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CHRONIC HYPERTROPHIC SPINAL PACHYMENINGITIS¹

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The immediate stimulus to the writing of the present article was our experience with a case of unusual interest, admitted to the hospital of the University of Pennsylvania, May 28, 1910. This case, before it came under the observation of the writers, had presented active symptoms for about one year, during which time several diagnoses had been made. The one most favored for several months by the physicians in attendance was that of grave hysteria, this diagnostic view having been reached largely because of the great variability in the symptoms presented, and also because of some mental peculiarities, which had developed during the progress of the case, these being chiefly a tendency to unreliability of statement and great suggestibility in connection both with the relief and the production of symptoms. The experience on which this paper is based, however, is by no means exclusively confined to this instructive and unusual case.

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Early in the professional experience of one of us a case of pachymeningitis, localized to the lower bulbar and upper cervical region, was diagnosticated during life as one of hydrophobia, necropsy showing its real nature. The bulbar forms or bulbar extension of hypertrophic spinal pachymeningitis are now comparatively well known, although the number placed on record is limited.

In another case recorded clinically during the life of the patient, although under an incorrect diagnosis, hypertrophic spinal pachymeningitis, confined chiefly to the lower cervical and thoracic region was discovered at necropsy.

An interesting case reported by Dejerine and Tinel shows the importance of an early diagnosis of pachymeningitis as well as its difficulty. In this case the meningitis had extended until it involved pontile, bulbar, and cerebellar parts. The Brown-Séquard syndrome was present with cerebellar symptoms, with epileptiform seizures, vomiting, and papillary stasis, resembling brain tumor more than a pachymeningitis. The absence of cranial nerve involvement with such extensive basilar thickening was remarkable in this case.

Dr. Mills and Dr. Spiller placed on record a case of generally diffused external pachymeningitis, but this represented a different type from that recorded in the present communication.

At the last meeting of this association in a paper on tumors and cysts of the spinal cord, Dr. Mills recorded a case of diffuse spinal meningitis with a subpial cyst, and referred also to other cases of this description which had been reported abroad and in this country, notably by Schlesinger, Horsley, Bliss, Krause, Oppenheim, Spiller, Musser and Martin; and Weisenburg. The cases referred to by these writers, however, were different in character from the subject of the present communication. They represented in part or together, cases of the so-called circumscribed serous meningitis. The point to which we wish to direct attention, however, is that in most of these cases the meningitis present was widely diffuse and was in some instances, at least in part, of the form of an internal hypertrophic pachymeningitis, adhesions having formed in single and separated portions of the inflamed membrane.

The present case had in its symptomatology much the appearance of the classical cervical hypertrophic pachymeningitis of

Charcot and Joffroy. Certain features in its symptomatology, however, which became more evident after operation and necropsy, served to separate it from the original Charcot-Joffroy type, and the presence of these features is among the reasons which would seem to call for the careful recording of the case. Atrophy and loss of power in the trunkal muscles were, for instance, among the symptoms.

Among the features of the case which call for special review are those concerned with the explanation of the variability in the symptoms, and the peculiarities in the sensory disturbance. The resemblance of the case to a cervico-thoracic tumor, to a somewhat aberrant form of syringomyelia, and to amyotrophic lateral sclerosis, is a matter of some interest. The existence of rudimentary cervical ribs is also of passing interest.

No feature in this case is of greater clinical interest than the variability of the symptoms presented by the patient up to two or three weeks before operation. This variability in symptomatology led to at least two erroneous diagnoses—at an early date that of hysteria, and later that of circumscribed serous meningitis. Almost a year before her death the patient was for a time bedridden, apparently unable to stand or walk, but chiefly under the influence of strong suggestion regained her feet and continued to stand and walk with occasional short periods of relapse, until six weeks before her death. The deep reflexes in the lower extremities presented so extreme a variation that on one day foot clonus and the Babinski reflex were present and persistent, while on the next or within a day or two these phenomena could not be elicited. Even the distal portion of the upper extremities varied considerably from day to day. The sensory symptoms also showed some variations and differences, both in the upper extremities and in the trunk and lower limbs.

The best explanation of these variations seems to be indicated by the microscopical findings.

