

Seeing that hydroquinone precipitates silver out of acid solutions, and taking into consideration that gold takes a higher place than silver in the electromotive series, this precipitation will certainly take place in the case of gold, so that our technique demonstrates gold, irrespective of the form in which it occurs in the tissue.

Summarizing, a method is described for the detection of gold in animal tissues by means of physical development in a solution of gum arabic,  $\text{AgNO}_3$ , hydroquinone and citric acid.

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**Neurology.** — *Clinical and histological observations on a case of primary cortical degeneration of the cerebellum.* By MARGARET A. KENNARD, M.D. (New Haven, Conn.). ROCKEFELLER Fellow 1934—'35. (Communicated by Prof. B. BROUWER).

(Communicated at the meeting of April 27, 1935).

Cases of late primary cortical degeneration of the cerebellum of the type first described by MURRI (12) in 1900, occur but seldom and the cases in the literature in which both clinical and pathological data have been presented are few. It has therefore seemed of value to report the following case seen recently in the clinic of Professor B. BROUWER in the Wilhelmina Gasthuis of Amsterdam.

Previous cases have been described under various titles: *Atrophie lamellaire des cellules de Purkinje* (A. THOMAS (1).); *Atrophie primitive parenchymateuse du cervelet à localisation corticale* (ROSSI (14).); *L'Atrophie cérébelleuse tardive à prédominance corticale* (MARIE, FOIX et ALAJOUANINE (11).). Such cases show a very definite picture characterised clinically by the development in adults with no history of familial cerebellar disease, of a slowly progressing cerebellar syndrome. Histologically, there is primary atrophy of the Purkinje cells of the cerebellar cortex with only slight alterations in any of the other cellular elements of the central nervous system.

#### CASE HISTORY.

The patient, H. K., a female, aged 59, was admitted to the Neurological clinic of the Wilhelmina Gasthuis on June 20, 1932, complaining of unsteadiness and inability to walk. She had been well until April 1932 at which time she developed vertigo and difficulty in maintaining her balance. A transient diplopia and blurring of vision also appeared at this time. Following this, tinnitus developed in both ears with gradual diminution of hearing which became poorer in the left ear than in the right. The difficulty in walking became so great that the patient was unable to stand alone, but coordination of the upper extremities remained normal. There was occasional frontal headache and vomiting. The patient, formerly cheerful, became very depressed.

She had always been well previous to the present illness. There was no history of cerebellar disease in her family. Her husband had died at 58 of heart disease. At one time he had been treated for syphilis. Two children were living and well, one had died in childhood.

*On Physical Examination, June, 1932*, the patient appeared in good general condition. All physical findings were normal except for a palpable tumor in the abdomen which was freely moveable and not tender.

*On Neurological Examination*, the mental status appeared normal. Cranial nerves were normal. The fundi and fields of vision were normal. There was no diplopia and no strabismus. Extraocular movements were normal. Pupils were equal and reacted to light and to accommodation. There was no facial paralysis, sensation in the face was normal and the corneal reflexes were present. There was slight deafness of both ears, greater on the left than on the right. WEBER's test was referred to the right. RINNE's test was negative bilaterally.

*Nystagmus*: There was no nystagmus when the patient looked directly forward but on looking to either side a vertical nystagmus appeared. Both canals reacted normally to the test of KOBRAK, i.e. with irrigation of the outer ear, horizontal nystagmus appeared toward the opposite side. The vertical nystagmus then disappeared but remained present on looking toward the side of the stimulated ear. The ninth through the twelfth nerves were entirely normal.

*Sensorium* was normal. Deep sensibility was intact and there was no astereognosis.

*Motor*: There was no stiff neck or KERNIG and no muscular atrophy. Muscle power was normal as was resistance to passive manipulation. Coordination was severely disturbed. The patient could not stand alone. There was also slight ataxia of the arms and hands. There was no dysdiadochokinesis, however. Writing was normal, and speech was intelligible.

The tendon reflexes of the arm and legs were equal and normal. There were no pathological reflexes of the sole of the foot.

July 5th 1932: Otological consultation confirmed the vertical nystagmus. It was stated that it was not due to labyrinthine infection but to intracerebral causes. The origin of the deafness was not clear.

*Laboratory*: Pulse and temperature were normal. Blood pressure 130/110. Blood WASSERMANN and SACHS-GEORGI negative. The urine contained albumin but was otherwise normal. Lumbar puncture showed an initial pressure of 130 and a normal QUECKENSTEDT. The fluid was clear and colorless, NONNE negative, PANDY negative, WASSERMANN negative. LANGE 2223211100.

