Multiple sclerosis; mode of onset and etiology

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Multiple Sclerosis
Mode Of Onset And Etiology

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Introduction

If one of the old masters of medicine were alive today and was to scan the diagnosis of all patients in any hospital, he would indeed feel "lost". It is true we believe we have a very good knowledge of many diseases but this is not the case for all pathological processes.

And so it is with Multiple Sclerosis. Here is a relative new disease, being first differentiated only ninety-nine years ago. Yet, it differs from many of our more recently recognized diseases in that the "mode of onset" and etiology has been in a turmoil—the onset up to just fifteen years ago and the etiology is still a much disputed problem. With this thought in mind, it is easily understood why Multiple Sclerosis is a disease which has assumed importance in the field of medicine only during the present century.
Mode of Onset

The primary purpose of this discussion is to de­
scribe the "mode of onset" of Multiple Sclerosis as we
know it to be today. However, a brief review of what the
more renowned authors in the past held as to the develop­
ment of symptoms of this disease is, I believe, fitting
and interesting.

We find that Hippocrates (1) used our present day
term of "paraplegia" when describing a palsy of all the
parts of the body below the neck following an apoplexy. Up
to the time of Galen (1) it seemed to be the belief that a
paraplegia had to be due to disease or injury of the brain.
Galen knew that there could be a partial paralysis due to
disease or injury to any special vertebra. Galen derived
this information from animal experimentation on monkeys and
from his predecessors, Erasistratus, a grandson of Aristotle,
and Herophilus of the Alexandrian school.

And so medical knowledge was slowly pieced together
until Carswell (1), in 1837, drew in color pathological
tissues of the central nervous system while being a medical
student in London. This appears to be the first attempt to
differentiate the different types of spinal paraplegia.
Among his drawings there is one of the spinal cord with the
pons and medulla showing superficial colored plaques and
this condition was described by Carswell as "a peculiar dis­
eased state of the cord and pons varolii accompanied by
atrophy of the discolored portions, all of them occupying
the medullary substance which was hard, semitransparent and atrophied. It begins on the surface of the white and extends to the gray substance."

In 1835 Cruveilhier (1) described a similar condition pathologically as well as clinically and our knowledge of Multiple Sclerosis really dates from the findings and descriptions of Cruveilhier. In his writings Cruveilhier states "this new tissue is dense--much more so than the cord itself. I cannot compare this tissue with any other morbid tissue of which I have knowledge". Cruveilhier then described a patient with this pathology and since this is the first case description of Multiple Sclerosis I shall quote him: "There seems to be a very incomplete controlling power of the will over the muscles which seem to obey imperiously some involuntary cause; and this conflict between the will and some involuntary cause produces incoordinate movements similar to those seen in chorea. If the patient is carried from bed to bed, the most violent reactions take place in the legs, and the attendants must exercise care not to be struck by them. These contractions take place when the patient is asked to move the limbs voluntarily. The only thing she can use moderately well is snuff tobacco. To do this she makes a sudden violent effort with the hand in which she holds the snuff, at the same time moving her head towards it; by the sudden combined movement of head and hand the snuff reaches the nostrils." Of course, what Cruveilhier described, is the intention tremor, as later emphasized by Charcot (2).

During the following thirty-five years various men recorded cases which resembled those described by Cruveilhier and Carswell (1). However, it remained for Charcot (2), whose
findings were published along in 1870, to more or less crystallize the earlier observations that had been made. In a series of lectures delivered to his students, Charcot gave an excellent description of the pathology of Multiple Sclerosis and it would indeed be well worth one's time to read Charcot's original pathological description.

As far as the clinical aspect of this disease is concerned, Charcot divided it into three forms, the spinal, the cerebral, and the cerebrospinal, depending upon where the pathology occurred. He stated that the latter form was by far the most common. At this time, it seems that Paralysis Agitans was frequently confused with Multiple Sclerosis and Charcot warned his pupils not to make this error. He then presented a case of Multiple Sclerosis, a female, age thirty one.

The first symptom which Charcot demonstrated in this patient was that of the "intention tremor". He emphasized that the tremor of this patient was not the "ordinary type of tremor one encounters" but it was only present when the patient attempted to perform an act which demanded muscular coordination. He believed this to be a very important symptom of this disease and said that it should always be present. He continued by demonstrating the difference in the handwriting of this patient with a normal individual and one with a tremor of some other etiology.

