THE CELL CHANGES IN AMAUROTIC FAMILY IDIOCY.[1]

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PLATES LXI–LXV.

The morbid anatomy of amaurotic family idiocy is now as safely established as are the clinical symptoms of this interesting disorder of early childhood. The changes in cell structure are as typical of this disease as are the mental defect, the marasmus, the blindness associated with the "cherry-red spot in the region of the macula lutea," and the family disposition.

Great progress has been made in the recognition of the pathology of the disease during the past twenty-three years, since one of us first thought of the disease as an arrest of cortical development (agenesis corticalis).[2] Eleven years later, following the researches of Hirsch[3] and others, the disease was seen to depend upon involvement of the gray matter of the entire central nervous system, and still more recently, owing particularly to the work of Schaffer, which we are able happily to corroborate, amaurotic family idiocy has gained additional importance in view of the extraordinary and constant changes in ganglion cell structure which it reveals. Incidentally, as Sachs has pointed out at the meeting at Budapest, this gravest and most fatal of all family diseases is a purely cellular disease. It is of no little moment to have established this one fact. It is the starting point for the future study of the pathology of other hereditary and family diseases of the nervous system.

Schaffer, Hirsch, Sachs, Spielmeyer and others, have insisted that in amaurotic family idiocy not a single ganglion cell escapes, and the cell changes are the same whether the cell examined be in

[1] Received for publication June 7, 1910.

[2] Sachs, *Jour. of Nerv. and Ment. Dis.*, 1887, xiv, 541.

[3] Hirsch, *Jour. of Nerv. and Ment. Dis.*, 1898, xxv, 538.

the cortex, in the basal ganglia, in the spinal cord or in the spinal ganglia or retina.

Our present contribution is to be devoted to an account of these morbid cell structures as revealed by the study of a typical case of amaurotic family idiocy, complicated by rickets.

A child, L.G., aged 2 years, was admitted to Mount Sinai Hospital, May 25, 1908. Through the couresy of Dr. Koplik it remained under observation until its death, June 5, 1908. Two other children of the same family had died of amaurotic family idiocy; one child had died of colitis. There is one healthy child 6 years old.

Our own patient had not passed through any of the infectious diseases of childhood. The parents stated that when the child was one year old, having the fate of the two other children in mind, it was noticed that the child did not develop normally. It did not hold up its head, would start suddenly on hearing noises (hyperacusis), and its vision evidently became defective. The parents noticed constant oscillation of the eyeballs and frequent twitchings of the extremities. They also observed a rapidly increasing emaciation.

At the time of the first examination, May 25, the general physical condition was poor, the head somewhat hydrocephalic and in great disproportion to the size of the body. The child would lie entirely listless until subjected to examination. Any attempt to move it would cause a stiffening and trembling of the arms and legs. The child was violently startled by the slightest clapping of the hands near its bed. The eyes were staring and showed marked rotatory and lateral nystagmus. It was evidently blind; its cry was feeble; respirations were fairly regular except for short intermissions. The anterior fontanelle was open, permitting two fingers; the occipito-frontal circumference was 50.5 cm. The child was wholly unable to sit up or to hold up its head.

As for the general condition, it was noted that there was a general morbiliform eruption over the trunk and exteremities. The right epitrochlear and the left axillary glands were slightly enlarged. There was also slight epiphyseal enlargement of the bones. There was normal development of the teeth considering the age of the child. A marked rachitic rosary was noted. The lungs, heart and liver were normal; the spleen palpable. The extremities were, as a rule, in a tetanoid position; the knee-jerks exaggerated; there was no Babinski. Plantar stimulation caused marked trembling of the entire lower extremity. There was no Kernig symptom. Examination of the fundus revealed the "cherry-red spot" in each eye. The disks were blue in color and sharply outlined.

The child's condition remained practically the same during the period of observation except for the progressing emaciation. At various periods during its stay in the hospital the temperature varied from 98.4° to 102.4°. Without any marked change in the symptoms, and without the occurrence of convulsions, the child died on June 5. The autopsy was performed within a few hours after death by Dr. I. Strauss.

