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Discussion of paralysis agitans

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A DISCUSSION OF PARALYSIS AGITANS

BY

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A Thesis

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INTRODUCTION

Paralysis agitans is a very old, complex and interesting disease. It was described very completely in 1812 by James Parkinson and since that time little has been added about symptoms, diagnosis or onset. But the opposite is true of the pathology, etiology and treatment. I doubt if any one syndrome in medicine has been subjected to such a variety of theories. Thus in this brief discussion I will attempt in each section to show what the original concept was and then point out the new theories that have been added, in an attempt to solve the mystery of etiology, pathology and treatment.

In a paper of this kind I have limited the subject to the primary form of paralysis agitans, that is the juvenile and idiopathic forms. But since the postencephalitic variety is so similar in many respects I have considered it in many instances merely for the sake of comparison. However, the postencephalitic complications open an immense field that could not be covered in this paper.

In covering the literature I have been forced to use mostly American articles; however, the majority of the early writings and even a great deal of the current literature is written in foreign languages.

From this paper it will be noted the lack of harmony that physicians have in their theories about etiol-

ogy and treatment and this syndrome still offers great opportunities in the field of future investigation.

I. DEFINITION AND HISTORY

In 1812 James Parkinson described very fully the condition we now call paralysis agitans. According to his description the shaking palsy was characterized by "involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace; the senses and intellects being uninjured" (74).

Compare this now with the present concept of the disease; in the first place, it is now regarded as a syndrome with a definite and characteristic complex of symptoms which may be caused by a variety of pathological lesions. Therefore paralysis agitans is a chronic, progressive organic syndrome of the central nervous system, which is characterized by weakness and slowness of movement, spontaneous tremor, and muscular rigidity. A mask-like expression of the face, a characteristic attitude, festinating gait, and a rhythmical shaking of the extremities are pathognomonic of this disorder.

Paralysis agitans represents a fundamental type of motor paralysis which is referable to the corpus striatum and the extrapyramidal motor system. In the central nervous system there are three systems which subserve the functions of motility: the segmental system with its various reflex functions; the striospinal system with its control of auto-

matic and associated movements; the corticospinal system with its higher function of dissociated movements.

The striospinal system has to do with the transmission and control of motor impulses underlying automatic and associated acts and movements, in contradistinction to the corticospinal system which conveys isolated synergic impulses of cortical origin. The shaking palsy in the striospinal system is the counterpart of spastic paralysis in the pyramidal system. Like spastic paralysis, it may occur as a primary affection or as a secondary manifestation (49).

Clinically, three types of the disease are recognized: the presenile and senile, the symptomatic, and a rare juvenile form. It is unlikely that an affection of this character, which is so diverse in its clinical manifestations, should have as its basis a uniform pathological lesion. The paralysis agitans group undoubtedly includes a variety of forms, which are related clinically as they present the chief symptoms of Parkinson's syndrome (rigidity and tremor) but which may be distinguished by differences in the localization and character of the underlying pathological lesions.

With this end in view Dr. J. R. Hunt (47) suggests a separation of the juvenile and early adult forms of paralysis agitans from the larger syndrome on the basis of the pathological alterations in the motor neurones of the

globus pallidus system. For this affection he would propose the name progressive atrophy of the globus pallidus, as best expressing the nature, characteristics and the localization of the abiotrophic process. Further pathological investigations will be necessary in order to show how frequently these same pathological changes are met with, when the disease begins in the later periods of life. Dr. Hunt suspects, however, that in the late forms of the disease, senile degenerations, vascular and perivascular lesions will play the more important roles.

Paralysis agitans has been called by a variety of names, the most common is the eponym, Parkinson's disease; shaking palsy; the trembles; chorea festinans; chorea pro-cursiva and sclerotynbe festinans. By many the term paralysis agitans is considered as inappropriate since, though there is muscular weakness, true paralysis does not occur except possibly as a complication, and it may not be accompanied with any tremor.

As has already been pointed out, James Parkinson was the first to speak of this condition as a clinical entity; previous to this time the condition was considered as belonging to the class of entities in which tremor (no matter what the type) was the outstanding symptom.

The shaking of the limbs belonging to this disease was particularly noticed, as will be seen when treating of the symptoms, by Galen, who marked its peculiar character by

an appropriate term. The same symptom, was accurately treated by Sylvius de la Boe. Tremor has been adopted, as a genus, by almost every neurologist; but always unmarked, in their several definitions, by such characters as would embrace this disease. "Tremor can indeed only be considered as a symptom, although several species of it must be admitted". In the present instance, the agitation produced by the peculiar species of tremor, which here occurs, is chosen to furnish the epithet by which this species of palsy may be distinguished.

Thus up until the first part of the nineteenth century paralysis agitans was not considered as a separate entity. At this time James Parkinson, an English physician, wrote his now famous "Essay on the Shaking Palsy". Only a few copies of this book seem to have been made and there remain only four of the original. A German named Willige obtained one of these original books and translated and published the book, and it is thought that some of Charcot's pupils did the same for the French. Thus for many years the book was not available for the English. But in 1922, Alfred Ostheimer (74) translated the essay and it was published in the Archives of Neurology and Psychiatry. In this work Parkinson describes and classifies tremors as they were understood at this time, 1812.

"It is necessary that the peculiar nature of this tremulous motion should be ascertained, as well for the

sake of giving to it its proper designation, as for assisting in forming probable conjectures as to the nature of the malady, which it helps to characterize. Tremors were distinguished by Juncker into active, those proceeding from sudden affection of the mind, as terror, anger; and passive, dependent on debilitating causes, such as age, palsy. But a much more satisfactory and useful distinction is made by Sylvius de la Boe into those tremors which are produced by attempts at voluntary motion and those which occur whilst the body is at rest. Sauvage distinguishes the latter of these species by observing, that the tremulous parts leap, and as it were vibrate, even when supported; whilst every other tremor, he observes, ceases when the voluntary exertion for moving the limb stops, or the part is supported, but returns when we will the limb to move; whence he says, tremor is distinguished from every other kind of spasm.

Under this authority the term palpitation may be employed to mark those morbid motions which chiefly characterize this disease, notwithstanding that this term has been anticipated by Sauvage's, as characteristic of another species of tremor. The separation of palpitation of the limb from tremor, is the more necessary to be insisted on, since the distinction may assist in leading to a knowledge of the seat of the disease. It is also necessary to bear in mind that this affection is distinguishable from the tremor by the agitation, in the former, occurring whilst the

affected part is supported and unemployed, and being even checked by the adoption of voluntary motion; whilst in the latter, the tremor is induced immediately on bringing the parts into action. Thus an artist, afflicted with this malady here treated of, whilst his hand and arm is palpitating strongly, will seize his pencil, and the motions will be suspended, allowing him to use it for a short period; but in tremor, if the hand be quite free from the affliction, should the pen or pencil be taken up, the trembling immediately commences.

Cases occur in which the muscles duly excited into action by the impulse of the will, do then, with an unbidden agility, and with an impetus not to be repressed, accelerate their motion, and run before the unwilling mind. In describing the gait Sauvage says, 'I think it cannot be more fitly named than hastening or hurrying scelotyrbé'" (74).

Parkinson in his original essay made no mention of the facial expression, yet today we speak of the "Parkinson's mask". Charcot, in his many writings, was the first to emphasize the diagnostic importance of the immobile "facies" in paralysis agitans. It is thus probable that the pathognomonic facies of paralysis agitans was not recognized - at any rate, it was not recorded. This raises the question, was this symptom present during the first half of the nineteenth century? Moreover, diseases do change their type from time to time; this may possibly explain the curious oversight of

this sign. But I think most will agree with Dr. A. J. Hall (42) that likely this symptom was neglected and not recorded in Parkinson's original essay.

From 1812 until 1885 very little new investigation was done on this disease, cases were recognized, viewed with pity and treated as best they knew. The doctors had little new interest in trying different things, or investigating by doing autopsies to find where the pathology really was. But after 1885 the field of investigation again was reopened and even if since 1812 little has been added as to the symptoms or course of this disease, since 1885 a great deal has been added about pathology and treatment. I wonder if there is a disease condition in medicine that has been the subject of such diverse ideas as to the fundamental seat of the pathology, or the ideal line of treatment to follow.

As we have said, after 1885 the field of investigation was again reopened first along the line of spinal nerve and cord pathology, then back to the brain as the seat of the trouble, then the endocrine glands came in for their share. Until now J. R. Hunt had led us back to the basal ganglia as the seat of the pathology.

Our knowledge of the structures and function of the basal ganglia has increased so rapidly in recent years that disorders of the extra-pyramidal motor system now take equal rank with the diseases of the pyramidal pathways.

