THE EVOLUTION AND TREATMENT OF PARKINSONISM.

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INTRODUCTION.

Parkinsonism as a clinical entity is well known to the profession, but the ramifications of the various syndromes which go to make up the complete picture, are perhaps not so well known. In addition to this the extra-pyramidal motor system, the minute anatomy and complete function of which are not yet fully understood, is an entity which might be more fully explained in the text-books of medicine. The average medical student knows extremely little of the extra-pyramidal motor pathway, and still less of the syndromes caused by disease of its structure.

The habit of calling a clinical syndrome a disease, is one which unfortunately still persists in the profession and especially is this unfortunate when the name of some investigator is added to it. Undoubtedly Parkinson, as will be explained later, was the first to set out clearly the signs and symptoms of the Shaking Palsy, which to-day is only a part of the whole of Parkinsonism, but that is no reason why the syndrome should be called Parkinson's disease. This is especially so, when after the epidemics of encephalitis in the earlier part of the century, a new syndrome was recognised, clearly in some ways resembling Paralysis Agitans, but only superficially so. This resemblance, striking at first sight, it is true, is found to be much less striking on looking more closely.

It is therefore the intention of the writer to describe first of all the signs of Paralysis Agitans, and then the syndrome which follows Epidemic Encephalitis. The causation and pathology of both will be described and then the treatment. The treatment of necessity takes up much more space than it probably deserves, because it is perhaps true to say that in no other condition has so much work been done, and about which has so much been written, without 'Eureka' being exclaimed. It is untrue and almost sacrilege to say that all this work has been of no avail, but it has strengthened the conviction that treatment is only palliative and will produce no more than symptomatic improvement.

This will, I hope, bear out the importance of clearly differentiating between the various syndromes, and not merely referring to them all as 'Parkinsonism'. It will, of course, be appreciated that in many instances it is extremely difficult to differentiate clinically between the various forms, especially if the patient is over forty, the age above which Paralysis Agitans usually commences, and if there is no history of any acute illness which might be interpreted as encephalitis. Confronted by two cases in which there is tremor, rigidity and a mask-like face, it would be indeed a bold clinician who would venture a diagnosis with no further pointers to guide him.

At the closing years of the last Great War there were epidemics of encephalitis lethargica and again the same may happen. This fact, and also the fact that I have been brought into contact with some cases showing residua from encephalitis following the last Great War, has made me venture to collect the data which is set down in the following pages.

As the subject under consideration is "Parkinsonism" a bold distinction must be made between the two conditions which are grouped together under that title. The Idiopathic type of case will therefore be called Paralysis Agitans or Pre-Senile Parkinsonism, while the late manifestations or residua of Epidemic Encephalitis will be referred to as Post-Encephalitic Parkinsonism. Parkinsonism used by itself in an unqualified state will mean both conditions, unless otherwise specified.

GENERAL CLINICAL DESCRIPTION.

In considering the clinical signs of Parkinsonism it is important to remember that the post-encephalitic type should, properly speaking, be designated by itself and not be included under the same heading as Paralysis Agitans. There is on first sight a distinct resemblance which led the French School to include the post-encephalitic group of symptoms under the heading of Parkinsonism or the Parkinsonian syndrome.

As Paralysis Agitans or Pre-Senile Parkinsonism is the older of the two diseases, it will be considered first and the post-encephalitic later.

Paralysis Agitans was first described in 1817 by James Parkinson, member of the Royal College of Surgeons in "An Essay on the Shaking Palsy".(54) It has therefore been called Parkinson's Disease, in addition to Shaking Palsy or Schüttellahmüng of German writers. In the majority of instances "the symptoms indicated by it are sufficiently prominent to make 'shaking palsy' one of the best names that have been conferred on any disease."(12) Starting in the earlier part of the later part of life, the condition is only rarely seen in patients under the age of forty, although a case in the twenties has been reported. The disease is more commonly found in men than women, Gowers' figures being

men : women; 156 : 78 in his series,[12] but Savill gives the percentage of male cases as 65.[15]

There are four prominent features of the condition, namely tremor, weakness, rigidity and the attitude, but, as the name implies, tremor and weakness are the most prominent of the four. The onset is extremely gradual, the tremor commencing in one hand or arm, accompanied often at the outset by rheumatic-like pains. As Parkinson says, "So slight and nearly imperceptible are the first inroads of this malady, and so extremely slow is its progress, that it rarely happens that the patient can form any recollection of the precise period of its commencement."[54] The tremor usually spreads to the ipso-lateral limb in the same way, very often, as in Parkinsonism consequent upon injury or encephalitis, constituting a hemi-parkinsonism. The rigidity may precede the tremor by several years, and for some time the only feature may be weakness in the affected limb. Paralysis Agitans may be recognised in the absence of tremor. Erb among 183 cases met with 37 cases of Paralysis Agitans sine agitatione.[37] Gradually the tremor spreads, perhaps within twelve months or more appearing in another limb, until it becomes generalised. It sometimes affects the neck and tongue, but seldom the head or eyes, although it is often more marked on one side of the body than the other. Charcot says that for a time it may be limited to one thumb.[27]

The tremor, which is almost invariably more marked in the arms than in the legs, is likened to pill-rolling, cigarette making, or "the movement in the hands may be likened to that by which the Arabs beat their small drums."(12) The tremor is moderate in amplitude, rhythmical and at the rate of five to seven per second. It occurs at rest, an important distinction from that of insular sclerosis, it tends to diminish on voluntary movement and disappears during sleep. The fingers are flexed and in the position of rest, with occasionally an overextension of the terminal phalanges, and the forearm is midway between pronation and supination. The hand as a whole is turned towards the ulnar side and resembles the configuration of the hand in rheumatoid arthritis. The toes have a similar tendency to curl over the sole of the foot.

Weakness accompanies the tremor and the stiffness gradually ensues. The attitude and aspect of the patient become typical. The face assumes a reptilian stare, a "sphinx-like" immobility, but it is not as expressionless as that found in Post-Encephalitic Parkinsonism. Parkinson in his essay made no reference to the facies and the use of the term 'Parkinsonian mask' is therefore rather unfortunate. The skin does not tend to lose its wrinkles in the same way, and, although there may be thickening of the skin, especially of the forehead, it is not as greasy as in the post-encephalitic.

Sialorrhoea is a prominent symptom and there is often saliva dribbling from the corner of the mouth. This is made worse by the fact that the control of the excess saliva is almost impossible by reason of the muscular weakness. The aetiology of the excess salivation is uncertain. It is not known whether it is an excess secretion or whether it is due to infrequent swallowing. The latter is the more probable.

The attitude is one of general flexion, the head appears to be fixed and is bent a little forward; the elbows are flexed and are held in to the sides; the spine is flexed and the knees are brought together by a movement of adduction, and are bent. The patient walks "thrown on to the toes and the fore-part of the feet, being at the same time irresistibly impelled to adopt unwillingly a running pace. In some cases it is found necessary entirely to substitute running for walking: since otherwise the patient in proceeding only a very few paces, would inevitably fall."(54) According to Trousseau, the patient appears in walking to chase his own centre of gravity.(13) The walking of the patient is made all the more strange by the loss of arm swinging, the arms being held rigidly to the sides in the same flexed attitude. If the patient is jostled on his way while walking, he will increase his pace until it becomes more than he can manage and he falls on the ground. This same phenomenon will be observed if the patient is pushed backwards. The gait is

described as 'festinating' and the phenomena as propulsion and retropulsion respectively. At other times the patient will rise from a chair, and intending to go forwards will go backwards, as if put into 'reverse gear' by an unseen hand.

The voice is often shrill and piping, a 'child treble', as pointed out by Buzzard. Sentences are carried out in a monotone, but the speech varies in speed. There is hesitancy in beginning and then an explosive finish, the patient hurrying through the rest. This is vividly in contrast to the scanning speech of insular sclerosis.

There is as a rule great restlessness, a sensory symptom known as akathisia, and a craving for constant change of position because of the feeling of restlessness. Although mental changes are rare, as contrasted with the Parkinsonism following encephalitis, yet the patient suffers from depression and may at times be exceedingly truculent and difficult. This distress is occasioned by "the restlessness which knows no relief, the continued discomfort, the fatigue which sleep only relieves and the depression by the consciousness of a malady which is found, only too soon, to resist every effort to lessen or arrest it."(12) There may be loss of memory, extreme irritability and a varying degree of senile dementia, especially in the later stages of the disease, but these might well be found in any person of the same age, not

subject to the shaking palsy. The occurrence of the associated failure of mind is not difficult to understand if we conceive the process to be a senile degeneration of the cortex: yet it is the occasion for many mistakes in diagnosis, especially in cases in which there is little tremor, and rigidity or muscular weakness are the chief symptoms.

Subjective sensations of heat without any obvious flushing may be complained of by the patient, and it may be present with a tendency to sweating on any exertion or external warmth. The sensation of heat may be a generalised or local phenomenon and may be present on one side of the body only. Charcot found an actual increase in surface temperature, up to as much as 6 degrees Fahrenheit, associated with that sense of alteration in temperature.(13) In other instances the patient complains continually of cold. Electrical reactions of the muscles affected elicit the fact that there is no hyperexcitability to faradism, in contra-distinction to that in hemiplegia.(71)

Clinical examination of the nervous system may reveal some increase in the deep reflexes, with clonus, but as a rule there is nothing of note. The clinical findings are dwarfed beside the subjective symptomatology.

Turning now to the consideration of the clinical signs in the Parkinsonism following encephalitis, the problem is found to be one of greater dimensions. It occurs as a residue or after-effect of encephalitis,(66) or some refer to it as the chronic stage of the disease and include in this all the later manifestations in the same way as we speak of the secondary and tertiary stages of syphilis. This stage of the disease may come on immediately after the acute attack and even some features of the acute attack may be superimposed on the chronic.(40)

The syndrome is noted for its incompleteness and as has been pointed out elsewhere, the clinical picture often contains nothing that Parkinson described, which makes one doubt the wisdom of including this condition under the same heading as Paralysis Agitans. In striking contrast to the generalised distribution of Paralysis Agitans, Post-Encephalitic Parkinsonism may show the complete syndrome or on the other hand, one hand may be affected and perhaps in the same subject there may be a slight residual paralysis of one eye muscle, but of all the residua of the acute disease, the most frequent is the strange clinical picture whose resemblance to Paralysis Agitans of advanced age is, in some respects, so close.

