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The Treatment of Post Encephalitis

Senior Thesis
N. Richard Miller, B. Sc. in Med.
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Preface:

The purpose of this paper is to discuss the treatment of Post Encephalitic conditions resulting from epidemic lethargic encephalitis, especially emphasizing the use of Datura Stramonium; also a brief summary of Lethargic Encephalitis, and its residuals.

A great part of the neuropsychiatric literature in the past ten years has been taken up by discussions of encephalitis and its calamitous residuals. The etiology at the present date is unknown, and the symptoms are very numerous and variable, which will account for the difference in opinion, as to treatment by many men who have studied these conditions.

Epidemic encyphalitis is probably centuries old, but the first available accurate report was in 1718, when a case was described in England. It became more prevalent on the continent, and from there spread to the United States in 1918, where there has been several epidemics, each of a somewhat different type symptomatically. In New York and some other districts it has become endemic.

Epidemic lethargic encephalitis is an acute inflammation of the brain, possibly toxic in character.

The Etiology is doubtful. No bacteriological evidence of botulism was demonstrated, although during several epidemics a considerable number of persons had recently partaken of sausages, shrimps, lobsters, etc. The spinal fluid is negative for bacteria and chemically. Over one-half of the reported cases occurred in individuals over 20, but some have been reported in children in the first year of life. Since the early epidemics in the United States coincided so closely with those of Influenza, it was thought that the condition was a complication of this disease. However, encephalitis appeared in Europe before the onset of the influenza epidemic. Influenza may be complicated by encephalitis, but this is not of the lethargic type. A more logical conclusion seems that the same environ-

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mental conditions favor an epidemic of both types. The disease has been said, by some authorities, to be caused by a filterable virus, but no convincing evidence is available.

Of late there seems to be an increasing number of cases following vaccination, but to date no definite connection has been established.

The symptoms in many cases closely resemble those caused by the spirochete, the lethargica resembling that of African Sleeping Sickness, and the resulting chronic neurological and mental symptoms resembling those of Tertiary Syphilis. Some men have considered a spirochete as the possible etiological factor, but lack any definite or convincing proof.

In the different epidemics, three distinct types of onset were noticed, each being somewhat peculiar to a definite epidemic. They are: the lethargic, the gastro-intestinal, and the influenzal. Even though the onset varied, there seemed to be no characteristic residual symptoms which followed any of the epidemics.

Many mistakes were made by all in the diagnosis of encephalitis so that when the neurological symptoms appeared months later, it seemed almost impossible to account for them, and only very careful questioning would show the possibility of a mis-diagnosed encephalitis at some previous date. A difficulty of this type can be readily understood when the symptoms of the acute phase are considered. In only one reported epidemic true lethargica occurred, and became increasingly rare in all others until it was seriously considered dropping the name as being unsuitable.

Some of the acute encephalitic cases may go on to complete recovery, but the far greater number acquire post or chronic encephalitic symptoms from a few months to years after to acute attack. It has been estimated by some that this number is anywhere from 70 to 75 per cent. Also, those cases which apparently go on to complete recovery may show some difficulty in school work and a lack of general interest following the attack. Acute encephalitis is on the decline since 1923, but the victims of the condition are beginning to appear in greater numbers.

Post Encephalitis may be defined as a nervous disease, usually of a progressive and chronic character, frequently phasic in its future development, the individual symptoms distinctly indicating the disseminated localization of the morbid process within the central nervous system, and has a pronounced predilection for certain definite areas of the nervous system. One of the chief characteristics of post-encephalitis is a variability in respect to both the grouping of the symptoms and their mode of development, which is by no means inferior to the clinical pictures of nervous diseases due to syphilis or to that of disseminated sclerosis.

There may be an interim from a few months to a few years following the acute stage of encephalitis. During this period the patient may remain comparatively free from all disease. Those without a nervous residue of some type or other are rare; although it may be only that of a slight facial paralysis. An example of a typical case may be given as follows: A child, who at all times has been apparently normal, interested

in his school work, thoughtful of the rights of other people, and well-behaved at home, suddenly begins to play truant from school, loses interest in his work, has violent temper spasms, and even may attempt suicide. Careful investigation most commonly shows that several years previous he had an attack of influenza, from which he made an uneventful recovery as far as could be determined. Later, definite neurological symptoms may develop which show, that, in stead of suffering from influenza the child actually had a mild attack of encephalitis unrecognized at the time; There seems to be no relationship between the severity of the initial attack to the gravity of the nervous or mental condition following.

The characteristic behavior changes are peculiar to children, and actual psychoses rarely develop; but these are of such a type that one would prefer to see actual mental deficiency rather than the maladjustment that develops from conduct that is absolutely incompatible with social adjustment. Such behavior changes are not duplicated by any other known disease, the closest approach being those resulting from cerebral trauma. Behavior difficulties of a lesser degree may develop in lues and chorea, but the diagnosis is seldom difficult to make in these conditions. These behavior difficulties are more commonly found in the types of encephalitis which are characterized by lethargica and oculo-motor symptoms. Our reform schools and other institutions for children are being filled with victims of this insidious disease. They are also forming an ever-increasing percentage of the children which is causing problems in our schools. Our courts are being stampeded by these

individuals, where they are mistreated unobtrusively, as the difference between their behavior, which is due to a disease process, is hard to differentiate from that which is due to maliciousness. It is practically impossible to lay too much stress on the fact that any sudden character change in children of a marked degree should be looked upon with suspicion. It must be remembered that neurological changes may not occur until some months after psychic changes have occurred. Idiocy may develop if the disease occurs before the child is five years of age. The majority of behavior difficulties occur between the ages of five and seventeen.

