U.M.

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Report

of

Committee on Examination

This is to certify that we the undersigned, as a committee of the Graduate School, have given Charles Edward Nixon final oral examination for the degree of Master of Science/In Neurology. We recommend that the degree of Master of Science/In Neurology be conferred upon the candidate.

Minneapolis, Minnesota

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C. M. Jackson

THE UNIVERSITY OF MINNESOTA

GRADUATE SCHOOL

Report

of

Committee on Thesis

The undersigned, acting as a Committee of the Graduate School, have read the accompanying thesis submitted by Charles Edward Nixon for the degree of Master of Science in Neurology. They approve it as a thesis meeting the requirements of the Graduate School of the University of Minnesota, and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science in Neurology.

H. E. Robertson
Chairman

E. T. Bell.

J. B. Johnston

May 29 1918 M. D. Sheldon

H. M. Watterson

THE PATHOGENESIS OF THE LESIONS OF THE NERVOUS SYSTEM FOUND IN CASES OF PERNICIOUS ANEMIA

A Thesis submitted to the
Faculty of the Graduate School of
the University of Minnesota

by

CHARLES EDWARD NIXON

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for the degree of

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THE PATHOGENESIS OF THE LESIONS OF THE NERVOUS SYSTEM FOUND IN CASES OF PERNICIOUS ANEMIA.

Charles E. Nixon, A.B., M.D., Teaching Fellow in Nervous and Mental Diseases, The Medical School, University of Minnesota.

Since Lichtenstern and Lichtheim noted changes occurring in the spinal cord in cases of pernicious anemia many observers have offered their explanation of the mechanism by which these lesions are produced.

That the blood picture of this disease is produced by a toxin there is fairly general agreement; in summarizing the theories regarding the genesis of pernicious anemia Squire mentions:-

(1) Splenic disturbances.

(2) A general disturbance of the lipoid mechanisms and functions of the body; thus the liberation of hemolytically active substances, as oleic acid.

(3) Gastro-intestinal disturbances leading to the distruction of sufficient mucosa to allow undigested proteins to leak through into the blood stream where their digestion (parenteral) liberates protein poison.

While the majority of neuropathologists believe that the lesions of the nervous system are caused by a toxin they are not agreed as to the way the toxin acts. Seyderhelm has recently made an interesting contribution to this phase of the subject. He was able to break the toxin "Oestrin" up into various fractions. The toxin was both hemolytic and neurotoxic; he found that the "blood poison" acts (both as a hemolytic and toxic agent) only by parenteral introduction.

It is not without interest to note that the suggestion has been made that anemia may sometimes be of central origin. Herrick gives a number of cases reports where pernicious anemia or severe anemia followed nervous shock. Pokrowski found changes in the cerebellum,

fourth ventricle and medulla, and was led to conclude "that the findings in the central nervous system must have had an influence, if not the sole influence in the production of the anemia." Schuele also referred to the possibility of the anemia being of neurogenic origin. Among suggestions as to relationship Langdon says "Does the impaired enervation at times lead to morbid functioning in the blood forming or blood destroying organs?"

The various theories that have been advanced to explain the lesions found in the cord and brain in pernicious anemia may be summarized as follows:-

(1) Hemorrhagic foci- it being supposed that numerous small extravasations of blood occur causing secondary degeneration.

(2) Primary vascular changes - consisting in thickening of the vessel wall, exudation around the vessel or thrombosis; through coalescence of these perivascular areas a pseudo-systemic disease is produced.

(3) Lymph stasis:- the dilated perivascular lymph spaces and the spaces of Obersteiner were thought by Schmaus to be the primary factor in the degeneration. Through the lymph stasis malnutrition or accumulation of toxins initiated the nerve changes.

(4) Nerve cell degeneration:- changes found in the gray matter, especially in the anterior horn cells and the cells of Clark's column have been supposed to be the primary cause of the degeneration in the white matter.

(5) Myelitis:- the marked degeneration with the picture of an inflammatory process presented in some cords has suggested the theory that the condition may be a myelitis with secondary degeneration.

(6) Anemia per se - i.e. the thickened vessel walls are supposed to produce degeneration through malnutrition because of the poor blood supply; apart from this the theory has been advanced that the blood condition itself is the cause of the nervous lesions.

(7) Toxin:- the toxic theory is the one most widely accepted; whether there is one or more toxins and what the modus operandi of the toxin is in production the lesions in the nervous system are points still to be agreed upon.

Hemorrhages.

Minnich(1892) in a study of cases that showed a few or no symptoms referrable to the spinal cord found two groups of lesions in the cord. The first consists of capillary hemorrhages and their result,miliary sclerosis, analogous to retinal hemorrhages. The second group shows a peculiar sort of softening. He speaks of the influence of the general "hydrame" and the local edema, especially of the posterior column, resulting in lymphstasis. The "Hydropischen Quellung" which he noted in these cases is also observed in the course of many severe diseases, as sepsis.

Bullock (1892) found blood extravasations in the spinal meninges.

Birulja (1894) noted numerous small hemorrhages.

Teichmüller (1896) emphasizes the importance of hemorrhages and the etiology of the cord lesions. The course of the changes is as follows: 1. Hemorrhages. 2. Increase of the connective and glia tissues. 3. The characteristic degeneration of the nerve fibres.

v.Voss (1897) noted small hemorrhages in the gray matter most numerous in the lower and middle dorsal and middle cervical regions. However, he states, the hemorrhages in no way explain the origin of the system disease.

Clark (1897) observed hemorrhages in the gray substance; these varied in size and were distributed chiefly about the central parts of the gray matter, the posterior part of the anterior horns, and in the neighborhood of the commissure.

Billings (1901) and Russell, Batten and Collier (1900) found practically no hemorrhages or traces of former extravasations.

Reuling (1904) likewise found no hemorrhages.

Hemorrhages.

Brown, Langdon and Wolfstein (1901) observed no small multiple hemorrhagic foci. They do not agree with Nonne that the degeneration is due to ascending and descending degenerations following multiple areas of softening of inflammatory or hemorrhagic character, which several areas become confluent and give the picture of a system disease.

Homen (1903) regarded the hemorrhages which he often found as caused by the same toxin that caused the degeneration.

Siemerling (1909) noted several hemorrhages in the region of vessels; these he believes to be agonal and not of significance in the production of the picture.

Pfeiffer (1915) found no hemorrhages.

Toxin as Etiological Factor.

The theory that a toxin was the primary factor in the production of the cord lesions in pernicious anemia was first promulgated by Lichtheim.

Burr (1894) favored the toxic theory and believed both the anemia and cord lesions were due to a common cause.

Nonne (1895) suggested that the anemia and cord changes were not dependent upon one another, but upon a toxin acting more upon the blood or cord in individual cases.

Petren (1896) also believed that the cord lesions were due to a toxin.

Russell, Batten and Collier (1900) state that the toxic body that they believed to be present may be supposed to produce a parenchymatous degeneration by its action on the nerve elements of the spinal cord.

Adami (1900) advances the theory that many of the sclerotic processes of the body are due to acute and chronic infections through the pressure in the tissues by bacteria or bacterial poisons which may be derived from the intestines.

Billings (1902) says "The fact that the brunt of the lesion occurs in that part of the tracts involved fartherest removed from the trophic centers, where the nerve fibre is least protected by its nutritive cell, is evidence of a toxic cause."

J. M. Clarke (1904) thought that the apparent relation to vessels might possibly indicate the route of conveyance of a toxin.

Reuling (1904) suggests that there is probably more than one toxin in pernicious anemia, one having a predilection for causing degenerative changes in the red blood cells, while the other seems to have a special affinity for the spinal cord fibres.

Siemerling (1909) thought the etiological factor was probably a toxin.

Toxic

Gordon (1909) thought that the poison, if it is one, does not necessarily follow the route of the blood vessels as the later are frequently found in tact, or very slightly altered. According to him it follows the route of the nerve fibres within the cord without strict regard, however, to the neurone systems. "The white matter of the cord is therefore the tissue of predilection in pernicious anemia." That toxins spread to the cord directly through nerve fibres is a well established factm as illustrated by tetnus.

White (1910) regarded a toxin as the etiological factor and stated that it may be a toxin which produces hemolysis or it may be one of the results of hemolysis.

Henneberg ( ) thinks that the pathologic anatomic process consists ~~primarily~~ apparently in a primary acute degeneration ofthe medullary sheaths; chiefly disseminated small areas caused by the presence of a toxin. The toxin may be conveyed by the vessels without at first causing vessel changes that are demonstrable, then later vascular changes are seen.

Lube (1912) concludes that "the degenerations are not the result of the blood changes, but of the toxin that causes the blood picture. The toxin is carried by the blood and has an affinity for the white substance of the central nervous system. However this toxin does not always directly involve the nervous substance, but may cause a degeneration through vascular changes.

Bramwell (1915) makes the following classification in regard to the action of the toxin. 1. Toxin acts entirely on the blood. 2. It acts chiefly on the cord. 3. The anemia precedes the cord symptoms. 4. The toxin involves the blood and cord at the same time.

Toxic

Pfeiffer (1915) states that "The changes affecting the nerve cells in the brain and spinal cord simulated the alterations of the neuronic elements which are encountered in states of chronic and subacute toxemia and obviously resulted from the action of the same toxic agent responsible for the degenerative changes in the white matter."

Blood Vessels and Lymph Spaces.

Birjula (1894) observed many lymphoid cells in the pericellular lymph spaces of the cortical cells.

Burr (1894) rejects the vascular theory because of the rarity with which he found changes in the blood vessels.

Nonne (1895) noted wide lymph spaces packed with products of degeneration. The small areas of acute degeneration were always in direct relationship to a vessel. He also noted the relation of areas to vessels which show terminal periarteritis and when such is the case the surrounding lymph spaces are markedly widened.

Bowman (1894) states" the blood vessels are found to be affected in proportion to the degree of interstitial change, being apparently healthy in areas where the nerve elements are solely or chiefly involved and presenting very obvious changes in the more densely degenerated parts. The earliest alteration consists in a proliferation of a nuclei in the sheaths of the smaller arterioles while in a later stage the sheaths is crammed with cells, the lumen of the vessel re remaining normal.

Riggs (1896) found that the arteries showed thickening of the endotheli um, and here and there an inward projecting growth of new connective tissue. He believed scleroses were of vascular origin.

Clarke (1897) found the walls of the smaller vessels to be much thickened and very many showed hyaline change.

Bastianelli (1897) found no alterations of the blood vessels in the places of beginning sclerosis. He refutes the view of Minnich and Nonne that the primary trouble is in the vessel.

v.Voss (1897) observed that sometimes there were diseased vessels in normal tissue. A serial section of a area showed vascular changes and nerve degeneration to be progressing together. He does not regard vascular changes as the primary cause of degeneration.

Blood Vessels and Lymph Spaces.

Russell (1898) agrees with v. Voss that the areas of degeneration are often seen in the neighborhood of perfectly healthy vessels, while on the other hand vessels with marked changes in the walls may be seen in parts of the cord free from degeneration, and further, small areas of degeneration occur with no vessel of any kind in their immediate neighborhood.

Jacob and Moxter (1899) found vascular changes in the healthy as well as the diseased areas. Sometimes ~~in areas~~ there were normal vessels passing through degenerated areas and he concludes therefore that the vascular alterations cannot be the primary cause of the lesions but are coordinate with the nerve lesions and produced by the same cause.

Henneberg (1899) noted high grade alterations of the vessels of the cord and pia.

Russell, BAtten and Collier (1900) noted engorgement of the vessels in the affected areas; the walls were thickened but there was no actual thrombosis. In unaffected areas however, the vessels were neither engorged nor thickened.

~~Billings~~ (1901)
Hughes and Spiller (1901) found both the intra and extramedullar blood vessels to have markedly thickened walls; the small intramedullary vessels were thickened not only where the sclerosis is dense but also where the tissue of the cord is normal. The thickening implicates all the coats.

"It must be therefore that vascular changes may aid in the development of the sclerotic tissue, but degeneration of the nervous tissue may begin before any thickening of the vessel walls is detected; it seems not improbable that some toxic substance in the circulation is the cause of the formation of the sclerosis ~~it~~ within the white matter and of the alteration of the vessel walls.

Blood Vessels and Lymph Spaces.

Brown, Langdon and Wolfstein (1901) found no marked vascular changes; in certain places the walls of the smaller vessels showed hyaline changes, but no evidence of inflammation.

Putnam and Taylor (1901) found insignificant vessel changes.

Schmaus (1901) regards lymph stasis as the primary pathologic change, this leading to a widening of the glia meshes. In the perivascular lymph sheaths there is often found a homogenous or granular substance.

Pickett (1902) noted some thickening of the vessel walls but the vascular changes were not confined to any region or tract.

Taylor and Waterman (1903) noted that the blood vessels in the cord were for the most part distended with blood, but beyond a slight thickening of the walls were normal.

Homen (1903) states that the vessels are clearly involved, especially in the older parts; in the dilated perivascular spaces there are detritus bodies and often leucocytes and fat granule cells. Not seldom there is thickening of the perivascular glia tissue. He believes that the vascular and spinal cord alterations are coordinate.

Clarke (1904) thinks the vessel changes are secondary because they are not evident in regions where the nerve degeneration is slight (and recent) and in areas of the cord where the only evidence of the disease lies in the presence of a few scattered degenerated fibres. The appearances in some instances suggest some relation to the vessels as the degeneration often seems to begin in the terminal distribution of the small arteries that run into the cord along the septum between the columns of Goll and the posterior external column. In some instances the increased connective tissue may appear to spread directly from the vessel walls. "These changes seem to me to be entirely secondary to the parenchymatous degeneration of the nerve fibres?

Blood Vessels and Lymph Spaces.

Camac and Milne (1910) found thrombosis of several of the smaller capillaries and veins most noticeable just above where the cavity was largest. The mechanical effusion of fluid with separation of the tissue may have been the cause of the destruction of the structures in the gray matter.

Thompson (1911) saw no evidence that the degeneration was due to vascular changes.

Henneberg (1912) states that in the initial stage, especially in the posterior columns, there is sometime a definite relation of the lesions to larger vessels. These areas lie at the division of the arteries, especially the artery interfuniculares. The vessels in the early stage may show little change. In early cases lymph vessel alterations are also lacking.

There is too great a regularity in the localization of the lesions for them to be of strictly vascular origin; further the exemption of the gray matter is against a purely vascular origin. If one would base the changes on a primary vascular condition they must be able to prove that in many cases the sphere of the posterior spinal artery is alone involved.

Pfeiffer (1915) found the capillaries of the gray matter often distended. He believed that the vascular changes in his cases of no primary importance.

Woltman (1918) believes that "the appearance of these plaques, not only around the blood vessels but also around some of the larger pyramidal cells, seems additional evidence that lymph stasis is an important factor in the production of these foci."

The Blood Supply.

The relation of the lesions to the arterial distribution in the cord. has been a favorite field of speculation for most of the writers on this subject. Various theories have been put forth as to the way the blood supply influenced the formation of the sclerotic areas. It has been explained on the assumption of increased blood supply thereby bringing more of the toxin, of a poorer blood supply causing a locus minoris resistentiae, through a hyaline exudate around the vessels causing a degeneration, through changes in the vessel walls themselves thus causing degeneration directly or by making the tissue more susceptible to the toxin and, finally, thrombosis of the terminal arteries.

