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PARALYSIS AGITANS AND SARCOMA.

REPORT OF A CASE, WITH AUTOPSY.

By Charles L. Dana, M.D.,
OF NEW YORK.

My interest in the pathology and pathological anatomy of paralysis agitans began some six years ago, when I read a paper before the Philadelphia Neurological Society upon this subject, and reported the results of an examination of two cases, with autopsies.[1]

A third case was reported by me in the *Post-Graduate* for July, 1896, special neurological number, page 332.

I recently, with the assistance of Dr. Fraenkel and Dr. Muskins, have been able to make a study of the pathological findings in a fourth case, and it is the result of this which I wish to submit. The patient was an inmate of the Montefiore Home, and most of the clinical study was made by Dr. Fraenkel, to whose notes I am indebted. The pathological examination was made by myself and by Dr. L. J. J. Muskins, who contributes some specially careful and laborious studies as to the degree of degenerative change in the cells.

The history of the case is as follows:

J. B., aged sixty-one years, occupation peddler, nativity Hungary, resident of the United States seventeen years. The family history shows us nothing of importance; father dying at sixty-seven, neither parent having any nervous or mental disease. The patient married at twenty-one, and had nine living and several still-born children; had malaria, but denied syphilis, and had been moderate in the use of alcohol and tobacco. Present disease began in 1891, seven years before

[1] Philadelphia Neurological Society, February 27, 1893; New York Medical Journal, June 10, 1893.

his death. The cause is unknown, but the patient ascribed it to a fright and fall on the street. The first symptoms were tremor in the left hand, followed by some weakness in that arm. The tremor progressed its usual way, from arm to leg, and from the left side to the right. It involved also, rather early, his speech. He was admitted to the Montefiore Home in 1897. At that time the examination by Dr. Fraenkel showed the following condition: His mental condition is fairly good, though he is slow in thought and not always correct in his calculations. His memory is good. Emotional condition is rather active, as is usually the case in this disease. The speech is monotonous, slow, and at times unintelligible. His physiognomy presents the flushed face and mask-like appearance characteristic of Parkinson's disease. He has the tremor in the arms and head, also in the legs to a less extent. This tremor, while in general slight and stable, increases at times on intentional movements. There is a very considerable rigidity of the limbs, as well as weakness, so that the patient walks with difficulty. He has also the usual trouble in initiating movement; thus when he first begins to rise from a chair he fails, and has to make several consecutive efforts before he finally succeeds. After about twelve or fifteen attempts he gets up quickly, uttering a sigh of relief; all the time his lips, hands, feet, and legs are trembling with more or less intensity. His station is that of the pronounced paralysis agitans type, and the gait is equally characteristic, the steps being quick and short, with a tendency to retropulsion when the patient stops.

The tremor affects the lips, the neck muscles, the arms and hands, and the legs equally. The head is flexed, trunk flexed, upper extremities adducted at the shoulder-joint, flexed at elbow-joint and the metacarpo-phalangeal joints, and extended in all the phalangeal joints. There is flexion at the knees and hips. The patient looks emaciated and very senile. The skin is dry and scabby, and in parts dotted with small hyperæmic-looking spots all over the body, showing the most of these disturbances in small or large areas, and localized, warty-like growths in the lower extremities, especially on the left. Some of these warts are ulcerating and discharging a bad-smelling hemorrhagic fluid.

The tongue is coated thickly, and when protruded trembles very perceptibly. Pharyngeal reflex is present and motility of soft palate undisturbed. There is inability to wrinkle the forehead, but the motility of the lower facial branches is normal. Pupils small, reaction good. Ocular movements very slow, and the patient cannot reach the extreme lateral positions. Vision and hearing seem normal, as do also smell and taste. There is some stiffness of the jaw and difficulty in swallowing. There is no disturbance of the sensibility of the skin. There is no ataxia or inco-ordination. Superficial reflexes are present and moderately lively; knee-jerks are present.

On electrical examination and stimulation there is a decided quantitative diminution of the direct reaction, and contraction is vermiform.

