Clinical and pathological survey of the corpus striatum

Herbert C. Modlin
University of Nebraska Medical Center

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A CLINICAL AND PATHOLOGICAL SURVEY

OF THE CORPUS STRIATUM

BY

HERBERT C. MODLIN

A senior thesis presented to the College of Medicine, University of Nebraska, Omaha, in partial fulfilment of the requirements for the degree of Doctor of Medicine.

1938
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INTRODUCTION
The recent ascendancy of problems connected with the anatomy, physiology and pathology of the corpus striatum and associated structures forms perhaps the most striking advance in contemporary neurology. In a brief period of less than thirty years the study of basal ganglion pathology has progressed from an occasional poorly classified report to a tremendously extensive literature. Few volumes of any neurological journal appear without a number of papers devoted to this subject.

Notwithstanding this immense activity, well substantiated conclusions on the pathology and function of the corpus striatum are minimal, and theory and speculation are still regrettably extant. Motor symptoms as widely divergent as a complex tic and a simple muscle twitch, as heterogeneous as palilalia and micrographia are alike attributed to striatal disease.

The corpus striatum is so situated that selective trauma cannot produce clear-cut lesions; its vascular supply is not derived from a single source; morbid processes involving it are seldom confined to the ganglia in question; and the immediate presence of the internal capsule confuses the picture. The inaccessibility of these structures has discouraged experimental work on the striatum, and most of our knowledge at the present time has been gained from clinico-pathological sources.

It became apparent at the outset of this paper that no one of the diseases of the corpus striatum could be separated from the
others and discussed as such. Many of these syndromes, originally described separately, have been found to overlap and intertwine; and other problems, at one time a unit, have been subdivided, added to and subtracted from, so that it is impossible to discuss adequately any one of the many pathological processes of the basal ganglia without examining its relationship to all the others.

Although, the pathogenesis of the striatal diseases is far from clear, it is the most absorbing phase of the subject, perhaps because of its obscurity. It is to the origin and functioning of the morbid processes underlying striatal disease that I shall devote most of this thesis. The syndromes themselves, as clinical entities, are interesting, but are merely an expression of altered architecture in certain bodily structures. The actual understanding of a disease, its definition, interpretation of symptoms, prognosis and treatment, all rest on the principles of pathogenesis which have been evolved for it. Many of the striatal diseases are poorly defined, inadequately interpreted and ineffectually treated, all because of the obscurity of their pathogenesis. This paper is chiefly an attempt to cull from the literature as much as is known of the pathogenesis and pathological physiology of striatal diseases, and consideration of the clinical aspects will be sacrificed to a discussion of morbidity.
History

The masses of gray substance placed deeply in the telencephalon, now known as the basal ganglia, have been recognized by anatomists from earliest times. They were mentioned by Galen and by his medieval disciples, but little significance was attached to them until Thomas Willis, in 1667, remarked that they probably represented "internodes by which the cerebrum coheres with the medulla oblongata."

The earliest English text available at this time is one by Samuel Solly on the Human Brain (1848). In it he described the anterior cerebral ganglion or corpus striatum and the posterior cerebral ganglion or optic thalamus as comprising the central ganglia. His interesting suppositions on physiology and pathology will be noted elsewhere. Fifty years later Solly's division of the basal ganglia was still used by Beevor (1898) and Gardinier (1899) in discussing the subject. During that time, however, more astute observers, particularly in Germany, were studying the central ganglia in more detail. The English translation of Jakob's text (1896) described the thalamus separately, and discussed the caudate nucleus, the lentiform nucleus with its two divisions, the putamen and globus pallidus, the claustrum and the internal and external capsules. This erudite pupil of the famous Dr. Strumpell founded the modern concept of the anatomy of the central ganglia.
Gross Anatomy and Connections

The basal ganglia are four gray masses deep within the forebrain and are known as the caudate, lentiform and amygdaloid nuclei and the claustrum. The two former, with the internal capsule which separates them, constitute the corpus striatum. The two latter have not been mentioned in any report on basal ganglion pathology involving the extrapyramidal motor system and may be presented briefly. The parts of the corpus striatum demand more attention.

The nucleus caudatus (Plate IV) is an elongated mass of gray matter bent on itself like a horseshoe, and is in close relation to the lateral ventricle throughout its extent. Its large rostral head bulges into the anterior horn of the ventricle, and the remainder tapers into a slender arched tail which curves around into the roof of the inferior horn and extends rostrally as far as the amygdaloid nucleus with which it is fused (Ranson, 1932). This latter structure is a small ball of gray matter in the roof of the inferior horn. It is continuous with the end of the caudate tail and with the cerebral cortex of the temporal lobe lateral to the anterior perforated substance (Landau, 1919).

The lentiform nucleus intervenes between the insula on one hand and the caudate nucleus and thalamus on the other. It is not a homogeneous mass but is divided into a lateral putamen and a medial globus pallidus, (Plate IV) the latter again divided into two
portions. The dividing tissues are called, respectively, the external and internal medullary laminae. Both portions of the lentiform nucleus are fused rostrally with the caudate head.

The claustrum is a thin plate of gray substance just lateral to and separated by the external capsule from the putamen (Plate IV).

The internal capsule is the broad band of white fibers separating the lentiform nucleus on the lateral side from the thalamus and caudate nucleus on the medial side. In a horizontal section it has the shape of a wide v, (Plate IV) the angle of which is known as the genu, and the sides of which are known as the anterior and posterior limbs of the internal capsule. The anterior limb, which separates the caudate and thalamus, contains corticipetal fibers from the thalamus to the cortex and corticifugal fibers from the cortex to the nuclei pontis. The posterior limb, which separates the lentiform and thalamus, contains the important corticospinal, corticobulbar and corticorubral tracts as well as the optic radiation, the temporopontine tract and the thalamic radiations.

A point in the histology of these bodies is of interest here. It is of no particular advantage to discuss the finer structure of the ganglia other than to point out that two types of cell bodies are found (Starr, 1896, Malone, 1912). Both are stellate cells of Golgi's type I and differ only in size and length of axon. The large cell with long efferent axon is found in the caudate and both divisions of the lentiform nucleus. The small cell with short, intraganglionic axon, occurs in the putamen and caudate but not in
the globus pallidus. Malone's classification shows them both to be motor cells.

The motor mechanism of the human central nervous system has two divisions, the pyramidal, consisting of the centripetal fibers of the cerebral cortex, and the extrapyramidal, which is again divided into two parts (Jakob, 1925), the more significant of which is usually termed the extrapyramidal pathway. This arises from the basal ganglia, thalamus and subthalamus and extends via the red nucleus and its tract to the sacral region of the cord. The second part of the "involuntary" system is the fronto-ponto-cerebellar pathway, which also terminates ultimately in the red nucleus and exercises its influence over lower motor neurones by the rubrospinal tract.

As has been indicated, there are other structures intimately related to the corpus striatum, and though they are not a part of it or of the basal ganglia, their importance in pathology and function necessitates a brief description of them here.

The subthalamus (Plate VI) is situated between the thalamus and the tegmentum of the mesencephalon and forms a zone of transition between these two structures. The red nucleus and substantia nigra project up into it from the mesencephalon, and it contains in addition a biconvex mass of gray matter known as the hypothalamic nucleus (Ranson, 1932). The German writers refer to this body as the corpus Luysii (Jakob, 1925), and ascribe to it a definite relation to the corpus striatum.
The substantia nigra of the mesencephalon is a broad thick plate of pigmented gray matter, observable to the naked eye, and therefore appearing earlier in neurological descriptions than many other structures. It separates the basis pedunculi from the tegmentum and extends from the pons through the mesencephalon into the hypothalamus. Its irregular pigmented nerve cells are motor in type and send their axons into the tegmentum (Ferraro, 1925).

The nucleus ruber (Plate VI) is the last structure to be examined. It is a large oval mass, of a pink color in the fresh brain, and located in the tegmentum of the mesencephalon at the level of the superior colliculus and termination of the brachium conjunctivum. The cells are of two types here also, the smaller sending axons into the tegmentum and the larger forming the long fibers of the rubrospinal tract.

For my discussion of the afferent and efferent connections of these central nuclei I have preferred to take the physiologic approach and display the interconnections of the system as a whole rather than to mention the pathways piecemeal with the descriptions of the various ganglia. The probable connections of the striatal systems are illustrated by plates I and II taken from Rasmussen (1935) and Plate III from Ranson (1932). The following account is from Jakob (1925) and Ranson (1932) except when otherwise stated.

The caudate nucleus and the putamen of the lentiform nucleus are grouped together as the striatum, since their connections and
function appear to be identical. Striopetal fibers extend to the caudate and putamen from the anterior and medial nuclei of the thalamus (Sachs, 1909), and striofugal fibers go to the pallidum (globus pallidus). According to Cajal the various parts of the corpus striatum also receive collateral branches from the corticospinal tract. It is Vogt's impression that afferents extend to the small cells and efferents lead from the large cells, and that the small cells are intermuncial from caudate to putamen and from putamen to globus pallidus (Plate III).

The pallidum, or globus pallidus, therefore, receives its fibers from the striatum and the thalamus; and its single large type of cell sends its efferent axons in a transversely directed bundle of fibers, known as the ansa lenticularis, to the structures diagrammed in plate II, namely the thalamus, motor trigeminal and motor facial nuclei, hypothalamic nucleus, red nucleus, substantia nigra and posterior commissure. The ansa lenticularis is, therefore, the common tract of the extrapyramidal motor system, and the globus pallidus is its site of origin. These efferent fibers are both crossed and uncrossed (Jakob, 1925) and innervate the nervous system bilaterally.

The corpus Luysi (Plate VI) receives its afferents from the pallidum and thalamus and sends its efferents to the two closely apposed structures, the red nucleus and the substantia nigra. Its connections are still somewhat obscure.
The substantia nigra also has some interrelations which are not clear. The most elaborate set of connections is established by Jakob (1925) who states that the area receives afferents from the cortex, pallidum, thalamus, corpus Luysi and red nucleus, and sends efferents to the basis pedunculi, corpora quadrigemini and tegmentum of the pons.

The red nucleus, besides having centripetal attachments to the cortex, thalamus, pallidum, substantia nigra and hypothalamus, also receives fibers from the dentate nucleus; and it therefore appears to be a coordination center for the entire motor system. Its efferents travel by the rubrospinal, rubroreticular and rubrothalamic tracts to the bulbar and spinal motor neurones and to the thalamus.

The corpus striatum draws its blood supply chiefly from the middle cerebral artery, a branch of the internal carotid. There is also a small vascularization from the anterior cerebral branch of the internal carotid. The anterior artery gives off a group of antero-medial ganglionic branches which supply the head of the caudate. The middle artery also forms a group of antero-medial ganglionic branches, which are arranged in two sets; one, the internal striate, passes upward through the inner segments of the lentiform nucleus and supplies it, the caudate nucleus, and the internal capsule; the other, the external striate, ascends through the outer segment of the lentiform nucleus and supplies the caudate.
nucleus and thalamus. One artery of this group, larger than the rest, is of special importance since it is the most frequently ruptured artery of the brain. It rises between the lentiform nucleus and the external capsule and ends in the caudate.

Comparative Anatomy

The study of the old and new motor systems from the standpoint of comparative anatomy is an essential preliminary to the perusal of the clinical phenomena of motor disease.

In the vertebrate series, the corticospinal tracts, with their origin from the cortical mantle, are first encountered in the higher reptiles. In birds, such fibers are few and not electrically excitable (Wilson, 1925), hence Ariens Kappers' view that in vertebrates the old motor system of lower motor centers acts vicariously for the new.

The fundamental motor unit of prepallial life is the neurone of the ventral horn of the spinal cord. It is the original and simplest unit of motor activity. The highest center of this lower motor neuron system is in the vertebrate corpus striatum at the base of the telencephalon. In amphibia the primordial striatum first shows subdivision into an olfactory and a somatic portion. In reptiles there may be identified a further division of the somatic striatum into a lateral afferent portion, the putamen, and a medial efferent part, the globus pallidus. The lentiform nucleus
is, therefore, an ancient structure and is built upon the same plan in man as in the turtle (Herrick, 1926).

The caudate nucleus, which arises partly from the olfactory striatum, forms, with the putamen, the neostriatum, the combined structure appearing first in reptiles. The globus pallidus is the paleostriatum and is older phylogenetically as well as ontogenetically; it is a well developed structure known as the nucleus basalis as low down in the animal scale as fishes (Grunthal, 1932). This last named structure forms in fishes the basal forebrain bundle and, with the motor fasciculus of the cord plus the posterior longitudinal fasciculus, forms the central motor mechanism (Hunt, 1917a).

This concept of the origin and division of the corpus striatum will be utilized in describing various points under physiology and pathology.
EXPERIMENTAL PHYSIOLOGY
As previously suggested, the laboratory research into the function of the corpus striatum has been meager compared to the large volume of clinical investigations. Due to early technical difficulties many of the first reports are of little value, and significant experiments date from the early part of the present century, beginning with reports on decerebrate rigidity.

Experimentation on the corpus striatum was started in 1820 by Flourens. His efforts consisted of attempted stimulation of the basal ganglia and resulted in negative findings. Magendi, 1841, also failed to get any response from stimulation experiments, but, when he destroyed the ganglia operatively, he beheld a peculiar leaping forward of the animal. In 1840 Budge exposed the intestines of his animals and, on electrical stimulation of the basal ganglia, observed increased peristalsis. Hitzig, 1870, reported powerful muscular contraction resulting from striatal stimulation. Ferrier, 1876, also noted contractions on the opposite side of the body. These reports are open to criticism since their authors doubtless included the internal capsule in the area stimulated. Numerous other similar experiments continued to accept and deny the excitability of the basal ganglia, but no definite tenet was established.

Two more recent experiments also showed diametrically opposed results. Wilson (1914) very thoroughly explored the corpus striatum of the ape with the stimulating needle but was unable to provoke any muscle movements. Grinker (1931) reported an unusual type of experiment;
he was able to examine a living newborn case of anencephaly in which, when the calvarium was removed, the corpora striata, later identified histologically, were projecting up from the base of the brain in plain view. He stimulated these masses electrically and procured slow flexion and the appearance of athetoid movements in the arms and legs.

Following Sherrington's classical experiments on decerebration, the study of the basal ganglia took a new turn. The bilateral posture of rigidity in extension assumed by these experimental animals suggested at once the rigidity of paralysis agitans, and contemporary thought began to consider this problem. Since decerebration is accomplished by interruption of the central nervous system at the level of the superior colliculus, and the corpus striatum is also separated from the lower motor neurones, our conclusions from simple decerebration must necessarily be reserved, for how much of the postural change is due to release from the cortical and how much from the extrapyramidal, is not known. Sir Victor Horsley (1909) removed the cortex from an animal and noted the resulting posture. It was his conclusion that the motor cortex was for the learning of new movements and the basal ganglia were for "stock movements."

