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A STUDY OF SOME PECULIAR CHANGES FOUND IN THE OXONS AND DENDRITES OF THE PURKINJE CELLS *

S. UYEMATSU, M.D.

HATHORNE, MASS.

INTRODUCTION

A peculiar balloon-like swelling of the dendrites of the ganglion cells was noted first by Schaffer¹ in amaurotic family idiocy. Later the same condition was observed in the apical dendrites of the Purkinje cells by Rogalski, Jansky, Schob, Bray, Sachs and Strauss,² Schaffer and others. This swelling of the dendrites was considered by these authors as one of the pathognomic findings of amaurotic family idiocy.

In 1906, Sträussler³ described the same kind of alteration among the dendrites of the Purkinje cells, together with similar swellings of the axis cylinders in a psychosis—in a woman 36 years of age—which manifested certain cerebellar symptoms associated with mental agitation and intellectual weakness. The cerebellum of this patient showed congenital malformation—defect of the granular layer. He attributed this peculiar change of the dendrites to their incomplete development and overwork.

In 1910, Sträussler, in a report on three cases of juvenile general paralysis, described a hypoplasia of the cerebellum and peculiar swellings of the dendrites and axis cylinders. He thought that these swellings were identical with those of amaurotic family idiocy and also with those shown in his previously described case. He believed, as a result of his studies, that there is an intimate relationship between juvenile general paralysis and hereditary family diseases, based on developmental defect of the central nervous system.

* From the Pathological Laboratory of Danvers State Hospital.

1. Schaffer: Zum normalen und pathologischen Fibrillenbau der Kleinhirnrinde, *Ztschr. f. d. ges. Neurol. u. Pathol.* **21**: 1, 1914.

2. Sachs and Strauss: The Cell Changes in Amaurotic Family Idiocy, *J. Exper. Med.* **12**: 685, 1910.

3. Sträussler: Ueber eigenartige Veränderungen der Ganglionzellen und ihrer Fortsätze im Centralnervensystem eines Falles von kongenitaler Kleinhirnatrophie, *Neurol. Centralbl.* **25**: 194, 1906.

So far as the writer has been able to determine from the literature these peculiar swellings of the dendrites have never been found in any other diseases than those mentioned above. As etiologic factors, most of the authors seem to favor congenital weakness, endogenous factors such as suggested by Sachs and Strauss in amaurotic family idiocy, and some external agent, such as overwork.

In the experimental study of Ramon y Cajal ⁴ the injured dendrites of cerebral as well as cerebellar cells showed, as a rule, no regenerative reactions; but in one young animal experimented on, the dendrites of the Purkinje cells presented various nodular enlargements. Their reaction to the injury was also shown by a change in diameter, as well as in the form, length and structure of the secondary and tertiary branches.

Swellings of the axis cylinders have also been noted by various observers, and the explanations of the nature of these have been almost equally varied.

Cajal was the first to describe the swelling of the axons of the Purkinje cells resulting from experimental lesion. He called attention to certain terminal sacs (*les boutons terminaux*), some belonging to Purkinje cells, others to afferent fibers of the white substance. Most of these sacs were situated rather far from the lesion in apparently healthy tissue, while in the neighborhood of the lesion Purkinje cells were markedly degenerated, presenting a granular appearance, with no trace of intracellular neurofibrils. This led Cajal to believe that the sac formation is a reaction of the living protoplasm, and that it represents a regenerative process of the axons, whose continuity has been disturbed.

Rossi also observed the same interesting changes among axons of Purkinje cells in a case of cerebellar sclerosis. The axon was replaced by a round or oval mass, single, more rarely double, of homogeneous appearance, though sometimes showing within it a few fibers. This mass was generally encountered within the granular layer at a distance from the Purkinje cell, to which it was attached by a filament. He found also similar masses at the level of Purkinje cells where the latter seemed to be lacking. Most of the Purkinje cells exhibiting these changes were smaller and presented fewer dendritic arborizations. Some of these swellings were provided with processes which often threaded their way to the molecular layer in which they mingled with other nerve ramifications, thus rendering it impossible to determine the manner in which they terminated. Rossi interpreted the latter condition as a regenerative process of the preexisting normal collaterals.

4. Cajal: *Histologie du système nerveux de l'homme et des vertébrés*, traduite de l'Espagnol par le Dr. Azouley, 1909.

When the integrity of the Purkinje cells has been impaired by some cause or other, they no longer possess the ability to regenerate completely, and therefore they try to reproduce some other paths for their compensatory efforts. According to Rossi, this is the most important phenomenon from the point of view of the function of the organ.

Later Marinesco⁵ described structures identical with those described by Cajal and Rossi. He reported cerebellar symptoms had been shown clinically in one case, and at necropsy a large cystic cavity was found in the cerebellum. In another case a cerebral tumor, involving the left auditory nerve and severely compressing the cerebellum, was found at necropsy. One patient, a man aged 67, exhibited areas of softening in the cerebellar cortex, while the remaining patient had tubercle deep in the white substance of the cerebellum. Clinically, this last patient was a victim of Pott's disease. Marinesco summarizes his conclusions on the study of these cases as follows:

The fibers of the cerebellum, like those of the medulla, show a decided tendency to grow, if interrupted. We have seen them penetrate the interior of the softened region to great distances. Those which have not been able to penetrate have given forth new fibrillation at the limits of the healthy tissue. This zone can, then, from all points of view, be compared with the central end of a divided peripheral nerve. As to the other phenomenon which we have discussed as "*boule des axones de Purkinje*," the swelling of the fibers, the hypertrophy of the neurofibrillar plexus, whether dendritic or axonal, etc., these may be classed as phenomenon of nerve regeneration. Some authors class them among the regenerative phenomena, others regard them as of a degenerative nature. In our opinion they do not represent anything but a special reaction of the nerve cell and fibers, due to a disturbance of nutrition.

In 1914, Schaffer studied the normal and pathologic neurofibrillar structure in material from normal cerebella, amaurotic idiocy, tabes, taboparalysis and senile dementia. He described a peculiar swelling of the axons in the Purkinje cells in all pathologic groups; in amaurotic idiocy there was marked swelling of the dendrites. This differed from the earlier descriptions of amaurotic family idiocy by Sachs and Strauss. These observers did not note axonal changes in the Purkinje cells, though they did state that "the apical dendrite of pyramidal cells and axons were rarely affected," adding that they had "no theory as yet to account for this peculiar selective activity of the degenerative process." Schaffer observed two types of local swelling of the axons: One is stained pale, showing a loosened neurofibrillar structure; the other is dark and homogeneous, characterized by an argentophilic condition. In the cerebellum, therefore, the neuron is affected in all its constituents, that is, not only the cell body with dendritic arborization,

5. Marinesco: *Nouvelles contributions a l'étude de la régénérescence des fibres du system nerveux central*, J. f. Psychiat. u. Neurol. **17**: 131, 1913.

but the axon. In addition to focalized enlargements of axons, Schaffer described diffuse hypertrophies and atrophies of the axon of Purkinje cells. Schaffer interprets the focalized swelling of the axon as resulting from two causes: first, from hypertrophy of the axoplasm, and second, from the loosening of the neurofibrils following a solution of the interneurofibrillary substance (*Axonkittsubstanz*). This process is followed by a local deposition of the waste products of pathologic metabolism, which is suggested by the general argentophilic condition of these portions. These peculiar changes of the axon were associated with degeneration and diminution of the tangential and basket fibers in cases of tabes and taboparalysis.

In a case of congenital atrophy of the cerebellum, Sträussler described the swelling of the axons as well as of the dendrites. He attributed both of these conditions to the wasting of the cell and to certain congenital predisposition. Sträussler also observed the same peculiar swelling of the axon in juvenile general paralysis.

In 1918, Professor Kure, Dr. Hayashi of the Tokio Imperial University, and I, observed the same peculiar swelling of the axons in three cases of senile dementia, and reported them at a meeting of the Tokio Medical Association. At the time we suggested that they were probably common in the cerebella of senile dementia.

The swelling of the dendrites and axis cylinders have thus been reported by various observers under various pathologic conditions, and their opinions concerning the nature of these swellings vary. This study was made to endeavor to determine in what diseases these changes are likely to be found, and what significance they may have.

METHOD OF EXAMINATION

The material for this study was secured from brains of the Danvers State Hospital Laboratory series. These brains had been preserved in 14 per cent. formaldehyd solution. Particular care has been taken in the selection of suitable material, especially with respect to proper fixation and the time intervening between death and necropsy. Brains not hardened well and those that came to necropsy more than twenty-four hours after death have been excluded from this study. Small pieces have been taken from the upper and lower vermes, superior and inferior lobes of both hemispheres. Frozen sections have been made at 5 microns and stained by the Bielschowsky method. Ten slides have been studied from each block. Each preparation has been observed under low and high magnifications and the entire section studied. The sections contained, on the average, ten cerebellar foliae. Thus, 600 folia from each cerebellum have been carefully examined for the particular neurofibrillar changes.

In addition to Bielschowsky's method sudan III, thionin, Scharlach R., Weigert's glia staining, and other general staining methods have been employed.

HISTOLOGY OF THE CEREBELLUM

In the study of this problem consideration of the normal histology of the cerebellum cannot be omitted, more particularly the knowledge of the nerve fibers which are closely related to the Purkinje cells and their prolongation. I shall therefore first summarize the normal histology that has hitherto been described by various authors, particularly by Cajal; second, I shall give my own observations, which are more or less different from those already described.

It is convenient to describe the finer structure of the cerebellum under the following heads: the molecular layer, the intermediate or Purkinje cell layer, the granular layer, the white substance, and the basket and cushion fibers.

The molecular layer is occupied by small and large nerve cells. The large cells are found in the deeper part of this layer. The axis cylinders of these large cells have a certain relationship to the Purkinje cells. They run horizontally over the Purkinje cell layer, giving off collaterals at regular intervals. They finally approach one of the Purkinje cells, arborize around it, and form a kind of basket (Koelliker and Cajal). The collaterals also form baskets around the Purkinje cells. These cells of the molecular layer are called, accordingly, basket cells.

At the lower limits of the molecular layer, that is, in the intermediate layer, are found a large number of Purkinje cells, the largest in size of the elements of the cortex, and from a physiologic point of view considered as playing the most active part in the functions of the cerebellum.

The Purkinje cells possess dendrites that run through the whole thickness of the molecular layer. This cell is a voluminous spherical or ovoid body. It has a fibrillary structure. The fibers seem to wind around the nucleus, then turn away to course to the peripheral prolongations. It is worthy of note that the Purkinje cell contains, in comparison with other large cells of the brain, spinal cord, optic thalamus, etc., and very few pigment corpuscles. The rod shaped Nissl bodies are arranged in circular order around the nucleus, those in the base being larger than those in the apex. The apical dendrites also show rod shaped Nissl bodies. In silver preparations one can observe the collaterals of the axis cylinders which have a tendency to turn back toward the surface of the cerebellum, arborize around the neighboring Purkinje cells and continue further into the molecular layer. The axis cylinders go down into the white matter without diminution of caliber.