The widespread obliteration or partial obliteration of the vessels of the membranes and cord would have caused much variation in the blood supply under the influence of general vascular states; even those vessels which were patulous were thickened and inelastic and would have failed to respond in a compensating way for differences in general blood pressure. The number of spinal cells having been greatly reduced, local

areas in the cord would also have been much more readily fatigued.

Cases of chronic hypertrophic pachymeningitis may, as in this instance, lead to difficulties in their diagnosis, the diseases most resembling it being amyotrophic lateral sclerosis, syringomyelia, multiple neuritis, cord tumor, circumscribed meningeal cyst, and supernumerary ribs. Hysteria, while diagnosticated as such in our own case, should not cause any difficulty where such distinct organic signs occur either early or late as were present. Hysterical symptoms might occur concomitantly, but should not obscure the organic condition present.

Amyotrophic lateral sclerosis presents a picture resembling in some respects that of pachymeningitis, but the absence of pain in amyotrophic lateral sclerosis is a distinguishing sign, and when pain does occur it is not intense and is due to fatigue or overstretching of muscles and joints, and cannot be definitely ascribed to nerve distributions. Paresthesias and objective changes in the senses of pain, temperature, and touch, are not found in this disease, although of frequent and often of early occurrence in pachymeningitis. Bladder disturbances if present are entirely against any diagnosis of amyotrophic lateral sclerosis.

Symptoms common to syringomyelia and chronic hypertrophic pachymeningitis are muscular atrophy and loss of power with loss of reflexes in the motor arcs affected, deep reflexes increased in those below the affected arcs, and objective sensory changes. These sensory changes may be to some degree dissociated in pachymeningitis, but generally they are not so marked or so distinctly defined as in syringomyelia. In the former, also, a preponderance of subjective sensory symptoms will be found as a rule, such as intense pain and paresthesias along the distributions of the nerves involved. A certain degree of spinal rigidity occurs in both these affections, but it is more marked in pachymeningitis. The atrophy in both cases involves more often and more extensively the muscles of the hands and forearms, with greater tendency to further extension in pachymeningitis and with greater trophic changes in syringomyelia. The so-called succulent hand (main succulente) of the French writers does not occur, or at least very rarely in pachymeningeal cases.

Multiple neuritis might be confused with a case of pachymeningitis at its incipency, as pain is then a most prominent symptom

in both diseases. The excessive tenderness of the nerve trunks in neuritis with the absence of early objective sensory signs would aid in the differentiation, while the later occurrence of muscular atrophy would add to the certainty of diagnosis of pachymeningitis. In multiple neuritis a decrease of the deep reflexes of the lower limbs occurs in contrast to the usual increase in pachymeningitis. A history of some predisposing or exciting factor in neuritis is of importance, such as previous alcoholism, infectious fevers, metallic poisons, etc. A history of lues or traumatism is of some etiological significance in cases of pachymeningitis.

Tumors of the cervical cord in some instances give symptom complexes very difficult or even impossible to distinguish from that of pachymeningitis. Muscular atrophies and loss of power and reflexes with increased reflexes below the affected arcs, paresthesias and anesthetics with subjective pain, all are prominent symptoms in both diseases. The pain is possibly more excruciating and sharper or more lancinating in tumor cases, while those of pachymeningitis often have some rigidity and soreness of the neck and aching of the shoulders preceding the violent pain by a period of months or even years. The occurrence of segmental distribution of objective sensory changes points more to tumor. The X-ray is of value in showing a new growth, though not always certain in the result.

In circumscribed cysts the picture may resemble that of tumor, and differential points of the former would be of almost equal value for this condition. However, pain here is usually of less intensity and often somewhat fluctuating. The fluctuation of the symptoms has been supposed by some to be pathognomonic of circumscribed cyst, but this rapidity in the change of symptoms occurred in our case. Any case of pachymeningitis could readily form a cyst, thus causing a compound condition. Motor loss and atrophy as a rule are not so marked in cases of circumscribed cyst as in those of tumor or pachymeningitis.

In cases of supernumerary ribs any muscular atrophy or other trophic changes, loss of power, or sensory changes are due to peripheral nerve or plexus involvement. No increase of deep reflexes in the lower limbs occurs, and no sign of organic cord or meningeal lesion such as pains and sensory changes in trunk or legs, and the presence of ankle clonus and dorsal extension of

the great toe upon irritation of the sole of the foot. Interference with vesical and rectal control also never occurs in cases of cervical ribs. The presence of the bony overgrowth may often be easily palpated, and is always distinctly seen in radiographs. Weakness in one or both radial pulses is very common, and this weakness becomes more distinct upon pulling back the shoulders and arms so as to cause pressure of the cervical ribs upon the subclavian arteries.