The action of the cerebellum must also be taken into account, although the work of Holmes (1922) and Pollock and Davis (1927) showed it to be an inhibitor of postural activity rather than a stimulant.

Graham Brown (1913), working with excitation of the mesencephalon
in decerebrate monkeys, reported that unipolar stimulation below the level of interruption produces a constant postural variant of the usual decerebrate picture. The attitude, which appeared after anterior (rubrospinal) or posterior (posterior longitudinal bundle) excitation, consisted of homolateral arm flexion and leg extension, contralateral arm extension and leg flexion, head extension with rotation of the face to the side stimulated, and tail erection with deviation to the homolateral side.

One of the important points to be gathered from these experiments is that the corticospinal system is functionally nonpostural, is phasic rather than static. Pyramidal motor reaction corresponds with the duration of stimulus, whereas extrapyramidal motor reactions do not (Wilson, 1929). The motor reaction in man, then, is of a double type, the phasic and the static.

There have been a number of reports on cases of complete interruption of function in both systems, i.e., decerebrate rigidity, in man (Wilson, 1920; Kraus and Rabiner, 1922; Walshe, 1923). The findings here are neither those of paraplegia or paralysis agitans but closely resemble the pattern-attitude of decerebrate animals, extensor rigidity.

One of the most recent experiments conducted from a somewhat different point of view, was Tower's cortical stimulation in cats after pyramidal tract interruption. She discovered that this maneuver resulted in a lessened initiative of voluntary moti...
produced stereotyped movements with no apparent loss of muscular activity. From this she deduced that the cortical mechanism is organized at four levels; the segmental level occurring in the cord regulates simple reflexes; the one in the brain stem accomplishes reintegration and produces posture and movement; that of the thalamic region provides further integration and controls pattern formation; and the one in the cerebral cortex effects the height of integration and pattern formation. Tower concluded that the cerebral cortex is both motor and inhibitory and may act through the extrapyramidal levels if direct pathways are interrupted.

In recent years quite another line of approach to the mysteries of the basal ganglia has developed. This is the investigation of the possibility that vegetative functions originate in or are controlled by the corpus striatum. Tokay (1931) attempted to study this problem by means of stab wounds into the corpus striatum, and found that as a result his animals developed fever, polyuria and chloride loss. His autopsy examinations disclosed the major insult in the caudate nucleus, and he designated this body as the control of at least these three vegetative functions.

Lhermitte and Trelles (1932) discussed this phase at length and concluded that the corpus striatum is a vegetative center, and as such modifies respiration, the digestive tract, arterial tension, glycogenesis, temperature and vasomotor control. They were unable to formulate any conclusions as to whether these activities
are of the sympathetic or parasympathetic type.

Söken (1934) found that seven cases of striatal epilepsy showed, during their seizures, marked hyperpnea and redness of the entire body, and indicated the apparent association of the striopallidal system with these vegetative functions.
Unquestionably senile paralysis agitans was a disease afflicting the human race long before 1817, but practically the disease was first acknowledged as a clinical entity at that time, the year James Parkinson published his celebrated pamphlet, "An Essay on the Shaking Palsy."

Senile shaking palsy was noted by Galen and by later authors such as Sylvius de la Boe and Sauvages. Sylvius named the condition tremor coactum and Sauvages, 1768, called it scetolyrbe festinans. It remained generally unrecognized, however, until the English physician Parkinson published a report of six cases with conclusions as to etiology, pathology, symptomatology and treatment. The future value of these little pamphlets was not realized at the time of their appearance, with the result that only five are extant. The work was translated into German many years ago, but it was not until 1922 that an English translation was made by Ostheimer. The quotations which follow are from this work.

Parkinson's definition of his disease was "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 running to a walking pace; the senses and intellects being uninjured." The onset of the disease is insidious, its progress imperceptible. The patient first notices a sense of weakness, with trembling, which fastens on a part of the body such as an arm, a leg or the head. The symptoms become more decided; the typical forward-stooping posture appears; difficulty
PARALYSIS AGITANS
in controlling the hand is evident, especially in delicate manipulations such as writing; and the characteristic shuffling gait, due to inability to raise the feet, appears. As the years pass, the posture becomes exaggerated, and the pronounced flexion of the trunk causes, at times, a forward propulsion into a running pace. There is continued degeneration until the powers of speech and deglutition fail, saliva dribbles from the mouth, sphincter control is lost, and the patient becomes bedridden until relieved by death.

Concerning the pathology of the shaking palsy, Parkinson believed that there is "a diseased state of 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... the 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."

The excellence of Parkinson's powers of clinical observation cannot be denied. For many years, textbooks such as those of Watson (1843) and Copeland (1850), simply quoted the original monograph at length and were unable to change Parkinson's picture in any respect. Both of these latter works cited two autopsies of Morgagni in which the pathology for the disease was presumably located in the medulla and upper cord.
It was not until another giant of clinical analysis, Charcot, turned his attention to paralysis agitans that any advancement in the study of the disease was made. The English translation of his text (1877) furnished several noteworthy additions to our understanding of the subject. He first gave an analysis of tremor, dividing this symptom into the rapid or alcoholic type, the moderate or hysterical type, and the slow type found in paralysis agitans and disseminated sclerosis. His second important contribution was the addition of rigidity to the syndrome, a symptom which Parkinson and his successors overlooked. He also described for the first time two of the secondary signs, the mask-like facies and the typical arm attitude - flexed at elbows with hands on abdomen. Perhaps his most significant finding was in differentiating for the first time between multiple sclerosis and Parkinson's disease, in which he laid particular stress on the age of onset, rigidity, ataxia and eye signs. Charcot had nothing to add to the question of pathogenesis except to refute theories advanced by others. He stated, "The pathology of this disease is yet to be discovered."

During ensuing years, as case by case, the disease was studied with increasing interest, attention was gradually drawn to the basal ganglia. Beevor's text (1898) remarked that the pathology for paralysis agitans lay probably in the central ganglia of the telencephalon. Jelgerma, one of the early workers of the German
school, which was to do so much with basal ganglion diseases in the first part of the twentieth century, localized the lesions in the lenticular and lateral thalamic nuclei and described a reduction in size of the ansa lenticularis (1908). Two other prominent papers by Lewy (1913) and Auer and McCough (1916) also gave special prominence to the lesions found in the lenticular nucleus. Lewy found, in addition, gliosis and degeneration in the dorsal motor nucleus of the vagus, and the paper by Auer and McCough mentioned further changes in the caudate nucleus and thalamus.

An even more detailed localization of pathology was accomplished in a series of comprehensive studies on paralysis agitans by Hunt in 1917 and 1918. He prefaced his remarks on pathology with a clinical classification, and a description of a new form of Parkinsonism (1917a). His types of the disease were presenile and senile of the original description, symptomatic of arteriosclerosis, lues, etc. (and now of encephalitis), formes frustes or incomplete and atypical types, and a fourth new form, juvenile paralysis agitans. In discussing this new discovery, he presented four cases with the first complete pathological investigation. He found the essential change to be an atrophy of the large cells in the globus pallidus with less profound changes in the large cells of the caudate and putamen. Hunt then named his new disease "progressive atrophy of the globus pallidus," and defined it as "a system disease clinically
of the paralysis agitans type, and pathologically associated with atrophy of the motor cells of the globus pallidus. The etiology is unknown; the symptoms are progressive paralysis, tremor and rigidity with the secondary signs of paralysis agitans; the pathology is as noted above; the diagnosis is made on early age plus Parkinson's syndrome with differential from multiple sclerosis and Wilson's disease; and the prognosis, as in paralysis agitans, is that the syndrome is progressive but compatible with many years of life. Hunt's description was completely substantiated by Bogart (1930) who examined in detail a case of juvenile paralysis agitans and found a degenerate globus pallidus and an intact striatum.

Continuing with this same general problem, Hunt showed, in another report (1917b), that these large cells of the pallidal system are motor in type and are the chief efferent pathway of the corpus striatum, forming the ansa lenticularis. He also described degeneration of these large cells in a case of presenile paralysis agitans (1918) thus substantiating the general premise he had derived from his first report on the juvenile form of the disease.

These observations of Hunt received considerable attention and corroboration in the years immediately following. Particularly, Lhermitte in France and McAlpine in England subscribed to localization of Parkinsonian lesions in the globus pallidus. These two investigators (1924, 1926) discovered a considerable increase in iron deposit in the globus pallidus of paralysis agitans brains and stated that this finding signified the position of the pathogenic
tissue. They also quoted 25 consecutive cases of Lewy, all with the pathology in the pallidum. A few years later Lhermitte and Cornil presented four cases of paralysis agitans with the remark that pathological changes were found all over the central nervous system, but that the most severe and constant changes were in the large cells of the striatum, the cortex and the substantia nigra. At the same time Foix presented seven more cases of Parkinson's disease with the degeneration limited to the large cells of the striatum and pallidum. This writer further stated that even among the workers who agreed on the globus pallidus as the pathological site, there were two conflicting groups when the interpretation of the nature of the paralysis agitans changes was made. The school headed by Hunt and supported by Lhermitte, McAlpine and Foix regarded the disease as a systemic degeneration, an abiotrophy of the large cells only (the pallidal system). Other authorities believed the disease to be the result of regional lesions, either vascular (Vogt) or infectious (Dana).

While the French and English workers were centering their attention on the pallidum, another line of investigation was being conducted in Germany. Closely following the World War a tremendously important new factor entered the field of basal ganglion research. In comparatively great numbers of patients, Parkinsonian syndromes appeared as a sequel to encephalitis lethargica, and the investigation became much larger in scope. In Germany, the wealth of material was fully utilized and a series of reports appeared with
findings somewhat different from those of Hunt and his followers. In 1923, Spatz presented fifteen carefully scrutinized cases of paralysis agitans in which he found the constant pathology not in the basal ganglia but in the substantia nigra. The important monograph of Jakob, 1923, from which he lectured in America (1925), also gave attention to the substantia nigra. Freeman (1925) reported two cases of post-encephalitic paralysis agitans with changes only in the substantia nigra; Hohman (1925) presented twelve similar cases; and Hassin and Bassoe (1926) added four more, with the remark that the classical paralysis agitans showed a degenerative change while the post-encephalitic syndrome exhibited degeneration and inflammation. Three more cases were introduced by McKinley and Gowan (1926), whose observations were taken from the micrometric method of cell counting and, therefore were of considerable value. These men found a 58-87% decrease in the number of cells in the substantia nigra of their cases.

In 1926 McAlpine wrote a significant article on post-encephalitic Parkinsonism and, neglecting his earlier support of Hunt's theory, ascribed to the view that the substantia nigra was the seat of localized pathology. He quoted McKinley and Gowan, Jakob, Freeman, Spatz and many others, and brought forward eight personal cases with degeneration in the substantia nigra.

In response to this new concept of Parkinsonian pathology, Hunt published another paper (1933) reviewing and reiterating his
original tenet. He presented another case of juvenile and two cases of presenile paralysis agitans and again described degeneration of the large cells of the corpus striatum. He cited Lhermitte and Cornil on the subject, stating that they detected changes in the large pallidal cells and the substantia nigra, but that they found the substantia degenerate in many other brain diseases, whereas the pallidal changes were peculiar to paralysis agitans.

There have been several authorities who have recognized both the pallidum and the substantia nigra as responsible for the Parkinsonism syndrome. Jakob, (1925) divided true paralysis agitans, with the lesions in both sites, from post-encephalitic Parkinsonism, with changes only in the substantia nigra. Russetsky (1931) described the hyperkinesis of tremor as due to pathology of both the pallidum and the substantia nigra. Winkleman (1932) pointed out that on the basis of Ferraro's experiments (1925) most of the pallidal efferent fibers went to the substantia nigra, and suggested, in view of the anatomical and pathological evidence, that the globus pallidus and substantia nigra be grouped together as the pallidal system.

Keschner and Sloane (1931) added a warning note to this subject when they stated that the general view that idiopathic Parkinsonism displays lesions in the corpus striatum, while post-encephalitic Parkinsonism shows lesions in the substantia nigra, must not be adhered to slavishly in attempting to differentiate between these two types of the disease. The diffuseness of the
encephalitic infection and the widespread degenerative lesions of senile paralysis agitans of many years duration often leave an obscure picture.

To retrogress for a moment, while the neurogenic theory of Parkinsonian pathogenesis was receiving the attention of most neurologists in many countries, the dawn of the 1900's saw the introduction of the myopathic theory and the endocrine theory of paralysis agitans by a few nonconformers. In 1907 Camp reviewed all three theories, much to the discredit of the nervous origin of the disease and to the advantage of the myopathic theory. He presented fourteen cases with no significant findings in the central nervous system except for a generalized arteriosclerosis. The muscle origin which Camp supported was first introduced by Blocq in 1894 and was sporadically recognized by several French and German workers until a thorough study of the tenet was made by Schwenn (1901). He pointed out the clinical resemblances between Parkinsonism and myotonia congenita and stated that the two diseases showed similar changes in muscular excitability. He described histological changes in the muscle, consisting of atrophy with connective tissue hyperplasia and, usually, fatty degeneration. These changes appeared at various places in various levels of the body and were not the same in all parts of any muscle. Camp subscribed heartily to Schwenn's findings and described very similar histological pictures in his fourteen cases. His theory of the pathogenesis
of such a change was that a circulating toxin of some sort, probably endogenous in origin, was the exciting factor. He also suggested that a disturbed endocrine balance, possibly thyroid or parathyroid, might be the toxin in question.

At about the same time that Camp was expounding the myogenic theory, Berkley in America, was advancing his theory of parathyroid pathology as the causative factor in paralysis agitans. In a long series of papers (1905-1918) he attempted to establish the doctrine of endocrinopathy in relation to Parkinson's disease. In 1905 and 1906, he reported improvement in Parkinsonians by the empirical use of parathyroid gland, without any pathological facts or autopsy findings to substantiate his theory. His reports aroused the curiosity of Thompson (1906) who studied the parathyroid gland in the next nine cases which came to his autopsy table. He was unable to find any changes in "number, size, position or histological structure of the glands." Berkley's next paper serenely ignored Thompson's results, although he was quite aware of them, and presented eleven post mortem examinations of Parkinsonism with diseased parathyroids. He also reported further clinical remissions of the disease with administration of glandular therapy. In 1916 and again in 1918, in spite of the great mass of evidence favoring the basal ganglia as the site of pathology, Berkley continued to champion his hypothesis. He stated (1918) that "the parathyroid theory is still within the bounds of reasonable scientific speculation."
Although his theory of etiology was not favorably received, the symptomatic treatment of paralysis agitans by the use of the gland was continued for some time. Kuhl tried parathyroid transplants in six patients and attained some improvement in four (1924). This was apparently the last active work done in that field.

