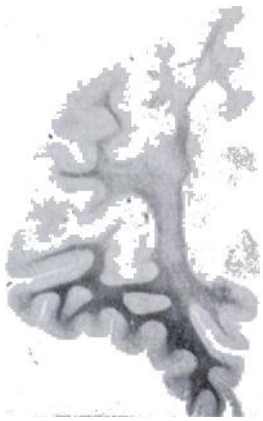

FIG. 3.—Case 1. Left frontal lobe, showing pallor of myelin staining of dorsal part of white matter. Loyez.

of nerve cells. There was a very slight diffuse gliosis of the *globus pallidus* on each side, with accentuation around some of the vessels. The nerve cells and myelin sheaths in the *putamen*, *globus pallidus* and *caudate nucleus* on both sides were normal in appearance. Dilatation of the perivascular (Virchow-Robin) space was more marked around the vessels in the white matter of the frontal lobe than those in the occipital lobe, a few lymphocytes being present between the collagenous fibres.

CASE 2

Clinical History

This child was born normally at term, and, though kept for a long time in a "warm bed", developed normally until the age of nine months, when high fever and convulsions developed

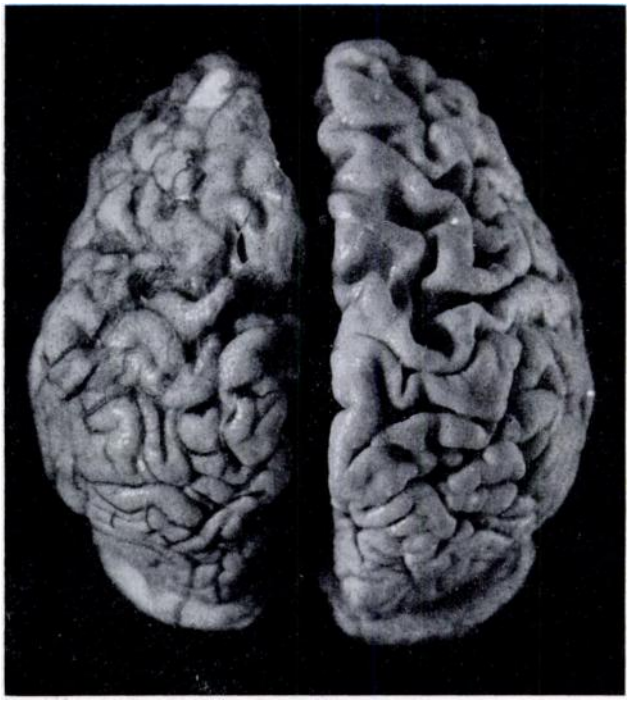

FIG. 4.—Case 2. The brain viewed from above showing atrophy of the dorsal parts of both cerebral hemispheres.

https://doi.org/10.1192/bjp.101.424.610 Published online by Cambridge University Press

suddenly in the course of an otitis media. The child remained for six months in the Children's Clinic in Leipzig, but failed to make any further progress, never sitting up or being able to talk. He was transferred to a home and then, at the age of 5 years, to the Landesanstalt at Chemnitz-Attendorf, where he was found to be in poor general condition with his body extended and rigid, though it was possible to move the limbs passively without spasm occurring. The tendon reflexes were slightly increased. No further convulsions occurred. The child was quite unclean, apathetic, and frequently burnt himself. He made no further mental progress and died at the age of six years from acute tonsillitis and lobar pneumonia.

No details are available as to the findings at autopsy, but through the kindness of Professor W. Scholz, I am able to give the following details of the examination of the brain which was carried out at the Deutsche Forschungsanstalt für Psychiatrie in Munich.

Examination of the Brain

The brain, which was fixed in formalin, weighed only 380 gm. Both cerebral hemispheres appeared to be normally developed, but were severely atrophic so that there was gaping of the sulci between convolutions which were firmer than normal. These changes were most marked on the mesial and basal aspects of the occipital lobes, but were also prominent further forward on the dorsal aspects of the frontal and parietal lobes (Fig. 4). There was marked dilatation of the lateral ventricles, especially in the region of the posterior horns. The ependyma was smooth. The corpus callosum was normally formed but extremely thin. In coronal sections through the frontal lobes, the cortex was narrowed, especially in the depths of the sulci. The white matter was shrunken and harder than normal, but retained its white colour. The basal ganglia appeared normal to the naked eye. The white matter of the cerebellar hemispheres was very hard and yellow, and the foliae appeared atrophic.

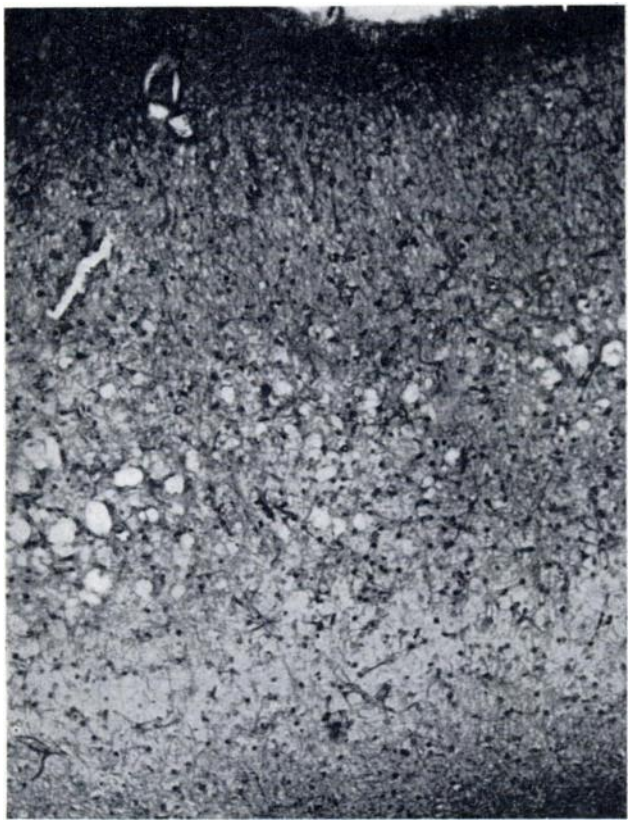

FIG. 5.—Case 2. Basal region of occipital lobe, showing dense gliosis of cortex, with status spongiosus of the third layer. Frozen section, stained with Holzer. ×100.

https://doi.org/10.1192/bjp.101.424.610 Published online by Cambridge University Press

Histology

Blocks were taken from the basal part of the occipital lobe, through the entire cerebral hemisphere at the level of the optic tract, the central region, the frontal lobe and the cerebellum. Frozen sections were stained with Holzer and Spielmeyer and celloidin sections with Nissl.