Cervical tabes, a condition of rare occurrence, although frequent enough to enter into consideration, has a complex of symptoms greatly resembling the present case. The shooting pains in the arms with the lost reflexes and presence of paresthesias or even areas of objective sensory changes, might point toward either condition. Further, a difference in the pupillary reactions of the two sides might occur in pachymeningitis where the sympathetic fibers are involved at their exit from the cord, but a typical Argyll-Robertson pupil would not be obtainable and there might be other evidences of unilateral sympathetic involvement. The absence of knee-jerks and Achilles reflexes would be a feature of tabes strongly opposed to the heightened lower limb reflexes of pachymeningitis cervicalis hypertrophica, although the loss of reflexes is often lacking in cases of tabes cervicalis. Ataxic conditions of the arms would probably be more marked in tabes. Romberg's sign with areas of hypesthesia, bladder and rectal disturbances showing involvement by tabes of the lower parts of the cord, could later occur and clear the diagnosis, while ocular palsies and optic nerve atrophies are of further diagnostic significance.

The question of operative treatment in cases of this sort is of much practical importance. While no harm was done and death was here probably deferred rather than hastened, nevertheless the results to be obtained from surgical procedure in such a case are not sufficient to warrant it. The operation in this case was decided upon chiefly with the hope of discovering a circumscribed serous meningitis or a cervical tumor or pachymeningitis so localized as to be removable.

The case summarized is as follows: The patient was a woman about forty-five years old. For several years she had had occasional pains at the lower part of the back of the neck, and between her shoulders, and thirteen or fourteen months before she came

under observation she first experienced severe pain in her back between the shoulders, followed in a few days by weakness in the right arm and hand. About two weeks later she lost power in the lower limbs so that she was unable to walk, the right limb being more affected than the left. After a few weeks she recovered power in the lower limbs, losing it again a few weeks later. Seven months later she had an attack of severe pain in her head followed by nausea and vomiting and a convulsion. Her position in this and in some subsequent convulsive attacks, was that of opisthotonos. She would remain unconscious or partially so for several hours. Altogether she had a half dozen of such attacks. During five months before she was first seen she showed a curious condition of varying power in the lower extremities, being sometimes unable to walk, while at others she could go about a room or the house holding on to furniture or other supporting objects. This variability in her power to use her lower extremities was so marked that her attending physician was strongly inclined to believe that the case was one of hysteria.

Examination showed mentality clear but memory defective. The patient was inaccurate in her statements.

The ocular movements were free in all directions. The pupils were slightly dilated, the left being a little larger than the right. Both reacted promptly to light and accommodation.

Examination showed no impairment of the muscles supplied by the 5th or 7th nerve. The tongue when protruded deviated slightly to the left of the median line; it showed slight fibrillary tremor. Sensation was intact on the face, head and neck. The vision and hearing were good. There was no stiffness of the neck.

Both upper extremities were weak, the right considerably more than the left. In the distal portions of the limbs the weakness amounted to almost complete paralysis on the right side, especially for movements of the hand and fingers. Atrophy was very marked in the forearms and in the hands, involving the thenar and hypothenar eminences and interossei muscles. This atrophy was more marked on the right. Some contracture and deformity was present in accordance with the paralysis and atrophy. Relatively, power was largely retained above the elbows. Touch and pain senses were retained but diminished in the upper extremities. The patient apparently failed to locate the pain. Temperature appeared normal in the upper arms but was markedly affected in the forearms, most notably on the ulnar side, and was lost in the right hand. The same conditions were present but not so positive on the left side. Sense of position was retained on each side, but the patient could not recognize objects properly, in the main because of loss of power. Some objects could be recognized in the partially paralyzed left hand. These notes as to sensation were taken when she was first

examined. Later hyperesthesia appeared in the entire left upper extremity.

The tendon and muscle jerks in the upper extremities showed some increase and variation.

Wasting was general of the muscles of the trunk, especially of those of the back. The patient was unable during the eight weeks of her stay to sit up in bed without support, apparently because of the weakness of the trunkal muscles.