The percentage of cases of Parkinsonism following each epidemic of encephalitis has in the past varied according to some observers. Thus according to Sicard,[41] the 1916-1917 outbreak was non-Parkinsonian, that of 1918 but slightly so, 1919 highly Parkinsonian, and 1920 non-Parkinsonian, but the percentage of cases of encephalitis showing residua of some form or another has been remarkably high, estimated by some at roughly one quarter, but Parsons found residua in 40 per cent of the 3,000 cases followed up.[52][69] 541 cases of the so-called Parkinsonian syndrome following encephalitis were reported to the Ministry of Health in 1919; 1025 in 1923 and 4605 in 1924.[37]

The resemblance of the syndrome to Paralysis Agitans is in some ways remarkably close, but although that is so, the differences are many also, and of the signs and symptoms to be described, only occasionally are they all seen in the one case. The most common of the signs is the immobile face. It is staring, mask-like, and expressionless, although not quite completely so, as the lingering smile of Parkinsonism is well known. There is a loss of the natural wrinkling of the skin of the face and this adds to the staring expression. The skin itself is greasy and there may be localised sweating of the skin of the forehead. There is infrequent blinking, ocular fixity and a loss or impairment of the power of ocular convergence. The mouth may be partially open and

there is sialorrhoea, usually much more marked than in Paralysis Agitans. Although opinion on this subject seems to differ, my experience, and the opinion of most of those to whom I have spoken, seems to be that excess salivation is much more common in Post-Encephalitic Parkinsonism. Voluntary movements of the face are weak and ill-sustained and voluntary retraction of the orbicularis oculi causes tremor of the eyelids. Retraction of the lips is feeble and the naso-labial furrows are poorly marked.

Tremor is much less prominent, and may be absent altogether, and for this reason Charcot found fault with the use of the term Paralysis Agitans to describe the sequelae of encephalitis.(37) When tremor is present it resembles closely that found in its counterpart, and the tremor may occur at rest or in action, or in both, and it may be inhibited by voluntary movement and intensified by emotional upset. The muscular rigidity is however a much more prominent symptom, and in some cases weakness also is much to the fore, but not in all cases, and this is another reason why the term Paralysis Agitans is unsuitable, as the muscular weakness may appear only very late in the disease. Almost any forms of katatonia and perseveration of movement may be met with and action being contemplated it may be half carried out, and then there is an inability to execute completely the movement. The rigidity is of the 'cog-wheel'

variety and the hypertonia differs from that found in pyramidal lesions in that it is equal in opposing groups of muscles and there is this interrupted resistance to passive movements, from which 'cog-wheel' rigidity receives its name. In the hands, abduction of the thumb and fingers is weak and micrographia is a cognate symptom of the condition.(14) The muscular weakness affects the muscles of the face and larynx, and this weakness of the lips, soft palate and tongue all contribute to the slurring inarticulate speech. The immobility of the larynx gives to the voice a monotonous tone. Both articulation and phonation are impaired and in some cases, as in Paralysis Agitans, the voice may be shrill and high-pitched.(16)

In other cases there are varied disorders of respiratory movement. Thoracic expansion is diminished, the chest is fixed in the position of expiration, and the diaphragmatic movements are therefore of necessity increased. Paroxysmal tachypnoea and bradypnoea may come on in attacks lasting from a few minutes to a few hours and these attacks may be so severe as to require confinement of the patient in a mental hospital.(29) In many cases these attacks are looked on as hysterical. There may be a spasmodic cough, explosive, of a dry and violent character and tending to recur in the evening.(11) Breathing may be deep as well as fast and hyper-ventilation tetany may develop. On the other

hand bradypnoea may be as slow as six per minute, the breathing deep, and often noisy and panting. Sighing may occur, with apnoeic pauses and breath-holding, the latter also tending to occur towards evening. It may be very dramatic. The head is thrown back, the limbs placed in grotesque attitudes and consciousness may be lost in the longer attacks. Respiratory tics, such as hiccough, yawning, sniffling and sneezing are usually found in children of school age. These signs are all normally found in subjects affected with some degree of mental derangement.(11)

Excitomotor residua are met with in varying degrees. Bradykinesia is one of the commonest, or as defined by Levy, "slow regular rhythmic movements of great amplitude."(60) The movements exhibit an astonishing rhythmicity and occur regularly so many times a minute. It may be flexing of one thigh and raising of the opposite arm, or any other combination of movements. These excitomotor phenomena are not, strictly speaking, typical of Post-Encephalitic Parkinsonism.

In a considerable number of cases there may be oculogyric spasms - in fact they are found in no other condition. It is a spasmodic conjugate ocular deviation, usually in an upward direction, lasting about half an hour. Any attempt to deviate the eyes to the horizontal causes spasm of the lids. There may be accompanying disorders of the blinking or oculo-palpebral reflex. Normally a person

blinks two or three times a minute, but the Parkinsonian may go on for one or two minutes without blinking. If one places an object suddenly close up to the patient's eyes, the lids are not shut immediately as they would be in a normal person, but instead there is a strong trepidation which lasts as long as the object is held there, probably due to hypertonicity in the opposing groups of muscles.(11) Again the patient may close his eyelids and instead of the eyes opening again, they remain closed for some considerable time and on opening them there is a fluttering of the lids as if there were some resistance to be overcome before this can be accomplished. It is not a marked inconvenience to the patients as a rule, but a case is recorded in which this symptom was the one for which medical advice was sought.

The gait may resemble that found in Paralysis Agitans but an interesting additional phenomenon is that of 'kinesia paradoxa'(14) or an ability on the patient's part to perform movements which require effort, more easily than those which do not. Thus a patient who cannot walk may run with ease and jump with even greater ease. In many instances there may be mirrored movements, - that is, if the patient is asked to execute a movement of one limb, especially on the more affected side, the same movement will be less vigorously carried out on the opposite side.

Enfeeblement is almost a constant sign of the so-called asthenic syndrome which is seen in Post-Encephalitic Parkinsonism but in which the physical signs may be slight. The complaint is of a more or less persistent sense of fatigue, both mental and physical, not as a rule mere inertia, but inertia accompanied by the discomfort of a great weariness. The feeling of weariness may not, like that in myasthenia gravis, be dispelled by sleep and rest. This has been referred to as the 'myasthenic' form of Post-Encephalitic Parkinsonism, but this should not be used, as between it and myasthenia gravis there are many essential clinical distinctions and complete pathological divergence.(29)

The mental symptoms vary from slight change of disposition, apathy and an inability to concentrate, to complete change of character and even in some cases, insanity of an acute or chronic kind. The shrinkage or impoverishment of emotional life may eventually make the patient content to sit about all day in idleness. The unknown poison which causes Post-Encephalitic Parkinsonism affects any part of the central nervous system with an especial predilection for the cranial nerves rather than the spinal part.(22) The area and the extent varies but the disabilities can be divided into 'somatic' as evidenced by Post-Encephalitic Parkinsonism and 'psychical' affecting the mind or morals.(2) Both may appear together. There are mental changes, no matter how slight, in a large

proportion of the cases, and there may be suicidal attempts, impulsive acts of violence against the patient himself, sexual outbreaks and thefts or excessive pugnacity, but the number of cases requiring certification has been proportionately small, in this country at any rate, according to Hall.(11) In children also, the after effects of encephalitis affect both the mental and physical condition, but the mental changes in children may be more outstanding than in adults.(25) The changes vary from complete idiocy to slight mental deficiency. The children in many instances become aggressive, quarrelsome and cruel, may show morbid sexual tendencies and steal, whilst others show suicidal or even homicidal tendencies. They become completely outwith the control of their parents.(11) Hall's classification in children falls into four types, namely the idiot, Parkinsonian, apache, and naughty child types.(32)

Nocturnal excitement may become a troublesome feature. It is very commonly seen in children, and may also be found in adults. There may be nocturnal insomnia alone or associated with diurnal somnolence - turning night into day.

Adiposity is sometimes a marked feature of the disease,(30) some patients becoming repulsively fat. Hyperidrosis remains in some cases as a residuum from the acute stage when it is very common. Again there might be

excessive dryness of the skin suggesting hypothyroidism.(11)

Residual paralyses are uncommon compared, for example, with poliomyelitis. Even the parts most affected by the acute attack may recover completely. The eye is perhaps the most affected by residual paralyses, but even then, although the squint may last for some considerable time after the acute illness, it is only seldom seen as a complication in Post-Encephalitic Parkinsonism. Pains and paraesthesiae of various kinds and in various parts may be seen in the syndrome as a complicating feature, also tics, myoclonic movements especially of the face and torsions of the limbs.(68) The movement known as 'trouser-hitching' is well known and a patient has been described who at regular intervals rose and ran round the room because of a queer feeling in his head.

The clinical picture may be complete or extremely incomplete and it is usually "the combination of symptoms, each of which alone might be pathognomic, which makes the clinical picture recognisable, in spite of its infinite variety."(11)

CAUSATION.

In Idiopathic or Pre-Senile Parkinsonism, the syndrome which was originally described by Parkinson, and which was the only entity to bear his name until twenty or thirty years ago, also called Paralysis Agitans or Shaking Palsy, the illness comes on insidiously, usually in the earlier part of the later part of life. No direct cause can be given for its onset, but various theories have been put forward. The condition may be due to simple arterio-sclerotic changes in the brain, or to a system degeneration similar to that seen in progressive muscular atrophy. It has been suggested that there may be some unknown toxic factor at work, which may be responsible, as in the cases of hepato-lenticular degeneration, where there is an associated cirrhosis of the liver. Prolonged and depressing mental emotion may be a cause,(12) and in support of this theory the tremor of fear, closely allied to mental emotion, has been known to persist and eventually assume the same symptom complex as that of Paralysis Agitans. Therefore it has been said that excessive worry, as in business, may be a causal factor and there is no doubt that the constant tension caused by prolonged trench warfare in the last Great War may have been the deciding factor in many cases, coupled with the fact that many of the men were blown up and even injured on more than

one occasion. Direct heredity in these cases is rare, but there may be an inherited influence, and the patients often belong to families where there are, or have been, other nervous disorders.