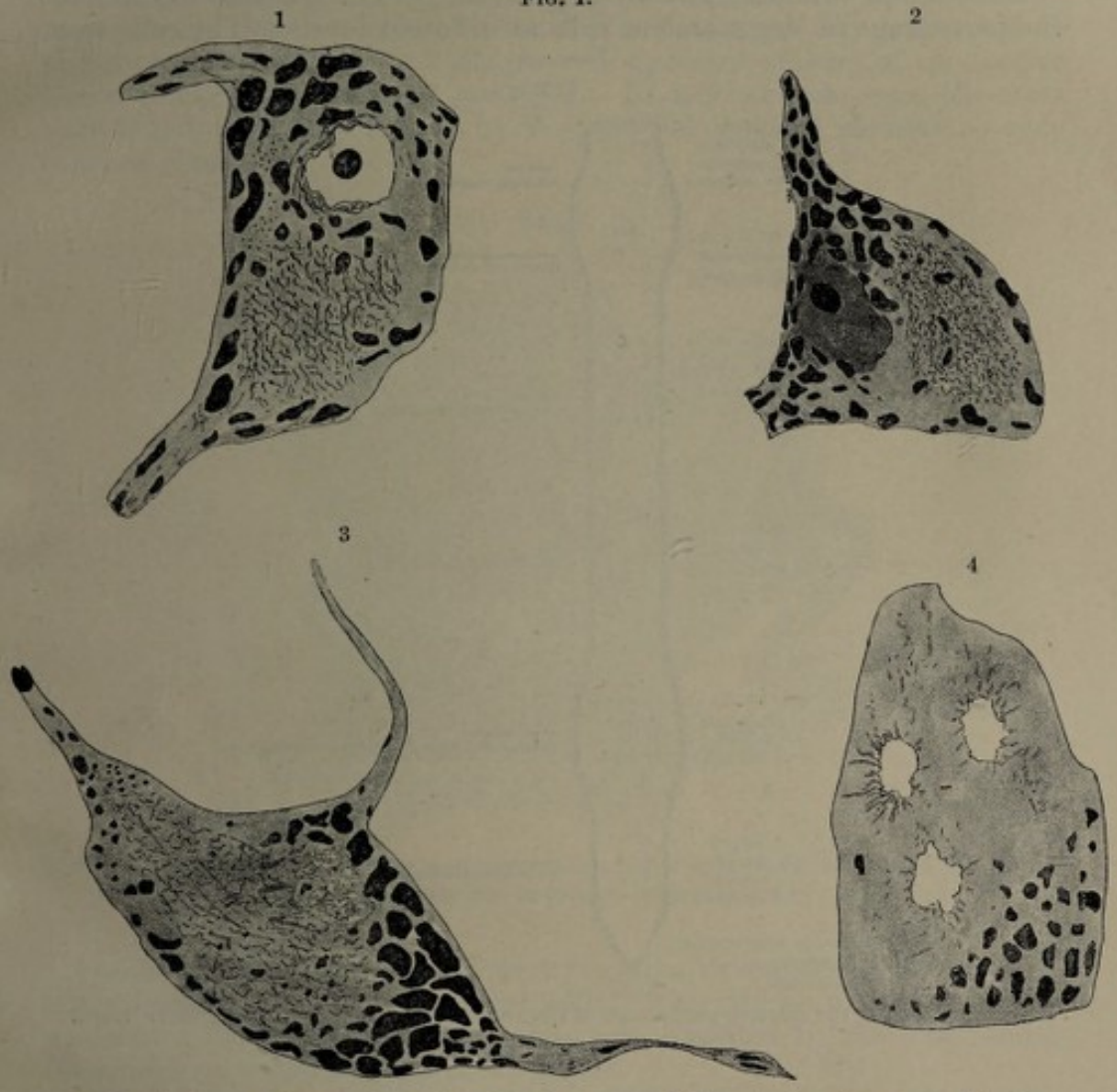
The condition outside of the nervous and muscular field is as follows: The pulse is 72, somewhat hard; temperature, 97.5°; respiration normal; heart and lungs are normal. Manner normal, and there are no anatomical stigmata of degeneration. The mouth is without teeth.

The patient's condition did not markedly change during the rest of his life, except that there was a steady increase in weakness, rigidity, and emaciation. The warty and ulcerating nodules of the skin, which

were diagnosed as sarcoma, increased and added to the exhaustion of the patient, who died finally of exhaustion after his illness had lasted *eight years.*

Post-mortem examination was made by Dr. Onuf, who carefully preserved the cord, brain, and parts of the sympathetic in formalin, alcohol, and in Mueller's fluid. The post-mortem, outside of the nervous centres, showed no lesion of importance except the cutaneous sarcoma.