The basal region of the occipital lobe showed complete destruction of the cortical architecture with status spongiosus in the third layer. There were many compound granular corpuscles both in the perivascular spaces and disseminated through the cortex. There was a dense gliosis of the cortex with accentuation, both in the superficial layers and around the spaces in the spongy third layer (Fig. 5). The white matter showed a uniform, moderately severe, diffuse pallor of myelin staining, with slightly less pallor of the optic radiation. With higher magnification, the myelin sheaths were seen to be reduced in number and showed at intervals, globular or fusiform swellings or a varicose outline. There was a very dense, uniform, fibrous gliosis throughout the white matter. There were numerous fat-laden compound granular corpuscles in the Virchow-Robin spaces, but none elsewhere in the white matter. There were also moderate numbers of lymphocytes in the Virchow-Robin spaces, but the latter were not notably dilated, though the space of His was unusually wide. There was a marked increase in the astrocytic nuclei, which were of normal form, and there was a moderate diffuse increase in microglia. A section through the *hemisphere at the level of the optic tract* showed a less dense though still marked fibrous gliosis affecting the lateral part, and especially the digitate white matter, of the parietal lobe, with a very slight gliosis of the rest of the white matter (Fig. 6). The dorsal part of the parietal lobe also showed a marked fibrous gliosis of the upper two layers of the cortex and status spongiosus of the remaining layers.

Central region: Few nerve cells remained in the cortex, but those present had a normal appearance. There was an increase in astrocytes, some of which were hypertrophic. Formation of glial fibres in the cortex was only slight, but a status spongiosus was present. In the white

FIG. 6.—Case 2. Section through cerebral hemisphere at level of optic tract, showing fibrous gliosis of dorsal part of hemisphere, largely confined to white matter. Frozen section stained with Holzer.

https://doi.org/10.1192/bjp.101.424.610 Published online by Cambridge University Press

matter there was a moderately dense fibrous gliosis. Pallor of myelin staining was only slight, but the myelin sheaths were reduced in number and those remaining showed beading and varicosity. Moderate numbers of compound granular corpuscles were disseminated throughout the cortex and concentrated around the vessels in the white matter. In the *frontal lobe*, there was marginal gliosis in the cortex, with a moderately severe fibrous gliosis of the superficial two layers and status spongiosus of the deeper layers, as in the occipital lobe, though more moderate in degree. Over the most severely affected areas of cortex, the arachnoid was thickened and contained mononuclear cells in its interstices. *Insula:* There was an occasional nerve cell with homogenizing cell change. *Ammon's horn:* There was marginal gliosis of the hippocampal gyrus and gliosis of the subiculum. There was status spongiosus and extensive outfall in cells from Sommer's sector. *Cerebellum:* In the atrophic foliae, the molecular layer was very shrunken and the granular layer was reduced to a narrow strip. The molecular layer showed a dense fibrous gliosis, in the midst of which many Purkinje cells remained, though others had disappeared, their former situation being indicated by a focal proliferation of the Bergmann cells (Fig. 7). There was also a severe fibrous gliosis of the white matter and dentate nucleus.

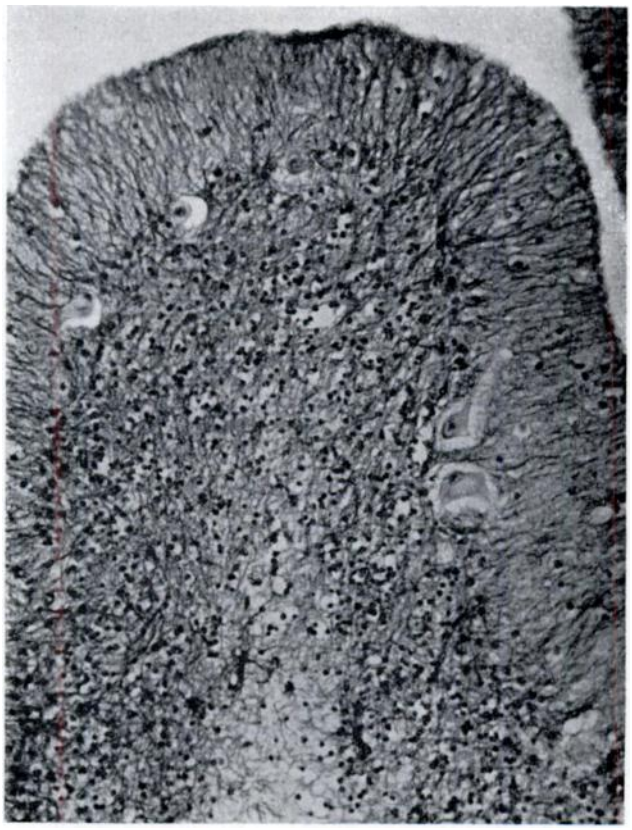

FIG. 7.—Case 2. Lateral lobe of cerebellum, showing gliosis and atrophy of molecular layer, with persistence of many Purkinje cells. Frozen section, stained with Holzer. ×180.

I am indebted to Dr. Ludo van Bogaert for permitting me to report Case 3 which was investigated by him at the Institut Bunge, Antwerp.