He then entered into a discussion of the visual disorders found in Multiple Sclerosis. He believed that diplopia was only a transitory symptom and not important, a view held today. He said that the presence of amblyopia is more important as a visual symptom but the most common and helpful
ocular symptom was that of nystagmus. Charcot believed that nystagmus, as the intention tremor, should be present in every case of Multiple Sclerosis. The patient that he demonstrated at this lecture had a severe horizontal nystagmus, so much so, that he referred to the patient as if "her eyes are to pop" out of her head.

The third symptom which he discussed was the difficulty of enunciation that this patient presented. The patient spoke slowly in a drawling manner as though the tongue was too thick. However, as he pointed out, the tongue was of normal volume, and there were no signs of swelling in the mouth. He spoke of this as a "scanning speech" and this is the third of the important group of symptoms which he emphasized and which later authors call "Charcot's triad of symptoms".

However, our later writers really do Charcot an injustice as they leave the impression that the above triad is all that Charcot used in diagnosing a case of Multiple Sclerosis. This is not true. The author continued his clinical lecture by pointing out that following the scanning speech, bulbar symptoms are apt to appear. The patient which he presented had difficulty in deglutition and of circulation and respiration and the author said that the patient will probably continue until a typical syndrome of progressive bulbar paralysis appears. He then called attention to the fact that vertigo is often present in these cases and it is the type of vertigo where all objects revolve about the patient. He believed that it was important to have this particular type of vertigo.

He demonstrated the peculiar facies which this disease produces. The patient which he presented had a vague, uncertain look, the lips hung half open and there was a stolid
expression. He said that at times the expression is that of a stupor. He continued by saying there was an enfeeblement of memory, that conceptions are formed slowly and the intellect and emotional life of the patient is blunted. He said that at times a condition of euphoria is present, and at times an opposite, a depression.

Charcot continued by saying that spasticity of the lower limbs occurs frequently in the extensor position. He added, however, that this spasticity occurs in the flexed position late in the disease. He made, what today is termed a gross error, by stressing the absence of disorders of sensibility. He admitted patients often complained of numbness but said this was a transient sign and little marked. Cutaneous sensibility, he pointed out, is usually normal; the patients can determine the position of the limbs or toes with their eyes closed. He stated the closing of one's eyes had no effect upon their mode of walking and continued by saying the sphincters are only rarely effected by the weakness of the muscles. He stressed the fact that the enfeebled muscles retained their shape and firmness, in other words, there is no atrophy present. He continued by saying it is possible to get epileptiform or convulsive attacks in Multiple Sclerosis.

Charcot (2) believed the onset of Multiple Sclerosis could be divided into three periods. The first, as he expressed it, extends from the time the first symptom is noticed, until the limbs become spastic. He said that for years there is usually nothing but a paresis of the lower limbs which progresses to the upper extremities. During this first period the remissions, which are characteristic of this disease, occur. Also, during this period vertigo and diplopia may suddenly present themselves.
His second period was the time during which the patient was confined to bed or barely able to take a few steps about the room but while the patient still preserved the integrity of her organic functions. He believed this period to be usually of considerable length and during this time all the symptoms become more marked and spasmodic contractures, which he previously referred to, occur. The third period started at the moment when the functions of nutrition began to suffer in a marked manner. During this time all of the symptoms of the disease would become simultaneously aggravated. He continued by saying that diarrhea frequently developed in this stage. He pointed out that this was the time when the "scanning speech" and other advanced symptoms developed. The sphincters are paralysed, the bladder inflamed, and eschars develop at this period.

And so, as will be emphasized later, Charcot had a remarkable knowledge of this disease for as little pathological and clinical recording that had been done at that time. It is true that he did not emphasize the earlier symptoms as well as should have been done but he did mention some of them and suggest others. His records stand as a milestone in the development of our understanding of Multiple Sclerosis.

It remained for Oppenheim (3) to emphasize the importance of the sensory findings in Multiple Sclerosis. He based his knowledge on the anatomical situation of the larger sclerotic patches in the cord producing a disturbance in reciprocal sensory cutaneous areas.

In 1896 Gowers (4) stated that "the variation in the character of the symptoms extends to their order and to their mode of onset". Thus, we find that it was beginning to be
realized that Multiple Sclerosis does not have a hard and set rule by which it begins and progresses in all patients. Gowers (4) believed that in some cases the peculiar incoordination in the hands was the first indication of the disease. In others, he thought the legs first became weak or the patient was unsteady in standing or walking. He realized the importance of sensory disturbances because he said that dull pains in the limbs may trouble the patient a year or two before the actual onset of the disease, or there may be a sense of "numbness" in the hands and feet which may occur and then pass away and recur. He said that occasionally a cranial nerve palsey occurred at the onset or the speech is peculiar but he believed in the majority of cases the limb symptoms preceded the others. Gowers considered the "intention tremor" of Charcot and Cruveilhier and eye symptoms to be late findings.