Disregarding all macroscopical changes in the brain, and without heeding the question whether or not minor changes in fissuration are of any importance, we pass to a consideration of the morbid process as it affects the ganglion cells of the central nervous system. It has been intimated before that the pathological process is essentially the same whether the cell examined be from a section of the cortex, of the cerebrum or of the cerebellum, or from a section of the spinal cord. The most striking evidence of degeneration is found in the enlargement of the cell-body. The normal concave contour disappears and the circumference of the cell becomes well rounded. The Nissl substance in the body of the cell begins to disappear; it does not disintegrate but undergoes a gradual absorption. In the vicinity of the nucleus the Nissl bodies can be recognized for a considerable period of time, but in the end they disappear there also, as well as from the dendrites. At first the cell appears to contain a finely granular detritus, which is probably the remains of the disintegrated endocellular network. As the morbid process continues the cell-body is converted into a homogeneous mass.

In frozen sections stained with scarlet R. the ganglion cells take on a red stain, which indicates that the degeneration has resulted in the formation of some lipoid substance. So far as we know, this reaction has not been previously noted. The nucleus is displaced to the margin of the cell at an early period of the disease. In the pyramidal cells of the cortex it is found almost invariably at the base of the apical dendrite. As a rule, the nucleus is irregular in outline, somewhat shrunken, and contains a distinct nucleolus, but very little chromatin. It remains recognizable within the degenerating cell until the final disintegration has occurred.

Next to the degeneration of the cell-body, we are struck by the peculiar balloon-like swelling of the dendrites, to which Shaffer was the first to call special attention. This enlargement may be said to be pathognomonic of the disease. The swelling of the dendrites is especially characteristic of the ganglion cells of the cerebral cortex, as well as of the cells of Purkinje in the cerebellum. In the former the basal dendrites are invariably affected. They may be so dilated as to be considerably larger than the cell-body. The swelling of the

dendrites of the Purkinje cells is also very marked. This same change is found to a lesser degree in the ganglion cells of the spinal cord. In striking contrast to this is the fact that the apical dendrites of the pyramidal cells and the axones are rarely affected. We have no theory as yet to account for this peculiar selective activity of the degenerative process (Plate LXI, Figs. 1 and 2; Plate LXII, Figs. 3 and 4).

In his excellent study on amaurotic family idiocy, Schaffer[4] observes that "Sachs' disease may be diagnosticated by the appearance of the fibrillæ." We cannot subscribe fully to this statement. Somewhat similar changes in the fibrillæ, their disappearance in the cell-body and their persistence in the dendrites and axone have been described in other diseases, as shown by Goldstein's[5] findings in dementia præcox. Before entering upon the description of the changes in the fibrillæ of the ganglion cells of the central nervous system in amaurotic family idiocy, it will be best to review briefly the present-day knowledge of neurofibrils. . . . Within the cell-body, but very near its surface, is a well-defined network of fibrils. This network is also present in the dendrites and in the axone. It is called the epicellular or ectocellular network of neurofibrils. This network receives fibrils from beyond the cell, and by some it is thought to be connected with a finer fibrillary network occupying most of the cell-body, and known as the endocellular network. The meshes of the latter network are smaller, and around the nucleus it is denser in appearance. This denser part is designated as the pericellular network.[6]

Bethe describes the epicellular network, which he considers the same as the Golgi net, but denies that there is any endocellular network. He claims that the fibrils pass through the cell without forming anastomoses. Donaggio, however, with a slightly different method has demonstrated an endocellular network. Cajal, and many of those using the silver method, describe primary fibrils

[4] *Zeit. f. d. Erforsch. u. Behandl. d. jugendlichen Schwachsinns,* 1909, iii, 53.

[5] *Arch. f. Psychiat.,* 1910, xliv, 1062.