Nonne (1895) believed the areas were especially in the region of the a. a. reticulares post. and a. a. interfuniculares, and that the spinal cord changes came about through a softening caused by a toxin circulating in the blood stream. He agrees with Minnich that the lesions are in the region of the terminal branches of the small vessels of the periphery.

v. Voss (1897) observed that the destruction of the nervous tissue was mostly in the region of the connective tissue septa and the blood vessels contained in the same.

Boedeker and Julisburger (1898) noted early there were circumscribed areas in the region of the instreaming septum in relation to branches of vessels. In some places there were edematous fibers arranged along the septum. They also found small acute areas giving the picture of a subacute myelitic process standing in close relation to the vessels.

Jacob and Moxter (1899) state that the process nearly always begins with the formation of perivascular and periseptal areas, which partly through confluence and partly through production of secondary degeneration finally produces "strangförmige" degeneration.

Blood Supply

Marburg (1900) noted myelomalecia like areas usually containing a blood vessel. In some of these areas the central-placed vessel is thickly bordered with fatty granule cells surrounded by a wide meshed, sieve like tissue containing many fat granule cells. He explains the fact of the preponderance of lesions in the cervical region by a better "supply" of toxin to these parts and also explains the involvement of the dorsal segments in a similar way.

Russell, Batten and Collier (1900) state "that the topographical distribution of the degeneration of the white matter of the cord depends on the vaacular distribution there seems to be little question. The blood supply of the cord is mainly from two sourses, the anterior median artery in the anterior median fissure and the peripheral arteries derived from the vessels of the pia. The former supply the anterior horns and the white matter bordering on them and the neck of the posterior horns including Clarke's column, while the latter supply nearly all the rest of the white matter.

The distribution of the lesions in the white matter is that of the peripheral vessels; the only part played by the vessels is in bringing the toxic material to the areas. " They do not believe that we can assume that the middle dorsal region is most involved because of less blood supply for the anatomical evidence rather indicated that the lower dorsal and lumbo sacral regions are least well supplied with blood.

Putnam and Taylor (1901) agree with Russell, Batten and Collier "that the peculiar and relatively constant distribution of the lesions in the cord depends upon the anatomical arrangement of the pial blood vessels, an idea first advanced for combined lesions by Marie." However, they believe those areas of the cord most efficiently supplied with blood under normal conditions are likely to suffer first under abnormal conditions.

Pickett (1902) quotes the doctrine of Marie that the ~~dorsal~~ late dorsolateral white matter is involved because of a less copious blood supply, but mentions Russell, Batten and Collier pointing to the paradox th that the cervical and upper dorsal regions are most involved and yet these are the more abundantly supplied with blood.

Church (1902) states that the "changes in the cord are in a sense mechanically located. That is, those portions of the cord which are less well supplied with blood are the first to suffer."

Homen (1903) noted the relation of the lesions to the septa and vessels and a predilection for the distribution of the arteriae interfuniculares and its divisions. The areas found early around a septum or vessel whose wall is thickened and whose perivascular lymph space is dilated sometimes reminds one of a "myelitic" lesion.

Camac and Milne (1910) observed that the destruction and cavity formation present in their ~~days~~ cases corresponded almost entirely to a branch of the anterior spinal artery.

Pfeiffer (1915) states "the anatomical data, however, do not seem to support the assumption ~~as most of the evidence at hand indicates~~ that the cervical and upper thoracic regions of the cord are less efficiently supplied with blood than other parts, as most of the evidence at hand indicates that the lower part of the dorsal as well as the lumbar and sacral regions of the cord, are not as well supplied with blood." ~~They~~ He also states that researches regarding the vascular ~~p~~topography of the spinal cord make the plausible vascular theory of Marie untenable.

Anemia.

Bowman (1894) rather "regards the anemia as the primary and probably the cause of the changes in the cord."

Goebel (1896) also looks upon the anemia as the causal factor in the production of the cord lesions.

Editorial J A M A (1913) states that the nerve cells of different classes show differences in the sensitiveness to anemia.

Bramwell (1910) and Cadwalader (1916) believe that the cord lesions to be independent of the anemia.

Changes in the Ganglia and Peripheral Plexuses.

Sassaki (1884) believes that the gastrointestinal form of pernicious anemia depends on the primary (i.e. not secondary to the anemia) atrophy of Meissner's and Auerback's plexuses.

Putnam (1891) found changes in the interveterbral ganglia which were examined in one case.

Meninges.

Jacob and Moxter (1889) found infiltration and vascular changes in the pia.

Bullock (1892) noted that the pai was cloudy over the vertex of the brain and markedly thickened in the cord.

Bowman (1894) found the pia free from change.

Herringham (1894) reports a case of "pachymeningitis hemorrhagic", as termed by some, in a case of pernicious anemia.

Thompson (1911) found the meninges to be normal.

Kauffman (1914) noted round cell infiltration of the pia.

Schröder (1914) found the pia thickened but not infiltrated.

The Nerve Fibre and Sheath. System Degeneration.

Bowmann (1894) states that in the earliest lesions the most obvious alteration is found in the nerve fibres themselves. The degenerative changes are for the most part not strictly limited to definite tracts of long fibres ?

Nonne (1895) observed that the intremedullary white substance was alone affected by the toxin.

Teichmüller (1899) believed the posterior columns to be involved because here was a locus minoris resistentiae against the degenerative process.

Dana (1899) states that it is the peripheral ends of the neurone which are especially affected and explains this as being due to the distance from the trophic center.

Jacob and Moxter (1899) observed that the degenerative area first approaches the triangular and then becomes "L" shaped. In their second case the lesions involved the intramedullary bundle of one or two neughboring upper sacral roots. There was not a localized lesion in the root entrance zone.

Billings (1901) states that the whole neurone is not involved.

Brown, Langdon and Wolfstein (1901) agree with Burr and others who consider the lesion as a primary system degeneration, i.e. primary as far as the cord is concerned and distinctly neuronic, but secondary etiologically to some condition superinduced by pernicious anemia.

Reuling (1904) thought the lesions were due to a diffuse degeneration affecting certain fibre columns.

J. M. Clarke (1904) states "These changes, though fairly regular and possible indicating thatthe fibres of the posterior columns which run the longest course are earliest degenerated, do not exactly map out special tracts, but are somewhat patchy in distribution, often varying at different levels for no obvious reasons.

Bennett

The Nerve Fibre and Sheath. System Degeneration.

Barrett (1911) found in the brain extreme reaction of the nerve fibres adjacent to the blood vessels.

Thompson (1911) states that the axis cylinder undergoes, as a rule, less rapid degeneration than the medullary sheath. It ultimately disappears.

Hassin (1917) sums up the spinal cord lesions as regressive changes in the nerve fibres and progressive ones in the glia. The pathological process is confined only to the long fibres which make up the tracts of Goll, Burdach, the spinocerebellar tracts (especially the direct ones) and the crossed pyramidal fibres. Early the fibres are "in a condition peculiar for peripheral neuritis."

"As the morbid changes found in subacute cord degeneration and peripheral neuritis are alike it would seem proper to characterize the changes in the former as central neuritis, because the central fibres exhibit changes peculiar to the latter." He refers to Meyer (1901) who introduced the term "central neuritis" and hinted at its possible occurrence in subacute cord degeneration and concludes "My present studies seem to sustain the correctness of Meyer's suggestion."

The Gray Matter.

Minnich (1892) found the gray matter to be normal except for a few hemorrhages.

Bulloch (1892) noted abundant hyaline in the gray substance. He thinks the hyaline material had exuded from the blood vessels and surrounded the nervous structure of the cord leading to their destruction. The ganglion cells were converted into granular masses sometimes, while others were represented by hyaline masses the shape of the original ganglion cells.

The greatest amount of hyaline was in the region of the blood vessels. The central mass so apparent, seems to have been derived from filling up the canal with hyaline which had exuded from the central arteries of the cord. He considers the previous condition of the blood vessels to be the prime factor. The composition may have been altered and some albuminoid product formed.

Bowman (1894) states that the ganglion cells and gray matter is generally normal.

Rothmann (1895) considered pernicious anemia of endogenous origin, conditioned through a primary disease of the gray substance. He concludes that in a great number of cases there is demonstrable disease of the gray substance and that a primary affection of the gray substance best explains the entire process of combined degeneration.

v. Voss (1897) noted that the ganglion cells were somewhat shrunken and the paracellular spaces widened in the upper lumbar region in one case.

Clarke (1897) found the changes in case II were almost confined to the gray substance. There were small areas in which the gray matter was partly disintergrated of sclerosed. The cells of the dorsal and cervical region were excessively pigmented and contained a number of coarse deeply staining granules arranged concentrically around the nucleus in the cell protoplasm.

The Gray Matter

Boedeker and Julisburger (1898) think that while the lesion is not primarily in the gray substance yet the latter cannot be said to remain free from alterations.

Scagliosi (1898) noted that the Nissl bodies had disintergated in nearly all of the pyramidal cells of the cortex. Chromatolysis of the anterior horn cells had occurred. He thinks these changes are due to a lack of oxygen.

Henneberg (1899) found the ganglion cells of the upper dorsal region to be diminished in number and partly sclerotic. The Marchi stain showed the anterior horn cells to be sometimes completely filled with black masses. There was a diminution of the cells in Clarke's column.

Jacob and Moxter (1899) did not find sufficient changes in the gray substance to explain degeneration.

Bastianelli (1895) (But after Rothman) disagrees with the endogenous theory of Rothman and others; the alterations in the gray substance were too few in his cases to explain the degeneration. "On the other hand the localization in the zone radicullaris merlia in the lower levels and Golls in the upper sections speaks for an exogenous origin of the degeneration.

Russell, Batten and Collier (1900) found the gray matter practically normal in their cases; no vascular changes were or degenerations were found.

Putnam and Taylor (1901) report practically no involvement of the gray matter.

Billings (1902) observed in one case that the cells of Clarke's nucleus were small and much decreased in number. The cells of the lateral horn showed disintergration of the Nissl bodies.

The Gray Matter.

Prebrajensky (1902) noted that the cells of the anterior horn were edematous and that chromatolysis, especially peripheral, had taken place. There was staining of the achromatic substancea and the contour of the nuclei was indistinct. In the cortical pyramidal cells stained by the Marchi method there was seen a great number of fine, black, round bodies found chiefly in the periphery of the cell; at times scattered throughout.

Clark (1904) found no important changes in the gray matter. The most common change here was an unusual amount of pigment in the anterior horn cells and the cells of Clarke's column.

Gordon (1909) found some destruction of cells in the cervical segment.

Bramwell (1910) states that many of the nerve cells of the anterior horn in the dorsal, lumbar, and cervical regions, and the cells in Clarke'S column were degenerated.

Barrett (1911) found that a number of pyramidal cells in the brain cortex showed the axonal type of cell change.

Pfeiffer (1915) states that a majority of the anterior horn cells showed no obvious alterations; in some of them, however, evidence of a degenerative process was present; a number of these cells appeared shrunken, elongated and stained more deeply than usual. Other cells were somewhat swollen, their nuclei eccentrically placed and chromatolytic changes were present. The alterations were more intense in the cells of the posterior horns. He does not agree with Rothmann and others that the alterations in the white matter are consequent to a primary disease of the gray, but thinks rather that the elements of the gray matter are affected simultaneously with, or subsequently to, those of the white substance with through the activity of some toxin.

Central Canal and Cavity Formation.

Although not a common finding definite cavity formation in the cord has been reported by several authors.

Bäumler (1887) found cavity formation extending from the upper cervical to the lower dorsal region involving the posterior horn; the pathogenesis was apparently a degeneration of a diffuse gliosis.

Henneberg (1899) reports two cases with cavity formation. The first was in the lower cervical region involving the anterior horn; the walls of the cavity showed no special structure; it was formed from the products of destruction in which "Körnchenzeller" and "Spinnenzellen" are found. The second was in the mid cervical region; it was a small frontally placed split formed by the central canal; there was also in the lower cervical and upper dorsal regions a widening of the canal. An increase in the ependymal glia was noted. The epithelial covering was lacking in the posterior wall in many sections. Individual sclerotic ganglion cells were found in the gray matter surrounding the central canal.

In Bullock's case (1892) there was a marked cavity formation extending anteriorly by a wide opening and also extending posteriorly and into the lateral cord. Below this in the dorsal region the cavity was more like a fissure and in the lower cord there were well defined hyaline masses in the region of the central canal with ill-defined cellular elements in its center.

Teichmuller (1896) noticed extensive involvement of the gray matter by an irregular cavity formation.

Pickett (1902) found the central canal somewhat dilated throughout.

Camac and Milme (1910) considered thrombosis as the cause of the cavity formation in a case reported by them. In this case the cavity occupied almost exclusively the gray matter.

Degenerative Products.

Minnich (1892) noted that the granule cells are found in greatest numbers in association with the "Lücken" and believes that they have to do not only with the resorption of the hyaline particles, but also with that of the unaltered myelin and that probably these mobile cells are recruted out of the earlier fixed cells of the glia network.

v. Voss (1897) observed fat granule cells and looked upon them as resulting from a granular destruction products of the nerve substance

Boedeker and Juliusberger (1896) noted staff like structures in the Marchi specimens associated with the anterior horn cells.

Margurg (1900) found peculiar cells of cyst like character in the meshes of the sieve like fields, especially in the cervical regions these when stained by Van Gieson present a pale violet substance with the nucleus either central or excentric and staining rather intensively. These may be "Fettkörnchenzellen" but are more epitheloid in character.

"Spinnenzellen " were found in conjunction with "Gitterzellen" seemingly indicating that the Gitterzeller are the mother cells of the Spinnenzellen. The glia processes were swollen.

Putnam and Taylor (1901) speak of the "small tendency of the neurolgia to proliferate."

Henneberg (in Lewandowsky) noted that in some cases there was a swelling of the glia protoplasm which takes on a Qgitterformige" structure and forms free granule cells; there was also an increase of large pale nuclei, formation of protoplasmic "spinnenzellen" and formation of glia fibrils.

Barrett (1911) found,in the brain a tendency to group arraggement of the neurolgia and forms showing progressive types of reaction were common. Rod cells were frequently seen.

Degenerative Products.

Pfeiffer (1915) With the Marchi stain found fat droplets of various sizes and shapes lying in the peri

The cord showed "small focal disintergrations of the myelin and an accumulation of the eiptheloid cells actively phagocytic for the fatty products of the disintergration; around the area the neurolgia showed progressive reaction changes.

Pfeiffer (1915) with the Marchi stain found fat droplets of various sizes and shapes lying in the perivascular spaces. These were distributed irregularly. He found large proliferating glia cells constructing a thick net work between the disintergrating nerve fibres. Cresent shaped "Körnchenzellen " were especially numerous along borders of the glia network where products of degeneration are abundant.'

There were many scavenger cells lying within the meshwork wurrounding the blood vessels. The neurolgia tissue was increased. Progressive neurolgia changes had occurred in the vicinity of the degenerating ganglion cells, the intensity of the glia proliferations apparently corresponding to the degree of the cellular alterations.