Jelgeroma in 1909 recorded certain pathologic

changes in the basal ganglia in paralysis agitans. Dr. J. Ramsay Hunt (49) in 1917, in both the juvenile and presenile types, showed the essential lesion to be a primary atrophy of the efferent neurons of the corpus striatum - the efferent striatal and pallidal system. According to his conception, paralysis agitans, like spastic paralysis, is not a disease, sui generis, but a paralytic syndrome which may result from a variety of pathologic causes.

II. ANATOMY AND PATHOLOGY

Since the basal ganglions seem to be the seat of the primary pathology, before we discuss the pathology it would be well to consider the anatomy of this region in more or less detail.

The basal ganglia are represented by an aggregation of important nuclei beneath the lateral ventricle at the base of the brain. They are the corpus striatum, the optic thalamus, and the claustrum. The corpus striatum has close anatomic and physiologic relationship with important subjacent centers, the red nucleus, the substantia nigra, and the corpus subthalamicum, which also play an important role in extrapyramidal function.

In man the corpus striatum is divided by the passage of the internal capsule into two structures, the caudate nucleus and the lenticular nucleus. The nucleus lentiformis is still further subdivided into an external segment, the putamen, and an internal, the globus pallidus. These divisions are based on gross appearance of the cells and fiber systems.

The caudate nucleus and putamen have the same origin and histologic characteristics and together form the neostriatum of the comparative anatomy.

The globus pallidus is an older structure phylogenetically and is termed the paleostriatum. It consists of two segments; an external and an internal, the segmental

appearance being produced by the massing of nerve fibers in the lateral, mesial and accessory medullary laminae.

In the study of lower forms of life we see the phyletic significance of these structures. In fishes, the paleostriatum represents the highest center for correlation of motility. In reptiles, the neostriatum is developed as an accessory, to the paleostriatum and supplies the inhibitory elements which are so essential for terrestrial motility.

In the higher vertebrate forms, the corpus striatum is an important center for the control of automatic associated acts and movements. The optic thalamus is also an important addition to the system.

The corpus striatum has no direct connection with the cerebral cortex. A cortical influence, however, is exercised on this structure through cortico-thalamic fibers and the numerous fiber radiations passing between the optic thalamus and the striatum. It has important connections also with the inter-brain and the mid-brain by way of the strio-thalamic radiations.

The corpus striatum, through its connections with the red nucleus, the corpus subthalamicum, the locus niger, and other subordinate centers of the mid-brain, exercises control over the extrapyramidal pathways of which the rubro-spinal tract and the fasciculus longitudinalis dorsalis are the ones best known. These systems regulate the older forms of motility, paleokinesis, and are chiefly concerned with

automatic-associated acts and movements.

In the neostriatum we find two distinct types of ganglion cells, a small type and a large cell type. The axons of the small cells terminate in the striatum and constitute a short association system which unites the small and large cells of the caudate nucleus and putamen. The axis cylinder process of the large cell type terminates in relation to the cells of the globus pallidus, while others pass to the nucleus ruber; the substantia nigra and the corpus luyssi. Thus, the stratum stands in direct relation with the pallidum and the important sub-pallidal nuclei through the efferent striatal system (49).

It is according to Dr. Hunt's (48) conception that the fibers which unite the caudate nucleus and the putamen to the globus pallidus are merely an inhibitory and association system for the corpus striatum. This short neostriatal system undergoes atrophy in Huntington's chorea and is the essential lesion underlying the choreiform manifestations of this disease.

The globus pallidus contains these large cell types. They have long axis-cylinder processes which course in the ansa lenticularis and ansa peduncularis, terminating in the thalamic and hypothalamic regions. There are also connections with the corpus subthalamium, the nucleus ruber, and the substantia nigra. This is the efferent pallidal system. The efferent striatal and pallidal systems are the essential

motor pathways of the corpus striatum and are involved in paralysis agitans.

The nature of the mechanism by which the cortical and striatal activities are harmonized is largely speculative. It now appears highly probable that the corpus striatum has no direct connection with the cerebral cortex. The pyramidal tracts, however, as they transverse the striatum send off numerous collaterals to all parts of the structure, so that a certain relationship between the motor cortex and the corpus striatum could be maintained through the medium of such collateral fibers. The optic thalamus also stands in very close relationship with all portions of the cerebral cortex by its afferent and efferent fiber systems; and as very close intimate associations exist between the thalamus and the corpus striatum the influence of the cortex on the striatum could be exercised in this manner. Dr. Hunt assumes that the motor system of the corpus striatum is essential for the control of automatic and associated movements, and that it exercises this function through the medium of the rubro-spinal system, and other extrapyramidal motor tracts which as yet are not well understood (48).

The blood vessels of this region are abundant and it is noteworthy that no one structure receives its whole blood supply from any one arterial source. The anterior cerebral and middle cerebral give off branches that supply this region. Among these vessels is the well-known lenticulo-

striate, the artery of cerebral hemorrhage. The anterior choroid nourishes the tail of the caudate nucleus, the nucleus amygdalae, and part of the putamen and globus pallidus. It is this vessel which is particularly liable to thrombosis in carbon monoxide poisoning.

Below are some important points about the corpus striatum that will be helpful to keep in mind, to clear up points in other parts of this paper.

I. The fiber system of the corpus striatum may be divided into four main groups:

(1) Fibers arising and ending within the corpus striatum (internuncial);

(2) Fibers arising in the corpus striatum and ending elsewhere (striofugal);

(3) Fibers arising elsewhere and ending in the corpus striatum (striopetal);

(4) Fibers passing through the corpus striatum, but arising and ending elsewhere (fibers of passage).

II. Things to remember about the anatomy of the corpus striatum:

(1) It is independent of the cerebral cortex;

(2) The putamen and caudate are closely linked to each other, and both to the globus pallidus;

(3) The main striofugal and striopetal fiber groups are related to the globus pallidus only, and not to the putamen and caudate directly;

(4) The striofugal groups preponderate, and link the globus pallidus with the optic thalamus and the regio subthalamicum and substantia nigra;

(5) The corpus striatum is not connected directly with the spinal cord;

(6) The corpora striata, directly at least, are independent of each other (95).

Thus we see since Parkinson's time there have been many notable contributions to the pathological physiology of this subject, as well as a vast amount of pathological research in an effort to find and identify the essential lesion of the disease. Many theories have been promulgated and a glance at the monographs of recent years will show the various and complicating points of view, the great diversity of pathological findings, and the absence of any well defined and harmonious conception as to the true nature of this interesting malady. The theories, even of today, include such widely dissimilar structures as the cerebral cortex, cerebellum, basal ganglia, the brain-stem and the spinal cord. Even the glandular and myogenic conceptions are still upheld by some.

Parkinson was not able to do posts on his patients so he merely formed a number of what he thought were logical conclusions.

He considered the symptoms caused by a diseased state in the medulla spinalis, in that part which is contained in the canal, formed by the superior cervical vertebrae, and

extending, as the disease proceeds, to the medulla oblongata.

"By the nature of the symptoms we are taught, that the disease depends on some irregularity in the direction of the nervous influence; by the wide range of parts which are affected, that the injury is rather in the source of the influence than merely in the nerves of the parts; by the situation of the parts whose action are impaired, and the order in which they become affected, that the proximate cause of the disease is in the superior part of the medulla spinalis; and by the absence of any injury to the sense and to the intellect, that the morbid state does not extend to the encephalon" (74).

A study of the literature shows that after the original description of the disease by Parkinson in 1812 practically no pathological studies were made until 1861 and 1862. Under the stimulus to pathology given by the Vienna school, a number of autopsies were done, but the results were of little value. The disease was not sufficiently known to be surely recognized, and the microscopical examinations were very incompletely made.

In the next decade, when Charcot had taught the profession to distinguish shaking palsy from coarser organic disease, many more cases began to be reported. The results, however, were still reported negative. Since this time numerous autopsies have been done with a great variety of findings.

Other men at this period thought the symptoms of paralysis agitans to be due to an irritation of the regulating

or coordinating fibers in the voluntary motor tract of the brain, which fibers pass from the peripheral grey matter of the cerebrum through the motor ganglia (probably the caudate nucleus) and the peduncle cerebri to the cerebellum (61).