These behavior changes in children are probably due to the fact that the brain is still immature and the character habits are not yet firmly established. Rarely are there two cases coinciding in their symptoms. The child may be hyperkinetic, and garrulous. His attention may become erratic. There may be uncontrollable outbursts of crying or laughing. There may be irritability, with marked temper tantrums during which there may be attempts at homicide. The use of abusive language and destructiveness are not uncommon. The children may become habitual truants, pilfering and begging. All these symptoms, as in adults, are associated with bradyphrenia, or extreme fatigability of initiative interest and psychomotor activity.

In adults the psychic symptoms are markedly different than those found in children. If any character deterioration occurs in adults, which is found only in rare cases, it usually denotes a previous psychopathic personality aggravated by the disease process. Insomnia and headaches with

drowsiness during the day may occur. A tachycardiac or bradycardia associated with precordial pain may be found.

Neurological symptoms are much easier to recognize, Paralysis or partial paralysis of any of the cranial nerves may be monosymptomatic. Involvement of the facial nerve is the most common.

Parkinsonism is the most marked neurological manifestation. It may emerge almost directly from the febrile state, although it too may follow an afebrile attack or delay several months before its appearance. In parkinsonism there is an increasing hypertonicity of the muscles with the typical facial expression of paralysis agitans. Accompanying there may be such a difficulty in passing from a state of rest to activity that a condition resembling catatonic dementia praecox may result. Automatic movement may occur without difficulty. In contrast to the true paralysis agitans there may be no tremor or if tremor is present it is not accentuated by active movement. Laziness due to stiffening of the muscles must not be confused with bradyphrenia, which is frequently present. Speech difficulty may go on to mutism which disappears in reciting or reading which is more or less automatic. In reality, it appears to be more of a laziness in thought. Spasmodic speech and explosive laughter occur which are not found in true parkinsonism.

There are intermediary neurological types which are less clearly defined and therefore offer considerable difficulty in diagnosis. They are not found as commonly as parkinsonism and only a mention of their existence will be made in this paper. The "Catalepsy" type, or one in which there is a maintained position. There may be involvement of the basil

ganglion and pyramidal tracts which is called the "Pallidopyramidal."

There is a "chorea" type in which the manifestations are wide irregular choreic movements, which may be accompanied by dystonia. The "Ocular" type presents ptosis, orgyll-Robertson pupil, nerve paralysis with nystagmus, and rarely a choked disk. The spinal cord and peripheral nerve lesions in which there are root pains, but no muscular atrophy as in anterior poliomyelitis. In the "Bulbor" type we find increased salivation along with cardiac and respiratory arhythmias. The epidemic of hiccoughing which was prevalent in 1926 and 1927 has been shown to be encephalitic in character. In several cases there were late eye manifestations (paraxysmal rotation of the eye balls) which is known as "Oculo-gyric crises".

¹
Jelliffe reported 200 cases in the literature up to 1929. All of them were most commonly seen in conjunction with a parkinsonian state, although some did not show a parkinson residual of encephalitis. Jelliffe believes that these are organic pathologic changes with over emotional response producing the spasms of the eye.

Before entering in to the phase of treatment, it may be well to say a few words about the diagnosis differential and pathology of parkinsonism. The earliest symptoms may be so slight as to pass unnoticed. Generally however, the patient's appearance, or behavior, arrests attention. He also becomes aware there is something wrong, feels weary, and there is reduction of vigor. There is also usually lethargy or insomnia over various periods of time before the gross physical signs of parkinsonism appear, viz: greasy face, starey eyes, open mouth, fixed expression, sialorrhoea, muscle

rigidity and tremor, muscle palsies, myoclonus and pupillary abnormalities. Of paramount importance is an accurate history, although an acute phase is often associated with one of the epidemic influenza years it is not necessary for making a diagnosis. Such symptoms as neuritis, neuralgia, cutaneous hyperesthesia, or irregular pyrexia, or mental symptoms may precede the development of the parkinsonian state and lead to mistakes in diagnosis. It is necessary to note the totally different characteristics of the manifestations in children, where effects are chiefly in the psychic sphere. (An example of which has already been given in this paper.) This psychic sphere usually disappears when a parkinsonian state develops. In adults physical signs predominate.

Little if any difficulty is experienced in the diagnosis of a well-developed case of parkinsonism. There may, however, be some doubt in very early cases, exacerbations or atypical cases. The following disorders should be differentiated:

Paralysis Agitans -- The mask-like faces of parkinsonism show none of the deep furrowing of the brow that is so prominent a feature of parkinson's disease. The localized distribution of muscular spasm and the "kinesia paradoxa" often found in parkinsonism never occur in paralysis agitans. Tremor rarely predominates the parkinsonian syndrome as it does in paralysis agitans. The tremor in parkinsonism is less marked, and, unlike that of paralysis agitans, occurs as a rule only during voluntary movement or the maintenance of an active posture. In addition the tremor is found elsewhere, giving rise to such signs as shaking of the head, clicking of the teeth, to and fro movements of the tongue, and a rhythmical sucking

action of the lips. There is nothing in paralysis agitans comparable to the metabolic disturbances seen in parkinsonism. In parkinson's mask, the skin of the face has not the thick greasy look that it has in parkinsonism, and it is not associated with sialorrhoea. In parkinsonism the rigidity is more likely to be localized; e.g., one arm, leg, or the face, and the rigidity and loss of associated movements are more accentuated. In parkinsonism there occurs more frequently mental changes, e.g., explosive laughing and crying, or nervous phenomena such as myoclonus. The onset is usually at an earlier age than paralysis agitans, the latter occurring in individuals over forty years of age.