FIG. 1.



1. Anterior horn cell, second lumbar, showing central pigmentation. 2. Second lumbar, lateral displacement of nucleus. 3. Anterior horn cell, upper dorsal, central pigmentation. 4. First dorsal, vacuolation loss of nucleus. (Nissl stain. 1/12 objective.) (MUSKINS.)

Examination of the Spinal Cord. Nissl stains were made by Dr. Muskins of the sections taken from the mid-cervical, upper dorsal, third and fourth dorsal, seventh dorsal, middle lumbar, and upper sacral regions. These showed very striking degenerative changes in the cells of the anterior horns. The changes consisted in marked pigmentation of the cell-body, chromatolyses, loss and displacement of the nucleus, atrophy, and loss of some of the dendrites. The absence of or defect in dendrites is common (Fig. 1). The pigmentation occupied, in some

cases, the periphery, involving nearly half the body of the cell, in other cases attacking the centre of the cell-body and following it out, leaving a peripheral portion of fairly healthy substance. In many cases the pigmented part had apparently dropped out, leaving vacuoles, and vacuolization of the cells is a more striking phenomenon than is often seen. This, I think, however, may be largely due to the bad preservation of the specimen, or, at least, due to a post-mortem chemical and mechanical change, caused by putting the tissue through various hardening processes.

An attempt was made, at my suggestion, by Dr. Muskins to estimate the percentage of degenerative cells at different levels. The cells were

FIG. 2.

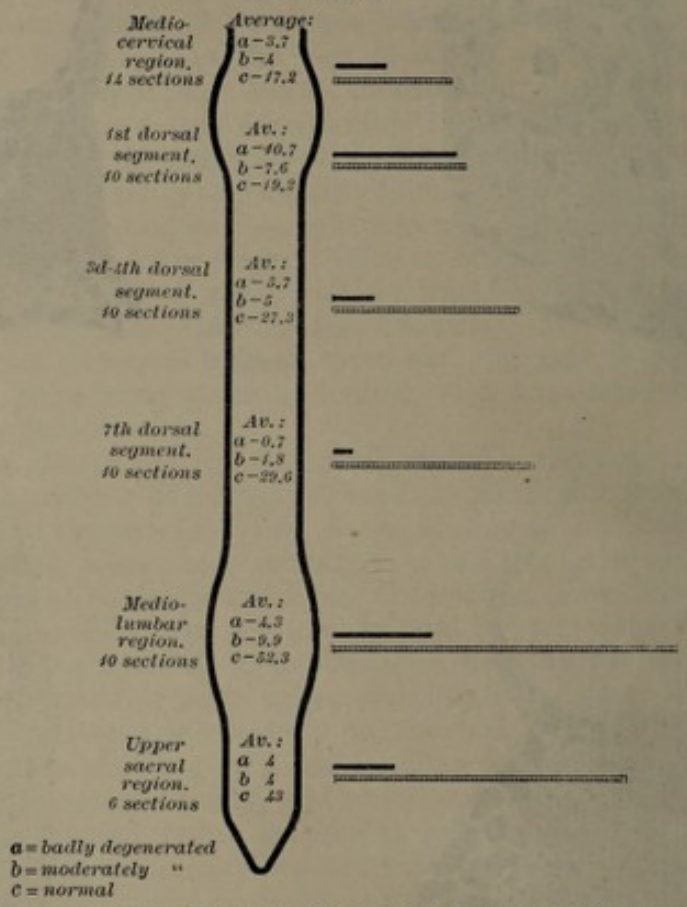


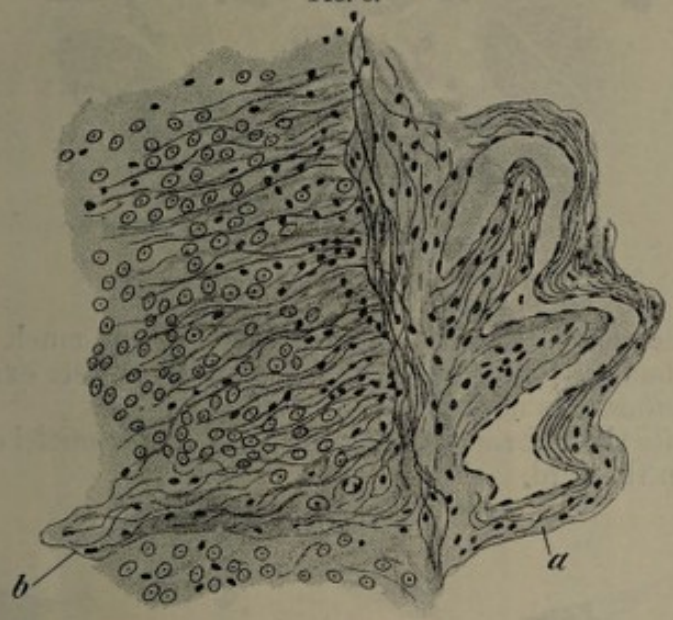
Diagram showing the relative percentage of degenerated nerve-cells in the anterior horn. Dark lines represent cells *a* and *b*.