It is generally accepted that all the axis cylinders of the Purkinje cells pass through the cerebellar cortex to terminate in the cerebellar ganglions of the white substance. From the apex of the cell a short thick main stem of the dendrite is usually given off, which soon divides into two main stems that extend horizontally in opposite directions. From these two branches many other smaller branches are given off which extend toward the surface of the cortex, these in turn giving rise to many still finer branches which penetrate through the entire molecular layer. The atypical form of Purkinje cell, described by Cajal and others is triangular, conical or often star shaped, and is usually located in the molecular layer. Schaffer described this atypical form of the Purkinje cell in which he occasionally found two nuclei, one smaller than the other. The nucleus of this atypical form is, according to Schaffer, often of oval shape, while the nucleolus is always spherical.

Schaffer described more accurately the relation of the axis cylinders to the cell body. The axons, it is asserted, do not always spring from the base of the cell body, but sometimes originate in the lateral periphery. They arise from a conically shaped elevation of the protoplasm, immediately become very thin and stain faintly. A short distance from the cell the fiber suddenly becomes thicker and stains more darkly. This increased caliber of the fiber is probably due to the beginning of the myelin sheaths. Schaffer observed the collaterals of the axon mostly at a great distance from the Purkinje cell body, given off at acute angles and in directions contrary to the general course of the axon, noting also a bridge of some plasmic substance between the axonal stem and the collateral branch.

The granular layer is almost entirely composed of an agglomeration of small cellular elements of spheroidal shape. Each one possesses protoplasmic prolongations and an axis cylinder. The protoplasmic prolongations are three or four in number; they are short and thin, and, with few terminal branchings, they end in the granular layer. The axis cylinders of these cells ascend in the molecular layer and divide in a T-shaped manner, the branches extending horizontally and terminating freely among the end-arborizations of the dendrites of the Purkinje cells. In the granular layer, there are also several kinds of large nerve cells. Schaffer differentiates two kinds: one, a spindle form in the Purkinje cell layer, the other, a star shaped or multipolar cell, located in the deeper layer. The spindle shaped cells are of two types: one located in a horizontal position in the Purkinje cell layer with its long axis horizontal, and the other located in the upper part of the granular layer and disposed in either an oblique or in a perpendicular position. The dendrites of the first type share in the forma-

tion of the so-called cushion fibers. The prolongations from the lower pole of the second group arborize in the granular layer, while the prolongations from the upper pole mount into the molecular layer, mixing with the basket fibers of the Purkinje cells. The star shaped cells are rather large and possess a great number of prolongations which arborize freely in the immediate vicinity of their own cell bodies, thus forming a sort of network in the meshes of which a large number of granular cells may be enclosed. Some of these prolongations, however, mount upward to terminate in the molecular layer. Schaffer also described a peculiar basket formation around those nerve cells located near the Purkinje cells—a formation similar to that found around the Purkinje cells.

The white substance is formed by a mass of myelinated fibers which extend in opposite directions; one set of fibers is centrifugal, the other centripetal. The centripetal fibers are of two kinds: the mossy fibers of Cajal and the climbing fibers of Cajal and Koelliker. The mossy fibers arborize in the granular layer and enter into relation with granular cells. The climbing fibers ramify principally in the molecular layer and terminate at the dendrites of the Purkinje cells. The centrifugal fibers are entirely derived from Purkinje cells. Schaffer, Bielschowsky and Wolff observed and described the climbing fibers. Schaffer, however, asserted that the ascending fibers did not always follow the course of the dendrites of Purkinje cells but sometimes left them to terminate in the gray substance of the molecular layer. After leaving the dendrites, they take either a horizontal course or an oblique or perpendicular course, attaching themselves transitorily to the dendrites and again losing themselves in the molecular layer.

Basket and Cushion Fibers.—The Purkinje cell layer is a place of rendezvous of fibers of different origin. These fibers arrange themselves chiefly in a vertical direction, that is, they extend from the base of the cell toward the main dendrite. Many fibers run partly in an horizontal, partly in an oblique, direction. These fibers thus form a kind of envelope around the Purkinje cell, as well as a cushion-like support. The enveloping fibers are called basket fibers and the fibers that extend horizontally are called cushion fibers. The basket fibers are derived, according to Cajal and Koelliker, from the basket cells of the molecular layer. Schaffer described these fibers accurately and illustrated them in his paper. The following are the important points of his description: Each collateral of the axis cylinders of the basket cells traverses the main dendrite and cell body and after sending a branch to the right and one to the left, sinks deep into the cushion fiber layer (*Polsterfaserschicht*) and becomes a part of the constituent elements of the cushion. It then runs either to a neighboring Purkinje

cell to take part in the formation of its basket, thus uniting two neighboring Purkinje cells, taking its course in the cushion fiber layer, passes on for a distance corresponding to two or three Purkinje cells, and there terminates around a Purkinje cell; meanwhile its caliber gradually diminishes. Schaffer also states that some of these collaterals, after they have shared in the formation of the basket, pass into the granular layer, the fiber accompanying an axon of the Purkinje cells, then take a sharp turn again finding their way to the fiber basket of the same Purkinje cell, while the others assume a curved course to join the fiber basket of remote Purkinje cells. Ascending fibers were also described by this observer: fibers from the granular layer to the elements of the basket, such as fibers from the spinocerebellar tract, dendrites of Cajal's star shaped ganglion cells of the granular layer and screwlike, winding, thick fibers, their origin unknown but probably derived from the white matter. Some observers have described direct communication between the fiber basket and the Purkinje cell body, but Schaffer contradicts these authors.

PERSONAL OBSERVATION ON NORMAL HISTOLOGY OF CEREBELLUM

Site of Purkinje Cells.—The Purkinje cells are usually found in the intermediate zone, that is, between the molecular and granular layers. A small percentage of these cells are found in the molecular layer, usually immediately above, and occasionally fairly far from, the normal location of the Purkinje cells (Fig. 1). Since this condition of dislocation of the Purkinje cells is commonly found in normal cerebella, it cannot be regarded as an heterotopia. If, however, Purkinje cells are found in the deeper parts of the granular layer or in the upper parts of the molecular layer, an interpretation of heterotopia is justifiable.

Atypical Form of Purkinje Cells.—Although the normal form of the Purkinje cells is spherical and somewhat depressed like a lens or the seed of a pumpkin, it presents several other forms. In the early part of the development, as shown in my study of several fetal brains, there is often a resemblance to a boat, the long axis being horizontal and situated partly in the molecular and partly in the granular layer. Some cells, however, are fairly far above the normal location in the molecular layer and wholly within this layer. The two extremities of the boat are dendritic prolongations which approach nearer and nearer in the course of development, finally meeting and forming the apical dendrite. There are, therefore, in the normal fully developed cerebellum, many transitory forms between the original and fully developed types. Some Purkinje cells have two main dendrites given off from the side of the cell body, while others present two main pro-

jections at the apex of the cell whose courses are in opposite directions, giving the cell the appearance of a uterus with tubes. Those cells which possess a single main stem also show a varied manner of branching, some dividing directly above the cell body, others at a distance from the apex, some having branches of equal thickness and others having branches of considerably different caliber. Purkinje cells found out of their normal position display more or less atypical forms in the general shape of the cell body, as well as in its mode of branching. A small number of cells, however, although normally located, present atypical forms even in normal cerebella. The small dendrite sometimes seen at the side of the cell body is regarded by some authors

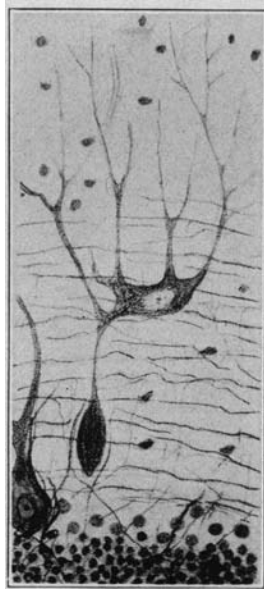


Fig. 1.—An abnormal location of the Purkinje cell whose axis cylinder is swollen.

as a pseudodendrite. The writer does not consider this a good term, since this is only a transitory stage in the formation of the apical dendrite and is purely a developmental characteristic. This, it seems to me, is important for the interpretation of the nature of the peculiar changes found in the cerebellar cortex.

The original embryonic shape of the Purkinje cells may assume in the course of development a variety of shapes—conical, stellar and bizarre forms. The radiating dendrites from the several parts of the cell body may at times be as many as four or five in number.

Dendrites of the Purkinje Cells.—The manner of arborization for the main stems has already been described. The Purkinje cells located in the sulci between the folia show generally an irregular arborization. Some Purkinje cells have dendrites that extend to great distances, while others possess short branches that terminate comparatively close to the cells. The dendrites given off from the sides of the cell body, which some authors regard as pseudodendrites, are sometimes very thin and have a few secondary branches which do not appear like ordinary branches of dendrites. The protoplasmic bridge between the two dividing branches, described by Schaffer, is frequently found, and should not be considered as pathologic. The spindle-like thickening of the main dendrites, which gives rise to a number of small arborizations, is also not a rare finding in the normal cerebellum. But when these swellings are found together with obvious pathologic changes of the bodies of the Purkinje cells or their dendrites, it is sometimes difficult to decide whether they are pathologic or normal.

The Axis Cylinders of the Purkinje Cells.—A knowledge of the normal anatomy of the axis cylinder is especially important for the study of our problem. The axis cylinders of the Purkinje cells are usually difficult to demonstrate, although in pathologic conditions they are likely to be increased in thickness, which makes their course and termination easier to follow. For this study of the normal structure, however, pathologic changes in axis cylinders or tissues from manifestly pathologic cerebella cannot be regarded as suitable. For the study of normal axis cylinders cerebella were used from three patients with manic depressive disease, from three with dementia praecox and from two subjects that were not insane, all in the third to fourth decades. While most of these cerebella were derived from subjects dying of psychoses, there were no gross pathologic changes in either cerebellum or cerebrum and no outstanding pathologic alterations in the cerebellum of any of the subjects.