About 1900, neurologists began investigating fiber tracts and peripheral nerves and a group of men thought they found the seat of the pathology in the peripheral nerves for the following reasons: (1) the tremor ceased during sleep, this is when the function of the hemisphere is least active, but in cases in which tremor is known to be due to cortical involvement the tremor does not disappear during sleep. When a case of paralysis agitans in which all four extremities are affected develops a hemiplegia, the tremor disappears on the paralyzed side. This, if invariably true, proves that the nervous impulses which by their perversion cause the symptom originate in the cerebral cortex, but it does not prove where the perversion of impulse in this disease takes place. Whether in origin, transmission or in their reception ultimately by the muscle, the result of a complete cessation of the impulse would be the same: (2) the uncommon combination of mental changes: (3) the paraesthesia and the subjective sensations of heat and cold (which are due to peripheral defects); (4) the constant failure of any change in the sphincter reflexes. These reasons have led many of the older men to believe the symptoms of this disease are due to an irritation from the presence of an increased amount of neuroglia in the posterior

column producing an excitability of the reflex collaterals of the posterior nerve roots arborizing about the ventral cornual cells which results in an increase in the normal rhythmic discharges of energy from these cells, producing at first tremor and later the rigidity. (19).

Notwithstanding the prevailing opinion as to the cerebral location of the lesion and the essentially nervous character of the affliction, it was apparent that, for a period of one hundred years, searching study of the nervous system had failed to disclose a definite pathologic foundation for the disease, and that the muscle tissue, the most conspicuous anatomic structure concerned in the mechanism of motion, had not been thoroughly investigated. Although the myopathic nature of the disease had been discredited, the occasional early involvement of the small muscles of the hand, and the fact that there are in the skeletal musculature a variety of nerve terminals which had not been carefully examined, suggests that the somatic neuromuscular tissue might be profitably studied. Since there is such a wide difference in autopsy findings, with this indefinite and contradictory state of knowledge regarding the pathology of paralysis agitans, encouraged Dr. Byrnes (17) that further information might be derived from a study of nerve terminals.

(1) Evidence has accumulated within the last few years that indicates that the postencephalitic Parkinsonian syndrome and genuine paralysis agitans are often accompanied

by a lesion in one or more of the basal ganglionic structures; nevertheless, it has been quite impossible to determine the exact location of the lesion. There is much in the clinical course of paralysis agitans to suggest that in some instances, at least, it may be dependent on a morbid process situated in the peripheral mechanism concerned in the production and maintenance of muscle tone, and unsuccessful attempts have been made to locate the lesion in the muscle itself. Dr. Byrnes in his examination of the muscular tissue obtained by biopsy from fourteen cases of genuine paralysis agitans gives no evidence that the disease is of myopathic origin.

(2) There is, however, in the neuromuscular bundle a constant lesion characterized by edema, early degeneration of the intrafusal nerve and final disintegration of the entire spindle. The intramuscular nerve trunks are normal, and the surrounding musculature is, as a rule, unaltered. The lesion in the neuromuscular bundle is, therefore, essentially neuropathic and involves a specific system of proprioceptive nerve terminals.

(3) That the lesion in the spindle is primary and not secondary to the tremor or the rigidity is indicated by the failure to discover any abnormality in the light spindles obtained from a case of the postencephalitic Parkinsonian syndrome in which these symptoms had persisted throughout a period of five years.

(4) Although studied in a variety of diseases, no

lesion similar to that observed in paralysis agitans has been discovered in the neuro-muscular bundle. Because the spindle has not been examined in all cases under the same technical conditions, Dr. Byrnes cannot, however, make the unqualified assertion that the lesion is pathognomonic of paralysis agitans. Nevertheless, had a spindle lesion similar to that exhibited in his microscopic sections existed in any other disease, it could not have escaped detection by the simpler technical methods there employed.

(5) There is reason to believe that the lesion is a toxic parenchymatous degeneration of the intrafusal nerve terminals. The cause of the lesion is not known, but it is conceivable that one or more toxic substances of metabolic or glandular origin might exhibit a selective affinity for the neuro-muscular bundle, and the early edematous change in the spindle suggests an irritant chemical action or osmotic process.

(6) It is generally taught that the muscle sense, but apparently disease of the neuro-muscular bundle causes no appreciable abnormality in the perception of this sense. It is therefore reasonable to conclude that the spindle does not subserve this function.

There is, however, much evidence that it plays an essential part in the mechanism of muscle tone, and it is Dr. Byrnes' belief that the spindle is the afferent inhibitor of the striothalamic tonectic centers.

(7) Hypertonia of the Parkinsonian type might originate, therefore, from either central or peripheral disease of this system of fibers, and it is suggested that the central lesion finds its chief exponent in the postencephalitic syndrome, while genuine paralysis agitans, in its typical form, is characteristic of the peripheral lesion. This assumption does not preclude, however, the possibility of a combination of the two lesions in certain types of Parkinson's disease in which the symptoms are wide-spread and fully developed in the early course of the disorder (19) (17).

Next in the early part of the twentieth century the endocrine glands were coming into importance, and it was Dr. Berkeley who was one of the first to link parathyroid gland disturbance to that of paralysis agitans. Dr. Berkeley's (12) reason for thinking paralysis agitans due to parathyroid deficiency need be only summarized: (1) the symptoms appearing in rabbits and other convenient experimental animals upon removal of the parathyroid glands are suggestive; shivering and twitching of the voluntary muscles, rigidity, convulsions, salivation, and often a quite typical "propulsion" may be observed; (2) the disease has been reported several times in conjunction with myxedema, and with exophthalmic goitre, where the contiguity of the diseased thyroid might well be supposed to work mischief on the parathyroids; (3) the parathyroid glands have been reported in a diseased condition in a fair percentage of autopsies; (4) the use of a properly prepared

parathyroid extract by the mouth, or better by hypodermic administration has been productive of remarkable benefit in a majority of the cases treated.

In 1911 Mendel published a comprehensive account of the disease with a critical review of the pathologic studies recorded up to that period. Evidence has accumulated which suggested that the lesion might be situated in one or more of the central nuclear masses. Brissaud, Maillard, and Jelgersma had observed changes in the substantia nigra, in the red nucleus, and in the lenticulostriate and hypothalamic structures; but the lesions were often diffuse, wide-spread, and of uncertain meaning. Similar observations were recorded later by Levey, Monschot and Aver and McCough.

"The substantia nigra was involved in every case except one diagnosed clinically as arteriosclerosis in which it showed only evidences of vascular sclerosis. The lesions in the locus caeruleus, parallel to some extent those in the substantia nigra. The pallidum seemed to have been mostly affected in the idiopathic cases. As to the involvement of the other basal ganglia, it did not seem to make much difference whether the case was encephalitic, idiopathic or arteriosclerotic so far as the site of the pathologic process was concerned, the deciding factor being the nature of the process. In the present state of knowledge there is altogether too little definite information as to the effects of disturbances of function and their relation to structural changes

in the neural mechanisms as to the basis of symptomatology of the various diseases of the extra-pyramidal system".

McAlpine holds that in the postencephalitic Parkinsonism is caused by destruction of the substantia nigra, and that the "idiopathic" form is caused by a lesion of the globus pallidus.

A way out of this impasse has recently been opened up by the investigation of Ferraro, who showed that the axones of cells in the substantia nigra end almost without exception in the lenticular nucleus. Thus the destruction of these neurones either at their source in the substantia nigra or at their termination in the lenticular nucleus may cause the development of paralysis agitans.

The findings in these cases support Tretiokoff's contention that the substantia nigra is severely altered in paralysis agitans, and tend to show that this degeneration is the actual cause of the disease. The alterations in other parts of the brain were insignificant in comparison. The afferent pathway to the substantia nigra is not definitely known, although it probably comes from the cortex. It has been shown that the efferent pathway is to the lenticular nucleus. Probably the substantia nigra furnishes impulses to the globus pallidus that serve to inhibit the muscular rigidity, but the mechanism is not clear (32).

Deposits of iron have been found in abnormal forms in the various basal ganglion in cases of paralysis agitans,

chorea and other diseases, but in other cases we do not find any iron deposits. It makes one wonder if the iron deposits were not the result of some preceeding pathology and not the primary cause (62).

Most of the work that I have mentioned on pathology has been theories grounded only on gross autopsy findings. It is true that some of these men have been very systematic in their work, but not enough detail was paid to microscopic examination of brain sections. In 1912 Dr. J. R. Hunt (48) made his important finding on paralysis agitans which is still considered today as the real primary cause of the symptoms.

The most striking pathologic changes noted were in the large motor cells of the caudate nucleus and putamen. The cells were reduced in size, the bodies were shrunken, atrophic and shrivelled with an elongated contracted nucleus, occupying a lateral position in the cell body. Pyknosis of the nuclei was a striking feature in many cells, while in others the entire cell was much shrunken and diffusely stained. The motor cells of the globus pallidus proper were not reduced in number and in comparison with the giant pallidal cells of the neostriatum were well preserved.

With the exception of the pathologic changes in the efferent pallidal system, namely chronic atrophy of the giant pallidal cells of the neostriatum, a reduction in the fiber network of the globus pallidus and atrophic thinning of the fibers of the ansa system, the central nervous system appear-

ed normal.