In vascular cerebral lesions one should note unilateral signs, of paralysis, pupillary abnormalities, and coma. In coma following vascular lesions the patient can not be aroused, whereas in epidemic encephalitis the patient can be aroused.

Myasthenia gravis -- In parkinsonism the feebleness is not, as a rule, much diminished by rest. Symptoms resembling myasthenia may come on soon after the acute phase, or a long time after the development of the parkinsonian syndrome. A history of the acute phase, or certain symptoms of the parkinsonian syndrome will aid in the correct diagnosis.

Disseminated sclerosis -- This is diagnosed by absent abdominal reflexes, eye signs (nystagmus), presence of spastic paralysis, ankle clonus, babinski reflex, and pallor of the optic discs. Often, for a time, at least, the diagnosis may be impossible.

Meningitis -- Examination of the spinal fluid and culture of the

organisms, along with high pressure in spinal canal.

Typhoid fever -- Difficulty in diagnosis may arise in the case of children. Accomplished by perusal of the history, blood culture, Widal reaction, and physical examination.

Polio myelitis or Polioencephalitis -- One should note the season of the year, and localizing symptoms. Persistence of paralysis is in favor of infantile paralysis. The cerebral spinal fluid contains polymorphonuclear cells (average 50 - 250) in the early state. The course of the disease is also very valuable in assisting in diagnosis. In poliomyelitis, paralytic symptoms develop their maximum intensity in a few days, whereas in epidemic encephalitis, paralysis occurs after a prolonged course.

Chorea -- The history, time of year, less marked arm movements in epidemic encephalitis, and heart examination will help to clear the diagnosis. Myoclonic, choreic, and athetoid symptoms have been more frequent following the late epidemics and may be related to a gradual attenuation of the virus, or change in the site of the lesion.

Cerebral tumors -- These are easily mistaken for encephalitis. Lethargy is often marked, especially in the frontal lobe tumors. One should look for optic neuritis, projectile vomiting, headache, localized paresis, and Jacksonian epileptic attacks. An X-ray should be taken for all intra-cranial growths.

Cerebral disease -- In this disorder we find characteristic gait, or decomposition of movements, absence of Rombergism, and inability

to execute opposite kinds of movements quickly and regularly.

Acute infectious diseases accompanied by meningismus -- If in doubt, it is best to do a lumbar puncture, in which case the spinal fluid is usually normal. The history, clinical picture, and physical examination will lead to a proper diagnosis.

Appendicitis -- Many cases of epidemic encephalitis have been operated on for appendicitis. A history of myoclonus, associated with, or followed by, pain and cutaneous tenderness, or radicular distribution is in favor of epidemic encephalitis. A history of lethargy and eye signs warns one to be careful.

Neurasthenia -- In parkinsonism the patient does not tend to feel better as the day goes on.

Hysteria -- This may be simulated by forms of encephalitis with respiratory anomalies, such as grunting, hissing, and spitting movements. The effect of urging in hysteria usually increases the disability, whereas in parkinsonism, the reverse is true.

The pathology of all Post Encephalitis residuals, as in Lethargic Encephalitis, is a perivascular round cell infiltration, accompanied by definite evidence of degeneration in the region of the mid-brain, substantia nigra, basal ganglia, pons and medulla, depending on the type of residual one is dealing with. The acuteness of the pathological picture of encephalitis is lacking; but as many authors have state, Post Encephalitis could more properly be called chronic encephalitis, as they believe that the interval between the intial attack and the onset of the

residuals is merely a latent period in the disease. In this respect it has been compared with the latent stages of lues, but all attempts to prove a definite etiologial relationship have failed. Pardee cites several cases in which the encephalitis was supervened on a syphilitic. But no definite evidence out side of a syphilitic vascular accident was present in his article.

It may be well, at this time, to differentiate from a pathological stand point between encephalitic parkinsonism and senile paralysis agitans. There are distinct clinical differences in the two syndroms and their pathological lesions are localized with the greatest intensity in areas of the brain, some what removed from each other. In paralysis agitans the main incidence of neuronc degeneration is in the globes pallidus, while in encephalitic parkinsonism the destructive lesions are most extensive in the substantia nigra.

The short review of the Etiology, Symptomatology, various types, pathology, diagnosis, and differential diagnosis of epidemic encephalitis is by no means complete, but a more detailed account is beyond the scope of this paper.

It might be well, at this time, to discuss briefly the most accepted treatment of epidemic encephalitis. (1) Injection of Normal Horse Serum 20 - 30 c.c. three doses, two days apart. (2) At the same time administration of alkalies to the point of alkalinization. (3) Glucose intravenously or by rectum. (4) Continued rest in bed and removal of any probably focci of infection. There are many modifications and additions to this treatment, but from clinical observation and the results obtained from their use is hardly warranted.