And so our knowledge of the "mode of onset" of Multiple Sclerosis began to take form. However, ideas of early symptoms and signs were still so mixed as late as 1920, that the association for research in nervous and mental diseases made a very extensive review of all the literature and published what they considered to be reliable data. Some neurologists up to this time would hesitate to make a diagnosis of Multiple Sclerosis unless the classical Charcot triad of symptoms was present.

It was the associations' (5) belief that in an early case there is usually a gradual development of weakness, especially in the lower extremities. Along with this there is usually an increase in the deep reflexes. The upper extremities are less frequently involved in this general loss of power and a cerebellar ataxia and adiadokokinesia may
precede by months the development of weakness or paralysis of
the upper extremities. In both the upper and lower extremities
weakness or paralysis is associated with a very moderate de-
gree of spasticity. Due to the fact that the diseased patches
occur at various levels in the pyramidal tracts and in the
cerebellar pathways the motor symptoms are of a varied nature.

Even though the deep reflexes are increased a diminu-
tion or loss of the abdominal reflex occurs and this is a
very important sign when one is confronted with a possible
early case. Monrad-Krohn (6), a Scandinavian writer, pub-
lished a paper on the abdominal reflexes and he holds that
these reflexes are present in all healthy individuals with
normal abdominal walls and that there is a pathway connecting
the spinal arc with the sensory motor cortex. Of course the
loss of the abdominal reflex as well as a positive Hoffman
is a sign of pyramidal tract involment and according to the
associations (5) report, the only apparent way of explaining
this loss in Multiple Sclerosis is that in view of the ex-
tensive character of the disease the reflex pathways with
their cerebral connections are certain to be hit somewhere
by one or more of the sclerotic patches.

Uhthoff (7) was the first to point out the pallor of
the temporal halves of the optic discs in Multiple Sclerosis.
Today, the ocular changes are considered very important in
an early case. The characteristic plaques develop in the
optic nerve or tract at any point, but with greater frequency
in the axial fiber bundle of the optic nerve. The axones
from the ganglion cells in the macular region of the retina
run in the temporal portion of the optic disc and farther
Back in their course reach the center of the optic nerve to
form the axial bundle. In the plaque the exudate at first
merely compresses the optic nerve fibers and interferes with their function. Later the medullary sheaths break down and the glia tissue proliferates but since the axis cylinders are not destroyed restitution of vision frequently takes place. After an interval of from one to six weeks pallor of the disc usually appears and remains permanently, even though vision is restored to normal again. Of course the pallor of the disc varies with the extent and location of the plaques. A diffuse pallor of the discs is found in cases where there is a greater amount of involvement and this type of pallor is also found in tabes and other general atrophies. But, the temporal pallor, so frequently seen in Multiple Sclerosis, indicates an involvement of the axial bundle alone and this type of pallor is to a certain degree characteristic of this disease.

The defects in the fields of vision in Multiple Sclerosis are of three types: one, a peripheral contraction, two, central or paracentral scotoma, and three a combination of both peripheral and central defects. The peripheral contraction is usually on a functional basis rather than organic. It is generally considered that this is due to a fatigue field and that is is suggested by the examiner to the patient. In Multiple Sclerosis the mental state of the patient is often one in which suggestions are readily seized upon, as I shall attempt to show later.

The more characteristic defects in the field are the central and paracentral scotomata. Often a typical picture of retrobulbar neuritis develops and it is sometimes one of the earliest signs of Multiple Sclerosis. It may be as late as nine months to years until other symptoms of the disease
develops. The eye is tender and the eyes pain the patient when moving them about and there is often the complaint of blurred vision. The onset of the visual disturbance is acute in about half the cases and in a large percentage both eyes are affected. The disturbance of vision may remain stationary and then either improve or grow worse. Remissions, relapses and extensions may alternate for years. With a central scotoma the patient cannot read, but he can go about without difficulty.

The association (5) further points out that a nystagmus is often present in Multiple Sclerosis, especially in a far advanced case. Generally a horizontal nystagmus is present which is moderately coarse and rapid. It must be remembered that a few normal individuals develop a nystagmoid type of movement and this must not be confused. Once the nystagmus is present it is less likely to partake in a remission than other symptoms. This may be explained, the association continued, by the fact that it is usually a late finding and the patient is entering the terminal stages of the disease. The lesions responsible for this disorder probably lie in the vestibular nuclei or their connections with the posterior longitudinal bundles or directly in the longitudinal bundles. But, the cause of the nystagmus is difficult to determine because there are so many lesions which are disseminated throughout the nervous system.