Syphilis, alcohol and sexual excesses do not seem to enter into the aetiology,(52) although Walker reports that it may follow Syphilis.(43)

It is an established fact that Parkinsonism may follow trauma, not only to the skull, but also in the limb or limbs subjected to the trauma. This syndrome was described by Faure-Beaulieu and it presents the following features. There is a definite time lag between the original injury and the onset of the tremor. Between these times the injured limb remains weak, painful and paraesthetic. The tremor and the rigidity begin in the affected limb and then, as often happens in the post-encephalitic type, the syndrome extends to the other limb on the injured side, thus constituting a hemi-parkinsonism. There are never any accompanying mental symptoms.(1) It should be noted, as was stated above with relation to the persistence of the tremor of sudden alarm, that this may be the mechanism for the onset of Parkinsonian tremor after injury, but it much more frequently follows trauma to the arm than to the leg.(12)

Cases of Parkinsonism coming on after pregnancy have been reported, although it must be pointed out that there

had been a previous acute attack of Encephalitis, but that the onset of Parkinsonian symptoms had coincided with a pregnancy, suggesting that the pregnancy had acted as a trigger or hair spring for the commencement of the sequelae. Meyer(42) reported a case where a woman had an acute attack of encephalitis in February 1920 with an apparent complete recovery. One year later she became pregnant and lethargy occurred for two months. About the six month, symptoms of Parkinsonism followed. A normal child was born at full time, and for a week after, all her symptoms cleared up, only to be followed by a much increased return, auggesting a recrudescence of the disease.(11) Levy records a similar case with a Post-Encephalitic Parkinsonian syndrome coinciding with a pregnancy, two years after the acute attack. The child need not be infected in utero or afterwards, but the pregnancy definitely seems to aggravate the existing syndrome.(60)

Exposure to cold, any of the acute diseases and fevers, especially malaria, have been given as causes for the onset of the Pre-Senile Parkinsonian syndrome. Also it may follow poisoning by gold, manganese, cyanide and carbon disulphide,(1) but it is interesting to note that the poisons which cause tremor do not cause the tremor of Pre-Senile Parkinsonism.(12)

Less than 50 per cent of the cases of Parkinsonism are due to a previous attack of Encephalitis Lethargica, and most of the cases which are residual, have occurred in childhood. From this one infers that residua may be more likely to follow in a child than in an adult. In a certain proportion of the cases no acute attack can be traced, and there is no evidence even of a febrile illness. These are the so-called "occult" cases and in these some sign of the chronic stage is often the first indication that there is anything wrong with the patient.(5) Young patients showing signs of mental or moral change, and in whom no history of any acute attack can be traced, may belong to this type of "occult" case. The term "chronic epidemic encephalitis" which was almost unknown twenty years ago, now covers a wide and varied selection of cases.(5)

The time lag in these cases between the acute attack and the onset of chronic symptoms varies tremendously. The chronic stage may come on almost immediately, the immobile facies, which is often one of the first signs, being evident within a few days, or in one of Hall's cases,(11) within a fortnight. In one of Buzzard's cases the tremor had begun at the very onset.(11) On the other hand, the delay may be anything up to four years, and "the limit of safety from the residuum cannot be stated."(11) In Young's(58) series the average time lag was seven months, but McAlpine reported

a case in which the interval was 3¾ years.[62] This interval may be one of apparent good health, in which the patient knows nothing of the Sword of Damocles that is hanging over his head. De Lisi, according to Hall, states that in most of the ten cases seen by him the period was one of good health, and in some the evidence of this is surprisingly clear. Thus Renaud writes of a soldier who suffered from Encephalitis in March 1920, a mild attack only. He returned to military duty and in due course he was discharged as fit; he was again called up for duty on the Rhine in the Spring of 1921 and again discharged. In June 1921 he had the complete picture of Post-Encephalitic Parkinsonism. Another case, between the acute attack in January 1920 and the onset of rigidity in his legs in November of the same year, served as a mechanic on board ship, as a cowboy, labourer and a Post Office official.[11]

The severity of the initial attack has no bearing on the severity or quality of the residual symptoms. Some of the worst cases of Encephalitis Lethargica recover completely, while in others most serious and disabling residua have followed a mild attack, or "an almost forgotten slight and transient period of ill health." In every 100 cases of Encephalitis, to quote Hall, 25 die, 25 recover practically completely, while 50 recover with residua of which perhaps 25 have some degree of Post-Encephalitic Parkinsonism.[11]

This is of necessity only a rough approximation to the true figures, but will serve as a rough guide.

The reason for the latent period between the acute attack, whether obvious or not, and the chronic stage is that the virus of Encephalitis does not, like Poliomyelitis, as a rule, cause any permanent damage, and the nerve palsies, choreiform movements, myoclonus, acute nerve pains and profound myasthenia, which are so often present in the acute stage, pass off before the damage which causes the chronic stage has made itself felt.

PATHOLOGY.

Parkinsonism is one of the few common extra-pyramidal syndromes that is available for clinical investigation. The pathology of the Post-Encephalitic type will be dealt with first. There is probably no doubt that it is an affection of the extra-pyramidal motor pathways that we are dealing with, and one in which the cell stations and neuronic pathways play an important part. The first light on the extra-pyramidal motor pathway was shed by Kinnear Wilson in 1912, who then described the disease which is now known by his name.(59) Degeneration of the lenticulo-striate nuclei was found in association with a variety of motor disorders which did not, except by chance, include signs of involvement of the pyramidal tracts. Five or six years later the outbreak of Epidemic Encephalitis provided a fresh and ample supply of material for investigating those problems which centred round the structure and function of the extra-pyramidal system. The mutual relations, as put by one writer, between its constituent parts, instituted through years of evolution are not readily subject to analysis in terms of structure and function, and such generalisations as have acquired currency are based on observations of the spontaneous experiments of disease. The residua of Encephalitis are however dependent also on the pyramidal

motor pathway, for the syndrome disappears in a limb which has been paralysed by a stroke, only to return as the power returns.(17)

The corpus striatum, so called because the fibres of the internal capsule traverse its grey matter and give it a striated appearance, consists of the caudate and lenticular nuclei. The lenticular nucleus is divided into two parts, the putamen, of recent origin, and an inner more ancient part, the globus pallidus. Fibres pass from one to the other and so to the red nucleus and the substantia nigra in the mid brain and once more into the rubrospinal tract, in the extra-pyramidal path, to the motor cells in the anterior horn of the spinal cord.(44)

The pallidal syndrome is that of rigidity and tremor, and that of the putamen, or neostriatal system, choreiform and athetoid movements, as a result of loss of inhibitory impulses from the putamen and globus pallidus. Huntingdon's chorea is supposed to be associated with disease of the putamen and caudate, Wilson's disease with degeneration of the lenticulo-striate system and Post-Encephalitic Parkinsonism with degeneration of the substantia nigra. Some observers maintain that the motor functions of the corpus striatum are complex and others, such as Foerster(8) that the symptoms of its disorders may be much more simply explained. The view expressed above is opposed by Kinnear

Wilson. He considers that a steadying influence is exerted by the corpus striatum by way of the extra-pyramidal path on the innervation of the lower motor neurone from the pyramidal path. "Both the pyramidal and extra-pyramidal paths exert influences on the anterior horn cells, the resultant of these forces passing out along what Sherrington calls the final common path, i.e. the lower motor neurone. If the steadying influences are removed from the final common path, tremor occurs, which is increased by the increase of pyramidal action." This tremor and the rigidity must be closely allied and long ago Hughlings Jackson suggested that there was an intimate relationship between the two. "Tremor is rigidity spread thin, and rigidity is tremor run together."(17)

There is very little in the morbid anatomy of the acute attack of Encephalitis which might cast any light on the causation of the chronic stage. The gross appearances of the brain are in no way characteristic, but it has been noted by some workers that small haemorrhages are very often found in the floor of the fourth ventricle, and in some cases there may be a massive haemorrhage in the cerebrum. The lesions of Post-Encephalitic Parkinsonism, as opposed to the acute attack, are found in the substantia nigra and in the cruri cerebri. There are parenchymatous lesions such as are found in the acute stage and consist of a certain degree of chromatolysis, eccentricity of the nucleus and finally the

disappearance of the cell body. Removal of these damaged cells by phagocytic glial cells is uncommon compared with that in poliomyelitis. Perivascular cuffing of the vessels with lymphocytes is found in the chronic stage and it is a characteristic of the acute stage. These changes, according to Muir, represent not only the damage done in the acute stage, but also that there is a persistence of the virus in the brain. The cerebral and cerebellar cortex escape to a remarkable degree.(18)

No definite organisms have been found on microscopic examination, but small bodies have been demonstrated occurring inside and outside the nerve cells and in the leucocytes. They may be either parasites or tissue elements.(18)

A distinction can be drawn between those cases which came to post-mortem in the acute stage and those which came after a prolonged Post-Encephalitic Parkinsonian illness. The lesions in the long-standing case do not resemble an inflammation, or in other words a process which is still active, nor do they appear to resemble in any way syphilis, tubercle, malaria or trypanosomiasis, all chronic diseases of the central nervous system. Ivy McKenzie considers that because of these facts "it is more likely that the Post-Encephalitic Parkinsonian sequelae are the expression of a disordered function of the whole compendium of reflexes related to the basal nuclei of the cerebrum, mid-brain and

the vestibular apparatus and concerned with the regulation of those phases of automatic posture which make voluntary movement possible." The destruction of the substantia nigra cannot account for all the symptoms, in the same way as the destruction of the anterior cornua of poliomyelitis, or the motor cortex in the hemiplegia of the upper motor neurone variety. There is practically no evidence of any disease of the cerebral cortex, in the red nuclei, or in the anterior cornua of the cord. As is noted by Ivy McKenzie, "it is a Paralysis Agitans without the vegetative disorder and a ketatonia without the stupor."(29)

No special lesions have been found in the organs of internal secretion but there is a gradual accumulation of facts showing that there is an associated multiglandular dysfunction, as well as the lesion of the central nervous system. Adiposity may occur in some cases, and whereas in young people this may be regarded as physiological, in others it is clearly not so. This increase in weight may often be accompanied by other signs of hypophyseal involvement, such as shrinking of the genitals, lack of sexual desire and Barkman records a case in which a male patient's appearance had become quite feminine.(11)

According to various observers, e.g. Ottonello, and Runge and Hagemann(24) there is an indication of an inefficient

liver function, a practically constant feature of the condition. This liver disorder, if it exists, is probably due to the implication of the liver during the acute stage of the disease, in the same way as in any other acute toxaemic condition. In due course the liver function becomes a dysfunction, and this disorder should be borne out by the laevulose tolerance tests for liver function, but according to the work of McCowan and others this is not the case. They carried out the laevulose tolerance test in 16 cases. After a twelve hours fast, 40 gms. of laevulose were given in 8 oz. of water and for two and a half hours blood sugar estimations were done at half hourly intervals. The results of this investigation did not bear out the hepatic inadequacy stressed by the other observers already mentioned.(36)

In the same investigation the blood sugar tolerance tests to glucose were done and the results pointed to there being a definite derangement of carbohydrate metabolism. The curves obtained by taking blood sugar estimations at half hourly intervals for two and a half hours after the ingestion of 50 gms. of glucose in 8 oz. of water fell into three distinct classes. Firstly curves which were normal in shape, but which were followed by a secondary hyperglycaemia. The blood sugar percentages reached their maximum, and fell to the normal level within the usual one and a half hours, but thereafter rose to a considerable height. These curves

resembled normal curves with a reactionary rise, which is sometimes obtained, but not to so great an extent. Secondly, curves which were more or less normal in contour but the maximum level was in most of them high, above 0.2 per cent. These curves resemble those found in hyperthyroidism, but there was apparently no evidence of it in the cases investigated. The third type of curve showed a sustained hyperglycaemia, and resembles that found in melancholia, and in many of these cases there was in fact a melancholic background. The explanation given for these abnormal blood sugar tolerance tests was that they strengthened the feeling that chronic encephalitis is after all a chronic infection, similar to para-syphilis. According to McCowan the majority of cases of Post-Encephalitic Parkinsonism show a hyperglycaemia after glucose ingestion, and this hyperglycaemia is marked in 50 per cent of the cases.(36) These findings have not been corroborated in the present investigation.