In investigation of different forms of treatment of Post or chronic encephalitis, which are likely to be of some benefit, it soon becomes apparent that no actual curative effect is possible; as the signs and symptoms result almost entirely from neuronal destruction. In such a case all treatment must revolve itself into what is essentially palliative treatment under which the patient has permanently to remain to avoid relapse. Failure to do so by in-cooperative individuals may possibly account for the inconsistent results obtained in many cases. A vast number of remedies were experimented with in the large clinics in both Europe and America, and it is a well known fact that this type of patient is the hardest to convey the importance of remaining on such treatment religiously and also to report regularly to the clinic, so progress can be noted and records accurately kept. This has not been the case in those individuals suffering from post encephalitic residuals, as there is such a marked relief from symptoms when the patient is taking his medicine as directed, and such a sudden relapse as soon as the routine is discontinued, that it rarely takes more than one or two relapses to convince the patient that this is his only opportunity to live a happier and useful life.

The atropine group of alkaloids have been used extensively and have a pronounced effect on these encephalitic residuals. Their pharmacological action in parkinsonism is some what obscure. They are known to act on the para-sympathetic nervous system, giving rise for example to paralysis of the nerve endings of the secretory fibers to salivary glands, also of the fibers to the spluncer papillae and of the vagus nerve. In addition they depress the nerve endings of the secretory fibers to the sweat glands

throughout the body, and as most authorities agree that these fibers originate from the sympathetic nervous system rather than from the parasympathetic, this action would suggest some effect upon the sympathetic nerve-endings. In experimental animals there is evidence of slight depression of ordinary sensory and motor nerves. So one can conclude that this group of alkaloids tends to paralyze all nerve-endings, the effect being most marked upon those of the parasympathetic system. These alkaloids are also known to act centrally, atropine especially, producing a general cerebral stimulation with a subsequent depression. Hyoscine produces only a short stage of stimulation and a more pronounced stage of depression. The action of Hyoscine on nerve-endings is more pronounced but does not last as long. Atropine is composed of equal parts of levo and dextro rotatory hyoscyamine. As the latter is said to be comparatively inactive, the effects of atropine are due to the levo-rotatory hyoscyamine, which is the hyoscine in *Datura Stramonium*, which also contains atropine as well as some unknown alkaloids, which might tend to make it more toxic and less specific. On the other hand it may have effects which atropine or belladonna would not exhibit.

According to the theory of dual innervation of muscle, postural tone is said to be maintained by impulses passing down sympathetic nerve fibers to skeletal muscles. On this hypothesis the tonic excess of muscle tone in parkinsonism suggests an excess of postural tone, which is probably diminished by a depressant action of the atropine group of alkaloids on the sympathetic nerve-endings. To be sure this theory has considerable against it, since some of the distinctive characteristics of parkinsonism are relieved by them, namely bradyphrenia and tremor, and such relief must necess-

arily be central in origin. On the other hand the relief of sialorrhoea is almost certainly due to peripheral action. In parkinsonism the hypertonicity is probably due to destructive lesions involving an area of the brain of which the function is the inhibition of the lower centers concerned with the central origination of postural muscle tone. It has also been suggested that specific palliative effect of the atropine group of alkaloids on parkinsonian rigidity is due to a depression of those centers over which inhibition has been diminished by the disease process.

Before attempting to use any of the above mentioned alkaloids in the treatment of this condition all foci of infection should be taken care of. This should be accomplished by giving the patient a thorough mouth examination, carious teeth are filled or removed if necessary, and pyorrhoea is treated. If the latter is pronounced, extraction is the only sure cure. Usually very noticeable improvement occurs after proper dental treatment, as so many of these patients tend to have foul mouths. The ear, nose, and throat should not be neglected in these cases. The investigations of certain workers leads one to believe that definite improvement follows washing out of the nasal mucous membrane and accessory nasal sinuses. It has been suggested that the infection in epidemic encephalitis is a symbiotic process, and that the portal of entry is through the nasal mucous membrane, damaged by some organism of the catarrhæ group. The etiological them supposedly enters the tissues and reaches the brain, possibly by the peripheral lymphatics, or along the

first division of the Trigeminal nerve, or the branches of the olfactory nerve, and not through the blood stream. On this basis there has been recommended the prolonged daily use of an oil solution to the nasal mucous membrane of an efficient coagulation antiseptic to prevent further infection by the original etiological factor or secondary germs. Any definite pathology should immediately be taken care of in order to eliminate other sources of infection from the ear, nose or throat.

The results obtained from the different methods of treatment used in parkinsonism often varies greatly in apparently identical cases. As a rule this paradoxical result is only apparent for while the cases are superficially alike and are also alike in many respects they differ in others. Postural reflexes show a part of this difference. The Parkinson Syndrome, whether senile or post-encephalitic should be considered a possible combination of three elementary conditions: a bradykenetic, a hypertonic and pyramidal. The bradykenetic condition, i.e., a slowness of movement, was isolated by Cruchet and Verger, as dissimilar as progressive lacunar cerebral sclerosis, senile parkinsonism and post-encephalitic parkinsonism and post-encephalitic parkinsonism. Verger thinks that bradykinesia results from a defect in the automatic function of habit. At the present time there is no drug known that can stimulate this function and only the will can accomplish it by sustained attention in the execution of movements. The hypertonia is due to considerable exaggeration of the postural reflexes. These postural reflexes are mechanisms of arrest that tend to fix attitudes taken. From clinical and physiological studies there has been shown that there are two agents which may overcome the exaggeration of

these reflexes. The first of these agents is active or passive mobilization which tends to decrease the intensity of the postural reflexes for the time being. The second agent is scopolamin which on sugcutaneous injection (one and a fourth milligrams of 1:2000 solution of the hydrobromide) completely abolishes the postural reflexes in about 45 minutes. The postural reflexes are exaggerated by prolonged immobility and inactivity of the muscles, thus leaving a vicious circle: immobility increases the postural reflexes and these reflexes increase the immobility. It becomes imperative to all that this vicious circle must be broken.