CASE 3

Clinical History

The patient was a boy aged seven years when he first came under the care of Dr. van Bogaert. He was the youngest of six children. His birth had been normal, and, apart from whooping cough at the age of a year and a half, he had been in good health until he was three.

https://doi.org/10.1192/bjp.101.424.610 Published online by Cambridge University Press

At the age of three years and one month, a chill was followed by severe pneumonia commencing on one side but becoming bilateral. There was severe cyanosis and it was thought unlikely that he would recover. However, on the ninth day his condition improved. Several days later, he had pyuria with occasional febrile episodes. Twenty days after his temperature returned to normal, he suddenly became comatose and then developed convulsions. Ten days later, consciousness returned, but he was found to have paralysis of all four limbs and was blind. He was subsequently admitted to the Bachten Mental Hospital under Dr. Devos, where there was found to be a spastic quadraplegia with choreoathetoid movements of the toes. The lower limbs were in extension and crossed scissor fashion and there were contractures in extension of both big toes. The upper limbs were half flexed and half pronated, the fist was in line with the forearm, the fingers were spread out and showed occasional involuntary movements. There was no wasting. He was completely demented and uttered no sound. He swallowed normally. He was completely blind. The pupils were dilated but reacted to light. The optic fundi were normal but there was a pericapillary pigmented zone and abnormal pigmentation of the macula. The following year, the upper limbs became flexed but the lower limbs remained as before. There were frequently a series of rhythmical movements of the head to the right or left, two or three movements being made in a minute; these movements were accompanied by rhythmical contraction of the orbicularis oculi with the same frequency. Lumbar puncture yielded a fluid containing 3 cells per cub. mm. and 20 mgm. protein per 100 ml. The Wassermann reaction was negative both in the blood and the cerebrospinal fluid. The patient died of bronchopneumonia at the age of eleven years.

Only the brain was available for study.

Histology

Blocks were taken so as to incorporate the dorsal half of one hemisphere at the level of the anterior and centromedian nuclei of the thalamus respectively and also from the dorsal half of the occipital lobe. Frozen sections were taken from these blocks and stained with Holzer and Spielmeyer. Celloidin sections from a block incorporating an entire hemisphere, cut in the coronal plane through the centromedian nucleus, were stained with Nissl. Sections taken from a block obtained by sagittal section of the other hemisphere in the sagittal plane, were stained by Weigert-Pal.

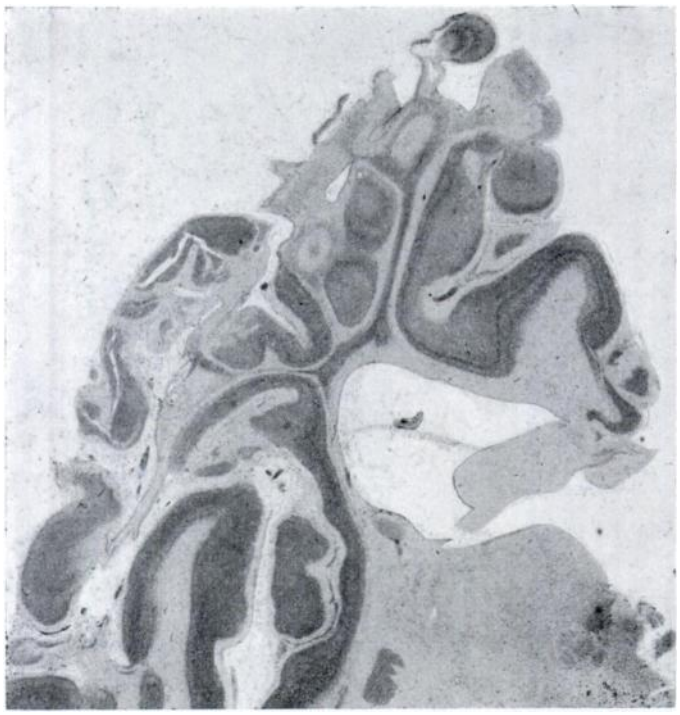

FIG. 8.—Case 3. Parietal lobe, showing ulegyria and the narrow, centrally placed line of dark staining in the digitate white matter. Note ulegyria of Heschl's gyrus. Nissl. ×2¼.

https://doi.org/10.1192/bjp.101.424.610 Published online by Cambridge University Press

Findings

The severest changes were confined to the *parietal* and *occipital lobes* on the two sides and were symmetrical. The gyri on the lateral aspect of the hemisphere dorsal to the Sylvian fissure, together with the posterior part of the *superior temporal convolution*, were, for the most part, ulegyric with almost complete destruction of the cortex, which was reduced to a narrow band of glial tissue. The underlying white matter was greatly shrunken and, in Nissl preparations, showed with the naked eye a central line of dark staining due to the increase in astrocytic nuclei and processes (Fig. 8). Passing further forward to the level of the *centromedian nucleus of the thalamus*, the cortex was seen to be intact except for the tip of the two most dorsal convolutions, where gliosis continued from the shrunken white matter through a cortex atrophic at these points only. There was a diffuse pallor of myelin staining in the deeper part of the digitate white matter and the greatly shrunken centrum semi-ovale, just external to the lateral angle of the ventricle, showed an approximately pentagonal area of complete destruction of myelin, the greatest breadth of which was 0·4 cm. Laterally, the border of this area was sharp, but mesially, towards the corpus callosum, many palely staining, irregularly swollen sheaths crossed the border so as to make the latter less distinct. This area could still be seen in sections through the *anterior nucleus of the thalamus*, but the pallor of myelin staining was no longer complete. The demyelination was accompanied by a fibrous gliosis of loose texture. At this level, there was still more severe shrinkage of the white matter of the centrum semi-ovale and of the most dorsal convolutions and the convolutions dorsal to the Sylvian fissure on the lateral aspect of the brain. The *cingulate* and *paracentral gyri* appeared normal, but the *precentral gyrus* showed marked shrinkage and pallor of myelin staining, with moderate gliosis of its white matter, though the cortex was not atrophic. The two more ventral convolutions, however, showed ulegyria, with more severe gliosis and shrinkage of the white matter. The section cut in the sagittal plane and stained with Weigert-Pal, showed that the deep white matter beneath the ulegyric convolutions at the *occipital pole* was completely demyelinated and that some pallor of myelin staining was present in the centrum semi-ovale as far forward as the frontal lobe.

