CEREBELLAR AGENESIS

By

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DEVELOPMENTAL defects of the cerebellum may take various forms: agenesis of the entire cerebellum; aplasia of one or both hemispheres, or aplasia limited to the vermis. It is the purpose of this communication to review the first two groups and to place on record the clinical and pathological features of a case in which but for one small fragment the cerebellum was wholly absent.

COMPLETE ABSENCE OF THE CEREBELLUM

The earliest recorded case, reported by Combettes (1831), was that of a low-grade epileptic imbecile, Alexandrine Labrosse, who died at the age of eleven. She did not speak until her third year and her articulation was always very defective. She had weakness of the lower limbs and did not learn to walk until she was five years old. Often she fell. She used her hands freely and could feed herself. For the last four years of her life she was confined to bed and usually lay with her head inclined to the left. At the post-mortem examination it was noted that the meninges were normal, the tentorium cerebelli was present and the cerebral hemispheres a little larger than normal. In the space normally occupied by the cerebellum there was a gelatinous membrane connected to the medulla by membranous pedicles. In their neighbourhood there were two detached pea-like masses of white matter. The quadrigeminal bodies were intact and at a lower level the aqueduct of Sylvius could be identified in the midst of tissues which seemed to have undergone some form of softening. In the medulla this softening had to some extent encroached on the restiform and olivary bodies. There was no fourth ventricle, no pons Varolii and the pyramids diverged to enter directly the crura cerebri. Flechsig (1883) also reported a total defect in a new-born child but the details of the case are too fragmentary to have any value.

A third example of total absence of the cerebellum has been described by Priestley (1920). Her patient was a spastic hydrocephalic infant of four months. There was no vestige of cerebellum, peduncles or pons. "On exposing the brain it was found to be extremely distended; the brain matter formed a thin layer over the ventricles which contained about 1½ pints of clear fluid. The fourth ventricle was covered by a thin sheet (0·5 mm.) of tissue running from the corpora quadrigemina to the dorsal surface of the medulla. On the ventral surface the pyramidal tracts appeared to run up to the corpora quadrigemina. The base of the skull showed three pairs of fossae but there was no tentorium cerebelli. The lower end of the vertebral column was ill-developed; the arches of the fourth and fifth lumbar vertebrae were absent, as, too, were all the sacral segments."

PARTIAL AGENESIS

In cases of partial agenesis of the cerebellar lobes and vermis the extent of the developmental failure varies widely and of the numerous reports which have appeared the following are the most noteworthy.

In a rhachitic cretin of 19 years who during life had difficulty in walking and speaking, Verdelli (1874) found a minute cerebellum measuring not more than 2 cm. in its transverse diameter. Leyden (1876) reported two cases of

almost total agenesis. In the first the cerebellum was reduced to the size of a bean and in the second it was represented by two minute masses, possibly "rests" of the flocculi. Other developmental anomalies present in both cases were hydromyelia, syringomyelia and meningocele. In the case described by Borrell (1884) the left cerebellar hemisphere was the size of a haricot bean and the right only slightly larger.

Ferrier (1886) described the brain of a female imbecile, aged 15, who was said to have walked well and steadily, though she was never known to have run. The cerebellum was of a most rudimentary character. The left lobe which constituted the main portion, possessed a superficial area of not more than one half inch square. In an imbecile woman aged 48, Fusari (1891) found almost total absence of the cerebellum. The failure of development involved the lateral lobes, the vermis and the flocculus.

The case recorded by Warrington and Montserrat (1902) was that of a female infant, aged six weeks, who presented a lumbar spina bifida, hydrocephalus and paraplegia. The cerebellum showed a very marked degree of arrested development; in many places it was unconvoluted and represented by an undifferentiated mass of embryonic tissue and small cells. In a few areas of the lateral hemispheres there was a cortex in which the three strata of molecular, granular and Purkinje cells could be recognized. There was no trace of central gray nuclei, no olives and no arcuate fibres; the cerebellar peduncles were practically absent. The spinal cord showed a general attenuation and the presence of hydromyelia and syringomyelia.