5

Delmas-Marsalet in their article published in 1927 recommend a subcutaneous injection of Hyosine hydrobromide, one and a fourth milligrams of 1:2000 solution, to be given on an empty stomach. This dose does no harm, although it may produce a temporary onirism. The hyonine hydrobromide brings about a complete abolition of the postural reflexes, which enables the patient to make rapid movements after about an hour. But as the action of this drug is only temporary, the free period should be utilized to decrease the postural reflexes by voluntary movements. So the patient should be made to get up and walk or work. In this way voluntary movement is substituted for the temporary effect of the hyonine and therefore prolongs the action of the latter. Delmas-Marsalet found that by this procedure the effect of a single injection of hyonine hydrabromide may be prolonged fro 12 to 15 days; at the end of this time the procedure should be repeated, as the postural reflexes return to their original condition. In this way they received the same therapeutic effect that they received from continuous scopolamin treatment which is more complicated

and more harmful. Delmas-Marsalet found that this simplified matters, and that it would be entirely successful if it were not for the third pyramidal factor. The existence of this third factor is shown in some cases of parkinsonism by simple clinical examination, but in others they may be shown by the scopolamin test. An injection of one and one-half milligrams of a 1:2000 solution of hydrobromide of scopolamin makes latent pyramidal symptoms appear as soon as the postural reflexes are abolished. This makes it look as if the pyramidal symptoms were masked by the exaggeration of the postural reflexes; and as soon as the postural reflexes are abolished the pyramidal symptoms become evident. The scopolamin test shows a great variability in the intensity of the pyramidal symptoms. In some cases they are no more than a baninski sign or a little ankle clonus; in others they consist of an initial parkinson contracture. When this is the case the scopolamin only substitutes for a Parkinson contracture a pyramidal contracture which is just as troublesome from the point of view of function. The failure of many patients to improve on scopolamin may be explained by a change in the nature of the contracture.

Before treating a case of Parkinsonism one should determine whether the postural reflexes are exaggerated and then to determine whether there are pyramidal symptoms. After determining this the case can be placed in one of four classes: (1) Simple bradykenitic parkinsonism without exaggeration of the postural reflexes, and without any pyramidal symptoms, even after scopolamin. (2) Cases of bradykenitic parkinsonism with exaggeration of the postural reflexes but without pyramidal signs. (3) Cases of bradykenitic Parkinsonism with exaggeration of the postural

reflexes and pyramidal signs shown by the scopolamin test. (4) Cases of bradykenitic parkinsonism which show pyramidal symptoms spontaneously.

In class one the atropine group of alkaloids have only a slight effect for it does not influence the bradykinesia. In class two the use of these drugs is ideal for they act on the exaggerated postural reflexes. In class three their usefulness must be determined by test, if only slight pyramidal symptoms appear without contracture their use is strongly recommended, but if there is marked pyramidal contracture their therapeutic effect will be greatly decreased. In class four the postural reflexes are abolished or very much decreased, but the pyramidal contracture takes its place, and may cause spasticity that is very harmful, so they should not be used.

These facts explain the variable results of treatment reported by different authors.

6

Chavany recommends the use of scopolamin in the form of the hydrobromide. He gives it subcutaneously in a series of twenty injections. The addition of 5 milligrams of morphine hydrochlorid to 0.3 milligrams of scopolamin increases the action of the scopolamin, but is not advisable in such a long continuous treatment as parkinsonism requires. Chavany reports several cases in which the patients took the drug for months without interruption and without any signs of intolerance in doses varying from 0.5 to 0.6 of a milligram to 0.13 to 0.14 of a milligram. When given subcutaneously the drug produces headache, dryness of the throat, etc., for about an hour. The signs of true intoxication which necessitates stopping the drug are vertigo, prostration, somnolence and vomiting. In case the scopolamin produces too great a

depression Hyoscin may be used. The signs of intolerance are the same as those of Scopolamin. Atropin was tried on several cases. It has a definite effect on the hypertonia and tremor, but it appears to be less active than the above mentioned drugs; although Chavany believe that it is indicated particularly in cases in which there is sialorrhoea. It may be given by mouth, half a milligram of neutral atropin sulphate per tablet 2 to 4 times a day.

7

Blum in his paper published in 1929 strongly favors scopolamin hydrobromide, 5 drops of a 1 per mille solution, three times daily, slowly increasing and decreasing until the individual optimum is reached. In order to avoid intoxication, scopolamin should be given for five days followed by a pause of two days. Blum had little success with atropin, Banisterin or Harmin, and he used opiates only to combat pain. In addition to treatment with scopolamin he used exercises, massage and psychotherapy. With Protien therapy he had little or no success. Eighteen cases were treated with Endolumbar Serotherapy, in eleven of these definite improvement was noticed which lasted for about six months. The serum injected was an auto serum, 10 - 20 c.c. being injected into the lumbar canal after the removal of an equal quantity of cerebral spinal fluid. After the injection the patient must lie down for 24 hours with the pelvis raised. Slight symptoms of meningism may occur, as also temperature. None of these symptoms lasted for more than a week. In none of the eighteen cases was hypersensitiveness to the serum noticed. This injection should be repeated ever 10 to 14 days, four to five injections being made altogether. Blum in his treatment of children used an indi-

vidualized treatment by occupation under supervision. Better results were brought about in an institution than in the child's own home.