Comment

These three cases, which show between them most of the important features of Acute Infantile Cerebral Diplegia, present many points of similarity with a case reported in 1937 by Bailey and Hass, in which the superior longitudinal sinus was found at autopsy to be completely occluded in its middle half by organized thrombus. The case was that of an infant, who, in the course of an attack of diarrhoea at the age of four weeks, suddenly became flaccid, as if dead, and shortly afterwards had a convulsion lasting twenty minutes. Three similar seizures followed within an hour. The temperature was 105° F. Another convulsion occurred on admission to hospital, when the lower extremities were noted to be held rigidly. After a week, he was sent home, where he had one to three seizures daily. At two months the head measured 16½ in. in circumference. The arms and legs were rigid so that he could support his weight on his legs. The cerebrospinal fluid was xanthochromic and contained red blood cells. There was hydrocephalus. He died from gastroenteritis at three and a half months. The similarity between this clinical history and that of our three cases, suggests that the latter may also have suffered a thrombosis of their superior longitudinal sinuses. If this vessel had been available for histological examination in the cases reported in this paper, this possibility could easily have been tested and if the opportunity for making such an examination in similar cases were likely to present in the near future, there would be little excuse for writing this paper. However, opportunities for carrying out post-mortem studies on cases of Acute Infantile Cerebral Diplegia in the chronic stage rarely present and when they do, examination of the dural sinuses is apt to be superficial. Organized thrombi in the sinuses are often inconspicuous and it may be useful to illustrate with an example (Fig. 9) from the straight sinus of a child who had a febrile episode heralded by convulsions at three weeks and died aged ten months at the Hospital for Sick Children, Great Ormond Street. The inconspicuousness of the resultant fibrous nodule emphasizes the need for histological confirmation in such cases.

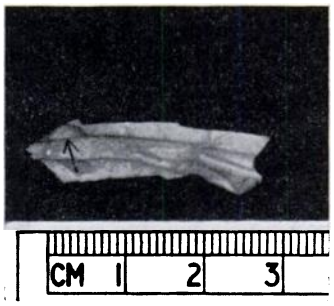

FIG. 9.—Organized thrombus (arrow) in the straight sinus of a child dying 9 months after the probable onset of the thrombosis.

It seems, therefore, worthwhile examining the evidence for and against an origin for the cerebral diplegia in thrombosis of the superior longitudinal sinus, in our three cases.

Firstly, we may consider the antecedent conditions and the clinical course. In Case 1, there was cervical adenitis following tonsillectomy, Symonds (1937) has reported a non-fatal case (his Case 2) in which he considered that thrombophlebitis of the right lateral sinus had arisen from a peritonsillar abscess and spread to the superior longitudinal sinus and thence into one of its tributaries draining the right precentral cortex. He thought, following Goldman (1936), that the thrombotic process had started in the jugular vein. Courville and Nielsen (1935) have indicated the not infrequent spread of otitic thrombophlebitis of the lateral sinus to the superior longitudinal sinus *via* the vein of Labbé and the superior anastomotic and superficial middle cerebral veins. The clinical features in Case 1 are fully consistent with a spread of thrombosis in this way to the superior longitudinal sinus from the left jugular vein. The neurological symptoms were ushered in by convulsions indicating a lesion of the precentral gyrus near the Sylvian fissure on the left side. Oedema over the mastoid process indicated the probability of thrombosis of the lateral sinus with interference with the blood flow in the mastoid emissary veins. The pulse rate fell in three days from 160 to 70 per minute although the patient remained febrile. At operation the dura was bulging. Thus there appeared to be raised intracranial pressure, though there was no papilloedema as was seen by Bailey and Hass in their first two cases of thrombosis of the superior longitudinal sinus. Whatever the process responsible for the convulsions was, it appeared to be capable of spontaneous arrest, as the intracranial pressure returned to normal and the patient became ambulatory, though spasticity in both lower limbs continued to develop for several years, while her intellectual status was that of idiocy and she subsequently became afflicted by minor epileptic seizures.

In Case 2, the convulsions at the onset were associated with otitis media and accompanied by high fever. The association of thrombosis of the lateral sinus with otitis media is classical and the same route of spread to the superior longitudinal sinus can be envisaged as that just mentioned. The state of the patient in the chronic phase was similar to that in Case 1, with the additional involvement of the arms.

In Case 3, coma and convulsions, followed by a spastic quadraplegia, occurred ten days after a pyuria of unknown origin. Here we may recall Symond's (1937) case (7), where he suggested that thrombosis of the superior longitudinal sinus had followed a thrombophlebitis migrans, probably secondary

to a perirectal abscess. Some form of pelvic suppuration may have been present in Case 3, spread of the thrombosis occurring from the pelvic veins to the dural sinuses as a thrombophlebitis migrans or as venous thromboembolism *viâ* the vertebral venous plexus as postulated by Batson (1940, 1942).

Thus all three cases of Acute Infantile Cerebral Diplegia have a clinical history consistent with venous thrombosis spreading to the superior longitudinal sinus. It is intended now to show, that the changes found in the brains from these cases are equally in accord with such a pathogenesis.

The changes in the brains from each of the three cases were strikingly similar. In each, there was a very severe and diffuse sclerosis of the white matter of the dorsal parts of the two cerebral hemispheres. The area of sclerosis was poorly demarcated, fading gradually into the surrounding tissue. While in Case 1, the frontal and left temporal lobes were the most severely affected, in Cases 2 and 3, the occipital lobes had suffered most. The sclerosis was accompanied by a much milder pallor of myelin staining. There was little evidence of the products of the breakdown of myelin, which form so prominent a feature in cases of classical "Diffuse Sclerosis". In the most atrophic areas, there was evidence of loss of nerve cells and cortical degeneration varying in severity through laminar sclerosis up to complete atrophy and ulegyria.