Sternberg (1912) described the accidental discovery at autopsy of what at first sight appeared to be total absence of the cerebellum. His patient was a woman who succumbed to carcinoma of the stomach in her 46th year. On removal of the brain the tentorium cerebelli was seen to be represented by a slender crescent which lay above a shallow posterior cranial fossa. Removal of the meninges revealed on each side strands of white matter bearing on their surface a number of parallel fissures resembling those normally seen on the surface of the cerebellum. From their position the author inferred that they represented the flocculus. The quadrigeminal bodies were small and a rudimentary pons blended with the medulla, conspicuous for the large size of the pyramids. The olivary bodies appeared to be absent. The cranial nerves and vessels at the base were completely normal. Of the five cases reported by Vogt and Astwazaturow (1912) the first was found to have only traces of the cortex of the hemispheres and vermis. The olivary and red nuclei were normal.

Anton and Zingerle (1914) reported the case of a child, aged six and a half years, in whom there were severe disturbances of the motor system; ataxia, adiadochokinesis, difficulties in swallowing and speaking, convergent strabismus and horizontal nystagmus. Movements of the hands were freer in the recumbent posture than when the child sat up. The cerebellum was almost completely absent but two fragments of the flocculus were found, each possessing a well differentiated cortex in which Purkinje cells were present. In the distended fourth ventricle islets of tissue containing granule and molecular layer cells were present. There were no olives and the restiform bodies were rudimentary. Baker and Graves (1931) described the brain of a low grade imbecile, aged 19, who learnt to speak a few words and who could walk if helped. The cerebellum was reduced to proportions approaching complete absence; its stage of development corresponded to that normally reached in the middle of the third month of foetal life. A normal tentorium cerebelli separated the cerebral hemispheres from an almost empty posterior fossa below. Folia present on the surfaces of

the attenuated lateral lobes indicated that cortical differentiation had taken place. The medulla showed absence of the olives and an extremely wide rhomboid fossa. There was no evidence of hydrocephalus. In the case of Rubinstein and Freeman (1940) in spite of extreme attenuation in cerebellar development, ante-mortem signs did not develop until two years before the death of the patient at the age of 71 years. Detailed studies of the brain disclosed two fairly developed flocculi, a trace of vermis and three simple folia of the right lateral lobe.

In the two instances of cerebellar aphasia recorded by Lichtenstein (1943) the condition was to a large extent unilateral and is therefore of lesser interest.

The case now reported was at first considered to be an example of total absence of the cerebellum for it was not until naked-eye examination of the brain stem had been supplemented by careful examination with a hand lens that a single minute fragment of cerebellar substance was discovered. It lay beneath thickened pia-arachnoid closely applied to the right side of the pons and the piece of tissue had a superficial area of approximately 10 mm. and a thickness of 1 mm. Microscopic examination showed that it possessed the molecular, nuclear and Purkinje cell layers which characterize the cerebellar cortex. Though in this way deprived of the interest which attaches to complete agenesis, the developmental defect was of a degree more marked than in any of the examples referred to above and seems therefore to merit a full description.

Case Report

The patient, Samuel W., was born in 1883. Delivery was difficult owing to the large size of his head and was associated with asphyxia. His appearance at birth was evidently abnormal as the doctor is said to have remarked that it would be better if the baby were to die. It is not known at what age he started to crawl but he did not learn to walk until his seventh year. Speech was acquired late and his articulation, although it improved as he got older, never became distinct. All movements were clumsily performed and according to his sister "his fingers were all thumbs". He was very slow in buttoning and unbuttoning his clothes and often he required assistance. In adolescence he learnt to smoke and was able to fill a pipe and to hold a cigarette. He stood balanced on his heels with his legs far apart and when seated hunched himself up on the edge of his chair. He had frequent falls but was able to climb stairs unaided. In bed he lay curled up and had a habit of rolling his head. He played with toys and was friendly with other children. In spite of his obvious mental defect he remained at an ordinary elementary school until the age of fourteen. Apparently he learnt nothing and when he left school could neither read nor write. He was kept at home where he looked after the feeding of hens and goats. He went out by himself and was well known in the village, finding amusement in watching things and in talking to people. He had a ravenous appetite and ate everything placed in front of him. For 39 years he was looked after by his mother, and on her death he was sent to a public assistance institution where he remained for nearly ten years.

