

1937

The Parkinson syndrome of epidemic encephalitis

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THE PARKINSONIAN SYNDROME OF
EPEDEMIC ENCEPHALITIS

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Submitted to
the faculty of the
University of Nebraska College of Medicine
in partial fulfillment of
the requirements for
the Degree of
Doctor of Medicine

480842

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I wish to acknowledge my indebtedness to Dr. C. W. M. Poynter, Dr. H. A. Wigton, Dr. Richard Young, Dr. W. A. Willard, and Dr. O. C. Nickum, all members of the faculty of the University of Nebraska College of Medicine, for the references they have given me for my bibliography, for their constructive criticisms of the first draft of this thesis, and for their discussions of cases of epidemic encephalitis which have come under their care.

Willard Brinegar

THE PARKINSONIAN SYNDROME OF
EPIDEMIC ENCEPHALITIS

INTRODUCTION

During the World War and the years immediately following, the medical profession witnessed the appearance, development, and spread of what was, to all intents, a new and very interesting disease. This disease was a type of encephalitis which differed in its neurological manifestations from the types with which the medical world was familiar. It was first described by von Economo of Vienna(82) in May of 1917, and he believed at the time that it was an entirely new disease. However, since that time historical investigations have revealed that several epidemics which resemble closely this disease have occurred in the past.

It soon became apparent that many cases of this new disease were not permanently cured when the acute manifestations of the disease had passed, but that the acute phase was often followed by a number of interesting and distressing sequelae. The most frequent and perhaps the most interesting of these

was a symptom complex resembling paralysis agitans, or Parkinson's disease. Because of this resemblance, the syndrome is usually spoken of as a parkinsonian state. The purpose of this paper is to discuss this parkinsonian syndrome as a sequel of lethargic encephalitis.

In this discussion of the parkinsonian syndrome of epidemic encephalitis it is necessary to say a few words about the acute disease. Epidemic encephalitis belongs to the general group of diseases known as the nonsuppurative encephalitides. They may be divided into four general groups: (31)

1. The form associated with measles, smallpox, vaccinia, and antirabies inoculation;
2. The group known as toxic or disseminated encephalomyelitis, seen most commonly in children and usually associated with varicella, infections of the upper respiratory tract, otitis media, a variety of acute gastro-intestinal diseases, pneumonia, septicemia, and pertussis;
3. Hemorrhagic encephalitis which occurs in association with influenza, bronchopneumonia and arsphenamine poisoning;
4. The epidemic encephalitides. This is the

only group with which we are concerned since the parkinsonian syndrome has never been reported as following encephalitis of the first three groups.

Recent authors have divided this fourth group again into two divisions. Since there is reason to believe that the endemic encephalitis of Japan and the disease recently prevalent in St. Louis (and to a lesser extent in other parts of this country), is of a somewhat different nature from the lethargic encephalitis of von Economo. Therefore the epidemic lethargic encephalitis of von Economo will be designated as encephalitis type "A", and these other varieties as type "B". Although only the former seems to be associated with the parkinsonian syndrome, the two show so many points of similarity that both diseases will be treated very briefly before taking up the detailed discussion of the parkinsonian syndrome.

LETHARGIC ENCEPHALITIS OF VON ECONOMO OR
EPIDEMIC ENCEPHALITIS TYPE "A"

Epidemic encephalitis type "A" may be defined as a specific inflammatory process involving the central gray matter of the cerebral hemispheres and brain stem which is characterized by both acute and chronic symptoms.(31) It is usually epidemic but may be sporadic.

The etiology is as yet unknown although a great deal of work has been done in an attempt to determine the etiology of this condition. The responsible organism has never been isolated, but there is a good deal of indirect evidence that the disease is due to a filtrable virus.

This disease was first described by von Economo of Vienna in 1917.(82) However, a condition that was probably the same disease was prevalent in the Balkans in 1915 and 1916. Ford (31) estimates that over 100,000 cases developed throughout the world between 1917 and 1920. The highest incidence occurred in 1920 with a second lower peak in 1924. The Italian epidemic called "nona" in 1890, and the epidemic of sleeping sickness of Tübingen, Germany in 1712, may

have been this disease.

The disease is ordinarily most prevalent during the winter, although the English epidemic of 1924 occurred during the spring and summer.

It has been noticed that epidemics of this disease seem to be associated with epidemics of influenza. The actual connection between the two diseases is still a question. Some writers believe that they are caused by variants of the same etiological agent, but the most general opinion seems to be that influenza lowers the general resistance of the community, and so allows encephalitis to gain a foothold. In support of the latter view is the fact that there seems to be no cross-immunity between the two diseases, but also that many individuals who did not have influenza later developed encephalitis.