The sensory investigations showed differences at different examinations. In one examination, for instance, impairment of tactile sense was present up to the mammary region. Pain and temperature sensations were impaired to a level below that of the tactile diminution. A late examination for sensation made by Dr. Mills on June 10th gave the following results:

On the ulnar aspect of the hand and forearm the patient called cold, hot; rarely hot, cold. The temperature sensation for cold was somewhat delayed. The areas for impairment of temperature sensation were not definitely outlined, but the preponderance of change seemed to be on the ulnar and postaxial aspects of the hand and forearm. Examination of the upper thorax on the left showed a confusion of hot and cold sensations. The pain sense at this investigation did not appear to be changed, like that of temperature.

Voluntary power in the lower extremities on several examinations was almost gone. The patient could not draw up the limbs while in bed, but flexion and extension of the foot were preserved on each side. No wasting of the lower extremities was detectable. Touch and pain senses were not impaired in the lower extremities, but temperature sense was much disturbed, and so irregularly that the areas of disturbance could not be definitely outlined.

At an early examination after admission to the hospital the knee-jerks were very prompt. The Babinski reflex was present on each side. Slight foot clonus could be elicited on the right side but only at times, while on the left it was not present. A few days later the knee-jerks and ankle-jerks were about normal and no foot clonus or even the extensor Babinski response could be elicited. Two days after this the deep and superficial reflexes were slightly exaggerated. Persistent foot clonus and the Babinski extension of the toes were present on both sides; there was also a tendency to lateral clonus. The von Bechterew, Sinkler and Oppenheim reflexes were all obtained.

The extraordinary variability in symptoms, in both the upper and lower extremities, especially in the motor and reflex symptomatology in the lower extremities, was a striking feature in the case up to a few days before operation. The reflexes and sensation were varied as above indicated. At one examination the patient was unable to move her hands on her wrists, or to draw up either

lower extremity; at another she had considerable power in the flexors and extensors at the wrist and could forcibly draw up the lower limbs.

The patient had complete loss of control over the bladder and rectum, both when lying down and when sitting up supported.

As some of the symptoms indicated the possibility of cervical ribs, these were examined for and it was believed were detected by deep palpation. A Roentgen-ray examination was then made by Dr. Henry K. Pancoast, with the following results:

Supernumerary ribs turned downward were found on each side. These ribs were rather rudimentary, the one on the left side being somewhat longer.

The usual vascular symptoms of cervical ribs were not much in evidence. The radial artery on each side was patulous and the pulse well defined on elevating the arms. The pulse volume diminished somewhat when the arm was drawn fully backward.

The etiology of this case may be regarded as uncertain. Although the patient's husband had a specific history, she had not had any miscarriages, and evidences of infection were lacking. Her mother died of tuberculosis, as did also one sister. Another sister died of cancer of the uterus, the father of some form of stomach trouble.

As the patient had been thoroughly treated with iodides and mercury without any improvement, and as the Wassermann and Noguchi tests, made by Dr. E. P. Corson-White were negative, the question of operation was taken up and it was finally decided to have a cervical laminectomy performed for the purpose of exploration, and also for the removal of a growth or of the thickened membranes. The operation was performed by Dr. Charles H. Frazier, June 20, 1910. The following are the notes of the operation:

Under nitrous oxide, ether anesthesia, preceded by morphine grain $\frac{1}{6}$, atropine grain $\frac{1}{150}$, patient lying upon her left side, an incision was made having the 7th cervical vertebra as its center. The spines and laminae were removed from the 5th, 6th and 7th cervical vertebrae. Upon exposing the dura it was found to be much thicker than normal with dense adhesions between the dura and pia, but not between the dura and bone. The pia also was found to be thickened and there were dense adhesions between the pia and cord. It was quite evident from the appearance of the cord that we were dealing with an inflammatory lesion and not a neoplasm, and that the lesion was of such character as not to be amenable to surgical therapy. Consequently after these exploratory measures we proceeded to close the wound. The pia was closed with fine catgut suture but in order to afford some relief of pressure the dura was left unsewed. The muscles and fascia were sutured with a continuous catgut, and the skin with a continuous silk suture. A small cigarette drain was inserted

through a stab wound near the lower angle of the wound. The patient left the operating table in excellent condition but shortly afterwards her temperature began to rise rapidly and her pulse to become more frequent, until within a few hours her temperature was over 104° and her pulse 130.