Sclerosis of the white matter in excess of demyelination is an interesting pathological change. Similar demyelination, but without notable gliosis has been described in oedematous areas around cerebral tumours by Greenfield (1939). The absence of gliosis in these cases of cerebral tumour is probably due to the short duration of survival after the onset of the oedema. Thus, only in animals surviving ligation of the superior longitudinal sinus by more than two months, does fibrous gliosis appear and become increasingly dense (Putnam, 1935; Woolf, 1954). These changes were attributed by the latter author to oedema resulting from venous stasis. Scholz (1949) has shown, in cases dying from thrombosis of the superior longitudinal sinus in the acute stage, that the area in which the effects of oedema can be observed is more extensive than that showing the effects of anoxia. While oedema principally affects the myelin sheaths, the nerve cells are most susceptible to anoxia. This was found to be the case in the animals with ligation of the superior longitudinal sinus, where, in the presence of a widespread diffuse gliosis, only the cortex adjacent to the sinus was degenerated. The prominence, though not dominance, of atrophic changes in the cortex in our three cases, suggests that if these lesions were, in fact, due to a thrombosis of the superior longitudinal sinus, then a considerable degree of anoxia must, on occasion, accompany the oedema in the areas with the greatest degree of venous stasis. The anoxia, cannot, however, be of the severity present in most cases of arterial obstruction since none of the three cases showed softening of the brain, a feature present in the vast majority of cases, where the supply rather than the return of blood is impeded.

In the literature, haemorrhagic infarction with softening is frequently regarded as the typical sequel to thrombosis of the superior longitudinal sinus. While this may be correct for the rapidly fatal cases, it is certainly not so for cases surviving for longer periods. A case studied at The Hospital for Sick Children, Great Ormond Street is illustrative of this point. The patient was a child aged thirteen months suffering from an obstructive hydrocephalus. Its lateral ventricles were drained into the pleural cavity. Aspiration of the fluid that accumulated in this cavity was followed by extensive cerebral venous thrombosis, which was shown at autopsy, a month later, to have affected the anterior third of the superior longitudinal, the straight and both transverse

sinuses and to have spread into the veins on the convexity of the left hemisphere (Fig. 10), the thrombosis having apparently started in the transverse sinus and spread into the vein of Labbé in the manner suggested by Courville and Nielsen.

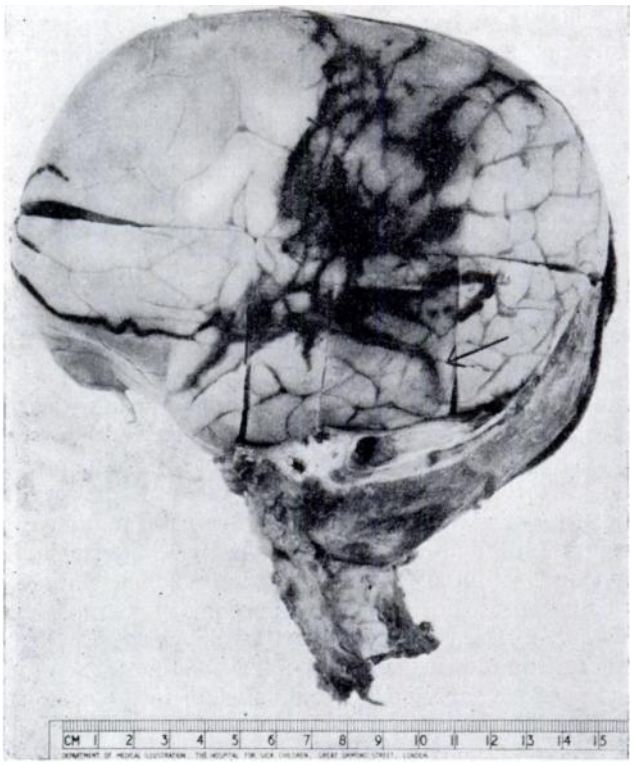

FIG. 10.—Hydrocephalic brain, showing thrombosis spreading on the convexity of the brain from the transverse sinus *viâ* the vein of Labbé (arrow) to the superior longitudinal sinus. Note thrombosed vein coursing across the ventral part of the frontal lobe. The thrombosis occurred three weeks before death.

The great vein of Galen and both internal cerebral veins were thrombosed. In spite of this extensive involvement of the venous system, as well as the additional embarrassments of a left subdural haematoma and the hydrocephalus, infarction visible with the naked eye was confined to a softening the size of a pea deep to one of the pre-Rolandic veins on the convexity of the hemisphere. There was, however, severe haemorrhagic infarction of the basal ganglia on the left, but this was no doubt due to the thrombosis of the Galenic system and could not be attributed to the thrombosis in the superior longitudinal sinus or its branches.

The method of spread of the thrombophlebitic process, so clearly illustrated in this case, would explain very completely the distribution of the lesions in Case 1, the severe affection of the left temporal lobe corresponding to thrombosis of the overlying vein of Labbé.

Before leaving this illustrative case, attention should be drawn to the thrombosed vein coursing across the convexity of the ventral part of the left frontal lobe. This vein ran into a short, unnamed, dural sinus passing just above

the orbit, which finally emptied into the anterior part of the superior longitudinal sinus. Oedema over the orbit was a valuable diagnostic feature in this case and was probably due to obstruction of diploic veins draining into the unnamed sinus. Similar obstruction of diploic veins may have a bearing on the extremely thick calvarium over the anterior and middle fossae in Case 1.