The incubation period is not definitely known, but probably varies between about two weeks and several weeks. The mode of transmission is also unknown but it is believed to be transmitted mainly by healthy carriers of the virus. The portal of entry is probably the upper respiratory tract.

The incidence is greatest in the second and third decades of life, but no age is exempt. Males and females

seem to be affected with about equal frequency. It is interesting to note that in one epidemic the incidence among physicians was sixteen times that of the general population. (88)

The onset of the disease may be sudden or gradual, tending to be more abrupt in severe epidemics, in which case sudden loss of consciousness may be the first symptom. Usually there are first present symptoms of a mild upper respiratory infection, such as coryza, pharyngitis, or bronchitis. G-I symptoms may be present. Prodromal symptoms such as headache, vertigo, restlessness, irritability, insomnia, and drowsiness may be present for several days before definite neurological disturbances appear. There are several more or less distinct clinical forms of the disease.

The most common of these is the somnolent-ophthalmoplegic type. The patient is in a deep stupor but usually can be aroused temporarily. True coma is rare but may occur. There is early involvement of the third, fourth, and/or sixth cranial nerves, the third being affected most frequently and most severely. The resulting palsies are usually bilateral but are often incomplete, involving only part of the muscles supplied by the affected nerve. The pupils may be

dilated or contracted and are generally unequal and often irregular. Diplopia and ptosis of the eyelids are common. The light reflex and accommodation reflex are usually diminished and either or both may be completely absent. Eye ground examination will usually show congestion of the optic nerve head, but true papilledema is rare. Nystagmus and facial palsies sometimes occur. Some less common symptoms which may occur in this type are hemiparesis or actual paralysis of the extremities, increased or decreased tendon reflexes, focal or general convulsions, and symptoms of meningeal irritation.

The so-called myoclonic type resembles the somnolent-ophthalmoplegic type except that in addition to any or several of the above symptoms myoclonus is the most prominent symptom. There are sudden contractions of various muscle groups of arms, legs, face, and abdominal or respiratory muscles. These are usually rhythmical and often various groups of muscles contract in more or less regular sequence. The fever does not necessarily parallel the somnolence and there is no characteristic temperature curve for this disease. Acute symptoms vary in duration from a few weeks to

several months.

The hyperkinetic form is more severe and has a higher mortality than the above mentioned, and is most apt to occur during severe epidemics. Its onset is almost always sudden and the fever is high. There is at first insomnia instead of somnolence, and chorea-like movements are common. A reversal of the normal sleep rhythm is often found, especially in children. The mental state consists of delerium, excitement, and anxiety. Hallucinations are common. Myoclonus may also occur in this type. As a rule, the duration is shorter than in the somnolent type of the disease.

Fulminating cases in which the patient dies within a few hours after onset occasionally occur during the peak of severe epidemics. The picture may be of sudden coma or wild delirium followed by collapse and death. Convulsions or a fulminating bulbar palsy may close the picture.

Abortive cases are probably much more common than is generally realized, because the symptoms are so mild that the patient is not seen by a physician. The only symptom may be a mild drowsiness for a few days, or neuralgic pains, insomnia, and headaches may occur. These cases are important because they may be followed by the parkinsonian syndrom or other sequelae.

In the acute disease the spinal fluid contains from 20 to 500 or more lymphocytes. The spinal fluid protein is slightly increased and sugar is normal or very slightly increased. The red blood count is normal and there is a polymorphonuclear leukocytosis, the white count varying between 15,000 and 30,000. The blood chemistry is essentially normal. The urine is usually normal but may contain a little albumin or sugar or both.

The pathological findings in acute cases which have come to necropsy show: (11,23)

Gross: The brain stem has a pink appearance grossly due to vascular engorgment which is more pronounced on the venous side than on the arterial side. There are usually small hemorrhagic areas and some small thrombi both in the meninges and in the brain substance.

Microscopic: The pia mater shows injection and round cell infiltration. The cells of the affected nuclei show cloudy swelling, eccentric nuclei, and obscuration or disappearance of Nissl bodies. Ameboid glial cells cluster about the degenerated motor cells.

The pathologic changes involve the entire nervous system as well as other parts of the body. Courtney (23)

says that, "Chronic lethargic encephalitis is a systemic toxemia of which the resultant brain inflammation is the most striking and most dangerous expression."

The changes are both parenchymatous and interstitial, the former principally involving the cortex, and the later the peduncles, internal capsule, lower pons, bulb, and cord. In the basal ganglia and mid-brain both parenchymatous and interstitial changes are pronounced. The pathology more closely resembles that of African sleeping sickness caused by *Trypanosoma gambiense* than that of acute anterior poliomyelitis or traumatic or experimental encephalitis. (11)

The possibilities for outcome of the acute disease may be listed as follows: (31)

1. Acute encephalitis with fatal outcome,
2. Acute encephalitis with more or less complete remission followed eventually by the development of a chronic phase of the disease,
3. Acute encephalitis merging imperceptibly with the chronic phase without any definite remission,
4. Acute encephalitis followed by more or less complete recovery without any subsequent symptoms. This is probably very rare in cases where the diagnosis is undoubtedly

encephalitis type "A".