Hassin (1917)"The axones were frequently broken up into smaller fragments which were inclosed within various gliogenous formations, as, myelophags, granular bodies, or myelin globules." The cellular elements of the glia tissue appeared unusually rich in protoplasm which was frequently granular and vacuolated.

Other Diseases Giving Similar Cord Changes.

Many conditions have been reported as giving cord changes similar to those found in pernicious anemia; among these may be mentioned diabetes, ergotismus, pellagra, diphtheria, melaena, carcinoma, nephritis, malaria, Addison's disease, tuberculosis, syphilis, typhoid, influenza, scarlet fever, chronic jaundice, chronic alcoholism, leukemia, bothriocephalus, tetanus, leprosy, and the metallic poisons.

Experimental.

Considerable work has been done in the endeavor to produce either the blood and cord picture, or the cord changes alone, found in pernicious anemia. Mott found that very small amounts of abrin or ricin will cause marked change in the appearance of the nerve cells when injected into animals; the Nissl bodies disappear, the cells are stained uniformely and show a fine colored dust all through the protoplasm and cell processes. "All the nerve cells are affected and the cause of these alterations would indicate a changed condition of the blood and lymph rather than a selective influence of the cells for the poison."

Edinger found that rats poisoned with pyrodin showed degeneration with the Marchi method only in the posterior roots if they were kept at rest, but iff made to do hard work then the posterior columns and the peripheral parts of the antero-lateral columns showed definite changes.

Shimazono quotes Bignami and Dionisi as having found in pyrodin dogs hydropic changes in the cord such as Minnich described in pernicious anemia.

Types of Lesions

Minnich (1892) reported a symmetrical degeneration of a part of Goll's column and a patchy degeneration in the middle root zones.

Bowman (1894) states that the minute changes suggest that the process is rather of a parenchymatous than an interstitial character, at least primarily.

Boedeker and Julisburger (1898) notes two distinct histological pictures. (1) The acute degenerative process in the nerve fibres. (2) The reaction on the part of the connective tissue in the form of sclerosis. "The clearly symmetrical sclerosis in the region of the posterior columns makes one think that here another type of degeneration of the nerve fibres had occurred - viz a primary pure atrophy (without adema) with reactive connective tissue proliferation. However in the direct neighborhood of the posterior columns sclerosis, indeed within the tissue of the latter itself was found acute "Quellungsherde " so that probably there not two processes (i.e. one with and one without edema.)" Also against two processes is the fact that in the lateral and anterior columns there is a more or less outspoken reaction of the connective tissue so they believe it is possible that if the duration of the disease were longer these areas might show as symmetrical completely sclerosed areas.

Jacob and Moxter (1899) noted three types of alteration in the white substance of the cord. (1) Pure "strangformige". (2) Pure "herdformige". (3) Mixed "herd" and "strangformige".

Russell, Batten and Collier (1900) state "there were obviously two distince processes at work in relation to the alteration found in the spinal cord in these cases.

(1) A focal destructive lesion. The earliest process consists in a swe ling of the medullary sheaths, the axis cylinder remains, apparently, unaltered. There next occurs a fatty degeneration of the

Types of Lesions.

sheath and this in turn is absorbed and at the same time the axis cylinders disappear, a space being thus formed surrounded by the connective tissue of the cord.

(2) A system lesion. The long tracts of the cord exhibit a degeneration similar to that found after transverse lesions of the cord, that is, there is degeneration of the medullary sheaths and axis cylinders and a gradual replacement by connective tissue giving rise to definite sclerosis.

THEY found these processes often to be merged into one another so closely that it was impossible to definitely separate them.

Putnam and Taylor (1901) refer to the characteristic degeneration consisting of a vacuolation with slight neurolgia proliferation. The degeneration occurs in discrete areas, varying from segment to segment and does not occur in the same manner in any other condition. This vacuolated appearance is no doubt to be explained by a rapidity of the degenerative process. The excessive number of fatty cells furthermore bears out this supposition.

Billings (1901) states that two processes are often seen side by side; the one apparently chronic with a tendency to neurolgia proliferation; the other, acute and sometimes very extensive.

Preobrajensky (1902) observed two sorts of areas in the white substance of the cord, medulla oblongata and cerebellum.

(1) Miliary- found along the vessels.

(2) Areas of destruction of the nerve tissue; a more or less marked swelling of the nerve fibres or axis cylinders; significant reduction in the number of fibres; presence of round homogeneous bodies of verying size and definite increase in the leucocytes.

Pickett (1904) agrees with the theory held, then abandoned, by Putnam that there are two types of processes - one systematic, the other diffuse. Pickett believes his case sp

supports this conclusion.

Grinker (1908) states that the processes of vacuolation and neurolgia formation were found side by side in nearly all the sections examined.

Weigert:-L 1:- Pathology is limited to posterior columns; the changes are somewhat patchy and consist in small areas of sclerosis together with groups of and scattered dilated sheaths. The changes are more in the central part of the posterior columns. One of the areas showing no sheaths is in apparent relation to pial vessel.

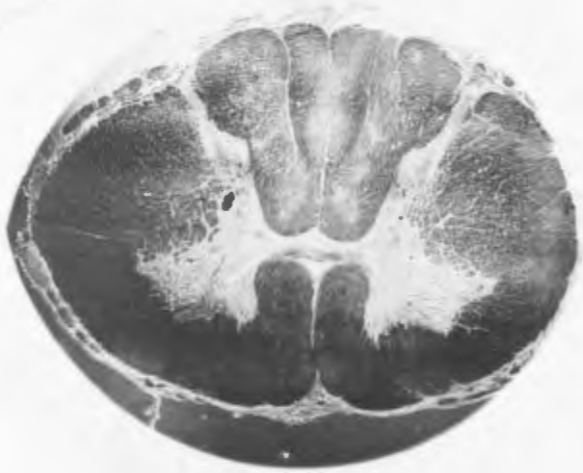
D 9:- The degeneration still somewhat diffuse.

D 4:- The degeneration is rather diffuse in the posterior columns and there is some tendency towards involvement of area on either side of the central part of the median fissure. There are a few ballooned fibers in the pyramidal tracts. Root zones are little if any diseased.

C 8:- The degeneration is most marked along the posterior median fissure and in the central parts of the posterior columns There is considerable ballooning of sheaths, mostly in lateral part of posterior columns. Some of the peripheral areas seem to be at terminations of the pial arteries.

C 5:- Both old and recent degeneration is seen in the posterior columns. There is an area of old sclerosis along the median fissure in its central part; this area has intact sheaths scattered through it. Lateral to this is a strip of more or less normal tissue; the sheaths immediately adjoining the posterior median septum are fairly normal appearing but in one column of Burdach there is an area of old sclerosis running parellel to the posterior median fissure in its central part; also, there are several small areas of sclerosis on this side; several near the periphery are possibly in relation to a vessel or septum; scatter through both columns of Burdach are numerous ballooned sheaths. There are a few sheaths undergoing alteration in the lateral column.

Sections from this cord, as from others, show an unstaining



N. 10. C 5. Weigert.

area, apparently a ballooned sheath with axone destroyed surrounded by normal sheaths that appear somewhat pressed together.

Marchi: In the dorsal regions black dots are seen along vessels in the posterior horn and to some extent along the posterior median fissure in the areas of degeneration in the posterior columns. There are a few fat granule cells in the sclerotic patches. The cells of Clark's column are especially dotted with black granules.

General Histology:- In the less densely sclerotic areas there are numerous protoplasmic glia cells with ramifying processes.

The blood vessels are thickened in the gray matter and several of the lumen of several of the smaller vessels is almost obliterated.

Myelin sheaths in the posterior columns are in various stages of disintergration. The perivascular spaces are not especially widened although a few are notable and are filled with glial elements.

Lower in the cord, in the lower dorsal and upper lumbar regions a few corpora amylacea are seen - more along the posterior median fissure. In the cells of Clarke's column there is a peripheral arrangement of the chromatin substance; the nucleus is frequently absent; some of the nuclei are swollen and irregular; the pericellular lymph spaces are widened. The glia cells are much increased in Clark's column. The anterior horn cells show definite change in cyto-architenture. Corpora amylacea are seen along vessels and in relation to degenerating ganglion cells.

This section shows definite and extensive involvement of the gray matter.

Cervical:- The anterior horn cells of all groups seem altered; the external lateral group perhaps more than the other groups.

Weigert: - Mid-lumbar region:- the posterior columns are rather densely sclerosed in an area on either side of the posterior ~~xxxxxxxx~~ two thirds of the median fissure with the exception of a border of intact sheaths along the fissure. Lateral to the denser sclerosis is an area of sieve-like structure which extends nearly to the posterior horns.

Throughout the sclerotic area are sheaths thatare normal or slightly changed. Just posterior to the central part of the commissure is a small patch of sclerosis with a vessel near the center.

The ~~xxxxxxx~~ pyramidal tracts show the densest sclerosis at the outer part. Sheaths, more or less intact, are seen throughout the sclerotic area.

In the anterior white matter there are several areas near the periphery and along the anterior fissure in which the medullary sheaths are swollen.

11 Dorsal:- Dense sclerosis in column of Goll and at the periphery of the posterior columns involving also the root entrance zone. The crossed pyramidal tract still shows rather marked sclerosis but there are more ballooned sheaths than in lower levels. The cerebellar tracts contain many edematous sheaths. The degeneration in the anterior columns extends along the periphery and on either side of the fissure; the fibers lateral to the dense sclerosis are swollen.

1 Dorsal:- Old sclerosis in a triangular area in the posterior columns - the apex at the middle of the posterior median fissure and the base atthe periphery. Around the periphery of the posterior columns there is no trace of medullary sheaths. The sclerosis

shades out upward and latera ly with many normal sheaths scattered through. There is almost complete loss of fibers in the outer pert of the cerebellar tracts. The degeneration in the anterior columns is more of a reticulated character. There are several streaks of degeneration extending in from the periphery.

Lower Medulla:- Old sclerosis in columns of Goll and Burdach and cerebellar tract; patchy, sieve-form degeneration in both pyramidal tracts.

General histology:- There are definite changes in many of the anterior horn cells and cells of Clarke's column. In the dorsal cord many corpora amylacea are seen - ~~xxxx~~scattered through posterior and lateral columns, around vessels, at root entrance zone, at periphery of posterior columns and along septa.

Modified glia cells are numerous; glia nuclei of various sizes and with varying amounts of protoplasm are to be seen. Glia nuclei are especially numerous around blood vessels. Gitterzellen are more numerous in the posterior columns and large spider cells are more apparent in the pryamidal tracts.

In the more recent areas myelin sheaths are seen in all stages of disintergration, the glia meshes enclose edematous sheaths, corpora amylacea and fat granule cells.

The anterior spinal vessels have thivkened walls; in the posterior columns in the dorsal regions there is an increase of nuclei in the Adventia. Widened perivascular lymph spaces contain many Gitterzellen.

The meninges are somewhat thickened.

N. 45. D 8-9. Weigert.

The only tissue available was a block of cord from the mid-dorsal region.

Weigert:- The lesions are somewhat patchy in one posterior column in the other they consist of a single area which seems to be in relation to a vessel and a few ballooned sheaths scattered through the posterior columns.

The vessels in relation to hyaline like areas do not have obliterated lumens but apparently have thickened walls; the swollen sheaths are not especially in relation to these patches. There are some intact sheaths scattered through the areas. The areas are more in Burdach's than Goll's column.

There are probably several hemorrhages - one in the anterior horn and one in the posterior column.

The pericellular lymph spaces are much enlarged. The vessels in both the cord and meninges are engorged with blood.

In the lateral columns there are a few ballooned sheaths scattered through them.

Marchi:- There are many black dots seen in the pyramidal tracts in the posterior columns there are collections of black masses around the blood vessels.

Weigert:- L 1:- There is marked posterior and lateral involvement and slight anterior degeneration. The posterior columns show an area of normal tissue on either side of the median fissure; lateral to this in the middle third is an area of older sclerosis with intact sheaths scattered through it; in the rest of the posterior columns, except for a border of normal sheaths along the gray matter and periphery, there are seen many ballooned sheaths staining with varying intensity; in one posterior column there is an area of older sclerosis somewhat centrally located.

D 8:- The posterior columns contain an area of dense sclerosis somewhat "V" shaped. Outside of this area are many ballooned sheaths occupying most of the column of Burdach and the peripheral part of Goll's columns. Many reticulated bodies are seen in the sieve-like area corresponding to the size of the glia meshes. They are extremely numerous in this area. Scattered through the sclerotic areas are normal appearing sheaths. The vessel in the posterior median fissure is engorged and thickened but the tissue on either side of the peripheral part is fairly intact.

The lateral change is limited to the pyramidal tracts and like the change in the anterior columns consists in ballooning of the sheaths.

D 7:- The sclerosis in the posterior columns is far advanced and consists of an area of dense sclerosis along the median fissure triangular in shape and extending from the upper part of the fissure and including most of the periphery; lateral to this is seen more recent degeneration; the posterior root entrance zone is degenerated. The change in the lateral columns is extensive but more recentin character. In the anterior columns there is a patch of old sclerosis on either side of the peripheral part of the median fissure surrounded by ballooned fibers. There is a hemorrhage in the

N. 46. D 7-8. Weigert.

posterior columns at the edge of greatest sclerosis. The smaller vessels in the sclerotic area have thickened walls and are engorged with blood. On the other hand areas with little or no change show vascular involvement. The meningeal vessels are thickened.

D 5:- The lesions here are similar to the above section except for slight variations in extent and degree of sclerosis.

Cervical:- The old sclerosis is much less extensive; it occupies a wedge shaped area on either isde of the peripher l half of the median fissure. Lateral to this is considerable normal tissue with ballooned sheaths and patches of older degeneration scattered through it. There are also several areas of sclerosis at the periphery, possibly in relation to the pial vessels.

The change in the lateral columns extends to the periphery and includes both cerebellar paths; the sheaths are dilated, There is also fairly marked change anteriorly with some sclerotic tissue and border of ballooned fibers on either side of the median fissure. The root entrance zone is decidedly degenerated on one side.

Marchi:- The lower levels show degeneration throughout most of the posterior columns, at least the central part of each column. In the higher levels the Marchi changes are more peripherally and extending slightly into the central part.

General Histology:- L1:- The anterior spinal vessels show rather marked thickening of the adventilia. The blood vessels in the white matter generally and especially in the posterior columns are definitely involved.

In the areolar areas of degeneration many modified glial cells are seen in the posterior, lateral and anterior columns. The are especially marked in the lateral columns.

D 7 In the posterior columns the glia cells are very numerous. There is a moderate number of reticulated cells here; the nuclei of these cells are in various stages of disintergration. Many of the glial meshes are occupied by these "Gitterzellen", others, appear empty. In the denser parts the vessels show some hyalinization of the walls; in the less dense areas of degeneration the adventitia is thickened. In most of this area the perivascular lymph spaces are markedly filled with cellular elements. While the fat granule cells are fairly numerous in most of the sclerotic areas they are especially numerous in the somewhat less densely sclerosed areas and the nuclei are usually more distinct. A few of them appear to contain amyloid bodies. In the more areolar portions more protoplasmic glia cells with long branching processes are seen. In the sclerotic areas the blood vessels stand out more distinctly. The vessels in the gray matter appear somewhat enlarged and some of them are engorged with blood. The nuclei of the ganglion cells seem normal but about half the cells give an abnormal staining reaction.