During the present century, the more permanent investigations into the nature of paralysis agitans have been proceeding along three general lines. One of these, the localization of pathology, has previously been mentioned. The other two are the elucidation of clinical signs and symptoms and a group of miscellaneous reports using biochemistry, bacteriology, electrical stimulation and other laboratory methods for study.

In addition to Parkinsoin's original clinical interpretation of the findings, two other papers on signs and symptoms, those of Charcot (1887) and Hunt (1917), have already been presented. The syndrome of tremor, rigidity and weakness, with the secondary findings of arm attitude, immobile facies, shuffling gait, generalized flexion, forward propulsion, etc., which Charcot described, remained intact for a considerable time; and Hunt's classification of senile, juvenile, formes frustes and symptomatic types is still unexcelled. A very complete clinical summary was presented by Foerster (1921) which listed the following points: (1) tremor during rest, (2) increased plastic tone, (3) increased muscle resistance to passive stretching, (4) tendency to passive fixation
(5) tonic prolongation to electric stimuli, (6) absence of postural reactions during complex movements and tonic prolongation of reflex response, and (7) slowness, limitation of range and absence of associated movements in voluntary movement. Foerster's paper deserves more attention and we shall refer to it regularly as we proceed.

With this clinical resume as a preliminary, I wish to discuss in some detail an important and extensive study of the subject of paralysis agitans and its clinical manifestations presented by Kinnier Wilson at the Croonian lectures and subsequently published (1925, 1929). Such is the thoroughness and excellence of Wilson's presentation that I thought it best to include my other references and material into the subject, as outlined in his lectures, rather than to continue with a simple chronological presentation as in the preceding part of this section.

Accepting Wilson's outline, then, our first consideration is the voluntary motor system in striatal disease. It is almost a platitude to point out that many of the symptoms attributed to the Parkinsonian patient are derangements of actions which, in undisease persons, are termed "voluntary." "Voluntary" presumably means those actions which we have reason to believe are affected through the corticospinal tracts, to some extent, because in the experimental animal, movements can be produced electrically via these tracts. It is probably that a large part of every voluntary
movement is outside consciousness, and only the end results of movement and joint displacement are conscious. Similarly "paralydis" as a term is equally vague. Usually it is understood as motor incapacity of the cortex-innervated structures, and is to be differentiated from the motor helplessness of the extrapyramidal system. A third term to be mentioned is "synergy." Following the early work of Winslow (1772) on primary and secondary muscles in a given action, Beevor classified the muscles as (1) primary movers or agonists, (2) synergic muscles, (3) fixation muscles, (4) antagonists. Wilson combines (2) and (3) as synergists for simplicity.

The excellent contribution of Tilney and Pike (1925) on cerebellar action and muscle coordination is at variance with this interpretation of Beevor and Wilson, which is based on Sherrington's law of reciprocal innervation (1906); but for practical purposes of description, it is convenient to classify the muscles as agonists, synergists and antagonists.

According to Wilson, discussion of the voluntary motor system includes the following points:

1. Power of movement. This is definitely diminished in paralysis agitans according to dynamometer records of the author. This is especially evident in unilateral cases. The small muscles are particularly affected, and the feebleness is inversely proportional to the mass of the muscle being tested. Deficient eye action and convergence–accomodation and the phenomenon
of micrographia are presumably the result of small muscle weakness. It is Wilson's contention (1916, 1925) that micrographia is not always associated with eye disturbances and not always related to striatal pathology, since the micrographia occurs at times without ocular changes and in diseases of the cortical system (lues, arteriosclerosis).

2. Quickness of movement is definitely impaired. The measurements of Worster-Drought (1924) average .24 seconds for reaction of normal persons to a visual stimulus, compared to .36 seconds for the paralysis agitans patients.

3. Poverty of movement rather than actual paralysis is the phenomenon of Parkinsonism. The general akinesia is due to several factors including a reduction in the will to act, a voluntary unwillingness to exert extra effort and rigidity of the peripheral motor system. The motor weakness is not due to defect of the corticospinal system proper, and Foerster's postulate of a special cortical tract through the globus pallidus, which is destroyed in Parkinsonism, is without anatomical or experimental grounds. Another observable corollary is the akathisia or paradoxical activity of some of these patients. Even though immobility is a prominent symptom, it at times becomes so intolerable that the patient must get up and walk about even though extra effort is required.

4. Synergic action is unimpaired in paralysis agitans, according
to Wilson's accurately tabled experiments (1925), a conclusion which is again in opposition to Foerster's belief of the corpus striatum as the central control for coordinate action. Tilney's papers (1919, 1925) substantiated Wilson on this point, and Young (1927) presented a careful clinical analysis of fifty cases of senile and postencephalitic Parkinsonism which also showed normal agonist-antagonist action.

5. The presence of movements of cooperation and association are not missing in striatal disease. Arm-swinging is an example of a movement which, although often lacking due to the increased effort necessary for its accomplishment, is not at all lost to the patient. Not only that, but some associated movements appear only with the onset of Parkinsonism. These include mirror movements of the opposite arm in a unilateral case, and the blinking sign of the eye lids.

6. Loss of movements of reaction and defense, if carefully tested for, are not found to be absent. Wilson quotes experiments with many cases to prove this contention.

7. Movements of expression are minimal because of the muscular weakness and poverty of movement discussed above, but are not entirely absent in striatal lesions. No theories attributing emotional disorders to disease of the corpus striatum alone are acceptable.

8. The role of the antagonists in muscle action probably follows
Sherrington's rule of reciprocal innervation; however Winslow at an early date (1772) and Tilney and Pike recently (1925), hold to other conclusions. Their view is that co-contraction, rather than reciprocal relaxation, is the movement which occurs. In either case, the normal function of muscle groups is unimpaired in paralysis agitans and cannot be considered as a function of the corpus striatum.

We come now to the all-important question of muscle tone, or postural contraction, in paralysis agitans. Again there are two conflicting theories of action. The dual hypothesis, developed especially by Hunter (1925), postulates one type of muscle fibers for tone, innervated by the autonomic system, and another type for movement, activated by the anterior horn cells. In contrast to this picture of Hunter's is the theory of uniform muscle construction and innervation. In support of it are the demonstration of actual tongue movement by the old Vulpian phenomenon of autonomic stimulation (Langworthy, 1924), the demonstration that the action currents of tone and movement are similar (Wilson, 1925), the conclusion that tone fuses with and reinforces contractions (Holmes, 1922), and the well recognized theory that movements are merely successive tone positions (Sherrington, 1906). The dual theory has recently been supported by Hunt (1932) in a form somewhat different from Hunter's account. It was Hunt's contention that the kinetic systems, the pyramidal and extrapyramidal, innervate
the red-fibered units of skeletal muscle while the static system, the cerebellar, innervates the white fibers. He states that the role of the sympathetic system in skeletal muscle action is not yet well understood, and is possibly a fixation mechanism.

A study of the rigidity of the average case of Parkinsonism does not favor either of these theories since the symptom may be explained by both. The hypertonus in these cases is universal and not selective; it may fluctuate from time to time; and the lengthening and shortening reaction of the decerebrate animal is absent. Catatonic reactions are absent in paralysis agitans also; limbs placed in one position do not tend to become fixed; and the typical passive fixation, noted by Kraus and Rabino (1922) and Walshe (1923) in decerebration, is not present. In addition to these points, the cogwheel phenomenon, which is a jerky catching feeling with quick passive extension of a limb, and the striatal attitude of generalized flexion are to be mentioned. There is no good explanation for the latter phenomenon, but it is obviously not in the same category with decerebrate rigidity. Another report on rigidity was made by Pollock and Davis (1930), whose investigations showed that the rigidity of paralysis agitans is dependant on the integrity of the reflex arc and disappears when the posterior roots are cut. They also demonstrated that atropine diminished that part of the rigidity in decerebrate animals due to the proprioceptive arc, and concluded that its action in paralysis agitans
is probably the same.

We come now to a consideration of the last member of the classical triumverate of Parkinsonism (paralysis, rigidity, tremor). The organic tremor of the Parkinsonian is characterized by a rate from 5 to 8 per second, a definite rhythm, a wide variation in range, and a localization in the small muscles particularly. This tremor may be reduced, or even arrested completely for a short while by numerous extrinsic stimuli such as a pin prick, a loud noise, or even a change in posture of the affected limb. It is usually sharply differentiated from the intention tremor of cortical diseases; but it is Wilson's contention that the two types tend to run into each other and that neither is pathognomonic of a particular mechanism. The proof of this statement lies in observations that patients with multiple sclerosis may have a rest tremor, and patients with progressive lenticular degeneration have exacerbation of their rest tremor with voluntary movement (Wilson, 1925). A series of Parkinsonian cases analyzed by Patrick and Levy (1922), disclosed thirteen patients with intention tremor and five without any tremor.

It is apparent that tremor is purposeless and without meaning, and, therefore, of a low physiologic order. Organized to a high degree, tremor is systematized and incapable of variation. It is not associated with complete paralysis; on the contrary relative motor integrity is essential. A number of cases are on record of
the disappearance of a tremor with the onset of apoplexy or other cortical pathology \cite{Wilson1924}. Tremor may be associated with hypertonia, as in the rigidity of paralysis agitans, or with hypotonia, as in cerebellar lesions \cite{Holmes1922}; but it is not present with complet atonia. Pritchard \cite{Pritchard1929} demonstrated by means of electromyographic studies that the tremor of paralysis agitans is the same type of motor discharge as a normal voluntary movement. Jackson believed that tremor and rigidity are different aspects of the same process, differing only in degree. Pritchard's results seemed to confirm this early theory, and Wilson, after showing that these two symptoms are present in paralysis agitans in inverse proportions, also supported Jackson. Walshe, however, declared this view to be wholly untenable \cite{Walshe1924}. He abolished Parkinsonian rigidity with muscular injections of novocain, but the tremor remained. A general conclusion, with which both theories are in agreement, is that tremor is an involuntary movement belonging to the old motor system.

In opposition to this complete and well-entrenched treatise of Wilson on senile and postencephalitic paralysis agitans are the views of the French school. In the same volume which contains Wilson's lectures \cite{Wilson1925}, is a lengthy article by Cruchet presenting the theory of the bradykinetic syndrome, which consists of slow movement, immobile facies, characteristic attitude and paradoxical
kinesia. This syndrome is common to the two conditions of senile and symptomatic paralysis agitans, but the classical form also has hyperkinetic symptoms of tremor and even mental unrest. The English school finds tremor and rigidity in the syndrome as well as the disease, and is unable to accept the French view. Critchley (1931) remarked that bradykinesia is an associated condition of rigidity and poverty of movement rather than an isolated phenomenon.

In this section, I have presented those papers on paralysis agitans which have been of most significance in the development of our present concept of the disease, without attempting, by any means, a comprehensive survey of the literature. In addition to the reports I have mentioned, there are literally hundreds which are merely case reports or repetitions which would in no wise add to this presentation. There is another small group of papers dealing with isolated problems of etiology, laboratory aids to diagnosis, and kindred points, which are interesting and occasionally give up fragments of important information. Among these may be mentioned liver function tests. The first work was done by Hurst (1926) in an effort to discover whether, in common with hepatolenticular degeneration, there was any liver damage in paralysis agitans. He found the levulose tolerance test to be within normal limits in all cases. Haug (1934) using galactose, obtained somewhat different results. His series of eleven cases, four of which were senile and five post encephalitic paralysis agitans,
showed liver impairment in eight cases. He also employed the urobilinogen test and found ten cases with liver damage by this criterion.

Several reports have been concerned with sensory changes in Parkinsonism. Krebs (1925) explained a case with complete unilateral anesthesia, and Worster-Drought and Hill (1931) reported 25 cases with impairment of vibratory and deep-pressure pain. Both of these papers attributed pathology for sensory losses to the thalamus.

Munch-Peterson and Wernoe (1932) declared an "adrenalin-liquor-saccarum reaction" and a "Bimanual faradic irritation test" to be diagnostic aids. The former recovers a lower amount of glucose from the spinal fluid in corpus striatum diseases, and the latter gives atypical or absent pronation and flexion of the forearm in striatal disease.

Another problem of paralysis agitans, the possibility of trauma as an etiologic factor, has been supported by many, including Kraftchung (1898), Pearce (1901), Ruhemann (1904), Starr (1909), Gierlich (1920), Gumston (1921), Patrick and Levy (1922). Recently, however, Heyde (1932), Miller (1934), and Grimberg (1934) have produced refutations. Grimberg analyzed 85 cases from the literature and found only two which could not be discounted. He concluded that trauma was not a causative factor in Parkinsonism. Heyde reviewed some 600 cases and found none in which the factor of trauma was not questionable.
PSEUDOSCLEROSIS
At the outset of this paper attention was called to the difficulties in organization due to the intertwining and subdividing of the various divisions of basal ganglion pathology. This is attributable, for the most part, to the bewildering state of the pseudosclerosis group. The various parts of the subject have been alluded to in the literature as Westphal's disease, Westphal-Strumpell's pseudosclerosis, Hosslein-Alzheimer's disease, Wilson's disease, Wilson-Westphal's pseudosclerosis, and hepatolenticular degeneration. In addition, there have been several closely associated diseases such as Vogt's syndrome, Hollervorden-Spats disease, status pigmentatus, and others which add to the confusion. As will be seen, all of these syndromes have some similarity, and should be placed in one large group. I shall attempt to give in chronological order the developments in the present concept of pseudosclerosis from a purely objective view, and summarize my impression of the present clinical and pathological status in a future chapter.

Fortunately the origin of our subject is clear and its early development uncomplicated. The original article was written by Westphal (1883) and described a chronic degenerative disease, pathology unlocated, which the author considered an aberrant form of multiple sclerosis. He described a syndrome of onset in youth, general mental impairment, slowing of muscular movements, tremor, and difficult speech. A few years later Strumpell (1898, 1899) reported three cases of Westphal's disease and defined the syndrome
as one with purely motor symptoms of general paralysis, spasticities, tremors, and ataxia, and, in some cases, apoplectiform attacks or remissions. The voluntary movements are retarded, the facies are fixed and immobile, the ataxia is paretic, the tremor is of the intention type, speech is disturbed, epileptic seizures and psychic deterioration may occur, and there is no nystagmus or loss of sphincter control. Strumpell also emphasized the early age of onset - 10 to 20. He examined the various parts of the central nervous system of his cases and found only a diffuse "Kirnsklerose" of the cortex, thalamus, corpus striatum, cerebellum and parts of the mesencephalon. He named the disease "Westphal's pseudosclerosis."

Germany continued to be the seat of investigation of this new sclerotic brain disease for several years. Three very important articles concerned with its development appeared in 1911. One of these was by Hosslein and Alzheimer, giving the first pathological investigation of value. They described a clinical condition not far removed from the picture of Strumpell. The symptoms were listed as onset at a very early age, mental deterioration, increased tonus to the point of contractures, and inconstant tremor. The disease, according to these workers, was a gradually progressive degeneration of the corpus striatum, thalamus, pons and dentate nucleus.