Other possibilities are:

1. Subacute encephalitis slowly becoming chronic,
2. Chronic epidemic encephalitis without any discoverable evidence of an acute phase.

The prognosis is given by Ford (31) as follows:

"It is usually stated that the mortality during the acute stages of the disease varies between twenty and forty per cent, but it is probable that these figures are too high, since many abortive cases are not included. The mortality varies within wide limits in various epidemics. Among those who survive the acute stage, many if not most make a complete recovery for a time. The ultimate outlook for these patients is still not entirely clear. The earlier reports were optimistic and stated that a large number of these patients remained well, but more recent articles are rather gloomy, for year by year the incidence of parkinsonism and other late symptoms increases. The writer has seen such symptoms develop after a remission of ten years' duration, so a long period of observation is required to be sure that late symptoms will not develop. A recent follow-up of patients who were thought to have acute encephalitis during the years 1919 and 1920,

revealed that those in whose cases the diagnosis was well established were almost all dead or helpless, and that the incidence of complete recovery was highest in those in whom the clinical picture was atypical and the diagnosis doubtful. One gains the impression, therefore, that if we exclude errors in diagnosis, the outlook of continued good health in epidemic encephalitis, type "A", is very bad indeed. This is of course only the writer's opinion and is not shared by all authorities."

While parkinsonism is the most common of the late symptom groups we will list here others which may occur. As we will see later, any one or more of these may occur in conjunction with parkinsonism but they may occur without it: (31)

1. The myoclonic movements which are so typical of the acute stages of the disease may persist for a number of years afterward.
2. Choreiform movements may also persist for years.
3. Bradykinesias--slow movements of large amplitude occurring at a rate of fifteen to twenty per minute and almost rhythmical.
4. Dystonic syndromes such as torticollis,

rotations of hips or shoulders, retraction of the head, and holding the mouth widely open. These are most apt to occur in children.

5. Tic-like movements.

6. Oculogyric crises. As we will see later, this is very common with parkinsonism, but may occur separately. The attacks may come several times a day. At the onset of the attack there is usually a fixed stare for a few minutes. Then the patient's eyes roll upward or upward and to one side, and are fixed in that position by a strong muscular spasm. By a strong effort he can often move the eyes down to a horizontal plane for a moment, but this cannot be maintained for long. As we will see later, various emotional reactions usually accompany these attacks.

7. Paroxysmal disturbances of respiration. These will also be more fully discussed later since they sometimes accompany parkinsonism.

8. Paralysis of extremities.

9. Progressive muscular atrophy and amyotrophic lateral sclerosis.

10. Disturbances of sensibility, usually numbness and paresthesias. Anesthesias occur but are rare.

11. Various disturbances of the autonomic system

such as seborrhea of extraordinary intensity, excessive salivation, hyperhydrosis, local edemas, cyanosis, and vasomotor disturbances.

12. Disturbances of metabolism such as obesity, failure of genital development in children, precocious puberty with unrestrained eroticism, and states resembling thyrotoxicosis with exophthalmos, loss of weight, tremor, hyperhydrosis, and intense restlessness.

13. Mental disturbances, especially in children with complete personality change and behavior problems. Such children commit all kinds of sex offenses, lie, steal, commit arson, etc. There is usually a defect in intelligence, especially if the disease develops during infancy.

EPIDEMIC ENCEPHALITIS TYPE "B"

This is an edemic and epidemic encephalitis which resembles epidemic encephalitis tye "A" closely but presents several fairly definite differences, notably an absence of a chronic progressive phase which is so characteristic of von Econom's disease.

The endemic encephalitis of Japan, of which there has been several epidemics, (1912, 1919, and 1929), the "disease" of Australia, and the recent epidemic of encephalitis in St. Louis are considered to be of this type.

The etiological agent has not been isolated but recently many investigators believe they have successfully transmitted it to laboratory animals and that it is a filtrable virus. (13,17,46)

Ford (31) gives the following description of the pathology based on Japanese descriptions: "In general the process is similar to that of epidemic encephalitis type "A". The brain and meninges are congested, and there is a diffuse inflammatory reaction throughout the entire central nervous system. The small blood vessels are surrounded by cuffs of lymphocytes and cellular foci are also found in the parenchyma. There

is a moderate microglia reaction with phagocytosis of broken down lipoid products. The inflammatory process is apparently most intense in the basal ganglia of the forebrain and in the midbrain, but is said to be more diffuse and more acute than that of encephalitis type "A". Cortical lesions are relatively severe. The extensive destruction of neurons in the substantia nigra, which is so characteristic of von Economo's disease, is not found and this fact probably explains the absence of the severe sequelae which are characteristic of that disease."