Upper D:- Masses of fat granule cells are seen in the center of the posterior columns with the Weigert stain these areas appeared as dense sclerosis. In the lateral columns there are more spider cells.

Cervical:- The anterior horn cells are fairly normal but there is considerable widening of the pericellular spaces. There is an increase in the number and size of the glia cells in the gray matter. Many modified glia cells are seen in the posterior and lateral columns. The blood vessels are thickened and their dilated perivascular spaces contain many cellular elements. There is no special tissue reaction around the vessels.

N 46.

These sections show fairly definitely the greater ballooning of the fibers in the upper portions of the pyramidal tracts and the more complete destruction of the sheaths and axones lower in the cord. The reverse seems true in the afferent tracts.

In this cord we have the picture of a fat granule cell myelitis as far as the white matter is concerned. The areas appearing densely sclerotic in the Weigert sections are seen to be made up largely of masses of granule cells occupying the glial meshes.

This cord shows especially distinctly the various stages of myelin sheath and axone involvement.

Weigert L 1: There are well defined areas of sclerosis in the posterior and lateral columns. The area in the lateral columns shows few ballooned sheaths. In the posterior column the central part of each posterior column is fairly densely sclerosed with ballooned sheaths especially at margins.

8:- In the posterior columns there is a "V" shaped area of fairly dense sclerosis with the apex at the upper third of the posterior median fissure; many sheaths of fairly normal appearance are seen in the sclerotic portion; ballooned sheaths are scattered through the rest of the posterior columns. In the upper part of Burdach's column there is an area resembling the dense central area that is in apparent relation to a patent blood vessel and which has many normal appearing sheaths in it.

D 1:- The old degeneration in the posterior columns is more definitely circumscribed. It is triangular in shape with the apex at the commissure and the base about ~~xxx~~ one sixth the length of the fissure from the periphery; there are several areas of ballooned fibers - one well defined area being in Lissauer's zone.

In the lateral columns there is fairly marked sclerosis with some swollen sheaths outside the area of denser sclerosis.

The anterior columns are probably degenerated on either side of the median fissure.

C 4:- The involvement in the posterior columns consist in a somewhat "V" shaped area of dense sclerosis on either side of the posterior median fissure and joining at the middle half of the fissure, it contains a

N. 49. Post. col. C l. Weigert.

number of intact sheaths; scattered through the posterior columns are a number of areas apparently surrounding a vessel and ~~with~~ containing some intact or thinned medullary sheaths.

The lateral columns present many ballooned sheaths giving a sieve-like appearance; there are a few swellen s sheaths in the anterior columns. The anterior cerebellar tracts are apparently ~~d~~endely sclerosed.

L1:- The area of old sclerosis in the posterior columns curves outward from the upper third of the median fissure around the periphery to the posterior horns; there is a strip of nearly normal sheaths between this area and a streak of less dense sclerosis containing many sheaths running on either side of the posterior median septa.

The pyramidal tracts contain little or no dense sclerosis; there is some sclerosis in the cerebellar tracts.

Marchi:- Mid D:- There are collections of black masses around the small vessels and elsewhere ~~on~~ on either side of the posterior median fissure; There is marked degeneration in the pyramidal tracts but not in the other lateral tracts.

Bielschowsky:- show various swollen and tortuous fibers.

Lower Dorsal: On either side of the anterior median fissure near the commissure a few corpora amylacea are seen in an area with a dew ballooned sheaths. There is a moderate increase of the glia cells. The blood vessels are little ahanged.

In the posterior columns there are many corpora amylacea especially at the periphery and in the posterior root entrance zone. Few ballooned sheaths are seen. The ~~xxx~~ blood vessels are nearly normal. In the more reticulated areas many protoplasmic glia cells but almost no fat granule cells are seen.

In the lateral columns there is a moderate amount of sieve-like structure. In the more central part there is a rather large dense area of sclerosis with very few corpora amylacea. The area of more advanced sclerosis contains many glia nuclei. Many fat granule cells are seen.

Mid D: Many corpora amylacea are seen especially in the posterior third of the posterior columns. The long sections show many corpora amylacea - sometimes several in a row. Protoplasmic glia cells are extremely numerous in the lateral columns; often several are seen more or less in rows. An occasional myelophage is seen. Some of the corpora amylacea appear to have a granular center. The blood vessels show slight changes.

Lower Medulla: In the posterior columns many small and moderate sized ~~xxxx~~ glia cells are seen especially in Burdach's column. In Goll's column some axones are seen but staining very indistinctly but practically no sheaths remain.

In the pyramidal tracts there are considerable number of spider cells and also some fat granule cells. There is an increase in glial fibrils. A large number of sheaths and axones are gone. A few corpora amylacea are seen. In the central part there is a markedly reticulated area. The vessels present slight changes. Ballooned sheaths are scattered through the tract; the axone is often pushed to one side. Another similar area is seen somewhat more centrally.

Weigert:- S 4 There is possibly some change in the pyramidal tracts and the large posterior root bundlex fibers appear thin and pale.

S 2 - The section is probably negative except for the paler staining area laterally and the alterations in the posterior root bundle fibers.

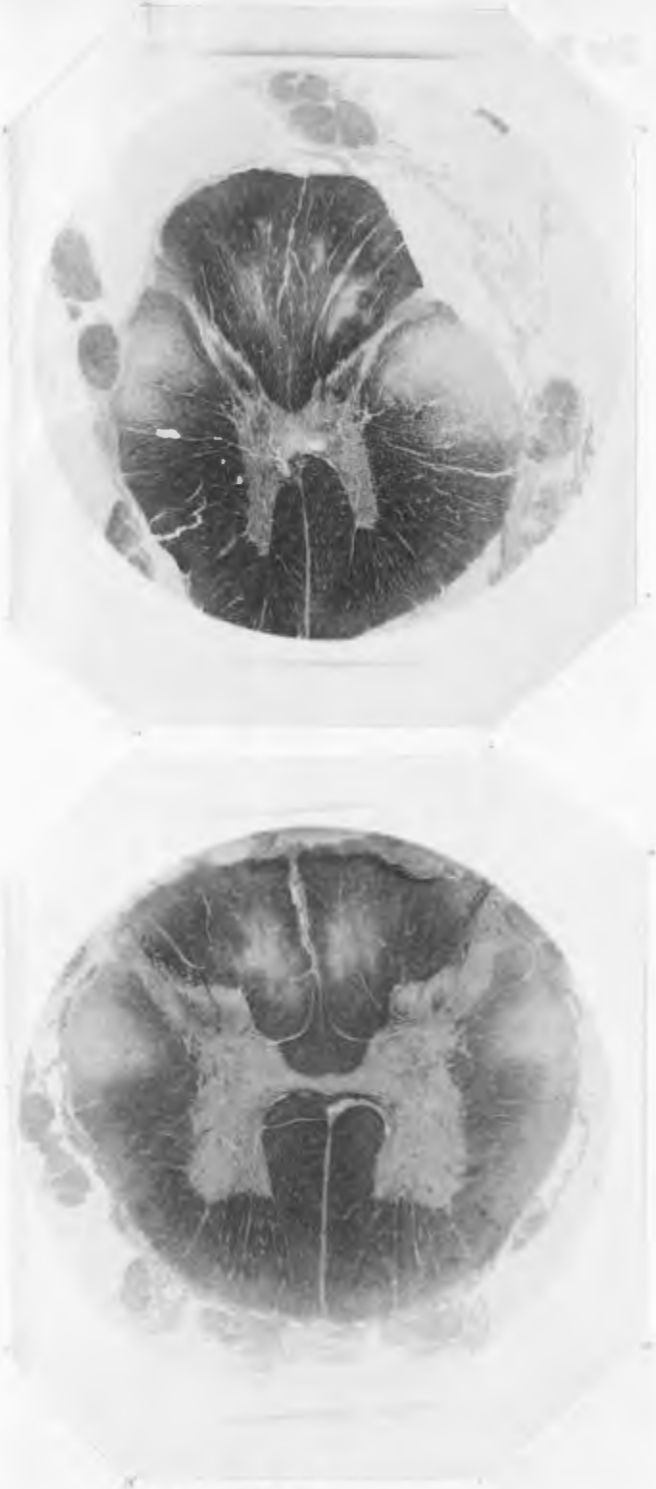
L 3 - A rather dense patch of sclerosis in the center of the posterior columns is somewhat diffuse and of some duration of time; sheaths that appear normal or but slightly involved are scattered through the sclerosis in the posterior columns; there are practically no ballooned fibers.

In the lateral columns there is a well marked area of degeneration somewhat triangular in shape with the base at the periphery. The part of the periphery anterior to this area is pale staining but there is no definite degeneration.

L 2 - There is marked lateral and fairly marked posterior column degeneration. The lateral area is still wedge shaped. The posterior column involvement somewhat more circumscribed but still has a number of more or less intact sheaths scattered through it, especially in the outer parts of the area.

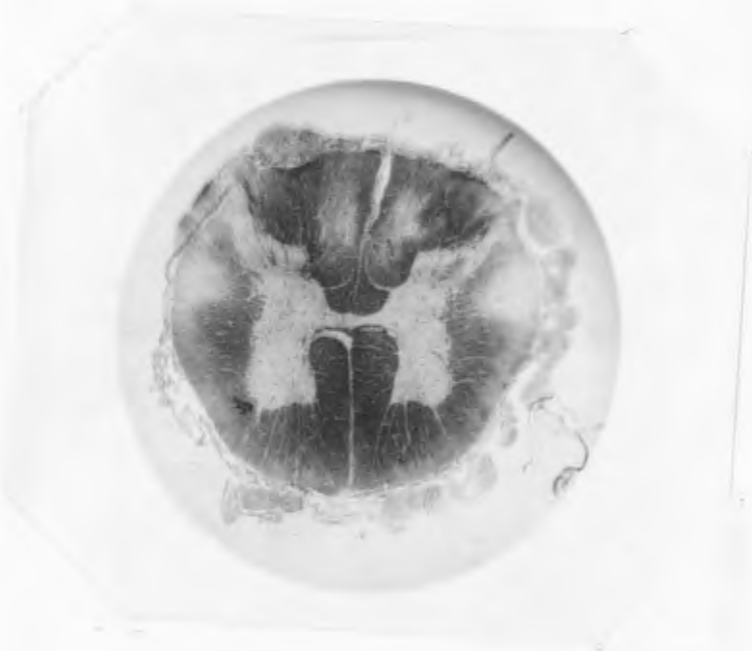
L 1 - The degeneration is well marked in the posterior and lateral columns. There is a somewhat diffuse well marked patch in both posterior columns midway dorso-ventrally but nearer the median fissure. Both anterior and posterior roots appear degenerated.

Upper D - Old degeneration in the lateral columns is well marked at periphery but centrally towards the apex of the area more and more intact sheaths are seen. In the posterior columns the degeneration is somewhat diffuse and patchy and involve the column of Goll more than Burdach's column but especially on one side the sclerosis extends well into the fusiculus cuneatus.



N° 71. Weigert.

Upper - D 7. Lower - 2.



N. 71. L l. Weigert.

The relation of the areas in the posterior columns to the vessels is indefinite; the vessels appear thickened in both the posterior columns and in the fray matter but do not seem especially more involved in the sclerotic areas then in the gray matter except for a vessel near the center of a sclerotic patch in the posterior columns. Longitudinal sections show a peculiar anatomical distortion in the lumbar region.

Marchi: Cells of the anterior horn and Clarke's column are markedly pigmented with fine granules; in some of the cells the nucleus is likewise involved; sometimes the Marchi dots are fairly well limited to the ~~pi~~ poles of the cells. In the lower thoracic region there is definite degeneration in the roots.

General Histology: - Many glia cells are seen in all the areas. The ganglioncells show various stages of chromatolysis; in some the chromatin substance in the nucleus is arranged in masses around the periphery of the nucleus; in others no nucleus is seen and the cell is diffusely stained.

A hematoxglin-eosin section of the lower medulla shows swollen medullary sheaths in the cerebellar tracts. The cell of the nu. gracilis and nu. cuneatus are diffusely stained throughout and show other chromalytic changes. The glia cells are markedly increased in the posterior area. The pyramidal tract also shows an excess of glia cells with varying amounts of protoplasm. The vessels in this region appear to have a hyaline exadate around them.

The peripheral nerve (sciatic) shows many black dots with the Marchi stain. The Weigert sections show less definite degeneration.

Weigert.

Sacral cord:- no change in the Weigert sections.

Lumbar region: L2 In central part of one posterior column there are a number of ballooned sheaths with little evidence of sclerosis.

In the other posterior column in the central part there are a few dilated sheaths.

Dorsal region:- 11 D Patches of somewhat similar character but slightly less extensive.

Mid dorsal:- no definite involvement of the posterior columns but peripherally in one lateral column there is a small patch of sclerosis.

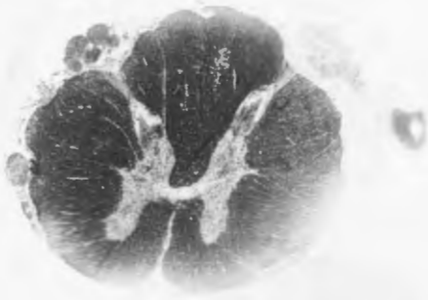
Marchi:- There is an excess of pigment in the anterior horn cells.

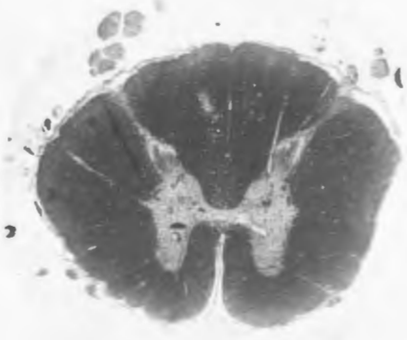
Hematoxylin eosin:-

Lumbar:- at the periphery of the posterior columns, there are many corpora amylacea. There is an area of swollen sheaths seen in the central part of the posterior median septum. The tissue surrounding a cross section of a vessel in the posterior median septum has been separated from the vessel by an extravasation - possibly a hemorrhage. Hyalin degeneration has occurred in some of the smaller vessels in the posterior columns.

Lower Dorsal:- few corpora amylacea and an increased number of glia cells seen on longitudinal section.

Mid D:- The corpora amylacea are more numerous at the root entrance zones. There are a few dilated sheaths in the posterior columns. The cells of Clarke's column show chromalytic changes.





N 100. Weigert.

Upper - D 8.

Lower - D 11.

N 118.

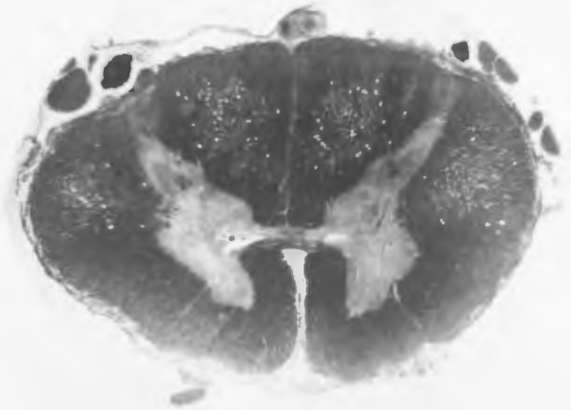
Weigert: L 5 Except for a slight degeneration laterally and a questionable change in the roots the section is negative.