July 7th, 1932. The ataxia, deafness and vertical nystagmus persisted. There was occasional vomiting. Speech had at this time become blurred. At times the BABINSKI reflex was positive on the left. The patient occasionally had difficulty in urinating.

Sept. 1932. Dysarthria had become much more marked. Ataxia was unchanged. On lumbar puncture, the fluid was normal except that NONNE and PANDY tests were both positive.

From this time on until death the symptoms gradually increased in severity. There was incoordination of all movements of the trunk and extremities and the ataxia was so severe that the patient had been in bed since September 1932. Speech was almost impossible to understand. The patient complained frequently of headache and, at times of diplopia. There was still no paresis of the eye muscle to be seen objectively. Vertical nystagmus persisted. There was questionable papilledema of the left optic disc. The reflexes of the legs had become increased.

Death occurred on December 1st, 1933.

#### PATHOLOGICAL REPORT.

Autopsy, Dec. 2nd, 1933 (Dr. TER POORTEN).

At autopsy a terminal bilateral lobular pneumonia was found. There was a patent foramen ovale. Pyelonephrosis was present and thrombosis of the left iliac vein. There was a carcinoma of the right ovary with metastases to the lymph-nodes, the peritoneum, stomach, intestine, liver and spleen. There were no metastases to the lungs.

The skull and brain showed no gross abnormalities. There were no signs of increased intracranial pressure. The cerebellum appeared normal on external inspection. *There was no atrophy.* But, on section, the dentate nuclei appeared shrunken and gray. Brachium conjunctivum, thalamus, capsula interna, nucleus ruber and hypophysis were normal. Dura and falx were also normal as were the blood vessels at the base of the brain.

*Histological examination:* Serial sections of the entire cerebellum and the adjacent brain stem were made and alternate sections were stained with VAN GIESON and with WEIGERT-PAL stains. Small portions of the cerebellum were also stained with the NISSL and the HOLZER method and with the BIELSCHOWSKY. NISSL and Haematoxylin-eosin sections were made from portions of the dentate nucleus. From the cerebral cortex, NISSL and Haematoxylin-eosin preparations were made from the frontal, temporal, and occipital cortices.

*Cerebellum:* The general contour of the cerebellum was normal. Pia-arachnoid and blood vessels were normal. There was no evidence of meningitis or of any type of infection. The one striking abnormality was the practically complete absence of PURKINJE cells. This condition was the same throughout the entire cerebellum, the vermis, hemispheres and flocculi. Occasionally in discrete isolated areas a few shrunken PURKINJE cells were to be seen, usually sunk down into the granular layer. No normal PURKINJE cells were seen. This phenomenon was present in both NISSL (Fig. 1) and in Haematoxylin-

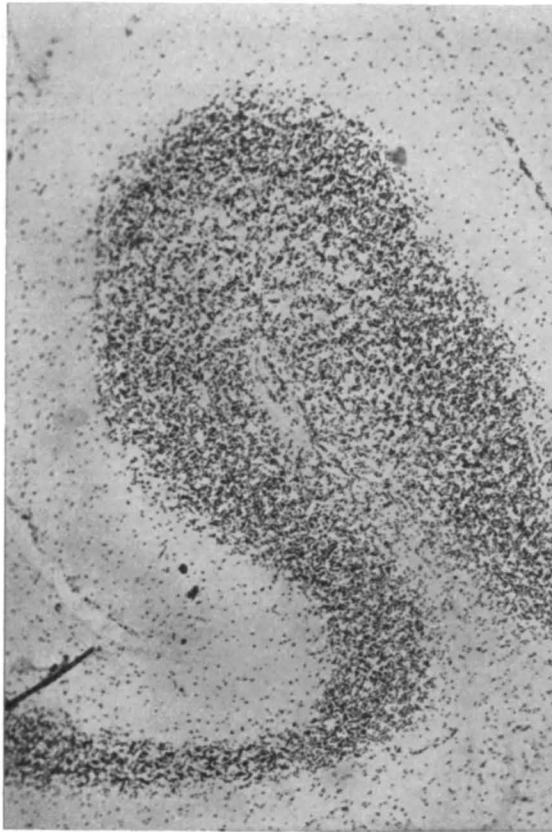


Fig. 1. Cerebellum. — NISSL stain; molecular and granular layers with complete absence of PURKINJE cells.

eosin sections. With BIELSCHOWSKY silver stain the absence of PURKINJE cells was very striking. The empty basket cells remained very numerous and with very marked collateral fibres extending laterally along the region between the molecular and granular layers (Fig. 2). The fibres of these basket cells seemed more dense than normal.