The association (5) continued by pointing out that the "scanning speech" of Charcot does not tell the whole story as far as the speech involvement is concerned. In addition there may be other forms of dysarthria. The speech may be purely tremulous or bulbar or cerebellar in character.
Grinkler (8) states that the speech in Multiple Sclerosis is in no way any different from that caused by any cerebellar lesion. So, dysarthria in itself is no absolute sign of Multiple Sclerosis. It is considered that the speech disturbance in this disease is due to a disturbance in the cerebellar system which may be in the cerebellar nuclei or the afferent connections with the cervical cord.

The association (5) continued by reviewing Charcot's finding of "intention tremor". They point out that the lower extremities are less frequently affected as severely as the arms. They believe the tremor is probably an oscillation of the limb about a point it should occupy due to a faulty innervation of antagonist, fixator and cooperative muscle groups.

Muscular weakness gradually develops, with or without remissions, into a spastic paraplegia. The legs often "jump", especially at night, and this is believed due to stimuli from the bed clothes acting on a spinal cord in which certain lesions have affected a partial spinal release and with the further physiological release of sleep the jumping occurs. They continue by saying that the spasticity is usually of the extensor type and paraplegia in flexion rarely occurs. The gait of the patient is stiff and the patient drags the limbs along the ground alternatingly tilting each side of the pelvis in order to slide the legs along. The babinski reflex is often positive. This spasticity is usually present in the lower extremities but it may occur in the upper extremities if the lesions occur at a high enough level in the cord.

Bladder troubles are almost always present to some degree. Charcot, as I previously stated, failed to observe
this fact. It is difficult for anyone to decide whether these disturbances are due to an involvement of the voluntary or involuntary muscles. The association was of the belief that with the type of sclerotic patches that occur in this disease there probably is a blacking off from the central nervous system and automaticity of the bladder might result. In some cases there is even paralysis of the bowels. The milder forms of paralysis are manifested by constipation.

In most cases of Multiple Sclerosis there is a tachycardia present. This may be as high as 120 and was in a case that the writer observed. The association found that in moderately well advanced cases the thyroid had a tendency to be underactive. Such patients may present scaling, dryness of the skin, and falling out of the hair. Kraus and Pardee (9) attempt to explain this on the chronic nature of the disease. However, in the same case referred to above which the writer observed, a hyperthyroidism developed during the latter part of the first exacerbation of the neurological disorder. There are apparently no other such cases reported in the literature and I hesitate to even attempt to explain the etiology of the hyperthyroidism.

Many authors do not consider sensory changes in Multiple Sclerosis important. This is a gross error. Sittig (10) presents a very valuable article on this aspect of the subject. He believes pain sense is rarely affected. However, transient sharp pains through the body often are experienced. The proprioceptive sense is the sensory quality most often involved. Loss or decrease of vibratory sensation in the lower extremities is a common finding and often is an early finding in the disease. Often there is a decreased or absent sense of
position and passive motion. Asterognosis is sometimes found and gives rise to a useless limb. Of course these symptoms suggest that the posterior columns are more susceptible to damage and when involved are only mildly damaged as pointed out by Grinkler (8).

Trigeminal neuralgia has appeared in some patients along with other signs of Multiple Sclerosis. Parker (11), in 1928, described several such cases. In one case which he was able to follow with necropsy, the lesion was in the dorsolateral border of the pons at the entrance of the fifth nerve. In 1929 Lhermitte (12) described a case in which sudden, transient shocks, spreading down the body into the legs when the patient flexed the head forward, occurred and he offered this as an early sign of Multiple Sclerosis. But, as pointed out by Grinkler (8), the phenomenon may occur in other neurological diseases as subacute combined cord degeneration and cervical cord injuries.

Apoplectiform seizures are seen rarely. Nattrass (13) has described this as a possible part of the symptomology in some cases. However, it is so rare that it is generally not considered and it is mentioned here merely to show that cerebral localization of the disease is possible.

Mental symptoms in Multiple Sclerosis are often seen and are important because they help to formulate a diagnosis when present. Of course there is not a group of such symptoms as consistent in Multiple Sclerosis as there is in Paresis. However, when one considers the euphoria, first recorded by Charcot (2), about ninety per-cent of the cases show mental symptoms according to the association's (5) findings. They are often disregarded because they are overshadowed by the
physical symptoms and often are not of a character to introduce an element of alarm. There is apparently no predisposition to mental disease in the make-up of these patients. So the mental symptoms seem more dependent upon the organic brain disease than upon an underlying tendency.