The characteristic symptoms of primary atrophy of the efferent neurons of the corpus striatum are: paralysis, rigidity and tremor. These symptoms may be secondarily induced by a variety of lesions. In many cases, especially of the senile type, both primary and secondary involvement of these systems exist. The term primary paralysis agitans, however, should be reserved for the rarer system type of lesions in which primary atrophy and degeneration of cells is the essential lesion, thus harmonizing the pathologic changes in the striospinal with those in the corticospinal system.

Levey, in a large series of cases, also emphasized the wide dissemination of senile atrophy in the central nervous system in paralysis agitans. Lesions are found in the basal ganglia, cerebellum, thalamus, vegetative nuclei, spinal cord and cerebral cortex. He emphasized, however, the greater degree of involvement of the cells of the corpus striatum, and the characteristic symptomatology, paralysis, tremor and rigidity, was referred to this region.

Primary paralysis agitans is due to a degeneration of the parenchymal cells and fibers of the central nervous system of obscure origin, but resembling most closely the group of the senile degenerations, although senile plaques and senile fibrillar changes are commonly lacking. This degeneration is especially marked in the striopallidal mechanism, which underlies the essential symptomatology of paralysis

agitans.

Paralysis agitans, as expressed in Dr. J. R. Hunt's original monograph, is not a disease but a syndrome referable to the efferent neurons of the corpus striatum (striatal and pallidal). This syndrome may be induced by a variety of pathologic lesions, primary atrophy, senile degeneration, and vascular, inflammatory and neoplastic lesions. There are three system syndromes of the corpus striatum; (1) the chorea syndrome, which is related to the small cell striatal system; (2) a paralysis agitans syndrome, which is related to the large cell striatal and pallidal systems. This syndrome may be still further subdivided into a tremor type of paralysis agitans, which is related to the large cell efferent striatal system, and a rigid type of paralysis agitans, which is related to the efferent pallidal system. All regional syndromes of the corpus striatum - striatal, pallidal and striopallidal - represent fragments and combinations of these cellular systems (50).

An attempt is also made to distinguish the juvenile form of paralysis agitans from the larger syndrome on the basis of certain definite pathological changes in the motor cells of the corpus striatum, this is, the globus pallidus mechanism. The juvenile type of paralysis agitans should be regarded as a pure system disease, characterized by a slowly progressive atrophy of the motor neurons of the globus pallidus mechanism, while the paralysis agitans of later life,

the presenile, senile and the symptomatic forms are dependent upon senile and vascular degenerations in the course of this same mechanism (19) (47).

This juvenile and to a lesser extent the senile form of palsy are produced by a disease of the motor or efferent system of the globus pallidus, which exercises a controlling influence upon the extra-pyramidal motor system. The large motor cells of the globus pallidus system occupy in the automatic motor nervous system the same position as the cells of Betz in the cortico-spinal system, the corpus striatum controlling automatic and associated movements, while the higher cortical centers are concerned with isolated synergistic movements.

Both of these motor systems in addition to their function of innervation also exercise a certain control or inhibition upon muscle tonus, so that a destructive lesion produces not only paralysis but an increase of muscular tonus as well. Both types of central palsy are therefore associated with rigidity, and a paralysis of either produces a characteristic and distinctive symptomatology. A lesion of the pyramidal track system is followed by the phenomena of spastic paralysis; a lesion of the pallidal system by the phenomena of paralysis agitans.

One great disadvantage encountered by previous observers has been the advanced age of the subjects upon which pathological studies have been made, so that senile degenera-

tive, vascular and perivascular lesions have dominated or obscured the histological picture.

In a case of juvenile paralysis agitans the only discoverable lesion was a wide-spread atrophy and disappearance of the cells of the globus pallidus mechanism, that is, the globus pallidus proper, the nucleus basalis of Meynert and especially the large cells of the neostriatum. Dr. J. R. Hunt therefore regards this affection as a progressive atrophy of the motor cells of the globus pallidus mechanism, and this mechanism as the essential motor or projection system of the corpus striatum (47). He also holds that the same pathology causes the symptoms in senile agitans, but that the cause of the pathology may be different. Also in the senile type other lesions may be found due to senility that have no true relationship to the symptoms.

III. SYMPTOMS AND DIAGNOSIS

Before I try to correlate the symptoms with the pathology, I think it would be well to quote from Parkinson's "Essay" and show how completely he described the course of this malady some 124 years ago.

"So slight and nearly imperceptible are the first inroads of this malady, and so extremely slow is its progress, that it rarely happens that the patient can form any recollection of the precise period of its commencement. The first symptoms perceived are, a slight sense of weakness, with a proneness to trembling in some particular part; sometimes in the head, but most commonly in one of the hands and arms. These symptoms gradually increase in the part first affected; and at an uncertain period, but seldom in less than twelve months or more, the morbid influence is felt in some other part. Thus assuming one of the hands and arms to be first attacked, the other at this period becomes similarly affected. After a few more months the patient is found to be less strict than usual in preserving an upright posture, this being most observable whilst walking, but sometimes whilst sitting or standing. Sometime after the appearance of this symptom, and during its slow increase, one of the legs is discovered slightly to tremble, and is also found to suffer fatigue sooner than the leg of the other side; and in a few months this limb becomes agitated by similar tremblings and suffers a similar loss of power.

Hitherto the patient will have experienced little inconvenience; and befriended by the strong influence of habitual endurance, would perhaps seldom think of his being the subject of disease except when reminded of it by the unsteadiness of his hand, whilst writing or employing himself in any nicer kind of manipulation. But as the disease proceeds, similar employments are accomplished with considerable difficulty, the hand failing to answer with exactness to the dictates of the will. Walking becomes a task which cannot be performed without considerable attention. The legs are not raised to that height, or with that promptitude which the will directs, so that the utmost care is necessary to prevent frequent falls.

At this period the patient experiences much inconvenience, which unhappily is found daily to increase. The submission of the limbs to the directions of the will can hardly ever be obtained in the performance of the most ordinary offices of life. The fingers cannot be disposed of in the proposed directions, and applied with certainty to any proposed point. As time and the disease proceed, difficulties increase; writing can now be hardly at all accomplished, and reading from the tremulous motion is accomplished with some difficulty. Whilst at meals the fork not being duly directed frequently fails to raise the morsel from the plate, which, when seized, is with much difficulty conveyed to the mouth. At this period the patient seldom experiences a suspension

of the agitation of his limbs. Commencing for instance in one arm, the wearisome agitation is borne until beyond sufferance, when by suddenly changing the posture it is for a time stopped in that limb, to commence, generally in less than a minute, in one of the legs or in the arm of the other side. Harassed by this tormenting around, the patient has recourse to walking, a mode of exercise to which the sufferers from this malady are in general partial, owing to their attention being thereby somewhat diverted from their unpleasant feelings, by the care and exertion required to insure its safe performance.

But as the malady proceeds, even this temporary mitigation of suffering from the agitation of the limbs is denied. The propensity to lean forward becomes invincible, and the patient is thereby forced to step on the toes and fore part of the feet, whilst the upper part of the body is thrown so far forward as to render it difficult to avoid falling on the face. In some cases, when this state of the malady is attained, the patient can no longer exercise himself by walking in his usual manner, but is thrown on the toes and fore part of the feet; being, at the same time, irresistibly impelled to adopt unwillingly a running pace. In some cases it is found necessary entirely to substitute running for walking since otherwise the patient, on proceeding only a very few paces, would inevitably fall.

In this stage, the sleep becomes much disturbed.

The tremulous motion of the limbs occurs during sleep, and augments until they awaken the patient, and frequently with much agitation and alarm. The power of conveying the food to the mouth is at length so much impeded that he is obliged to consent to be fed by others. The bowels, which had been all along torpid, now, in most cases, demand stimulating medicines of very considerable power; the expulsion of the faeces from the rectum sometimes requiring mechanical aid. As the disease proceeds towards its last stage, the trunk is almost permanently bowed, the muscular power is more decidedly diminished, and the tremulous agitation becomes violent. The patient walks now with great difficulty, and unable any longer to support himself with his stick, he dares not venture on this exercise, unless assisted by an attendant, who, walking backwards before him, prevents his falling forwards, by the pressure of his hands against the forepart of his shoulders. His words are now scarcely intelligible, and he is not only no longer able to feed himself but, when the food is conveyed to the mouth, so much are the actions of the muscles of the tongue, pharynx, impeded by impaired action and perpetual agitation, that the food is with difficulty retained in the mouth until masticated; and then as difficultly swallowed. Now also, from the same cause, another very unpleasant circumstance occurs; the saliva fails of being directed to the back part of the fauces, and hence is continually draining from the mouth, mixed with particles of food, which he is no

longer able to clear from the inside of the mouth.