McCordock et al (56) report the following findings in a series of post mortem examinations of patients who died during the St. Louis epidemic:

1. The meninges showed more intense infiltration with monocuclear cells than usually was found in the lethargic type;
2. Degenerative changes in the nerve cells were more frequent and neuronophagia was more marked;
3. The inflammatory foci were more widespread throughout the brain, often occurring in great numbers in the cerebral cortex, and were not restricted to the midbrain or basal nuclei;
4. The cranial nerve nuclei, especially the third, rarely showed degenerative changes such as are

frequent in the von Economo type;

5. There was more extensive involvement of the spinal cord in the St. Louis type;

6. Pathologic changes resemble closely those found in Japanese type "B" encephalitis.

The onset may be sudden or gradual. Generally there are mild prodromal symptoms such as slight fever, headache, pains in the extremities, symptoms of upper respiratory infection or G-I symptoms.

Then the fever rapidly rises and restlessness, delirium, and stupor or coma develop. There are almost always signs of meningeal irritation. Generalized muscular rigidity and tremors and twitchings of groups of muscles are common. Oculomotor palsies are rare. Tendon reflexes are usually increased early and later become diminished. Abdominal reflexes were usually absent in the St. Louis epidemic. If the patient does not die during the first two weeks from pneumonia, nephritis, hyperpyrexia, or respiratory paralysis, rapid improvement may be expected. There is no characteristic temperature curve.

The red count is unchanged; the white count varies between 10,000 and 35,000. This leukocytosis is polymorphonuclear. The spinal fluid pressure is increased and the cell count varies between 300 and

1,000 lymphocytes. Protein and globulin are slightly increased and sugar is normal.

The mortality in St. Louis was about twenty per cent, while in Japan it ranged from thirty to seventy per cent.

Sequelae are mild and rare. It is doubtful if parkinsonism ever develops following encephalitis type "B". Hemiplegia, reduction of memory, personality changes, deafness, disturbances in speech, headache, and vertigo have been described as sequelae. (31)

THE PARKINSONIAN SYNDROME

Clinical Description

The onset is invariably gradual. In some cases the first symptoms are tremor and muscular rigidity which makes recognition easy, but many cases show other changes months or years before the characteristic parkinsonian tremor or rigidity appear, so that many cases which later proved to be parkinsonism have been at first treated for a variety of other conditions.

In many cases the patient's associates notice a change in him some time before he himself realizes that anything is wrong. The individual's facial expression may change in a manner described as fixed, blank, starey, or expressionless. Motor activities become slower in the field of automatic associated movements such as the swinging of the arms in walking, or the manner in which he sits down on or arises from a chair.

Those who recognize changes in themselves notice that they do not blink as often as they formerly did, that their arms do not swing when they walk, that they feel stiff and awkward, and feel incapable of responding quickly in a motor sense. These symptoms are usually associated with a feeling of weakness and

fatigue. Often they are accompanied by some degree of hypersomnolence, with or without nocturnal insomnia, or sometimes intractable insomnia without a trace of diurnal somnolence. The lingual and throat muscles are often sufficiently hypokinetic to produce conscious dysphagia and accumulation of saliva which drools from the mouth when bending over in the daytime and runs out of the mouth in bed at night. There is probably also an actual increase in the output of saliva due to disturbances of the autonomic nervous system.

In some more rapidly developing cases the first symptom may be tremor, usually occurring at first only when the affected limb is in some certain position, or only while the patient is under some mental or emotional strain. At first it can usually be stopped by voluntary fixation of the involved muscles. When the development of a tremor is the first symptom, it is often followed by a rapid loss of weight, in which case the progress of the disease is apt to be rapid.

Ornstein (65) describes what he calls "parkinsonian fragments" which often appear months or years before a completely developed parkinsonian syndrome is manifest. These are especially apt to occur in patients who have been well for a long time since the

acute encephalitis, or in patients who had such a mild attack that it was not recognized as encephalitis at the time. He lists the following parkinsonian fragments as the most common:

1. Abnormal automatic associated movements.

The most common of these is an automatic flexion of the forearm during walking. It is a slow but steady upward movement of the hand. The patient is usually not conscious of this movement unless he happens to see it, and the tendency of this movement to bring the hand to the region of the genitalia is often quite embarrassing.

Sometimes only the fifth finger is strongly abducted and extended. Such movements may occur only during writing or only during mental activity.