[6] The principal studies on neurofibrils have been made by Bethe and Donaggio, using a method which depends upon the action of ammonium molybdate upon methylene blue. Cajal and Bielschowsky have pursued the same researches, relying upon a method of silver precipitation.

which are thick and pass through the cell but at the same time anastomose with a finer set of fibrils which form a dense network about the nucleus. In order to harmonize the views of Bethe and Cajal, Economo, a pupil of Bethe, working under his supervision and studying the same materials by the various methods, concluded that the epicellular network is a well-defined structure connected with the fibrils of the cell-processes and that it is also frequently connected with fibrils coming from beyond the cell. In his opinion the thickening of the primary fibrils of Cajal and the appearance of interlacing are due to the silver nitrate's causing the fibrils to shrink and to be approximated to each other, thus simulating a network. According to Economo the endocellular network is due to thorough impregnation of the protoplasmic reticulum. The isolated fibrils lie in this reticulum. He and Bielschowsky believe that the isolated fibrils run over and pass the nucleus and that the perinuclear network is an artifact due to the method of impregnation.

In his first studies of the fibrils in amaurotic idiocy Schaffer described an outer network of coarse anastomosing fibrils which he considered identical with the Bethe-Golgi net, or the epicellular network of Economo. Schaffer also described an inner network which he regarded as equivalent to the endocellular network of Donaggio. He observed that the outer network of fibrils is very evident in the dendritic processes and that the fibrils anastomose with each other and are connected with the inner network. Bielschowsky questioned this connection between the two networks and claimed, in agreement with Economo, that the inner was an artifact and was caused by the impregnation of a protoplasmic reticulum. In his latest work Schaffer still claims that his preparation showed the presence of the two networks, but because the endocellular one has the staining characteristics which Economo and Bielschowsky ascribe to the protoplasmic reticulum, and because of its behavior in the degenerating cell, he agrees with the writers just mentioned in the observation that this is not a true neurofibril structure.

We find that the pyramidal cells of the cortex, the Purkinje cells, and the large anterior horn cells, which we have studied by Bielschowsky's method, show the epicellular network very distinctly

(Plate LXIII, Fig. 5). The fibrils are seen in the dendrites as parallel strands closely approximated and freely anastomosing with one another. This anastomosis may be due to the blending or shrinking together which Economo claims gives rise to this appearance in tissues treated by Cajal's method, but in sections in which the dendrite is characteristically swollen one can often see the fibrils separated by a considerable space from one another and also having branches which unite them. The epicellular fibrils from the dendrites can be traced into the cell-body where they form a superficial network (Plate LXIII, Fig. 6). Schaffer has pointed out that there is a distinct network of strands of still finer calibre occupying the greater part of the cell-body within the endocellular network. Around the nucleus this network appears to have more numerous strands and finer meshes so that it has a denser appearance. This denser network forms the perinuclear network. We have observed the fibrils from the epicellular net of the dendrites passing over and around the nucleus, apparently not forming any connection with the perinuclear net. We have also observed the fibrils from the dendrites passing directly into the perinuclear net and joining the endocellular neurofibrils. The neurofibrils in the axone usually form a single black strand. Frequently they can be seen entering the cell-body, spreading out in funnel-fashion, and merging into the perinuclear network. We have not been able to corroborate Economo's description of the color characteristic of the endocellular network. The epicellular fibrils differ from the endocellular in being stouter and more deeply stained, also more permanent. It would seem that the endocellular network was the first to show evidences of degeneration (Plate LXIII, Fig. 7; Plate LXIV, Fig. 8). The fibrils become granular and often disappear leaving a granular detritus. The perinuclear network remains for a considerable period of time, but even after the cell has become a large, swollen, balloon-like structure, and after the nucleus has become either degenerated or has entirely disappeared, the dendrites may still remain and show the presence of fibrils (Plate LXIV, Fig. 9). The last of all the cell structures to disappear is the axone with its fibrils. Schaffer argued originally that the early disappearance (Plate LXIV, Fig. 10) of the endocellular neurofibrils proved that

they were not functionally an essential part of the cell, but that the interfibrillary substance must be the conducting element.

According to his latest views, Karl Schaffer is inclined to believe that the morphological endocellular network is connected with the epicellular net, but since it disappears very early in cells which still retain fibrils in the dendrites and in the axone, it does not represent a true neurofibril structure. This conclusion of Schaffer's does not seem wholly warranted. It is nothing unusual to find a structure which is more vulnerable in one part than in another, and for this reason alone we are not compelled to assume that there is any structural difference between these parts. In a nerve which has been cut the degeneration of the fibrils in the proximal part proceeds to Ranvier's node, and yet no one for this reason would assume that there is any difference in the structure of the axone fibrils at any part of their course. If Schaffer's contentions were correct, we should be compelled to assume that the fibrils and the dendrites of the axone were different in character, because the former disappear in the degenerating cell while the latter remain.