In temperament he was good natured and easily managed. Though sexually mature he took no interest in the opposite sex. He had no knowledge of time and often stayed out until he was fetched home. He had, however, a good memory for faces and could recall people he had known long after his admission to hospital.

The family history contained little of importance. The patient was the fourth and only abnormal child in a family of seven. The father, a canal wharf man died of heart disease, aged 60. His mother died from the effects of a stroke at the age of 64. A maternal aunt had a mentally defective child with a large head and defective gait.

In 1932 Samuel was certified and sent to the mental hospital at Hatton, Warwick. He was then in his 49th year. On admission, he was observed to be a small, thin man with a high forehead (Fig. 1). He walked on a broad base, bending his knees very little and with his arms held away from his sides at an angle of about 30 degrees to the vertical. He could stoop to pick up a ball and could throw it quite easily. He dressed himself and managed his food quite well. His habits were clean. When he spoke he had a habit of developing a convergent strabismus. His articulation was indistinct, monotonous, rather staccato and slightly nasal. Vision was good and he could recognize people from a long distance. Mentally, he was an imbecile. He recognized coins and knew the names of the staff and of other patients with whom he associated. With great difficulty he could write his own name. He had a good memory. When excited by other patients he became spiteful and struck out. In 1934 he was reported to be occasionally noisy and abusive and to chatter unintelligible rubbish. From this time onward he showed an increasing tendency to fall but it was only a serious handicap during the last

twelve months of life. A year before death pallor of both discs was observed with a normal right pupil; the left showed no reaction to light or accommodation. There was hypotonia of all limbs. The plantar reflexes were normal; the tendon reflexes exaggerated. The Wassermann reaction was negative in both blood and cerebrospinal fluid. In April, 1938 the patient became confined to bed. He went downhill rapidly and on 5 May succumbed to lobar pneumonia. He was 55 years old.

FIG. 1.—The patient S.W. There is an obvious degree of hydrocephalus and the widely separated fingers of the left hand suggest the presence of dysmetria.

POST-MORTEM EXAMINATION

The necropsy was performed approximately 24 hours after death. Apart from the appearance usual in lobar pneumonia the pathological findings were limited to the central nervous system.

EXAMINATION OF THE BRAIN

As it was proposed to preserve the brain as a museum specimen, it was immersed in Kaiserling's solution, but after three weeks in this medium it was transferred to a solution of formalin. Large, and obviously hydrocephalic, the cerebrum had undergone some degree of distortion in the fixing medium. It had also been damaged, particularly at the base where there was an almost complete tear through the pons. Furthermore, in the process of fixation the brain stem had acquired an acute anterior flexion at the junction of medulla and pons so that the floor of the fourth ventricle was exposed to view. These artefacts together with the preliminary fixation in Kaiserling's solution made the subsequent task of microscopic examination one of considerable difficulty.

Cerebrum

The lepto-meninges and vessels on the superior surface of the brain were normal. The two hemispheres were slightly asymmetrical; the right was a little smaller than the left and its parietal and occipital lobes were on a plane inferior to those of the other side (Fig. 2). The convolutions were large, simple and slightly flattened, there being a moderate degree of internal hydrocephalus. At