The pentagonal focus of demyelination and gliosis seen in the centrum semi-ovale, adjacent to the lateral angle of the ventricle in Case 3, is of interest since it suggests a milder degree of the paraventricular softenings reported by Norman (1953) as possibly resulting from thrombosis of the great vein of Galen. There were, however, in Case 3 none of the lesions in the basal ganglia usually associated with thrombosis of the Galenic venous system. However, these lesions need not follow obstruction of this system as was suggested by Bedford's (1934a, b) experiments in which he placed a clip on the great vein of Galen and particularly strikingly demonstrated by the following case in which thrombosis of this vessel was an unexpected post-mortem finding. This case has the additional interest of showing that cerebral oedema due to obstruction of cerebral veins may produce its effects wholly unaccompanied by the effects of anoxia and in this way resemble exactly the oedema associated with cerebral tumours.

CASE 4

Clinical History

The patient, a man aged forty-seven, was admitted to the Bethnal Green Hospital on the 24 May, 1951. The details of the clinical history are not relevant to the subject under discussion and we need only mention that he died a few days after developing pneumonia. Post-mortem examination showed sub-acute bacterial endocarditis with mitral stenosis.

Examination of the Brain after Fixation in Formalin

The brain was large, weighing 1,570 gm. The ventricles were not enlarged. The vessels at the base of the brain were a little more rigid than normal, but showed no obvious atheroma. The posterior cerebral artery was opened up on the left side, its lumen was patent and it contained no embolus. On opening the great vein of Galen, a whitish, cord-like, adherent thrombus was seen to occlude the lumen almost completely. Anteriorly, extensions of the thrombus were seen to pass into the internal cerebral veins. They were, however, not adherent to the walls of the vessels. There was marked uncinate herniation, more marked on the right than on the left. There was also marked tonsillar herniation. The ventral part of the *left occipital lobe* showed a greyish discoloration of the digitate white matter, within which were numerous, distended, small veins which were filled with fresh blood clot (Fig. 11). The adjoining cortex, which was

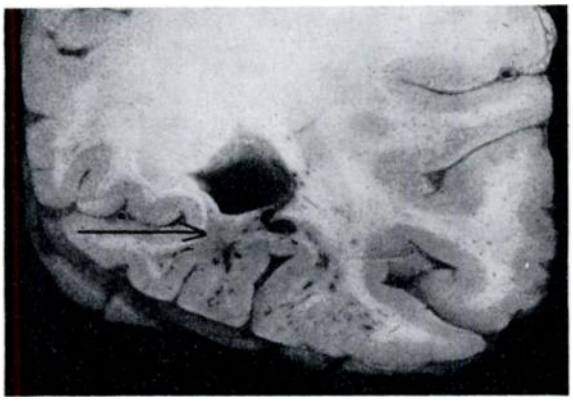

FIG. 11.—Case 4. Occipital lobe, showing area of greyish discoloration (arrow) in white matter, with sparing of the cortex.

https://doi.org/10.1192/bjp.101.424.610 Published online by Cambridge University Press

separated from the greyish white matter by apparently intact, subcortical fibres, appeared macroscopically normal. Passing anteriorly, there was seen to be a crescentic cleft embracing the white matter beneath the *collateral sulcus* on the left side. The cleft was filled with a gelatinous fluid and ante-mortem clot and was narrowly separated from the cortex by sub-sulcine "U" fibres. The veins lining the left posterior horn were very distended and one of them obviously communicated with the cavity described. On dividing the slab, which contained the cavity, into two, by a further coronal section, a fusiform, ante-mortem blood clot 0·7 cm. long ×0·3 cm. wide was seen to lie within the collateral fissure. As it extended towards the surface it tailed off into a cord-like structure, apparently an obliterated vessel. Following it inwards, it was seen to be continuous with the clot in the cavity described above.

Histology

Frozen sections were taken from the ventral portion of the left occipital lobe and stained with scharlach R, Holzer, and the Takiya-Siko modification of Weigert-Pal. Frozen sections were also impregnated by Penfield's modification of Hortega's method for microglia. Blocks were also taken from the dorsal and ventral portions of each occipital lobe, from both central regions, both frontal and temporal lobes, both lentiform nuclei and at five levels through the thalamus. These blocks were embedded in celloidin and sections stained with haematoxylin and van Gieson, cresyl violet and phosphotungstic acid-haematoxylin. Sections through the left occipital lobe were also impregnated with Gros-Bielschowsky.

Findings

Sections through the great vein of Galen showed that the thrombus it contained had been completely converted into fibrous tissue and was densely adherent to the wall of the vein. Sections through the ventral part of the occipital lobes showed that the veins in the white and grey matter were very distended, especially on the left. The distension was most marked in the white matter of the left fusiform gyrus. An occasional vein, in the white matter, was completely occluded by a fibrous plug. The veins immediately medial to the inferior horn of the lateral ventricle, were very distended and some of them had necrotic walls and were surrounded by red blood cells. One small vessel—probably an arteriole—was surrounded by a homogeneous material staining like plasma. It contained a few clumps of red blood cells

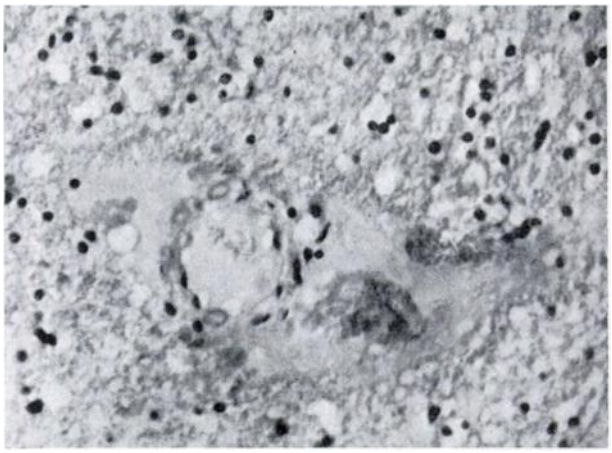

FIG. 12.—Case 4. Section from discoloured white matter, showing perivascular exudate. H. van G. ×350.