The proximal portion of the axis cylinder is very delicate and consists of axoplasm and neurofibrils. After a short distance it increases in thickness, due to an addition of the so-called "Kittsubstanz," (gymnaxostroma and myeloaxostroma of Bielschowsky and Wolff). I have found that not all axons of the Purkinje cells enter the white matter. A certain number of axis cylinders, after extending a short distance into the granular layer, turn back toward the surface of the cerebellum in a bowlike curve to arborize around its immediate neighbor or perhaps around more distant Purkinje cells. When the axis cylinder arborizes around neighboring Purkinje cells, it soon gives off a number of collaterals which seem to take part in the formation of the baskets. Some of these axis cylinders, even after reaching a fairly deep part

of the granular layer, turn back to terminate around the neighboring Purkinje cells. It may be questioned whether or not we are here dealing with collaterals of the axis cylinders instead of with the main stems. The caliber of the fibers, however, is always the same, and they show no abrupt turn in their course. Moreover, we do not normally see collaterals in the immediate neighborhood of the cell body. Certainly, those fibers that take a horizontal course from the sides of the Purkinje cells to the neighboring ones can only be explained, as axis cylinders. Another peculiarity of the axis cylinder is its round about course in the granular layer. Some of the axis cylinders which

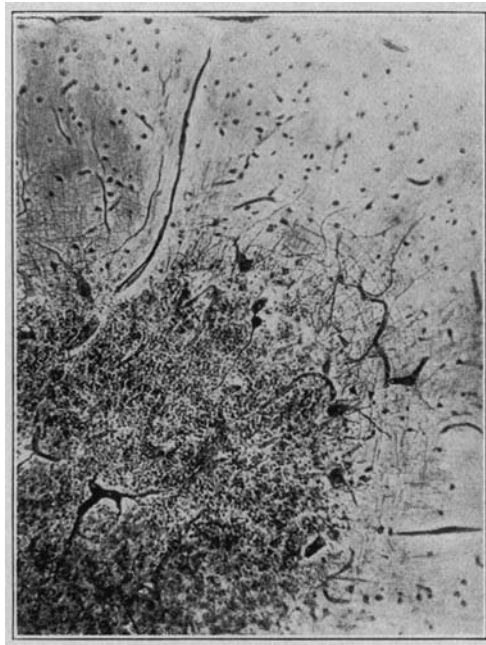


Fig. 2.—Senile cerebellum showing degeneration of dendrites, tangential fibers, Purkinje cells and spheroidal cells of the granular layer. The vessels are relatively increased.

enter the white substance do not do so directly, but extend backward in a horizontal direction for a fairly long distance, finally curving in the opposite direction and entering the white matter.

The axis cylinders of the Purkinje cells usually extend from the base of the cell body; occasionally they extend from the side of the cell. In atypical Purkinje cells of the molecular layer axis cylinders frequently extend, not only from the abnormal part of the cell body, but also from the dendrites, and sometimes from dendrites far from the cell body (Fig. 2).

The collaterals of the axis cylinders are usually given off far from the cell body at an acute angle and directed toward the molecular layer. They divide, while in the granular layer, into several branches, which help in the formation of the cushion fibers and also share in the formation of the basket fibers. The collaterals seem to terminate in the molecular layer. Purkinje cells, therefore, seem to stand in an intimate relationship to each other, either by means of their axis cylinders or their collaterals.

Basket Fibers of the Purkinje Cells.—As for the basket formation around the Purkinje cells, we found about the same condition as described by Schaffer. In addition to this we observed axis cylinders and their collaterals taking part in the formation of the baskets. In a few instances I have also seen axis cylinders of the spindle formed cells included in the formation of the baskets.

Ascending Fibers of the Molecular Layer.—Not only so-called climbing fibers but all fibers ascending the molecular layer tend to lean against or pass over the dendrites of the Purkinje cells. This has been asserted also by Schaffer. I have clearly seen collaterals and axis cylinders from Purkinje cells and large cells of the granular layer as well as tangential fibers climb along the apical dendrites of Purkinje cells for a considerable distance. The fibers, therefore, climbing along the dendrites are not always the "climbing fibers" of Cajal and Koelliker.

STUDY OF PATHOLOGIC CASES

The swelling of axis cylinders and dendrites, in various pathologic conditions, has been noted in the foregoing. I have selected forty-one cases in which all the patients died of psychoses. These forty-one cases have been grouped under nine different categories to determine, if possible, the relationship of these peculiar changes to the following groups of diseases: (1) senile dementia, (2) arteriosclerotic brain disease, (3) general paralysis, (4) congenital brain diseases, (5) dementia praecox, (6) manic depressive insanity, (7) alcoholic and toxic psychoses, (8) brain tumors and (9) myxedematous psychosis.

GROUP I. SENILE DEMENTIA

CASE 1 (Case No. 20719, Aut. No. 2114).—Female; psychosis of four years' standing; died at the age of 78 from bronchopneumonia.

CASE 2 (Case No. 20150, Aut. No. 2116).—Female; died at advanced age of lobar pneumonia.

CASE 3 (Case No. 19760, Aut. No. 2008).—Male; psychosis of two years' standing; died at the age of 72 of arteriosclerosis.

CASE 4 (Case No. 19817, Aut. No. 2035).—Male; psychosis of ten years' standing; died at the age of 97 of bronchopneumonia.

CASE 5 (Case No. 19922, Aut. No. 2036).—Female; psychosis of several months' standing; died at the age of 71 of arteriosclerosis.

CASE 6 (Case No. 20887, Aut. No. 2086).—Female; psychosis of five years' standing; died at the age of 65 of cardiorenal disease with hypostatic pneumonia.

CASE 7 (Case No. 20507, Aut. No. 2082).—Female; psychosis of eight years' standing; died at the age of 73 of metastatic tumor of the mediastinum.

CASE 8 (Case No. 16964, Aut. No. 1990).—Male; psychosis of ten months' standing; died at the age of 76 of arteriosclerosis and hypostatic pneumonia.

CASE 9 (Case No. 19981, Aut. No. 2003).—Female; psychosis of one years' standing; died at the age of 87 of chronic nephritis and mitral regurgitation.

CASE 10 (Case No. 16657, Aut. No. 1924).—Female; psychosis of five years' standing; died at the age of 76 of arteriosclerosis.

CASE 11 (Case No. 19202, Aut. No. 1932).—Male; psychosis of two years' standing; died at the age of 80 of chronic nephritis and chronic valvular disease.

CASE 12 (Case No. 20064, Aut. No. 2026).—Male; psychosis of two years' standing; died at the age of 89 of interstitial myocarditis.

CASE 13 (Case No. 19458, Aut. No. 2027).—Female; psychosis of several months' standing; died at the age of 77 of arteriosclerosis and bronchopneumonia.

CASE 14 (Case No. 17444, Aut. No. 2030).—Male; psychosis of nine years' standing; died at the age of 74 of gangrene of the left lower extremity.

CASE 15 (Case No. 20558, Aut. No. 2050).—Male; died at advanced years of coronary sclerosis.

CASE 16 (Case No. 18638, Aut. No. 1877).—Female; died at the age of 87 of chronic nephritis.

Pathologic Observations on Group 1.—All patients in Group 1 presented fairly abundant senile plaques with or without Alzheimer degeneration of neurofibrils. Some patients presented softening and hemorrhagic areas due to cerebral arteriosclerosis, but these latter were included in this group because they exhibited senile plaques and diffuse fatty degeneration of ganglion cells.

In interpreting peculiar changes of dendrites and axis cylinders described in this paper one must not lose sight of the general associated pathologic changes shown in these cerebella and their possible causative or resultant relationship. Hence a description of both the general and special changes will be given.

The pia mater, in most cases, was thickened and showed a considerable amount of pigment substance. The walls of the pial vessels were thickened and revealed a more or less advanced degenerative fatty change. The molecular layer was diminished in width, particularly at the summit of the folia. The tangential fibers were reduced in number. The basket cells, which give origin to tangential fibers, showed marked changes of disintegration and many had disappeared. Together with the disappearance of the greater part of the dendrites, which will be

described later, the above mentioned condition gives the architecture of the molecular layer a very simple plan. Vessels that showed more or less sclerotic changes, however, appeared to be increased, owing largely, I think, to a diminution of intervacular nervous elements. It is to be regarded only as a relative increase of the vessels and unlike the proliferative processes of vessels which Alzheimer and others pointed out as occurring in general paralysis and some other chronic degenerative processes of the brain. In senile dementia, at least in our cases, the regenerative and proliferative processes of the vessels have not been observed.

Amyloid corpuscles were, in general, increased, particularly in the uppermost and deepest portions of the molecular layer, while in the middle portion of this layer they were rarely encountered. These corpuscles were readily stained by Bielschowsky's method, and took silver diffusely.

In striking contrast to the diminution or disappearance of other nerve elements, that is, tangential fibers, dendrites, Purkinje cells, etc., the number of basket and cushion fibers surrounding the Purkinje cells were not much impaired. These fibers, chiefly those in the intermediate or Purkinje cell layer, even seemed to be increased. Where atrophic Purkinje cells with a few stumps of dendritic arborization remained and even where Purkinje cells had disappeared, these fibers, more particularly cushion fibers, showed enormous masses of tangled fibers. This condition was most markedly observed in cases 4, 9 and 12, (Plate 1, Fig. 1), the patients being 97, 87 and 89 years of age, respectively. Most of the basket and cushion fibers were derived, as explained before, from the so-called basket cells, and it is difficult to explain why these fibers appeared to be increased while the cells from which they originated degenerated and decreased in number. Whether or not these seemingly increased fibers are to be interpreted as a compensatory proliferation of fibers from some other source of origin or merely as a relative increase due to emaciation and disappearance of the Purkinje cells, is difficult to determine. Schaffer, in his study of pathologic changes in neurofibrils of the cerebellum, observed the disappearance of basket and cushion fibers in cases of amaurotic family idiocy, taboparalysis and senile dementia. In our study of sixteen cases of senile dementia, the opposite condition obtained.

In the intermediate layer, there were more or less numerous fat corpuscle cells, more abundant than found in any other part of the cerebellum. The granular layer showed a diminution in small spheroidal cells, and the whole layer appeared to be lighter than normal. This condition made it rather easy to follow the course of the axons and afferent fibers of the white substance.

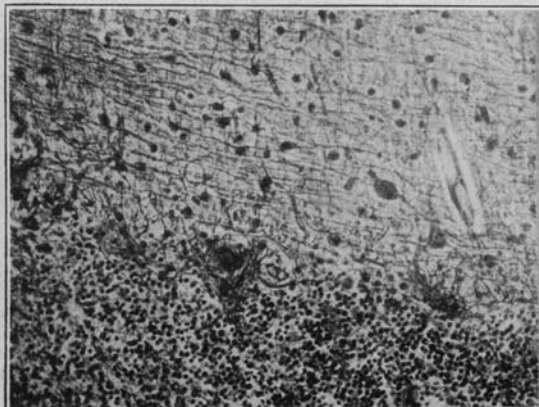


FIG. 1



FIG. 2

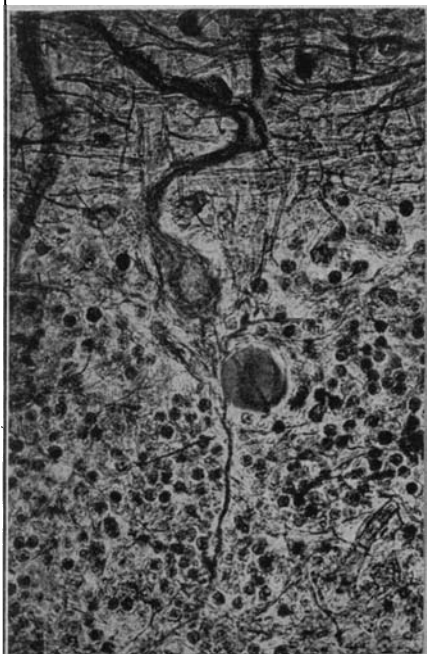


FIG. 3

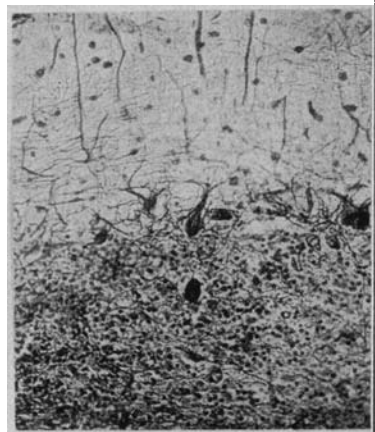


FIG. 4

PLATE 1

- Fig. 1.—Senile cerebellum, showing enormously increased cushion fibers.
 Fig. 2.—Spindle formed swelling of an axis cylinder.
 Fig. 3.—Pedunculated form of the axonal swelling.
 Fig. 4.—Spherical swelling of an axis cylinder.

