Review.

An Attempt to Classify Cerebellar Disease, with a Note on Marie's Hereditary Cerebellar Ataxia.

It is unnecessary to insist on the need of some method of classifying primary disease of the cerebellum: it has become almost imperative owing to the confusion which has arisen from the introduction of the term "Hereditary Cerebellar Ataxia" by Marie, as under this title many cases have been described without any regard to the exact nature and the localisation of the pathological lesions.

The numerous published cases of cerebellar disease have been already several times collected together and reviewed, but as the object has been to determine the symptoms due to affection of the cerebellum, or to adduce some facts with regard to its function, all cases have been indiscriminately grouped together without any regard to the nature of the lesions. In the reviews of Nothnagel, Thomas, and Adler [1] little attention was paid to whether the disease was congenital or acquired, or whether it was a primary affection of the functional tissue or a degeneration of this secondary to vascular or interstitial lesions; while Mingazzini [33], who has alone attempted to classify cases according to their morbid anatomy, has, apart from distinguishing congenital from acquired lesions, more or less disregarded the nature of the disease.

As it is essential to base any classification of disease on morbid anatomy and its pathogenesis, only those cases will be included in the present review in which the nature and the extent of the pathological changes were determined by *post-mortem* examination. But even with this restriction it is difficult to classify many of the published cases, owing to the meagre clinical and anatomical records which are available. This is especially so with the cases which were described before more exact methods of examination were in use; many of these must be consequently excluded, as they can be of nothing more than historical interest. The large number of recorded cases of aplasia or congenital lesions of the

cerebellum must be also excluded from this review, but it is not always possible to do so with certainty, as we must rely on the history of the onset and of the course of the disease, as well as on the histological changes found in the central nervous system.

The following mode of classification seems the most natural and the best possible:—

(I.) Primary parenchymatous degeneration of the cerebellum.

(II.) Olivo-ponto-cerebellar atrophy.

(III.) Progressive cerebellar disease due to vascular or interstitial lesions.

(IV.) Acute cerebellar lesions.

In these four groups all cerebellar diseases, apart from tumours and focal lesions of vascular origin, may be included. It will be seen, however, that it is also advisable to discuss the two following groups of cases here; for although in them the cerebellum is not affected, their most prominent symptoms have been described as those of cerebellar disease.

(V.) Degeneration of the spino-cerebellar tracts, the cerebellum being normal or small only.

(VI.) Congenital smallness of the central nervous system associated with cerebellar symptoms.

There are cases which do not fully conform to the type of any of these classes, but when there are main and general resemblances in both the clinical symptoms and the morbid anatomy it seems advisable to attempt to place them in one or other group. This is frequently the most we can do in any branch of medicine, as neither nature nor disease draws lines of sharp distinction.

Class I.—Primary Parenchymatous Degeneration of the Cerebellum.

The cases which I have described in the present number of this Journal [21] seem to be the best examples of primary parenchymatous disease of the cerebellum, with the rest of the central nervous system intact or only secondarily affected.

Fraser's cases [18] probably fall into the same group. A brother and a sister were similarly affected, but there was no other case in the family. The symptoms were present from early childhood and increased slowly in intensity. They were very similar to those in my cases; a reeling and staggering gait,

incoördination of the arms, nystagmoid jerking of the eyes on lateral movement with, in addition, strabismus, which may have been congenital, slow, guttural and hesitating articulation, and tremor of the head in one case at least. Vertigo was prominent in one case, and in both there was primary optic atrophy. The central nervous system of the brother was examined. The cerebellum was reduced to less than half its normal weight, its cortex was little more than half the normal thickness, very few Purkinje cells remained in it, and these were atrophied and shrunken. The white matter of the folia was less affected. The spinal cord, which was examined by the naked eye only, appeared normal, and no other disease was detected in the central nervous system. Fraser's cases have been included among the congenitally small cerebella, but the progressive course of the symptoms, as well as the nature of its morbid anatomy and its familial incidence, make it to my mind most probable that the disease was a primary degeneration of the cerebellar cortex.

In the case of a woman reported by Thomas [64] the symptoms began with slowly progressive affection of gait at the age of 40. There was no similar case in the family; the patient had had syphilis and admitted excessive indulgence in alcohol. She walked on a broad base, reeling from side to side, and there was marked disorder of movement, of the intention-tremor type rather than ataxia, of the lower limbs, but the upper extremities were not affected. All muscles were very hypotonic. Articulation was nasal and scanning, and there was irregular nystagmus on lateral movements of the eyes. Sensation was unaffected, the knee-jerks were brisk and the plantar responses were of the extensor type. She died at the age of 54. The only pathological changes found in the central nervous system were disappearance of the Purkinje cells from many of the folia of the cerebellum, atrophy of these cells in others, though in some they were normal; in the folia from which the Purkinje cells had disappeared there were degenerative changes in the molecular and granular layers, with secondary neuroglial proliferation. There were no vascular or meningeal lesions.

In a case recorded by Mingazzini [33] the cerebellum was very small, its cortex was atrophied and narrow, and the Purkinje cells were diminished in number and in places absent. The white matter and the myelinated fibres of the cortex were also atrophied. The central nuclei were imperfectly developed and the medial portions of the superior peduncles were degenerated.