As the debility increases, and the influence of the will over the muscles fades away, the tremulous agitation becomes more vehement. It now seldom leaves him for a moment, but even when exhausted nature seizes a small portion of sleep, the motion becomes so violent so not only to shake the bed hangings, but even the floor and sashes of the room. The chin is now almost immoveably bent down upon the sternum. The slops with which he is attempted to be fed, with the saliva, are continually trickling from the mouth. The power of articulation is lost. The urine and faeces are passed involuntarily; and at the last constant sleepiness, with slight delirium, and other marks of extreme exhaustion, announce the wished-for release" (74).

The symptoms may follow a variety of pathologic lesions primary atrophy, senile atrophy, degeneration, arteriosclerotic changes in the corpora striata, with secondary involvement of the cells or fibers of the striopallidal systems; also inflammatory and degenerative lesions, epidemic encephalitis, syphilis and tumors having this localization.

The three cardinal symptoms of this condition are paralysis, rigidity and tremor. The great variation in the clinical picture is dependent upon the distribution, the extent of involvement, and the degree in which these fundamental symptoms are present. In the common form of the disease, all three symptoms are usually present in combination. In other

cases, especially in the earlier stage, one symptom may dominate the clinical picture or even be present alone and special clinical types are, therefore, recognized.

The onset of the disease is insidious, the progress is very slow and gradual. The first symptom may be a tendency to a fine slight rhythmical tremor of the hand or fingers. This is at first slight and inconstant, but soon becomes permanent and is present even during rest. Associated with the tremor are a peculiar weakness and a stiffness of the movements of the fingers. The stiffness has a certain wax-like quality and interferes with the finer movements of the parts. The tremor, weakness, and rigidity gradually increase in severity and eventually make their appearance in other members. Usually, the leg on the same side is next involved, giving a hemiplegic aspect to the case. The tremor may be the only sign or it may be associated with rigidity and paralysis or one symptom may be the only sign of the disease.

(1) Tremor: the tremor type is due to the involvement of the efferent striatal system. The tremor is fine and rhythmical in character and ranges from four to seven vibrations to the second: it persists during rest and is associated with a peculiar interosseal posture of the hand and the fingers, giving rise to the characteristic pill-rolling movements of the older writers. Its most frequent site is in the flexors and extensors, adductors and abductors of the fingers; the flexors and extensors, pronators and supinators

of the hand. As a result, there is a characteristic pill-rolling movement of the hand. The tremor is present at rest and is momentarily lost by movement, to reappear (38).

It is most frequent in the upper extremities, especially the hands and fingers. One interesting feature of the tremor is the maintenance of the same tempo in all the parts affected, although its intensity may vary from time to time under psychic stress or excitement. It usually stops during muscular activity, and it practically ceases during sleep. As a rule, with the increase of weakness and the rigidity, in the later period of the disease, the tremor also lessens, but is usually still manifest in some portion of the musculature, even in the advanced paralytic stage.

Dr. Stanley Cobb (23) has done a great deal of experimentation on the tremor of paralysis agitans and has reached the following conclusions about this tremor.

(1) The tremor of paralysis agitans is remarkably constant, the average being 5.8 per second. Little variation is observed in any one case when re-examined months later.

(2) The tremor of paralysis agitans gives a characteristic electro-myogram, with large slow waves at the time of muscular contraction and smaller, more frequent waves between these tremor-like contractions.

(3) In young people the rate of the tremor may be much more rapid.

(4) Scopolamine may stop the tremor, but does not seem to slow the rate when acting less completely.

(5) Various muscles in the same person show practically the same rate of tremor.

Dr. J. R. Hunt (47) holds that the rhythmical tremor of the Parkinson type is one of the characteristic symptoms resulting from loss of the globus pallidus mechanism. The factors underlying the causation of the tremor are not definitely known. It has been suggested by some observers that it is a part of and dependent upon the degree of muscular rigidity and to use the words of Hughlings Jackson "tremor is rigidity spread thin, and rigidity is tremor run together".

Dr. Hunt suggests the possibility of an inhibitory tremor center in the hypothalamic region which is under the control of the globus pallidus mechanism, and when this is diseased the center is released from control and the tremor disturbance results. In this way one could explain satisfactorily those cases of paralysis agitans with rigidity or tremor alone.

Going still further in the cause of this tremor Hunt reasons, as the striatal muscle fiber has a dual innervation and function, a correlating center or group of centers for the control of these two systems is believed to exist. One of these controls the anisotropic disk system (the large anterior horn cell fibers) which subserve the function of the quick contraction or the twitch; the other controls the sarco-

plasmotic substance (sympathetic fibers) and the more plastic contraction of the muscle. The loss of the inhibitory influence of the motor cells of the corpus striatum in paralysis agitans would release these lower centers from control with the static symptoms. The tremor follows the release of the inhibitory mechanism governing the anisotropic disk system; the rigidity follows the release of the center controlling the sacroplasmotic substance of the muscle. The tremor of paralysis agitans, therefore, should be regarded as an involuntary form of motor activity, not dependent on the rigidity per se as was suggested by Hughlings Jackson, but produced by loss of the inhibitory functions of the pallidal system on a lower mechanism governing rhythmical movements of the anisotropic disk system of the striated muscles (48).

(2) The rigidity begins locally and then gradually extends and becomes generalized. The hypertonicity of the musculature is of a plastic quality. The plastic quality of the musculature is quite evident on making passive movements of the extremities, which meet with a smooth, waxy resistance, quite unlike the elastic quality of spastic muscle. Often there is a tremor-like sensation of movement on passively flexing and extending the elbow and is called cogwheel symptoms. The general rigidity gradually causes changes of facial expression, posture and attitude, which are quite characteristic of the disease. The face is masklike and without expression; although the facial muscles may be voluntarily innervated, they

fail to respond to emotional innervation. The attitude is characterized by slight flexion of the head, trunk, and both upper and lower extremities. The fingers are held in the interosseal position, with flexion of the basal and extension of the distal phalanges. One curious feature of the disease is the so-called poverty of movement. Patients with this disease will sit motionless by the hour, and even the winking reflex is diminished.

In motility three types of movements are recognized; reflex movements, automatic and associated movements, and isolated or dissociated movements of cortical origin. The motor disturbance of paralysis agitans shows the paralysis to be limited to the automatic and associated movements of the body. For this reason, those motor activities which are concerned with walking, running, sitting, rising from a sitting posture, show most marked and early involvement.

It has been proven that both automatic and associated movements depend on some type of anatomic patterning in the central nervous system. Allowing in full for the effects of rigidity, the grace of some of these movements is seriously disturbed in Parkinsonism, while that of others is left relatively untouched. Since the lesions of Parkinson's syndrome are most constantly and frequently found in the corpus striatum, it seems almost inescapable that the perfect patterning of many of the phylogenetic automatic associated movements is a striated function, while that of the individually acquired ones is a

process of some other part of the brain, presumably some part of the cortex.

(1) Attention is called to the existence of a group of automatic associated movements that are individually acquired, and that can be contrasted with those that are phylogenetically grounded.

(2) The latter group is seriously impaired in Parkinson's syndrome, while the former may escape. Thus we have added evidence that both groups depend on some type of anatomic patterning.

(3) Therefore, the rigidity alone cannot account for the impairment of movement in Parkinsonism, and this organ shows that the patterning of phylogenetic automatic associated movements is a striatal function.

(4) The patterning of the individually acquired movements is presumably a function of some part of the cortex (64).

In these movements the automatic and associated activities of massive muscle groups are impaired and it is only by great effort of will that the defect is overcome. The facial expression is masklike, and the patients are not able to show any emotions.

The purely reflex act of swallowing is not generally affected, even in the last stages of the disease, and in advanced cases, with complete anarthria and general rigidity, solid and liquid nourishment may be taken without great dif-

difficulty, by virtue of the purely reflex mechanism of deglutition.

There is a loss of muscle association in both upper and lower extremities. In walking, for example, there is a failure of the associated flexion thigh, knee and foot which accompanies the normal act of stepping. Instead the foot hangs as the knee is lifted, which adds to the slow dragging movement and the shuffling gait which is characteristic of the disease. The condition is often associated with a peculiar tendency to festination which is characterized by a progressive acceleration of the step and a tendency to pitching forward of the body, so that the patient breaks into a shuffling run and is only able to stop his precipitate progress by throwing himself against some object in his path.

In advanced cases the association mechanism is completely lost; if the patient is pushed over while standing on a large mattress, the fall is passive and complete, and occurs without any of those muscular attempts to break the fall which are present in all other conditions of palsy.