The second report in 1911 on pseudosclerosis was presented by
Voelsch. He reported a case with the now well established symptoms of rigidity, tremor, slowness, fixed facies, dysarthria, dementia and absence of pyramidal signs. Voelsch's autopsy examination disclosed, in addition to the brain lesions, a silent nodular cirrhosis of the liver, which was the first description of a combined brain and hepatic damage and which was to attract considerable attention in the future.

The third paper, published by C. and O. Vogt described a new disease somewhat related to the pseudosclerosis group in that rigidity, spasticity and mental defects were present, but the chief characteristic of the disease was athetosis, which will be described in detail under that heading. In 1920 Madame Vogt described another syndrome which was subsequently enlarged upon by Hallervorden and Spatz in 1922 and is often known by their names. This disease was also characterized by some of the symptoms of the Westphal-Strumpell type but usually presented athetotic manifestations.

In 1912 still another variant was originated by Wilson in England and was called by him progressive lenticular degeneration. This disease also had cirrhosis of the liver as a prominent accompaniment of the neurological symptoms and was finally classified with the pseudosclerosis of the Germans. The great importance of Wilson's original monograph, coupled with the earlier individuality of this disease process, warrants a separate treatment, even though
most investigators at the present time consider the two as different aspects of the same fundamental mechanism.

Rausch and Schilder (1914) were among the first to study Wilson's disease and pseudosclerosis together, and were the first to suggest that they belonged in the same category. They were particularly interested in the familial aspects of this group and re-emphasized the non-familial aspects of the pseudosclerosis syndrome as opposed to the "exquisitely familial character of Wilson's syndrome." A rather comprehensive paper by Spiller (1916) summarized the two diseases and, although ascribing the pathology in both to the lenticular nucleus, made a nice clinical differentiation between them. Of pseudosclerosis he stated that it is rarely a familial disease, age of onset at 14-26, characterized by progressive changes to death by 40, and identified by tremor, rigidity, slow scanning speech, epileptic attacks and psychic disturbances.

The investigations into the pathology of the pseudosclerosis group have not added much to our knowledge of the basal ganglia. This is due to the fact that many of the symptoms are a part of the paralysis agitans syndrome, and the pathology of that disease entity, as has already been thoroughly discussed, is still somewhat in doubt. All of the investigators of the Wilson-Westphal group are agreed on the lenticular nucleus as the site for the lesions, and most of them further localize the point of destruction in the putamen. Freishhacker (1924) and Jakob (1925) both place the pathology in the large cells of the putamen and, to a lesser
extent, in the caudate nucleus. Jakob also, together with Uchimura (1930), propounded a separate type of histopathological changes for this group of syndromes consisting of the appearance of the large glial cells of Alzheimer and a heavy deposit of fat in all parts of the corpus striatum.

With the exception of the tendency to classify pseudosclerosis with Wilson's disease, there has been little change in the clinical concept of the disease during the past two decades. Following Spiller's suggestion, many workers decided that the pseudosclerosis group should include Wilson's disease and possibly others of lesser note. Barnes and Hurst (1925), Wechsler (1928), Strumpell (1931) and Gardberg (1933), among many others, were of this opinion. Barnes and Hurst, in addition, included Oppenheim's dystonia muscularorum deformans.

Besides the matter of classification, which will be considered again in the next section, there have been a number of articles published which deal with the obscure problem of etiology. Woods and Pendleton (1925) reported a series of fourteen simultaneous cases in the same village, due presumably to an endogenous poison of some kind. As far back as 1888 Poelchen remarked on the susceptibility of the corpus striatum to toxins, carbon monoxide in the particular case he was reporting. This point has been re-emphasized by Meyer and Earl (1936) as well as by Woods and Pendleton. In the opinion of these men, the basal ganglia's blood supply is hardly
more than adequate for ordinary needs; and ischemia easily occurs here. As we have seen, with the possible exception of the head of the caudate nucleus, the vessels to the ganglia are an end-type of circulation with no collaterals. Wilson (1912) believed that an endogenous toxin from the liver produced a specific effect on the lenticular nucleus. This theory has been recently revived by several workers. Pollock (1930) described a case with hepatic disease for ten years and the onset of Parkinsonism three months before death. The post mortem examination disclosed a cirrhotic liver and patchy degeneration of the caudate, putamen and substantia nigra. Crandall (1933) induced experimental hepatic damage with alcohol and recovered a toxin from the blood serum which acted destructively on fresh rat spinal cord in a test tube. Sjovall (1934) also described a case with hepatic damage, followed in two years by the typical picture of pseudosclerosis. Meyer (1934) reported a series of cases of icterus neonatorum gravidum in which the basal ganglia showed severe selective damage. Haug's galactose tolerance test (1934) on eleven cases showed hepatic damage in eight of the patients. Brouwer (1936) contributed findings on two cases of icterus neonatorum gravidum with pathology in the globus pallidus and subthalamic nucleus. These men felt little doubt that there is some definite connection between an endogenous hepatic toxin and alterations in the basal ganglia.

The infectious theory for the origin of some pseudosclerotic
cases has been advanced by Westphal and Sioli (1922) and by Campbell (1924) who reported cases following encephalitis and erysipelas, respectively. The factor of actual organic disease has been assumed by such authors as Economo (1910) who found tuberculous necrosis in the corpus striatum, and Keys (1932) who recovered ciliomycese from the gastrointestinal tract of patients with striatal disease.

There is one other point of interest to be mentioned in regard to the pseudosclerosis group of diseases. This is the presence of the Kayser-Fleischer ring on the cornea, a copper-brown colored deposit in the form of a partial or total ring, composed of iron pigment within the layers of the cornea. It was noted by Kayser in 1902 in a patient suffering with rigidity, tremor and mental aberrations, and in the same patient was discussed more in detail by Fleischer a year later, after a diagnosis of pseudosclerosis was made. Hall (1921) was so impressed by its appearance that he declared it to be pathognomonic of pseudosclerosis and Wilson's disease and a good point of differentiation from multiple sclerosis. It has recently been reemphasized by Curran (1932) who found four out of five patients with pseudosclerosis, all members of one family, with the Kayser-Fleischer ring. That the corneal deposit is not a characteristic of pseudosclerosis alone, is held by such men as Barnes and Hurst (1925), who noted it in a case of torsion spasm.
WILSON'S DISEASE
The clinical investigation of striatal disease has produced no more valuable single publication than the historic monograph of S. A. Kinnier Wilson on "Progressive Lenticular Degeneration" (1912). Here, for the first time, was the presentation of a pure striatal syndrome with a definite clinical picture and consistent autopsy findings. Since lenticular degeneration is a comparatively rare condition, this work is not nearly so well known as the original paper on paralysis agitans, but Wilson's treatise shows a clinical acumen equal to Parkinson's essay and has a physiological and pathological significance which supersedes by far the earlier writing.

Wilson's careful survey of the literature previous to his publication disclosed only four cases which were of the same type. Two of these were seen by Gowers in 1888 and 1889 and subsequently presented in a paper (1906). In 1890 independent reports were made by Ormerod and by Homen, and all three men, without knowledge of each others' work, described cases remarkable for their similarity. Gowers called his cases tetanoid chorea; Homen nominated the spirocheta pallida as the etiological agent in his case; and Ormerod was unable to arrive at any definite conclusions regarding the nature or etiology of this strange malady.

Wilson reviewed these four cases and added six of his own, and arrived at the following classic definition: "It consists of involuntary movement, nearly always bilateral tremor of both upper
and lower extremities, the head and neck also being sometimes involved - a tremor usually rhythmic but occasionally irregular, and increased with volitional movement; there is pronounced spasticity of the limbs and of the face, the latter usually being set in a spastic smile, while in the latter stages contracture of the limbs develops; there is a dysphagia and dysarthria, the latter eventually developing into complete anarthria; there is sometimes spasmodic laughing and emotion. As a result of the extraordinary degree of stiffness of the musculature there is considerable difficulty in maintaining equilibrium. Little or no true paresis or paralysis occurs, however, inasmuch as most ordinary movements, if not all, can be executed, although it may be slowly and feebly. In some cases certain mental symptoms, of a transient nature, manifest themselves, and their significance will be duly discussed. In spite of the great degree of motor weakness and helplessness, in a pure case the abdominal reflexes are preserved and a double flexor response is obtained."

It seems advisable to discuss the lenticular syndrome from the original monograph since, years later (1929), Wilson stated that he had found little to add concerning the disease which bore his name.

The specific etiology is still not well understood. At the time of his original presentation Wilson advanced the following hypothesis: the disease is sometimes familial but often acquired
and not congenital; it is toxic but not syphilitic; the toxin may be elaborated in the liver and has a specific action on the lenticular nucleus. The many recent findings in support of this early hypothesis have been enumerated in the preceding section. In addition to this direct etiologic factor there are two important points on predisposing factors, first the familial but non-hereditary character of the disease, and second, its occurrence early in life. Wilson found the onset to be from 10 to 25 years, with an average age of 14.

The symptoms may be acute, with a fatal termination in a few months, or, more commonly, may run a chronic course for several years. In the acute form there is fever, in both forms tremor, spasticity, contractures, dysarthria and dysphagia, muscular weakness and emaciation, minimal sensory changes, normal reflexes in a pure case, and mental changes of docility, childishness and narrowing of the horizon.

The name selected by Wilson for this disease indicates the region of pathology - the lenticular nucleus. Homen (1890) pointed out three important problems of pathology, namely, the presence of a severe fatal nervous system disease with insignificant gross findings, the presence of hepatic cirrhosis in one so young and the absence of all symptoms of cirrhosis. More specifically Wilson noted cirrhosis of the liver and enlargement of the spleen, together with degeneration and disintegration of the putamen and, to a
lesser extent, of the globus pallidus. There was no endarteritis or infiltration, but gliosis and disintegration, causing cavitation, together with the appearance of the large glial Alzheimer cells.

The prognosis is fatal in all cases, being several months in the acute form and from two to seven years in the chronic.

As is true of all original presentations of a clinical disease, Wilson's monograph occasioned the appearance of many papers and reports in subsequent years substantiating and condemning, proving and disparaging various points in his syndrome. It is significant that his proponents far outnumber his antagonists, and the latter at most have been able to challenge only his interpretation, never his clinical acumen.

The familial character of the disease was particularly stressed by Rausch and Schilder (1914), Spiller (1916) and Curran (1932). Rausch and Schilder also mentioned a point already discussed in part in the section on pseudosclerosis, namely the close relationship between Wilson's disease, Vogt's syndrome and Westphal-Strumpell's pseudosclerosis. Wilson had already taken cognizance of the 1911 reports of C. and O. Vogt but declared their etat marmoratus quite distinct from his lenticular degeneration. Rausch and Schilder, however, indicated that these two processes had much in common.

Following the initial papers of 1912-14, many articles appeared
describing cases of Wilson's disease (Spiller, 1916; Hamilton, 1916; Jakob, 1925; Ostertag, 1926; Halford, 1933; Baltzan, 1936), but none of them added anything to the original clinical description except confirmation. The only clinical advance was made with the discovery of the Keyser-Fleischer ring as a common finding in the disease. This has already been discussed in the preceding section. In addition to Hall (1921) and Curran (1932), previously quoted, Dermitte and Muncie (1930) made particular note of this corneal pigment in Wilson's disease. However, since Herman and Schilder (1933) described a typical case of the lenticular syndrome with the Fleischer phenomenon absent, and Barnes and Hurst found it in diseases such as torsion spasm, its clinical significance is not of paramount importance.

Perhaps the most salient contribution to the development of Wilson's disease, exclusive of the original paper, was the work of Barnes and Hurst (1925) in grouping Wilson's progressive lenticular degeneration, Gowers' tetanoid chorea, Westphal-Strumpell's pseudosclerosis and Thomalla's torsion spasm into a disease group known as the hepatolenticular degeneration. In 1925, they presented four cases typical of Wilson's disease or pseudosclerosis and found liver and lenticular damage in two of these on which necropsies were performed. Subsequently (1926, 1929) the post mortem findings on the other two cases were reported. All of these cases showed typical liver cirrhosis, splenic fibrosis and lenticular degeneration,
particular in the putamen. At this time they concluded that the nervous symptoms of this disease do not appear until liver damage occurs. The liver cirrhosis probably is the result of an acute hepatitis caused by bacterial toxins in the gastrointestinal tract. This phrase of Barnes and Hurst, "hepatolenticular degeneration," was accepted by many workers, Greenfield and Poynton, Garberg, Halford, Brouwer, and Baltzan among others writing articles on hepatolenticular degeneration.

In a paper on the relationship of hyperthyroidism and paralysis agitans, Wechsler and Savitsky (1931) drew an analogy between the subject of their discussion and hepatolenticular degeneration. In both a toxin is present, and in both a somatic gland and a localized structure in the central nervous system are the seat of pathology. In Wechsler's cases, however, Parkinsonism antedated thyrotoxicosis, while the consensus of opinion on Wilson's disease is that liver damage comes first.

Loewy (1931) reviewed the literature on diseases with hepatic and nervous system damage and studied the time relation between the onset of hepatic and nervous symptoms. He found that no conclusion could be drawn since in half of the cases the hepatic findings appeared first and in half they appeared second. He then attempted to correlate the spongy degeneration of Wilson's disease, the gliosis and formation of Alzheimer's cells in pseudosclerosis, the Kayser-Fleischer ring and the nodular hepatic cirrhosis. Again he
was doomed to indecisive conclusions as his tabulations showed no constant relationship among these factors. In his summary Loewy stated that coexisting lesions of the brain and liver do not stand in any causal relationship to each other but develop as coordinated parallel processes.

Following the reports of Barnes and Hurst no new developments have occurred in the pathology or symptoms of Wilson's disease, excepting the recent tendency to group it with the pseudosclerosis group. This change has been fully noted previously.
CHOREA
Chorea is a disease characterized by "an irregular and involuntary clonic contraction of some of the voluntary muscles, which, however, are not wholly or constantly withdrawn from the government of the will....There is no loss of consciousness; no defect of volition; the ordinary movements of the body can be performed in some degree, or sometimes under the direction of the will; but it would seem as if some other power wantonly interfered to excite them when they are not needed, to render them unsteady and imperfect, to arrest the natural action, and to give a new direction to the limbs and to cause the patient to gesticulate and grimace like a Merry Andrew. Moreover, these apparently absurd movements do not occur in paroxysms, but continue throughout the day, sometimes for weeks together, but they generally cease during sleep."

When Sir Thomas Watson (1843) wrote the above classic definition he was speaking of acute infectious chorea, or chorea minor, which was first described by Sydenham in 1686 in his "Schedula Monitoria." Following the original presentation by Sydenham, the choreic syndrome was referred to in the literature but was confused with many diseases such as myelities, epilepsy, etc. It was not until the beginning of the nineteenth century that the disease took on complete individuality. At that time Sydenham's chorea became associated with rheumatic fever, and Prochaska first alluded to the theory of reversion of choreic movements to those of infancy. By the middle of the century chorea was a firmly established disease
entity as Watson's excellent description indicates. In 1881 Gowers gave the first presentation of paralytic chorea, a rather rare form in which flaccidity and weakness predominate.