In the white substance, fat corpuscle cells were less numerous than in the Purkinje cell layer. In some cases a degeneration of myelin sheaths was observed, always accompanied by arteriosclerotic changes in the cortex or white matter.

In the cerebrum all cases of this group exhibited fairly abundant senile plaques and most of them showed typical so-called Alzheimer degeneration of the neurofibrils. In the cerebellum senile plaques were found only in Case 1. The Alzheimer degeneration, while abundant in the cerebrum, was not encountered in the Purkinje cells.

The Purkinje cell changes were of various kinds and were not always the same for each case of the group. The cells were more or less reduced in number, especially at the summit of the folia. The summit of the folia seemed to be the most vulnerable part of the cortex of the cerebellum. Of sixteen cases, eleven (Cases 3, 4, 5, 9, 10, 11, 12, 13, 15 and 16) showed perceptible diminution of cells, marked and universal in Cases 4, 13 and 15.

Most of the Purkinje cells were somewhat swollen and the Nissl bodies had partly or entirely disappeared. Some cells, however, were sclerotic, protoplasmic substance and Nissl bodies being stained dark. The protoplasmic prolongations in both of these cells were stained well and could be traced to a considerable distance. Cases 8, 12 and 16 showed extremely advanced fatty degeneration, while Cases 1, 2, 3, 4, 5, 9, 10, 11, 14 and 15 presented fairly marked fatty degeneration. This condition of fatty degeneration did not show any parallelism with the age of the patient or the stage of arteriosclerosis of the cortex. It is well to note that the fatty degeneration in the Purkinje cells in Case 1, which presented typical senile plaques in the cerebellum, was less marked than in the other cases which did not show senile plaques.

The most interesting findings in our study of the cerebellum were certain peculiar changes in axis cylinders and dendrites, which form the basis of this paper. I shall first describe the manifold changes of the axis cylinders and then those of the dendrites. There are roughly distinguishable two kinds of changes in the axis cylinders; a diffuse hypertrophy and localized swellings. A combination of these two may be encountered.

In the majority of cases of Group 1 the axis cylinders of the Purkinje cells were increased in thickness, not only the axonal stems but also the collateral branches. These hypertrophic axons were stained homogeneously dark; their neurofibrils were not visible. Associated with this was a diffuse disappearance of spheroidal cells of the granular layer which made it easy to determine the course of the axis cylinders. In this group were observed many instances of axis cylinders of Purkinje cells which did not enter the white substance of the

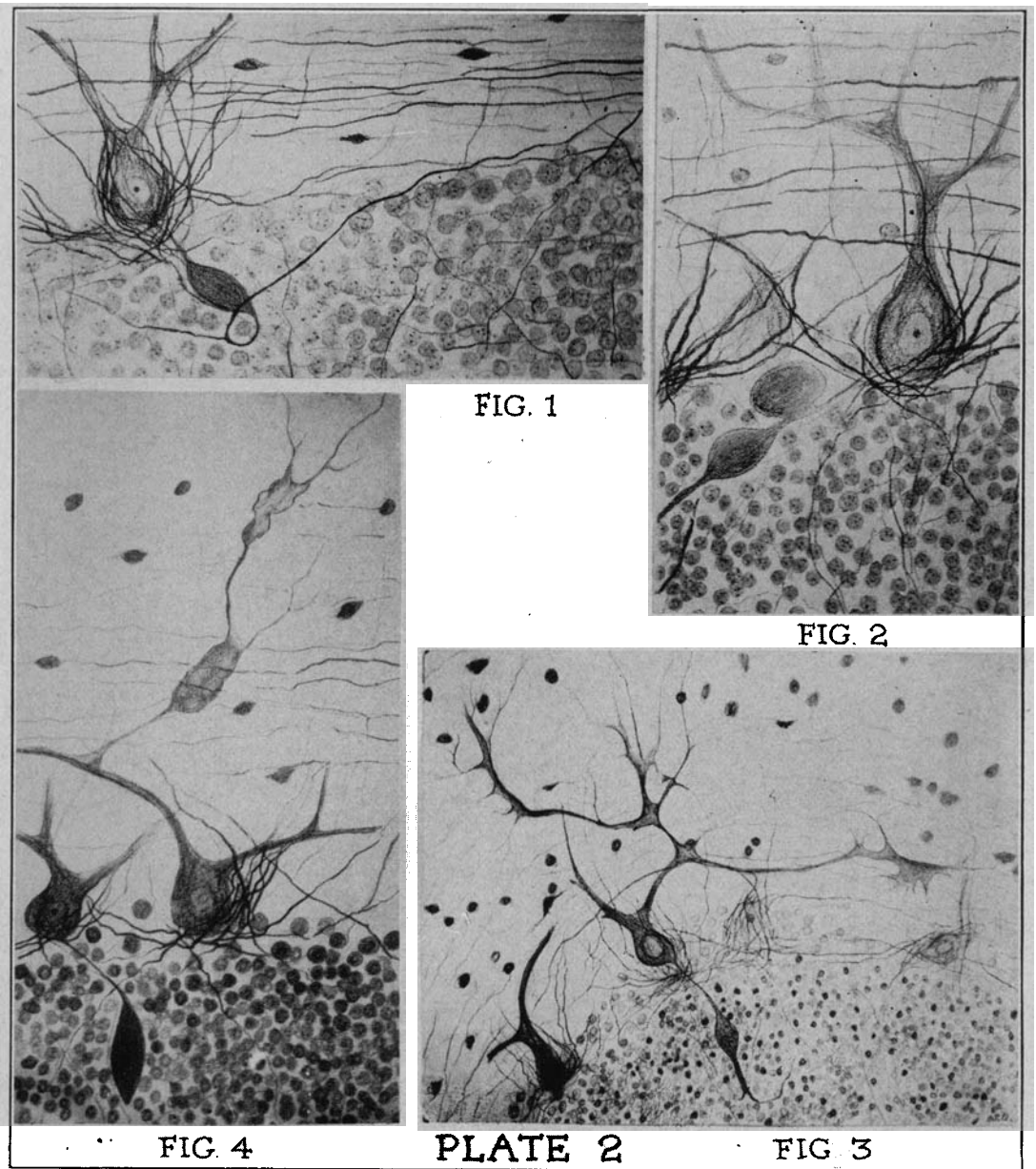


Fig. 1.—The axis cylinder presents a spindle formed swelling from which the axonal stem extends backward into the molecular layer.

Fig. 2.—A combination of pedunculated and spindle formed swellings of the axis cylinder.

Fig. 3.—Axonal and dendritic swellings of one and the same Purkinje cell.

Fig. 4.—Axonal and dendritic swellings.

cerebellum but which took their course to neighboring Purkinje cells, around which they arborized. This condition is normal, as mentioned in the consideration of the normal histology of the cerebellum, but in these cases it was decidedly noticeable because of the destruction of other nervous elements resulting in a simpler fiber pattern.

The localized swellings of axis cylinders which were identical with those described by Cajal, Rossi, Marinesco, Sträussler and Schaffer, were found in all the cases of senile dementia. They were most numerous in Cases 5, 6 and 11, numbering more than 50 in a small section (about 10 folia). The other cases, with the exception of Case 13,

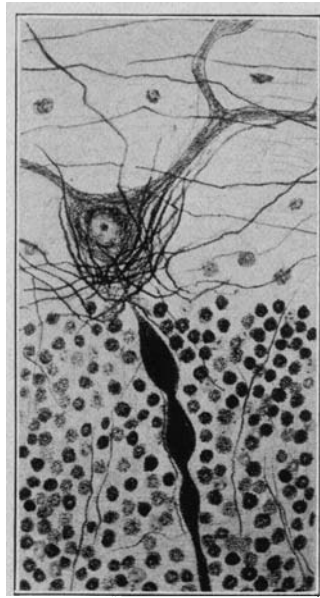


Fig. 3.—Beaded form of the axonal swelling.

exhibited from 5 to 20 swellings in a section of about the same size. In Case 13 only from 1 to 3 swellings were observed. Case 13 showed the most advanced cortical devastation, extreme fatty degeneration, marked disappearance of the Purkinje cells, considerable increase of amyloid corpuscles, etc. The histology of Case 5, which showed the most numerous examples of swellings, in contrast to Case 13, was comparatively normal, although individual Purkinje cells were more or less atrophic.

As a rule, Purkinje cells showing swellings of their axis cylinders are more or less atrophic, but not extremely degenerated. This perhaps explains why there were few axonal swellings in Case 13, in spite of the most marked degeneration of the cerebellar cortex, while in Case 5,

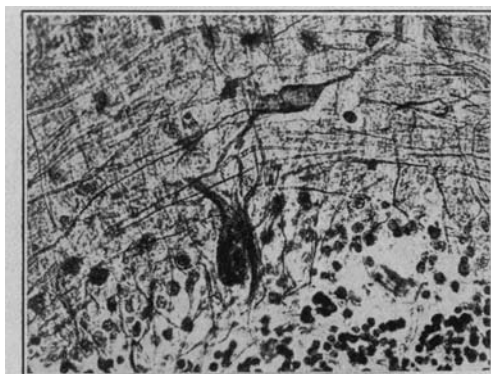


FIG. 1

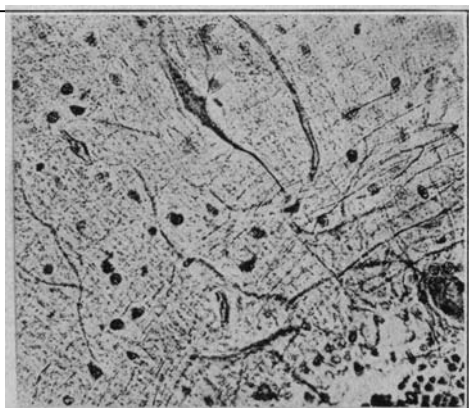


FIG. 2

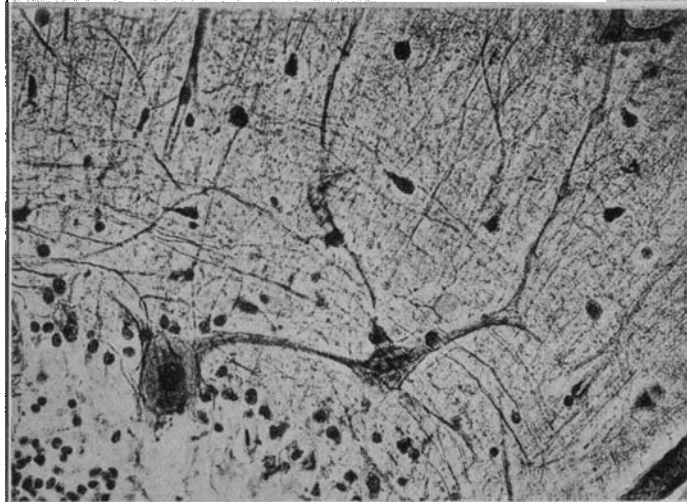


FIG. 3

PLATE 3

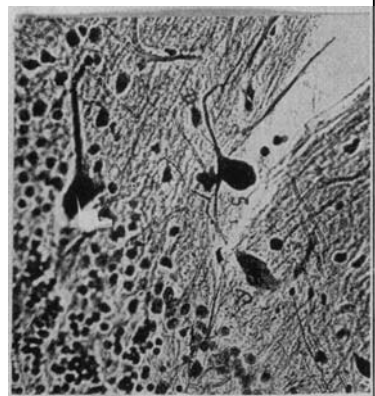


FIG. 4

Fig. 1.—Spindle formed dendritic swelling.