The tendon reflexes in the early period of disease are normal, or may be exaggerated. As the rigidity develops the tendon jerks are usually diminished, but are never abolished. The Babinski is never present and sensations are normal.

The patient may carry a slight fever due to the tremor and the fever is increased by muscular activity. The

intelligence as a rule is not affected (49).

There are subjective sensations of heat, accompanied by local flushings, especially of the face and chest, by local and general elevation of temperature; attacks of sialorrhoea, diarrhoea, and outbreaks of sweat, which may or may not coincide with the flushings just spoken of, do occur (24).

There is marked slowness in all his motions. The cranial nerves are usually normal and the sensibility is not affected. Quite frequently the patient complains of pain and sometimes early, before other manifestations, there is a peculiar drawing dull pain often found in the shoulder. It may be the first sign of a beginning rigidity of the musculature. Another early sign of Parkinson's disease is the uneven spacing of the outstretched fingers.

A review of juvenile forms shows that there are certain points of difference which distinguish them from the presenile type. These are the early age of onset, the more rapid progression of symptoms, the comparatively early involvement of the bulbar muscles, the rarity or perhaps absence of the rigid form without tremor, and the infrequency of subjective sensory symptoms, and the affection is inclined to progress more rapidly (47).

The rhythmical tremor of the hands which persists during rest, the general muscular rigidity, together with the absence of all signs of pyramidal tract involvement, the mask-

like expression, and the peculiar posture, also the loss of certain automatic and associated movements are all important signs that make the diagnosis fairly easy.

Before we discuss some of the problems of differential diagnosis it would be perhaps interesting to see what Parkinson (74) had to contend with during his era of medicine.

"Palsy, either consequent to compression of the brain, or dependent on partial exhaustion of the energy of that organ, may, when the palsied limbs become affected with tremulous motions, be confounded with this disease. In those cases the abolition or diminution of voluntary muscular action takes place suddenly, the sense of feeling being sometimes also impaired. But in this disease, the diminution of the influence of the will on the muscles comes on with extreme slowness, is always accompanied, and even preceded, by agitations of the affected part, and never by a lessened sense of feeling. The dictates of the will are even, in the last stages of the disease, conveyed to the muscles, and the muscles act on this impulse but their actions are perverted.

Unless attention is paid to one circumstance, this disease will be confounded with those species of passive tremblings to which the term shaking palsies has frequently been applied. These are tremor tremulencies, the trembling consequent to indulgence in the drinking of spirituous liquors, that which proceeds from immoderate employment of tea and coffee; that which appears to dependent on advanced age; and

all those tremblings which proceed from the various circumstances which induce a diminution of power in the nervous system. But by attending to that circumstance alone, which has been already noted as characteristic of mere tremor, the distinction will readily be made. If the trembling limb be supported, and none of its muscles be called into action, the trembling will cease. In the real shaking palsy the reverse of this takes place, the agitation continues in full force whilst the limb is at rest and unemployed, and even is sometimes diminished by calling the muscles into employment".

Often times in chronic Parkinsonism it is nice to know if we are dealing with an encephalitic, or the genuine, so-called idiopathic paralysis agitans. Of course past history is the important thing but often we do not get any history of preceeding encephalitis. The difficulty is especially great in persons who have reached an age at which cerebral arteriosclerosis may be expected, and who, in addition, give a history of an infection of the upper respiratory tract, or grip preceding the onset of the syndrome.

Hall mentioned the following characteristic of Parkinsonism due to encephalitis: typical "pill-rolling" tremor is absent or minimal; tremor may be absent no matter how general the rigidity is; whereas in so-called idiopathic paralysis agitans it is not unusual for one extremity or one side of the body to be affected at first and, as a rule, for the condition to extend fairly soon; in encephalitis cases, as the

years go on such extension does not occur, muscular jerkings, lethargy, pupillary signs, great restlessness, spasmodic fixation of the jaws, nystagmus and disturbances in ocular convergence are more common than in the idiopathic cases; the fixed facies develops much more slowly and later in the encephalitic than in the idiopathic cases; in the encephalitic cases the Parkinsonian syndrome may remain stationary and even improve; such is never the case in the idiopathic type. From their observations the encephalitic type is characterized by a fairly acute onset of symptoms and signs of Parkinsonism that is within two or three days after the acute onset of the encephalitis. Another diagnostic feature of encephalitic Parkinsonism is a diurnal variation in the patient's motor activities. Sleep disturbances in the nature of a "reversal of sleep" and various disorders of breathing, such as grunting, hyperpnea, dyspnea, and all sorts of respiratory tics are also never observed in genuine paralysis agitans.

The arteriosclerotic Parkinsonism occurs in persons with evidence of peripheral and retinal arteriosclerosis, and the symptoms generally appear later in life than in the idiopathic type. A history of previous vascular accidents seems to be fairly common. Comparatively speaking, the progress of the disease is more rapid in arteriosclerotic, than in idiopathic Parkinsonism, and it may advance by a series of sudden exacerbations due to repeated apoplectiform insults. But while it seems rather simple it is very hard to make the

diagnosis in many of these cases (56).

Multiple sclerosis in its cerebellar form very closely resembles paralysis agitans, and which may be distinguished by the tremor occurring only upon movement, being wider in range and more irregular than in paralysis agitans, though intention tremor may occur early in paralysis agitans. Multiple sclerosis rarely commences after 40, paralysis agitans rarely before 30. Multiple sclerosis is usually accompanied with nystagmus, loss of abdominal reflexes and slight optic nerve atrophy, with pallor of the temporal half of the discs.

Senile tremor is recognized by a fine tremor of limbs and head (the latter being rarely involved in paralysis agitans, and then late in the course of the disease), the tremor being finer than in paralysis agitans, and affects the head early, involves both extremities about the same time and is unassociated with rigidity (13).

Dr. M. Moyer (72) thinks he has found a very important diagnostic sign for the malady. The extremities often show a certain sign that is elicited by the examiner grasping the wrist with one hand and steadying the arm with the other, above the elbow. Rapid flexion and extension of the arm is made. Instead of an even movement without resistance, one, two or perhaps three slight hinderances to the movement are experienced by the hands of the examiner, which communicates to the hands of the examiner a jerky feeling. This seems to be a rather early symptom.

Thus we see that the diagnosis of this disease is hardly ever in doubt, the tremor is so characteristic, the facies, the paralysis, rigidity, onset, absence of positive laboratory findings, lead to little difficulty in sustaining the diagnosis.

The disease is very slowly progressive, especially in the adult forms. The finer movements of the hands are usually affected quite early by the tremor and rigidity, in late stages the patient may even be bedridden as the rigidity sets in, the tremor diminishes. Death is usually caused by some intercurrent disease.

The affection is organic and incurable, and the most that can be hoped for is an arrest of the progress of the disease, and some slight amelioration of the distressing tremor, weakness, and general disability. The course is usually very slow, in some instances, long intervals may occur during which the disease makes little progress, but sooner or later there is a recrudescence and the progressive course continues. Death results, not from the disease itself, but from a general reduction of the physical strength and vitality.

But Dr. D. S. Booth looks upon the prognosis in a little different light. "While it is true that the results usually obtained are not encouraging, we believe it largely due to the fact that treatment is ordinarily not sought or given until late in the course of the disease, and owing largely to medical nihilism, the treatment is neither system-

atic or intensive. Certainly degenerated organs or tissues cannot, with our present knowledge, be regenerated, but it appears that the degeneration may possibly be arrested, as has been demonstrated in locomotor ataxia, so that if treatment be instituted early, a clinical cure may be possible."

IV. ETIOLOGY AND TREATMENT

In this paper so far we have told how accurately Parkinson described this syndrome. But it is in the field of etiology that we find he had most peculiar ideas, but this should not be considered very strange in the light of the scientific knowledge at that time.

"The great degree of mobility in that portion of the spine which is formed by the superior cervical vertebrae must render it and the contained parts liable to injury from sudden distortions. Hence therefore may proceed inflammation of quicker or of slower progress, disease of the vertebrae, derangement of structure in the medulla, or in its membranes, thickening or even ulceration of the theca, effusion of fluids.

But in no case which has been noticed, has the patient recollected receiving any injury of this kind, or any fixed pain in early life in these parts, which might have led to the opinion that the foundation for this malady has been thus laid. Whilst one has attributed this affliction to indulgence in spirituous liquors, and another to long lying on the damp ground; the others have been unable to suggest any circumstance whatever, which, in their opinion, could be considered as having given origin, or disposed, to the calamity under which they suffered." In a series of cases reviewed by Parkinson he seems to think that rheumatic conditions are found in the great majority of the patients (74).