Many patients, even though they know they are suffering from a serious disease, do not think their condition serious nor do they seem deeply concerned about it. As Grinkler (8) points out, there is a marked inconsistency between the patient's mood and his physical disability. The patient often smiles and giggles at the slightest provocation. Forced laughter or forced crying may occasionally be seen. Slight stimuli such as the presence of food or water in the mouth may set the patient into uncontrollable peals of laughter without the emotion of pleasure. Cottrell and Wilson (14) believe the lesions which produce these emotional changes are in the ventricular region of the thalamus.

In a progressive organic brain disease as Multiple Sclerosis it seems probable that a mental deterioration would occur in all patients. But this is not the case. Deterioration may or may not occur. It progresses, as the association (5) pointed out, to different degrees in different patients but only occasionally becoming profound. A few cases show a mild disturbance of the memory of which they are entirely aware. Auditory hallucinations occur at times and when they do they are without insight and occur as a feature of a delusional trend. It is believed these hallucinations arise on some irritative or toxic basis, either in the higher visual centers or in the pathways leading to them. Patients with Multiple Sclerosis generally
retain the same personality except for the changes brought about by the euphoria. Even though deterioration may occur the patients do not as a rule show any marked moral or ethical changes. Of course a group of mental symptoms may develop, as the association said, that are secondary to the disease. That is, the delusional states and depressions which may appear arise as a result of the handicapped and incapacitated condition in which the patient finds himself. There may even be suicidal attempts but all of these depressive type of reactions are usually overshadowed by the euphoria present.

In 1921 Birley and Dudgeon (15) emphasized the importance of a proper history in a case of suspected Multiple Sclerosis. In their opinion there is no disease where accurate history taking is more important. They state that in a large proportion of cases a diagnosis can be made from the history alone. The patient's description of the onset and character of the various symptoms is usually sufficient to make it clear that widely separated areas of the central nervous system have been affected at the same or at different times. This feature alone differentiates Multiple Sclerosis from all other common diseases of the central nervous system with the exception of cerebrospinal syphilis. These men further point out that the history demonstrates that the course of the disease is not always slowly progressive and uneventful but is more often interrupted by acute and unexpected disturbances.

In a disease presenting such marked pathological changes as Multiple Sclerosis one would expect to find abnormalities in the cerebrospinal fluid. Yet, this is not the case. The
spinal fluid is usually under moderate pressure but not consist­ently so. A pleocytosis occurs in some cases but it is never very high and there does not seem to be any definite relation to the acuteness of severity of the disease with the cell count. The cell count of the spinal fluid is very rarely over twenty-five in Multiple Sclerosis. Most authors agree that in about fifty per-cent of the cases a goldsol reaction may be obtained, often of the paretic type. The Wasserman reaction is always negative. As far as the blood findings are concerned, we are again disappointed, as they are negative. Occasionally, the association pointed out, there may be a slight blood leucocytosis in the acute stages along with an occasional fever. Of course one cannot say that the cerebrospinal fluid is entirely negative except rarely, but there are no consistent findings. There are no findings which are a help in the diagnosis or prognosis of a case.

Trophic lesions in Multiple Sclerosis are so uncommon, except for eschars, that they are almost unknown. Gowers (4), in 1896, states that they have been observed in rare cases, but does not attempt to explain the lesions. Starr (16), some thirteen years later, states that in his opinion such trophic changes as herpes, dental caries, changes in the nails, and alopecia are evidence of an involvment of the spinal cord, and are, therefore, important in Multiple Sclerosis when they occur. Just a few years ago Levinger (17), while discussing the causes of hypertrichosis, stated that he has noted a widespread overgrowth of hair in a female patient suffering from Multiple Sclerosis. The nervous symptoms had existed, in this case, for six years when there was a sudden
and rapid growth of hair on the legs, breast, back, arms and face. This growth was so great that frequently it was necessary to shave the patient. This patient was given malarial therapy for the neurological condition and this seemed to cause a marked increase in the hypertrichosis.