2. Hyperkinetic and tonic manifestations.

The hands or feet may show slow rhythmic movements. The patient is usually unaware of these until someone calls his attention to them. There may be attacks of tonic spasms of the muscles of the extremities, the flexors being affected more often than the extensors. Sometimes the hand will involuntarily grasp an object such as a pen while writing, and the patient is unable to let go quickly. Ornsteen describes a patient who experienced considerable difficulty in driving a car

because he was often unable to release his tight grasp on the steering wheel for some seconds when he wished to shift gears. In some cases, especially children and young adults, there are tic-like movements of the corners of the mouth or slow rolling movements of the lower jaw.

3. Oculogyric crises and blepharospasm.

Oculogyric crises come on usually without warning, although a few patients experience a definite aura, visual, auditory, olfactory, or other sensory disturbances prior to an attack. They are generally tonic and the deviation remains for minutes or hours. Much more rarely they are clonic with the eyeballs moving rapidly upward and downward. Some patients can control the tonic oculogyrations by great effort, bringing the eyes down to a horizontal plane temporarily. However, this effort usually produces severe pain and is often accompanied by a painful blepharospasm which persists until the eyes are allowed to turn upward again. These attacks are often accompanied by vertigo, and in some patients by severe mental and emotional disturbances. Ornsteen reports five cases who committed suicide during one of these attacks.

4. Disorders of the respiratory mechanism.

The most striking of these is an attack of typical Cheyne-Stokes respiration while the patient seems to be in good health. These attacks occur at irregular intervals. The individual may lose consciousness for a short time during the periods of apnea. Other disturbances which may occur are attacks of hyperpnea or bradypnea or a sighing type of respiration. Some patients have various nasopharyngeal and palatal tics resembling habit spasms which cause sniffing, snorting, clearing of nose and/or throat, and the making of various laryngeal sounds. Rarely there are paroxysms of coughing.

5. Postencephalitic dyspituitarism.

Menstrual disturbances are common, the usual disturbance being complete amenorrhea for many months or years. Obesity is another common result, some patients gaining fifty or sixty pounds in a year or less. Seborrhoea facialis is found in most cases, occasionally it is present to a marked degree before other symptoms appear.

6. Miscellaneous parkinsonian fragments are listed as: mental depression, chronic tiredness, loss of initiative, broken sleep, hypochondriacal tendencies, diurnal drowsiness, persistent aching of one limb, vertigo, loss of weight, subjective awareness

of slowing of thought processes, personality and character changes (especially in children), and involuntary opening of the mouth (especially in young adults).

Ornsteen gives a diagnostic triad consisting of three tests for the early recognition of parkinsonism:

1. Note the increased flexion of the interphalangeal joints of one hand so that the thumb and forefinger are brought into apposition while in the opposite hand the finger and thumb have a normal appearance of relaxation while the hands hang by the sides.

2. Have the patient extend his upper extremities foreward with the fingers separated. On the affected side the thumb is not abducted as much as in the less affected extremity and the other fingers are irregularly spaced or closer together than in the opposite hand.

3. Have the patient close his hands before his face and then attempt to rapidly and repeatedly bring the tips of his forefinger and thumb together. In the affected limb the height of the excursion is less than in the other hand, the movement is less eumetric,

and it is liable to become exhausted until it gradually stops, while the other hand continues the movements.

These signs, which indicate an early increase in tonus of the affected limb, are usually positive before other symptoms appear, according to the author.

The symptoms usually begin on one side, and the tremor and rigidity are apt to affect the arm before the leg. The tremor and rigidity gradually spread until almost the entire skeletal musculature is involved. The rate of the tremor is usually four to six times per second. Due to the gradually increasing muscle tonus the head is bent forward, the spine somewhat flexed, the arms tend to become flexed at the elbow and sometimes at the wrist, and the legs become partially flexed at the hip and knee. The ankles are extended so the foot is in the equinus position, and the patient walks on his toes. Due to the rigidity of facial muscles the face shows little expression. The normal wrinkles and folds of the skin are smoothed out, the eyelids rarely blink and the eyes have a peculiar fixed stare. There is usually a marked seborrhea. These peculiarities of the face give it a characteristic appearance known as "mask face".

The skin changes are not confined to the face (73) but tend to involve the entire skin surface. A generalized seborrhea is common but the face and scalp are most severely involved. In a series of cases studied by Rattner (73), all patients had one or more moles, fleshy or pigmented, on the face. Acne vulgaris was common, as was acne rosacea. Hyperhidrosis of the palms and soles was found in most of these cases, and many were troubled with folliculitis and furunculosis.

All motor activities of these patients were slowed up. They often sit for hours without moving, because all motor activity requires a great deal of conscious effort. When they look to one side only, the eyes move while the head usually remains fixed. There is a tendency toward festination of gait when walking, which in some cases is so severe that the patient will fall forward unless someone catches him or he finds some object to lean against. The speech often also shows festination.