L 2 - Definite change laterally and posteriorly. The lateral columns are lighter staining and show slight sclerosis; the medullary sheaths are somewhat swollen. The involvement of the posterior columns is somewhat diffuse and consists in groups of ballooned sheaths, which may have some relationship to the vessels.

L 1:- Well marked change in posterior and lateral columns; the posterior columns show extensive ballooning of the sheaths, especially in the central part of the columns; intact sheaths are seen in relation to the involved sheaths and scattered through what appears to be old sclerosis. There are no changes in the area adjoining the posterion horns. Both the anterior and posterior roots appear diseased.

D 7:- The lateral columns show extensive ballooning the fibers fairly well limited to the pyramidal tracts; the cerebellar tracts are not involved. The degeneration in the posterior columns is patchy in character and consists of dense sclerotic areas in the region of the median fissure and of groups of ballooned fibers in Burdach's column with some sclerotic tissue. There is a questionable small hemorrhage in the margin of one of the patches. Just posterior to the commissure there is a blood vessel with a moderately thickened wall surrounded by a small area of sclerosis containing some intact sheaths; the sheaths outside the area are normal in appearance.

D 3:- The degeneration is more marked and more diffuse both posteriorly and laterally. The degeneration in the lateral columns is recent in nature and consists mostly of ballooned sheaths. The changes in the posterior column are older in character.



N. 118. Weigert.

Upper - D 7.

Lower - T 1.

N 118.

There is an area of degeneration in each column of Goll and Burdach which are separated to some extent by a more normal area; the area near the median fissure is the older. Lissauer's zone is probably diseased.

Lower Medulla;* Extensive recent involvement in Tr. spinp-cerebell. and fasiculus cuneatus.

Marchi L 5:- shows well marked degeneration in the posterior columns in the central parts and along the periphery, and also in the lateral columns. There is no grouping of black masses along the vessels Roots are distinctly degenerated. The anterior horn cells are distinctly pigmented.

Upper D:- In the pyramidal tract and around a central sieve degeneration the medullary sheaths are shown to be degenerated by the Marchi stain. The anterior and posterior roots are still clearly diseased.

Cervical:- Fatty granule cells are seen in the posterior columns.

Medulla:- The cerebellar tracts are extensively involved. Burdachs column also shows evidence of recent degeneration. The cells of the nu. gracilis contain an excess of pigment granules.

Medulla:-(section through the XII nu.) Degeneration in the corp. restiformis and in the pryamidal tracts.

Pons:- Marchi dots are seen in the brach. conj.

General Histology :- In the mid dorsal region many corpora amylacea are seen in the posterior columns; also, many glia cells. The blood vessels are not especially involved. There is some chromatolysis in the cells of the anterior horn and of Clarke's column. A few "Gitterzellen" are found in the posterior and lateral columns. There are a number of spider cells in the lateral columns.

N 118.

Longitudinal sections of the dorsal cord stained with hematoxglin erosin show rows of corpora amylacea and fat granule cells in the posterior columns, especially Brudach's. In the cervical region there is also an increase in glia cells in the posterior columns and to a less extent in the lateral columns.

Lower D:- Many corpora amylacea at the posterior root entrance zones; they are more numerous in the central and lateral part of the posterior columns. On longitudinal section they are seen more or less in rows, around blood vessels, and at the periphery. Thionin and kresyl violet stains show rather marked chromatolysis in the cells of the anterior horn and Clark's column. In a vessel in the anterior horn there is a clump of bacteria.

Heidenhain's iron hem. shows many corp. amy. along the vessels and septa in the lateral column as well as scattered throughthe sieve-like area; also in the posterior columns and posterior horns at the periphery. There are a considerable number of "Spinnenzellen" in the lateral columns. The wide meshed glial spaces and swollen sheaths in various stages of disintergration are beautifully seen in the lateral columns the same is true of t the axones though apparently here the changes are later in time than in the sheaths. Some of the vessels in the posterior and lateral columns are thickened but are not in definite relation to the areas of sclerosis.

The lymph spaces around the vessels in the posterior and lateral columns are dilated and contain cellular elements. The spider cells are more numerous in the reticulated areas.

In the gray matter of the dorsal cord there is some widening of the perivascular and pericellular lymph spaces.

The peripheral nerves are definitely involved.

Weigert:- This cord presents a rather clearly circumscribed area of degeneration beginning in the central part of the posterior columns in the upper throacic region and approaching the posterior median groove until in the upper thoracic and cervical regions the sclerotic area is "V" shaped. This degeneration extends in to the medulla oblongata in the column of Goll.

The anterior roots, and to a less extent, the posterior roots are degenerated.

Marchi:- In the lower dorsal regions a rather small area of dense sclerosis is seen surrounded by ballooned sheaths. In the reticulated portions of the area many Marchi dots are present. There is an excess of black granules in the cells of Clark's column.

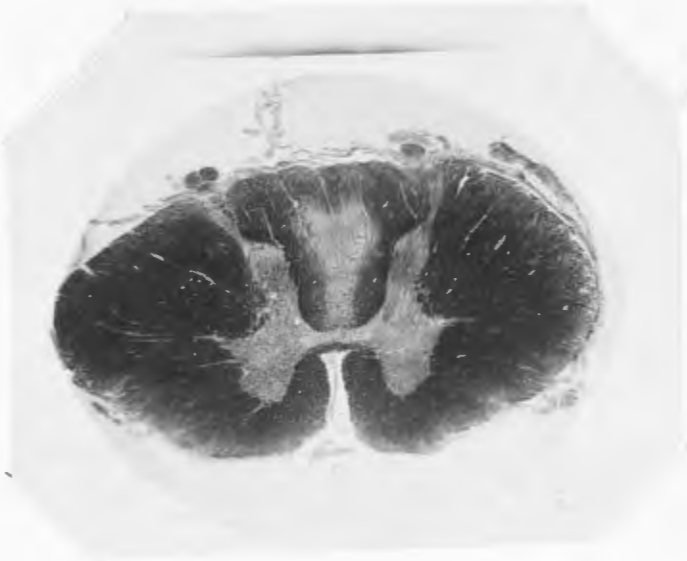
The mid-dorsal cord shows very little evidence of degeneration with the Marchi stain. In the upper levels of the cord the dots are mostly at the margin of the area of sclerosis.

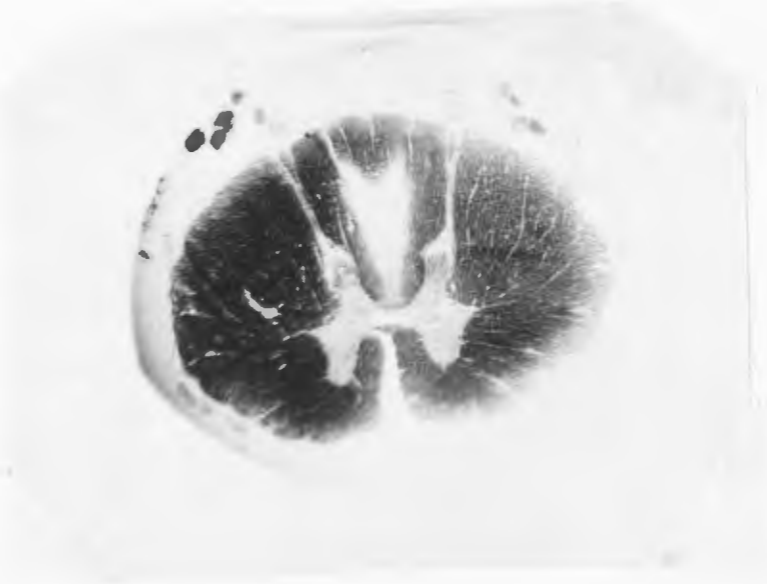
There is a definite degeneration in the posterior columns in the region of the posterior root entrance zone.

Ford Robertson and Bielschowsky:-Swelling and slight varicosities of the axones are seen; in the Bielshowsky preparations the axones are seen to be decidedly nodular.

General Histology:- The changes in the cells of the anterior horn and Clark's column are well marked. The chromatin substance is frequently arranged in irregular masses around the periphery of the cell in irregular masses. The nucleus is absent or in various stages of disintegration. In some of the cells the ce nter is filled with pigment.

In the lower medulla there is extensive sclerosis in Goll's column and to a much less extent in Burdach's. Large protoplasmic





N 127. Weigert.

Upper -D 2.

Lower - D 6.

glia cells are seen. There are more corpora amylacea in Goll's column. The cells of the nucleus gracilis show definite tigrolys.

In the dorsal regions the glia cells are very much increased in the diseased portion of the cord.

The blood vessels show definite hyalinization, especially in the old sclerotic areas.

Weigert:- There are no marked changes in any part of the cord; there is possibly a slight pallor in the posterior column.

General Histology: A few corpora amylacea are seen along the vessels and in the lateral part of the posterior columns; also in the lateral columns. The most marked increase of the corpora amylacea is seen in the posterior root entrance zone or Lissauer's zone; this is constant in the dorsal sections. The pericellular lymph spaces are widened, especially in Clark's column. The glia cells are increased in size and number in the posterior columns, and in the lighter areas in the Weigert sections, there is possible a slight swelling of the myelin sheath.

The cells of Clark's column shows definite chromatolysis; the changes in the anterior horn cells are slightly less marked. The nucleus is often partly or entirely disintegrated and the chromatin substance arranged in irregular masses around the periphery of the cell.

Bielschowsky:- Some of the fibers in the posterior columns appear nodulated.

Weigert:- L 1:- There is marked degeneration in the lateral and posterior columns. In the posterior columns the involvement is extensive being of an old character in the central part and more recent in the lateral parts. The sheaths on either side of the lower two thirds of the median fissure and bordering on the gray matter are intact.

The sclerosis in the lateral columns is older and has many fairly normal sheaths scattered through it.

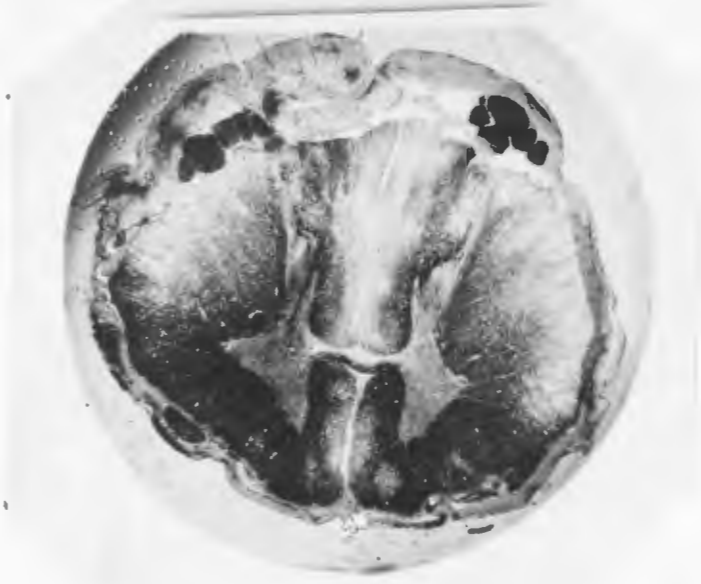
B 11:- The changes are similar to the above but the area in the posterior columns is slightly more circumscribed. There are a few ballooned fibers in the anterior column along the anterior median septum.

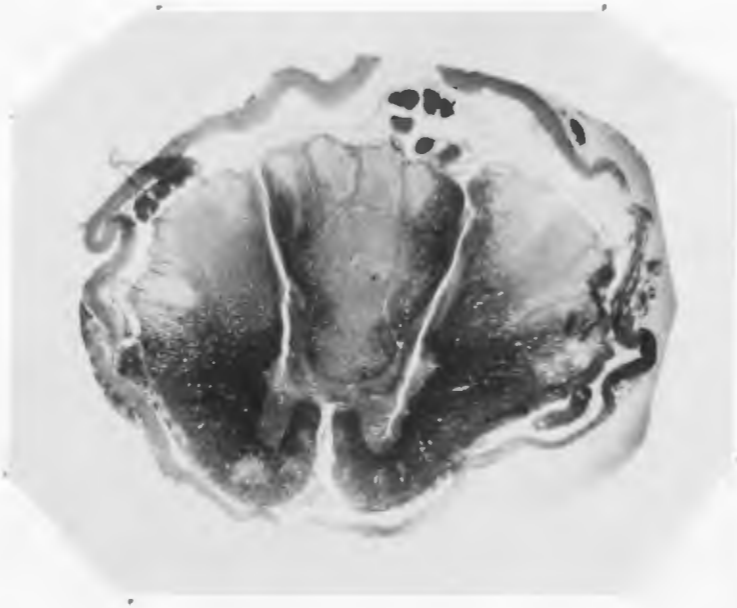
D 7:- There is marked sclerosis of all the posterior columns except a small "V" at the end of the posterior median fissure and a narrow border of normal or ballooned sheaths along the posterior horns. As a whole the sclerosis is most marked next to the median fissure and about the center of the fissure. The changes in the column of Burdach are more recent.

In the lateral columns there is fairly marked sclerosis in the pyramidal tracts and recent degeneration in the cerebellar tracts. A few groups of ballooned sheaths are seen anteriorly.

D 2:- There is marked sclerosis in the posterior columns especially in the column of Goll; there is a small "V" shaped area of fairly normal fibers at the extreme periphery of the posterior columns; there are many ballooned sheaths in the lateral part of the posterior columns.

C 8:- There is marked degeneration of all of the posterior columns except a band along the posterior horns and even here there is considerable ballooning of sheaths especially toward the periphery

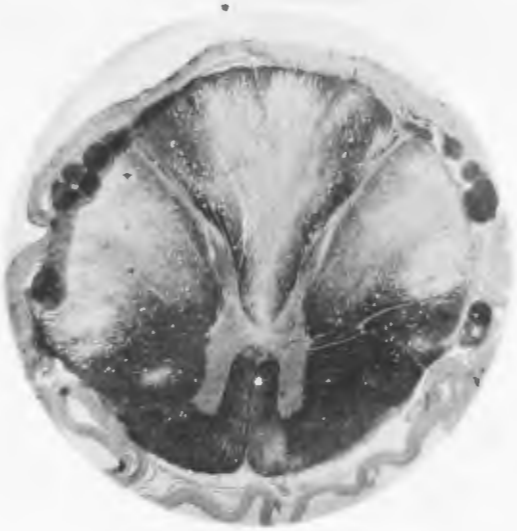




N. 127. Weigert.

Upper - C 3.

Lower - upper D.



N. 127. Weigert.

Upper - D 7.X

Lower - D 12.

The sclerosis in the pyramidal tracts is not as dense as in the lower levels; there is well marked degeneration along the anteriior median fissure.

The longitudinal Weigert sections show sheaths in various stages of disintergration in the areas involved.

Marchi:- In the lumbar region there are m ny fat granule cells especially near the median fissure.

Dorsal:- There are mahy fat granule cells in the lateral columns as well as in the posterior columns.