divided into three categories: (*a*) Those that were extensively pigmented and degenerated, (*b*) those moderately so, and (*c*) those that were nearly normal. Cells of these three categories were counted in the different levels and percentages made out. In all the cells in sixty sections at different levels were counted. The percentages of cells indicated in group *c*, and degenerated cells, indicated by groups *a* and *b*, are shown diagrammatically in light and dark lines, respectively, upon the accompanying diagram (Fig. 2). It will be seen that the greatest proportion of degenerated cells was in the lower cervical and first dorsal sections—the area where the tremor first starts; next to that in the mid-cervical region, then in the mid-lumbar and upper sacral regions. The least affected portion seemed to be the middle dorsal and upper dorsal.

Examination of the columns of Clarke showed some degenerative changes, but, on the whole, their condition was fairly good, certainly much better proportionately than that of the cells of the anterior horns. It is impossible to place any very great weight upon the changes in this area.

The study of sections stained by carmine and Delafield stains, for purposes of determining the condition of connective tissue, showed slight increase in the interstitial connective tissue of the white matter. This is more marked in the marginal columns than in either the pyramidal tracts or the posterior columns, but it is not a very striking increase in either case. The anterior roots showed a greater amount of connective tissue thickening than the posterior. In neither case were the roots very much affected. Stains by Weigert-Pal method showed no very marked change.

FIG. 3.



Showing tortuous vein in posterior septum and slight connective tissue infiltration in posterior column. *a*, Vessel. *b*, Connective tissue. (Delafield stain.) (MUSKINS.)

Stains by the Marchi method were negative, except to show very strikingly degeneration of the cornual cells. The degree of degeneration was shown to be more extensive than was revealed by the Nissl stain. *There was no reaction in the white matter.*

Throughout the whole area of the cord, both in the gray and white matter, there were many large vacuolar areas, such as are often seen in degenerated spinal cords that have been hardened in alcohol. They indicate not only that there has been some general atrophy of the cord and connective tissue proliferation, but probably also some corresponding vascular congestion and dilatation of perivascular areas (Fig. 3).

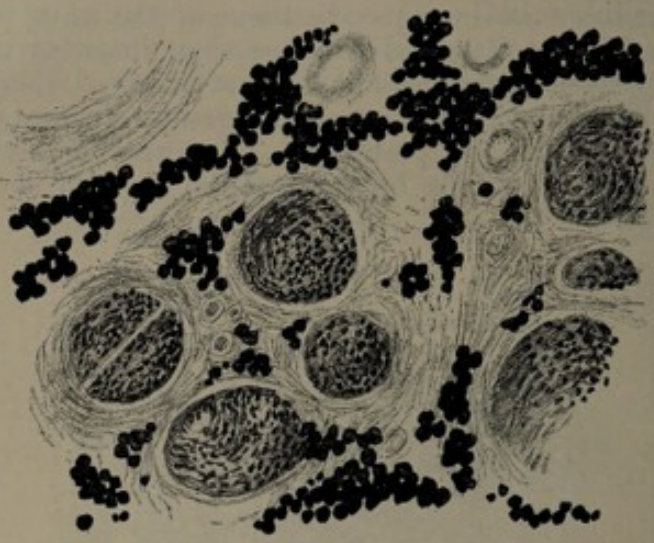
Occasionally one could see thickened bloodvessels, but on the whole the changes were slight. *There was no general arterial sclerosis.*

The sciatic and ulnar nerves were perfectly normal to Marchi and Weigert stains (Fig. 4).