The most important conclusions to be drawn from a study of the fibrils of the ganglion cells of amaurotic idiocy are (1) that the endocellular network is most susceptible to the degenerative process, and since there is good reason to believe that the cells preserve their function in the earlier stage of degeneration, these fibrils cannot be the conducting elements, and (2) we must note the remarkable independence of the axone and its fibrils from the rest of the cell. This is shown not only by the persistence of the axone near the cell, but by the absence of degenerated fibers in the cord.

Schaffer was the first to describe the presence in the cortex of round structureless cells with the nucleus rich in chromatin. He noted that they were found in fewer numbers in the white matter directly under the cortex. He thought them glia cells undergoing retrogressive metamorphosis. In his latest article he refers to Eisarth's studies on "The Histology of the Human Neuroglia," in which such cells are described as being characteristic of changes in the glia in the degenerative psychoses of early life. We have noticed these peculiar cells in large numbers both in the cerebral and in the cerebellar cortex (Plate LXV, Fig. 11). They are also

fairly abundant in the subcortical white matter. Their cytoplasm, however, is not structureless as Shaffer thought, but when the cells are stained with scarlet R. they are found to be filled with fat droplets. The nuclei vary in size from those of the normal glia cells to one considerably smaller and more deeply stained, at least in those cells which are filled with fat. These cells frequently occur in nests and can often be seen not only in the vicinity of the degenerating ganglion cells, but they also actually invade them (Plate LXV, Fig. 12). They appear to play the rôle of neuronophagocytes. These cells, it is interesting to observe, are also found in considerable numbers in the perivascular spaces of the vessels of the cortex Plate LXV, Fig. 13) and also in the subpial space over the surface of the cortex (Plate LXV, Fig. 14).[7]

There can be no doubt that these peculiar cells, which we agree with Schaffer in interpreting as altered glia cells, bear a striking resemblance to the granular cell which is found in brain tissue bordering upon an irritating lesion. In the brain of the amaurotic idiot the presence of these granular cells is explained by the degeneration of the ganglion cell acting as an irritant to the surrounding tissue. There is no reason to claim that the morbid process is at all inflammatory in character.

The glia shows an increase of fiber growth in the cortex and in the antero-lateral ground bundle and direct pyramidal tract region of the cord. This growth may be partly of a substantive nature which is due to the degeneration of the cortical ganglion cells and partly to the inhibited development of the motor paths in the cord. Possibly some of this growth is due to the same exciting cause which is responsible for the process of degeneration.

In several previous publications Sachs called attention to the striking absence of the degeneration of the white fibers in the brain and spinal cord. In the present research this same fact has been observed. There is a twofold reason for this: first, as has been shown by Schaffer and by us, the axone remains apparently unaffected by the disease process, and, secondly, we must suppose that some, if not many, of the cells retain some trophic influence

[7] We are indebted to Dr. F. S. Mandlebaum, Pathologist of Mount Sinai Hospital, New York, for the photographs reproduced in this article.

over the peripheral fibers in spite of the marked change in morphological structure. Such slight changes as have been noted by us and others in the pyramidal tracts are not due to a true degeneration, but are the expression of imperfect myelinization. As is well known, the fibers of the pyramidal tracts are the last to acquire their myelin sheaths; hence it is not surprising that they are less deeply stained than are the other spinal tracts at this early period of life.[8]

The attempt to interpret the pathological findings in amaurotic family idiocy has led to an apparent conflict of opinion regarding the origin of the disease. In previous publications one of us defended the theory of an arrest of development affecting the ganglion cells. The thought that the disease was due to an *agenesis corticalis* was abandoned a number of years ago, after Hirsch had found that it was not the gray matter of the cortex, but the gray matter of the entire central nervous system that was involved in this disease.