Just a few months ago Byrnes (18) published an interesting article concerning trophic lesions in Multiple Sclerosis. The patient was a female of twenty-one years of age. Shortly after entering a hospital two peculiar skin lesions appeared simultaneously on the lateral surface of the left leg and the flexor surface of the right thigh just above the knee. Dr. L. W. Ketron, a dermatologist, examined these lesions and made the following note: "On the outer side of the left leg is an irregular palm-sized patch, the central portion of which is necrosed and covered by an easily detached horny layer. The edges are undermined by a slightly cloudy serous fluid". This lesion could not have been due to pressure, the author points out, because of extensive paralysis of the extremities pressure in the above locations was impossible. However, such lesions are very rare, and not a common enough thing in Multiple Sclerosis to be of any assistance in diagnosis.

And so we have seen that the "mode of onset" of Multiple Sclerosis is indeed very variable. However, as a case develops, paresthesia is one of the most common early symptoms. Of course it is often transient as many of the earlier symptoms of this disease are. But, these subjective disturbances are absolutely definite. They are variously described as "tightness, tingling, numbness, boring pains, aching, rheumatism, like water trickling down the skin, coldness, and as if my
body and legs were in plaster". Another early sign in this disease is the change in reflexes, the deep reflexes are increased in activity and the abdominal reflex is generally absent, as well as a positive Hofmann. The ocular disturbances, when present, are very valuable. In fact, any case with a diagnosis of "retrobulbar neuritis" should be watched very carefully for some form of paresthesia or altered reflexes.

Muscular weakness is another early manifestation of Multiple Sclerosis. As the condition develops the so-called "useless arm" often becomes manifested. This may occur before or after any paresthesia are noticed by the patient. As a rule it is unilateral and there is a loss of deep sensation, proprioceptive, astereognosis, no vibratory response and sometimes wild, uncontrollable movements. It must be remembered that at any time during the onset of this disease remissions are apt to occur and the patient is perfectly normal, or nearly normal, for a few months or years before another exacerbation occurs. When an exacerbation does occur after a remission, the future remissions are usually not so complete as the first. As the condition continues to develop we have seen that the patient presents the classical picture which Charcot (2) described. Through all phases of this disease the possibility of the mental symptoms, previously discussed, must be kept in mind. Often, at the very onset of the disease, a distinct euphoria is present.

Thus, it must be remembered that there is no symptom or particular group of symptoms which are pathogenomic of Multiple Sclerosis. Nor are there any laboratory aids to this problem of much practical worth. A patient with sus-
pected Multiple Sclerosis must, by all means, be viewed as a whole, the entire patient must be considered, and a proper history, as emphasized by Birley and Dudgeon (15), is exceedingly valuable as only by the history can one appreciate the slow, chronic development of this disease with its remissions and exacerbations.
Etiology

Seventy years ago Leyden (19), in one of the earliest papers on Multiple Sclerosis, pointed out that exposure to cold and dampness, concussions to the body and psychic trauma appear to play a significant role in the onset and etiology of the disease. This observer seems to be the first to suggest a group of etiological factors.

As has previously been pointed out in this paper, Charcot (2) was the first to attempt to study Multiple Sclerosis intently. Charcot's theory as to the cause of this disease was that extreme worry seemed to be the etiological factor. He offered no organic cause whatsoever for this disease. He demonstrated the psychogenic factor behind each case of Multiple Sclerosis which he presented to his students in the series of lectures which were later published.

It must be remembered that during the latter part of the nineteenth century and earlier portion of the twentieth century it was not agreed among neurologists as to the symptomatology of Multiple Sclerosis. Therefore, many of the earlier theories are incorrect as the cases upon which these theories were based were inaccurately diagnosed. Also, the development of the knowledge of the pathology of this disease was essential before any plausible theory as to the etiology could be advanced.

Dejerine (20) and Marie (21) in 1884 held that the primary lesion was in the blood vessels leading to altered nutrition of the surrounding tissue causing a degeneration
of nerve fibers or an extension of the so-called inflammatory process to the perivascular tissue, with subsequent or simultaneous glial proliferation. The conception of Multiple Sclerosis as an infective disease was originated by Marie (21). He held that it arose as a sequel to acute specific fevers such as typhoid fever, malaria, influenza, acute rheumatic fever, diphtheria and the childhood infections like measles and scarlet fever. His work at this time was purely hypothetical as no experimental work had been done at all. Even today frequently a history of some specific disease, as those stated above, may be elicited in the history of a case of Multiple Sclerosis as occurring just prior to the onset of the neurological disease. However, it does not seem possible that these are true etiological factors since the specificity of the lesions in Multiple Sclerosis point to one common cause and it does not seem probable that it could be due to infective agents of so different a nature and varied origin per se.

Redlich (22) in 1896 offered a few words on the pathology of the disease. He said that the change in the myelin sheath is the primary lesion and of the nature of an acute degeneration, analogous to that occurring in periaxial neuritis found in toxic diseases. The changes in the glia were considered to be secondary to this parenchymatous degeneration.