Brain. The cells of the central convolutions show a considerable degree of degeneration. They are not much pigmented, but the nuclei

are often very large, and are surrounded by a bright area, showing that they are splitting away from the body; they are sometimes seen lying at the edge of the cell. There is chromatolysis, making the cell-body look like an open network—a kind of granular degeneration seen also in a previous case described by me. The cells are not much atrophied,

FIG. 4.



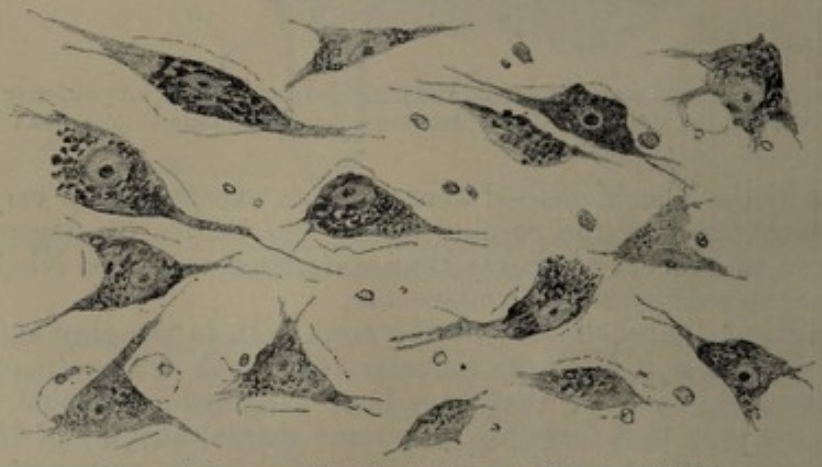
Ulnar nerve.

and the processes look fairly well. There is not much vascular or neurogliar change. Only the central convolutions were examined.

The *cerebellum* was normal.

The *medulla* showed some degeneration of motor nuclei cells—not as marked as in the cord.

FIG. 5.



Group of degenerated cells of olivary body. ¼ objective.

The *inferior olivary body-cells* showed moderate degeneration in nearly all cells, a change that has been noted by others (Fig. 5).

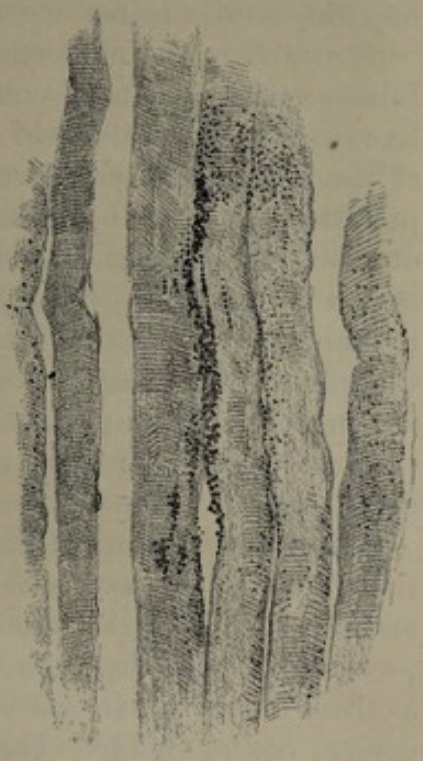
Examination of the Muscles. A piece of muscle from the adductor pollicis and another from the palmaris brevis were removed and stained with picro-carmine, and afterward by the Marchi method. The picric acid stain showed a striking difference between the coloring of different

muscle fibres, which was thought to be due, perhaps, to accidental differences in the impregnation with the dye. Examination by the Marchi method, however, showed that a large number of the fibres took on a dark stain, and were full of minute black granules of osmic acid, due to the presence of fat. Upon closer examination it could be seen that there was a slight fatty degeneration of many of the muscular fibres, while the others were apparently perfectly healthy. This staining was usually rather diffuse, but here and there in nearly every field one could see little patches of particularly dark staining, which appeared to be the nerve terminations (end-plates) upon the muscle. Staining by hæmatoxylin showed no increase in the nuclei, no proliferation of connective tissue, and no disease of the bloodvessels. The muscle fibres, apart from

FIG. 6.

Fatty degeneration of muscle (adductor brevis). ⅔ objective.

FIG. 7.