8

Adams and Hays in their recent article of last year strongly emphasize the findings of Bremer, who proved beyond any argument the hyposensitiveness of patients with the parkinsonian syndrome to atropin. Thirty-five patients were given a 0.5 of 1 per cent solution of atropin sulphate, beginning with one drop three times a day and increasing each dose a drop a day until as high as 35 drops three times a day were taken, which is an astonishingly large dose of atropin. Of these thirty-five patients, twenty-nine were incapacitated for work and eighteen were in need of personal care. At the end of the treatment twenty-three were able to work and all were able to care for themselves.

8

Stemplinger also reports twenty-six cases treated with a 0.5 of 1 per cent solution of atropin sulphate, beginning with one drop three times a day and increasing one drop each dose until 21 drops three times a day were taken. No ill effects were reported on any of the patients.

At the Eastern Oklahoma Hospital twenty-one patients were placed on this treatment. A few were given doses up to 21 drops three times a day, but most cases were found to show marked improvement while taking from 10 to 18 drops. When this point of improvement was reached, this was determined the optimal dose and the patient was carried on the same from day to day. The effects from the atropin group will be noted in the first week, the muscle contracture will improve, the mask-like face will relax, the gait will become more steady, erect and rapid, the movements of the hands will be more free, the patient will be able to feed and dress

himself. In many cases the mental condition also shows improvement, he is less irritable, sleeps better, the appetite improves and he begins to put on weight. In beginning a treatment of this kind on a patient, who has marked symptoms, it is wise to have him in an institution as a certain percentage of the cases will show alarming symptoms before the optimal dose is determined.

A large percentage of the cases may be restored to a useful life by continuing the treatment in their homes. When the optimal dose is established the patient may be fitted with proper glasses to overcome the marked dilation of the pupils and the atropin may be taken indefinitely without any bad results.

From 1924 on Datura Stramonium has been used by many investigators throughout the United States and Europe with remarkable results.

9

Laignel, Lavastine and Valence began treating all of their cases of parkinson syndrome resulting from epidemic encephalitis with datura stramonium in 1924. Twenty-four were followed very closely and they report two as typical examples. Both of these cases presented were very characteristic. They showed a mask-like face, generalized rigidity, tremor particularly marked on rest, loss of automatic balancing of the arms; they could only walk by leaning far forward and the weight of their body pulled them forward so that they began to run, showing a high degree of paradoxical hyperkinesia; they struck violently against objects. Considerable psychic retardation, probably due to mental weakness, was present in both cases. The patients were conscious of their condition and from time to time talked about suicide, but neither made any attempt to carry it

out. At first scopolamin treatment was tried and then belladonna, without any distince change in their condition. Dried preparations of datura stromonium were then used in doses of 0.1 gm. in the form of pills prepared from the powdered leaves. This was given three times a day in increasing doses. On the ninth day after 0.9 gm. datura stromonium they were almost normal. The mask-like expression was gone, they walked in an upright position, speech was easy and they believed that they were cured. At this stage the treatment was stopped for seven days and both fell back into their original condition and their mental condition was even worse. A second series of treatment brought about the same results as the first, and the syndrome re-appeared again when the pills were stopped. As long as the patients were kept under treatment the syndrome would disappear, but as soon as treatment was discontinued for from five to eight days there would be a recurrence.

In the majority of the cases treated with stromonium by Laignel,⁹ Lavastine and Valence the symptoms disappeared, and in about eight per cent of the cases the patients felt much better subjectively. But the threshold of toxicity of the drug is quite low and it has to be given in the doses near the level of toxicity before the desired effect is received. At about the fourth day of the treatment the patients begin to have defective accommodation and mydriasis which does not stop until two or three days after the treatment is discontinued. Dryness of the mouth quickly follows the initial period of decrease of the sialorrhoea. These are the two most constand toxic effects of the drug and the latter is a

good thing for the patients. The same is true of the toxic diarrhea which overcomes the constipation of parkinsonism. There were a few cases reported in which the treatment failed, either from lack of improvement or because the patients became intoxicated so rapidly that it had to be given up. In cases of arteriosclerotic Parkinsonism little if any improvement was noted.

10

Moren cites six cases which he treated with stromonium. Three of these improved very little, discontinuing treatment due to the toxicity produced by the drug. The other three got along very nicely, all have returned to work and have had no relapses except when they discontinued the drug. Moren states that from his experience with stromonium "It seems to benefit the ocular crises best." It certainly influences the rigidity, but has less effect upon the tremor. There are some cases which do better with scopolamin than with stromonium. It does not act as well in elderly people. It seems to me that stromonium is a drug well worth trying in these cases, and we have an opportunity select another sedative drug other than scopolamin or hyoscine."

11

Worster-Drought, and Hill took six typical cases of chronic encephalitic parkinsonism and treated them originally with Tr. Stomonium B.P. given three times a day; beginning with doses of 20 to 30 minims and increas gradually to 90 to 120 minims, which is 8 times the maximum pharmacological dose. Definite improvement resulted in all cases and the result was distinctly better than that obtained from hyosine grains 1 - 200 to 1 - 100 given orally, but was less than that which was obtained by the hypodermic injection of hyosin hydrobromide. In addition

the patients on stramonium exhibited no symptoms of intolerance ever over a period of several years.