The theory of an arrest of development has to be given up since embryologists limit this term to the conception of an arrest due to the cessation of the normal morphological growth, whereas so far as we know the brain of the amaurotic idiot is morphologically normal at birth and for some time after. Others must abandon the idea that so strictly a family disease can be due to a definite infectious or toxic agent acting from without.

Amaurotic family idiocy is unique among congenital diseases because of the specific and pathognomonic change in the ganglion cells, and of the involvement of every part of the nervous system. The gray matter of the brain and spinal cord is morphologically well formed and, so far as we know, functionally normal up to the age

[8] Through the courtesy of Dr. Spielmeyer we have been privileged to study some of the sections from his case of the juvenile form of amaurotic idiocy. While there is a superficial resemblance between the cell changes in these two varieties of amaurotic idiocy, the differences are still more striking. In the juvenile form, the disease process is not as universal as in the infantile form; there are many relatively normal cells, the cell contours are not completely obliterated and we fail to find the typical balloon-like enlargement of the cell bodies and the swelling of the dendrites which are so characteristic of the cells in the Tay-Sachs type.

of four or six months. Then there gradually occurs a degeneration of all the ganglion cells and a consequent loss of function. The tendency to this degeneration must be born with the child and must reside in the germ plasm. Unfortunately, our knowledge of the laws of heredity as yet furnishes us with no idea as to the nature of this inherited taint. It is, however, not sufficient merely to predicate an impairment of the germ plasm; this would not explain the normal development of the nervous system through the early months of infancy and its degeneration a few months later. We must suppose that at about the fourth or sixth month some endogenous factor, related to the metabolic processes of the body, intervenes and affects the cells which have inherited a lessened resistance to this agent. The factor may be one which is present in all children but does not affect the nervous system of those who are not born with this inherited weakness.

Hirsch supposed that the change was due to an infection conveyed through the mother's milk, but his theory has been positively disproved by the fact that several of the children described by Sachs and Schaffer have not been nursed by their own mothers, and inasmuch as several children in the same family have been raised by different nurses, this theory falls absolutely to the ground. Poynton, Parson and Holmes, who have opposed Sachs's original idea of an arrest of development, are convinced that "The disease is due to some inherent bio-chemical property of the protoplasm of the cells." After all, the "bio-chemical property" is "inherent" in the cell, which is equivalent to saying that there is something in the cell born with it and not acquired by it. An additional factor must be assumed to explain the late appearance and the specificity of the degeneration.

EXPLANATION OF PLATES.

PLATE LXI.

FIG. 1. Pyramidal cells from the cortex. Balloon-like swelling of body and basal dendrites, displacement of nucleus to base of apical dendrite, degeneration and disappearance of Nissl substance. × 560.

FIG. 2. Anterior horn, spinal cell. Enlargement, balloon-like (?), degeneration, displacement of nucleus, remains of Nissl substance. × 280.

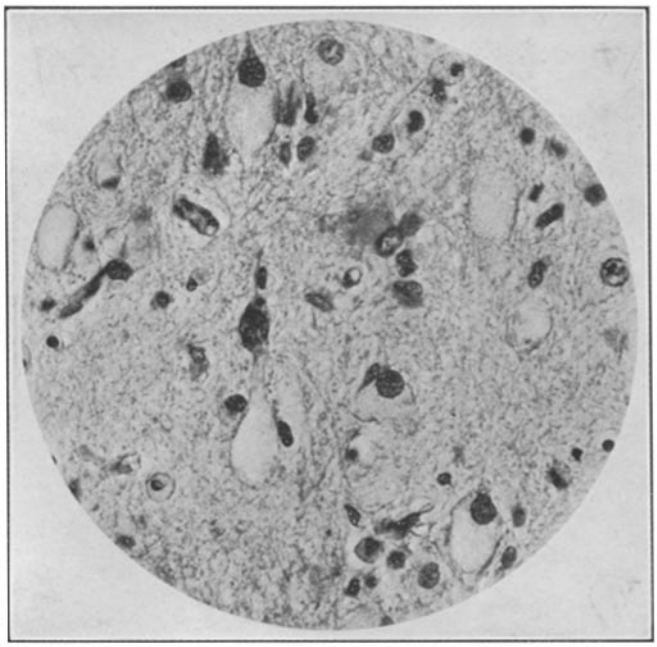


FIG. 1.