The middle peduncles and the transverse fibres of the pons were also slightly atrophied. There was, in addition, thickening of the pia mater over the whole central nervous system, and probably as a result of this a slight peripheral degeneration of the cord and atrophy of the cerebral cortex, but these may be regarded as only coincident changes. The patient died at the age of 18. There is no history of the course of the disease, and no similar case in the family. The symptoms and signs were convergent strabismus, nystagmus on movement of the eyes, scanning articulation, rhythmical tremor of the head, slight rigidity of the limbs and ataxia of the intention-tremor type, a reeling and staggering gait with great difficulty in equilibration, and active tendon reflexes. The patient was an idiot and had frequent epileptic convulsions. Mingazzini regarded his case as a partial agenesis and aplasia of the cerebellum, and, though this was most probably its nature, it is cited here as a possible case of cerebellar degeneration.

The cats which were examined by Herringham and Andrews [20] were possibly also instances of primary cerebellar disease. The four kittens of a litter appeared healthy at birth and were for a time able to walk quite naturally. Two of them soon became weak on their legs and gradually incapable of movement, and were destroyed. Later the other two were similarly affected; in these the symptoms were certainly not present from birth. The optic discs and the functions of the cranial nerves were normal; there was marked inability to maintain equilibrium both in rest and in motion: on a smooth surface they attempted to walk on a broad base, reeling and falling from side to side, the defect being chiefly in the movements of the hind limbs. The one kitten was killed at four months, the other at eight months of age, and the central nervous systems were carefully examined. The cerebellum of each was small; the molecular layer of its cortex was only half the normal breadth, the Purkinje cells were scattered all through the granular layer, but they were apparently normal and not appreciably diminished in number; the granular layer was narrow and in places hardly recognisable. The white matter, the central nuclei and the peduncles of the cerebellum, as well as the rest of the central nervous system, were unaffected. The authors regarded the condition as a primary degeneration of the molecular and granular layers of the cerebellar cortex, the distortion of the Purkinje cell layer being secondary to the sclerosis and contraction of the molecular layer. Risien Russell [50] found a somewhat similar condition in the puppy which he examined. All the members of the litter had apparently the

same symptoms, viz., an ataxic and reeling gait and constant oscillation of the head and trunk while at rest, but it is not certain whether the symptoms were present from birth or were acquired. The breadth of the molecular layer was very irregular; in places it was increased, in other places diminished; the granular layer was similar, and the Purkinje cells, which were absent in a considerable portion of the cortex, were in other places heaped up into masses which extended into the granular layer. He regarded the condition as a defective development. Southard [58], too, found a somewhat similar condition in the cerebellum of an epileptic imbecile who had apparently exhibited no symptoms of cerebellar disease during life. The author regarded this condition as a developmental anomaly. The evidence from these cases of Russell and Southard makes it probable that the pathological changes described in the kittens by Herringham and Andrews were also developmental abnormalities, and not degenerative, as these authors assumed. The absence of any secondary degeneration in the white matter of the cerebellum tends to confirm this view. There is evidence that cerebellar symptoms may develop late in life on the basis of congenital abnormalities (see the cases of Nonne and Miura).

Class II.—Olivo-ponto-cerebellar Atrophy.

The second type of primary cerebellar degeneration may be known by this title given to it by Thomas, as the grey matter and fibres of the pons and of the inferior olives undergo simultaneously primary degeneration. It seems to be the form of cerebellar disease which is most easily classified. It is chiefly to Thomas that we owe our knowledge of its clinical and anatomical features. This author published his first case in his well-known thesis on the cerebellum in 1897 [62], he added another case in 1903 [63], and, a third in collaboration with Dejerine [14]. His summary of its main features is, "a type characterised *anatomically* by atrophy of the cerebellar cortex, of the bulbar olives, and of the grey matter of the pons; by total degeneration of the middle cerebellar peduncles, by partial degeneration of the corpora restiformia, and by relative integrity of the central nuclei of the cerebellum; *clinically* by the cerebellar syndrome. It is neither hereditary, familial nor congenital. It comes on at an advanced age and progresses slowly. It falls into the group of primary cell atrophies." This general description covers the three cases, though there were points of slight difference between them. Clinically the most prominent feature was a great defect in equilibration in

standing and walking, to which the typical cerebellar "*démarche ébrieuse*" was due, although the individual movements of the lower limbs were not in the same degree ataxic, and Romberg's sign was absent. In two of the cases the movements of the arms were well coördinated, but in the third there was intention-tremor on movement. Articulation was slow and scanning in all three cases, and nystagmus was observed in two. Anatomically there was slight pallor of the crossed pyramidal tracts of the cord in two of the cases, but the other spinal tracts were normal. The degeneration of the transverse fibres and nuclei of the pons and of the inferior olives was practically complete, and the affection of the cerebellar cortex was very severe, involving all layers, but it was not uniform either in degree or distribution. Emphasis was laid on the very slight amount of neuroglial sclerosis which was found in the degenerated parts. Thomas' second case was complicated by the co-existence of disseminated sclerosis, which, however, the author regarded as independent of the cerebellar disease.