Then for over fifty years men took more or less

for granted the work of Parkinson and did not speculate on the cause of this disease, but in 1893 Dr. Dana (26) brought forth his theory. Dana says "My own theory and belief are that paralysis agitans is due to a toxin, microbic or humoral; that this toxin circulating in the blood has an especial affinity for certain areas of the spinal cord and medulla oblongata and to a less extent of the peripheral nerves. This toxin, while at first simply of an irritating kind, such as leads to tremors, pains and vasomotor disturbances, eventually destroys some of the parts which it at first irritates, and thus we find in the later stages of the disease a destruction and atrophy of nerve fibers and nerve-cell processes. The source of this toxin is not known."

Men began to wonder about the source of this toxin and it was suggested by Lundborg, of Stockholm, in 1904, and by Berkeley (7) independently in 1905, that chronic dyscrasia or insufficiency of the parathyroid gland, is quite possibly the cause of the disease, but it seems even more plausible that other glands are either primarily or even secondarily involved. It has been noted that the parathyroid glands (1) exert a control upon calcium metabolism and (2) have an anti-toxic action, the chief purpose of which have a predilection for nervous tissue; from which the possible involvement of these glands in paralysis agitans as well as in other diseases of the nervous system become apparent.

Paralysis agitans has all the marks of a chronic

chemical poisoning. The symptoms following parathyroidectomy are remarkably like those of paralysis agitans. In certain stages of illness a parathyroidectomized rabbit has propulsion, tremors, rigidity and salivation as perfectly as these signs ever appear in Parkinson's disease. Also in exophthalmic goitre and in myxedema paralysis agitans has not infrequently occurred as a complication or sequela, and it is by no means too wild a suggestion that the diseased thyroid has damaged the adjacent glands by contiguity of tissue. On autopsy of paralysis agitans patients they often find parathyroid pathology. Often the response to parathyroid therapy is very gratifying (6) (7) (8) (9) (10) (11) (12) (36).

Subsequently another group of men began to think that the seat of the pathology was in the muscle spindles, and they developed two theories as to the cause of this trouble. (1) There may be a primary degeneration of the muscles themselves, beginning in a muscle frequently after some local exciting cause; it gradually progresses from part to part. (2) A second hypothesis is that there is a toxin circulating in the body which causes these changes in the muscles. This toxin may be an actual one, or it may be some deranged hormone or from some pathology in the parathyroid gland that is so frequently seen (19).

The question, too, has been raised whether, in a syndrome such as hepatolenticular degeneration, the disease of the liver causes the changes in the brain or, conversely,

the involvement of the striatum leads to secondary disturbances in the liver.

The speculation is also justified as to whether the tremor of hyperthyroidism is not in effect the result of secondary changes in the striatum. In view of all this, the question now arises whether exophthalmic goitre may not in some way be the result of some altered physiologic or pathologic change of the hypothalamic vegetative centers. The proximity of these structures to the regions affected in paralysis agitans and the occurrence of hyperthyroidism with Parkinsonism in two cases in which the one syndrome preceded the other may possibly furnish clinical confirmation of these theoretical views. But it may be just an accidental association, because it is not found in all cases. But considering all this, the question still remains unanswered whether actual exophthalmic goitre can be caused by involvement of those centers. Very often the goitre precedes the paralysis agitans by a number of years (91).

While in recent years the idea of parathyroid relationship has been losing ground, other ideas have been becoming more firmly grounded and today the modern idea is that it is a combination of a number of conditions. There is no recognized specific cause of the disease. It belongs essentially to the degenerative period of life or the period of senility, and occurs most frequently in the fifth decennium and next in the forties. Before the present appearance of epidemic en-

cephalitis cases of paralysis agitans below forty years of age were very uncommon. Willige, in 1911, was able to collect only about 20 such cases from the literature up to that date and of these, the earliest age of onset was 18 to 20 years (41). But juvenile, presenile and senile types are recognized.

It is about twice as frequent in men as in women and is sometimes hereditary. Heredity findings are not significant except in the form of "neuropathic heredity" in about 25 per cent of the cases. The juvenile form not infrequently displays a familial incidence. It is, however, interesting to note the consanguinity of the parents, which is so frequently encountered in other system and degenerative affections of the central nervous system may play its part also (22).

Out of the nervous cases in the New York Medical Hospital 1.3 per cent had paralysis agitans. All races of men appear susceptible, even a case has been reported in a negro, at last proving this race not immune. It is found most often in Irish people; it may be that the Irish, being a very emotional race, are more vulnerable to the attributed exciting causes of paralysis; shock, anxiety, worry, depression, etc. It seems to be as much environmental as inherent. Occupation does not seem to play such an important part. It has been frequently stated that acute and chronic diseases of various kinds have a predisposing influence to the occur-

rence of paralysis agitans.

Among apparent predisposing or exciting causes may be mentioned depressing emotions, physical exhaustion, and injuries. A slight injury to an arm or leg has sometimes preceded the tremor, but in such cases the relation of cause and effect is very doubtful. Acute infections have sometimes preceded the onset of the disease, and this is also true of syphilis.

Primary paralysis agitans is preceded by atrophic and degenerative changes in the large cell efferent system of the corpus striatum. The chief factors inducing such changes are an inherent biologic inferiority of degeneration, especially those of senility. In primary paralysis agitans the cellular changes are those of primary atrophy, and are of the same pathologic nature as those of primary lateral sclerosis.

Secondary paralysis agitans from involvement of these neurons is more common than the primary form of the disease. Inflammatory (encephalitis) and vascular lesions (thrombosis, hemorrhage) are the common causes of the secondary form. Toxic degenerative processes due to manganese, carbon monoxide or other toxins, and neoplastic involvement of the corpus striatum also occur (49) (38).

This brief review of the etiology of paralysis agitans shows that the most important factors are age, sex, nationality, morality, violent emotions, especially depression, direct and indirect heredity, and infectious disease.

We have already shown the rather peculiar idea that Parkinson has as to the location of the pathology, and in view of this it is not surprising the line of therapy that he advocated. "All that has been ventured to assume here, has been that the disease depends on a disordered state of that part of the medulla which is contained in the cervical vertebrae. But of what nature that morbid change is and whether originating in the medulla itself, in its membrane, or in the containing theca, is, at present, the subject of doubt and conjecture. But although, at present, uninformed as to the precise nature of the disease, still it ought not to be considered as one against which there exists no countervailing remedy. It is to be hoped that a remedy will be found that will be of use in stopping the progress of the disease process. At this time the medical men assumed the symptoms were due to irritation of the coverings of the medulla, resulting in pressure symptoms. In such a case then, at whatever period of the disease it might be proposed to attempt the cure, blood should be first taken from the upper part of the neck, unless contra-indicated by any particular circumstance. After which vesicatories should be applied to the same part, and a purulent discharge obtained by appropriate use of the sabine liniment, having recourse to the application of a fresh blister, when from the diminution of the discharging surface, pus is not secreted in a sufficient quantity. Should the blisters be found too inconvenient, or

a sufficient quantity of discharge not be obtained thereby, an issue of at least an inch and a half in length might be established on each side of the vertebral column in its superior part. These, it is presumed, would be best formed with caustic, and kept open with any proper substance as cork, etc.

It is obvious that the chance of obtaining relief will depend in a great measure on the period at which the means are employed, as in every other disease, so here, the earlier the remedies are resorted to, the greater will be the probability of success. As slow as is the progress of the disease, so slow in all probability must be the period of the return to health.

But it seems as if there existed reason for hoping for more. For supposing change of structure to have taken place, it is extremely probable that this change may be merely increase in mass or volume by interstitial addition, the consequence of increased action in the minute vessels of the part. In that case, should the instituting of a purulent discharge, in a neighboring part, act in the manner which we would presume it may, should it by keeping up a constant discharge, not merely alter the determination, but diminish the inordinate action of the vessels in the diseased part: and at the same time excite the absorbents to such increased action as may remove the added matter; there will exist strong ground for hope, that a happy, though slow restoration to health, may

be obtained.

The weakened powers of the muscles in the affected parts is so prominent a symptom as to be very liable to mislead the inattentive, who may regard the disease as a mere consequence of constitutional debility. If this notion be pursued, and tonic medicines and highly nutritious diet be directed, no benefit is likely to be thus obtained; since the disease depends not on general weakness, but merely on the interruption of the flow of the nervous influence to the affected parts.

Although unable to trace the connection by which a disordered state of the stomach and bowels may induce a morbid action in a part of the medulla spinalis, yet taught by the instruction of Mr. Abernethy, little hesitation need be employed before we determine on the probability of such occurrence"(74).