The residua of Encephalitis Lethargica have been ascribed to vascular disturbances within the brain and these findings have been confirmed by various authors. Calcification of the brain has been found in cases of Post-Encephalitic Parkinsonism and this change is seen microscopically in the deposition of lime salts in the walls or even the lumen of vessels, and calcareous degeneration of the vascular walls and clots, according to Greenfield.(9) In Durck's cases,

according to Hall,[11] there was no ordinary arterio-sclerosis, but the deposits of lime salts occurred either as (i) incrustations round the ganglion cells, (ii) free flakes in the tissue substance, or (iii) deposits in the vessel walls, the last two being the most common and the most extensive. The calcification of vessels occurred most frequently in the corpus striatum, and in McAlpine's series six cases were seen all with calcification in the brain to some extent, and in all the cases the calcification was limited to the anterior part of the globus pallidus. Three cases of Pre-Senile Paralysis Agitans were examined at the same time as a control and they all showed calcification of the vessels at the anterior part of the globus pallidus. McAlpine in the same communication reports the most constant findings in two cases of Post-Encephalitic Parkinsonism and these findings included subacute inflammatory changes and some recent perivascular haemorrhages. In only one case was there marked degenerative change in the substantia nigra, while in the others this area appeared normal, but in this case there were large haemorrhages of arterio-sclerotic origin in the basal ganglia, and these "considerably modify the negative findings in the substantia nigra."[62]

For the pathogenesis there appear to be two opposing schools of thought, one that the lesion lies in the globus pallidus, this school being represented by the Vogts,[65]

Ramsay Hunt[64] and others, and the other school believe that the lesion is in the substantia nigra,[23][61] and this school is led by Tretiakoff[10] and supported by Pierre Marie. Lhermitte and Cornil,[11] on the other hand, as reported by McAlpine,[62] found alteration in the cells of the substantia nigra in cases other than Paralysis Agitans, i.e. specific combined sclerosis, syringomyelia, cerebral tumour, two cases of complete section of the cervical region of the cord and senile dementia. McAlpine examined the substantia nigra in one of each of the following diseases; myasthenia gravis, cerebral syphilis, subacute combined degeneration of the cord, primary dementia, myotonia atrophica and recurrent cerebral haemorrhage. In none of these cases did he find a diminution of the number of cells, or any depigmentation of any pathological importance.[62]

Turning to Paralysis Agitans we find that the degeneration is very often, although not always, found in the globus pallidus, but it "is not justifiable to regard the disease as purely one of the globus pallidus." Dunlop does not believe there is sufficient evidence to prove that the lesion is one of the corpus striatum[67] and Jakos believes that it is the large cells of the corpus striatum which are mainly affected in Paralysis Agitans.[63] The cause of the degeneration is not known. It may be in the nature of a senile atrophy. Because the condition has

certain features resembling those found in old age, it has been suggested that it is the result of premature senility affecting certain portions of the brain. This may be perfectly feasible, because although our organs age they do not do so uniformly, nor does the same sequence of events follow in two different persons. No special lesions have been found in these cases in the organs of internal secretion.(13)

It is interesting to note that Parkinson, in 1817, in what was probably the first thesis on the disease which now bears his name, gave the supposed proximate cause as "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." He noted that there was complete absence of any injury to the senses and the intellect and concluded "that the morbid state does not extend to the encephalon."(54) This fact remains true today, inasmuch as the subjects of the idiopathic type of Parkinsonism do not show mental changes, apart from those which may affect a subject of that age, in other words, a senile dementia, unconnected with the predominant illness. This disease of the medulla spinalis may, according to Parkinson, be caused by injury to the medulla itself, or "of the theca helping to form the canal in which it is enclosed."(54)

When the Parkinsonism follows injury in the syndrome

described by Faure-Beaulieu, then the condition may be due to a destructive lesion in the basal nuclei, and one theory is that the destructive lesion may be caused by a wave of cerebro-spinal fluid set in motion by the impact or injury.(17) This however is not a satisfactory explanation when one remembers that Parkinsonism may follow injury to a limb, or even to a part of a limb, without injury to the skull or spinal cord. As described under "Causation" the only explanation that can be given for the tremor in a hand or arm of the subject of trauma, is that the tremor is the persistence of the tremor of sudden alarm occasioned by the shock of the original injury.

There is nothing of note found on examination of the cerebro-spinal fluid in these cases.(39)

TREATMENT.

Even in 1817 when Parkinson first described, with the hand of a master, the disease which now bears his name, the chapter on treatment was headed "Considerations respecting the means of cure."(54) Ever since that time means and ways have been tried, without success, to prevent extension of the troublous condition or even relieve it, Parkinson conjectured, apologising for not being more precise, that the disease was dependent on a disordered state of that part of the medulla which is contained in the cervical vertebrae, and although uninformed as to the precise nature of the disease, maintained that it ought not to be considered as one against which "there exists no countervailing remedy."(54) Progress has hardly been made since then, except that we are now more convinced that no countervailing remedy has as yet been found. The patient can be made fairly comfortable, but we are still without the magic potion which will arrest the progress of the disease. As Gowers said, "of all the degenerative lesions of the central nervous system this is the least amenable to therapeutics and the least capable of arrest."(12)

Parkinson wrote that "at whatever period of the disease it might be proposed to attempt a cure, blood should first be taken from the upper part of the neck, unless contra-indicated by any particular circumstance. After which

vesicatories should be applied to the same part, and a purulent discharge obtained by appropriate use of the Sabine liniment; having recourse to the application of a fresh blister, when from the diminution of the discharging surface, pus is not discharged in a sufficient quantity. Should the blisters be found too inconvenient, or a sufficient quantity of discharge not be obtained thereby, an issue of at least an inch and a half in length might be established on each side of the vertebral column, in its superior part. These would be best formed with caustic, and kept open with any proper substance" cork being recommended as it possesses lightness, softness, elasticity and sufficient firmness. It is recommended that the treatment be resorted to early in the disease, as so greater will be the probability of success. The basic idea behind this apparently drastic form of treatment is that by causing such a purulent discharge the thecal ligament, the membranes, or the medulla itself may pass into the state of simple excitement or irritation whicn "may be gradually succeeded by such a local afflux and determination of blood into the minute vessels, as may be terminate in actual but slow inflammation." This then would eventually cause thickening of the structures in the medullary portion of the brain stem and by pressing on the unyielding walls of the spinal canal would "intercept the influence of the brain upon the inferior portion of the

medullary column, and upon the parts on which the nerves of this portion are disposed."(54)

Internal medicines were not considered advisable until more was known about the nature of the disease, but mercury might be tried as it had so often "manifested its power in correcting derangement of structure." Tonic medicines and a highly nutricious diet might be tried, but no good could be expected to follow from them "as the disease is not one consequent upon mere constitutional debility."(54)

A certain Mr Abernethy reported that a disordered action of the bowels might induce a morbid action in a part of the medulla spinalis, but Parkinson was unable to trace the connection "by which a disordered state of the stomach or bowels may induce a morbid action in a part of the medulla spinalis" but there follows a history of such a case in which a man"of temperate habits and regular state of the bowels, became gradually affected with slight numbness and prickling with a feeling of weakness in both arms, accompanied by a sense of fullness about the shoulders, as if produced by the pressure of a strong ligature, and at times a slight trembling of the hands..... Before adopting any other measures, and as there appeared to be no marks of vascular fullness, it was determined to empty the bowels. This was done effectually by moderate doses of calomel, with the occasional help of epsom salts; and in about ten days, by

these means alone, the complaints were entirely removed."(54)

There is very little in the literature about the treatment of Pre-Senile Parkinsonism, but with the advent of the Post-Encephalitic type of Parkinsonism, interest in the treatment of these affections of the extra-pyramidal system was revived. In 1919 Buzzard referred to Post-Encephalitic Parkinsonism as "a new problem." There is no other avenue of treatment in Parkinsonism, Pre-Senile or Post-Encephalitic, other than medicinal, except in so far as one may use psycho-therapeutic measures and re-education, but the condition is without the field of neuro-surgery at the present state of our knowledge of the causes and pathology of the disease, although the lower cervical sympathetic ganglia have been removed if the tremor was particularly troublesome in one arm, but the operation was attended with little success.

The furthest point that has been reached in treatment, in so far that some definite and lasting improvement was obtained with continued use of the drug or drugs, is with the Atropine series. It is especially useful in the relief of the slowness and poverty of movement. The use of this series of alkaloids has been known at least from the beginning of this century, although no actual reference to its first use has been discovered in this investigation. Hyoscine was certainly used in 1910, 4-5 minims of a 1:1,000

solution being given three times a day,[12] and Atropine, Hyoscine and Stramonium have remained the "stand-by" of the physician. Each of the atropine series has its own particular advantages and disadvantages and the high dosage atropine therapy, first advocated by Anna Kleemann[3] in Germany for the Post-Encephalitic type, held sway for some time after its introduction in 1929. Atropine was given in doses of ½ mgm. daily, increasing the dosage until no further subjective improvement ensued. Then the dose was decreased until the subjective symptoms appeared and finally increased to the optimum maximal dose. This was found generally to be in the region of 3-7 mgm. daily and 12-24 mgm. in severe cases. The temporary paralysis of accommodation which ensues can usually be met with glasses or Eserine Sulphate in doses of ½ gr. and the dryness of the mouth was found not to be a contra-indication, nor need the treatment be stopped on account of flushings, palpitation, vertigo or stomach symptoms. Pilocarpine could be given in doses of 1/10 gr. or more for the dryness of the mouth. The same investigator dispersed the idea that hyoscine was an isomer of atropine, as it was formerly thought to be, and noted the fact that it has a pronounced depressant effect on the higher centres.