(Fig. 12). Throughout the white matter of the ventral part of the occipital lobe, frozen sections showed swelling and beading of the myelin sheaths, with formation of free-lying globules of myelin. The cortical myelin sheaths were tortuous and varicose, otherwise the cortex was little affected. The axis cylinders were displaced by the dilated veins, but were not swollen. There were occasional twinning astrocytes and a conspicuous lipofuscin content of both astrocytes and nerve cells. In cortex and white matter, there was hypertrophy of microglial cells without any great increase in their number. Phagocytes containing fat were never seen, but some of the distended veins in the white matter contained large globules of neutral fat. The astrocytes in the white matter were considerably increased in number especially along the course of the vessels. They frequently showed regressive changes, the nuclear chromatin being arranged around the periphery of the nucleus under its membrane and staining more darkly than usual. The cytoplasm was bulky, ragged, stained palely and often contained large vacuoles. Eventually

the nuclei of these cells shrank, became very pale and finally faded away completely. A few astrocytes appeared activated and there was a light formation of glial fibres. The oligodendroglial cells were pyknotic but showed no other abnormality. The rest of the brain including the Ammon's horn and cerebellum was normal.

COMMENT

In this case, the thrombosis of the great vein of Galen probably occluded the entrance of the periventricular veins draining the ventral portion of the occipital lobe. The vein was probably never completely occluded as the basal ganglia were unaffected. The greyish discoloration of the white matter was due to a degeneration of the myelin sheaths with only an insignificant gliosis. Presumably a more prominent gliosis would have occurred if the patient had survived longer.

Degeneration of the myelin sheaths without formation of compound granular corpuscles is characteristic of "oedematous necrosis" (Jacob, 1940). While the changes in this case fall short of necrosis—in spite of the regressive changes in the astrocytes—the presence around the veins of a homogeneous material, staining like plasma is practically diagnostic of oedema. Exudates with a similar appearance were reported by Jaburek (1935) in oedematous areas near cerebral tumours, but the histological effects of oedema may occur without any stainable perivascular exudate as Greenfield (1939) has shown and as Woolf (1954) found in animals whose superior longitudinal sinus had been ligated experimentally. Scholz (1949) has related the unstainability of such exudates to their low content of protein. It may, of course, also be that the exudates were present at the time when the oedema was developing but had been absorbed during a period of dehydration, immediately before death, without sufficient time elapsing for the swelling of the myelin sheaths to subside. The presence of globules of sudanophil material in the greatly dilated veins is of interest in that it suggests that the products of the breakdown of the myelin sheaths were being transported towards the vessels by a humoral mechanism, emulsification occurring in the excess of fluid in the tissue spaces and then passing, in the form of globules too small to demonstrate by staining, through the perivascular space and vessel wall into the lumen of the vessel. Here they coalesced with the production of globules of demonstrable size. Probably the latter would never have been seen were it not for the stagnation of flow in the veins, consequent upon their obstruction by the thrombosis.

What is of particular importance in this case is the complete absence of degeneration of the nerve cells in the cortex overlying the discoloured white matter. While it is tempting to see in this absence of anoxic effects, a striking confirmation of Scholz's postulation that oedema is always more extensive than anoxia in cerebral venous obstruction, it may also be related to the territory normally drained by the periventricular veins, which may not include the cortex.

The area of greyish discoloration in the white matter in this case may well represent an early stage in the development of the gliosis seen in Cases 1 to 3, but to find lesions comparable with this more severe sclerosis, cases surviving for longer periods must be studied.

There do not seem to be in the literature any cases of this nature, where survival was long enough to enable sclerosis to develop and where the pathological investigation was sufficiently meticulous to allow such changes to be demonstrated. In several cases, such as Russell's (1949) Cases 46 and 47, attention was focussed on areas of haemorrhagic infarction and the possibility

of an extensive sclerosis and demyelination, of the type seen in our Cases 1 to 3, existing beyond the borders of the infarcts, cannot be excluded. Indeed, in reference to the haemorrhagic infarction in the right cerebrum of her Case 47, Russell refers to a peripheral zone of early gliosis.

Hallervorden (1939) reported the case of a boy aged 2½ years whose birth was said to have been premature and to have been followed at a short interval by epilepsy and then by a spastic paralysis of the right arm and both legs. Just before he died, from a lung inflammation, there were convulsions of the left side and face. At autopsy, there were old changes in the left parasagittal region with extensive shrinkage of the cortex, with laminar destruction, and atrophy of the white matter. The accompanying microphotograph showed a diffuse demyelination of the atrophic white matter. Unfortunately, there is no note as to whether the demyelination, which closely resembled that seen in Cases 1 to 3, was accompanied by a similar sclerosis or whether there was the same inconspicuous formation of compound granular corpuscles. There was an organized thrombosis of the superior longitudinal sinus, occluding the left superior cerebral vein. A remarkably similar case, also with symptoms dating from the neonatal period, was described in greater detail by Norman (1936).

These cases strongly suggest that the changes in Cases 1 to 3 were also due to thrombosis of the superior longitudinal sinus.

Thus a considerable amount of evidence has been put forward in favour of an origin of Acute Infantile Cerebral Diplegia in thrombosis of the superior longitudinal sinus. It is not suggested that thrombosis of this vessel only produces lesions of the type seen in Cases 1 to 3. It will, in fact, be shown in a paper to be published later, that liquefactive changes may dominate if the thrombosis occurs in the first few weeks of life. Russell's cases show that "healed" softenings may be the most striking feature. There seems no doubt, however, that the morbid anatomical syndrome of sclerosis and demyelination of the white matter drained by the thrombosed sinus may occur with great purity, i.e. with little or no involvement of the overlying cortex and without even incomplete softening.

Although no other cause for Acute Infantile Cerebral Diplegia seems as likely as thrombosis of the superior longitudinal sinus, it must be admitted that the changes seen in the brains from our three cases, resemble closely lobar sclerosis, which has recently been postulated by Scholz (1951) as one of the sequelae of convulsive seizures in childhood. It must be pointed out, however, that although there is good evidence that patchy palings may be found in the cerebral cortex as an immediate sequel to epileptic seizures (Meyer, 1939), there is far less certainty that lobar sclerosis is, in fact, the result and not the cause of epilepsy.