Near the end of the century the abilities of the eminent English neurologist Hughlings Jackson were brought to bear on the subject, and some of his concepts, made at that time, are still potent factors in the modern controversy of choreic pathogenesis. In addition to some of his general tenets, which are applicable to the problems in chorea, he made some specific observations on the subject. Of particular importance were his theories on the nature of involuntary movements. He stated that the phenomenon of chorea, and other spontaneous movements, occur during the action of healthy nervous arrangements and constitute a problem of "physiology in difficulties." Involuntary motions, therefore, are derivatives of living mechanisms rather than of destroyed tissue. Jackson also expressed himself on the theory of excitation as the genetic factor in chorea. He voiced many objections to the idea that involuntary movements of many years duration should be due to an irritation mechanism. He preferred to think of the action as a release phenomenon from the inhibition of higher centers. Along these same lines Jackson further observed that the nature of movements in chorea are not mere spasms or cramps but are an aimless profusion of movements of considerable complexity, very near to the purposive movements of health. He believed that the variety and complexity of
the actions were strong evidence that the diseased part serves in highly specialized and complex coordinations.

The latter half of the nineteenth century saw also the discovery and development of another type of chorea. This disease appeared in America and was first noted by Dr. C. O. Waters of Franklin, N. Y. (Good, 1900). Lyon, in 1863, published the first article on the condition, a chronic degenerative disease of middle life; and Huntington, in 1872, gave an admirable description and stimulated wide interest in the disease.

Investigation into the pathology of this new disease attracted the interest of Osler in 1893. He decided that the disease was of a neurodegenerative character with changes in the vascular, gangli-onic and neuroglial tissues of the brain. Good's review of the literature (1900) listed isolated pathological findings by contemporary investigators which included dural tumors, pachymeningitis, arteritis, dura adherenta, and atrophic cortex.

A note on the pathology of Sydenham's chorea was written in 1906 when Poynton and Holmes re-emphasized the association of chorea to rheumatic fever and reported the recovery of an identical diplococcus from autopsy material of both of these diseases. They cultured these organisms and injected them into cats and observed that these cats developed peculiar movements not unlike the choreic motions of humans. They called their discovery "diplococcus rheumaticus" and declared it to be the etiological agent.
Two years later Jelgersma, who first localized the pathology of paralysis agitans in the basal ganglia, introduced the striatal theory of pathogenesis in chorea by reporting a case of Huntington's chorea with atrophy and gliosis of the caudate nucleus. Real impetus to the striatal theory was given by Alzheimer (1911) who published results of a thorough examination of the brains from three cases of chronic and four cases of acute chorea. He found severe degeneration of the caudate and lentiform nuclei in the chronic phase and generalized infiltration and gliosis in the acute. In addition, he noted cortical atrophy and changes in the medulla, pons and optic thalamus in all cases.

Alzheimer's localization was widely accepted, and it is interesting to note that while his predecessors had found the basal ganglia normal, his successors discovered pathology in them.

It seems best to digress here and, instead of pursuing the whole problem of chorea, paper by paper, in chronological order, to present first one and then the other of the two theories of choreic pathogenesis which are still being argued and supported at the present.

The striatal theory was originated by Jelgersma and Alzheimer and was immediately supported by Kleist (1912) and Marie and Lhermitte (1914), whose cases, thoroughly investigated by modern methods, described lesions in the caudate and putamen. Marie and Lhermitte also found a degree of cortical atrophy in some of their
cases. Schroeder (1922), working with chorea minor, and Lloyd and Winkleman (1925), studying symptomatic posthemiplegic chorea, also found selective lesions in the neostriatum. Jakob's complete survey of striatal disease (1925) was an important contribution in support of this theory. He attributed Huntington's chorea to degeneration of the small cells of the striatum, especially the caudate nucleus; he identified Sydenham's chorea with consistent lesions in the striatum; he explained symptomatic and senile chorea on the basis of striatal lesions also. It was Jakob's theory that the pathological change producing chorea is an outfall of the small striatal cells; and the consequences of this destruction of the intermuncial neurones is an interference with the static and kinetic coordinating mechanism of the corpus striatum.

The most extensive piece of work was accomplished by Dunlap (1927a, 1927b). He studied seventeen cases of true Huntington's chorea, twelve cases clinically Huntington's chorea but with doubtful heredity, and thirty cases with other lesions of the striatum, largely vascular and luetic. His pathological conclusions for chronic chorea, from this comprehensive group of cases, were that reduction of the cells of the putamen and the caudate nucleus are associated with cortical involvement.

In 1931 Meyjes attempted an indirect reply to the cortical theory of choreiform movement, which had been developing simultaneously with the striatal concept. He pointed out that in cases
of acute infectious chorea, chorea gravidarum and chronic chorea, striatal lesions are found without exception, and it is only in cases with large, gross vascular lesions that striatal pathology without symptoms and choreic symptoms without striatal lesions occur. He further stated that the striatal concept cannot be applied absolutely, because there are a few exceptions in the literature, but it appears to be the most constant anatomic factor.

Neustadter (1933) made a thorough review of the literature in his article and cited Kiesselbach, Vogt, Foerster and Beilschowsky, in addition to many others, to prove the striatal hypothesis. At the same time he gave due consideration to the work on monostriatal localization.

The most recent work, that of Putnam (1933, 1938), is a report on operative procedure in 23 patients with extrapyramidal disease. He succeeded in severing the anterior funiculi of the spinal cord, which contains the extrapyramidal tracts, and obtained remission or improvement in sixteen cases of athetosis, dystonia, ballism and other types of involuntary movement. Three additional cases died, and the four unimproved patients were afflicted with paralysis agitans. This work apparently demonstrates that the pathway for excessive involuntary motions is the extrapyramidal tract from the red nucleus, and supports the striatal theory of choreic pathogenesis. It is true that none of these patients treated by operative interference were choreic, but, as will be
shortly seen, choreic and athetoid movements appear to vary only in degree and not in character, and are probably initiated by the same pathological mechanism.

The essence of the striatal theory of pathogenesis for involuntary movements rests on the assumption that the inception of these movements lies in destructive lesions of the basal ganglia, particularly the neostriatum. This conclusion is a direct result of observation of post mortem material and is not a concept based on any particular theory of biological reasoning or cause to effect functioning of the motor system. It is almost a platitude to point out that chorea is an increased activity of the motor system, not a reduction; and it is also obvious that destructive lesions of motor nuclei, with atrophy and disappearance of cells, cannot result directly in hypermotility of striated sarcomeres. These two points are not compatible, and it is upon this basis of physiologic reasoning, in spite of the demonstrable necropsy findings of the striatal school, that the proponents of the cortical theory build their case.

The pioneer of the cortical theory was Hughlings Jackson, whose concepts of choreic motility, made at a time before any controversy over pathological localization had appeared, have been previously presented. In brief, he was convinced that choreic movements are complicated actions similar to purposive motions; that chorea is the manifestation of increased activity of a system,
not that it is a destruction; that involuntary actions are a release phenomenon from higher center inhibition.

The cortical theory began, therefore, as a deduction of physiology and was built upon chiefly by the pupils and followers of Jackson in England. Cobb (1919) studied chorea by electromyograph and found that the action-current curves for voluntary and choreic movements are essentially the same except for shortness and lack of sustainment in the latter. Wilson (1920), while studying decerebrate rigidity in man, discovered that certain choreic postures - pronator sign, choreic hand, etc. - are indicative of a partial release of mechanisms from voluntary control, which are wholly released in decerebrate rigidity. A complete survey of chorea was made by Wall in his Bradshaw Lecture (1920), and pathology was discussed from the viewpoint of cortical action. Wall's theory was that the disease causes disturbances in the corpus striatum, the steadying influence on the pyramidal system, and that in chorea this inhibitory effect is lost.

The chief champion of the cause of the English school was Wilson, who, in his Croonian Lectures (1925), gave a complete analysis of the cortical theory. Wilson's thesis discussed some preliminary points, most of which were derived from Jackson. First, he pointed out that involuntary movement must be attributed to activity, not to paralysis or destruction of the motor mechanism. "A hole in the corpus striatum - for that is what outfall of
parenchymatous cell-fibre-systems means - cannot cause any movement whatever." Second, as an obvious corollary, if after development of chorea, a destructive lesion leads to cessation of movement, then some neural mechanism must have been in operation to cause the movements. Third, the Jacksonian theory of inhibitory action of higher motor centers on lower is of importance. The well-known phenomenon of increased activity of lower centers in the absence of control from higher centers rather than irritation, seemed to Wilson to be a better explanation of involuntary movement. Fourth, chorea and tremor are fundamentally dissimilar types of movement, and the probability that they are transmitted by different mechanisms is almost a certainty.

In discussing chorea, Wilson mentioned the following clinical characteristics:

(1) The spontaneous movements of chorea offer a marked resemblance to those of volition. They are as complex and coordinated, as elaborate and purposeful as voluntary actions. Wall (1920) also supported this Jacksonian doctrine. "The movements, although occurring independent of the will, are of the same type as movements executed as the result of volition."

(2) A further feature is their brevity and abruptness. It is of especial significance that these traits are noticeable in much of the patient's voluntary actions after recovery. The sudden, explosive character of both voluntary and involuntary actions tends
to disprove a diverse mechanism for each.

(3) A third point is the separateness of the movements. According to many observers, the choreic motions, however rapid, still do not blend but remain discrete. This is not wholly true, since there are some exceptions, and if a leg or arm is fixed to minimize displacement a confusion of movements occurs. Wilson's records of such muscle contractions in choreics substantiates his contention that "Sherrington's law of reciprocal innervation no longer holds, disease having led to its negation."

(4) Wilson next quotes instances of lack of synergy in several patients, and concludes that interruption of the physiological laws of coordination in agonists, synergists and antagonists is evidenced in chorea.

(5) The choreic hand, which is distinguished by flexion at the wrist and hyperextension at the metacarpophalangeal joints, the phalanges being straight or moderately overextended, was first described by Francis Warner in 1885. This posture, which is the opposite of normal posture, is more pronounced on the side of the body with more frequent spontaneous movements, and appears to be linked with the same mechanism implicated in the expression of these movements. To Wilson this hand means a postural change associated with abnormal function of the corticospinal system.

(6) Other signs in chorea point to disorder in the pyramidal system. Among these are the Babinski extensor plantar reflex,
the pronator sign, and hypokinetic chorea. The first is often absent and is not of great importance. The pronator sign of the forearm is another of the postural changes mentioned by Wilson in a previous paper (1920). The hypokinesis, or weakness with relative inactivity, is seen in some cases of chorea. This condition, although the opposite to hyperkinesis, or increased movements, is obviously also a derangement in the same process.

(7) Muscle tone is less than normal in chorea, allowing for increased range of motion. This state is opposite to the rigidity of paralysis agitans due to striatal pathology.

(8) The last point concerns the frequent display of emotion on the face of the choreic, which Wilson interprets from his theory of emotions (1924) as caused by abnormal (choreic) stimuli with efferent discharge over an involuntary motor mechanism.

In summary, Wilson stated, "It is difficult to resist the conclusion that choreic motor disorder manifests itself through the pyramidal (corticospinal) tracts, which must be in a condition of relative integrity for hyperkinetic symptoms to appear, and yet exhibit some defect of function as indicated by the above-mentioned minor signs."

Wilson discussed athetosis in his lectures also, and found in this allied disease further evidence of abrogation of reciprocal innervation, of postural activity - the athetoid hand -, of hypotonia, and of athetosis as a dysfunction of the corticospinal system.
His concept of the pathogenesis of choreoathetosis begins with the argument he stressed in his clinical discussion, namely, involvement of the corticospinal system in the production of characteristic movements. In addition to the evidence presented above in Wilson's eight points, there are several cases in the literature which offer additional proof of this theory. One patient with athetosis developed epilepsy, and immediately after her seizures the athetosis disappeared, undoubtedly due to cortical exhaustion. A second case of severe athetosis was operated by Horsley (1909) and the right post-central gyrus was removed. Athetoid movements vanished entirely. A third case with athetoid motions, presented by Foerster, experienced a sudden flacid paralysis from cerebrovascular accident, and the athetosis disappeared, never to return, even though the patient regained partial use of her limbs. There are other similar cases, and Wilson stated that it is significant that no case is known of spontaneous movements coexistent with corticospinal paralysis. At a later date (1928) Wilson found a case in his own practice which illustrated his tenet of corticospinal continuity in chorea. The case was found at autopsy to have a lesion in the post central area and an intact striatum.

Another line of evidence signifies afferent paths to the cortex from the cerebellum as the site of the lesion. Hypotonia and dysynergy are proof of alteration in cerebellar action, and Wilson, in addition, introduced many cases of cerebello-mesencephalo-cortical
disturbance with accompanying spontaneous movements.

A third step in Wilson's reasoning is the postulation of a higher motor center than the Betz cells, a precentral area which controls and inhibits the Betz area. It is here that the cerebello-thalamic afferents are transferred into efferent impulses to activate the Betz cells, and it is here that the pathology of chorea rests. The mental route by which Wilson arrived at this new "pre-motor" area is lengthy but logical, and recent experiments, to be presented shortly, bear out his hypothesis.

In summary, the cortical theory for the production of choreic and athetoid movements, as conceived by Wilson, is that chorea "represents a complex type of involuntary movement, for the carrying out of which motor mechanisms of cortical site are requisite. No single and invariable anatomical site for lesions underlying its development is to be expected; it is the expression of disorder of a system. To its continuance afferent cerebello-cerebral defect of regulation contributes, and transcortical control over its manifestations is very imperfect. As I have on several previous occasions strongly urged, any theory attributing its origin uniquely to striatal destruction is impossible."

Wilson's arguments were readily endorsed by many authorities. In 1930 Mayendorf presented a case of unilateral chorea with intact corpus striatum and a lesion of the right supramarginal and post-central regions of the cortex. He stressed particularly the
disturbance of sensory stimuli to the cortex in his interpretation of choreic pathogenesis. In the same year Lhermitte and Pagniez found pathology in the cerebellum and putamen-caudate, but agreed with Wilson that increased movement cannot be caused by destructive lesions. Davison, Goodhart and Schlionsky (1932) and Goodhart, Balser and Bieber (1936) also indirectly supported Wilson. The former found it impossible not to agree with the cortical theory, and presented three cases with cortical atrophy and inconstant corpus striatum findings. The latter group of workers performed a series of encephalographic studies in cases of extrapyramidal disease and stated chorea tended to indicate a cortical rather than a striatal involvement. Klingman (1936) discovered several cases in which cortical inhibition with alcohol produced cessation of athetoid and choreiform movements. Winkleman, in discussing the paper of Goodhart, et al, stressed the fact that there is no distinction in function between small and large cells in the striatum and that both are involved in chorea.