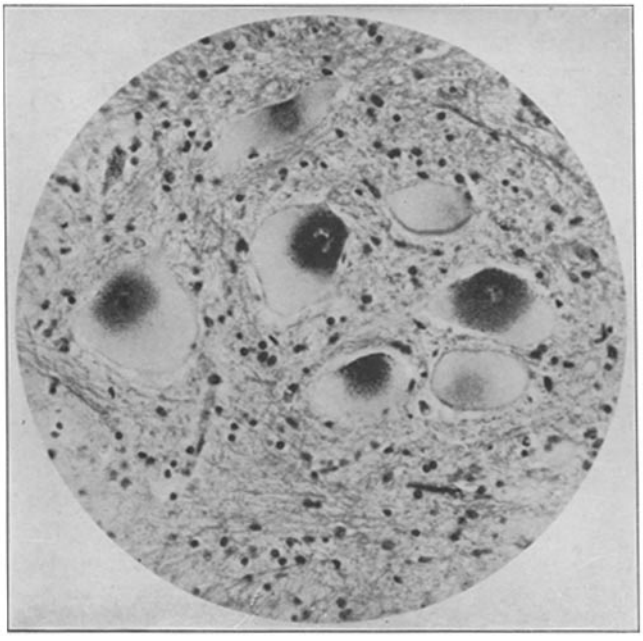


FIG. 2.

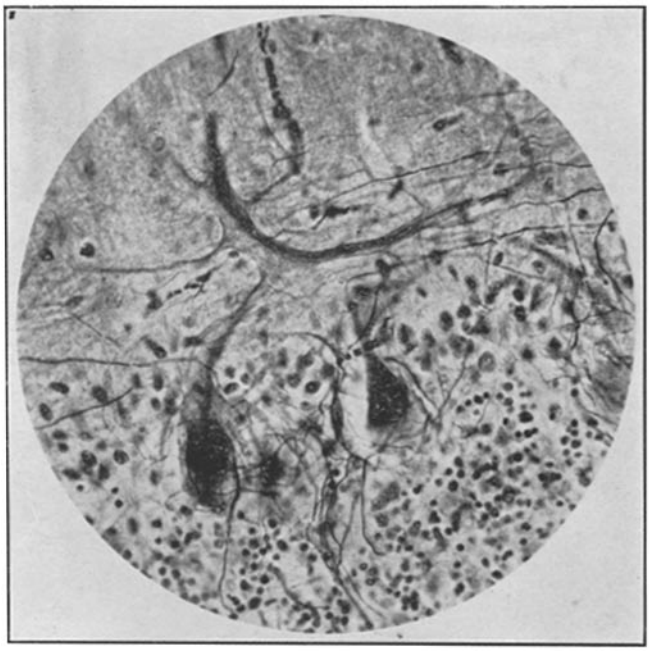
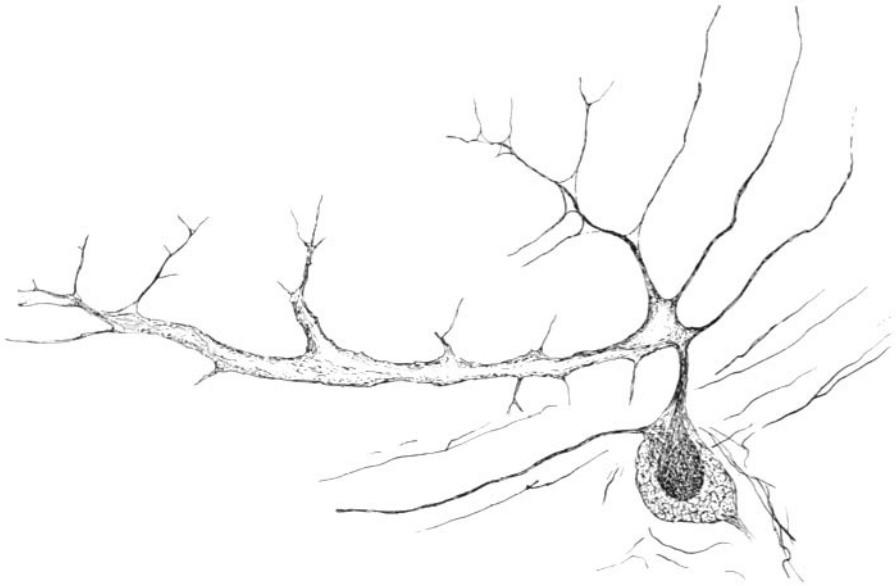


FIG. 3.