Fatty degeneration of muscle (adductor brevis). ⅙ objective.

the peculiar parenchymatous degeneration shown by the Marchi stain, were healthy in every way, there being no particular swelling nor breaking up of the fibres anywhere, and the striæ were distinct (Figs. 6 and 7). This degeneration of muscle fibre and of end-plates in paralysis agitans is, so far as I am aware, a new observation in the pathological anatomy of the disease, and I must credit my assistant, Dr. Muskins, with preparing the specimen and calling my attention to it.[1]

[1] Under the head of "Intrafibrillary Fatty Degeneration of the Muscle Fibres in a Hemiatrophic Tongue in Tabes," Prof. H. Obersteiner describes (Arbeiten, 1895, iii. p. 183) a somewhat similar condition. In this case there was no nuclear lesion, and the degeneration was ascribed to neuritis. In my case, as the drawing shows, section of the ulnar nerve showed perfectly normal fibres, and my case also the degeneration shows itself more localized, as though end-plates were affected.

The recent observations upon the Marchi stain, particularly by Nonne, seem to show that in its light degrees it indicates *trophic* disturbance of the nerve-tissues, and probably of muscle tissues, and that this degeneration is not incompatible with the *functional integrity* of the organ. It is interesting to find that a muscle which has undergone as many contractions in the last eight years as had this particular one shows this peculiar degeneration alone. The tremor in my patient's case early affected the hand muscles, and, estimating that the tremor was continuous, as in fact it was, from the beginning, during the waking hours, and that the contractions occurred at the rate of about five per second, during sixteen waking hours for eight years, I estimate that this particular bit of muscle had contracted during that time about *eight hundred and forty million times.*

SUMMARY. The anatomical changes may be summed up, then, as follows: Some general atrophy of the cord, moderate increase in connective tissue, and dilatation of perivascular spaces; no special thickening of the bloodvessels, either veins or arteries; no meningeal thickening; pronounced changes in the anterior cornual cells, consisting of atrophy of these cells, pigmentation and vacuolization, loss of dendrites, diminution in the richness of the plexus formed by the dendritic processes; the process most marked in the upper cervical and lower dorsal region; Clarke's column is not markedly affected; the brain cortex shows slight degeneration of cells; the olivary nerve-cells degenerated; the peripheral nerves normal; the muscles and end-plates showing some fatty degeneration.

COMMENTS ON THE PATHOLOGY AND PATHOGENY OF THE DISEASE. There are two views prevailing regarding the pathological anatomy of paralysis agitans. One is that it represents merely a premature condition of senility, and that the changes are the same as those found in extreme old age, the differences being a matter of degree, not of kind.[1] The other view is that the nervous system in cases of paralysis agitans presents changes which differ from those of senility, and although these have not yet been thoroughly studied

[1] In a recent article by Nonne upon the spinal cord changes in cases of pernicious anæmia (Deutsche Zeitschrift für Nervenheilkunde, vol. xiv, Parts III and IV, p. 192), the author states that he has examined the spinal cords of ten old people, and also the spinal cords in two cases of paralysis agitans, and that he does not find any differences between the conditions in these two cases, nor could he tell the difference in the appearances between the cord of a very old person and that of a person who had had paralysis agitans. To this I can only say that, in the first place, Nonne gives no account of how he has examined the cords of his cases of paralysis agitans, nor whether he has used all possible means of examining them by Marchi's method, the Nissl stain, and so on. In the second place, I can show from my specimens that the cord in the case of paralysis agitans here studied by me does not present the appearance of the senile cord as described by Nonne. There is not the extreme sclerosis of neurogliar increase, and the bloodvessels are positively very little diseased. Third, I must say, again, that paralysis agitans is clinically entirely different from old age, and that if we have not yet discovered the pathological anatomy, it does not follow that we shall not do so, or that the question is fully settled.

out, further research will in time discover them. It is this latter view which I most decidedly share. There are, to be sure, many changes in the spinal cord, brain, and even nervous system of paralysis agitans which are more or less identical with those found in the senile nervous system. But to say that paralysis agitans has underlying it nothing but the premature senility is to go utterly against the facts of clinical experience. The symptoms of rigidity and palsy are not those of premature senility. The vasomotor disturbances, the burning and lightning pains, the peculiar rigidity, the hitching of the voice, the sharp interruptions in volitional efforts, are also unlike the phenomena of senility. Even the tremor is essentially different, for the tremor of old age is larger in sweep and involves the head more often, and interferes relatively less with the active movements and comfort of the individual. The tremor of old age is benign as compared with the crippling tremulousness of Parkinson's disease. There is, indeed, little room for argument upon this point. The dissimilarity is so striking, and the symptoms in paralysis agitans are so progressive, severe, and malignant, that it is impossible to believe that there is not a distinctly different anatomical change underlying them. There is, probably, a common condition of increase in interstitial tissue and of proliferative neuroglia natural to advanced years; but I do not find in my cases of paralysis agitans such profound changes in the bloodvessels or such extensive arterial sclerosis as is seen in extreme old age. The pigmentation of the cornual cells exists in both cases, but it may yet be discovered that the neuronic degenerations in paralysis agitans are peculiar in degree and localization, as well as in the way in which they involve the cell-bodies.