With the dried stramonium leaves in 12 cases previously treated with hyoscin hydrobromide, definite improvement was noticed in three months over the effect produced by hyoscin hydrobromide hypodermically. They estimated that one grain of dried stramonium is equivalent in effect produced to grains 1 - 100 of hyoscin hydrobromide given hypodermically. The patients were then transferred to the dried stramonium extract in order to improve the method of administration (.25 - .37 gr. t.i.d. orally). The great improvement was fully maintained, and in this way getting away from the bulk of the dried preparation of stramonium leaves.

In the series of cases treated at the University of Nebraska Dispensary (recorded on pages 26 to 31) the tincture of stramonium U.S.P. was used. In every case there was definite improvement, all being able to return to work, and able to take care of themselves. The advantage of tincture of stramonium given orally makes it more convenient for the patient and the physician, than hypodermic injections of either hyoscin or scopolamin, and the same therapeutic effect is produced. The patients were usually started on minims 10 to 20 t.i.d. and increasing to 120 minims unless toxic symptoms appeared. Several cases were able to tolerate a much higher daily dosage, but this is without an individual characteristic as the therapeutic effect produced, was practically the same in all cases.

In a series of eight cases of encephalitic parkinsonia, Worster-Drought and Hill report very definite relief in all the cases with the

Dried preparations; but relative failure with the tincture. It is interesting to note that the cause for their failure is that tincture of stramonium B.P. is twenty times weaker in content of alkaloids than the extract stramonium U.S.P. This has been proven by transference of patients from preparation to another using equivalent amounts of the alkaloids, and the therapeutic effect being the same.

Case 1. I.B., age 28, single, white, entered the University dispensary March 6, 1917, complaining of a languid feeling a desire for food, but no appetite. She had felt nauseated and dizzy for some time. She had had pains under her arms and across the chest. At this time she was given cod-liver oil and showed slight improvement. February 1, 1919, entered with a broken clavical which was reduced and treated. July 8, 1920, patient was in the hospital (University) with a spinal fluid containing many lymphocytes and a diplococcus gram positive organism resembling the pneumococcus. Recovery was slow but continuous, with the patient complaining of a tired feeling and inability to read long at one time. October 24, 1920,, she showed a twenty per cent increase in her

condition, but still complained of a tired and weak feeling. Physical examination was essentially negative at this time, and her wasserman (blood) was negative. She delivered a normal child on August 20, 1923. Since that time she has had considerable pain in the back. Taping and binding gave no relief, and was still complaining of the low back pain in 1926. At this time she contracted G.C. and Lues. Has received constant treatment for both conditions. On August 27, 1930, was sent to Neurology Department. Here she was diagnosed parkinsonian with oculogyric crises. She was started on tincture of stramonium September 10, 1930. Patient was taking 100 drops and she, herself noticed some improvement. Dosage was increased to 110 drops p.c. On the 27th she was much improved, having had only 2 crises since last visit. The stramonium was increased to 120 drops. Urinalysis was negative, but the patient did complain of frequency. October 11, 1930, still complaining of frequency, stramonium decreased to 100 drops with instructions to decrease to 80 drops if bladder

symptoms do not disappear. November 8, 1930 patient feels much better, had one crises on October 26, 1930 lasting about thirty minutes. Stramonium increased to 100 drops. November 22, 1930, had occulo-gyric crises last Tuesday lasting thirty minutes, and it occurred again later in the day, but lasted only a few minutes. Patient states that she is feeling fine but still has some frequency. Continue on 100 drops of stramonium. Fowler's solution also perscribed. December 20, 1930, has had four spells since last visit. Increased stramonium to 110 drops. The frequency is still present but not marked. January 17, 1931, patient states that she is getting along fine. No ill effects from the stramonium, to continue on 110 drops. March 14, 1931, condition good, only one attack since January. Frequency does not bother her any more. April 25, 1931, has had one mild attack, feels fine otherwise, is taking 110 drops of stramonium. July 8, 1931, is taking 120 drops daily, and feeling fine. No ill effects. (To date the patient has not returned.)

Case 2. E.N., age 31, colored. Entered the dis-

pensary February 8, 1928, complaining of drowsiness. She falls asleep when ever she sits down. Sleeps well at night, but is tired out in the morning. These complaints began to appear about September, 1927. In June, 1927, she was separated from her husband. Previous illness limited to Mumps. Family history essentially negative. Physical examination shows sluggish reaction of eyes to light, but all right to accommodation, some scoliosis of the spine to the left in the mid dorsal region; otherwise not remarkable. Neurological examination essentially negative, except for slight tremor of tongue. Patient was referred to Neurology where she was diagnosed post encephalitic and sent to hospital for removal of foci of infection (tonsils and teeth). In the hospital cerebral spinal fluid negative to cells and wasserman, colloidal gold test of a parëtic type. She was dismissed improved with no further treatment. In May, 1931 brought to hospital suffering from Acute Nephritis. Nephrectamy was done June 18, 1931. Good recovery. January 30, 1932 came into dis-

pensary complaining of extreme nervousness, unable to do anything because of shaking of right side, speech slow and sluggish. Complains of being slow in doing everything. At this time she was placed on tincture of stramonium 20 drops t.i.d. increasing 1 drop at each dose daily. Also place on Bland's gr. v. t.i.d. in addition to stramonium. February 3, 1932, patient shows definite improvement, feels better; talks better and not so nervous. To continue with stramonium increasing as directed. March 2, 1932, much improved, talks better, appetite good, is working. To continue perscription. To return in May, 1932.