Ford Robertson:- Farious changes in the axone are shown; the fiber is apparently early involved but is not entirely destroyed until the sclerosis is well advanved.

General Histology:- There is marked chromatolysis of the anterior horn cells in the upper lumbar region.

In the dorsal regions the cells of the anterior horn and Clark's column show definite changes; various degrees of chromatolysis and staining of the achromatin substance.

Spider cells are very numerous in the sieve like areas especially in the lateral columns. There are also many fat granule cells in the lateral columns but they are more numerous in the posterior columns.

Longitudinal sections of these areas show rows of "Gitten zellen", some of them are of mammoth size and contain a double nucleus. The cells often contain very large vacuoles.

Quite a number of corpora amylacea are seen around the vessels in the posterior columns and in the glia meshes. The vessels show thickening of the adventitia, especially those in the posterior columns, but the vascular changes are not marked as a rule.

The anterior horn cells show some fuchsin ophilie granules but not marked.

In this cord again we have the picture of a fat granule cell myelitis in the white matter, also with definite changes in the grey matter without extensive vascular involvement. The various changes in the tissues are beautifully demonstrated here. We have the beginning reaction of the medullary sheaths through the stage of enlargement and pale, irregular staining until they finally disappear; the glia cell history is well brought out in these sections; all stages are seen from the early increase of the number and size of the neuroglia through the large protoplasmic glia cell to the stellate spider cell and the fat granule cell which is so common in this cord up to the stage of dense sclerosis.

Weigert:- The changes are relatively slight in the Weigert preparations. No isolated islands of degeneration are seen. In the posterior columns slight changes consisting of an obscurely outlined band along either side of the median groove. The change is most marked in the cervical region.

In the lateral columns a somewhat paler staining area is seen; it is most marked at the ninth thoracic segment.

In the upper thoracic cord a peculiar enlargement of one posterior horn near the commissure is to be observed. It is suggestive of the lesions reported by Baumler, Bullock, and Camac and Milne. However there is no evidence of cavity formation.

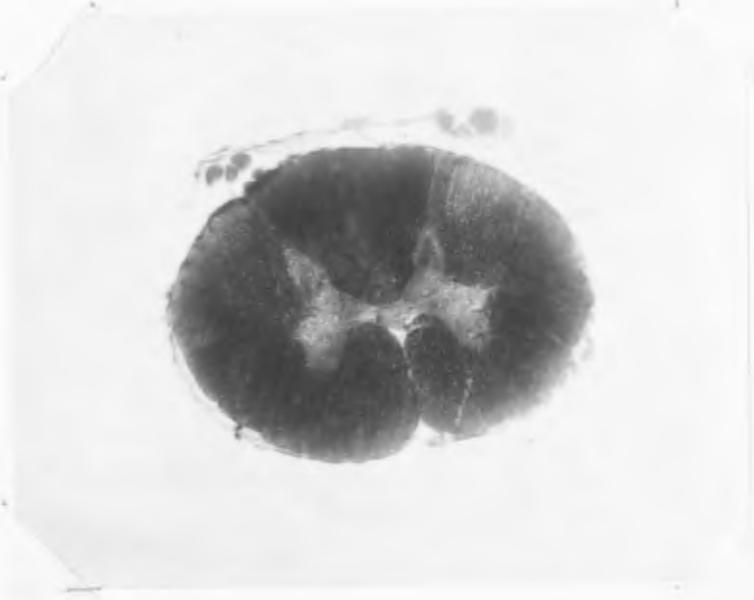
Lissauer's zone appears definitely abnormal but the change is rather diffuse.

Marchi:- The cord appears negative except in the anterior and posterior roots many Marchi dots are seen.

General Histology:- There is decided chromatolysis of the cells of Clark's column. The anterior horn cells present less evidence of degenerative changes. The pericellular spaces are markedly dilated around the cells of Clark's column. In the upper part of the cord an occasional sheath in the posterior column is seen to be edenutous. The lateral column shows definite involvement of the myelin sheaths and the neurofibrils are somewhat ir irregular. Fig 11

In the lower dorsal region the lateral columns contain many spider cells and corpora amylacea; and a few fat granule cells. The posterior column in this section shows only a slight increase of glia and very few corpora amylacea.

In the longitudinal sections an occasional row of several protoplasma glia cells are seen; these cells contain large nuclei



N. 130. D 5. Weigert.

and some have a marked amount of protoplasm.

There is some swelling of the sheaths and nerve fibers in the posterior root entrance zone.

Weigert : Mid D - in the central part of each posterior column there are several patches of sclerosis that are in apparent relation to vessels or septa. Scattered through the posterior columns, somewhat more in Burdach's column there are a number of ballooned sheaths.

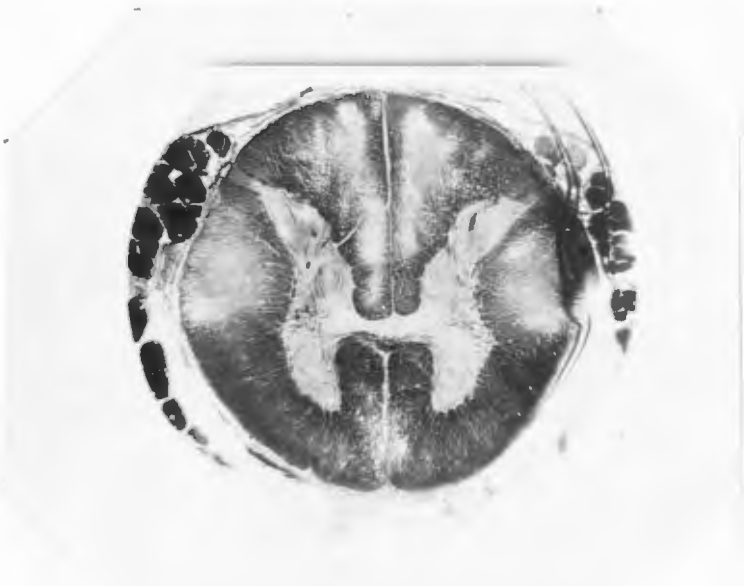
The lesion in the lateral columns consists of a well circumscribed reticulated area. There is comparatively little sclerosis in this area.

Marchi :- There is no Marchi degeneration seen around the vessels or in the patchy areas in the posterior columns; in the sieve-like areas, especially in the lateral columns many Marchi dots and granule cells are seen.

The roots are definitely involved.

General Histology:- In the posterior columns a few corpora amylacea occupying glia meshes are seen. Spider cells are found in the area of ballooned sheaths The blood vessels show little involvement. In the lateral columns there are many fat granule cells; a number of them show large vacuoles. The medullary sheaths are in all stages of destruction.

The peripheral nerves show some degeneration by the Marchi method.



N.9. 12 D-1 L. Weigert.

Nerve Cells.

Changes in the nerve cells have not commonly been looked upon as an important part of the findings in subacute combined degeneration. Many writers have referred to various grades of alterations in the anterior horn cells and in the cells of Clarke's column. Our sections showed definite and often marked chromatolysis of the cells of Clarke's column and to a less extent of the anterior horn cells. In cases where the cord changes were otherwise slight the cells of Clarke's column were distinctly involved.

Not infrequently there was staining of the achromatin substance so that the cell appeared more or less uniformly stained; often the cells stained very deeply. The common arrangement of the tigroid substance was in irregular massesaround the periphery. These cells often had lost their processes and nucleus.

The earliest change was an exxentric position of the nucleus with an excess of pigment in the cell. The nucleus was apparently gradually extruded or disintergrated. In some sections we see all stages of cell change- rounded cells without processes, spindle shaped cells, cells with excess of pigment, cells with abnormalaties of the nuclei, dark rather uniformly staining cells, peripheric arrangement of the chromatin substance, and finally cells that are almost unstained appearing as shadows of the former cell.

The anterior horn cell changes are not unlike those seen in multiple neuritis. The involvement of the cells of Clarke's column is very definite and constant and seemingly must play some part in the degeneration of the white matter in the cerebeller tracts. The changes in the anterior horn cells are probably due to the involvement of the peripheral nerve which we found to be constant.

Blood Vessels and Lymph Spaces.

Whether or not the distribution of the vessels is a factor in the location of the lesions it is certain that the sclerosis is not due to changes in the vessel walls. In isolated instances hemorrhages and thromboses are seen but certainly are not the primary cause of the degeneration.

As the sclerosis advances vascular changes are more likely to be seen. Hyaline degeneration is the most common change. Intimal proliferation occurred relatively infrequently. Thickening of the adventitia with increase of the nuclei in the vessel wall was fairly common. The vessels in relation to the earlier areas not infrequently are normal. The clump of bacteria found in one section was probably the result of a terminal septicemia.

The dilatation of the lumph spaces was a common, but not necessarily early, finding. In the stage where the "Körnchenzellen" are numerous the perivascular lymph spaces are usually notably widened and filled with cellular elements. The space of Obersteiner is often dilated around both the anterior horn cells and the cells of Clarke's column However chromatolysis is often very marked in cells with a fairly normal pericellular lymph space. Lymphstasis is probably a factor in the pathogeneses of the cell changes and sclerosis in the white matter but hardly the primary cause as changes occur in both instances without evident lymph stasis.

Neuroglia.

With this even more than with the other tissue elements the picture in any individual case is apparently modified by the degree of acuteness of the process and probably also by ability of the tissue to react to the stimulus. The glial elements show a marked sensitiveness to the supposed toxin for even before the fibers are appreciably affected there is an increase in the size and number of glia cells. It is not evident that the neuroglia proliferation initiates the parenchymal l chan es but rather progresses pari passu with the alterations in the nerve fiber.

There is an increase in the protoplasm of the glia cell and the nucleus stains very distinctly. As the ballooning of the sheath takes place the large protoplasmic glia cells form processes that surround the disintergrating fiber. At this stage the Weigert stainx shows swollen medullary sheaths and a little later the characteristic sieve-like area. These cells very greatly in size and not infrequently they present extensive processes which, by apparent anastomosis and inter lacing with processes of other glia cells, forms a most beautiful network. The fibrils often show a definite relationship to the v ascular structures.

As the sclerosis becomes more marked the spider cells are less and less distinctly seen and in place of the large protoplasmic branching glia cells forming a rather loose reticulum we see a mass of fibrils with comparatively few x nuclei.

The so called fat-granule cell or "Gitterzelle" is a very interesting part of the picture and seemingly plays an important, though not primary, roll in the destruction of the axone. These large protoplasmic cells present a reticulated appearance with the hematoxylin stains and a granular appearance when stained with osmic acid. They are often vacuolated. On cross section they are seen lying in glia meshes and on

longitudinal sections often appear in columns apparently occupying the space of the disintergrated axone - the fat granule cell being filled with myelin particles. These neurophages accumulate around the vessels and and often form a ring around a vessel filling the adventitial lymph space. In some sections the number of granule cells is so great as to possibly varrant terming the process at that level a "fat-granule cell myelitis". Sometimes areas that appear sclerotic in the Weigert sections are found to masses of Gitterzellen" is a gilal reticulum. In the late stages the nuclei of these scavenger cells show various grades of disintergration and finally they disappear.

The origin of the corpora amylacea has not been definitely determined. Rene Sand concludes that they are originated from destroyed axis cylinders. Obersteiner and many others believe that they arise from glia cells. Other than the fact of their being found in rows on longitudinal section there is nothing to indicate their origin from the myelin sheath. On the other hand the fact that the corpora amylacea are most numerous where glia numlei are seen in gre test abundance and that they are most prominent around vessels and septa is suggestive that they arise from glia cells. Around glia cells there is sometimes seen a faint eosinophin staining hyaline material which is probably the beginning of the amyloid body formation.

Axis Cylinder.

The Bielschowsky and Ford-Robertson section would seem to indicate an early involvement in the axis cylinder. In areas where the myelin sheath is apparently intact the axis cylinder may be showing the early change, indicent to degeneration. Pfeiffer found the axis cylinder process to be well preserved as shown by the Bielschowsky method; in the brain even where there was advanced nerve cell degeneration the neurofibrils were well preserved.

While it is fairly definite that the axis cylinders undergo slight changes early in the disease it is certain that the disintegration does not occur as rapidly here as in the medullary sheaths for axis cylinders are found in greater or lesser numbers in areas with extensive myelin sheath involvement. This is well illustrated in a peripheral nerve which showed marked demyelinization by the Weigert method but in which there was found to be present a number of axis cylinders.

The earliest changes are probably seen in the silver stained longitudinal sections showing a slightly swollen and slightly irregular axis cylinder; the neurofibril becomes definitely nodular and tortuous in its course. With the Hematoxylin eosin stain the axis cylinders are seen to be swollen and pale staining as the swelling of the sheath increases the axone is often found to one side of the ballooned sheath or after the sheath is practically gone the faint staining axis cylinder is sometimes seen in the glia mesh possible pushed to one side by a "Gitterzellen"

The axis cylinder becomes more granular and varicose and finally is apparently broken up into small particles from which, together with the disintegrated myelin sheath, are supposed to arise (Homen)

Medullary Sheath.

The changes in the myelin sheath are very distinctly presented in the various sections from these cords.

The transverse sections stained by Weigert and Van Gieson show the early swelling of the sheath; the longitudinal sections also show the enlargement of the sheath and the further stage of increasing tortuosity of the sheath. The staining is lighter than normal and becomes gradually lighter.

The medullary sheath gradually becomes thinned out until it has the appearance of dots connected by a fine thread and in a still more advanced stage only a faint ring can be made out. Groups of these ballooned sheaths with the axis cylinder pushed to one side or gone and fat granule cells possible surrounded by the faint line of myelin sheath of a fine glia network make up the sieve-like structure so frequently seen in subacute combined degeneration. The disintegrating myelin is apparently carried through the lymph spaces to the blood vessels by the fat granule cells.

In the moderately advanced stage the sheath is seen to be more or less broken up and the area filled with fat globules.

In another sort of area where a pale area surrounds a blood vessel the sheaths contained in the patch are either normal or smaller and paler than the other sheaths.

Discussion of the Pathogenesis.

It is evident that hemorrhages were not the cause of the degenerations in these cords, for in the many sections examined from various levels hemorrhages were rarely seen and in most of the cords they were entirely absent.

The vascular changes generally were even less than one would expect to find considering the extent of the changes in the other tissues. Our sections very definitely confirmed the observations of many neuropathologists that normal, or nearly normal, vessels may be found in sclerotic areas. In other instances where fairly marked vessel changes were present there was usually no definite relation between the vessels and the lesions. To a certain extent the vascular changes may be said to be coordinate with the alterations in the nervous tissue and neuroglia; but even this relationship is not always to be seen.

While noting the frequent lack of sufficient and constant vascular change to explain the cord lesions many observers have felt that there was a definite relationship between the vessels and the lesions. As stated in the introduction there has been widely diverging opinions as to the mechanism of this relationship. Neither has there been an agreement as to the level of the cord best supplied with blood. It has been explained that the gray matter of the cord is exempt from notable involvement because of its better blood supply through the anterior spinal arteries.

Pathogenesis.