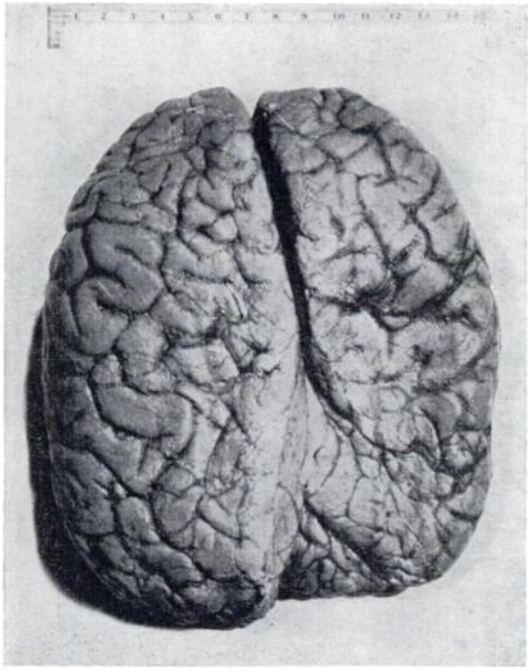

FIG. 2.—The cerebrum viewed from above, showing asymmetry of the two cerebra hemispheres.

the base, lying within the temporal and occipital lobes there was a large, roughly circular depression, covered by a conspicuous loose fold of pia-arachnoid which extended towards its anterior boundary. The cerebellum appeared to be entirely absent.

Proceeding from below upwards, it was possible to identify: a fragment of the cut cervical cord, remarkably normal in appearance; a flattened and attenuated medulla with, however, large and conspicuous pyramids; the bilateral absence of the inferior olives and the wide, flattened rhomboid fossa; the pons, very narrow in its width, bent caudally at the site of a transverse tear and joined to the midbrain by a continuation of the pyramids. The pons showed very little elevation on its ventral surface with no sharp demarcation between it and the cerebral peduncles, while the midbrain possessed a considerably dilated aqueduct, a relatively large tegmental area and a poorly developed basis pedunculi (Figs. 3 and 4). The corpora quadrigemina appeared normal and the roots of all the cranial nerves could be identified. On the ventral surface of the medulla the two vertebral arteries were prominent as they converged to form the basilar artery. On the right side of the brain stem at approximately the junction of the medulla and pons there was a loose membranous fold of tissue which when dissected off revealed the presence of a minute fragment of cerebellar

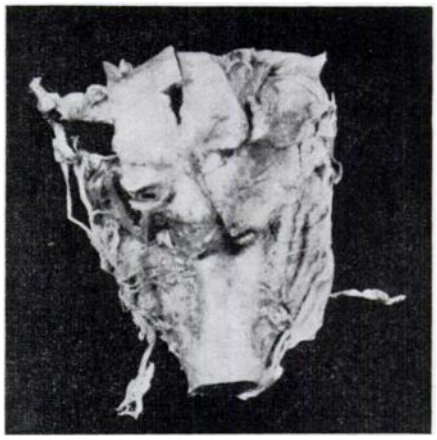

FIG. 3.—Ventral aspect of the brain stem. Note the relative smallness of medulla oblongata and pons. The midbrain shows a dilated aqueduct.

tissue. Inspection of the wide and shallow floor of the fourth ventricle showed that the striae acusticae were entirely absent. The roof of the cavity was represented by a partially detached thin membranous sheet, possibly of pia mater. The choroid plexuses were apparently absent.

FIG. 4.—Dorsal aspect of the brain stem. Note absence of the striae acusticae on the floor of the fourth ventricle.

MICROSCOPIC EXAMINATION

Frozen and paraffin sections were made of the cervical cord, the medulla at three different levels, the pons, midbrain, the vestigial fragment of cerebellum and the motor cortex.