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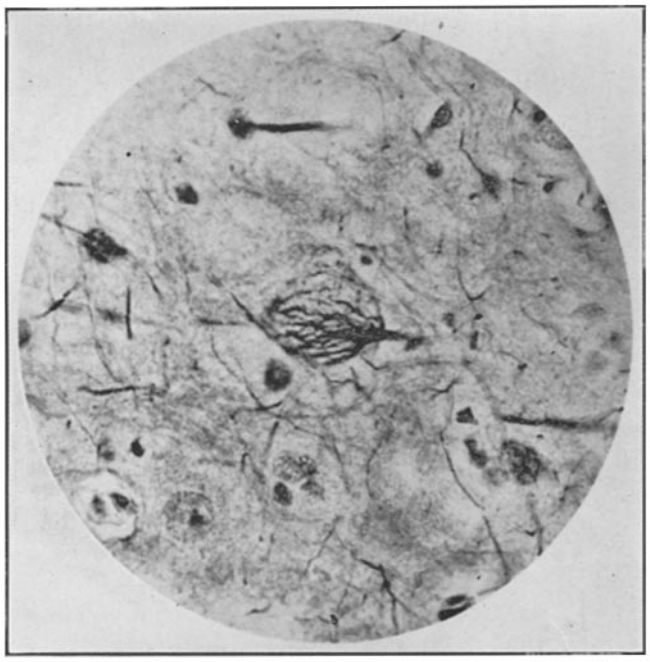


FIG. 5.

FIG. 6.

FIG. 7.

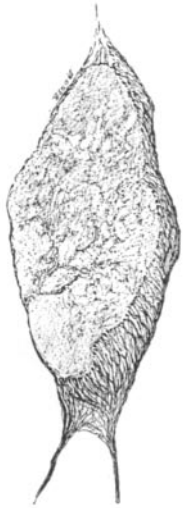


FIG. 8.

FIG. 9.

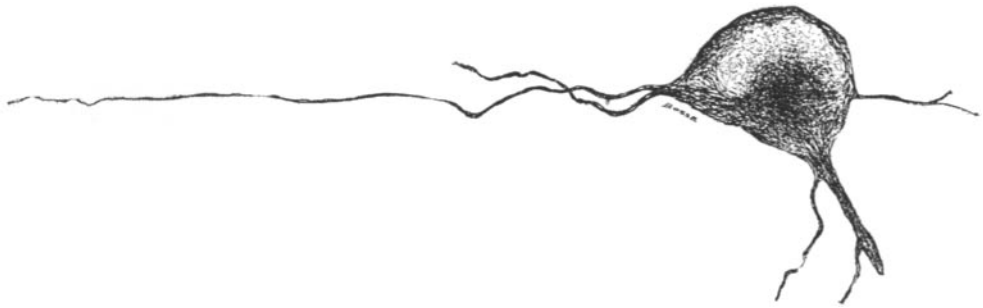
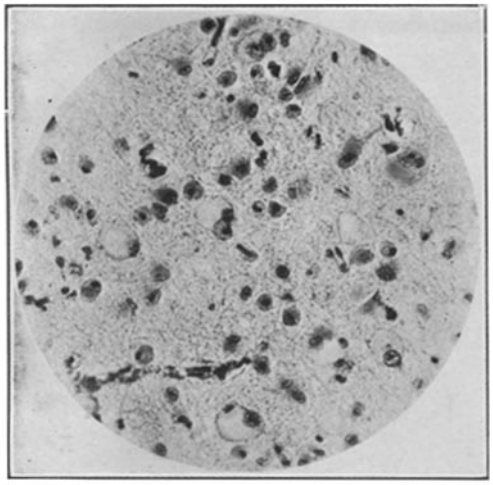


FIG. 10.