Jacob and Moxter, Russell, Batten and Collier, Putnam and Taylor and others regard the anatomical distribution of the peripheral arteries as the deciding factor in the location and symmetry of the lesions. In our sections there was one type of lesion found in apparent relation to the blood vessels or septa; these areas will be discussed later. The predominating change was in no arrangement of the pial vessels. On the other hand definite changes were found in the gray matter, even before the involvement of the white matter was well marked; furthermore this chromalytic process did not progress coordinately in all the cell groups as apparently should be the case were the changes dependent on vascular relationships.

Largely from the appearances of the Weigert preparations two types of lesions have been described; these are ordinarly termed "recent" and "old" or "areolar" and "sclerotic". These areas represent respectively early and late stages of the same process. The unstained "sclerotic" or "old" area seen in the Weigert sections differs in its histology according to the degree of advancement of the actual sclerosis; it varies from a mass of fat granule cells and other protoplasmic glia cells to a mass of glia fibrils with only a few nuclei seen in the sclerotic area. This type of degeneration is probably of toxic origin. The areas involved are not related to any special arterial distribution but do represent the long fibers of the posterior and lateral columns and exceptionally the longer fibers of the anterior column. As Putnam, Dejerine, Billings, Hassin and others have suggested the characteristic involvement is a degeneration of the long fibers of the cord and the process is, as Hassin states, essentially a "central neuritis" (Adolph Meyer) Besides the symmetry of the lesions, the location of the areas, and the pathological changes suggesting a toxic central neuritis, the character of the lesion in

them

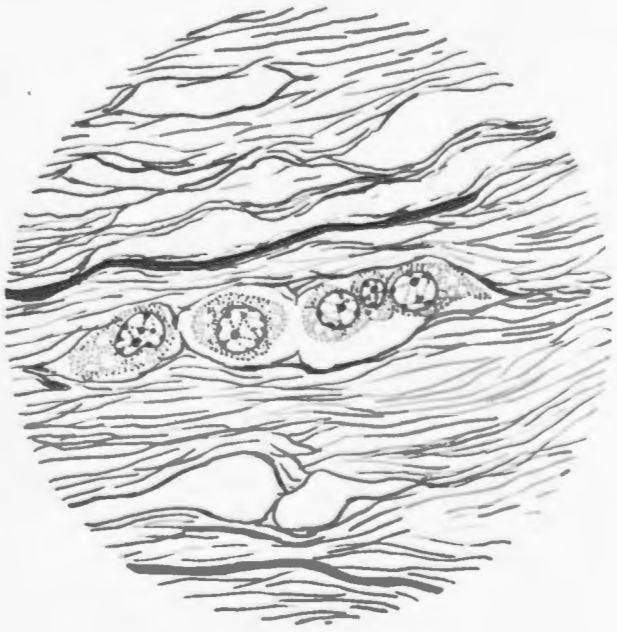
the the ascending and descending tracts at various levels would apparently confirm this view. The degeneration may be of the "areolar" type in one levle and the "sclerotic" type in a distant part of the same tract. The more advanced changes are found in the distal portions of the tracts and the recent changes - the ballooning of the sheaths and involvement of the neurofibrils are found nearer the cells from which the axones arise. Therefore in the upper cervical levels we find old sclerosis in the central parts of the posterior column with less advanced changes in the column of Burdach; likewise in the cerebellar tracts the changes are more advanced in the peripheral part of the tract. In the descending tracts the older lesions are in the lower levels of the cord with more ballooned sheaths seen in the upper regions. In other words it is, as has been pointed out, the parts of the nerones fartherest removed from their trophic center that is primarily involved and the descriptive term given to this disease by Dejerine - le syndrome des fibres radiculaires longues des cordon postérieur - is very apt.

Besides the above described type of lesion another sort of change is found fairly frequently though much less characteristic than the degeneration of the long fibers of the cord involvement in pernicious anemia. Areas of this type are in definite relation to blood vessels and appear in the Weigert sections as "sclerotic" areas surrounding a blood vessel or septum and containing a greater or less number of normal or atrophic sheaths. Ballooned sheaths are practically never a part of this picture and whenn found in relation to such an area it is probably a coincident. The vessels in these areas may have marked thickening of the adventitia but not infrequently they appear fairly normal. In the general stains the "sclerosis" is seen to consist of a hyaline like substance, although in some areas a number of granule cells are seen, especially surrounding

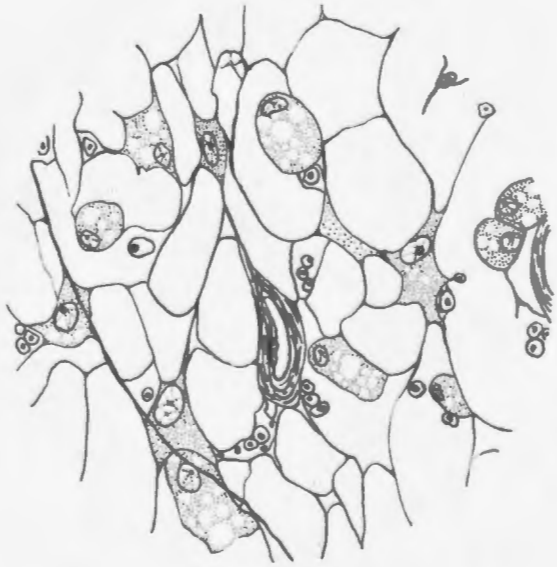
the vessel. These areas vary from segment to segment although it seems likely that a certain amount of secondary degeneration occurs as a result of these perivascular lesions.

Conclusions.

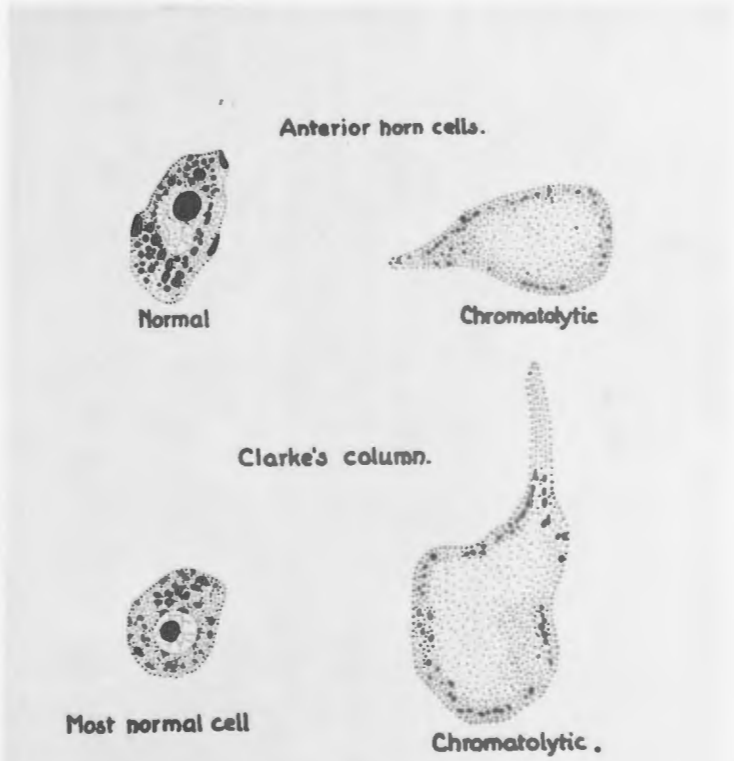
1. Two types of lesions predominate in the cord involvement commonly associated with primary anemia.
2. The lesion more characteristic of the changes in these cords consists of a degeneration of the long fibers of cord, especially of those in the posterior column. ~~Th~~ This type of lesion does not depend upon the arterial distribution.
3. A less distinctive process is a perivascular area having normal or atrophic sheaths scattered through the area. These discrete areas vary in different levels of the cord.
4. Changes in the cells of the anterior horn and Clark's column are often of early occurrence but are probably not the primary factor in the degenerate changes in the white matter since the involvement of the fibers occur wit hout marked changes in the gray matter. However, it is likely that the cells changes do play a role in the rapidity of the changes and possibly also in the character of the lesions.
5. Hemorrhages, thrombosis and adventitial thickening are found but are not constant or frequent enough to account for the degeneration.
6. The changes in the spinal cord are strongly suggestive of a toxic etiology.

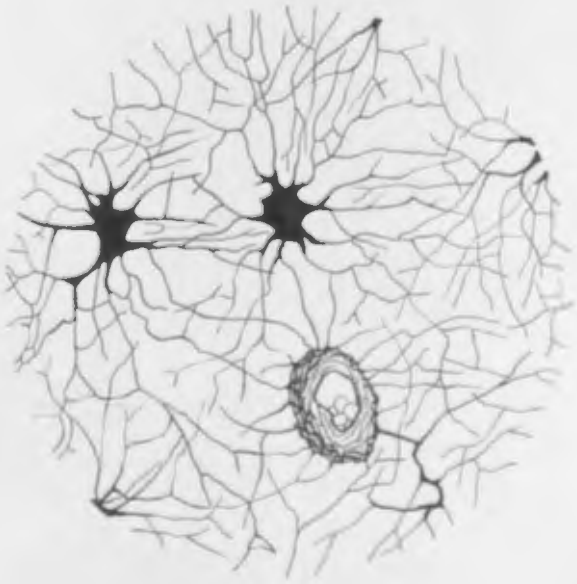


Row of fat granule cells.

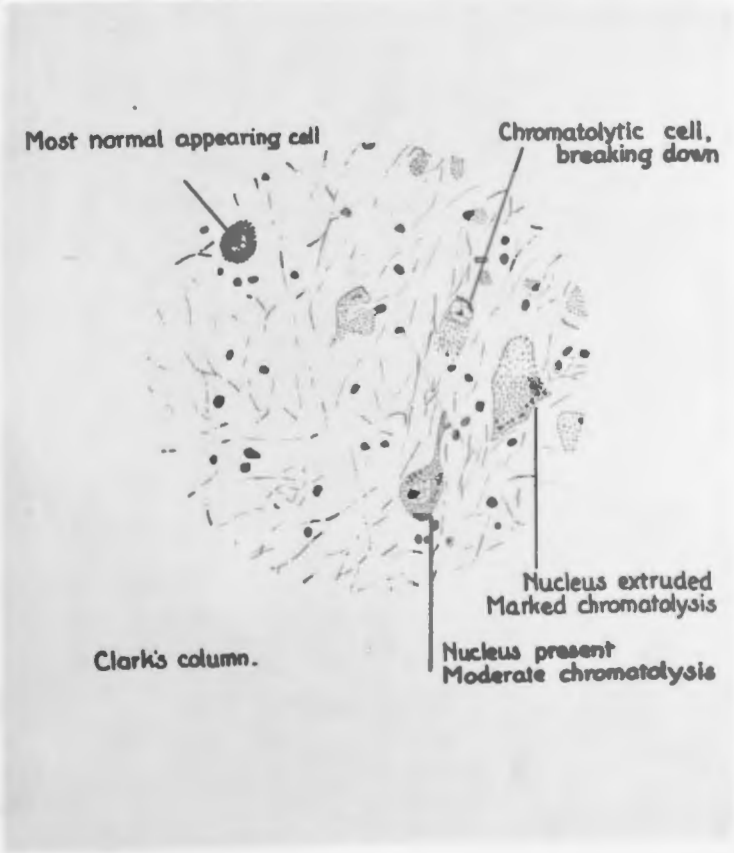


Posterior column
showing histogenesis of fatty granule cell.

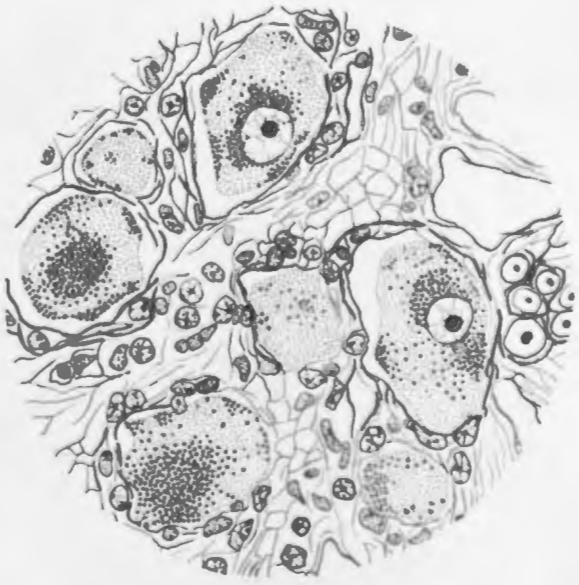

Anterior horn cells.
Normal
Chromatolytic
Clarke's column.
Most normal cell
Chromatolytic.



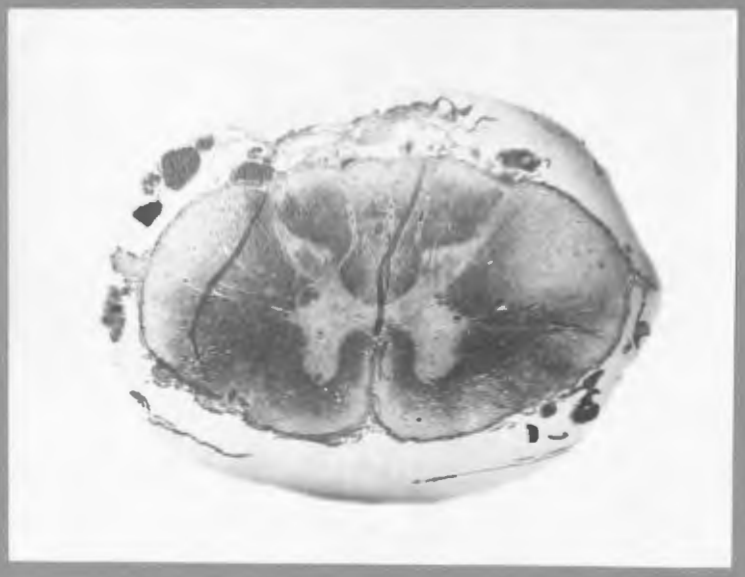
Cajal glia


Most normal appearing cell
Chromatolytic cell, breaking down
Nucleus extruded
Marked chromatolysis
Clark's column.
Nucleus present
Moderate chromatolysis

Degenerating myelin sheaths.



Posterior ganglion cells showing pigmentation.

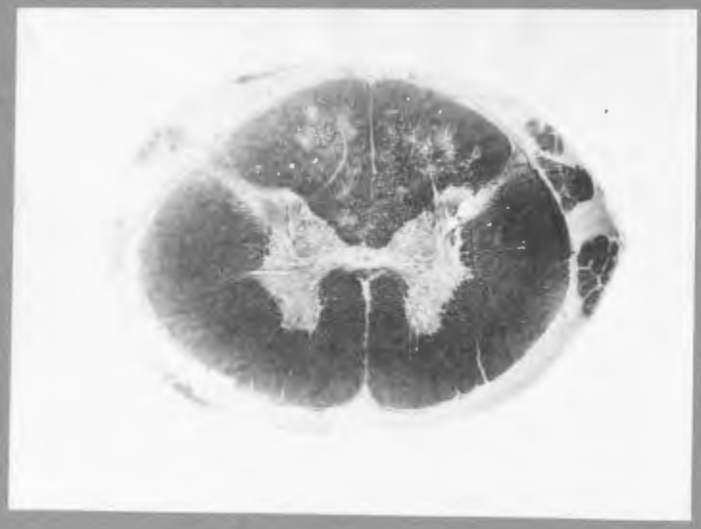


1

Fig. - (N35) Weigert. 11 D segment.