Sclerosis of the cerebellum in Case 2, might be put forward more confidently as a result of the epileptic seizures, although in this case the convulsions do not appear to have persisted beyond the acute stage. Furthermore, the cerebellar involvement may have been due to an extension of the thrombosis into the straight sinus. Softening of the vermis of the cerebellum may result from thrombosis of the straight sinus in the first month of life, and did, in fact, occur in the case illustrated in Figure 9. Possibly a similar obstruction later in life would have resulted in a more sclerotic lesion.

It must also be pointed out that while an origin in thrombosis of the superior longitudinal sinus explains the convulsions as well as the changes in the brain, a dependence of the lesions upon the convulsions leaves the origin of the seizures in obscurity. It is, of course, possible, or even probable, that con-

vulsions occurring in the chronic stage of Acute Infantile Cerebral Diplegia aggravate and extend the lesions in the brain.

In conclusion, it must be emphasized that cerebral diplegia is not the only possible sequel to thrombosis of the superior longitudinal sinus and it may not be inappropriate to quote again after more than twenty years, the concluding words of Byers and Hass (1933): "Nevertheless, if sinus thrombosis as a puzzling and often unsuspected complication of disease is kept constantly in mind, the aetiology of certain instances of 'encephalitis', spontaneous subarachnoid haemorrhage, cerebral palsy, cortical atrophy, mental defectiveness, epilepsy and hydrocephalus may then become apparent."

Summary

(1) The characteristic features of Acute Infantile Cerebral Diplegia were illustrated by clinico-pathological reports on three cases. The disease typically affects infants and young children who are suffering from fever with dehydration or suppuration in the head or neck. The onset is sometimes, but not always, ushered in by convulsions, which may be bilateral or unilateral. Coma may ensue. On recovery, the patient is di-, tri-, or quadraplegic and may show other manifestations of cerebral degeneration, such as blindness, aphasia or dementia. The chronic phase may persist for many years until death ensues from intercurrent infection.

The distinction from Little's Disease, i.e. Congenital Cerebral Diplegia, in which the disability is noticed at or soon after birth, was emphasized.

(2) The changes in the brains from the cases studied were remarkably uniform and consisted of a diffuse sclerosis of the white matter of the dorsal parts of both cerebral hemispheres, with less extensive laminar sclerosis or ulegyria of the cortex. Softening was not seen in the cortex or white matter and the demyelination shown by the latter was less marked than the sclerosis.

It was considered that the changes in the white matter were typical of the sequelae of oedema and that the cortical degeneration was due to an accompanying, but less widespread, anoxia, such as is seen in cerebral venous thrombosis. In view of the topography of the changes, it was considered that their most probable cause was a thrombosis of the superior longitudinal sinus. The clinical histories of the reported cases were shown to be consistent with this concept.

Acknowledgments

Cases 1 and 4 were studied in the Department of Neuropathology of the Institute of Psychiatry, London and Case 3 in the Department of Pathological Anatomy of the Institut Bunge, Antwerp. It is a great pleasure to acknowledge the constant stimulating interest shown by Professor Alfred Meyer and Dr. Ludo van Bogaert during the investigation of these cases. I also wish to express my gratitude to Professor W. Scholz for his generosity in allowing me to publish Case 2 and to Drs. Mildred Creak and M. K. Beattie for enabling me to study the brain from Case 1 and to Dr. Herbert Levy in respect of Case 4. Finally, I wish to thank Dr. Martin Bodian for allowing me to refer to the cases from The Hospital for Sick Children, Great Ormond Street, studied during the tenure of the Hydrocephalus Research Fellowship at this Hospital.

References

BAILEY, O. T., and HASS, G. M., *Brain*, 1937, **60**, 293.
BATSON, O. V., *Ann. Surg.*, 1940, **112**, 138.
Idem, *Ann. intern. Med.*, 1942, **16**, 38.
BEDFORD, T. H. B., *Brain*, 1934a, **57**, 1.
Idem, *Ibid.*, 1934b, **57**, 255.
BYERS, R. K., and HASS, G. M., *Amer. J. Dis. Child.*, 1933, **45**, 1161.
COURVILLE, C. B., and NIELSEN, J. M., *Amer. J. Dis. Child.*, 1935, **49**, 1.
FORD, F. R., in *Diseases of the Nervous System in Infancy, Childhood and Adolescence*, 1952, 3rd ed., p. 779. Charles C. Thomas, Springfield, Illinois.
GOLDMAN, I. B., *Laryngoscope, St. Louis*, 1936, **46**, 604.
GREENFIELD, J. G., *Brain*, 1939, **62**, 129.
HALLERVORDEN, J., *Z. ges. Neurol. Psychiat.*, 1939, **167**, 527.
JABUREK, L., *Arch. Psych. Nervenkr.*, 1935, **104**, 518.
JACOB, H., *Z. ges Neurol Psychiat.*, 1940, **168**, 382.
MEYER, A., *J. Ment. Sci.*, 1939, **85**, 927.
NORMAN, R. M., *Proc. R. Soc. Med.*, 1953, **46**, 627.
Idem, *J. Neurol. Psychopath.*, 1936, **17**, 135.
PUTNAM, T. J., *Arch. Neurol. Psychiat., Chicago*, 1935, **33**, 929.

RUSSELL, D. S., *Observations on the Pathology of Hydrocephalus*, 1949, p. 87. Medical Research Council. Special Report Series No. 265.
SCHLESINGER, B., and WELCH, R. G., *Great Ormond St. Journ.*, 1952, No. 3, 14.
SCHOLZ, W., *Arch. Psych. Nervenkr.*, 1949, **181**, 621.
Idem, in *Die Krampfschädigungen des Gehirns*, 1951. Julius Springer, Berlin.
SYMONDS, C. P., *Brain*, 1937, **60**, 531.
WOOLF, A. L., *J. Path. Bact.*, 1954, **67**, 1.