Due to the tremor and rigidity passive movements are resisted in a peculiar rhythmical fashion so that the diagnostic sign of "cogwheel" resistance may be elicited. When the muscle is stretched the resistance

varies due to the tremor as if a series of transient waves of increasing and decreasing tonus were occurring.

The tremor is, except in advanced cases, reduced during voluntary motion. Tremor is absent during sleep.

The above symptoms give the basic picture of almost any parkinsonian patient, but each case is different due to the appearance of any one or any combination of the symptoms described under "parkinsonian fragments", and also due to other sequels of encephalitis which may co-exist with parkinsonism. These other syndromes are listed under the sequels of encephalitis type "A", so I will not repeat them here.

An early incompletely developed parkinsonian syndrome may easily be confused with a variety of conditions, but if the "parkinsonian fragments" are remembered and watched for, and Ornsteen's triad of tests applied, the diagnosis can usually be made quite early.

A fully developed postencephalitis parkinsonian syndrome may sometimes be confused with paralysis agitans, but the following points will usually differentiate them. (65,1,5,9,27,55,50,12)

In true paralysis agitans the tremor tends to be slower. In paralysis agitans the tremor tends to be most marked in the fingers giving the characteristic "pill rolling" movement, while in the post-encephalitic parkinsonian states the tremor is usually most marked at the elbow and wrist. Paralysis agitans usually spares the tongue and face, while in the parkinsonian syndrome there is almost always a marked tremor of the tongue and the face is usually more or less involved.

The alterations in reflexes indicating a lesion of the pyramidal fibers which is so characteristic of this syndrome is rare in paralysis agitans. Cranial nerve palsies and mental impairment are seldom seen in paralysis agitans.

Paralysis agitans is more common in men than in women and usually occurs after the age of forty-five, while the postencephalitic condition occurs with equal frequency in both sexes and in most cases before the age of thirty-six. Postencephalitis is generally much more rapidly progressive and more subject to relapses and remissions than is true paralysis agitans.

The increase in salivation which is almost invariably found in postencephalitis is rare in paralysis

agitans.

Pathology

The following is a summary of the autopsy (47) reports of twelve cases of postencephalitic parkinsonism from John Hopkins hospital:

1. The process involves almost all of the central nervous system--cortex, basal ganglia, mid-brain, cerebellum, medulla, and cord, with especial localization in the basal ganglia and midbrain tegmental structures.

2. The process affects the parenchyma primarily and the cell changes are of the severe chronic degenerative sort with cell shrinkage and sclerosis, and also cell dissolution with neuronophagia. There is degeneration of the nerve fibers ranging from swelling of the axons to complete resorption of large areas of white matter.

3. There is some glial increase, mainly about the blood vessels.

4. Calcareous deposits are sometimes found in the walls of the blood vessels that cannot be accounted for on the basis of the age of the patient.

5. A striking feature is the finding of persistent signs of acute and subacute inflammation years after

the acute lethargic encephalitis. These consist of areas of round cell infiltration with plasma cells, lymphocytes, and occasional polymorphonuclear leucocytes. This infiltration is almost exclusively perivascular and involves the whole central nervous system.

6. There are fatty changes in the cells which vary from mere lipoid increase to fatty dystrophy.

7. The most profound degeneration is found in the substantia nigra. Reports of autopsies on true paralysis agitans shows a preponderance of degeneration in the globus pallidus, caudate nucleus, and putamen.

(47,50)

8. This degeneration of the substantia nigra consists of the disappearance of great numbers of the large pigmented cells, destruction of many fibers, a moderate increase in the glial elements with many pigment inclusions, and the presence of pigment masses lying free in the tissues. Some cases in this series were found with the globus pallidum practically intact. Unfortunately this article tells us nothing of the differences, if any, in clinical picture of those patients with an intact globus pallidum and those with this nucleus degenerated.

9. Next in severity of degeneration was the

striatum, (putamen and caudatus), third the globus pallidum, then the cortex, next the midbrain tegmental structures, then the cerebellum and the dentate nucleus of the medulla, and last the cord.

Hassin and Basso (44) say that the lesion in true paralysis agitans is purely degenerative while in the postencephalitic syndrome it is combined degeneration and inflammation. They report a case in which the substantia nigra is almost intact but the other basal nuclei, especially the globus pallidus showed marked degenerative and inflammatory changes. They believe that the globus pallidus and substantia nigra are so much alike histologically and physiologically (43) that injury to either structure will produce the same symptoms. Hunt (50) has still another idea of the functions of these nuclei. In discussing symptoms caused by lesions in the basal ganglia he gives this classification:

1. Lesions in the caudate nucleus and putamen cause athetosis, rigidity, and muscle spasm. (Cecile Vogt's Syndrome)

2. Lesions of the corpus striatum (more extensive) cause Wilson's Syndrome: chorea, athetosis, rigidity, weakness, and tremor.