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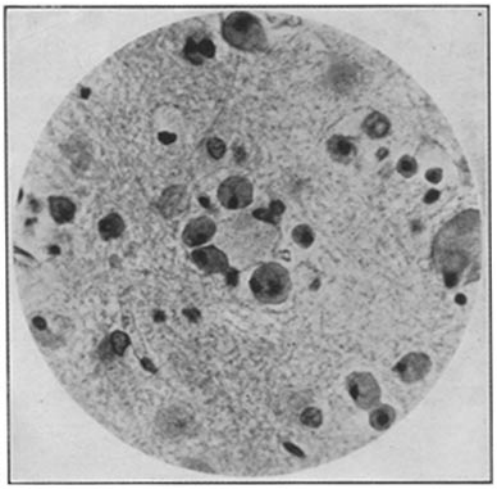

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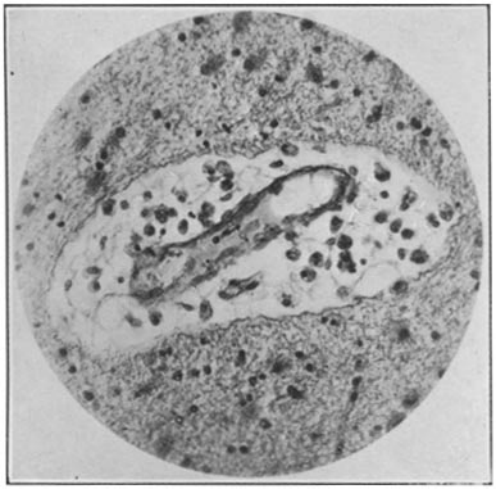

FIG. 13.

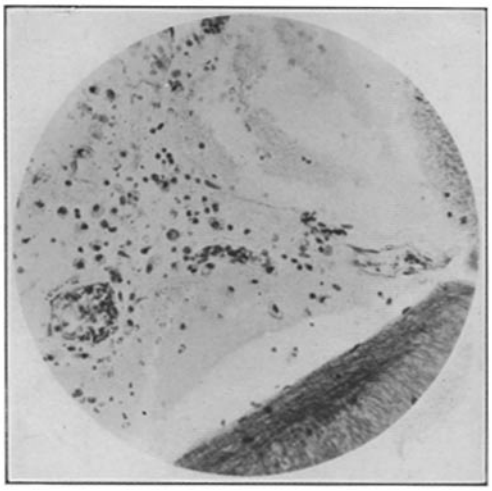

FIG. 14.

PLATE LXII.

FIG. 3. Purkinje cell showing very marked swelling of dendrite with remains of neurofibrils and their displacement. × 320.

FIG. 4. Purkinje cell showing very marked swelling of the dendrite and the remains of endocellular and perinuclear network (Bielschowsky).

PLATE LXIII.

FIG. 5. A large cortical cell showing the anastomosing epicellular network.

FIG. 6. Pyramidal cell of the cortex showing the remains of the cellular network (Bielschowsky).

FIG. 7. Same cell as Fig. 8. Different focus, showing changes in the endocellular network which are the result of degenerative changes (Bielschowsky).

PLATE LXIV.

FIG. 8. Spinal cord. Longitudinal section showing the epicellular network upon the surface of large anterior horn cell (Bielschowsky). Same cell as shown in Fig. 7.

FIG. 9. Purkinje cell showing disintegration of endocellular network, swelling of the dendrites and the peripheral position which the fibrillae assume in these swellings.

FIG. 10. Large pyramidal cell in cortex showing beginning degeneration of endocellular network. Cajal method.

PLATE LXV.

FIG. 11. Brain cortex showing degenerating ganglion cells and numerous granular cells. × 250.

FIG. 12. Granular cells in the brain cortex. The central group shows them in the rôle of phagocytes around a degenerated ganglion cell. × 500.

FIG. 13. Blood vessel in the cortex showing the granular cells in the so-called perivascular lymph space. They also can be noted in the surrounding brain substance. × 250.

FIG. 14. The pia over the cerebellum showing the presence of the granular cells. × 250.