In the same year Gowers (4) stated that Multiple Sclerosis occurs in both sexes in the same frequency. It was most common between the ages of twenty and thirty years. Previous to this time it had been suggested that heredity
might be a factor in this disease. As to this theory Gowers stated: "Direct heredity, or the affection of two brothers or sisters, has been noted in a few instances, but is quite exceptional; indirect inheritance is more common, shown by a family history of insanity, epilepsy, or of some form of chronic paralysis. Often, however, no hereditary predisposition can be traced and in about half the cases the disease develops without any recognisable cause, near or distant."

Thus, by Gowers' statement, it may be readily seen that in this period there was great confusion as to the diagnosis of almost all neurological conditions and the writers of this time, while citing cases of apparently the same condition, were often talking about different diseases. Gowers continues by saying that Multiple Sclerosis has been ascribed to such incidents as over exposure to cold, mental distress, over-exertion, and some acute disease, as suggested by Pierre Marie (21) of Paris. However, he continues by stating that any single exciting influence is to be traced in only a very small proportion of the cases and the most noteworthy fact regarding them is the occurrence of the disease at a time of life when general influences have, as a rule, no late sequelae. He has observed the disease to begin during a pregnancy, remain stationary until the next pregnancy, and then become progressive.

In the following year Borst (23) advanced the theory that the causal agent circulated in the blood and caused an arteritis of the vessels with chronic inflammatory and proliferative changes. He believed that these lead to nutritive disturbances and lymphatic congestion. However, he advanced no theory or idea as to where this causal agent originated,
but he did hold an organic etiological basis for this disease.

Oppenheim (24) thought that poisoning by mineral substances as lead, arsenic and tin might be responsible for Multiple Sclerosis. Von Jaksch (25) believed that poisoning by manganese was an etiological agent. J.J. Putnam (26, 27) in 1883 stated that a large number of neurological cases had come to him and lead intoxication was demonstrated in them. No special reference was made by Putnam to Multiple Sclerosis as a diagnosis in these cases but he did say that the neurological diagnosis were "Chronic Interstitial Myelitis, Cerebral Neurosis, and Lateral Sclerosis". So, it is very probable that his cases were similar to those which the European writers of this time were calling Multiple Sclerosis.

In 1898 Sachs (28) said that he did not believe a disease so widespread in distribution could have one etiological factor. Sachs pointed out that it was Oppenheim (24) who directed attention to the large number of cases of Multiple Sclerosis in which chronic metallic poisoning seemed to play a rather important part. It was Oppenheim, too, who referred to the importance of a puerperal condition as a predisposing cause.

Muller (29) held that Multiple Sclerosis was a congenital defect of the neuroglia or nervous tissue. There was no experimental work done to support this view.

Trauma has been suggested as a possible etiological agent, especially by Palmer (30) and Pemberton (31). It is true in some cases of Multiple Sclerosis a history of trauma may be obtained but it must be remembered, as pointed out by Barker (32), that patients who suffer from chronic nervous diseases are prone to incriminate trauma as a causative agent.
It has been assumed, by the above authors, that the trauma injures the blood vessels or by concussion it causes molecular changes in the nerve substance with a resulting necrosis in the parenchyma. However, Barker (32) shows no one has been able to reproduce the lesions of Multiple Sclerosis through experimental traumatism to animals. Of course injuries often occur in Multiple Sclerosis as a result of, rather than as a cause, and when the Multiple Sclerosis appears to develop after trauma a very careful inquiry into the previous history will often reveal the fact that the symptoms of the disease had been present earlier.

In 1911 Marburg (33) advanced the idea that a lipolytic ferment might be responsible for the destruction of the myelin sheaths in Multiple Sclerosis. However, Marburg did not attempt to prove his theory and it has only been but in the last few years that this theory has been investigated by modern research workers. The discussion of their work follows later in the paper.

The first experimental work on attempted transmission of Multiple Sclerosis from clinical material to animals was done by W.E. Bullock (now Gye) (34) in 1913. Bullock withdrew spinal fluid, under rigid aseptic conditions, from a case of Multiple Sclerosis and injected it subcutaneously into rabbits. He found it was possible to produce paralysis of the limbs in four rabbits out of five by doing this procedure. He apparently found the fluid to be potent after exposure to a temperature of zero degrees centigrade for fourteen days and after being filtered through unglazed porcelain. Histological examination of the spinal cord of
these rabbits showed, according to Bullock, vascular engorge-
ment and fragmentation of the myelin sheath in the early
stages and areas of degeneration throughout the cord in the
later stages of the disease. He regarded these histological
findings as being typical for Multiple Sclerosis.