Other recorded cases have considerable resemblance, both clinically and pathologically, to this type, and may be included in it. That published by Pierret [45] was probably identical; but if the history was trustworthy the symptoms appeared at a much earlier age—4 years—and there was much more tremor and incoördination of the upper extremities. Pathologically there was no essential difference, except a considerable amount of secondary sclerosis.

The clinical course of Royet and Collet's case [49] was typical except that there were contractures, but the cerebellum, which was small and appeared tough and sclerosed, was not examined microscopically. The degeneration of the pons and olives was very marked, and the spinal cord was normal.

The case reported by Arndt [3] differed from the type chiefly by the relatively slight affection of the cortex, in which there was only diminution and atrophy of the Purkinje cells, and by the more intense degeneration and sclerosis of the white matter of the cerebellum; the pons and the olives were completely degenerated. There was also slight affection of the pyramidal tracts. The author believed the degeneration of the nervous elements and the glial sclerosis were secondary to vascular disease; is seems, however, more probable that the definitely systematised degenerations which he described were independent of the vascular disease that was present, especially as the central nuclei and the superior cerebellar peduncles escaped. The symptoms began with vertigo and uncertainty of gait at the age of 66, four years before death.

The patient's gait was reeling and drunken, and his base broadened by separation of his feet. There was also slight dysarthria, paresis of the limbs without rigidity, and irregularity of the volitional movements, which were more or less of the intention-tremor type.

There was no accurate clinical observation of the case described by Redlich [47], but the pathological changes were very similar to those in Arndt's case. He regarded the case as a primary disease of the cerebellum, the Purkinje cells being the portion of the cortex which was first affected.

The subject of the recent publication by Schweiger [53] was a demented woman who died at the age of 58. Weakness of the legs and tremor of the upper extremities developed at the age of 51, and two years later articulation became affected. When she came under observation at 57 there was nystagmus, scanning speech, intention-tremor and slight spastic paresis of the arms, more marked spastic paralysis of the legs, paralysis of the sphincters, increased knee-jerks and ankle-clonus. The clinical diagnosis was disseminated sclerosis. The lateral lobes of the cerebellum were severely affected, the vermis less so, while the tonsils were normal. The central white matter of the lateral lobes had suffered the most severely, and that of the folia was also intensely degenerated. There was considerable atrophy of the granular layer of the cortex, the Purkinje cells were reduced in number, and those which remained were atrophied, but the molecular layer was almost normal. The inferior olives and the olivo-cerebellar fibres, as well as the middle cerebellar peduncles, the transverse fibres of the pons and the pontine nuclei, were completely degenerated. The dentate nuclei and the superior cerebellar peduncles were intact, but there was probably some affection of the roof nuclei. The case is remarkable owing to the degeneration of the cortico-pontine tracts, but the cortico-spinal tracts were normal. In the middle thoracic cord there was a focus which involved only the white matter and destroyed all its fibres, but the only secondary degeneration which resulted was of the distal part of the pyramidal tracts. This lesion was regarded as a patch of disseminated sclerosis, but it was not sclerosed; if this was its nature it must have been quite recent. I find it difficult to accept the author's interpretation of the pathological changes in this case. According to his view the original lesion was as sclerotic process, similar to the spinal lesion, of the central white matter of the lateral lobes of the cerebellum; the affection of the cerebellar cortex and of the pontine and olivary

systems was secondary to this. The degeneration of the pons and olives was so complete as to necessitate the conclusion that the primary lesion must have occurred in very early, or even in fœtal, life. He admits that there was no histological evidence of the primary encephalitic process which he postulates, but adds "nur so ist das Erhaltenbleiben der Purkinje'schen Zellen zu erklären." But on the contrary, if axones had been destroyed by an encephalitic process, the chief change would have been found in the cells from which those axones spring, and the Purkinje cells are the chief elements of the cortex which send axones into the central white matter. Further, it would be very remarkable if encephalitic foci had involved the two sides of the cerebellum symmetrically, and had, although seated in the central white matter, spared the dentate nuclei. From these facts it seems more probable that the olivo-ponto-cerebellar disease was of the type described by Thomas, and that the spinal lesion was a coincidence only.

Two cases in which, in addition to olivo-ponto cerebellar atrophy, there was tract degeneration in the spinal cord may be most naturally referred to here. The one was published by Menzel [31], the other by Thomas [62], (Obs. V.). There was probably a familial incidence of the disease in Menzel's case; the mother, who died at 60, had tremor of the head and uncertain gait; five of her seven children had evidences of nervous disease, and of these two sisters and a brother were probably affected similarly to Menzel's case. One of his daughters, too, had some form of hereditary ataxia. In the patient himself the symptoms appeared at 28 and progressed slowly. His gait was very unsteady and reeling, as well as slightly spastic; the volitional movements of his hands were wildly ataxic, and his upper extremities were feeble and rigid; his speech was slow and badly articulated, and there were involuntary movements of his head (probably a tic) and facial muscles. The knee-jerks were exaggerated. He died at the age of 46. In addition to degeneration of the cerebellum, pons and olives, the dorsal columns of the cord and the cortico-spinal and spino-cerebellar tracts were degenerated. The pathological changes in the cord were thus those of Friedreich's disease.