Fig. 2.—Localized hypertrophy of a dendritic prolongation.

Fig. 3.—Dendritic swelling of Type 4.

Fig. 4.—Pedunculated form of a dendritic swelling of an atypical Purkinje cell; *P*, Purkinje cell body; *S*, swelling; *D*, dendrite.

which presented most abundant swellings, the Purkinje cells were only slightly degenerated.

Axonal swellings were usually located not far from the cell body, some in the immediate neighborhood of the latter, others a little farther away, in the granular layer, but always in the upper half of the granular layer. In Case 6 the writer observed a swelling of an axon coursing from a Purkinje cell horizontally to a neighboring Purkinje cell. When atypical Purkinje cells which are located in the molecular layer display swelling of their axons, swelling is likely to be found in the molecular layer. In no cases studied was swelling observed in the deeper part of the granular layer or in the white substance of the cerebellum.

The swelling is of various shapes: (1) the spindle form, the most commonly observed in all of the cases (Fig. 1, Plate 1, Fig. 2) (2) the



Fig. 4.—A peculiar type of axonal swelling resembling leaves of the cactus. Note also the transverse course of the axon.

conical form, less common, the apex of the cone turning either upward or downward (Fig. 2); (3) the spherical form, more rarely encountered (Plate 1, Fig. 4); (4) the beaded form, still more rarely observed, characterized by two or more spindle forms arranged like a string of beads (Fig. 2); (5) the pedunculated form, the rarest, characterized by hernia-like protrusion at the side of axonal stems (Plate 1, Fig. 3; Plate 2, Fig. 2; Plate 3, Fig. 4), and (6) the cactus like form, encountered in Case 6 (Fig. 4) in which an axis cylinder was swollen and from the swollen body another swelling issued, giving a resemblance to the leaves of the cactus.

Structure of the Swelling: The internal structure of the swollen body is not always the same. The great majority of the swollen bodies appear homogeneous, without any visible neurofibrillar structure. These homogeneous types are of two varieties, one staining pale, the other

dark (strongly argentophilic). A smaller number of the swelling bodies display definite intra-axonal neurofibrils; these, however, are pushed apart by some interneurofibrillar substance giving a loosely



Fig. 5.—Alzheimer degeneration in the swelling of an axis cylinder.

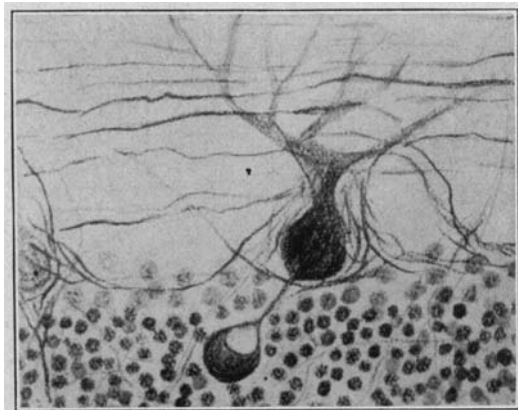


Fig. 6.—Vacuole formation in the swelling of an axis cylinder.

arranged appearance, the general direction of their course being unaltered. In a few cases I observed in one half of the swollen bodies a definite neurofibrillar structure and in the other half a more or less homogeneous argentophilic substance. I found in only two instances

thickening of neurofibrils and peculiar whirl-like structures suggesting Alzheimer degeneration of neurofibrils (Fig. 5). In the Purkinje cells, as mentioned before, no Alzheimer degeneration was found even after laborious search. This peculiar type of alteration found in two instances may possibly be of the same nature as Alzheimer degeneration. Other swollen bodies showed a coarse net formation, the inter-reticular substance being faintly stained. Still others displayed a dust-like substance in the swollen body, suggesting fragmentation of the intra-axonal neurofibrils. Vacuoles in the swelling of the axis cylinders, as shown in the illustrations of Marinesco's study, were not of

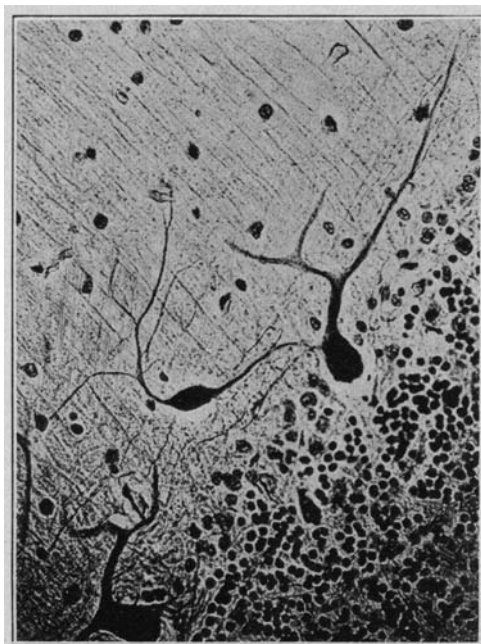


Fig. 7.—Spindle form swelling of a dendrite.

rare occurrence. Vacuoles were found mostly at the poles, rarely in the midportion of the swollen body (Fig. 6).

I tried to identify the substances in the peculiar swelling of axis cylinders by means of various methods of staining. In a small percentage lipoid substance, stained by sudan III and by the Marchi method, was demonstrated. The greater percentage of the swellings, however, showed no fatty content. A homogeneous substance with a glassy appearance was stained by the silver, in much the same manner as amyloid corpuscles, and some of these were markedly argentophilic. The exact nature of the substance is difficult to determine. Yet, the strong argentophilic character, the formation of vacuoles and

the deposition of fatty substance in some of them leads one to conclude that the processes are in part degenerative and in part regenerative, but that the latter are abortive.

Changes in the dendritic arborizations were not always alike for all the cases of this group. In Cases 1, 2, 6 and 8 the dendritic arborizations were well preserved, while in Cases 3, 7, 11 and 12 there was a partial disappearance of dendrites. Cases 4, 5, 9, 10, 13, 14,

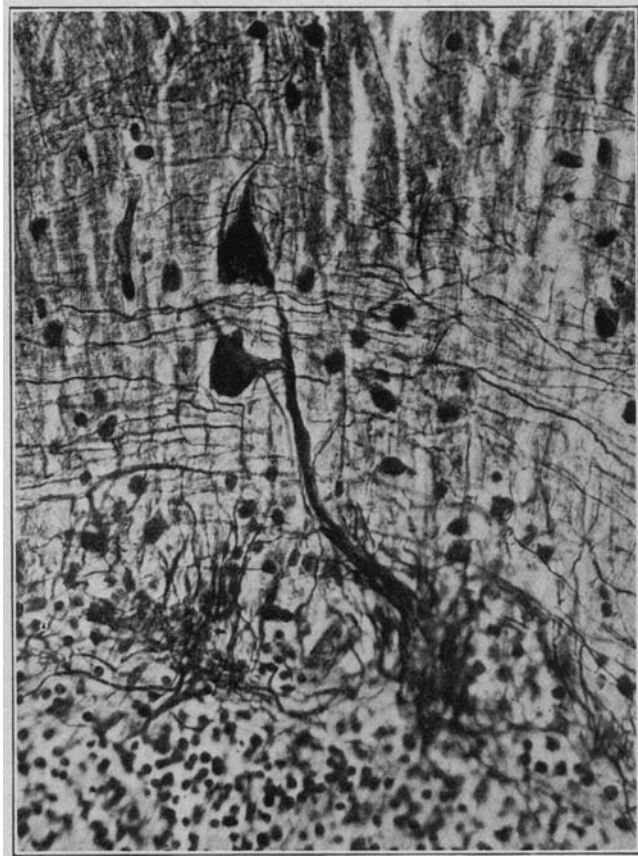


Fig. 8.—Pedunculated form of the dendritic swelling.

15 and 16 presented a well marked degeneration and an extreme scarcity of dendritic prolongations (Fig. 2). In these cases, Purkinje cells possessed only stumps of primary and secondary branches; other finer branches had all disappeared.

The peculiar swelling of dendrites, which I believe that I am the first to describe in senile dementia, were found in nearly all cases of this group, namely: 1, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 14, 15 and 16,

fourteen out of sixteen cases studied, or 87.5 per cent. These peculiar dendritic changes were not found in equal intensity in all of the cases. Cases 4 and 9, especially, showed only a few. Where the process was slight the changes were more likely to be found in sections from the worm, probably because this portion of the cerebellum is the most vulnerable. Cases 2 and 12, which gave negative results for these changes, might have shown the same peculiarities if sections from more parts had been studied.

The types of dendritic swellings found were: 1. Spindle Form: (Plate 3, Fig. 1). These swellings were usually located distant from the cell body and were similar in appearance and structure to those found in axis cylinders of the Purkinje cells. This form might also be found in the main stems of the apical prolongation or in the secondary and tertiary branches but they were most frequently found in the dendrites given off from the side of the cell body (Fig. 7). Marinesco, in his paper on cerebellar regeneration, illustrated a similar condition, which he described as a pseudodendrite. I could arrive at no satisfactory explanation as to why those dendrites given off from the side of the cell body were more frequently affected than the normal dendrites given off from the apex of the cell.

2. Pedunculated Form: This type varied in size and was usually found on the stem of the primary, secondary or tertiary branches. In Case 3, as illustrated in Figure 8, the main stem showed two peculiar sac-like swellings from which fibers were given off to terminate freely in the molecular layer. These fibers might possibly have been dendritic arborizations, but unlike them they took a more or less serpentine course.

3. Bulb-Like Form: This type was always found at the end of a fiber where it has much the appearance of an electric light bulb (Fig. 9).

4. The next type of swelling was more or less spindle shaped and was always found at the points of branching into finer dendrites (Plate 3, Fig. 3).

5. This type displayed enormously thickened dendritic stumps from which radiated a great number of fibers, which formed a more or less tangled mass (Figs. 10 and 13).

6. This type consisted of a diffuse thickening of primary and secondary branches (Plate 3, Fig. 2).

The contents of the swollen parts were as varied as the contents in the swellings of the axis cylinders. The spindle formed swellings usually contained a markedly argentophilic homogeneous substance and resembled similar swellings in the axis cylinders. Pedunculated swellings were either homogeneous glassy matter which in staining quality

is very much like amyloid. This homogeneous glassy matter was probably a semifluid metabolic substance, but this could not be determined. The diffusely hypertrophic dendrites usually had a neurofibril content. Some, however, stained homogeneously. Other swellings contained vacuoles, as in the case of axis cylinders. A certain number of these swellings presented fatty changes, which were readily stained by sudan III, Scharlach R. and the Marchi method, but in most instances I



Fig. 9.—Bulblike form of the dendritic swelling.

was unable to demonstrate any fatty substances. The strong argenophilic character, the homogeneous glassy appearance, the vacuole formation, etc., point, as in the case of axis cylinders, to their degenerative character. The cases presenting these peculiar swellings showed, in most instances, well marked dendritic disintegration, and their degenerative character.