In most recent corroboration has been a series of operations by Bucy. In 1932 he removed a portion of the precentral gyrus in a case of unilateral athetosis and the patient realized complete remission of symptoms for the next four years. In 1936 Bucy described in detail areas four and six of Brodman and their relation to involuntary movement, and in 1937 with Case, he told of good results in two more operations for athetosis. In these latter
two cases, working on the cortical theory of Wilson and the Brodman map of the cerebral cortex, Bucy exposed the cortex and then stimulated area six. This caused onset of involuntary motions, so he removed area six and the patients received complete abolition of their symptoms. The athetoic movements returned, however, in a few months, due to the fact that area four had been left intact. Bucy believed that involuntary movements are initiated from area six by a direct path rather than by its connection with area four, but otherwise he is in complete agreement with Wilson.

The recent experiments of Tomer (1936) indicate that there may be a sound physiologic and anatomic basis for Bucy's postulate of a direct extrapyramidal action of the cerebral cortex. Her stimulations of cat cortices after pyramidal tract interruption showed that the motor areas of the cortex are not solely dependent on the pyramidal pathways but effect stereotyped movements by some extrapyramidal path.

In the above discussion, cases presented as evidence have been chiefly those of chronic degenerative chorea, with an occasional case of Sydenham's. There are two other forms of the disease, seldom seen, which should be mentioned. In discussing the neurology of old age, Critchley (1931) presented a survey of senile chorea, which had first been defined by Graves in 1848. One must exclude cases with a family history of chorea, cases persisting from earlier life and cases with sudden apoplectiform onset before a
diagnosis of the rare, usually unilateral, senile chorea can be made. A note on senile chorea was made by Alcock (1936), who found the changes in the neostriatum as Dunlap had in Huntington's chorea. Brain (1933) listed Huntington's, Sydenham's and senile chorea and added a fourth type, electric chorea or Dubini's disease. He stated that this form was found only in Lombardy and neighboring parts of Italy and was first described by Dubini in 1846. The disease is fatal in a few days or months and is characterized by pains, myoclonic contractions, convulsions, paralyses and wasting.
ATHETOSIS
Athetosis is a condition which Hammond, who first described it in 1871, stated "is mainly characterized by an inability to retain the fingers and toes in any position in which they may be placed, and by their continual motion... the movements slow, apparently determinate, systematic, and uniform," in contrast to those of chorea which are "irregular, jerking, variable, and quick."

Athetosis as a symptom was noted in earlier works such as those of Charcot and Beevor and was even the subject for experimentation (Horsely, 1909), but it was not until C. and O. Vogt published their initial report in 1911 that athetosis was accorded the distinction of a separate disease. The work of the Vogts continued for many years, but unfortunately, with but rare exceptions, their papers were all published in the Journal fur Psychologie, to which I do not have access. With the exception of two small clinical reports my knowledge of their work is from intermediate sources.

The Vogts presented originally four cases of a disease characterized by double athetosis, progressive rigidity leading to peculiar postures, synarthria, dysphagia and in some instances by mental symptoms, pathological laughing and crying and convulsions. The primary evidence of this disease begins in the first months of life, and the Vogts considered it a congenital affection. The post-mortem findings in these cases were termed etat marmorate - marbling -
because of the blotches, stripes and irregular condensations seen in myelin sheath preparations. This marmorated pathological picture was observed only in the basal ganglia, particularly in the putamen and also in the caudate, and the effect is produced by a thick network of these irregularly medullated fibers traversing the atrophic neostriatum.

The athetoid disease of the Vogts was the first syndrome of the basal ganglia to be presented in the literature and was one of the important early contributions to the study of the ganglia. Hunt (1917a) accepted their syndrome of the neostriatum in his scheme of basal ganglion pathology, and Jakob (1925) also included the status marmoratus of Vogt in his concept of the striatal diseases, but, in direct contrast, localized the pathology for athetosis in the pallidum. During the years following 1911 many controversial points of the corpus striatum and its clinico-pathological investigations appeared. Wilson's progressive lenticular degeneration, and his extensive work on chorea and athetosis, Hunt's localization of paralysis agitans, and many other important papers cast doubt and controversy on the Vogts' original syndrome. In 1925 Wilson remarked that etat marbre was an interruption of neuronic activity from a fiber overgrowth. He also stated that "the Vogts have recently been compelled to admit that hyperkinesis of striatal diseases are substriatal in origin." Wilson thought "extra striatal" a better term. In the same year Madam Vogt published
an account of three cases of status marmoratus present at birth
and re-emphasized the congenital aspects of the disease. She also
declared that the pathological picture was not that of a sclerosis
but rather a dystrophy.

Scharapow (1928) reported a case of athetosis, convulsions,
disturbed gait, and indistinct speech, and on post mortem examin-
ation discovered etat marbre only in the putamen. The clinical
features of the original cases by Vogt were not questioned, and
Scharapow disagreed only in reporting a normal caudate nucleus.
The symptoms and signs were further substantiated by van Gehuchten
(1931), who reported a case in a premature child, and by Herman and
Schilder (1933), who presented a discussion of differential diag-
nosis.

Lowenburg and Malamud (1933) discussed the original report of
1911 in detail and pointed out that the Vogts considered status
marmoratus a definite clinical syndrome caused by a definite type
of lesion in a definite place. Lowenburg and Malamud discovered a
case with etat marbre in the cortex, and only nonspecific degener-
ative changes in the striatum. They concluded that the whole picture
was not as fixed as the Vogts supposed.

There have been few additions to our knowledge of Vogt's
disease in recent years. Hunt (1933) included the Vogt syndrome in
his discussion of the corpus striatum, but, as has been previously
noted, he believed that, while athetosis is a release phenomenon of
the striatum, rigidity is due to pallidal pathology. In this conclusion he ignored the rigidity without pallidal change which accompanied Vogt's athetoid disease. Putnam (Goodhart, et al, 1936) believed athetosis to be localized in the caudate nucleus.

Hallervorden-Spatz Disease

In 1920 the Vogts described a second syndrome of the corpus striatum characterized by onset in childhood, epilepsy, athetosis, and increased hypertonus to death. They included a case described by O. Fischer and one by Rothman in addition to three of their own. Pathological investigation showed destruction in the pallidum and striatum consisting chiefly of a decreased number of myelinated fibers with cellular atrophy and degeneration. They called this picture status dysmyelinnatus.

A thorough study of this condition was made by Hallervorden and Spatz in 1922. They had noted three cases of a familial disease of the pallidum and substantia nigra occurring in children, with essentially the same symptoms as the Vogts described. They classified their cases with those of the Vogts and added others of Ovari and Filimonoff. A more detailed examination by Hallervorden and Spatz revealed increased pigmentation in the globus pallidus and zona reticulare, the presence of the large Pick cells, increased pigment in the substantia nigra and dentate nucleus and a destruction of myelin in the ansa lenticularis and globus pallidus, which
was the most significant feature.

In contradistinction to the 1911 syndrome of the Vogts, and in recognition for their excellent work, the disease has been named for Hallervorden and Spatz. It is also called status dysmyelinatus and Vogt's pallidal disease in contrast to status marmoratus and Vogt's striatal disease.

The differential diagnosis between these two similar syndromes was discussed by Scharapow (1928) and van Gehuchten (1931). Both men described cases of both diseases and stressed the pallidal and acquired status dysmyelinatus as opposed to the striatal and congenital status marmoratus. Athetosis may be present in either, but is constant and prominent in the striatal affection; rigidity and contractures may be present in either, but are more prominent in the pallidal disease. Both diseases often include mental defects, but Vogt's syndrome may include convulsions and pathological laughing and crying as well.

Funfgeld (1929) added two more cases of Hallervorden-Spatz disease to the literature and observed marked alteration of the entire corpus striatum as well as the cortex, thalamus and substantia nigra. The course and prognosis of the two diseases of the Vogts concerned Ammosow (1931). He stressed the fact that the pallidal syndrome is a progressive disease with a fatal termination within a few years, and that the striatal disease is stationary or regressive and has a more lengthy course.
submitted three cases of Hallervorden-Spatz disease in a family of eight children, and stressed the familial occurrence of this and Wilson's disease as opposed to Vogt's syndrome. Hunt's report on the pallidal system (1933) agreed in all respects with Hallervorden and Spatz that rigidity is a result of pallidal pathology.

In 1935 Helfand produced a detailed discussion on the pathology of stat dyasmyelinique in which he differed from Hallervorden and Spatz in several particulars. His necropsies showed no pigmentation of the dentate and substantia nigra and no destruction of myelin. He did find increased pigment in the globus pallidus and zona reticulare and the presence of the large ballooned cells of Pick. Helfand suggested the name status pigmentatus for the disease because he believed that the essential change is a disturbance of pigment metabolism rather than myelin analysis.

Two more cases of stat dyasmyelinique were written into the literature by Meyer (1936a, b). Both of these cases showed mental deficiency, choreoathetosis, and progressive severe rigidity. Both exhibited selective sclerosis and demyelination of the globus pallidus and one showed degeneration in the substantia nigra. It was in connection with one of these cases that Meyer pointed out the susceptibility of the globus pallidus to anoxemia and suggested that this factor might play an important part in pathology of the nucleus.
General Considerations

In addition to the two specific diseases having athetosis as a prominent symptom, there are a number of general points to be discussed on the matter of pathogenesis. Most of the discussion will be of the same type as the presentation of chorea. Wilson and Walshe (1914) studied tonic innervation and motor apraxia and found it in athetosis but not in paralysis. Wilson later (1925) used this evidence to formulate his cortical theory of involuntary movements. Morgan (1927) attempted to add something to the controversy over involuntary movements by his experiments with cats. He concluded that "these facts seem to indicate that athetoid movements may have their origin either within the cortex or within the medial division of the globus pallidus," and gave no aid to one side or the other.

The often-quoted lectures of Wilson (1925) included a section on athetosis. In presenting the clinical qualities of this symptom, Wilson mentioned first the slowness and blending of the motions. He made a group of double tambour tracings and illustrated not only the slowness and blending but also his next point - the dys synergy and incoordination of muscle groups. He demonstrated here, as in chorea, the complete abrogation of normal physiological reciprocal innervation. He formulated also a description of the athetoid hand very similar to that of chorea. The phenomenon of tonic innervation, which is an inability to relax voluntarily a muscle group
contracted by voluntary action, is also observable in athetosis, and is an additional proof that muscle synergy is destroyed.

All of Wilson's clinical observations of athetoid motions substantiate his conclusions on the cortical theory of involuntary movement which were presented in the section on chorea. He found chorea and athetosis presenting many more similarities than differences and preferred to group them as choreo-athetosis. In consistent contrast with Wilson was Jakob (1925). He contended that athetosis is caused by a disturbance of pallidal origin in motor system coordination, and assigned the athetoid syndrome to the globus pallidus.

In 1930 Crothers and Cobb were able to examine a case of progressive athetosis with few or no other signs and symptoms, and discovered at necropsy atrophy of the caudate and lenticular nuclei. In contrast to this, on the cortical side, Klingman and Carlson (1936) presented observations on the effect of alcohol on choreo-athetosis, since this drug is a recognized cortical depressant. Their subjects claimed definite decrease in the intensity and duration of the motions under the influence of alcohol.

In 1932 Thomas presented a case of athetosis in a paralyzed limb. At autopsy, atrophy of the cortex for that limb was found together with degeneration of the corresponding portion of the pyramidal tract. Here was a case in refutation of Wilson - athetosis appearing in a limb devoid of cortical innervation.
Thomas preferred to support Jakob's view on the mechanism of involuntary movements.

The recent operative results of Bucy and Putman have already been presented. Those of Bucy lend strong support to the cortical theory while Putnam's may be interpreted in favor of either side.
BALLISM
Since 1920 there have appeared sporadic reports in the literature on a condition known as ballism, or, since it is commonly unilateral, hemiballism. Strangely enough, there have been no articles written in the English language on this subject, and further, the German periodicals, in which practically all of the work on hemiballismus has appeared, are chiefly those of the post-war period and not subscribed to by many libraries. I find myself forced by these circumstances to discuss the subject briefly from abstracts of five foreign articles which are available.

Ballism is defined as a violent jerking and twitching movement of the body. Hemiballism differs from hemiathetosis in being a larger and more rapid movement, and is differentiated from chorea also by its jerking, twitching, unpurposive character which is in contrast with the more coordinated choreic expressions.

An excellent description of a clinical case was given by Santha (1932). The patient, a woman of 57, developed recurrent attacks of twitching of her right hand, followed in a few minutes by a similar phenomenon in the right leg. This condition continued for a few weeks and then became gradually worse. The frequency and intensity of the involuntary movements increased, so at the time of examination she had a constant torsion-like throwing movement of the right arm and severe jerkings of the right leg. The head and neck were not involved. These movements could be stopped momentarily by placing the afflicted hand on the right shoulder blade, and ceased entirely during sleep. At necropsy senile plaques
of the cortex and softening in the left corpus of Luys were found. The damage to the body of Luys was in the caudal and posterior portions, the cephalic pole being intact. From this Santha postulated a segmental arrangement of the hypothalamic nucleus.

In much the same manner as were athetosis and chorea, hemiballism was recognized as a symptom long before any definite ideas on pathogenesis were evolved. The present tendency, particularly in Germany, is to connect hemiballismus with destruction of the contralateral corpus Luysi - the hypothalamic nucleus.

Guittain and Alajouanine (1924) described a peculiar form of choreoathetoid movements of one half of the body, characterized by an unusual hand with hyperextension of the fingers in which the movements are increased by exercise or emotion. They found this "hemichorea" due to degeneration in the body of Luys. Wenderowic (1928) later pointed out that hemiballism and hemichorea are closely related and probably of the same disease type. It was his contention that both of these symptoms result from an irritation to the cerebello-cortical pathway, as Wilson so vigorously claimed, and not to destruction of the subthalamus. He also stated that the hemialgesia and hemianesthesia, often associated with these motor changes, are caused by irritation of the thalamic nuclei.

In the same year Lhermitte arranged a survey of the corpus Luysi, and after perusing all of the literature and evidence stated
that neither the embryology, anatomy or pathology of the nucleus could clarify its function. He believed that destruction of the hypothalamic nucleus led most probably to excessive hemichorea, hemiballism and hemihypotonia of the contralateral limbs and trunk. Jakob (1928) submitted a case of intense hemichorea caused by hemorrhage into the body of the subthalamic nucleus.

Sjogren (1931) was able to present three cases of hemiballism with hypotonia, two of which showed athetoid movements of the fingers and toes as well as the jerking ballisms of the entire extremities. These movements diminished whenever the patient's attention was distracted, and disappeared completely in sleep. The author believed the body of Luys to be the seat of pathology and identified hemiballism and hypotonia as the syndrome of the corpus Luysi.