The medulla oblongata was much smaller than normal and the enveloping pia-arachnoid showed a considerable degree of thickening. Sections through the lower third stained by the method of Loyez had a contour unlike that seen in normal preparations. The transverse diameter greatly exceeded the antero-posterior measurement and consequently the rhomboid fossa was extremely shallow and devoid of lateral recesses. The two pyramids were disproportionately

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large and the olivary eminences entirely lacking. The dark staining fibres of the medial lemniscus were sharply defined and on the dorso-lateral aspects the wedge-shaped strands of cuneate and gracile nuclei were equally conspicuous. From their neighbourhood rather coarse bundles of internal arcuate fibres could be seen sweeping forwards to gain the medial lemniscus (Fig. 5). Closely applied

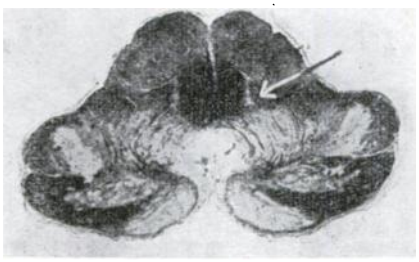

FIG. 5.—Section through the lower third of the medulla oblongata. $\times 3\frac{1}{2}$. The pyramids are relatively large and the internal arcuate fibres conspicuous. Arrow indicates the situation of olivary cells.

to the dorsal surfaces of the pyramidal tracts and separating them from the feebly represented formatio reticularis were two small areas of grey matter which in a rostral direction increased in size until they assumed the unmistakable appearance of olivary tissue.

In its middle third the medulla presented an even more abnormal appearance, its width being almost three times as great as its antero-posterior depth. As before the pyramids were prominent but they now presented on their dorso-lateral aspects two slightly convoluted bands of grey matter containing in very reduced numbers pigmented nerve cells characteristic of the inferior olive. To a considerable extent this part of the medulla owed its increased width to the presence on each lateral margin of closely aggregated bundles of nerve fibres which, if the cerebellum had been present, could legitimately have been regarded as entering into the formation of the restiform bodies (Fig. 6). Dorsal to these

FIG. 6.—Section through middle third of medulla. $\times 2\frac{1}{2}$. Loyez stain. Note the presence of two curved bands of olivary tissue.

fibre masses and lying almost on the floor of the fourth ventricle were two discrete oval bundles, obviously those of the fasciculus solitarius. Two symmetrically placed areas of pallor immediately latero-dorsal to the olivary grey matter suggested maldevelopment of the spino-cerebellar tracts.

In sections through the upper third the medulla maintained its flattened shape and the two bands of olivary tissue had become reduced in size and less curved in outline (Fig. 7). The two lateral areas of pallor noted above were more pronounced. No fibres could be found in the situation normally occupied by the olivo-cerebellar tracts.

Pons. This part of the brainstem was considerably smaller than normal and its partial destruction from tears together with its preliminary fixation in an unsuitable medium had rendered it almost useless for histological study. None-

FIG. 7.—Section through upper third of medulla. $\times 2\frac{1}{2}$. Loyez stain.

theless, in the fresh unstained tissue it was possible to note that of its two divisions the tegmental was considerably larger than the pars basilaris. In the latter the compact bundles of the pyramids were criss-crossed by very few transverse fibres. Stains such as those of Weigert-Pal and Loyez failed to give satisfactory results with sections of the pons but they did, however, succeed in bringing into sharp relief the small fragment of cerebellar tissue, attached by a pedicle on the right side of the pons at the junction of the tegmental part with the floor of the fourth ventricle (Fig. 8). It measured no more than 7 mm. $\times$

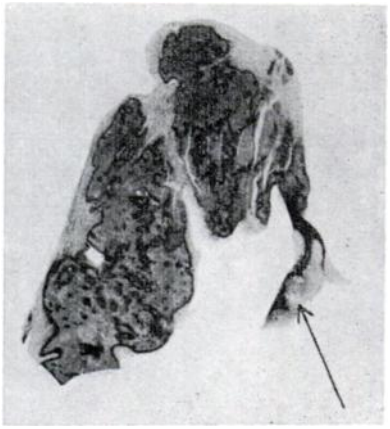

FIG. 8.—Section through pons. $\times 2\frac{1}{2}$. Loyez stain. The abnormal appearance is due to tears and the failure of the tissue to stain. Arrow indicates the situation of the cerebellar fragment.

3 mm. $\times$ 1 mm. A prolonged search on the opposite side failed to reveal any similar tissue. Thionin stained sections showed that it possessed the normal structure of cerebellar cortex and white matter though the Purkinje cells showed some irregularity of alignment and here and there gaps in their linear arrangement (Fig. 9).