But is this process only degenerative in character? I observed in many instances numerous small branches extending from the swollen body which were fusiform, sac form or irregular swellings of the den-

dritic stumps (Fig. 10). This and the diffuse hypertrophy of the dendrites would indicate the regenerative nature of the process, according to my interpretation. This will be discussed later.

GROUP II. ARTERIOSCLEROTIC BRAIN DISEASES

CASE 17 (Case No. 21348, Aut. No. 2118).—Male; psychosis of one months' standing; died at the age of 77 of arteriosclerosis and bronchopneumonia.

CASE 18 (Case No. 17300, Aut. No. 2115).—Female; psychosis of twelve years' standing; died at the age of 70 of arteriosclerosis.

CASE 19 (Case No. 21459, Aut. No. 2128).—Male; psychosis of four years' standing; died at the age of 92 of arteriosclerosis.

CASE 20 (Case No. 21142, Aut. No. 2103).—Female; psychosis of eight years' standing; died at the age of 48 of chronic vegetative endocarditis.

CASE 21 (Case No. 17376, Aut. No. 1915).—Female; psychosis of five years' standing; died at the age of 79 of profound cerebral hemorrhage.

Pathologic Observations on Group 2.—In the cerebrum, all cases showed areas of softening and hemorrhagic lesions. Cases 17 and 18 presented small hemorrhages in the white substance of the cerebellum, as well as in the pons. Case 21 exhibited a severe new intraventricular hemorrhage, which caused the death of the patient. The larger arteries of the cerebrum, as well as those of the cerebellum, were markedly sclerotic. This condition, however, was most profound in Case 21. Case 20, previously reported by the writer as an atypical form of arteriosclerotic brain devastation, presented a peculiar gross appearance quite like the moth-eaten condition (*état vermoulu*) of Pierre Marie. Histopathologically the latter revealed "spongy degeneration of the cortex," in addition to hemorrhagic areas and softenings. In none of these cases were senile plaques or Alzheimer degeneration demonstrated.

The general histopathologic findings of the cerebellum varied in each case, as the group is vascular in origin and the changes depend on the grade of vessel alteration and location of diseased arteries, in this particular respect differing from the cases of the senile dementia described in the preceding group.

The cerebellar pia of these cases was irregularly thickened and adherent to the cortex by brushlike glia fibers (Fig. 11). The glia fibers of the border were here and there enormously thickened, often times dipping down into the molecular layer in areas which were wedge-shaped, the base of the wedge directed to the periphery. In the areas of arteriosclerotic devastation, the entire molecular layer was remarkably reduced in width, measuring only from one-third to one-fourth of the normal thickness. Cells and nerve fibers were almost entirely destroyed. Scarcely any Purkinje cells or their dendrites were encountered. Glia fibers, especially Bergmann fibers, were greatly

increased throughout the molecular layer. Amyloid corpuscles were seen mostly in the meshes of proliferated glia fibers of the outer border and in the deepest part of molecular layer.

In the intermediate layer a great many fat corpuscle cells came to view when the process was relatively young.

The granular layer and the white substance suffered equally from arteriosclerotic degeneration, causing in the former the disappearance of spheroid cells and in the latter the degeneration of myelin sheaths.

The fatty degeneration of Purkinje cells was also focal, that is, well marked in the lesion or in the immediate neighborhood of the



Fig. 10.—A dendritic swelling from which a great number of finer branches are given off.

lesion, while in remote parts it was barely noticeable. In Case 19 fatty degeneration was general and in a considerably advanced stage, the patient being 92 years of age.

Case 20 presented a peculiar alteration of the cerebellum. The degeneration of the nervous element was so great that within the affected areas all parenchymatous elements had entirely disappeared, leaving only a framework (Fig. 11). In the molecular layer the Bergmann fibers which traversed it were almost the only constituents to be seen, the whole layer appearing like a slat fence. In the intermediate zone the Purkinje cells had almost disappeared. Glia cells

with large nuclei remained and marked the border of the molecular and granular layer. In the granular layer spheroidal cells, Cajal's star cells and other cells of parenchymatous nature had all disappeared. Glia cells and fibers formed a loose network. Here and there, where the devastation was still more complete, one could observe only a cystic cavity with no trace of supporting fibers.

Local swellings of axis cylinders, such as those described for the preceding group, were also encountered. These, however, were not so numerous as in the preceding group. In a small section (about ten folia) from two to five such swellings were found in Cases 17,

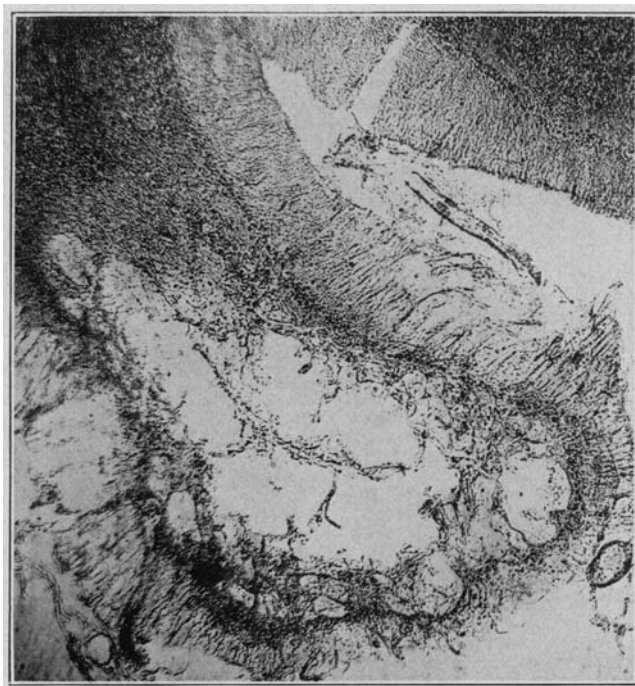


Fig. 11 (Case 20).—An atypical form of arteriosclerotic devastation of the cerebellum.

18, 20 and 21, and in Case 19 in from three to four sections of approximately the same size, only one or two swellings were seen. The last case showed an advanced fatty degeneration of the Purkinje cells. As a rule, however, swellings are not usually found associated with markedly degenerated Purkinje cells. Most of the swellings were found far from arteriosclerotic lesions in apparently healthy tissue, as was noticed by Cajal. I could not decide whether some of these swellings represented divided central ends of axons of Purkinje cells. On the other hand, I was able to follow, in a few instances, axis cylinders

with swollen bodies far down into the white substance of the cerebellum.

The association of swellings with relatively healthy Purkinje cells, their location at a distance from the lesion, and the fact that swollen fibers can be followed farther down into the white matter, suggest a reaction in relatively healthy Purkinje cells and fibers.

In Case 17, as shown in Figure 12, a peculiar sort of swelling was observed—two spindle formed swellings connected by a fiber filament, one of them located in the intermediate layer where normal Purkinje cells were found and the other in the granular layer. The upper spindle showed a fine netlike structure, while the lower one presented a coarse network arrangement. Whether or not the upper swelling

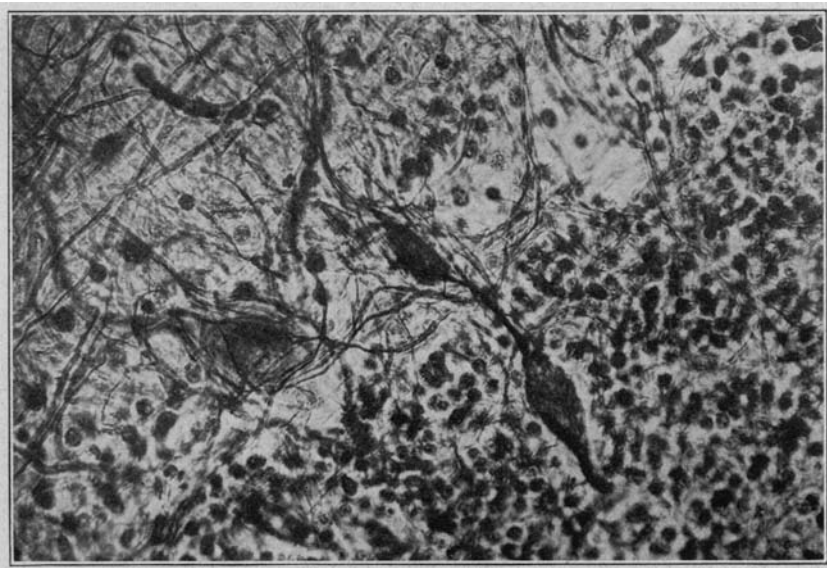


Fig. 12.—Photomicrograph of the cerebellum of the patient in Case 18.

was an atypical Purkinje cell or spindle formed ganglion cell, or a swelling of an apical prolongation from the spindle formed cell of the granular layer, is difficult to determine. The lower swelling might be either a local hypertrophy of a fiber, or it might be a cell body; but in any case, one of them was a structure of the type with which we are dealing. Swellings of fibers of unknown origin were found not only in the granular and the intermediate zones, but also in the molecular layer.

The dendrites of Purkinje cells were greatly affected within areas of lesions, but outside of them they were generally in fair condition. Case 21 presented a general scarcity of dendrites. The peculiar swellings of dendrites were found only in Case 21, and were fairly abun-

dant, being of many forms. A good example of Type 5 (described in the preceding group) was observed (Fig. 13). The ends of two dendrites were encountered which had the appearance of balls from which many very fine branches radiated. This condition suggested a regenerative rather than a degenerative process. The swollen or globular part was diffusely stained by silver. It did not contain any fatty substance. In other types of dendritic swellings a fatty substance

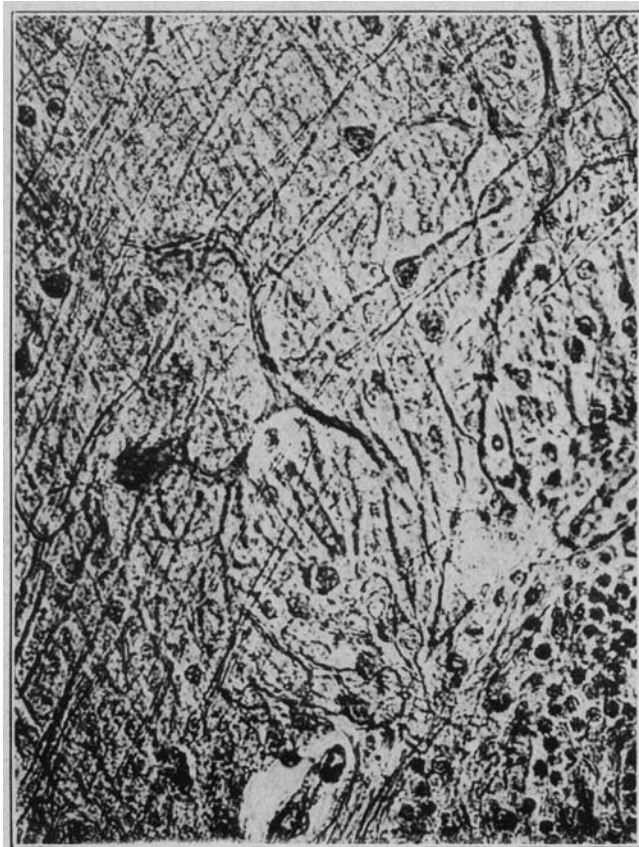


Fig. 13.—A type of dendritic swelling observed in Case 21. The ends of two dendrites show a ball-like swelling from which a number of finer branches are given off.

could be demonstrated, as well as a homogeneous semiliquid substance of an argentophilic character.