The patient's condition, however, gradually improved up to a certain point. The wound healed by first intention throughout, and the sutures were removed six days after the operation. Eight days later she was transferred again to the service of Dr. Mills.

The patient died a few days later.

The only necropsy allowed was of the spinal cord and its membranes. These were removed and were examined in the laboratory of neuropathology of the University of Pennsylvania by Dr. Williams. The following is a summary of the results of his examinations:

Macroscopically the dura and pia-arachnoid were very much thickened throughout the entire length. The area of greatest thickening extended from the highest cervical to about the second thoracic segment. The entire cervical enlargement was distorted and deformed, being flattened antero-posteriorly, the membranes here forming a solid mass, firmly adherent to the cord substance. Below this area the inner membranes were firmly adherent to the cord but the dura did not adhere as in the upper segments. Along the posterior portion of the cord in the lower cervical region was slight evidence of an old sub-dural hemorrhage, giving the appearance of a very narrow yellow streak on the pia-arachnoid.

Microscopically the thickening of the membranes was confirmed. The vessels were all very much congested and the changes were in detail as follows:

First Cervical.—The pia-arachnoid and particularly the dura are greatly thickened and the vessels congested. The shape of the section is somewhat irregular. A distinct zone of peripheral degeneration with some degeneration more or less diffuse throughout the section is present. The posterior columns, more markedly the columns of Goll, are so degenerated as to give a condition similar to that of tabes. Degeneration is more intense immediately surrounding the blood vessels and along the septæ of the white substance, these being considerably thickened throughout. The posterior root entering fibers are partly degenerated and none of them appear entirely normal, having a wavy, tortuous, and swollen appearance. The vessel coats are greatly thickened and their luminae very narrow. The congestion is great in both white and gray substance, especially in the latter, and in some places are perivascular hemorrhages, and some slight degree of vascular infiltration is present. The cells are for the most part normal, though different stages of degeneration can be seen in some of them.

Second Cervical.—The meninges here are much more thickened and a rather intense grade of infiltration can be seen. This is more marked posteriorly and is probably a post-operative reaction. The vascular congestion is only slight. Layers and clumps of newly formed connective tissue cells can be seen throughout the pia. These are particularly numerous about the thickened arteries. This is probably a reactive increase, and its intensity seems to depend in large measure upon the degree of closure of the vessels. Both the anterior and posterior roots contain only a few healthy fibers. The entering root zones show an entire absence of normal fibers, those fibers present being broken down and finely beaded. The anterior roots are divided into columns much more distinctly than normal by an excessive growth of the interstitial trabeculæ.

Many of these cell groups have linear nuclei of typical connective tissue type, while some show a round or oblong shape, this being due either to a transverse cutting of the nuclei as would occur if the connective tissue cells were in axis of the nuclei, or to their being young and round or oblong in shape and not yet having acquired cylindrical form.

The calcified vessels, particularly where the lumen is completely occluded, have the appearance of the arenaceous bodies described by Spiller and lend further proof to his suggestion concerning their origin. The intra-medullary vessels are congested and tortuous and the coats greatly thickened. The ganglion cells are only in a few instances degenerated sufficiently to show any change in structure.

Third Cervical.—The sections here are irregular in shape. The cord is partially twisted and rotated toward the left and flattened so as to form an irregular triangle, the base being formed by the ventral cord surface and the apex consisting of the right posterior horn area. The membranes are thickened, infiltrated, and firmly adherent to the periphery of the cord. The greatly thickened vessels are congested and calcified, the latter condition causing varying degrees of occlusion of the lumen. The posterior roots are greatly degenerated, particularly on the left, but it is doubtful whether any entirely normal fibers are present in the posterior or anterior roots on either side. A broad and distinct zone of peripheral degeneration can be seen and this degenerative change extends diffusely throughout the entire white substance, preponderating, however, in the white matter of the posterior columns. The vessels in the cord are congested and tortuous. The anterior horn cells are slightly changed, but a great many are almost normal. The posterior horn cells, however, are practically absent.