The most comprehensive report on hemiballism was written by Santba in 1932. According to his survey of the literature, hemiballism as a sign of a corpus Luysi lesion was first recognized by Jakob (1923). In 1927 Spatz wrote that this nucleus was the only part of the extrapyramidal system with a circumscribed function. In 1928 Santba concluded, on the basis of nine reported cases that hemiballism is impossible without some involvement of the body of Luys. He stated that since 1928 there have been five more cases written into the meager literature on the subject; one by Pelnar, 1929, with hemiballism of the right arm and hemorrhage in the left
corpus Luysi, one by Balthasar, 1930, two by Uberall and Samut-Ambrus, 1931, and one by Mikitius, 1932, which introduced the only dissenting note to the general rule, since the case showed hemiballism with an intact corpus of Luys and a lesion in the thalamus. Evidently Santha's perusal of the literature was not complete since he failed to mention any of the articles presented previously in this section.

In discussing the phenomenon of hemiballism, Santha was undecided whether to call it an irritation or an outfall. The bulk of evidence tends to select the latter but the mechanism of production of these peculiar movements is far from clear. As in chorea and athetosis, it is apparent that the pyramidal tracts must be intact for the appearance of ballism. Substantiation for this point was presented in Balthazar's case which displayed lesions in the corpus Luysi and also destruction of the pyramidal tracts. The patient evidenced no signs of hemiballism.
DYSTONIA MUSCULORUM DEFORMANS
The year 1911, which gave birth to Vogts' original presentation of etat marmoraté, which saw the first mention by Voelsch of a connection between the liver and the basal ganglia, and which fostered Hosslein and Alzheimer's classic investigation into the pathology of pseudosclerosis, also received the original presentation of still another disease related to the corpus striatum. In that year Oppenheim discussed four cases of a chronic progressive motor dysfunction which he called dystonia musculorum deformans.

A few months before Oppenheim's article appeared, Ziehen (1911) had remarked on five cases of a progressive spasm of muscles about the pelvis which had first been described by Schwalbe in 1908 and to which he gave the name of torsion spasm. These were essentially the same type of cases with which Oppenheim dealt. The latter writer identified and discussed these cases in considerable detail, and finally decided, since they could not be reconciled with hysteria, scoliosis, athetosis, chorea or any other extant classification, that they should be grouped alone and given a distinctive name. Dystonia musculorum deformans is still the accepted term, but in the literature the disease is also called progressive torsion spasm of children, Ziehen-Oppenheim's disease and tortipelvis.

Oppenheim described a chronic progressive disease, mostly of Russian-Jewish children, which appears from 8 to 14 years of age
and is characterized by deformity about the pelvis and tonic and clonic spasms of the musculature of locomotion. The muscles of the thigh, pelvis and lumbar region, in addition to spasm, also show alternating hypo- and hypertonia which disappears in sleep. The disease may begin in the arms, but the muscles of locomotion are the ultimate seat of disturbance. The patient has a characteristic pelvic deformity and a "dromedary" gait.

Oppenheim stated that the site of pathology is highly speculative but is probably in the cells controlling muscle tone. He discarded all cases of spasm, torticollis, etc., from his syndrome unless they had the characteristic pelvic findings.

Immediately following Oppenheim's presentation Collins (1912), Dana (1912) and Dana (1916) published cases of the same type, but disapproved of a separate classification. They regarded their cases as similar to tic and torticollis, and of psychic or hysterical origin. However, the organic theory for the pathogenesis of this class of disorder, which Oppenheim advocated, became more popular, and cases in support were presented by Spiller (1913), Bregman, Hunt (1916), Bernstein, Diller and Wright (1916), Hallock and Frink (1917), Dercum (1917) and many others.

Hunt placed the pathology in the striatal mechanism for tone control, and the basal ganglia have been considered the pathogenic site since that time. He also noted a conflict of synergists, agonists and antagonists in muscle group actions which he called
the paradoxical, or reverse, phenomenon of dystonia.

Diller and Wright (1916) made a thorough survey of the literature, presented two more cases, and suggested that the pelvic muscles were not alone susceptible to localized changes in tone and contraction, and that the disease might involve any muscle group. It was Keachner's opinion (1918) that while Diller and Wright were probably correct, practically, most patients developed pelvic changes sooner or later, and Oppenheim's original description held true in the majority of cases.

As dystonia musculorum became more generally recognized, the original restricted description of Oppenheim was found not to fit all the aberrant forms of the disease which arose. Wechsler and Brock (1922) examined six cases with unusual features such as decerebrate rigidity, myostatic variations, segmental distribution, and other striatal symptoms such as tremor and inconstant athetoid motions. These men postulated a static or postural phase and a kinetic or active phase, and stated that either may dominate in the disease.

In contrast to most of the striatal diseases presented here, the post mortem examinations of dystonia musculorum have been very few. The disease occurs at the end of the first decade of life, is not fatal, and unless the patient dies of intercurrent pathology, the neurologist who first makes the diagnosis almost invariably loses sight of the patient. Davis (1935) stated that "it (dystonia
musculorum) results from certain progressive lesions in the lenticular nucleus. While it is possible to conclude that the changes are degenerative, their exact cause is not yet clear."
TIC, SPASM, TORTICOLLIS
A tic is a recurrent spasmodic involuntary muscular action confined to a few muscles or muscle groups. It is sudden, rapid and abrupt and is usually clonic. It occurs without peripheral irritative cause, is presumably cortical in origin, and shows a functional pattern or ideational purpose.

A spasm is a sudden involuntary rigid contraction due to muscular action. It may be tonic or clonic and is often attended by pain. It has no purpose or pattern.

Myoclonus is a sudden irregular involuntary clonic twitching of a muscle or part of a muscle, which does not produce movement of a part. It is brief and rapid, has no rhythm or synchrony, and is a pure motor phenomenon.

Torticollis is a tonic or tonic-clonic spasm of the neck muscles which causes wry neck. It has the characteristics of spasm.

Until 1911 when Oppenheim separated dystonia musculorum from the larger group of spasms, the phenomena defined above were considered for the most part as functional in origin. This theory applied particularly to tics, and spasms and myoclonus were included since they were apparently a similar type of affliction. Following Oppenheim's demonstration of dystonia musculorum as an organic disease, several workers began to examine the other types of neuromuscular abnormality for a possible organic basis, and strife arose between the old psychogenic school and the followers
of Oppenheim. The newer concept of the pathogenesis of these conditions was not to be denied, however, and more and more neurologists began to see that at least some of these cases were organic in nature and probably caused by lesions in the basal ganglia.

A typical example of the controversy of the day may be found in Wilson's report before the London Neurological Society (1927). The author favored the functional view and stated in part, "The common association of tics with mental defects and imbecility, with such psychoses as paranoia and schizophrenia, with catatonic states, and, more widely, with mentalities of an unstable quality, effectively precludes any other view." Dr. Guillian declared, in response, that he and R. Marie had held to an organic origin for many cases of spasmodic torticollis, which were at the time appearing most frequently after encephalitis. He further stated that the basal ganglia are the structures involved. Dr. Cruchet attempted to mediate by suggesting that tic, being a movement of action, might be dissimilar to torticollis, which is a more prolonged spasmodic attitude.

It became apparent, however, that the organic theory was permanently established. Later in the same year (1927) Strauss reported two cases of post-choreic tic and suggested a close relationship among tic, chorea and myoclonus on a basis of common pathogenesis in the corpus striatum. However, Curran (1928), in his
survey of motor tic, reviewed the theories of the French school, the Freudians, and the followers of Adler and ignored any but functional hypotheses.

Grinker and Waller (1933) succeeded in performing an autopsy on a patient who, having been afflicted with uncomplicated torticollis for four years, died during an operation. They found marked alteration in the cerebellum and moderate changes in the cortex, thalamus and basal ganglia. They were unable to localize the lesion, but demonstrated an organic basis for torticollis. A paper by Freeman (1933) suggested the inferior olive as the faulty spot in a case of palatal myoclonus. Another report by Foerster demonstrated localized degeneration of the putamen in a case of "mobile spasm of the neck." Foerster mentioned the close relationship of athetosis and torticollis and stated that the latter is probably a localized type of the former.

The most recent survey by Putnam (1938) suggested that athetosis, dystonia, torsion spasm, spasmodic torticollis, ballism, chorea and myoclonus are all closely related phenomena, and that their pathogenesis is probably nearly identical. He described five cases, all with coexisting involuntary grimace, torticollis, athetosis, ballism of arms, dystonia, and torsion of the trunk. His report of nineteen cases of this class, all relieved by section of extrapyramidal pathways in the cord, was a valuable aid in establishing more firmly the organic genesis of these diseases.
CONGENITAL MUSCULAR HYPERTROPHY
The most recent of all the syndromes of the corpus striatum to be presented to the world of clinical neurology is de Lange's disease or congenital muscular hypertrophy. In 1934 de Lange wrote on three cases of a peculiar infantile disease characterized by hypertonia and rigidity of the entire body, resistance to passive movement, mental deficiency and large hyperplastic muscles. She stated that, to her knowledge, Bruck in 1889 reported the only other such case in the literature, and she prefaced her presentation with a thorough review of his case.

Bruck described a patient eighteen months old who was brought to him because of an extremely large tongue. Bruck removed pieces of the tongue on two occasions but it responded each time by replacing the lost tissue. He also remarked on the muscular hypertrophy of a wrestler which the child showed in his limbs and body. The infant experienced pronounced spasms, marked resistance to passive motion and no reflex changes. There were no especial findings upon post mortem examination.

De Lange described three cases remarkably similar to Bruck's, and evolved the following clinical description:

The disease is rare and apparently congenital but not familial. It is identified by muscular hypertrophy from birth, with a symmetrical over-development of the pectorals, deltoids, biceps and in fact all the muscles, by progressive rigidity and resistance to passive movement; by frequent spasms; and by mental deficiency.
The differential diagnosis from Thompson's disease, myotonia congenita, is made from the earlier age of onset, the clinical picture, the biopsy and the response to electrical stimulation. The last two points are altered in Thompson's disease but are normal in de Lange's disease. The prognosis is poor; all three of de Lange's patients died before reaching two years of age.

De Lange was able to secure a necropsy on only one of her patients. She reported a generalized porencephaly, communicating hydrocephalus, and congenital defects of the basal ganglia. In place of the caudate nucleus there was a group of small cells of an undifferentiated type, and no ganglion cells were present. The putamen was decreased in size; filled with cavities, and contained no ganglionic cells. The globus pallidus was small but with more fibers than the putamen.

A fifth case of this rare malady was studied by Hall, Sunder­man and Gittings (1936). The child in their case was a negro and, in contrast to de Lange's patients was alive at seven years of age. He demonstrated the typical picture of muscular hypertrophy, rigidity, spasms and imbecility. Hall and his co-workers ran a complete set of laboratory tests on the patient in an effort to discover more about the nature of his disease. A biopsy of muscle, x-ray plates of the skull and abdomen, blood Wassermann, tuberculin test, cerebrospinal fluid check including Lange gold curve, urogram and routine blood and urine analyses were all negative. The examination of the
blood serum was negative except for two factors; the potassium content was increased to 5.5, 25\% above normal, and the phosphorus content was increased to 7.3, 30\% above normal. In the urine creatine and creatinine were increased to two or three times their normal amount.

Hall's investigation is of interest even though most of his reports were negative. After summarizing the laboratory work he was unable to throw any additional light onto the nature of de Lange's disease.
MISCELLANEOUS
From time to time there have appeared unusual case reports or incidental statements in the literature relegating some rare and poorly understood disease to the basal ganglia. For the sake of completeness these will be considered here.

Jakob (1925) and Goodhart, Balser and Bieber (1936) mention the probability of basal ganglion pathology in Little's disease, or congenital spastic stiffness of the limbs. There is no doubt but what the pyramidal tracts are involved in these cases, and in some, due to birth injury, cerebral hemorrhage, etc., it is possible that the corpus striatum may be involved. The characteristic findings of spastic paralysis with exaggerated deep reflexes and a double Babinski are unmistakably those of the pyramidal system. Stiffness of the limbs is the main indication of extrapyramidal involvement, and this may well be secondary to the spasticity of corticospinal origin. Goodhart found porencephaly and internal and external hydrocephalus in his examinations and was unable to discover any involvement of the corpus striatum.

Gordon (1935) reported on four cases of a bizarre deformity in infants, probably congenital, which he attributed to pathology in the corpus striatum. These newborns suffered plastic rigidity without hyperkinesia and a characteristic deformity of extreme abduction and flexion of the hip and knee joints. Gordon called his patients "frog children" and suggested the corpus striatum as the most probable site of such deformity.
An epileptic variant called striatal epilepsy has occasionally appeared in various neurological reports. One of the best of these is by Soeken (1934). He reviewed seven cases of this malady, occurring in children from one to fourteen years of age, and noted as cardinal symptoms of the striopallidal system more or less marked rigor mobilis, occasional hypotonia, amimia, poverty of movement and tendency to rigidity. One of these cases came to necropsy and displayed degeneration of the pallidum. There were rather diffuse changes throughout the brain, but the pallidal degeneration was definite enough to be considered the causative factor in the striopallidal symptoms. In three cases Soeken noticed clonic twitchings. These children's seizures were severe and of the tonic type. Each patient assumed a body attitude consistent with the distribution of his rigor. These attacks were also associated with vegetative changes such as marked hyperpnea and general body redness.

The existence of a striatal form of epilepsy was discussed as early as 1925 by Wilson, but as little is known about this variant as about the whole subject of epilepsy.
SURVEY OF PATHOGENESIS
The pathogenesis of striatal disease, as Wilson so aptly stated, has one of the great characteristics of basements, viz., darkness, and there are times when one wonders whether attempts to bring to light the facts concerned merely intensified the subterranean blackness. The reader is no doubt keenly aware by now of the complexities of the subject and the need for a discussion to clarify the situation.

One of the most concise ways to summarize the majority of theories and facts on the diseased corpus striatum is to review the several complete syndromes of the striate body which have been presented piecemeal in the several sections of this paper. These have appeared in the literature conveniently spaced as to time and cover most of the important concepts on striatal pathology.

The first of these system-analyses was formulated by Vogt in 1911, and was quite general in nature. She listed the symptoms of her etat marbre (athetosis, rigidity, pseudobulbar palsy) and made of them a syndrome for the corpus striatum.

In the following year Wilson localized his symptom complex in the lenticular nucleus. It consisted of tremor, spasticity, dysarthria and dysphagia and weakness.

These two initial reports include all of the symptom groups of the corpus striatum. They are (1) involuntary movements, (2) rigidity, (3) spasms, (4) pseudobulbar palsy. Vogt was able only
to identify these findings with the corpus striatum in general, but Wilson localized them in the lenticular nucleus. We may deduce from this that the caudate nucleus has no exclusive hand in any of these symptoms and the corpus striatum as a whole produces no pathological findings which the lentiform nucleus cannot provide.