The molecular layer was slightly thinner than normal. Examination of the NISSL preparations showed a slightly increased number of cell bodies in this region. With

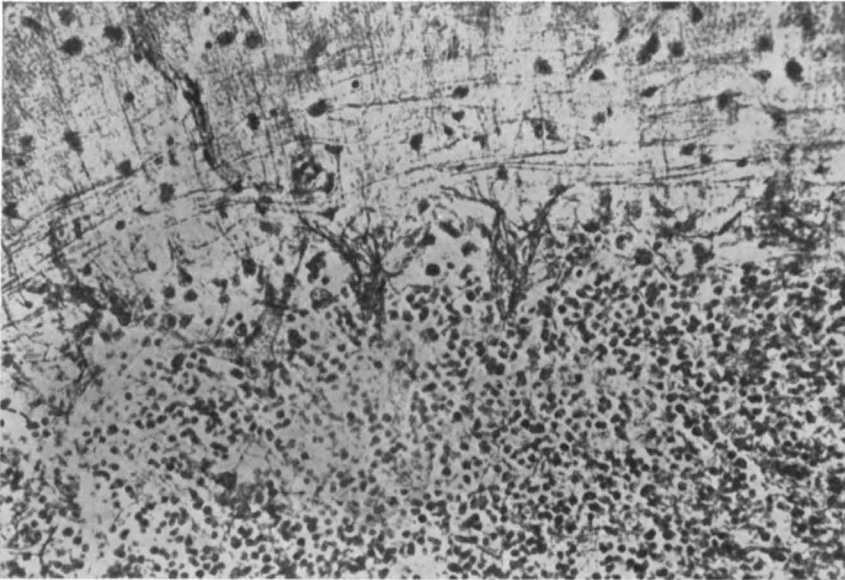


Fig. 2. Cerebellar cortex, — BIELSCHOWSKY stain ; showing empty basket cells with no PURKINJE cells.

HOLZER stain there was a slight gliosis of this layer. The granular layer was more nearly normal than the molecular but here also there was a slight gliosis.

In the WEIGERT-PAL preparations, throughout the entire cerebellum the transition between the granular layer and the white matter was very indistinct, probably because of the absence of the large deeply staining fibres which usually pass from the PURKINJE cells to the central nuclei of the cerebellum. These medullated fibres were somewhat more strongly marked in the flocculi than elsewhere in the cerebellum, but no normal PURKINJE cells were seen in the flocculi.

*Cerebellar Nuclei:* On gross inspection of the WEIGERT-PAL sections the dentate nuclei showed marked changes. The capsule or so-called fleece of the nuclei was absent (Fig. 3). The fibres of the white matter surrounding the nuclei were much less dense than normal, so that there was a marked pallor in the white matter about the nuclei. This was in sharp contrast to the heavy deep staining fibres leading off from the center of the nuclei to the brachium conjunctivum.

In VAN GIESON preparations the cell bodies of the nuclei were fewer than normal. The nuclei appeared thin and many preparations showed a marked gliosis. By NISSL stain very marked cell deterioration could be seen throughout every part of both nuclei. This was somewhat spotty in that there were certain areas containing no cells and others with only slight degeneration of the cell nuclei. Such differences occurred in very small adjacent parts of the nucleus dentatus, but there was no more degeneration in the ventral than in the dorsal or in the mesial than in the lateral part of the nucleus

as a whole. The cells were shrunken and degenerated with nuclei drawn to one side, often vacuolated and containing large amounts of fatty substance.

The roof nuclei, emboliform, globosus and fastigii showed the same type of degeneration but to a less marked degree (Fig. 4). Again there was thinning of the peripheral fibres entering these nuclei from the cerebellar cortex but the fibres leading



Fig. 3. Dentate nucleus, — WEIGERT-PAL stain; showing absence of fleece with thinning of fibres surrounding the nucleus but with normal fibres in the hilum.

from the emboliform nucleus to the brachium conjunctivum were well defined.