Case 3. R.W., age 43, white, married. Patient came to dispensary March 4, 1931 complaining of gradual loss of sight. Previous illnesses, Measles, Mumps, Chicken Pox, Small Pox, Acute Encephilitis (1919). Slept for about three weeks. Appendectomy, Tonsilectomy, and antrums were drained. Left ear is impaired, some tremor of hands, otherwise not remarkable. Family history evidentially negative, wasserman negative and urin negative. Neurological examination

shows tremors, drooling, masked expression, etc. Typical parkinsonian syndrome. Placed on tincture stramonium 20 drops t.i.d. and increase 1 drop each dose. April 1, 1931, condition improved. April 22, 1931 improvement marked. Now taking 140 drops stramonium. Complains of some dryness in mouth at night. No blurring of vision. September 30, 1931, now taking 165 drops. Much improved but loss of appetite, decrease stramonium to 140 drops. October 28, 1931, appetite still poor but tremor, drooling, and masked expression markedly improved. To decrease dosage to 130 drops. Urinalysis negative. (Patient has not returned.)

The three cases reported above were observed in the University Dispensary. All showed marked improvement without being hospitalized for the initial treatment, and the therapeutic effect was accomplished as quick as could be expected even in an institution.

The surgical possibilities in encephalitic parkinsonism is still in its infancy and the results reported are so varied and inconsistent, that a discussion here seems inadvisable.

It might be well to say a few words about the work which
 12 Ebaugh has been doing. He uses a one-tenth of one per cent solution of chemically pure sodium fluoride (1 gram per liter). Of this solu-

tion he gives drams one t.i.d. increasing after the first week to drams two t.i.d. The effect is usually manifested after two weeks with a marked relief in the tremors and rigidity in a large percentage of cases, although an occasional case proved refractory to this treatment. Sodium¹² fluoried does not affect propulsion or retropulsion. Ebaugh as yet considers this treatment in the experimental stage and has drawn no conclusions, although he considers some of his results to be exceedingly encouraging.

Conclusion:

Treatment of post encephalitic conditions like all chronic diseases is rather disappointing in its results. A great variety of drugs have been tried, only a few which have seemed to have any effect on the progress of the disease or control of the symptoms. The three measures which seem to have proven of the greatest value are: First, general alterative tonics such as arsenic and iron. These do not check the degenerative process at all, but they may correct any secondary anemia which is commonly present in these cases. Second, physical exercises for reduction of contraction of muscles. Third, sedatives to control the muscular rigidity, tremor, propulsion, etc. The drugs which seem to give the best results in the controlling of the symptoms are the atropine group of alkaloids, namely hyoscin, scopolamin and stramonium.

Atropine, hyoscin and scopolamin give definite relief from symptoms in the majority of cases. Atropin is probably the poorest of the three, as it produces toxic symptoms sooner, and is apt to cause ocular symptoms before either of the others, if taken over as long a period of time as is required in these cases of post encephalitis. The

results with hyoscin and scopolamin in the form of a hydrobromide are gratifying, but their maximum effect is only produced when given hypodermically. This usually necessitates hospitalization of even the milder cases at the beginning of treatment, and throws an extra burden of expense upon them. Of course, it is wise to keep every case under close observation during the beginning of treatment as the first appearance of any toxic symptoms is an indication to change the method of treatment.

With stramonium, in both the form of dried preparations and tincture, the results have been equally as good in an equal percentage of cases. This drug can be given orally, and can be accurately administered by the patient himself, necessitating only occasional visits by the physician. It can also be given over long periods of time without any permanent injurious effects. Patients get along on stramonium surprisingly well, and outside of an occasional loss of appetite or frequency of urination it produces no unpleasant effects. In the administration of stramonium the maximum dose which a patient can tolerate must be found, as the best effect is produced when stramonium is given in as near toxic doses as is possible. The patient must be informed that this is not a cure for his condition, and that he must remain on this treatment continuously for the rest of his life if he expects to be relieved from his present condition and suffer no relapses. Psychotherapy plays an important part in the treatment of these chronic cases. It is also wise to have the patient pursue a useful occupation, which aids materially in giving him a brighter outlook on life.

The treatment of these cases, if they do not respond to any of the above drugs is extremely discouraging. Their prognosis is exception-

ally poor. The behavior and psychotic types must be institutionalized. In children a definite regime must be carried out which fills the entire day. Some of these children learn to adjust somewhat better in the group but on releasing them from the institution they seem to have an immediate relapse.

There are many other measures such as good nursing, removal of foci of infection, diet, etc., which must be carefully looked into in post encephalitic conditions as well as in any other chronic disease.

In my opinion tincture stramonium is the drug of choice if the individual will respond properly, if not the rest of the atropin group may be tried. It is quite possible that I am prejudiced in this view point, as all the cases which I have been fortunate enough to have come in contact with have been treated with this drug, and the results have been very noticeable and surprisingly good in every case. In addition to this, the drug is easily administered by the patient himself, while hyoscin and scopolamin give their maximum effect when given hypodermically in the form of a hydrobromide.

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