In Thomas's case [62] there was a neuropathic heredity, but no other case of the disease in the family. The symptoms were complicated by the presence of hysteria. They commenced at the age of 25 with progressive feebleness of the limbs, failure of vision, a staggering gait and intention-tremor of the arms;

articulation became slow and scanning. In addition to atrophy of the cerebellum, pons and olives, which was similar to but not so severe as in the other cases of olivo-ponto-cerebellar atrophy, there was degeneration of the dorsal columns and of the spino-cerebellar tracts of the cord, and some atrophy of the pyramidal tracts, especially in the lumbo-sacral segments. Thomas regarded the cerebellar lesion in this case as a secondary atrophy of peripheral origin, the initial lesion being atrophy of the nuclei of the principal afferent tracts of the cerebellum, especially of the grey matter of the pons.

Class III.—Progressive Cerebellar Disease due to Vascular or Interstitial Lesions.

Although diffuse vascular or interstitial lesions of the cerebellum are often diagnosed, there is very little pathological evidence that they occur frequently. In Schultze's case [52], which was attributed to alcoholism, the onset occurred at 39. Gait became drunken and cerebellar in type, but Romberg's sign was absent; articulation was indistinct and slow, and there was intention-tremor of the arms and slight nystagmus. The symptoms progressed rapidly, and death took place at the age of 43. There was considerable atrophy and sclerosis of the cerebellum and brain-stem. The Purkinje cells of the cerebellar cortex were very scanty, and those which remained were atrophied; the molecular and granular layers were less affected. The lesions tended to be focal and very diffuse, and there was a large amount of secondary neuroglial sclerosis. The central nuclei were very atrophic, and the superior peduncles degenerated. The degeneration of the olives and of the transverse fibres of the pons was probably secondary to the cerebellar disease. The spinal cord was normal, excepting for slight pallor of the pyramidal tracts.

Michell Clarke [10] has published, as a case of sclerotic atrophy of the cerebrum and cerebellum of familial type, the history of a boy who was healthy till 7, when the symptoms began with choreiform jerkings of the limbs. Later, vision failed, the limbs became ataxic and spastic, the knee-jerks were exaggerated, and the plantar reflexes of the extensor type. Articulation was indistinct, and there was progressive mental deterioration. Two maternal uncles had been affected with the same symptoms, the onset occurring at the same age. *Post-mortem* examination revealed atrophy of the cerebral cortex, sclerosis of the white matter of the forebrain, and complete degeneration of

the cortico-spinal tracts. The cerebellar cortex was but little affected, but there were numerous patches of sclerosis throughout the white matter of the cerebellum.

Southard [58], in a congenitally syphilitic negro who died at the age of 23 with a history of progressive incoördination of the movements of the limbs, tremors, nystagmus and mental deterioration, found sclerosis of the cerebellum, absence of the Purkinje cells in many of its folia, and atrophy of its molecular and granular layers, in addition to chronic leptomeningitis and focal sclerosis of the forebrain. The medullæ of the folia were much degenerated, and there was an extreme amount of gliosis in the cortex, white matter, and central nuclei.

Finally Catolo [9], in a case which is difficult to interpret, found marked atrophy of the brain-stem and cerebellum, with diminution of the Purkinje cells of the cerebellar cortex and secondary sclerosis in their place, as well as patches of sclerosis without secondary degeneration throughout the cerebellum, some of them involving the dentate nuclei. Similar patches were found in the brain-stem. There was also partial atrophy of the olives and pons, and pseudo-system degeneration of the ventro-lateral columns of the cord. The vessels of the central nervous system were much diseased. The clinical symptoms, which were progressive, appeared at the age of 38 after an attack of cholera. They were nystagmus and diplopia, tremor of the head, intention tremor of the limbs, an ataxo-cerebellar and spastic gait, scanning speech and exaggeration of the tendon reflexes. The author regarded the case as one of disseminated sclerosis associated with cerebellar atrophy, the latter being probably due to the vascular disease.

Class IV.—Acute Cerebellar Lesions.

Batten [5] and others have attributed the cases of acute ataxia which occur relatively frequently in children during and after infective illnesses to lesions of the cerebellum. The pathological changes in several of these cases have been studied, but, with the exception of a case reported by Nauwerck [38] as cerebellar encephalitis following influenza, histological examination was possible only at long periods after the onset. It seems probable that while in some of the cases the disease is an inflammatory lesion of the nature of an encaphalitis, in others it is an acute degeneration of the nervous elements of the cerebellar cortex due to the action of toxins.

Clapton's case [11] is an excellent example. A healthy child

of 4 suddenly became unable to use her limbs or even to talk, after an attack of measles. She apparently remained more or less in this state for about six months; from that age improvement gradually set in, but till about 15 she could not use her hands properly and walked unsteadily. She died at 33. The cerebellum was less than a third of its normal weight, and on microscopical examination it was found that there was almost complete absence of the proper nerve substance of its cortex and great increase of neuroglia.

Hammarberg's case [19] was very similar. The onset was acute, with an attack of Hirnentzündung—" brain fever "—at the age of 7. For the first three months there was constant oscillatory movement of the head and limbs, and speech was lost. As these symptoms disappeared all volitional movements became wildly ataxic, articulation was scanning, gait reeling and uncertain, and there were choreiform movements of the fingers. Death occurred at 24. The pathological changes in the cerebellum were very similar to those in Clapton's case, but sclerotic foci were also present in the medulla and cerebrum.