*Cerebellar Peduncles:* All three of the cerebellar peduncles appeared normal. The restiform bodies were well marked and of the usual configuration in WEIGERT-PAL sections when they were compared with the same structures in a normal brain. The brachium pontis was also normal in appearance. The fibres of the brachium conjunctivum could be seen running from the dentate nucleus in a heavy band to the medulla. Mesial to these the fibres connecting the roof nuclei with the medulla could be seen.

*The Inferior Olives* and also the accessory olives were *entirely normal*.

*The Pons* contained normal nuclei throughout. The arcuate nuclei showed no pathological changes. The fibres running from the pons to the cerebellum were numerous and well myelinated and the fibres of the pyramidal tract seemed normal in size, number and distribution.

In the *Medulla*, about the floor of the fourth ventricle just rostral to the genu of the seventh nerve and in the region of the sixth nerve nuclei were numerous small and very

recent hemorrhages in both sides of the medulla. None of these were actually in the nuclei of the cranial nerves.

All nuclei of the cranial nerves from the third to the twelfth were normal. Because of the clinical history the sixth and eighth nerve nuclei were examined with special care but nothing pathological was found.

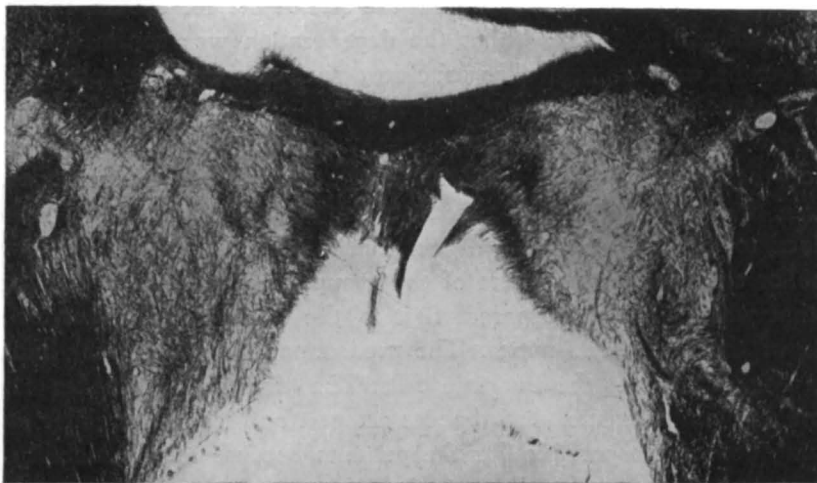


Fig. 4. Nuclei tecti, — WEIGERT-PAL stain; there is thinning of the surrounding fibres entering the nucleus.

The nuclei of the putamen, globus pallidus and caudatus of this case when compared to those of a normal brain showed no changes. The red nuclei were also normal as were the substantia nigra. The fibres of the brachium conjunctivum approached and surrounded the red nucleus in the usual fashion.

Sections from the frontal, occipital and temporal cerebral cortex showed no abnormal changes in NISSL or Haematoxylin-eosin preparations.

### *Discussion.*

This case is clearly one of late primary cortical cerebellar degeneration, for it possesses both the clinical and histological manifestations previously described as characteristic of this disease entity. The features of the syndrome, its pathology and the question of etiology have been adequately discussed before, notably by MARIE, FOIX and ALAJOUANINE in 1922 (11); by PARKER and KERNOHAN in 1933(13); and by LHERMITTE in 1922 (8) and in 1935 (9). In all, some nineteen cases have been reported in the literature since the original description by MURRI in 1900 (12). In each of these cases primary atrophy of the Purkinje cells was the predominating pathological feature.

Our case, together with three others of this group, however, should be of particular interest because in them the degeneration was confined entirely to the cerebellum. These four cases (the earlier cases of JELGERSMA (6),

BROUWER (3), and CASPER (4),) are strikingly similar both in clinical history and in histological findings. In them the pathological changes consisted of practically complete destruction of the Purkinje cells in both vermis and cerebellar hemispheres with no involvement of the cerebellar peduncles, inferior olives or other extra cerebellar structures. In these cases there was also little or no reduction in the size of the cerebellum. In all of the remaining fifteen cases either the degeneration was confined chiefly to the vermis, or extra cerebellar structures, such as the inferior olives, also showed pathological changes.