GROUP III. GENERAL PARALYSIS

CASE 22 (Case No. 19518, Aut. No. 1938).—Male; admitted at the age of 45; blood serum and spinal fluid positive; died two weeks after admission; cause of death was given as general paralysis.

CASE 23 (Case No. 18784, Aut. No. 1931). Male; admitted at the age of 48; fifteen years ago was infected with syphilis; blood serum and spinal fluid reactions positive. He died one year after admission to the hospital from lobar pneumonia.

CASE 24 (Case No. 18029, Aut. No. 1909).—Male; admitted at the age of 38; Wassermann reaction on blood serum and spinal fluid positive; died of bronchopneumonia after being in the hospital two years.

CASE 25 (Case No. 19395, Aut. No. 1924).—Male; admitted at the age of 39. He was admitted to this hospital eight years ago for the first time; at that time tests on spinal fluid were positive. He was admitted after eight years; died from general paralysis.

CASE 26 (Case No. 19091, Aut. No. 1971).—Female; admitted at the age of 51. Blood serum and spinal fluid reactions were positive; died one year after admission from general paralysis.

CASE 27 (Case No. 18681, Aut. No. 2030).—Male; admitted at the age of 60. Blood serum and spinal fluid reactions were positive; death at the age of 62 from general paralysis.

Pathologic Observations on Group 3.—The pia mater was thickened, its vessels being infiltrated by lymphocytes and plasma cells. The glia network of the outer border was considerably increased. The molecular layer was reduced in width, the structural plan being greatly altered. Tangential fibers and cushion fibers were diminished. The amyloid corpuscles were markedly increased; they were found, not only in the molecular, but also in the intermediate and granular, layer. Fat corpuscle cells were found around the infiltrated vessels in all layers. In the granular layer spheroidal cells were markedly diminished in number, especially in Cases 22 and 26. In the white substance there was a marked pallor of the myelin sheaths due to diffuse degeneration of fibers. Glia cells were increased in all layers, particularly at the outer border of the cortex, in the intermediate zone and in the granular layer. Glia fibers, as well as glia cells, were markedly increased, especially the Bergmann fibers.

The apical dendrites of the Purkinje cells tended to stain intensively and could be traced a greater distance than in the normal cerebellum. In Cases 22 and 26 the lipoid substance in the Purkinje cells was enormously increased; there was more of this substance even than was found in the most advanced cases of senile dementia. The Nissl bodies had disintegrated into a granular or dustlike substance. The nuclei of the Purkinje cells displayed various changes. They were mostly irregular in form and showed a dark stained nucleolus surrounded by a dark chromatin substance arranged in the form of a wreath.

All cases in this group displayed axonal swellings, but not so numerous as in the cases of senile dementia. These swellings were more numerous in Case 24. The character of the swollen bodies was the

same as that of the swollen bodies described in the cases of senile dementia. There was, however, less variety; most of the swellings were spindle or conical shaped.

Dendritic swellings were also observed in Case 22. In addition to localized swellings a few dendrites showed diffuse hypertrophy, with increased staining quality and with a loss of the neurofibrillary structure. The swellings of the dendrites, mostly spindle or bulb form, contained fatty substance, which was readily stained by Scharlach R. Not only the localized swellings of the dendrites, but also diffuse hypertrophic dendrites contained fat corpuscles. The dendrites in this case (Case 22) seem to have suffered more intensively from degenera-

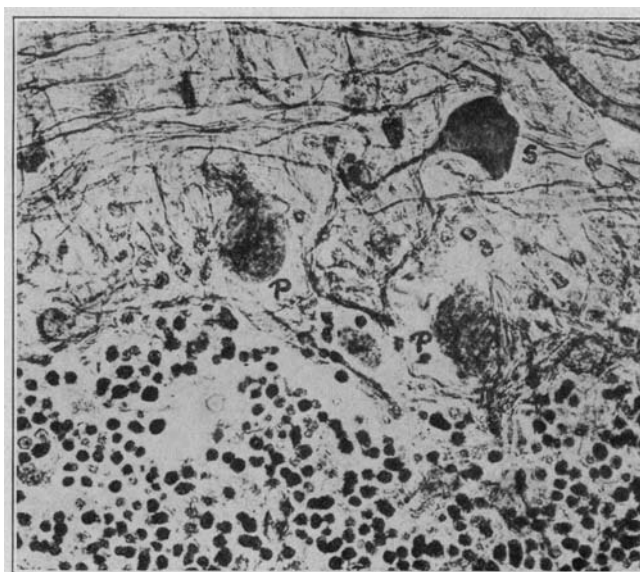


Fig. 14.—S, a swelling of a fiber whose origin is unknown; P, a Purkinje cell.

tion than in the remaining cases. Thus the swellings of dendrites appear to have a definite relationship to the general degenerative changes in dendrites. This may explain why dendritic swellings were found only in this case, for only in this case were general dendritic changes marked.

In Case 27 a few swellings of fibers were observed in the molecular layer in the immediate neighborhood of the Purkinje cells, but the cells of origin for these fibers were not determined. These swellings, however, may be fibers from spindle form ganglion cells of the granular layer, axons or collaterals of Purkinje cells, or dendrites given off from the sides of the Purkinje cell body, for I believe that any of these may show swellings of this sort (Fig. 14).

GROUP IV. CONGENITAL BRAIN DISEASES

CASE 28 (Case No. 16295, Aut. No. 2101).—Female; preceding the mental disturbance which occurred eighteen years ago, the patient had a "shock" following aphasia which lasted eight weeks. She died eighteen years after onset. Cause of death was given as chronic valvular disease.

CASE 29 (Case No. 19837, Aut. No. 2004).—Male; 8 years of age on admission; blind when admitted. He was untidy; he made no attempt to respond when questioned. He died eight months after admission; the cause of death was marasmus.

CASE 30 (Case No. 18551, Aut. No. 1999).—Male; admitted at the age of 62. The patient went to school but could not learn to read and write. He was classified as an imbecile. He died of tuberculosis.

Pathologic Observation on Group 4.—Case 28 was previously reported by the writer as a case of diffuse cerebrosplinal sclerosis. The brain was small, weighing only 870 gm., and was unusually firm in consistency. Histopathologically, a considerable increase of glia cells throughout the whole central nervous system was shown. Myelin sheaths in the centrum semi-ovale were diffusely degenerated. In addition to these remarkable changes, there was a cyst in the anterior part of the centrum semi-ovale of the right side, surrounded by softened areas.

The cerebellum presented also a considerable increase of glia elements in all cortical layers and in the white matter. The nuclei of glia cells displayed all possible varieties. In the Purkinje cell layer abnormally large, irregularly shaped, nuclei of glia cells were observed. Rod cells were abundantly encountered in the white matter. Glia fibers also were increased. The glia belt of the outer border was enormously thickened. The Bergmann fibers were prominent. Heterotopic cells, from two to three in a few sections, were observed in the upper portion of the molecular layer.

I include this case within the congenital group on account of the abnormally small brain, simple convolitional pattern, heterotopy of Purkinje cells and some anomalous organs of the body.

Case 29 showed microscopically no characteristic findings of amaurotic family idiocy, which would be expected from a reading of the history. Ganglion cells of the cerebrum showed well marked fatty degeneration. Dendrites of the ganglion cells, however, were not swollen. Glia cells were increased both in the cerebrum and cerebellum. The cause of the blindness was not determined, nor could we determine whether it was of central or peripheral origin. As there were a number of anomalies and malformations in the central nervous system, as well as in the body, this case was classified in the congenital group.

Case 30 did not show any chronic inflammatory processes of the meninges and brain substance. The brain was relatively small (1,050

gm.), and the gyri were of a simple pattern. The evidence which points to the congenital nature of the case is not so good as in the preceding two cases.

In Cases 28 and 29 tangential and cushion fibers showed some diminution. The Purkinje cells were perceptibly reduced in number. Apical prolongations stained unusually well, while Nissl bodies showed a granular disintegration and disappearance, especially in the peripheral and apical portions. With the exception of a slight diminution in the number of Purkinje cells, Case 30 showed no remarkable changes either in the cells or in the fibers.

All these cases showed axonal swellings. The first two cases displayed abundant examples of swelling, while the last case exhibited few swellings. Most of the swellings were of the spindle form; other types were rarely encountered.

Dendritic swellings were observed in the first two cases; they were abundant in Case 29 (Fig. 15) and less abundant in Case 28. Most of the spindle form swellings occurred in secondary or in tertiary branches. They were markedly argentophilic and showed no neurofibrils. In Case 29 the swellings were encountered chiefly in dendrites given off from the sides of the cell body or in one of the secondary branches of less thickness. This condition was also observed in some of the cases of the senile group.

GROUP V. DEMENTIA PRAECOX

CASE 31 (Case No. 19440, Aut. No. 2007).—Female; age on admission 40; hallucinated; indifferent, lost interest in her work; at times refused food and medicine; died of bronchopneumonia after being in the hospital about a year.

CASE 32 (Case No. 20069, Aut. No. 2112).—Female; admitted at the age of 32, with ideas of persecution; hallucinated; indifferent and untidy. She died at the age of 33. Cause of death was given as exhaustion.

CASE 33 (Case No. 20403, Aut. No. 2051).—Female; admitted at the age of 32; unclean and hallucinated; disoriented. The Wassermann reaction on the blood serum was positive; spinal fluid reaction was negative. She died of mitral disease at the age of 34.

Pathologic Observation on Group 5.—No remarkable histopathologic changes were observed in cases of this group. In Case 31 there was a slight diminution of Purkinje cells at the summit of the folia. The amyloid corpuscles, in comparison with the other two cases, were slightly more numerous at the outer border of the cortex and in the deeper part of the molecular layer. The Purkinje cells were apparently normal in appearance, the finer architecture well shown. No swellings of either axons or dendrites could be demonstrated in any of these cases.

GROUP VI. MANIC DEPRESSIVE CASES

CASE 34 (Case No. 18081, Aut. No. 1993).—Male; admitted at the age of 49. He had two attacks of depression. He was apprehensive and had a tendency toward suicide. Two and a half years after admission he died of septicemia.

CASE 35 (Case No. 20058, Aut. No. 2015).—Female; admitted at the age of 51; agitation, extremely restless and resistive; flight of ideas. She died from general streptococcic infection two weeks after admission.