3. The tremor of paralysis agitans is due to

lesions of the efferent striated system of the corpus striatum, while the rigidity is due to lesions of the pallidal system. Assuming this to be true it is easy to explain why rigidity and tremor do not necessarily parallel each other in either paralysis agitans or postencephalitic parkinsonism.

4. Chorea is due to atrophy of the small ganglion cells of the caudate nucleus and putamen.

In another publication (51) Hunt says that juvenile type of paralysis agitans is due to a progressive atrophy of the globus pallidus.

Prognosis and Treatment

The general attitude as regards prognosis may be summed up in the following paragraph by Carter (19):

"As to treatment, very little is to be expected. The damage has been done, the nerve cells have been destroyed, and I do not see how they can be restored by any sort of treatment."

In spite of the tremendous amount of work that has been done in this field there is at the present time no effective form of treatment from the immunological standpoint (65). Even if an effective immunological treatment for the acute disease is discovered it would probably be of little value in treat-

ing parkinsonism, except possibly in very early cases since the brain tissue has been destroyed and cannot possibly be repaired.

Artificial hyperpyrexia has done more harm than good in most cases (65).

A large number of different kinds of foreign protein therapy have been tried with little success. Recently von Economo (65) has used large quantities of iodine intravenously coupled with fever therapy but this method has had no success in this country.

Location and removal of foci of infection is usually recommended and some authors report remarkable but always temporary improvement.

Recently Fasting (30) has reported some improvement in a limited series of cases using alternately courses of treatment with eight cc. of lactic acid three times a day immediately after meals, followed by a course of ten grams of glutamic acid once a day, both given orally. The improvement was functional and he claims no cures.

Moore (61) recommends injection of thirty cc. of the patient's own blood serum. He gave two to seven injections.

Wigton (84) recommends Fowler's solution or solium cacodylate as a general tonic.

Ornstein (65) recommends:

1. Daily warm bath for thirty minutes followed by ten minutes under water passive and active exercise of the extremities.

2. General massage. He comments that this must be done by a person who knows the difference between medical massage and a rub down.

3. Reeducational postural and associated motor training using conscious control of motor behavior patterns to replace the lost automatic control. This will be more fully discussed under psychiatric treatment.

4. The solanaceous group of drugs (atropine, hyoscine, and stramonium). The dosages he recommends are:

Hyoscine hydrobromide 1/200 grain three times a day increasing as necessary up to 1/50 grain three times a day. If tremor is not controlled by hyoscine alone, one-half grain phenobarbital three times a day may be added.

Atropine sulphate 1/500 grain increasing as necessary to as high as 1/10 grain three times a day.

When after using hyoscine or atropine no more improvement results due to development of excessive

tolerance, switch to stramonium, twenty-three minims of the tincture, or its equivalent in fresh leaves or extract, three times a day increasing to as high as ninety minims three times a day.

Hall (42) reports good results with the Kleemann method of atropine therapy. This method consists of ascertaining the maximal dose of atropine that causes improvement. This is found by a daily graduated increase in dosage. When further increase causes no further benefit it is decreased day by day until symptoms begin to return. A dosage slightly higher than this is chosen as the patient's optimal dose and is used for routine treatment.

The patient should be in bed during the estimation of his optimal dose. Use a solution of atropine sulphate in distilled water either one-half or one-fourth per cent. The solution is given orally.

The first day the total dose is one-half milligrams given in two one-fourth milligram doses morning and evening.

The second day the total dose is increased by one-half milligram to a total of one milligram given in three doses; one-fourth milligram in the morning, one-half milligram at noon, and one-fourth milligram

in the evening.

The third day increase the total again by one-half milligram, making three one-half milligram doses.

Increase the daily dosage by one-half milligram each day as long as any objective or subjective improvement is noticed. Then keep on this maximal dose for a few days and then reduce the dose by one-fourth milligram per day until objective or subjective symptoms return. Then increase the daily dose by one-fourth milligram, divide it into three doses and let the patient get out of bed and continue on this dosage.

Patients who have received this treatment are said to have shown marked improvement. Speech became good in cases in which it was almost an inaudible whisper before treatment. General muscular movements became much more free. The sialorrhoea was controlled. Oculogyric crises were reduced in number and severity and the tremor was reduced in most cases. Most of the patients expressed a subjective sense of increased well being.

In using hyoscine or scopolomine the same procedure should be used to determine dosage. With scopolomine if sialorrhoea is still troublesome add 1/10 grain

pilocarpine nitrate three times a day.

The mode of action of the atropine group of drugs in parkinsonism is obscure. They are depressors of the parasympathetic system since they inhibit salivary secretion and inhibit the action of the parasympathetic vagus nerve. They also decrease sweating which, according to most authorities, is controlled by the sympathetics rather than the parasympathetics. They also have an action on the central nervous system: a short period of stimulation followed by depression and a longer period of depression than atropine. Stramonium contains both atropine and hyoscine and a group of other alkaloids about which little is known.