In view of the confusion which is today present in the literature concerning the functions of the cerebellum, both in man and in experimental animals, the symptoms found in man accompanying degeneration which is confined to the cerebellum are of extreme interest. In these four "pure" cerebellar cases as in the others of the group, the predominant symptom and that which always appeared first is the marked incoordination or ataxia of the *lower* extremities. The predominating pathological finding is the degeneration of the Purkinje cells. The disease first makes itself known by characteristic disturbances in gait and sooner or later even standing becomes impossible for the patients because of the inability to control the limb movements. Later in these four cases, the upper extremities became involved, but to a lesser degree. Speech was severely disturbed also. In most of the other cases of the series arm and head eventually became involved in this way.

In many of the nineteen cases, degeneration of the Purkinje cells was confined entirely to the vermis or to the vermis with the superior part of the hemispheres. In several cases the ataxia was practically entirely in the lower extremities. In an effort to localise cerebellar activity, correlation between these two facts is at once attempted, for it is conceivable that in this progressive disease, degeneration begins in the superior vermis, since in the majority of cases it is most involved, and that it spreads thence throughout the cerebellum. It is possible that the progress of the ataxia corresponds, but from these nineteen cases more cannot be inferred for the number of observers and the variety of the types of reports makes quantitative comparisons impossible.

*Nystagmus* occurred in the present case throughout the illness. The case of CASPAR also showed nystagmus but most of the nineteen cases report either no nystagmus or slight nystagmoid jerks only. In the present case the nystagmus must have been of cerebellar origin since vertical nystagmus does not occur in middle ear disturbances and since the nuclei of the cranial nerves were normal. That pure cerebellar nystagmus is possible is evident from a case described by FOERSTER (5) in which nystagmus was present in a child after extirpation of one cerebellar hemisphere only. This has persisted as the sole abnormal symptom several years after operation.

Another interesting fact observed in this case and also in the case of

CASPAR was that diplopia occurred. There was never any objective paralysis of the cranial nerves in the present case and there were no pathological processes involving the cranial nerve nuclei.

Hypotonia, a symptom usually referred to the cerebellum, is strikingly absent, or reported as only slight in the cases of this series.

The present case offers little toward the much-discussed problem of the etiology of the degenerative process. In this series, several cases do not occur in one family, nor can the disturbance be laid to an exogenous disease process. Yet the selective destruction of Purkinje cells is specific. But, together with twelve out of the nineteen, this case may be classed with MURRI's case of "Cerebellar degeneration due to enterogenous intoxication." This case and three other show carcinomatosis and the history of wasting illnesses in the other cases is most striking. ARCHAMBAULT (2) describes typhoid fever, and KIRCHBAUM and EICHHOLZ (7) acute rheumatic fever. Severe chronic alcoholism is reported as the influencing factor by STENDER and LUTHY (15).

One impressed that the "pure" case reported by CASPAR was reported as "toxic cerebellar atrophy in a case of carcinoma of the breast," and that MAAS and SCHERER (10) writing on types of cerebellar disease, describe one case as primary atrophy of the Purkinje cells. A second case they describe as a case of cerebellar atrophy due to *toxic causes* yet, on reading the two case histories one finds an almost identical clinical and pathological picture.

THORPE (16), in the latest case report of cerebellar degeneration occurring in adults, cites two cases, not included in the above nineteen, which occurred in epileptic brothers and which clinically resembles the above described syndrome. Histological examination of the brain of one of these individuals who died from pulmonary tuberculosis showed primary diffuse degeneration of the Purkinje cells with secondary involvement of the dentate nuclei. The second brother, still living, is an alcoholic and there was history of chronic alcoholism and of tuberculosis in the family.

From the above it would seem as though a severe wasting systemic disturbance of a "toxic endogenous" nature must be an etiological factor in degeneration of this type. The additional factor which is apparently not hereditary yet which makes selective degeneration possible in so small a number of individuals remains a mystery.

### *Summary.*

A case of primary cortical degeneration of the cerebellum is presented in which the degeneration is confined entirely to the cerebellum.

The clinical features usual in this disease entity were present: slowly progressive ataxia developed late in life and appeared first in the lower extremities. In this case, the upper extremities and speech became involved

later. The rare features of nystagmus and transient diplopia were present also.

The histological picture was of complete degeneration of Purkinje cells throughout the vermis and cerebellar hemispheres with some degeneration and gliosis of the central nuclei of the cerebellum, but with no involvement of extracerebellar structures.

This case, like several others, of the same type, possessed an exogenous toxic etiological factor: the carcinomatosis of the abdominal organs. It throws no additional light, however, on the selectivity of the toxin for the structure of the Purkinje cell alone.

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