The cases recorded by Huppert [22] and Sommer [57] were also similar. In each, at the age of 3 years, there was some form of acute brain disease, and thereafter gait was drunken and reeling, and there were other symptoms of cerebellar disease. Both children become idiots. The cerebellum of each was small and evidently sclerosed. In Sommer's case, of which there is a good description, the affection was not uniform; in the most affected parts all layers of the cortex were extremely atrophied, the Purkinje cells had disappeared, and the white matter was reduced and sclerosed.

Bond's case [7] was probably similar, but the history of the disease was not definite enough to decide with certainty if the onset was acute, or even if it was post-natal.

In the case which was examined pathologically by Spiller [59] the onset occurred apparently during an attack of scarlet fever at the age of 3 years, but the fact that the child was late in learning to walk raises the suspicion that the lesion may have been congenital. There was a gradual but not complete recovery from the symptoms; gait always remained staggering. Death occurred at 19. The cerebellum was small and widely affected by sclerotic foci, some of which extended sufficiently deep to reach the dentate nuclei. No cortex was present in the sclerotic areas; elsewhere its different layers were reduced in thickness. The cerebellar peduncles were small, and the olives and pons very atrophic.

The spinal cord was normal, but one cerebral hemisphere was under-developed and the corpus callosum was deficient.

In a case described by Sepilli [56] there was an acute onset during convalescence from an attack of typhoid fever, at the age of 28. The symptoms when the patient was later observed were general tremor and choreiform movements of the arms, ataxia of all voluntary movements, a reeling and drunken gait, and some affection of articulation. After death, which occurred four years after the onset, it was found that the cerebellum was very small, its cortex was extremely atrophied, and practically all its Purkinje cells had disappeared; the white matter of the folia contained very few myelinated fibres, and the dentate nuclei were also affected.

In the cat examined by Krohn [25] the history of acute onset was very definite. It occurred at the age of three months, when the cat suddenly became paralysed. Later, on attempting to walk, the animal reeled from side to side: "the hind limbs seemed to wish to go faster than the fore, giving a ludicrous effect." The movements of the limbs were ataxic, and there was considerable tremor, especially of the head. When the cat was killed at 11 months of age the cerebellum was found small and firm, its cortex was reduced to scarcely more than half its normal thickness, the molecular layer being the most severely affected, and the Purkinje cells were almost quite absent. The white matter was almost normal.

In the majority of these cases with acute onset the disease seems to have consisted of diffuse or focal lesions of the nature of encephalitis—that is, primary disease of the interstitial substance or of the vessels; but in the cat observed by Krohn, as well as in the two following cases, it was more probably a primary cell degeneration due to the action of toxins.

In the case recently recorded by Rossi [48] as primary parenchymatous atrophy of the cerebellar cortex, the symptoms appeared at the age of 59 after an attack of acute diarrhœa with pains in, and marked feebleness of, the limbs, and great disturbance of articulation. After a time there was some recovery, but later slight progression of the symptoms. Gait was staggering and of the cerebellar type, yet also somewhat spastic; there was asynergia and intention-tremor of the legs without any loss of power, articulation was slow and lisping, but there was no nystagmus. There was some analgesia of the legs and the plantar responses were extensor in type, neither of which can be regarded as cerebellar symptoms. Death occurred at 68. The cerebellum

was considerably reduced in weight and in volume, but the disease was practically limited to its upper surface. In the affected folia the molecular layer was much reduced in thickness; the Purkinje cells were completely absent, and the granular layer had lost many of its cells, but the white matter was little affected. In the other parts there was only a numerical reduction of the Purkinje cells. The central nuclei and cerebellar peduncles, as well as the rest of the central nervous system, were normal.

In connection with the etiology of the cortical degeneration in Rossi's case, it is interesting that Murri [37] has reported a case in which the Purkinje cells degenerated after an attack of enteritis, owing presumably to the action of toxins of intestinal origin. The clinical symptoms were those of cerebellar disease.

Lüthje [27] has insisted that the majority of these cases of acute ataxia which come on during or after the infective diseases, are due either to pure cerebral or diffuse cerebrospinal lesions. He cites the case of Ebstein's patient [15] who, when 48, during an attack of enteric fever, developed ataxia and paresis of the limbs, tremor of the head and limbs, and faulty articulation. The symptoms gradually diminished. He died eight years after the onset. The autopsy revealed diffuse focal perivascular and meningeal lesions throughout the cord and medulla; the cerebrum and cerebellum were normal.

Class V.—Degeneration of the Spino-Cerebellar Tracts, the Cerebellum being normal or small only.

The justification for including these cases among, or rather contrasting them with, those in which the cerebellum itself is affected, is in the clinical experience that their prominent symptoms are similar to, or may be identical with, those of cerebellar disease. Attention has been directed to this by the experimental work of Marburg [28] and Bing [6], who observed marked cerebellar symptoms after section of the spino-cerebellar tracts in the cord. A further reason for considering these cases here is the fact that some of the cases originally included by Marie in *Hérédo-ataxie cérébelleuse* belonged to this group.