The history of the disease shows that it is primarily a parenchymatous nervous disease. The onset of the trouble is sometimes very sudden, and shows the almost apoplectic-like disturbances of certain groups of nerve-cells. Where and what is this disturbance?

The clinical facts and the pathological examinations in cases of paralysis agitans lead one fairly to infer that the incidence of the attack falls (1) upon the dendrites of the cells of the anterior horns of the spinal cord or (2) else upon the end-brushes of the neuraxons that come from the voluntary motor tract and the cortical motor centres of the brain. We might in the latter case establish even a sort of analogy between paralysis agitans and locomotor ataxia. Thus while in locomotor ataxia the effect of the pathogenic poison is to produce a degeneration of the axis-cylinder of the posterior spinal ganglion cells, this degeneration, often apparently beginning in the periphery, and not closely involving the cell-body at first, in paralysis agitans the special poison affects the end-brushes of the axis-cylinders of the cortical cells of the brain, producing a destruction of them, but not involving the main trunk of the axis-cylinder.

This view is somewhat contraindicated by the fact that even in very old cases of paralysis agitans there is no special involvement of the pyramidal tracts.[1] On the other hand, in the very severe cases there is a correspondingly greater destruction of the anterior horn cells, and this destruction especially involves the dendrites and the cell-body, while, even in the bad cases, one sees the axis-cylinder process and the anterior roots still in comparatively normal condition. The most logical conclusion, therefore, that one can reach is that in paralysis agitans there is early a functional disturbance and later a degeneration and destruction of the dendrites of the anterior horn-cells which interfere with the even flow of motor impulses, and, finally, lead to motor weakness and rigidity, owing to the cell being practically cut off from the brain. The fact that in paralysis agitans there is rigidity, but no great increase in the deep or superficial reflexes, is explained also by this interference in the functional activity of the dendrites and the easy flow of impulses from cortical to spinal neuron, and from sensory to motor neuron; for, on account of this, the completeness of the spinal reflex arc is impaired. The difference between this condition and that found in spastic paraplegia, due to a sclerosis of the voluntary motor tracts, is manifest, for there the dendrites of the anterior horns which subserve reflex purposes are normal, while in paralysis agitans all are somewhat affected. The rigidity of this disease is much like that found late after total transverse cord lesions.

Pathogeny. It will, I think, be found that there is quite a number of degenerative diseases of the nervous system which are due to remote or secondary results of infections and poisons. Syphilis, for example, produces two results: one a direct injury by its exudates and irritating poison, the other a later, slowly degenerative process, due to some paralyzing effect which has been put upon the cell-life. It seems as though the circulation in the body of the luetic poison lessened the longevity of certain groups of nerve-cells, so that after ten or fifteen years the poisoned nerve-cell begins to die. In the same way I have seen persons subjected for years to slight degrees of lead-poisoning suffer at an early stage from a temporary lead paralysis, recover completely, then, twenty or thirty years later, undergo a progressive degenerative disease involving the peripheral nerves and the spinal cord, ending in an extensive sclerosis and terminal softening. The acute infection which causes anterior poliomyelitis is usually cured, and apparently the poison eliminated from the system; but sometimes twenty years after a degenerative process sets up in the anterior cornual cells, which slowly progresses until they all die, one after the other, and the patient himself becomes a paralytic wreck from progressive muscular atrophy.

[1] Marchi stains do not at all affect the white columns of the cord, but show strongly the cellular degeneration.