The high dosage atropine therapy certainly appears to have caused great improvement in the cases in which it was tried, according to Hall,[4] but only in the Post-

Encephalitic. The improvement noted is chiefly in the relief of muscular stiffness and in lessening the excess salivation. Opinion has differed as to whether atropine has any effect on the tremor. Kleemann in her original article asserted that the tremor was not easily controlled, but other investigators have found that the tremor may be considerably lessened in some cases. Oculogyric crises may be lessened in frequency and there may be some measure of control over the various other spasmodic symptoms. If the psychotic disability is the predominant feature of the case, then Hall states that there is not much improvement, but a psychotic disability secondary to Post-Encephalitic Parkinsonism may to a certain extent be relieved by the removal of the Parkinsonism.(4) It is also noted that under no circumstances does the Parkinsonism completely disappear and any lapse of treatment causes an immediate return of the symptoms.

High dosage atropine therapy is not without its dangers and discomforts. Kleemann did not cease treatment because of such discomforts as dryness of the mouth, gastro-intestinal upsets, etc. but these must be remembered if only for the sake of the patient. There may also be slight delirium and mental confusion, and some patients experienced difficulty in starting micturition. Cushny in 1936 noted that hyperthermia may occur during treatment - "Atropine often induces a marked rise in temperature, the cause of

which cannot be said to be definitely known." More than one fatal case of hyperthermia has been reported in Post-Encephalitic Parkinsonism, and according to Sollmann, "Atropine suppresses perspiration and thus causes a rise in temperature with moderate doses, notwithstanding the cutaneous dilatation.....with larger doses a fall of temperature is produced from lessened heat production."(4)

The Bulgarian treatment of Post-Encephalitic Parkinsonism was commenced in 1926 by the Bulgarian plant collector Ivan Raeff.(70) With this form of treatment, which will be described below in detail, the improvement was again much more marked in the Post-Encephalitic type of case. Of 34 patients, all Post-Encephalitic, 50 per cent were markedly improved, while 32 per cent were moderately improved. On the other hand, with the Pre-Senile type, or true Paralysis Agitans, of 18 patients, 17 per cent were markedly improved, and 33 per cent moderately improved. The treatment is symptomatic and must of necessity be continued indefinitely. The only effective component is the Bulgarian belladonna root, and the efficacy of it is decided by the proportion of alkaloids contained in it. There are various methods of extracting the active principle; wine decoction as was used by Raeff; cold extraction with alcohol; and if for economic reasons the alcohol must be omitted, then the cold extraction may be carried out by using an aqueous solution containing tartaric acid and a small amount of salicylic acid as a

preservative. The most effective percentage content of the three alkaloids was found to be 75-79 per cent hyoscyamine, 5-15 per cent atropine, and 1-5 per cent scopolamine. This was made up in an aqueous-alcoholic solution containing 3 mgm. of total alkaloids per c.c. and 66 per cent alcohol. Tablets were also made up and contained 0.5 mgm. of total alkaloids. The maximum clinical result was obtained by a total daily dosage of 2-3 mgms. but the mechanism of the effect on the central nervous system is as yet undetermined.(70)

Nicotine has been tried in the treatment especially of the Post-Encephalitic type of case. Those cases benefiting from nicotine therapy are those where voluntary muscle control is intact but movement is hampered by excessive plastic tone. The nicotine base is used with an initial dose of 1/30th gr. ter die and if there is no appreciable change in the pulse-respiration chart, as tachypnoea is one of the signs of intolerance, then the dose may be increased to 1/10th or even 1/5th of a grain ter die. The immediate results, according to the literature are indisputable. The signs of intolerance, in addition to tachypnoea, are nausea and fainting. During the course of treatment the patient is kept in bed.(20)

Although Hyoscine has been known for some time in the treatment of Paralysis Agitans, it was in 1926 that an article on its use in Post-Encephalitic Parkinsonism was

first published. Blood sugar tolerance tests were done on the Post-Encephalitic patients, and it was found that there were some abnormal curves, and usually the abnormality was a sustained hyperglycaemia. Hyoscine was then given and it was found that hyoscine depresses the blood sugar level, rendering the curve more normal in shape. The improvement noted in the cases was marked and it was said to be due to the specific action of the drug, although there was also undoubtedly an element of suggestion, which must count as a subsidiary factor when analysing the results. The effect of the hyoscine is only temporary and the drug must be given continually, but there are no deleterious effects from long continued use of the drug and apparently no increased tolerance is exhibited.(31)

Stramonium is probably the most used of all the drugs in the armamentarium of the physician today. It is as much used in the Post-Encephalitic as in the Pre-Senile type of case. During the first week 7 minims of the Tincture are given in water, and if no signs of intolerance, increased to 10 minims in the second week. In the fourth or the fifth week the dose may be increased to 15 or 20 minims and by the end of six weeks the optimum dose can usually be decided and is usually between 20 and 30 minims three times a day. The mechanism of the effect of the drug is not known, but the patients find great relief from exhibition of the drug, (50)

especially in its relief of muscular spasm. W. S. Hall stresses the danger of sudden cessation of administration of the drug, and advises starting with small doses, especially if the patient may be unable to swallow, as for example with a tonsillitis.(7) I have never found any ill effects from suddenly stopping the drug, but most of the patients concerned have taken the drug for a considerable number of years.

Whichever of these drugs or preparations is used it is necessary to give it continually in doses which are just enough to produce toxic symptoms, and it is a general experience "that Hyoscine is probably the most satisfactory member of the series in Paralysis Agitans and Stramonium in Post-Encephalitic Parkinsonism."(19)

It should be noted that Phenobarbital is contra-indicated in Parkinsonism. An article published in 1937(53) showed that a patient who was given Phenobarbital instead of Hyoscine, by mistake, developed such a marked degree of rigidity as to become completely bedridden, so "that the body could be moved as if made of one block." Immediately the drug was stopped the patient returned to his original state. The Phenobarbital was administered in three other cases with the same dramatic results. Barbiturates are frequently referred to as brain stem hypnotics but their predilection for this part of the brain still remains a matter for controversy. It is however undoubtedly a fact

that the administration of Phenobarbitone and probably other members of the barbiturate family is contra-indicated in Parkinsonism. Phenobarbitone by reason of its action on the brain stem, probably increases certain types of rigidity, and this may partly explain its action in Parkinsonism.

Working with the knowledge that cases of General Paralysis of the Insane can be improved with malarial therapy, Craig(38) in 1927 inoculated six cases of Post-Encephalitic Parkinsonism with the anopheles direct, the anopheles all known to be infected with a certain strain of tertian malaria, benign in nature. The aim to be reached in the therapy was to have nine rigors, a temperature of 105 degrees Fahrenheit or over being considered adequate. Tepid sponging was instituted at that temperature and the temperature was taken every quarter of an hour to make sure that the peak had not been missed. At the end of the ninth rigor, the malarial infection was checked by the exhibition of quinine. In these six cases, whose blood sugar tolerance tests were all within normal limits except one, some temporary improvement was noted in all, especially in the salivation, the facial expression, and in the speed of cerebration. Little or no improvement was noted in the exaggerated reflexes, rigidity or the tremor, and a decided difficulty was experienced in the induction of malaria in some of the cases.

At about the same time, McCowan and Cook[26] carried out a similar investigation, giving ten rigors at 104 degrees Fahrenheit or over and examining the blood of each patient every quarter of an hour to control the infection. They found no good result from this form of therapy and noted that it undermined the general health of the patient and necessitated a long convalescence as the poor recuperating powers of the encephalitic are well known. They had no hesitation in "condemning malarial therapy as a thoroughly useless and unjustifiable method of treatment in these cases."

Any improvement which could be noted must of necessity be slight as the damage to the basal nuclei has already been done, but that there was any improvement noted in one of the series investigated means that there is still some activity present in the extension into the mid-brain, and that the invasion or extension is still going on. This form of therapy must be a tremendous strain on the patient and I do not think that the results justify any further trial of this form of therapy.

The most recent addition to the long list of drugs used in the treatment of Parkinsonism is Benzedrine. This drug, which was introduced in 1935 for the treatment of narcolepsy, is β-phenylisopropylamine and is adrenaline-like acting on the vegetative nervous system. It paralyses intestinal activity and raises the blood pressure. In some cases it is found to interfere with sleep and it may cause psychological changes. There is no change in the blood sugar

level after the administration of the drug, nor any change in the B. M. R. or impedence angle.(43) The drug has been tested by means of intelligence scores, by giving children columns of figures to add up, before and after administration of the drug. A control was kept by giving another series of children the same figures to add, but they received a similar tablet in shape and size, but containing an inert substance. Two experimental groups showed an increase in the score of approximately 8 per cent but those given inert tablets showed no average alteration in the score after re-testing.(47)

It is known that Benzedrine may cause an increase in the blood-pressure and other effects of the drug on the cardio-vascular system have been noted, including the induction of a 4 to 1 heart block in a patient with an apparently stable cardio-vascular system.(48) Because of the vasopressive action of the drug, it is dangerous to use it in a hypertensive patient, but it is by no means a general finding that the drug does cause a rise in the blood-pressure. In 1938, 71 cases of chronic encephalitis from the wards and out-patient department of the Philadelphia General Hospital were treated with Benzedrine.(57) Three of the cases might have been classed as 'Pre-Senile' but it is recognised that the differential diagnosis is frequently extremely difficult to establish. 43 cases were men, and 31 women, and the ages varied from 15 to 68. In sixteen of these cases the blood-pressure was over 130 mm. Hg. at the commencement of treatment and it was at the end of treatment, decreased in ten, unaltered in three,

and increased in only three cases. In 58 of the cases the blood-pressure was less than 130 mm.Hg. at the commencement of treatment and was decreased in eleven, unaffected in four, increased in forty one and vaccillated in two, after the course of treatment was finished.