Midbrain. The fibre bundles constituting the crusta, mesial fillet and posterior longitudinal bundle presented a normal appearance but those of the superior cerebellar peduncle were few. The heavily pigmented cells of the substantia nigra and the cells of the red nuclei appeared to be present in their normal numbers.

Motor Cortex. In this area the moderate degree of internal hydrocephalus had caused no disturbance of the normal arrangement of cell columns, though

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possibly the Betz cells were less numerous than normal. Degenerate forms were present.

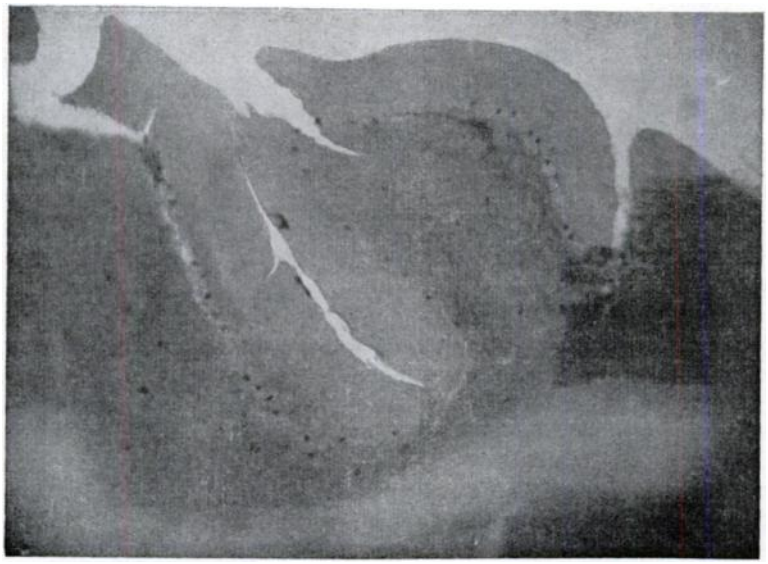

FIG. 9.—Fragment of cerebellar tissue. Cresyl violet stain, showing the almost normal differentiation into molecular, Purkinje and granular cell layers.

DISCUSSION

In an adult, the post-mortem discovery of a small cerebellum at once raises the question of whether it represents a failure of normal embryonic tissues to develop or a degenerative process of an atrophic or sclerotic character. When this doubt arises, a history of frank cerebellar signs is in favour of one or other of the many types of cerebellar disease for it is a remarkable feature of partial agenesis that it is not infrequently found in patients who during life exhibited no striking evidence of their serious structural anomaly.

In the case under consideration, though it was obvious that the patient was severely handicapped by disorders of voluntary movement which, as he grew older, became progressively worse, it seems clear from the post-mortem findings that his signs of cerebellar defect were the manifestations, not of an atrophic process, but of a true agenesis and of an extent so pronounced as to place the case almost in the category of complete aplasia. No loss of material, however severe, could be expected to reach the degree established in this case, for, as has been said, all that remained of the cerebellum was a single fragment of cortex and white matter, which on microscopic examination revealed the normal differentiation into molecular, granular and Purkinje cell layers. Moreover, the appearances in the brain stem and notably the conformation of the inferior olives were totally unlike those seen in a secondarily induced neuronal degeneration.

It is apparent that in the majority of cases of cerebellar agenesis the nervous system is affected at an early stage of its development and it will not have escaped notice that in the cases referred to above, in the more extreme degrees of agenesis it is almost invariably the pars floccularis which survives. Phylogenetically, the two flocculi are the primitive derivates of the roof-plates of the metencephalon. They constitute the oldest part of the cerebellum and in human