I have not space to expand this view of the subject of the secondary results of infection, but I believe it may be developed into the dignity of a broad pathological law, and this, I think, will in time give us some clue to the pathogeny of paralysis agitans. Sometime in the career of these cases the patients have been subjected to an infection or poison from which they have recovered. It has, however, left the imprint upon certain groups of cells and neuronic mechanisms, and when the degenerative period of life comes these less viable structures begin to go to pieces. What the primary infection in paralysis agitans is I do not know, but perhaps some autochthonous poison allied to that of rheumatism. At any rate, there is no other preceding history that is so often obtainable as one of rheumatism, and there are many facts in the clinical history of the disease which suggest a relationship between paralysis agitans and that form of rheumatic manifestation which is known as rheumatoid arthritis.[1]

A STUDY OF A CASE OF FAMILY PERIODIC PARALYSIS.[2]

By John K. Mitchell, M.D.,
of Philadelphia.

The curious condition of periodic paralysis is one of the utmost rarity, and in this country but three cases have been seen, with a doubtful fourth, previous to the ones herein reported. I should omit from the consideration the cases of Rich, where the paralysis was directly due to a hereditary susceptibility to cold, and was distinctly spasmodic in character. Gibney's cases, supposed by him malarial in origin, certainly do not belong to this group either.

I do not propose to enter into the history of the previous study of this disorder except incidentally. An admirable paper by Dr. E. W. Taylor, in the *Journal of Nervous and Mental Disease* for September and October, 1898, contains a very complete bibliography of the previous work, with analyses of all the cases hitherto reported, and to this I am not able to add anything except my own cases.

All the cases observed have presented, with small variations, the same type—a paralysis of the voluntary muscles, usually total except for the

[1] It has long since occurred to me that possibly the disease might be the result of some defect in glandular secretion. In order to test this as far as was possible, I have treated patients with all the known original substances of the body—namely, thyroid gland, thymus, pituitary body, cerebrin, testin, adrenal, etc. These substances have been given in doses running up as high as 60 grains a day, with the exception of the thyroid extract. The results were essentially negative so far as throwing any light upon this mode of pathogenesis of the disease was concerned. The use of thyroid gland makes the patient decidedly worse. The use of the pituitary gland in large doses quieted the patient for a time, but this is only temporary, and the quieting effect I have seen produced in other cases. The other substances had no effect whatever.

[2] Read before the Association of American Physicians, May, 1899.

head and face muscles, with loss of reflexes, with absence of electrical reaction, with no mental or sensory disturbance, and occurring periodically at somewhat regular intervals. Nearly all of the cases have instances in the parents or ancestors of the patient. In the family of my patient the first one known to have suffered from it was the maternal grandfather of the present victim, a Pennsylvanian by birth, a tinsmith by trade, who had in early life seizures like those from which my patient has suffered, but much less severe. A first cousin of this same grandfather had periodic attacks of paralysis quite as bad as any which have been described. His business kept him travelling much through the rough mountain districts of central Pennsylvania, and he used to say that he was often obliged to get off his horse and "have a paralysis." Both these persons, so far as known to their descendants, ceased to have the attacks in middle life.

The mother of the patient is one of six children. Of three elder sisters none have ever had any spells of the palsy. An older brother had one attack, brought on by overexertion, but has never had another. A younger brother has suffered in the same way, but the attacks did not begin with him until he was a grown man, and have since occurred only at long intervals. A daughter of this brother, now between twelve and thirteen years of age, has periodic palsies of the same sort, and full details of these two cases follow my patient's history. None of the other cousins except this one has ever had the family affliction. The mother of the patient began to have periodic paralyses when fourteen years of age, probably at about the time when her menstruation appeared. Their approach was sometimes announced by a slight sense of helplessness, which would last for a whole day. Going to bed with this, she would wake in the morning with total muscular paralysis, usually lasting thirty-six hours, seldom longer, and never more than forty-eight. The paroxysms recurred at long and rather irregular intervals, often months apart, and after she reached adult life decreased in frequency with the advance of years, and ceased altogether at about the thirty-eighth year. She is now forty-four years of age, and presents some interesting symptoms.

Mrs. E. J. is a well-looking woman, scarcely appearing as old as she is, calls herself perfectly well, menstruates regularly, and is active mentally and physically. She has a little difficulty in walking unless the ground is perfectly smooth; a very slight inequality makes her stumble, and if she stumbles she is very apt to fall. This is especially marked at night, when she cannot see where she is going, and has been noticed for some years. When sitting she gets up with some difficulty, rising as if her legs were weak, with a sort of wiggle, and aiding herself with the nearest object upon which she can lean. She thinks this is rather worse of late years, but she had not thought it bad enough to mention.