The dosage varies with the age and the systolic blood-pressure of the patient. The literature stresses the need for careful administration of the drug if there are any signs of hypertension or instability of the cardio-vascular system. For young people with a systolic pressure of 130 mm. Hg. or less, the dose is 60 mgms. daily, given in divided doses of 30 mgms. in the morning at 8 a.m. and a further 30 mgms. at 12 noon. If the drug is given in the late afternoon or in the evening, then there may be a disturbance of sleep. For an adult with a blood-pressure of over 130 mm. Hg. the dose is 40 mgms. daily divided in the same way. Larger amounts of the drug cause so much palpitation, tremor and rise in blood-pressure that the concomitant psychological changes are apt to be destroyed.(56)

The greatest difficulty is experienced in estimating the results of treatment, unless the patient can be relied on to give an accurate estimation of his or her subjective symptoms, but one index of improvement is the number of oculogyric crises which the patient has in a given time before and after the administration of the drug.(49) The results vary, but the most marked improvement is found in

the subjective symptoms. The very fact that the patient is being tried with a new drug may have a marked emotional and psychological effect, and so in most of the investigations which have been carried out, inert tablets were used in some patients as a control. Strong emotion may have an amazing spurt-like effect on the patient, but these spurts are emotionally driven and so of necessity are of short duration. "The improvement in writing and drawing is probably due to the general improvement in the extrapyramidal complex of symptoms and is a more accurate index of the degree of tremor and rigidity, and even the loss of habit movements, than the usual methods of estimating them." The degree of severity of each case also requires some standard, apart from the number of oculogyric crises, and in the Philadelphia General Hospital for this were used the strength of the grip, as measured by the dynamometer, the state of the handwriting and by taking motion pictures of ambulatory patients.(57)

From a survey of the available evidence it seems probable that there are signs of a definite improvement in the subjective symptoms of the patients treated with Benzedrine, and more so if it is administered with drugs of the Belladonna group. There is a reduction in the number and severity of the oculogyric crises, a decrease in the lethargy, and an increase in the mental alertness of the patient. A sense of well-being also is induced. Many patients have been able to resume responsibilities of which they have been incapable for years. It is a definite fact that treatment by Benzedrine

alone is not as good as that by synergism with stramonium, atropine, hyoscine or Bulgarian belladonna. Davis and Stewart[57] stated in their paper on the controlled investigation of Benzedrine in cases of Post-Encephalitic Parkinsonism that "in a disease respecting neither age nor sex, which marches so gradually and relentlessly to progressive helplessness, a drug which may stay its progress or offer some relief is worthy of trial."[54] The American observers found on an average that approximately 70 per cent of the cases were definitely improved, but British observers in the same type of case found that only approximately 50 per cent were improved, and even that improvement difficult to estimate in some cases. Khan in a correspondence on the subject, stated that he found improvement in practically all his cases with high doses of Stramonium to which Benzedrine Sulphate had been added.

The side-effects of Benzedrine are almost insignificant, although observers have noted a toxic effect on the blood-forming organs in some cases. Some cases have shown excessive sweating, some an increase in their already noticeable restlessness, and insomnia in those who took the drug late in the afternoon. There is no evidence of increased tolerance to long continued use of the drug. The reason for the effect of Benzedrine can be more easily understood when we realise that there is definite evidence in Parkinsonism of an autonomic dysfunction based on hypo-

thalamic lesions. The action of hyoscine, atropine and stramonium is sedative on the parasympathetic side of the autonomic nervous system, although a central brain stem effect must also be considered.(45) Benzedrine is a sympathetic stimulant or more accurately adrenalergic, and so Benzedrine enhances the activity of the drugs which are parasympathetic sedatives.(46) The adrenalergic action of Benzedrine also explains the signs of intolerance to the drug, the adrenalergic reaction being evidenced by tachycardia, insomnia, nausea and vomiting, dilated pupils and hypertension, an increase in the systolic pressure of 25 mm. of Hg. or more.

General treatment includes nervine tonics and Quinine, Arsenic and Strychnine have been tried, also Indian Hemp combined with Arsenic, Strychnine and an eighth of a grain of Cocaine. Bergmann has tried para-thyroid grafts and extract, and Guillain advises tincture of Arnica, beginning with 0.5 gm. daily and increasing to 3 gm. Sicard gave a vaccine prepared from the peduncles and striate region of a human encephalitic, and although some improvement occurred, it has generally proved to be without favourable results. Marie and Poincleux reported favourably on the intrathecal injection of fixed virus of encephalitis, and in four cases out of eight they found definite improvement.(11) Vitamin C has been used in concentrated doses with apparently favourable results.

Adjustment of the environment is important, in the home at first, and later in an institution when this becomes necessary. Baths of various sorts, with games and light occupational therapy may also be tried, and irradiation of the parotids has been advocated for the excess salivation. Many observers have advocated light massage and carefully regulated active or passive movements, while Meyer saw marked improvement when exercises were performed to rhythmic music.(11)

From whatever angle one approaches the treatment of the Parkinsonian syndrome, one is met by the same stone wall. The investigations that have been carried out and the monumental amount of work that has been done on the subject, have so far failed to produce a form of treatment that is curative. The best that can be said is that some drugs, notably those of the atropine series and stramonium, may, if used continually with a little hyoscine, certainly make the patient's life less of a burden, but still in many instances a heavy weight to carry. Nothing can detract from the feeling that it is an evil, from the domination of which there is no prospect of escape. We still have to find the means most appropriate of relieving a tedious and most distressing malady.

DIFFERENTIAL DIAGNOSIS.

Of the group of conditions now known as Parkinsonism, there are two clinical entities so similar that they are grouped together, but yet varying widely in some respects. As has already been pointed out, Parkinson's Disease originally meant Paralysis Agitans but with the advent of the sequelae of Encephalitis Lethargica, the term came to include both conditions. In this transference of the name Parkinsonism, or Parkinsonian syndrome, to include those post-encephalitic cases, one must remember that many of the clinical features in Parkinson's original description in 1817 are not seen in the post-encephalitic cases. The greatest difficulty is often experienced in differentiating the two conditions, especially when no history of an attack of Encephalitis can be found. The differences between the two conditions are well expressed by Hall[11] who states that Post-Encephalitic Parkinsonism is frequently something less than Paralysis Agitans, as in the former tremor is of all the symptoms the least prominent, whereas in the latter, as the name implies, tremor usually dominates the picture sooner or later while there may also be loss of associated and automatic movements, but these are the most prominent in Post-Encephalitic Parkinsonism. Paralysis Agitans is also much more complete in its distribution, whereas as has already been pointed out, the rigidity and slowness of movement may be localised to one limb or even part of a limb in Post-Encephalitic Parkinsonism. Secondly,

Post-Encephalitic Parkinsonism is frequently something more than Paralysis Agitans. Mental changes are common - some have been mentioned, especially with regard to children. The mask face may be seen in Paralysis Agitans but it is never so marked as in Post-Encephalitic Parkinsonism. Sialorrhea is common in the Post-Encephalitic case, but to contradict this Hall reports a case of Paralysis Agitans in which there was a super-added attack of Encephalitis at the age of 76, and loss of the excess salivation which had previously been a marked and disturbing feature of the case. Oculogyric crises are seen only in the Post-Encephalitic case, and, I believe, in no other condition. Recurrent attacks of lethargy, spasmodic fixation of the jaws, explosive laughter or crying, torsion movements, rhythmic 'tics', and repetition or perseveration of movements have all been noted in the Post-Encephalitic case, and are not as a rule seen in Paralysis Agitans.

The mode of onset and the age of onset vary in the two conditions. In many cases of Post-Encephalitic Parkinsonism the first sign is the typical facies, and the immobility of the face may be seen soon after the acute attack. There may also be preceding pain and stiffness in the neck, masticatory disorders and increased salivation, as pointed out by Levy. In Paralysis Agitans on the other hand, the characteristic facies usually arises later and by degrees

and is uncommonly seen as a sudden and initial sign. The age of onset of Paralysis Agitans is usually after the fortieth year, whereas cases have been reported as Post-Encephalitic Parkinsonism as young as eight years, certainly an uncommon occurrence, but cases at the age of the late 'teens were not so uncommon after the large epidemics. Kinnear Wilson recorded an early case in a girl of 17 years of age, and one of Hall's cases was a girl of nineteen.

Various other features distinguish the Post-Encephalitic from the Pre-Senile case. Slowness of movement may become so marked as to make muscular action stop for long periods altogether. A patient may lift a cup intending to put it to his lips and only manage to raise the cup half-way, where it may remain for interminable periods; or, when brushing his hair, lift the brush to his hair and get no further. Food may be put into the mouth and remain there for long periods without being eaten. Raimist, according to Hall, mentions a case in which a piece of bread was allowed to remain in the throat all night and had to be removed with a pair of forceps next morning. These forms of katatonia and perseveration of movements may be extremely varied, and Hall states that the irregular progress of the Parkinsonian syndrome is almost as striking as that of the original disease. On the whole the milder forms tend to remain more stationary than to progress towards the more complete picture, and as the

years pass this fact tends to separate them more and more from the idiopathic type of case. As Hall so aptly states, "the part of the picture which makes some of these Post-Encephalitic Parkinsonians so unlike cases of Paralysis Agitans is difficult to describe, but the case of Paralysis Agitans usually seems overwhelmed by the disease; the Post-Encephalitic Parkinsonian often seems as if he were a man caged."

Tremor is a feature to a more or less degree of the two types of Parkinsonism and this tremor must be differentiated from that which is found for example in Disseminated Sclerosis. In Disseminated Sclerosis the tremor is rhythmical and involves all muscles, including those of the head and tongue. It is the true type of intention tremor and may be distinguished from that of Chorea in that it goes straight to its goal, whereas in Chorea it takes a zig-zag course.(21) The tremor of progressive lenticular degeneration increases on voluntary movement and emotion increases the amplitude of the tremor. Hysterical tremor may simulate any type, and is commonly a part of that diathesis. The tremor of General Paralysis of the Insane is fine, vibratile and affects the lips and tongue usually more than any other part. Its recognition depends to a great extent on the recognition of the typical mental disorder which accompanies the tremor.

Parkinson[54] writes - "unless attention is paid to the circumstances, this disease (Paralysis Agitans) will be confounded with those species of passive tremblings to which the term Shaking Palsies has frequently been applied. These are the tremor tremulentus, the trembling consequent to indulgence in the drinking of spirituous liquors; that which proceeds from the immoderate employment of tea and coffee...." The tremor of chronic alcoholism is one of the most noticeable features of that condition, is especially noticeable in the hands, is small and vibratile, and is usually worst in the mornings. Mercury, lead and zinc, especially in vapour form, not infrequently produce tremor. This type of tremor is small and rhythmical and is seen best when the muscles are in action. It is accompanied to a varying degree by other signs of metallic poisoning. A small fibrillary tremor occurs in various toxaemic conditions, the most notable being the tremor of thyrotoxicosis, and then the other well known signs of that condition will be present to a greater or less degree. Nervous tremor, such as occurs in debility and neurasthenia, and also the tremor of organic nervous disease, such as brain tumour, lateral sclerosis and Friedrich's ataxia must be included in the differential diagnosis of the tremor.

Bilateral cortical degeneration with its slowly increasing rigidity and muscular weakness, but no tremor,

may resemble Paralysis Agitans, but it is accompanied by progressive mental failure, which is not a usual feature of Paralysis Agitans; there may also be an increase of the deep reflexes, sphincter troubles and other evidences of cortical degeneration.

THE NATURAL COURSE OF THE SYNDROME.