CASE 36 (Case No. 19918, Aut. No. 2017).—Male; admitted at the age of 45; depressed. He died three months after admission. Cause of death was given as arteriosclerosis.

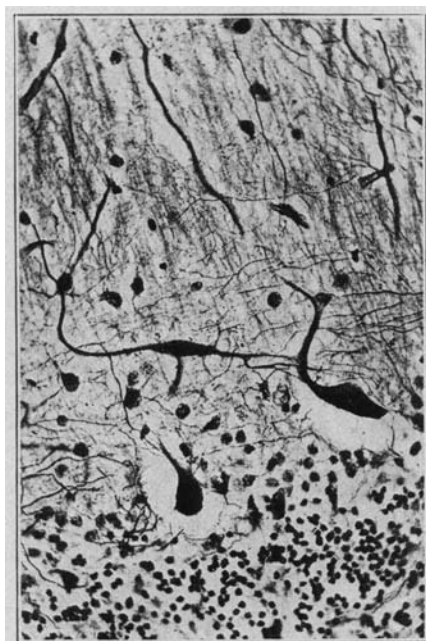


Fig. 15.—Spindle form swelling of a dendrite in Case 29.

Pathologic Observation on Group 6.—No remarkable histopathologic changes were found in these cases, with the exception of the changes in the Purkinje cells in the first two cases. In these cases a great many Purkinje cells had undergone a remarkable alteration. The nuclei, as well as protoplasm, stained poorly. The nuclear membrane had partly disappeared. The Nissl bodies were chromatolytic at the center, as well as at the periphery, of the cell. These changes of the Purkinje cells may possibly be associated with the terminal condition of the patients, who in both cases died of acute infectious diseases.

In none of these cases were the peculiar swellings of the axis cylinders and dendrites observed.

GROUP VII. ALCOHOLIC AND TOXIC CASES

CASE 37 (Case No. 9229, Aut. No. 1966).—Male; admitted at the age of 46 with a definite history of alcohol and attacks of delirium tremens. He died of lobar pneumonia after eighteen years in the hospital.

CASE 38 (Case No. 20036, Aut. No. 2067).—Male; admitted at the age of 50; definite history of alcohol. He died eleven months after admission of tuberculosis.

Pathologic Observation on Group 7.—The changes were marked and of the same character in both of these cases. Glia cells and glia fibers were slightly increased. The walls of the vessels displayed more or less fatty degeneration. Fat corpuscle cells were abundantly observed in the intermediate cell layer. The Purkinje cells were somewhat diminished in number, showing a marked increase of lipoid substance. Apical dendrites were rather deeply stained and could be traced for a considerable distance. The nuclei of the Purkinje cells showed some contraction and irregularity in form. The Nissl bodies had disintegrated. The tangential and cushion fibers seemed to be slightly diminished in number. Fat corpuscle cells were observed in the granular layer and in the white substance.

Swellings of the axis cylinders were observed in both cases, one or two in three or four sections. These were all spindle shaped and diffusely argentophilic.

Dendritic swellings were observed in Case 37. The swellings were spindle shaped or pedunculated. In Case 38 swellings of some fibers whose origins could not be identified, were found in the molecular layer not far from the Purkinje cells.

GROUP VIII. BRAIN TUMORS

CASE 39 (Case No. 21305, Aut. No. 2110).—Male; admitted at the age of 49; died ten days after admission.

CASE 40 (Case No. 20818, Aut. No. 2087).—Male; aged 50 on admission; aphasia; headaches with vomiting and vertigo.

In both cases the tumors were found to be gliomas. In both cases the cerebellum was flattened as a result of an increased intracranial pressure. Macroscopically, the cerebellar folia were generally flattened. Microscopically, the molecular layer was seen to be diminished in thickness, particularly at the summit of the folia, which gave them the appearance of a xiphoid process.

The most remarkable changes in this group were those in the dendrites of the Purkinje cells which coursed in a zigzag or serpentine manner (Fig. 16). Most of the finer dendritic branches had disappeared. The apical dendrites showed exceptionally good staining qualities. The Purkinje cells, basket and cushion fibers suffered very little. There was also a slight increase of glia cells and fibers.

The axis cylinders of the Purkinje cells disclosed the peculiar changes with which we are dealing. No dendritic swellings were observed.

GROUP IX. MYXEDEMATOUS PSYCHOSIS

CASE 41 (Case No. 21477, Aut. No. 2125).—Female; admitted at the age of 66. On admission she showed typical symptoms of myxedema. She died one month after admission. Cause of death given as myxedema.

Pathologic Observation on Group 9.—The ganglion cells of the cerebrum of this case showed cell changes due to a myxedematous condition of the brain matter. I have previously reported this case,

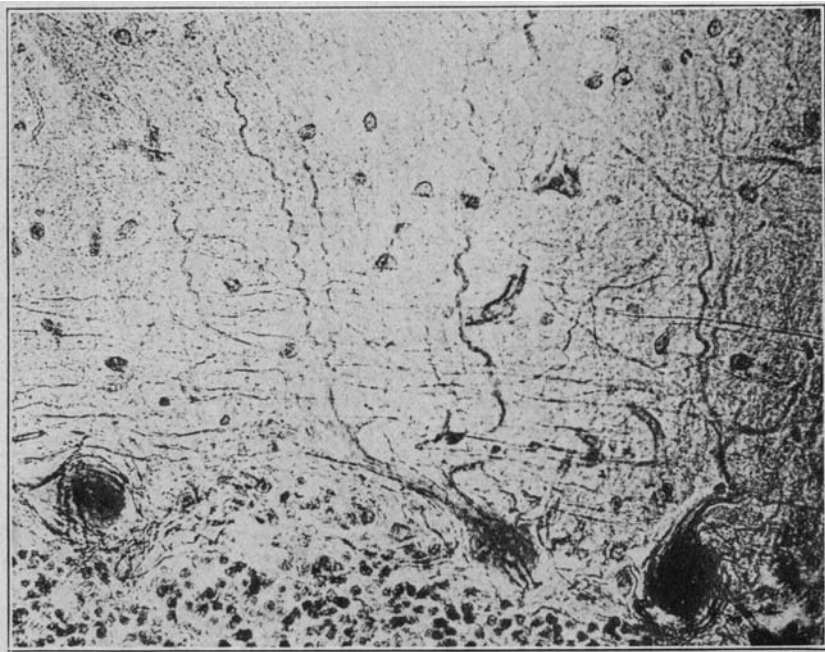


Fig. 16.—Serpentine course of dendrites due to pressure of the cerebellar cortex.

calling special attention to this type of cell change, which is believed to be pathognomonic for this disease. The Purkinje cells did not show this peculiar change. In the cerebellum the changes were very much like those of arteriosclerosis. The glia cells and fibers were increased. Fairly abundant amyloid corpuscle cells were found in the deeper portion of the molecular layer. The Purkinje cells contained only a moderate amount of fatty substances.

The peculiar swellings of axis cylinders, two or three in a section, were found. There were also some swollen fibers of obscure origin in the neighborhood of Purkinje cells.

SUMMARY AND CONCLUSIONS

The peculiar swellings of the axis cylinders and dendrites have been observed in various groups of diseases more commonly than was anticipated from a study of literature. These peculiar changes can, therefore, no longer be considered as specific changes. They are encountered in cerebella whenever there is a chronic degenerative process. This process may be either of an inflammatory character, the result of malformation, or of toxemia, as for example, from alcohol.

GROUPS OF CASES STUDIED, WITH THE PERCENTAGES OF AXONAL AND DENDRITIC SWELLINGS

Groups of Diseases	Cases Studied	Axonal Swellings	Percentage of Axonal Swellings	Dendritic Swellings	Percentage of Dendritic Swellings
Senile dementia.....	16	16	100	14	87.5
Arteriosclerosis.....	5	5	100	1	20.0
General paralysis.....	6	6	100	1	17.0
Congenital.....	3	3	100	2	66.7
Dementia praecox.....	3	0	0	0	0.0
Manic depressive.....	3	0	0	0	0.0
Alcohol, toxic.....	2	2	100	1	50.0
Brain tumors.....	2	2	100	0	0.0
Myxedema.....	1	1	100	0	0.0
Total.....	41	35	85	19	46.0

Axonal swellings are more frequently observed than dendritic swellings. Axonal swellings may be found in any disease in which the Purkinje cells have undergone degeneration. If, however, degeneration of the Purkinje cells is extreme, axonal swellings are either not to be observed or only a few are encountered as these swellings are stages of degeneration which these cells undergo. The dendritic swellings, on the other hand, are found even with fairly advanced degeneration of the finer dendritic processes and most commonly in senile dementia and congenital brain diseases. The dendritic and axonal swellings are not always of the same intensity in the same case though they are usually associated (Plate 2, Fig. 3).

What is the nature of these peculiar changes? Are they regenerative or degenerative in character? The swellings of the axis cylinders are not necessarily at the points of division of an axon by injury, although some swellings have no fiber continuing from them. From most of the swellings, however, a fiber may be followed down into the white matter. In cases which displayed coarse lesions, such as cystic cavities in the granular layer, the peculiar swellings were not found in the immediate neighborhood of the lesions but at a distance from the latter. Moreover, the swellings, as mentioned in the foregoing, have always been observed at a short distance from the Purkinje

cell body and always in the upper part of the granular layer. This fact and also the fact that the swellings are always associated with somewhat pathologic but not extremely degenerated Purkinje cells, lead to the assumption that the swellings are, in the beginning at least, a reactive process of pathologic but living protoplasm. The diffuse hypertrophy of axons and collaterals, which are found associated with focalized swellings, are to be regarded as a regenerative process. Thus the ill-nourished or slightly degenerating Purkinje cells appear to make a feeble attempt to increase the thickness of the axons. This increase of thickness may be, as Schaffer has asserted, the result of an hypertrophy of the axoplasm.

The "feeble attempt" at regeneration is, however, abortive. The Purkinje cells themselves, in diseases in which we find these peculiar changes, undergo degeneration, and their axons soon suffer a further process of a degenerative nature. This is expressed by the localized swellings of the axons caused by the accumulation of waste products of pathologic metabolism. The markedly argentophilic character of the swollen bodies, formation of vacuoles and deposition of fatty substances in the swellings, indicate the degenerative character of this phenomenon.

The dendritic swellings, though they are not so frequently observed as axonal swellings, probably are of the same character. Here I observed clearly that the dendritic stumps showed irregular swellings from which numerous finer branches were given off. This, and the diffuse thickness of the dendrites, leads one to conclude that the nature of the process is regenerative. Bulblike forms, which were found at the ends of thick dendritic fibers, may probably be compared to the central stump of the divided nerves, and are naturally of a regenerative character.

The regenerative process, however, is soon followed, as in the axis cylinders, by a degenerative one. The metabolic product which in most instances gives rise to the peculiar swellings is a homogeneously glassy substance. This substance shows a staining reaction similar to that of the amyloid bodies found in the central nervous system. I have been unable to determine the definite character of this substance. I have not yet arrived at a satisfactory explanation as to why senile dementia and congenital brain diseases are more likely to show this peculiar phenomenon than are other diseases. The inherited predisposition of the nerve element in congenital diseases and the acquired weakness in senile dementia may possibly play a great part.