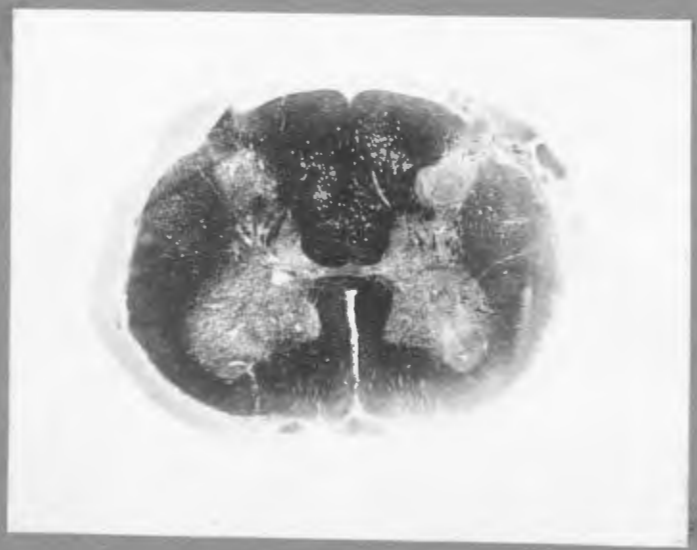
2

Fig. - (N46) Weigert. 1 D segment.



3

Fig. - (N10) Weigert. 1 L segment.
Showing several areas with vessels in center, also groups of and individual ballooned sheaths not in relation to vessels.

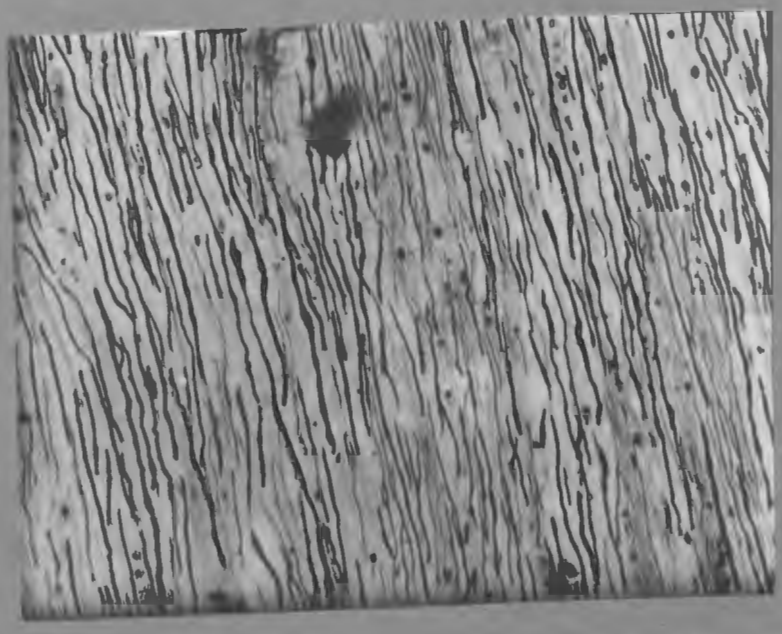


4

Fig. - (N118) Weigert. 2 L segment.
A number of ballooned sheaths are seen. These are not in any apparent relation to blood vessels. Practically no sclerosis is seen at this level.

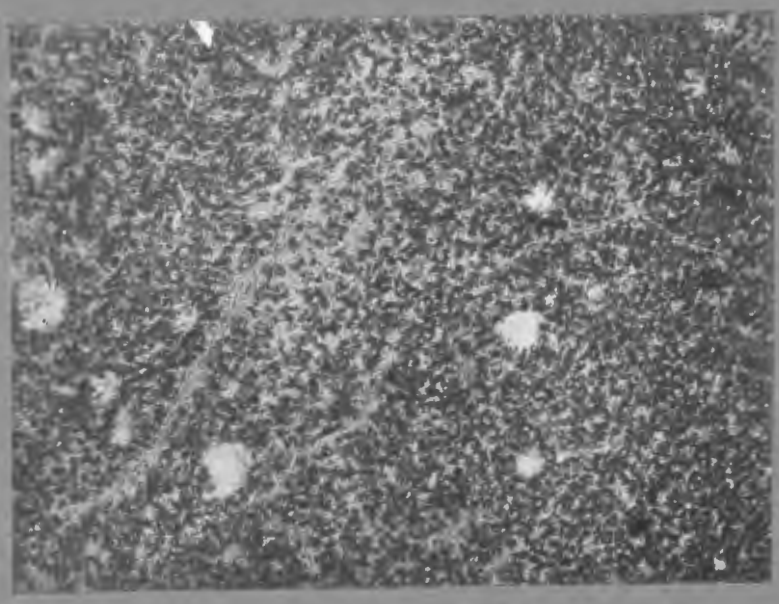
5

Fig. - (N137) Thionin. Posterior root ganglim. Excessive pigmentation and pale staining cells.



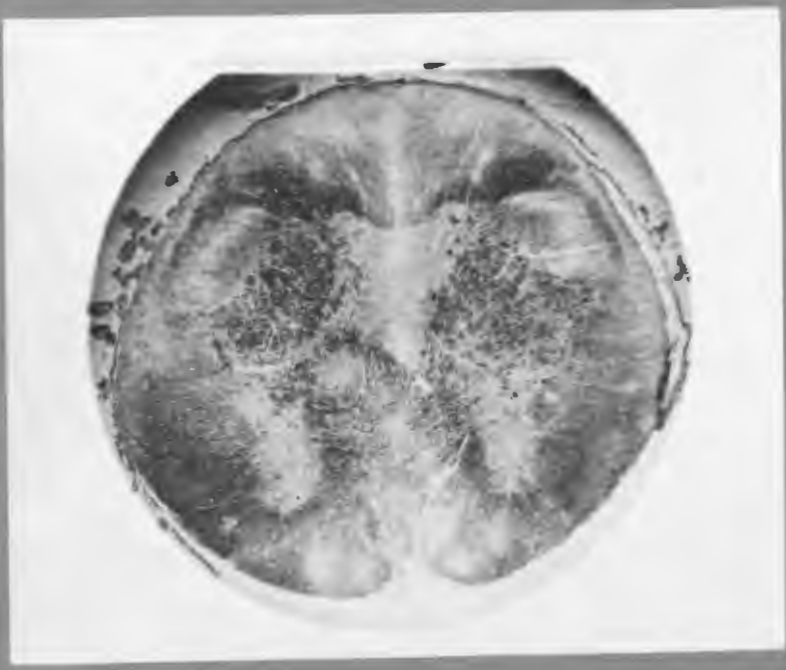
6

Fig. - (N125) Bielschowsky.
Some tendency to irregularities in the fibers.



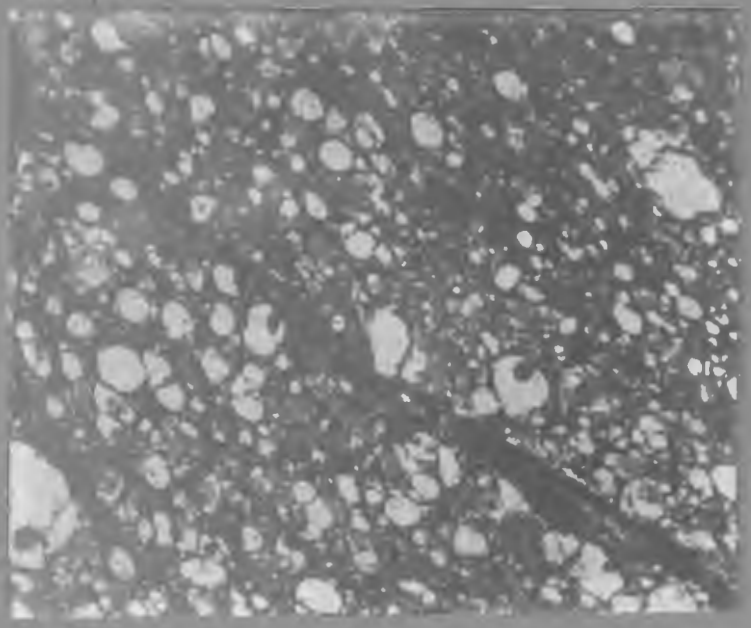
7

Fig. - (N10) Weigert. Showing an area in relation to a pial vessel containing no swollen sheaths. Ballooned sheaths are scattered through and in groups in the posterior columns.



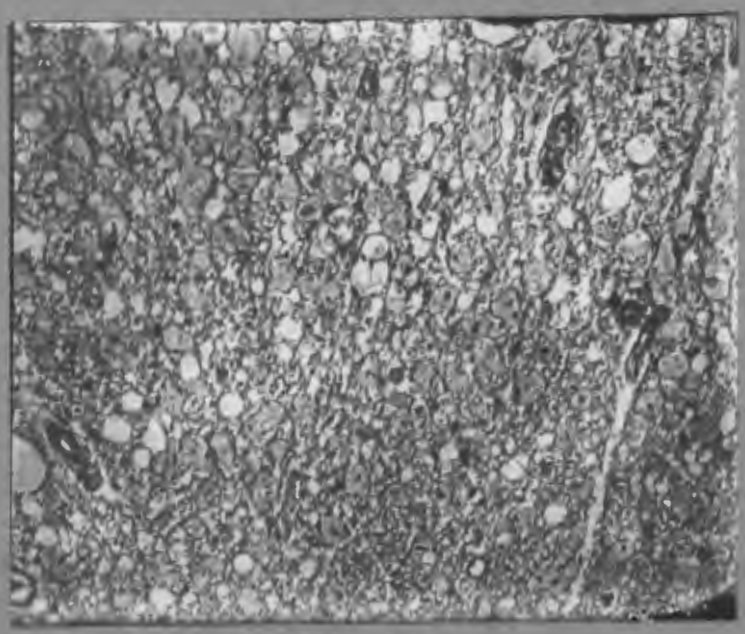
8

Fig. - (N35) Weigert. Lower medulla. Ballooned sheaths are numerous in the pyramidal tracts. Old sclerosis in the posterior column and cerebellar tracts.



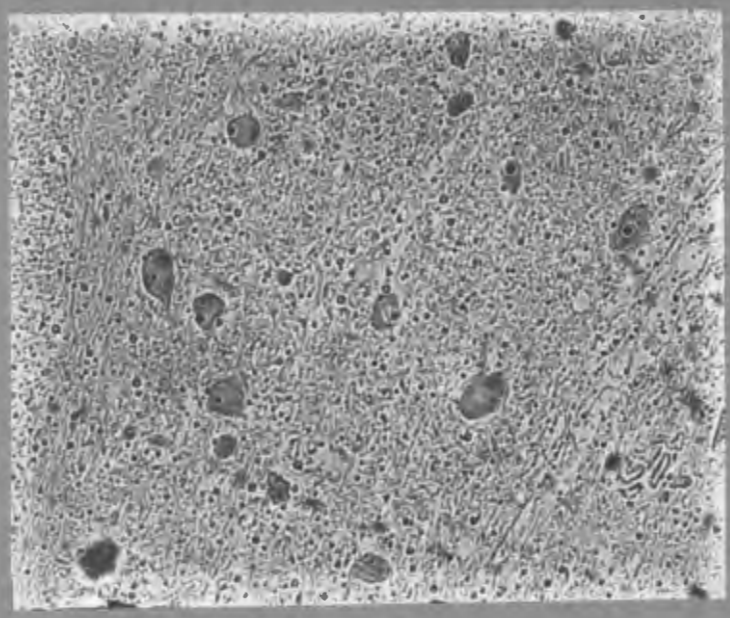
9

Fig. - (N137) Iron hematoxylin. 6 D segment.
Large numbers of fat granule cells are seen in the glia meshes.



10

Fig. - (127) Lichtgruenfuchsin.
Mid dorsal region; posterior column. Fat granule cells occupying the glia meshes and spaces in the ballooned sheaths

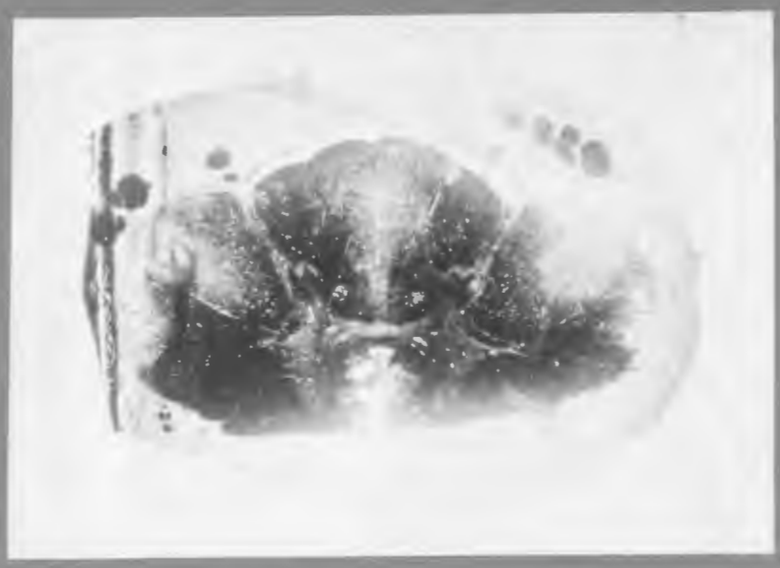


11

Fig. - (N130) Thionin. Chromalytic changes in cells of Clark's column.

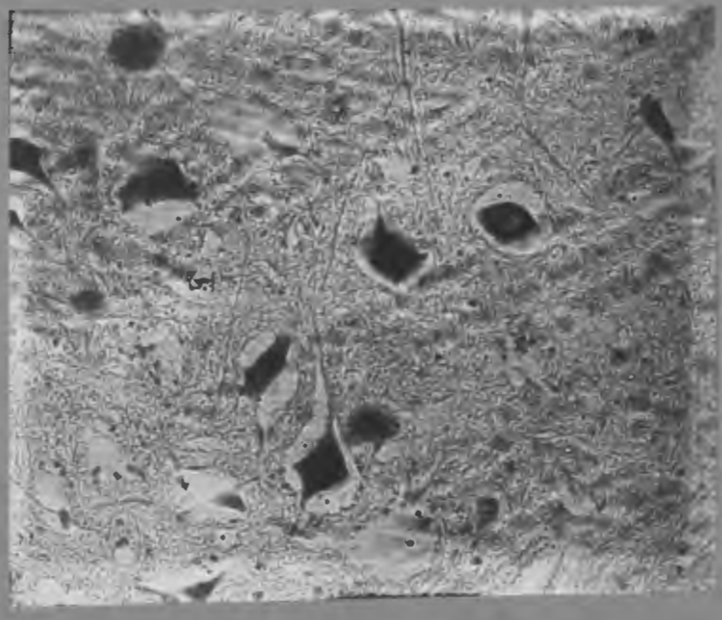
12

Fig. - (N10) Weigert. 7 D segment. A small perivascular area is seen in the posterior column.



13

Fig. - (N49) Weigert. 1 D segment.



14

Fig. - (N127) Kresyl - . Violet anterior horn cells. Dilated pericellular lymph spaces.