In both Post-Encephalitic Parkinsonism and in Paralysis Agitans the condition is a progressive one, although the progression may be very slow in some cases and almost non-existent in others, but to say that the course of Post-Encephalitic Parkinsonism is "not usually progressive" as Boyd does,(17) seems to be incompatible with the facts. Neither condition will necessarily terminate life, and it is generally accepted as true that Paralysis Agitans does not tend materially to shorten life, but this is not true in the case of the Post-Encephalitic type. The very symptoms of the disease tend to make the subject lead a life protected from the dangers and accidents of everyday life and therefore may seem to lengthen his life's span. Chronic diseases do not themselves terminate life, but the part they play is to produce a condition in which some intercurrent malady snaps the thread which has been reduced to extreme tenuity. It is to a certain extent true to say that the progress in the Pre-Senile type of case is normally slower than in the Post-Encephalitic, and that both may suddenly be cut short in their natural progress, but in the latter the final picture is often that of the wasted, bed-ridden patient who eventually dies from a pulmonary complication or from intercurrent disease, but the death is truly one from inanition. Periods

of spontaneous improvement may occur in both conditions, but still the tendency is for gradual downward progression, and the duration may be from two to twenty years, and is, as a rule, only too long. The final picture of striatal disease is one of complete motor helplessness, but there is no true paralysis. Charcot noted that in senile Parkinsonism the tremor ceases entirely a few hours before death.

I can do no better than quote Parkinson in describing the terminal scene as he saw it in Paralysis Agitans. "As the debility increases and the influence of the will over the muscles fades away, the tremulous agitation becomes more vehement. It now seldom leaves him for a moment; but even when exhausted nature seizes a small portion of sleep, the motion becomes so violent as not only to shake the bed-hangings, but even the floor and sashes of the room. The chin is almost immoveably bent down upon the sternum. The slops with which he is attempted to be fed, with the saliva, are continually trickling from the mouth. The power of articulation is lost. The urine and faeces are passed involuntarily; and at last, constant sleepiness, with slight delirium, and other marks of extreme exhaustion, announce the wished-for release."(54)

It is almost true to say that apart from nursing treatment, the course in Parkinsonism is the same whether the patient receives medicinal treatment or not, and

unfortunately, as has been pointed out, so far we know of no drug that will cut short or terminate the condition.

ILLUSTRATIVE CASES.

(Post-Encephalitic Parkinsonism.)

Case 1. H.L.G., aged 51.

In 1924 the patient found that although he thought that he was doing his work as a tailor well, his employer was beginning to ask him if "he had not this or that finished yet?" He was becoming slow in all his movements and imperceptibly so as far as he was concerned. About the same time, as far as the patient can remember, he began to notice some tremor of his hands and legs, but this has never been the predominant symptom. His previous health apart from two attacks of malaria while in the Army in 1916 and 1919, and occasional common colds, had always been good. He can remember no febrile illness or period of ill-health which could be interpreted as an attack of encephalitis.

The mode of onset of the disease was extremely gradual, and gradually he became slower in his movements, the attitude of flexion which he now has assumed being also gradual in its appearance. The spine is arched, the elbows flexed, and the knees bent. The face is that of a much older man, and the expression is fixed and staring, but there are lines on the face and there is no excess greasiness of the skin. A smile is produced slowly and lingers. Hypertonia is marked and there is noticeable cog-wheel rigidity. The gait is not the typical "chasing of the centre of gravity" but mainly because of his poverty of movement and the extreme flexion, he moves about with a chair in front of him to steady him.

Mastication and deglutition are apparently normal, but speech is hesitant and slow and is a good example of the hesitant beginning to the sentence and an explosive finish. Occasionally, too, he may stammer in commencing a sentence. The voice is monotonous and of average pitch. The hands are in the position of radial deviation with the fingers flexed and in the position of rest. There is a fine fibrillary tremor of the intrinsic muscles of the thenar eminence. There are no disorders of respiratory movement.

Tremor as a whole is not marked, but emotional upset and sometimes execution of a finer manoeuvre, such as the lighting of a cigarette, may increase the amplitude of the tremor. Oculogyric spasms occur only rarely, not more than twice or three times a year, and the patient finds them inconvenient only inasmuch as they prevent him reading for the half hour that they last. Tice and myoclonic movements occur occasionally in the lower limbs, especially the left, the power of which is much weaker than the right and this makes the manoeuvre of going upstairs very difficult. Sialorrhoea is not a prominent symptom, but it does occasionally occur, especially if the patient is excited. Sensory symptoms include a burning sensation in the legs and a feeling as if the left leg "were hollow". There are no mental symptoms, and as far as one can ascertain, there never have been.

Reflexes are all increased, but equally on both sides of the body, and no impairment of the sensory apparatus can be elicited. The distribution of the syndrome of Post-Encephalitis is bilateral. The case has recently been complicated by the finding, clinically and radiologically, of a carcinoma of the iliac colon.

Nothing of note was discovered on examination of the heart or lungs, and there was nothing in the urine. Blood pressure was 130/85 mm. Hg. An estimation of the blood-sugar tolerance to ingestion of 50 grammes of Glucose was done and the result was within normal limits.

As far as treatment is concerned, this patient finds most relief from Tincture of Stramonium, 15 minims being given three times a day.

Case 2. A.B., aged 61.

The most noticeable subjective symptom in this patient is tremor, and that was the first symptom complained of when the syndrome commenced in 1919. The mode of onset was gradual and the tremor was first noticed in the left hand, later appearing in the left leg and then in the hand and arm of the opposite side of the body. Stiffness then was noticed, but it has never been marked. The patient always enjoyed good health, and apart from measles as a child, he can remember no other illness, febrile or otherwise.

The attitude of the patient, after just over twenty years, is one of mild flexion which is best seen as the patient is walking, but to see him sitting, the attitude appears normal. The face has a loss of expression and there is slight greasiness of the skin. Wrinkles are present and the patient can produce a most pleasing smile. There is only a very mild degree of rigidity. The gait is shuffling and festinating, and Trousseau's description of "chasing the centre of gravity" is applicable to this case. There is no impairment of the power of ocular convergence and there have never been oculogyric spasms. The powers of mastication and deglutition are unimpaired, although the patient takes a long time to finish a meal. Speech is monotonous, of average speed and pitch, and sometimes hesitant. The patient can write easily and can execute all

the manoeuvres of everyday life as long as he is not hurried. If he is, then the tremor becomes much more noticeable, although it is not of the "intention" type. Thoracic expansion is normal and there are no disorders of respiratory movement. Sialorrhoea is variable in amount, at times being noticeable with saliva trickling from the corner of the mouth, at other times there being no excess. No sensory symptoms have been complained of by the patient, and the distribution is mainly left sided. Mental symptoms are occasionally marked, the patient divesting himself of his clothes and running round the room in small circles.

Reflexes are normal, and there is nothing abnormal to be made out on examination of the heart, lungs or abdomen. Urinalysis yields a negative result, and the Blood pressure is 140/90 mm. Hg.

The blood sugar tolerance curve obtained after the ingestion of 50 grammes of Glucose was within normal limits. Hyoscine was found to be the most effective drug in the alleviation of this patient's symptoms, and he now takes the equivalent of 1/75th of a grain in a mixture three times a day. If the drug is withheld the patient becomes highly excitable and distressed.

Case 3. J.D.E., aged 51.

In 1929 patient found that the power in his right hand was deteriorating, and movements which before were done with ease were now a strain. The left hand then became affected but not to the same extent, and the loss of power was also evident in both legs. The onset was gradual, and, almost imperceptibly, tremor ensued in all four limbs, as far as the patient can remember about six months after the illness commenced. Patient had had pneumonia on three occasions, in 1919, 1924 and 1926. He also received a gun-shot wound of the left thigh in 1917, and blames this as the causal factor for his illness.

Rigidity is marked, and the attitude is one of acute flexion at the upper lumbar region of the spine, and not the more gradual flexion of the spine as seen in other cases. The facial expression is staring and there is a marked furrowing of the brow, giving a "worried" look. A smile can be produced, but with difficulty, and once produced tends to linger. There is loss of conjugate deviation of the eyes, but the pupillary reactions are normal. Mastication and deglutition are normal. Speech is slow, slurred, hesitant and monotonous. The pitch of the voice is average, but is apt to rise to a crescendo if the patient becomes excited or annoyed in any way.

The hands are in the position of radial deviation, with flexion of the wrist and marked hyper-extension of the fingers at the metacarpo-phalangeal and inter-phalangeal joints, and resemble the 'rheumatoid' hand closely. Abduction of the thumb is weak, and the making of a fist is impossible, especially in the right hand. There is no evidence of any abnormality of the movements of respiration.

Tremor is fairly well marked, more so in the hands and arms than in the legs. Emotional upset causes a noticeable increase in the amplitude and velocity of the tremor, and the right side of the body is more affected than the left. Oculogyric spasms are a rarity, and an attack has not been noted for eighteen months or more. Sialorrhoea is a marked feature. Sensory symptoms include noises in the head and ears and patient is liable to have what are best described as 'brain-storms'. These attacks commence with acute 'home-sickness' and then the patient finds fault with someone, be it another patient, an orderly, nurse, or the medical staff. There is a definite persecution mania and everyone has a grudge against him, but the whole attack clears up as suddenly as it commenced.

Reflexes are normal. There is nothing abnormal to be made out on examination of the heart, lungs or abdomen. Urinalysis gave negative findings and the Blood pressure was 150/90 mm. Hg. The blood sugar tolerance curve to the

ingestion of 50 grammes of Glucose was within normal limits.

Patient at his own request does not take any medicine, so the effect of the various drugs has not been tried.

Case 4. J.A., aged 47.

In 1931 patient was confined to bed with a severe attack of Influenza. There was pyrexia and drowsiness, and from the patient's description of the illness there seems to be no doubt that it was an attack of Encephalitis. Immediately after the acute symptoms had cleared up, tremor was noticed in the left leg, and a few days later in the arms and hands. He was excitable and restless, and "his nerves were on edge." The acute stage lasted only fourteen days. The previous history contains nothing of any interest.

The attitude of the patient is now one of mild flexion, but the arms are held in to the sides and the elbows are bent. The back however is almost straight. There is distortion of the face due to a residual right sided facial paresis, (this was proved by inspection of a photograph of the patient before the acute attack). There is a further complicating factor in the loss of vision of the left eye, and a divergent strabismus. The result is that the expression is weird, but there are linear markings and the patient is able to smile quite easily. Rigidity is not marked, and there is no 'cog-wheel' sensation.