(1) Cases which do not belong to any well-recognised type of disease may be considered first.

Klippel and Durante's observations [24], which were subsequently completed by Londe [26], Vincelet [66], and by the authors who have described the anatomical examination of the central nervous systems, were made on three members of a

family, of which the mother and one of her sisters were apparently similarly affected. The onset occurred between the ages of 25 and 35 years, in two of the cases with cramps, violent pains and numbness in the legs, followed by a slowly progressive affection of gait, which was described as "démarche titubante," and Romberg's sign. The face was immobile, articulation hesitating, indistinct, and scanning; coarse nystagmoid jerking was observed on volitional movement of the eyes, and in two cases there was slight failure of vision, apparently without any disturbance of the pupillary reactions (on this point there are discrepancies between the reports of the different observers who published clinical details of the cases). Fibrillation in the limbs and facial muscles, and frequent intermittent muscle cramps which occasionally interfered very much with volitional movement, were prominent symptoms; it was to these cramps that Klippel and Durante attributed the disorders of movement of the different parts of the body. In addition there was rigidity and slowness and feebleness of movement and easy fatigue, but no true ataxia of either the upper or lower limbs. Contractures finally developed and produced deformities. In all three cases there was considerable diminution of cutaneous sensation, especially to heat and cold, on the legs and feet. The knee-jerks were normal or slightly exaggerated in two of the cases, though in the eldest brother they were diminished and finally lost. In the only case in which the state of the plantar reflexes was recorded, they were extensor in type. The three patients have died, and their central nervous systems have been examined by Thomas and Roux [65], Switalski [61], and Rydel [51]. The pathological changes found in all were so similar that they may be described together. The central nervous system was small, especially the cord, brain-stem, and cerebellum. The dorsal columns and the dorsal and ventral spino-cerebellar tracts of the cord were degenerated, and Clarke's column had lost most of its cells and fibres. There was also slight atrophy of the grey matter of the ventral horns. The only abnormality in the brain-stem was degeneration of the spino-cerebellar tracts, except in Switalski's case, in which the middle cerebellar peduncles and the ventral part of the pons were small. No histological change was found in the cerebellum. Thomas and Roux, in discussing the significance of the small size of the central nervous system, point out that though the age at the onset of the symptoms was in favour of it being due to a regressive atrophy, the absence of secondary degeneration and sclerosis favours the view that it merely represented incomplete development.

The chief clinical features of the twenty-one cases which Sanger Brown [8] observed in four generations of the one family were: onset, most frequently between the ages of 16 and 35, with ataxia of the legs and later of the arms, facial, ocular, head, laryngeal and pharyngeal muscles. The gait was described as a cerebellar reeling; there was no tendency to Romberg's sign. Later in the illness, palsies and permanent spastic contractures developed. There were also involuntary choreiform movements of the head and limbs "whenever it was attempted to maintain these parts in a fixed position by volitional effort." Optic atrophy was observed, with deficient pupillary reaction to light. Sensation was unaffected, the tendon-jerks were exaggerated, and there was no tendency to deformities, save those produced by the spastic contractures. Three of these patients have since then been examined pathologically, one by Meyer [32], and two by Barker [4], and in each of the three the same changes were found in the nervous system. The cerebrum was well developed and normal; the cerebellum was only very slightly, if at all, smaller than natural, and was normal in structure, except, perhaps, for slight diminution in the number of the Purkinje cells; in the brain-stem there were only insignificant changes. In the spinal cord, on the other hand, there were pronounced alterations; it was small in proportion to the rest of the central nervous system; the dorsal spino-cerebellar tracts and Clarke's column were completely degenerated; Gowers' tract was slightly affected, while in the dorsal columns there was degeneration of the middle root zones with ascending degeneration of Goll's columns.

In Perrero's case [44] there was no heredity, but from the age of 2 years the patient staggered and had tremor of the head. From the sixth year there was kypho-scoliosis, pes equino-varus, and a gradual deterioration of the power of walking. The anatomical change was enormous atrophy of the cerebellum and cerebrum, which was probably congenital, as microscopical examination revealed only the character of simple atrophy. In the spinal cord there was degeneration of the dorsal and ventral spino-cerebellum tracts, diminution of the cells of Clarke's column and degeneration in the dorsal columns. The special interest of this case is that, like Menzel's and others, it is regarded as forming a link between Friedreich's disease and hereditary cerebellar ataxia.

(2) Friedreich's disease is the best recognised type in which there is system degeneration of the spino-cerebellar tracts; a

short reference is necessary to the part the cerebellum plays in the production of its symptoms, owing to the repeated attempts to establish its identity with hereditary cerebellar ataxia—(Raymond [46]) or to insist that the two diseases are linked by intermediate forms—(Nonne [41], Londe [26], Seiffer [54]). To me it seems that the question needs little discussion, as Marie's disease, by which a primary atrophy of the cerebellum is generally understood, cannot be regarded as a disease in the ordinary acceptation of the term in modern medicine; the cases which have been included in it are not distinguished by constancy of their clinical symptoms, morbid anatomy, or pathogenesis.