development are among the earliest to make their appearance—probably not later than the second month of intra-uterine life. From this it may be inferred that the majority of cases of cerebellar agenesis occur after this period. In this case the position of the cerebellar fragment is not inconsistent with the view that it may have represented an imperfectly developed flocculus and its apparent limitation to the right side of the brain stem could easily have been due to the accidental removal of its opposite number on the left side of the pons. Small fragments of cerebellar tissue are readily overlooked and consequently, when based solely on unaided naked eye inspection, the claim for total absence of the cerebellum must remain open to doubt. In the case described by Combettes in 1831 his description of the presence of two small pea-like masses in the neighbourhood of the medulla resembles so closely that of Anton and Zingerle who were able to demonstrate the cerebellar structure of two nodules in a similar situation that it is difficult to avoid the conclusion that Combettes was describing a case which was not of total, but of partial, agenesis. Nor is the case recorded by Priestley wholly satisfactory since her claim for complete cerebellar deficiency rested on post-mortem appearances which were not supplemented by microscopic examination.

Normally, the development of the inferior olive affords an example of the embryological phenomenon of neurobiotaxis—the tendency of functionally related areas to establish connections—but from the findings in this case it is clear that a certain degree of independence is possible in the development of parts of the brain which are in closest connection with one another. Thus, though both palaeocerebellum and neocerebellum had all but failed to develop, the cells of the inferior olive which normally supply impulses to the cerebellum had survived to a considerable degree and showed no evidence of retrograde degeneration.

Foremost among the clinical features which deserve notice was the comparative freedom of movement in the upper limbs. Whereas in his station and gait the patient exhibited to a disabling degree the irregularities of movement which characterize cerebellar ataxia, except for the finer movements of the fingers, he was able to employ the upper limbs comparatively well. This has been noted in other cases of cerebellar agenesis in which both lateral lobes have been wholly wanting and is of interest inasmuch as the neocerebellum has developed through the ages as man became emancipated from the locomotive movements of the quadruped and learnt to use his fore limbs for more delicate purposive movements. It is therefore a paradox that deprived of his cerebellum the human subject should retain more command of his upper limbs than of his lower.

Attempts have been made to explain the absence of symptoms in cerebellar agenesis on the basis of compensations in neural structure. Anton and Zingerle (1914) concluded that compensation for the cerebellar defect is achieved by an hypertrophy of the dorsal sensory system, the spinal trigeminal and spinothalamic tracts on the afferent side, with hypertrophy of the pyramids and substantia nigra on the efferent side. It is, however, difficult to reconcile this view with the anatomical findings in the case described by Rubinstein and Freeman (1940). The cerebral peduncles were smaller than normal and in a much earlier study, Spiller (1896) made the same observation. In the case recorded above largeness of the pyramids was certainly a striking feature but microscopic examination of the motor cortex gave no indication of a compensatory hypertrophic development, nor were the cells of the substantia nigra more numerous than normal; if anything they were fewer in number.

More, perhaps, can be said for the alternative view that compensation can be achieved not so much through hypertrophy of extracerebellar tracts or nuclei as by a stabilizing function of the cerebrum. Hitzig (1884) based his support for this conclusion on the observation that his patient with unilateral cerebellar defect suffered no inconvenience until the brain was attacked by syphilis. Vogt and Astwazaturow (1912) subscribed to the same view as they, too, found that in pure agenesis tremor and ataxia were observed only in cases with concurrent cerebral disease. To these cases one can add that of Rubinstein and Freeman whose patient showed no signs of cerebellar disorder until generalized arteriosclerosis became cerebrally widespread.

In conclusion, it may be remarked that the frequency with which some degree of hydrocephalus has been found in conjunction with cerebellar agenesis suggests that in such cases the fluid accumulation and the cerebellar deficiency may have a common origin in some embryonic defect, possibly genetically determined.

SUMMARY

A male imbecile, who at birth was noted to have a slight degree of hydrocephalus, was handicapped throughout his life by unsteadiness of gait, clumsiness of the hands and dysarthria. He died in his 55th year. Examination of the nervous system showed that the cerebellum was represented by a single fragment of tissue attached to the right side of the pons. It measured 7 mm. × 3 mm. × 1 mm.

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