Fourth Cervical.—The entire section is irregularly flattened antero-posteriorly, and the anterior horns spread lateralwards. The extreme thickening of the dura and pia-arachnoid forms a

mass strongly adherent to the cord and portions extend as trabeculæ into the substance of the posterior roots. The marked peripheral degeneration has extended also along the septa and is particularly noticeable in the posterior columns and along the borders of the anterior fissure, Gowers' antero-lateral area, and the crossed pyramidal tracts. With the exception of the increased thickness and distorting effect, and the greater number of calcareous arteries (mostly in the postero-lateral portion), the meninges do not differ appreciably from the condition in other levels of the cord. The posterior horn cells are absent almost entirely. Those of the anterior horns are not greatly decreased in number, but many of them are greatly degenerated, and it is doubtful whether any of them are really normal cells. The nuclei in many instances are absent or they are indistinct and irregular in shape, and the cell pigment is increased far in excess of the normal. The vessels are extremely tortuous, congested, and sclerosed, and remains of minute perivascular hemorrhages can be found in the gray substance.

Mid-dorsal.—The sections have the irregular outline of a normal cord. The membranes are not so thickened as in the previously described areas, but otherwise are the same. The cord substance in addition to the zonal area of degeneration, shows degenerative changes extending into the substance, along the septa and the crossed pyramidal tracts, and those in the region of what is known as Gowers' area are almost totally destroyed. Cells are present in Clarke's columns and in both the anterior and the posterior horns, but only in a few in the posterior horn was there an approach to the normal condition, and none even of these could be called healthy functioning cells. Numerous amyloid bodies are seen throughout the posterior columns and in lesser numbers in the remainder of the section. The degenerated areas are replaced by an overgrowth of sclerotic tissue of a connective tissue character.

Second Lumbar.—The meninges are not so thickened nor so infiltrated as in the foregoing levels and the cord has a regular contour. The anterior roots are slightly degenerated, the posterior ones much more so; in these latter the fibers are very beaded in appearance. In both the anterior and the posterior roots the overgrowth of connective tissue trabeculæ is excessive, and the vessels are congested. The area of peripheral degeneration is not so broad as in the other levels. The changes along the septa are only slight. The most extensive degeneration is in the crossed pyramidal region. The posterior horn cells are almost absent, and those present are degenerated. The cells of the anterior horns are numerous and most of them are only slightly changed.

Correlating in summary form the gross and microscopical find-

ings, especially the latter, with the symptomatology of this case the following conclusions would seem to be justified.

In the first place, of interest microscopically would be the diffuse and extensive character of the meningitis, with the preponderance of the changes in the cervical enlargement. The infiltration was more excessive in the cervical region and particularly in the posterior part. This was probably due to postoperative reaction, but might have been confused with a possible luetic process. The degeneration involving so many of the fibers of the posterior columns, as well as those of the antero-lateral tracts, seems to have been greatly out of proportion to the minor degree of objective sensory changes. The excessive degeneration of the posterior roots and of the posterior horn cells throughout the cord would also lead one to expect greater sensory involvement. The greater involvement of the temperature and pain senses as shown in the clinical history of the case may find its explanation in the location of these areas of degeneration.

Degeneration of the anterior horn cells became very marked, first at and below the level of the fourth cervical segment, this explaining the greater loss of power and atrophy in the forearms and hands. The wasting and weakness of all the trunkal muscles were also attributable to the degeneration of the anterior horn cells in the dorsal region. The cellular constituents of the lumbar anterior horns being so well preserved accounted for the absence of any atrophy in the lower extremities, whereas the loss of power and the increase of deep reflexes were dependent upon the distinct degeneration in the cross pyramidal tracts. The vascular thickening and tortuosity of the vessels with calcification of their coats in many instances, and the extension of the degeneration from the immediate vicinity of these vessels and the trabeculae together with the overgrowth of the latter in both the cord and the root substance are of some interest.

The various degrees of closure of the luminae of the calcified vessels caused different degrees of increase of the surrounding connective tissue cells. The vessels which were completely closed having the appearance of corpora arenacea and thus gave more evidence to the theory of the vascular origin of these bodies. The variability of the clinical symptomatology might be accounted for by vascular conditions. When vessels are so sclerosed and their coats so thickened as in this case, it would not require great

systematic vascular changes to cause marked changes in the cord, such as anemia or congestion. On the other hand where there are so few normal cells present, these more readily become fatigued in such a way possibly as to cause this great variation in the symptoms.

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