Since 1812, the treatment of paralysis agitans has been rather faddish, as seems to be medicine in general. Whenever a new drug or idea was brought forth, someone had to try it on paralysis agitans. Thus all sorts of galvanic apparatus and electrical stimulators have been used. Then the endocrines have all been tried one by one, with no avail. But out of all this vast amount of experimentation we have found a few symptomatic aids at least.

As the disease is a degenerative atrophy of certain central neurons of the brain, the treatment is essentially

symptomatic and tonic. There is no known specific or curative agent. Although incurable, much can be done to ameliorate the condition and relieve distress. All possible measures should be taken to improve the general health and strength. The environment should be as quiet as possible, as these patients are very susceptible to the least excitement or stress, and their symptoms are exaggerated.

The characteristic mental depression should be met by encouragement and the assurance of relief, since the mental attitude has much to do with the result. The patient should be guarded against cold and so far as possible from emotional disturbances and mental and physical strain. Some men feel that constant motion is better for these patients. Hot or cold baths are to be used according to the likes or dislikes of the patient. Liquor, tobacco, tea and coffee should be used very moderately, if at all (13).

Massage, passive movements, and mild gymnastic exercises are helpful when given by a skilled attendant. Electric baths and general vibratory massage tend to reduce stiffness and counteract the development of deforming postures. Tremor may be helped by the use of galvanic current according to the work of Reynolds (81).

Swift (87) shows that with slow moving exercises taken for fifteen minutes three times daily benefited the patients and resulted in (1) a general constant relief of bad feelings, (2) occasionally an hour of complete relief

from all distressing symptoms, and (3) a quickly gained repose into sleep on retiring. The treatment, though giving marked relief from intense suffering even to the point of recovering normal conditions for hours at a time, proves no cure, and the symptoms all returned when the exercises were omitted, but they showed improvement again when resumed, and also again gave relief.

In the idiopathic and post-encephalitic paralysis agitans the tremor in the hands may be very violent. This can be greatly reduced in many cases by overstretching a group of muscles such as the flexors of the wrist. The slight discomfort of the splint is greatly outweighed by the relief gained from a greatly reduced tremor (20).

There are three drugs that seem to be of value, giving symptomatic relief; they are atropine, hyoscine and stramonium. There are other drugs which in the hands of the experimenter give excellent results but for others the results are very disappointing.

The first of these drugs is bulbocapnin, worked on by De Jong (28) of Amsterdam. He demonstrated that the tremor of paralysis agitans may be controlled by the use of bulbocapnin. Bulbocapnin is one of the eleven alkaloids from the larkspur (*corydalis cava*). This drug was used, according to Peters, as early as 1525. At that time it was recommended for diseases of the head and nerves and for trembling of the limbs. By administering doses of 200 mg. of bulbocapnin subcutaneous-

ly, they found it stopped the tremor of paralysis agitans. The duration of its effect when given subcutaneously is from three to six hours. De Jong has given it to patients over a period of several months, with no untoward effect, and has not found it to be cumulative. However, the treatment is palliative but not curative (68).

Dr. Grinker (38) commenting on this drug says "A drug which has been used experimentally, producing peculiar rigidity in animals, is known as bulbo-capnin. At one time, it was considered possible to use this drug to decrease the extrapyramidal tremor, but it has not worked out clinically. From the use of larger quantities, a very disagreeable increase in rigidity occurs."

As we have shown many men still contend that there is a definite relationship between parathyroid pathology and paralysis agitans. Using this as a basis they have divided therapy along two lines, Madlener (65) and Kuhl (58) have both implanted parathyroid glands from cattle into the muscles of the paralysis agitans patients. These men think they have seen some improvement but in the hands of others the results have been very disappointing.

Working on the same theory but on a different method of therapy, Dr. Wm. Berkeley (7) (8) (9) (10) (11) (12), by the administration of the parathyroid extract has reported very good results. The dose by the mouth is one capsule (one-fiftieth grain of parathyroid extract in milk sugar)

two to six times a day. The hypodermic solution is given in doses of one or two mils once or twice a day.

The benefits of treatment usually appear slowly. They consist in diminished rigidity, shaking relieved or arrested, restlessness abolished. There seems to be no contra-indications and there seems to be only a few toxic effects only if the dose is pushed too rapidly and then tremor is increased.

Improvement is often noticed in two weeks, very generally in two or three months; and it should continue for a few months more. After this the remedy should be indefinitely continued, but in smaller doses just enough to maintain the benefits already secured.

Eising reported good results in one case by the use of irradiated ergosterol. Calcium metabolism is known to play an important role in Parkinson's disease and to exert its action in some way through the activity of the parathyroids. Irradiated ergosterol is thought in some manner to stabilize calcium metabolism and would offer a sound rationale for its use in Parkinsonism (30).

Case of chronic encephalitis showing the Parkinsonian syndrome has been successfully treated by the injections of the dye trypan blue. The effects seem to be marked, and the tremor and rigidity are helped a great deal. This dye is supposed to be of value in the acute cases preventing the chronic complications (60).

It is in the relief of the common symptoms of increased muscular tone and tremor that treatment has so far been most successful. The slowness or poverty of movement to which the disease gives rise can in most cases, and to a certain extent, be made less by the action of one particular group of alkaloids, the atropine series.

The three members of the group which are most commonly used are atropine, hyoscine and stramonium. Each of these has its advantages and its drawbacks. Each, if prescribed in sufficiently large doses, is capable in certain cases of producing immediate effects as dramatic in character as any seen in medicine. Moreover, these effects can be maintained for long periods provided the treatment is continued.

During recent years a method of treatment by atropine, which was originally advocated by Kleemann in Germany, has been widely adopted in various countries. The method consists in ascertaining the maximal dose of atropine that causes improvement. This is found by a daily graduated increase of dose. When such increase yields no further benefit the dose is similarly decreased day by day until the return of the symptoms shows that the dose is too small. A dose slightly higher than this is then chosen as the optimal dose for that patient, and it is continued at that amount daily.

The patient should be in bed during the estimation of the optimal dose. A solution of atropine sulphate in distilled water ($\frac{1}{2}$ to $\frac{1}{4}$ per cent) is used, and is given oral-

ly. One should watch very carefully for signs of bladder and abdominal distension; when these symptoms occur one should temporarily discontinue the drug.

In many cases, even the most severe, quite marked improvement takes place. Speech, which for some time has been almost an inaudible whisper, becomes easily heard. General movements of the body and limbs become more free, and in some instances patients who had been almost totally dependent become almost independent. In some cases with troublesome sialorrhoea the relief secured is usually considerable. In some cases there has also been improvement in the tremor (43).

For the tremor hyoscine is to be recommended in doses of 1/200 to 1/100 grains twice or three times daily. Others say that this drug has little effect on the tremor but that it does have some value in combatting the rigidity.

Carmichael and Green and Hurst (51) proved that stramonium, which contains atropine and hyoscyamine, and they found that the mental as well as the physical condition of the patients showed great improvement. The drug can be given in doses as high as 45 to 60 mms. of the tincture three times a day. Also very often pilocarpine is combined with either hyoscine or stramonium; this makes possible the giving of larger doses without the undesirable effects.

Hurst begins by giving the patient 10 mm. of tincture of stramonium in half an ounce of water on waking, after

lunch, and after tea. If the stiffness causes disturbed nights by preventing the patient from turning over in bed, an extra dose is given before going to sleep. One drachm is added to each of the three doses of the mixture on alternate days, so that in eight days the total dose is doubled. The gradual increase in the dose is continued until the patient begins to complain of unpleasant dryness of the mouth or paralysis of accommodation. Pilocarpine nitrate grains $1/10$ is then added to the latest dose of stramonium and the mixture is prescribed in half an ounce of water. One drachm is again added to each of the three doses of the mixture on alternate days until sufficient relief is obtained or slight toxic symptoms appear; by this time the dose is generally at least 60 mm. of tincture of stramonium, with perhaps $2/5$ grains of pilocarpine nitrate. Finally a prescription is given for the full dose of stramonium and pilocarpine in a single half-ounce of water. The use of citrous fruits or candy offsets the dryness of the mouth. With the drug most men obtain the following results: (1) relief from the muscular tonus, (2) relief from the mental retardation, (3) lessening or at least relief from the tremor, (4) excessive salivation is relieved, (5) the masked facies and stare are rarely changed, although there may be a distinct change in countenance, conveying a more optimistic state of mind (51) (66) (15) (13) (44) (69).

In addition to make these people more restful and calm at night, bromides, luminal, cannabis indica, veronal,

are of definite value. Thus we see that while we have no specific treatment for this condition we do have many very good symptomatic drugs that are of very definite value. But paralysis agitans still remains the "sphinx" of neurology, both as regards cause and the specific line of treatment to be used.

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