The gait is typical of chasing the centre of gravity, and the patient is thrown forward on his toes. Speech is like that of a patient with a cleft palate, but there is no

deficiency of the palate in the patient under consideration. The rate of speech is slow and there is no hesitancy or explosive finish. Movements of the hands are only average, but the patient can write slowly, and can feed himself with little difficulty. Tremor affects the arms and legs, and is, if anything, more marked in the legs. There have been no oculogyric spasms in this case. This fact alone is interesting because, of the whole series of cases, this is the sole one in which a fairly clear cut history of an acute attack of Encephalitis can be obtained, and yet there have been no oculogyric spasms. So, while they may occur only in Post-Encephalitic Parkinsonism, they need not necessarily do so. Sialorrhoea has never been a troublesome feature, and there are no sensory or mental symptoms. Reflexes are normal. There is nothing of note on examination of the heart, lungs or abdomen, and the urine contains no abnormal constituents. Blood pressure is 135/80 mm. Hg. The blood sugar tolerance curve obtained after the ingestion of 50 grammes of Glucose was found to be within normal limits.

Case 5. J.B.S.H., aged 42.

In 1919 patient suffered from an attack of Influenza, and the year previously had been hit on the right parietal region of the skull with the butt of a riding stock, while in a Prisoners of War Camp in Germany. In 1925 the patient noticed that he was going to work as a Railway Fireman, tired and sleepy, and was tending to fall asleep at his work, and 'became a danger to himself and his mates.' The next symptom was that of slurring of the speech, and eventually his speech became so thick that he could not speak at all. Tremor commenced in the right hand about three months after the first symptoms were noticed, and a few days later the tremor appeared in the right leg. About six months later the left hand was affected, but the left leg was spared until about six years ago.

At the present time the patient's attitude is one of mild flexion when sitting, but more acute when walking. The facies is reptilian, smooth skinned and greasy. The mouth is open and saliva drops from the corner of the mouth, but on close examination, it is noticed that the patient swallows about once in two or three minutes, and when reminded about the excess saliva, swallows and the amount of saliva in the mouth is no longer excessive. Hypertonia is marked, more so in the legs than the arms. There is cog-wheel rigidity and extreme hypertonia. There is infrequent

J. B. S. H.

As far as I recollect how my sickness affected me
I was going to work tired and sleepy and falling asleep
on the Job until I became a danger to myself and my mates
then my speech kept on getting thicker and thicker until
I could speak at all and I kept falling all on the floor
then the shivering started, and I grew very bad tempered and
making trouble for my wife and kids, I was then sent to
Christie's Military Hospital Toronto Canada under their observation
I was kept there for three months, they could do no more for me
so I was sent home, then they started giving me Stramonia and the
shivering stopped and once more life became worth living and the
shaking eased up as well in fact it was nearly stopped on my left
hand. In 1932 I sold up and came home to the Old Country just to
see if the change would do me any good but it didn't I rang to
say but I kept taking the stramonia all the while and that kept
me on my feet I lived in England at this time in 1935 I took a bad
turn and the shaking started worse than ever so I decided to go home to
Scotland in 1934 and the Doctor there wouldn't give me the stramonia so
I grew steadily worse and began to lose the power of my arms and they
began to feed me then Doctor Adam of Forres sent me to Edinburgh in
1938 they gave me injections there which helped to steady me a great
deal but still I could not feed myself as there seems to be a nerve
connects the arm to the mouth that won't work together and it is still the
same I then met Doctor Slater of Edinburgh and he recommended me for
the leaf Stramonia and it kept me on my feet but it not kept
the shivering

blinking and tremor of the lids on attempting to close the eyes. The gait is festinating - on his toes and shuffling along - there is no way to express it better than chasing the centre of gravity. The eyes appear beady, and this is perhaps accentuated by the sparseness of his eyelashes. Conjugate deviation is absent, but the pupils react normally to light. The power of swallowing must be weak or else there would be no difficulty in getting rid of the saliva, but this lack of power is not perceptible to the patient. Speech is very difficult to understand, being slurring and very quiet, and the pitch fairly low. The hands are flexed at the metacarpo-phalangeal joints and hyperextended at the inter-phalangeal. The wrist is flexed and the thumb and index finger apposed in the position of 'cigarette rolling'.

Respiration is normal, the range of movement being within normal limits. Tremor is only second to the rigidity. It is more marked in the arms than in the legs, and more marked on the right side than the left. Emotional upset, even speaking to the patient increases the tremor. In spite of this the patient can write fairly well, and a specimen of his hand-writing is attached. There are oculogyric spasms once in every two weeks approximately. No tics, myoclonic movements or torsion spasms.

Sialorrhoea is marked, but more will be said about it in the treatment. No sensory symptoms, but patient

suffers considerably from headaches in the right parietal region of the skull, but X-ray and other investigations, including the examination of the cerebrospinal fluid have proved negative. Reflexes are exaggerated, but there is no clonus.

Treatment which has been most effective is the exhibition of Stramonium and Benzedrine. This is effective in decreasing the salivation, but there is also an increase in the energy output of the patient and the pressing feeling and headache in the right parietal region disappears.

There is nothing of note in the examination of the heart, lungs or abdomen. Blood pressure is 120/80. Urine contains no abnormal constituents.

The blood sugar tolerance obtained after the ingestion of 50 grammes of Glucose was within normal limits.

J. McD.

Case 6. J.McD., aged 43.

With no illness before in his life, that he can remember, the patient began to have shakiness of the left leg in 1923. This tremor followed the usual routine and spread to left arm a few months later. Later the right leg was involved and finally the right arm. Slowness was another noticeable feature and poverty of movement. The tremor, which is the most marked of the symptoms, has gradually increased in intensity and now dominates the picture. As the patient lies on the couch his whole body shakes, although the actual tremor is confined to the arms and legs and is distributed equally. Tremor is the only complaint made by the patient and the rigidity, which is fairly well marked, does not seem to inconvenience him as much as one would have expected.

Flexion is very marked and every time that I see this patient walking, I am reminded of Parkinson's essay - "the propensity to lean forward becomes invincible, and the patient is thereby forced to step on the toes and the fore part of the feet, while the upper part of the body is thrown so far forward as to render it difficult to avoid falling on the face." Only short distances can be accomplished by the patient without assistance, and unless his objective is near, he normally does not venture to change his position,

because he would inevitably fall. The face is not expressionless but there is a loss of the linear markings and there is a tendency to excessive greasiness of the skin of the forehead. Conjugate deviation is lost and there is a marked arcus senilis for a man of 43 years of age. Speech is slow and hesitant, the voice being almost piping in nature. The patient seldom speaks and when he does, seldom goes further than monosyllables.

Sialorrhoea is marked, only when the patient is smoking a cigarette; at other times there seems to be no difficulty in the control of saliva. No sensory symptoms have been noted and no mental symptoms. Reflexes are sluggish.

Stramonium has been found to give the greatest symptomatic relief, and he therefore is given the drug regularly in doses of 30-40 minims of the Tincture three times a day.

The blood sugar tolerance curve was within normal limits.

SURVEY.

From the investigations into the literature it would appear that more emphasis should be laid on distinguishing between the senile and pre-senile forms of Parkinsonism, and the term Parkinson's Disease should be discarded altogether. Strictly speaking, neither the senile nor the pre-senile type are diseases, but rather are they syndromes, and they should be referred to as 'Pre-Senile Parkinsonism' or 'Vascular Parkinsonism' when referring to what we understand as Paralysis Agitans, and 'Post-Encephalitic Parkinsonism' when meaning the syndrome which is a residuum of Encephalitis Lethargica.

The deeper the subject is pursued, the more striking are the differences between the Pre-Senile and Post-Encephalitic syndromes, and therefore the greater reason for the careful naming of them.

Pre-Senile Parkinsonism is, as the name suggests, a syndrome which occurs most commonly in older people, but the exact cause is not clearly understood. Undoubtedly it must be a degenerative process associated with age, whether it be the condition of the arteries, or even the nerve cells themselves. The pallidal syndrome is that of rigidity and tremor, and most probably the lesion in this senile form is situated in the globus pallidus, although this is not the

whole picture, as the tremor must be dependant on the pyramidal system to some extent, as the tremor will disappear in a limb paralysed by a stroke, only to return as the power returns.

Considering treatment, there is no drug, combination of drugs, operational measures, or any other therapy which so far has been found materially to affect the condition to such an extent that one could say that the insidious process had been halted, or even slowed up. The drugs of the atropine series are however definitely palliative, and may bring much subjective relief to the patient. Hyoscine is definitely the most useful drug in the senile type of Parkinsonism.

The post-encephalitic syndrome is due to a previous attack of encephalitis, a virus disease, and probably a filter-passing virus, but one which has not yet been successfully cultivated outside the body. In most cases attempts to transmit the disease to other animals have failed. It may be a type of anterior poliomyelitis, according to some observers, and according to Muir,[18] encephalitis and anterior poliomyelitis are allied, though distinct affections. The proportion of cases of encephalitis which show residual symptoms varies between 25 and 40 per cent. There is a latent period, varying in length, between the acute attack and the onset of Post-Encephalitic Parkinsonism. The ensuing syndrome may simulate Pre-Senile Parkinsonism closely, but in

other cases there is absolutely nothing common to both. Pathologically the lesion is a degenerative one, and is situated in the substantia nigra and in the red nucleus. The pigmented cells of the former may completely disappear.

Treatment is again, unfortunately, merely palliative. 'Prevention is the best cure' and it will be interesting to note in future epidemics, whether early recognition of the acute stage and prompt exhibition of the sulphonamide group will have any effect on the residua of the disease, and whether it may help in preventing the occurrence of the disturbing sequelae.

The blood sugar tolerance curves were investigated in six cases after the ingestion of 50 grammes of Glucose, and estimations of the blood sugar content were done by the method of Hagedorn and Jensen at half-hourly intervals up to two hours. The results do not fit in with those obtained by other workers, but the explanation may be that after fifteen years the chronic toxaemia has become less active and any liver damage that there may have been has been repaired.

It is interesting to note that in six cases of fairly clear cut Post-Encephalitic Parkinsonism, only one can give a history of an illness which could be Epidemic Encephalitis. The remainder must be included in that class of so-called occult cases.

CONCLUSIONS.

Parkinsonism is a syndrome which may be idiopathic in its origin or may follow Epidemic Encephalitis. It may also be seen in a very small percentage of cases after injury, and after certain metallic poisonings.

The main components of the syndrome, namely Paralysis Agitans and Post-Encephalitic Parkinsonism have been described. The causation and pathology have been investigated. The treatment, which is in most cases unavailing, has been mentioned in some detail.

The description of six cases illustrating Post-Encephalitic Parkinsonism has been given. Their blood-sugar tolerance has been examined and found to be normal.

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