The work of Hunt (1917a) was the first authoritative effort to subdivide the corpus striatum in relation to production of disease symptoms. He presented his concept that the globus pallidus is the site of pathology in paralysis agitans, and as such is responsible for the appearance of tremor and rigidity. In 1916 Hunt had located the peculiar spasms of dystonia musculorum deformans in the striatum, and Jelgerama, Alzheimer, Lhermitte and others had relegated the involuntary motions of Huntington's chorea to the putamen and caudate, so Hunt formulated the following syndrome of the corpus striatum:

1. Striatum - choreoathetosis, tonic and clonic spasms
2. Pallidum - rigidity, tremor

Further support to Hunt's classification appeared after C. and O. Vogt described their second disease in 1920 and after Hallervorden and Spatz had localized its pathology (1922). This syndrome, particularly characterized by progressive rigidity and severe contractures, was caused, according to the work of Scharapow, van Gehuchten, Meyer and others, by a selective destruction of the
globus pallidus. As experimentation progressed, two diseases of the Vogts formed themselves into a corpus striatal syndrome.

1. Striatum
   a. Akinesis - incoordinate speech, walking and standing
   b. Hyperkinesis - choreoathetosis, spasms, tremor

2. Pallidum - general rigidity

A point of controversy arose in 1923 when Spatz and Jakob both favored the substantia nigra as the point of destruction in paralysis agitans. It gradually became apparent that the substantia nigra is diseased chiefly in post-encephalitic cases, and many investigators proposed to separate idiopathic paralysis agitans with lesions in the pallidum from symptomatic paralysis agitans with lesions in the substantia nigra. Winkleman (1932) expressed the idea that, since many fibers from the globus pallidus enter the locus niger, and since they are both concerned in the production of Parkinsonian symptoms, they should be grouped together as the "pallidal system."

The present tendency is to accept both the globus pallidus and substantia nigra as factors in producing tremor and rigidity. Even Hunt, who first identified the globus pallidus with paralysis agitans (1917a) and who refused for many years to accept the substantia nigra (1933), has recently admitted (1935) that the pathology in encephalitis has a particular predilection for the corpus striatum and the locus niger.
Perhaps the most elaborate classification of pathological physiology of the corpus striatum was presented by Jakob (1925).

1. Striatum
   a. General - mild paresis, synergic incoordination, akinnesia, tremor, parakinesia
   b. Small cells - chorea
   c. Large cells - rigidity

2. Pallidum - athetosis, torsion spasm, rigidity, contractures

3. Corpus of Luys - hemiballism

4. Substantia nigra - Parkinsonism

As may be seen, Jakob differs from most authorities on one important point, namely, the localization for athetosis. The preponderance of evidence supports the view that athetosis is caused by lesions of the striatum rather than the pallidum. Another point in question is the advisability of attributing different pathological functions to the two cell types in the striatum. In the section on anatomy, the view was stressed that the small cells are internuncial in character, receiving afferents to the corpus striatum and not sending efferents from it. This is the accepted theory at present, and, according to Winkleman, has clinico-pathological as well as anatomic evidence to support it.

A third problem introduced by Jakob's classification is the status of the corpus Luysi and the relationship of hemichorea and
hemiballism to the striatum. Most authorities who have concerned themselves with the body of Luys are of the opinion that hemiballism and hypotonia are effected by its becoming diseased. The known connections of the body have been mentioned and illustrated, but as yet the exact significance of its symptoms is still not definitely established.

In 1933 Hunt presented a second outline of the abnormal functions of the corpus striatum, a much less complex system than that of Jakob.

1. Striatum
   a. Small cells - chorea
   b. Large cells - tremor

2. Pallidum - rigidity

These are the three syndromes of the corpus striatum, according to Hunt. All other signs and symptoms are referable to these three fundamental pathological changes. Athetosis and spasms he classified with chorea; contractures he placed with rigidity. Hunt's results as were Jakob's are here open to question in that the advisability of separating the striatal symptoms on a histological basis is doubtful.

Pseudosclerosis, characterized by tremor, rigidity, slow speech, epilepsy and mental changes, and de Lange's disease, with rigidity, spasms and muscular hypertrophy, are additional diseases of the corpus striatum which have been discussed in this paper. Neither has been well localized because each presents characteristics
of both striatal and pallidal pathology.

Before concluding this brief review of pathogenesis in diseases of the corpus striatum, the Jackson-Wilson theory of choreoathetosis should be mentioned. The conflict between the striatal adherents and the disciples of Jackson is one of the most persistent in contemporary neurology. The workers who adhere to the striatal theory have a great number of necropsies on which to base their tenet, while the supporters of the cortical concept have the neurologic law of modern physiology on which to rest their case. In spite of repeated autopsy findings to the contrary, it is impossible to ignore the impressive logic of Wilson and his co-workers. The views of each school of thought have been presented previously, and as yet no settled opinion one way or the other can be made. The recent work of Bucy, whereby removal of a part of the cerebral cortex gave cessation of athetoid motions, is undoubtedly an important contribution to the subject, and perhaps the recent trend toward operations on human material will be the means of answering the question.
SUMMARY AND CONCLUSIONS
I Paralysis agitans

A. Types
   1. Senile and presenile
   2. Juvenile
   3. Symptomatic
   4. Formes frustes

B. Symptoms - tremor, weakness, rigidity, secondary signs of flexed posture, propulsion gait, slowness and poverty of movement, masked facies, salivation, etc.

C. Lesions
   1. Senile and juvenile - globus pallidus
   2. Symptomatic - corpus striatum and substantia nigra

II Pseudosclerosis

A. Symptoms - tremor, rigidity, dysarthria, slowness of movement, convulsions, dementia

B. Lesions - lenticular nucleus, particularly the putamen

III Wilson's Disease

A. Symptoms - tremor or athetosis, spasticity, contractures, dysarthria, dysphagia, muscular weakness, dementia

B. Lesions - lenticular nucleus, particularly the putamen

IV Chorea

A. Types
   1. Sydenham's
   2. Paralytic
3. Huntington's
4. Senile
5. Electric

B. Symptoms - complex spontaneous movements, choreic hand, ataxia, weakness, psychic changes

C. Lesions
   1. Sydenham's - infiltration and gliosis
      a. Cerebral cortex, or
      b. Striatum
   2. Huntington's and others - chronic degeneration
      a. Cerebral cortex and striatum

V Athetosis

A. Types
   1. Vogt's syndrome
   2. Hallervorden-Spatz disease

B. Symptoms
   1. Vogt's - double athetosis, rigidity and postures, dysarthria, dysphagia, convulsions, pathological laughing and crying, dementia
   2. H-S - hypertonus, rigidity and contractures, athetosis, convulsions
   3. Symptomatic - athetoid motions

C. Lesions
   1. Vogt's - striatum
2. H-S - pallidum, and striatum to a lesser extent

3. Symptomatic - striatum usually

VI Ballism

A. Symptoms - typical ballistic motions, hypotonus, weakness

B. Lesions - corpus of Luys

VII Dystonia musculorum deformans

A. Symptoms - pelvic torsion, spasms, alternating hypertonus and hypotonus

B. Lesions - probably in the striatum

VIII Torticollis, tic, spasm, myoclonus

A. Symptoms - twitches, brief contractions, etc.

B. Lesions - corpus striatum in at least some cases

IX Congenital muscular hypertrophy

A. Symptoms - muscular hypertrophy, rigidity, spasms, mental deficiency

B. Lesions - congenital defect of the basal ganglia

X Striatal epilepsy

A. Symptoms - epileptic seizures with myoclonic twitchings, spasms, rigidity between convulsions
BIBLIOGRAPHY
*denotes abstracts from Archives of Neurology and Psychiatry


Barnes, S., and Hurst, E.W., 1925, Hepatolenticular degeneration, Brain, 48:279-333.

......1926, A further note on hepatolenticular degeneration, Brain, 49:36-60.

......1929, Hepatolenticular degeneration, Brain, 52:1-5

Bazett, H.C., and Penfield, W., 1922, A study of the Sherrington decerebrate animal in the acute and chronic conditions, Brain, 45:185-265.


*Bogaert, Ludo van, 1930, Primary juvenile paralysis agitans, Rev. Neurol., 2:315.


Bucy, P.C., and Buchanan, D.N., 1932, Athetosis, Brain, 55:479-492.


Copeland, James, 1850, Palsy and Apoplexy, Lea and Blanchard, Philadelphia, pp. 79-83.

Crandall, L.A., and Weil, A., 1933, Pathology of the central nervous


..., 1927, Structural changes in Huntington's chorea, Brain, 50:631-636.


Ferraro, A., 1925, Experimental contribution to the study of the


Gardberg, M. 1933, Hepatolenticular degeneration, J.A.M. A., 100: 482-484.


.........1924, Relation of the cerebellum to the static system and its role in posture synergy, J. Nerv. and Ment. Dis., 60:337-346.


.........1933, Primary paralysis agitans, Arch. Neurol. and Psychiat., 30:1332-1349.


Jackson, Hughlings, 1895, Neurological fragments, No. XV, Lancet, 1:476-478.


*……1928, Hemichorea due to hemorrhage into the hypothalamus, Arch. argent. di. neuroul., 2:1.


*Loevy, Hansi, 1931, Relationship between striatum and liver, Nervenarzt, 4:653.


Malone, E.F., 1928, the general relation of histological character to function in mammalian neurines, Cowdrey's Special Cytology, P. Hoeber, Inc., New York.


Miller, H.C., 1934, Causal relationship of trauma to paralysis agitans, Nebraska M.J., 19:165-168.


McAlpine, Douglas, 1926, The anatomo-pathological basis of the Parkinsonian syndrome following epidemic encephalitis, Brain, 49:525-566.


Ranson, S.W., 1932, Anatomy of the nervous system, W.B. Saunders Co., Philadelphia.


Ruhemann, Konrad, 1904, Aus der psychiatrischen, und Nervenklinik

*Russetzky, I.I., 1929, Paradoxical hypermotility in Parkinsonism,

Russetzky, Joseph, 1931, Sur les hypercinesies, Encephale, 26:739.

Sachs, E., 1909, On the structure and functional relations of the
optic thalamus, Brain, 32:95-126.

*Santha, K. von, 1932, Hemiballism and the corpus Luysi, Ztschr.

Scharapow, I., and Taschernomordik, P.M., 1928, Pathology of basal

Schroeder, L.C., 1922, Observations on the etiology and pathology

Schwenn, P.F., 1901, Ein Beitrag zur Pathogenese der Paralysis

Sherrington, C.S., 1906, Integrative action of the nervous system,

*Sjogren, V.H., 1931, Concerning the syndrome accompanying les-
ions of the corpus hypothalamicum of Luysi, Acta psychiat. et
neurol., 6:301.

*Sjovall, Einer and Wallgren, Arvid, 1934, Some aspects of hepato-
tolenticular degeneration and its pathogenesis, Acta psychiat. et

*Socken, G., 1934, Striatal epilepsy, J. f. Psychol. u. Neurol.,
46:326.

Solly, Samuel, 1848, The human brain, Lea and Blanchard, Phila-
delphia.

Spiller, W.G., 1913, A Case of dystonia musculorum deformans, J.

......1916, Family form of pseudosclerosis and other conditions
attributed to the lentiform nucleus, J. Nerv. and Ment. Dis., 43:
23-36.
113


Voelsch, Max, 1911, Beitrag zur Lehre von der Pseudosklerose,


Wall, Cecil, 1920, Bradshaw lectures on chorea, Lancet, 2:1081-1092.


....1924, The muscular rigidity of paralysis agitans and its relation to trauma, Brain, 47:159-177.


....and Brock, S., 1922, Dystonia musculorum deformans, Arch. Neurol. and Psychiat., 8:538-547.


....1914, An experimental research into the anatomy and physiology of the corpus striatum, Brain, 36:427-492.

....1916, Dysemetropsia and its pathogenesis, Tr. Ophth. Soc. U.
Kingdom, 36:412-444.


Winkelman, N.W., 1932, Progressive pallidal degeneration, Arch. Neurol. and Psychiat., 27:1-21

Window, J.B., 1772, Anatomical exposition of the human body, Donaldson and Elliot, Edinburgh.


ILLUSTRATIONS
FIBER CONNECTIONS OF CORPUS STRIATUM (AN EXTRA-PYRAMIDAL SYSTEM)

PLATE I

(After Rasmussen)
PLATE II

FIBER CONNECTIONS OF THE CORPUS STRIATUM
(EXTRA PYRAMIDAL SYSTEM)

- Cerebral cortex of frontal lobe
  - Frontothalamic fasciculus
    - Medial and ventral portion of thalamus
      - Brachium conjunctivum
        - Cerebellum
          - Motor nucleus of trigeminal nerve (V)
          - Motor nucleus of facial nerve (VII)
  - Motor cells of anterior central gyrus
  - Cerebral cortex of frontal lobe

- Pyramidal system (collaterals)
  - Caudate nucleus
    - Putamen
    - Globus pallidus
      - Ansa lenticularis and lenticular fasciculus
        - Subthalamic nucleus
          - Substantia nigra
            - Posterior commissure
            - Reticular formation
              - Nucleus of the medial longitudinal fasciculus
                - Reticulospinal fasciculus
                  - Nucleus ruber
                    - Rubrospinal fasciculus
                      - Lower motor centers

(After Rasmussen)
(After Ranson)
Legend for Plate IV

1. Caudate nucleus
2. Putamen
3. Globus pallidus
4. Claustrum
5. Thalamus
6. Internal capsule, anterior limb
7. Internal capsule, posterior limb
8. External capsule
9. Septum pellucidum
10. Corpus callosum
13. Lateral ventricle
14. Third ventricle
19. Cerebellar vermis
Horizontal section of the human brain
Legend for Plate V

1. Caudate nucleus
2. Putamen
3. Globus pallidus
4. Claustrum
5. Thalamus
6. Internal capsule, anterior limb
7. Internal capsule, posterior limb
8. External capsule
9. Septum pellucidum
10. Corpus callosum
13. Lateral ventricle
14. Third ventricle
19. Cerebellar vermis
Horizontal section of human brain

(Ventral to section in Plate IV)
Legend for Plate VI

1. Caudate nucleus
12. Corpus mamillare
13. Lateral ventricle (posterior horn)
15. Cerebral aqueduct
16. Red nucleus
17. Hypothalamic nucleus
18. Basis pedunculi
20. Pons
Frontal section of human brain through mamillary bodies
Legend for Plate VII

1. Caudate nucleus
2. Putamen
3. Globus pallidus
4. Claustrum
6. Internal capsule, anterior limb
8. External capsule
10. Corpus callosum
11. Anterior commissure
13. Lateral ventricle
14. Third ventricle
PLATE VII

Frontal section of human brain through anterior commissure