Postural tone is said by many physiologists to be due to impulses passing down the sympathetics to the skeletal muscles, although anatomists are unable to find any definite evidence of this. If this is true the inhibition of these impulses by atropine and similar drugs may account for the decrease in rigidity that treatment with these drugs produces. Atropine also has a central action which is obscure. The hypertonicity of parkinsonism is probably due to destruction of areas which normally inhibit lower centers concerned with muscle tone. Atropine may

furnish these lower centers with the inhibition which has been lost by this destruction.

Marshall (59) reports definite improvement in all of a series of nine cases which he treated in the dispensary of the medical college at Northwestern University without the use of drugs. Some of these had been on drugs of the atropine group but they were taken entirely off drugs for the experiment.

The work was done on the theory that the patients lose self-confidence due to their inability to effect the ordinary movements which are ordinarily accomplished in the course of a day's routine. Therefore the patient considers himself a cripple and acts accordingly.

They were treated with psychotherapy, relaxation, physiotherapy, and occupational therapy. The psychotherapy was carried on along psychoanalytic lines. Physiotherapy was similar to that used by Ornstein (65) which has been previously described. Patients were taught how to relax. Then they were shown the movements that normal people use in such actions as walking, and taught to imitate them. Movies were used to measure progress and to encourage the patients.

The author believes that the mental catharsis he was able to give these patients was responsible

for most of their improvement.

He claims no success in treating oculo-gyric crises but claims to have reduced tremor and rigidity and reeducated patients in walking and other motor acts which are ordinarily automatic. He controlled festination of gait in one patient.

Parkinsonian patients certainly should not be treated in the ordinary state and municipal psychiatric hospitals as is far too often attempted at present. Most, if not all, Parkinsonian cases show a mental slowing, although this does not necessarily depend on the severity of the Parkinsonism. However, careful psychometric examinations have failed to demonstrate a presence of any real intelligence defect. von Economo has emphasized this observation in his latest publication on encephalitis lethargica and its sequelae (70).

These patients usually show narrowed fields of interest and at times indifference in regard to personal affairs, but they still maintain an effective contact with their families, as well as unimpaired memories, judgment, and orientation. Many physicians fail to appreciate these facts because the appearance of the patient, especially in advanced Parkinsonism,

as well as his reactions and responses may lead one to assume that the patient is an advanced case of dementia.

The reason for admission of most of these patients to state and municipal institutions for the insane is that the family has been told that he has a chronic progressive disease with no hope for a cure. He has become a burden at home and his relatives have lost interest in attempting to please the patient and make him happy. This attitude means neglect of the patient, who, as might be expected, usually becomes despondent on this account. He realizes that he has been in the way and, because he is a burden, he is making his relatives unhappy.

These patients should not be classified as psychotics and consequently should not be kept in institutions for the insane. They have a marked degree of insight and realize the type of institutions they are in. The mere fact that they are in the society of other persons who show psychotic manifestations that they themselves can recognize, gives them anxiety and makes it exceedingly difficult to attempt the type of psychological treatment which will produce the best results. These patients are frequently admitted

to the acute neurological wards only to be transferred to the chronic wards. They realize that they have been labeled as incurables, that they are detained in an institution for the insane, as one of them, which places them in a poor state of mind for psycho-therapy.

The most satisfactory results are obtained when individual attention is given to the patient, not only from a medicinal point of view, but from every angle, including regulating daily routine, outlining diet, and planning activities both as to recreational and occupational therapy. He must realize that he is a patient and not merely an inmate or boarder. It is often valuable to arrange competitive games in the form of tournaments of checkers or card games, as these patients are capable of entering in competitive enterprises, and it gives them a pleasant diversion to keep their minds off their troubles.

The general physical condition must be carefully watched; the care of the teeth is especially important and is apt to be neglected. Since the basal metabolic rate is low, in many cases infections produce a greater drain upon the system than they would in a normal individual, so foci of infection should be

carefully watched for and removed when found. The weight should be recorded regularly and the diet regulated accordingly. It is necessary to watch the fluid intake of many of these patients, since even the effort of eating and drinking is too great for some.

Perkins (70) in a recent article in the N.Y. State Medical Journal makes an appeal to the state to build an institution to be used exclusively for the care and treatment of post-encephalitic Parkinsonism. He says that an institution of this sort would also provide a much needed opportunity for investigation and research in this disease.

In conclusion, the treatment of this syndrome is characterized by its inefficiency and is entirely symptomatic. All we can hope to do is to make the last months or years of these patients more comfortable and pleasant by the use of drugs, physiotherapy, and psychotherapy and prolong the usefulness of the individual in some cases which we see early in the course of this progressive disease.

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