Senator [55] some years ago argued, in opposition to Schultze, that the symptoms of Friedreich's disease were due to concomitant spinal and cerebellar lesions, but without any definite proof of his assertion. More recently, Phillipe and Oberthur (cited by Raymond) found in a case of Friedreich's ataxia general atrophy, without sclerosis of the cerebellar cortex and white matter, of the inferior and middle cerebellar peduncles, and of the transverse fibres and nuclei of the pons. The only other reference to lesions in the cerebellum in Friedreich's ataxia with which I am acquainted is by Mott [35], who found, in a patient who died twenty-one years after the onset of the symptoms, atrophy of the nuclei dentati and of the Purkinje cells of the cortex, associated with severe vascular degeneration, which was probably the causal factor. In two advanced cases in which I have examined the cerebellum by modern methods I failed to find any definite evidence of disease; here and there the Purkinje cells were placed rather far apart, but it is known that their arrangement in the normal brain is often irregular. It seems, then, probable that the pathological changes in the cerebellum and its peduncles which Phillipe and Oberthur found in the case of Friedreich's disease which they examined, can be regarded only as an exceptional coincidence, and there is thus very little justification for Raymond's assertion of the identity of this definite disease with the ill-defined groups of cases which have been described under the title "Hereditary Cerebellar Ataxia." Even if lesions of the cerebellum are found in Friedreich's disease they may be only secondary to the degeneration of the spino-cerebellar tracts which terminate in its cortex. In cases of combined system degeneration of the cord, in which the spino-cerebellar tracts degenerate, I have found foci of degeneration of all layers of the cerebellar cortex. It seems possible that this change was secondary to degeneration of the cerebellopetal fibres; on the other hand

it may have been merely the result of the direct action of the toxins to which the spinal degenerations are generally attributed. This view is made probable by the fact that Sträussler [60], whose recent paper is confirmatory of the observations of Weigert and Raecke, found similar degenerative changes in the cerebellum in general paralysis, which he attributed to the action of toxins circulating in the cerebrospinal fluid. Although there is no positive evidence that atrophy or degeneration of the cerebellum may follow degeneration of the spino-cerebellar tracts, it seems probable from analogy, as the cerebellum is very prone to undergo regressive changes as a result of cerebral lesions. The atrophy may travel by the superior peduncles, as probably occurred in the case of Mott and Tredgold [36], in which the molecular and granular layers of the cortex were atrophied and all Purkinje cells had disappeared from some of the folia; or through the pons and middle peduncles, as in the cases of Ferrier [16] and Cornelius [12], in which similar changes were observed in the cerebellar cortex. In the majority of these cases the primary cerebral lesion was congenital or occurred early in life, and the cerebellar changes were consequently regarded as due to arrest of development; but in the case described by Ferrier [16] the cerebral lesion occurred at the age of 30, and Cornu [13] has observed crossed cerebellar atrophy due to destruction of the contralateral basal ganglia by a tumour which had given rise to symptoms for only fifteen months before death. These cases indicate that this form of cerebellar atrophy is not merely a condition of arrested development, but is due to active regressive changes.

Class VI.—Cerebellar Symptoms associated with Congenital Smallness of the Central Nervous System.

This class is represented by the familial cases described by Nonne [40] and Miura [34]; the former were originally included by Marie in his paper on "Hereditary Cerebellar Ataxia."

Nonne recorded the cases of three brothers in whom the onset of the disease occurred at the ages of 10, 14, and 30. The first symptom to appear was awkwardness and uncertainty of gait, which increased slowly; Romberg's sign was absent. Articulation became loud, nasal and explosive, and was accompanied by excess of facial movement. There was optic atrophy with contraction of the visual fields, and various ocular movements were limited in range and interrupted by nystagmoid jerkings of the eyes. The movements of the limbs were ataxic, and there was

difficulty in relaxing contracted muscles, but no paresis. Sensation and the reflexes were unaffected. There was marked mental deterioration during the course of the disease. The pathological changes in one of the cases was described in Nonne's original paper, and since then the central nervous system of another has been examined [41]. In both the condition was the same. The whole central nervous system was small, the weight of the cerebellum and brain-stem was less than three-quarters of the normal. In one case the spinal cord was normal in size, in the other only equal to that of a boy of 10 years. No definite disease could be found in any part of the nervous system; the symptoms could consequently only be regarded " als Ausdruck einer mangelhaften Anlage, speciell des Kleinhirns."

Miura has described the cases of two brothers; their mother and two maternal cousins were probably similarly affected. The disease began with unsteadiness in walking, in the one at the age of 25, in the other at 33. Later, gait became reeling and ataxic, but Romberg's sign was absent. Vision became dim, and articulation explosive and stuttering. The facial expressions were remarkably fixed and stupid. Nystagmus was observed in one case, in the other it was absent. The limbs were tremulous, very ataxic in movement, and their strength was poor. Sensation and the reflexes were intact. The nervous system of one of the brothers was examined. The cerebellum and brain-stem were small; the former, which was little more than half its normal weight, appeared sclerosed, but no histological abnormality could be detected on microscopical examination. The cord was also small, but its tracts were normal. The clinical and anatomical similarity to Nonne's cases is obvious, and, as in those cases, the symptoms can be ascribed to a developmental defect only. But it is difficult to see why such prominent symptoms should first appear in early manhood and progress to the total disablement of the patient, if they were due only to a congenital deficiency to which neither degenerative nor regressive changes were superadded. More especially is this so with regard to the symptoms which were referred to the cerebellar deficiency, when it is remembered that with many cases of congenitally small or deformed cerebella, in which the disease was either bilateral (as in the cases of Otto [43], Ingels [23], Major [30], and probably in Ferrier's [17]) or unilateral (Neubürger and Edinger [39], Nonne [42]), no abnormal symptoms were associated; and that in other cases in which symptoms of cerebellar disease were present these gradually diminished with the increase of age (Anton [2]).

"Hereditary Cerebellar Ataxia" of Marie.

It will be remembered that Marie [29] attempted to define a new clinical type under this title by collating the cases which had been published by Fraser, Sanger Brown, Nonne, and Klippel and Durante, and that when his paper was originally published he himself had not observed any case which he could include in it. At that time the nature of the disease had been determined by *post-mortem* examination in two only of these cases.

The justification for Marie's definition of this new type must be therefore sought, in the first place, in the subsequent history and further analysis of these cases, and, secondly, in our clinical experience of its utility.

It must be again insisted that the classification of disease must be based on morbid anatomy and pathogenesis, and not on clinical symptoms alone. The constant association of a set of symptoms or physical signs may justify classing cases together provisionally under a single term, but only so long as it is impossible to determine accurately the pathological changes to which they are due. Consequently, in a discussion on "Hereditary Cerebellar Ataxia," only those cases in which a *post-mortem* examination has been made must be considered.

But an analysis of the clinical records of the cases which Marie orginally collected together shows that the symptoms of even these cases were by no means identical or even similar. The disease was hereditary in the cases described by Sanger Brown and by Klippel and Durante, but there was no similar case in the ascendant or collateral lines of the families observed by Fraser and by Nonne. Thus the term "hereditary" was not entirely justified; the disease was undoubtedly familial, and there was consequently in all probability an hereditary tendency to it, but this does not justify the use of the adjective.

One of the points of difference which has been adopted in many text-books between Marie's disease and Friedreich's ataxia, is that in the former the symptoms first appear in early adult life; but in Fraser's cases they were present from early childhood, and in some of Sanger Brown's they were observed as early as the eleventh year.

Finally, many of the symptoms exhibited by one or other of these patients could not be referred to disease of the cerebellum; for instance, the severe lancinating pains, the anæsthesia, and the inactivity of the pupils to light which were present in Klippel and Durante's cases. Nor could disease of the cerebellum explain the

intermittent spastic contractions of the muscles which were a prominent symptom in these cases, and to which these authors attributed the other abnormal symptoms. Optic atrophy, another symptom of " Hereditary Cerebellar Ataxia," could be regarded as only a coincident dystrophy; it was observed in some instances only.

But any justification there may have been for including the cases originally collated by Marie under the title " Hereditary Cerebellar Ataxia," has been shattered by the anatomical examination of the central nervous system. The morbid anatomy of the disease which affected the different families has been now determined in one or more members of each family, and has been already described in this review. In the cases of Klippel and Durante, and of Sanger Brown, the structure of the cerebellum was normal, and this organ was at the most only very slightly smaller than natural. In the spinal cord, on the other hand, there was degeneration of the dorsal columns and of the spino-cerebellar tracts. In Nonne's two cases no pathological changes were found, but in both the cerebellum was unnaturally small, and in one of these the whole central nervous system was considerably below the normal size. Only in Fraser's case was there the slightest evidence of acquired cerebellar disease.

Nor does a review of the large amount of literature which has appeared on " Hereditary Cerebellar Ataxia " since Marie's original publication help to justify its existence. The majority of the cases of progressive cerebellar disease which have been published belong to the class of the olivo-ponto-cerebellar atrophies, and in not a single one of these were the symptoms either hereditary or familial, and in almost all of them the onset occurred in advanced life. The same points of difference separate Thomas' and Rossi's cases from Marie's hypothetical group. As far as I am aware, no other case of cerebellar disease, with the exception of those published by myself [21], has been recorded in which the symptoms resembled those of Marie's syndrome, and in which the disease has been limited to the cerebellum.

We are consequently driven to the conclusion that no form of disease exists to which the term " Hereditary Cerebellar Ataxia " can be aptly applied. This title has been a convenient pigeon-hole in which to group together cases of obscure nature with some symptoms in common, and it may have been of service in drawing attention to such cases till it was possible to classify them accurately; but neither clinical nor pathological experience justifies its retention as the descriptive title of a form of disease.

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GORDON HOLMES.

PUBLICATIONS RECENTLY RECEIVED.

[Notes on a book under this heading do not preclude a subsequent heading.]

The Borderland of Epilepsy. By Sir WILLIAM R. GOWERS. Pp. 121. London: Churchill, 1907.

This is an interesting reprint, with additions, of the lectures published in the *Lancet* and *British Medical Journal*. It deals with various paroxsymal manifestations not definitely epileptic in origin. It is written with all Sir William Gowers's accustomed ease, and the chapter on "Vagal and Vaso-Vagal" attacks breaks new ground.