Bullock's work was widely read and it seemed to defin-
itely establish the etiological agent of Multiple Sclerosis
on an organic basis. During the next ten years there was
considerable research work done as to the cause of this disease.

In the following year Siemerling and Raecke (35)
published a lengthy article on the pathogenesis of Multiple
Sclerosis. They considered that the primary and essential
feature of the pathological process was a localized destruc-
tion of nervous tissue, the process being closely related to
changes in the vessels, which showed definite inflammatory
phenomena such as congestion, perivascular infiltration with
small lymphocytes, polymorphs and Plasma cells, and in many
cases capillary hemorrhages. They described the early changes
as being characterized by a focal destruction of axis cylinder
fibers, with which is associated a considerable destruction
of the medullary sheaths. The foci tend to coalesce and the
medullary sheath destruction becomes more and more complete.
In the cerebral cortex and periventricular region the lesions
were grouped according to the distribution of terminal arteries
and resemble infarcts, the cortical foci usually having a
pial vessel in their center. Immediately consequent to the
destruction of nervous tissue a marked proliferation of the
glia occurred, which acts as scar tissue and helps to pro-
tect the tissues from further damage. The early stages of
the glia reaction are characterized by a richness of glia nuclei, which later on are reduced in number to be replaced by a thick network of glia fibrils. The authors continue by saying that associated with the myelin sheath destruction numerous scavenger cells make their appearance, arising mainly from the neuroglia and to a less extent from the blood elements. These cells which effect the transportation of the products of destruction, are chiefly compound granular cells, and are most numerous in fresh lesions and in the lymphatic spaces outside the vessels. These men did not believe they are ever as numerous as in cases of softening due to arterio-sclerosis, and are much scarcer in the cortex than in the white matter, since myelin destruction is negligible in extent in the cortex as compared with the white matter. These cells contain a large, deeply-staining, round nucleus and their protoplasm is frequently packed with fatty granules staining orange-red with scharlach. Owing to the excessive glia reaction neighboring foci tend to be bound together in a common sclerotic plaque. Moreover, the authors continue, the individual foci do not pass directly over into normal tissue, but are surrounded by a broad intermediate zone characterized by a pronounced increase of glia nuclei. In these zones the authors observed a tendency to recurrence of capillary hemorrhages, while the presence in them of plasma cells was regarded as indicating a lighting up of the active process.

Secondary degenerations, according to the authors, were found in distant parts of the nervous system, and mingling with the essential focal lesions produced a complicated and confusing histological picture. They explained this secondary
degeneration as a result of axis cylinder destruction. The ganglion cells, although more resistant than the nerve-fibers, also show changes when involved in the primary lesions, but the changes were limited to the focal lesions and were never systemic as in "General Paralysis".

They continue by stating occasionally the glia over wide areas undergoes definite proliferation with an abnormal richness of both nuclei and fibrils and a few pathological spider cells. A section of such an area would certainly give the impression of a primary glia proliferation, but the authors are of the opinion that there are in reality no grounds for postulating a primary gliosis, and they explain the appearances by a leakage from the disease areas into the periphery of a virus or toxin in a concentration too weak to evoke a focal inflammatory lesion, but sufficiently strong to give rise to a diffuse glia reaction.

These men consider that the whole anatomical picture is in complete harmony with what they believe the clinical one to be, that is, acute lesions giving rise to acute symptoms which tend to clear up. They conclude that Multiple Sclerosis is infective or toxic in origin, that the virus or toxin reaches the central nervous system through the blood vessels, and they regard the presence of plasma cells as strong evidence in favor of an infective process and most probably a parasitic one.

In 1916 Dawson (36) examined nine cases histologically and came to much the same conclusions as Siemerling and Raecke (35), although differing somewhat in his interpretation of the histological details. Dawson describes six stages in the development of the essential lesion:
1. A commencing reaction of all the tissue components and degeneration of the myelin sheath

2. Glia cell proliferation and commencing fat granule cell formation.

3. "Fat granule cell myelitis"

4. Commencing glia fibril formation

5. Advancing sclerosis

6. Complete sclerosis

He regards the primary degeneration of the myelin sheath as the most constant and uniform feature of the histological picture, and considers that the relative persistence of axis cylinders and ganglion cells is abundantly confirmed. Secondary degeneration occurs, but affects scattered fibers and not tracts in their entirety. He traced the development of the essential lesions from their earliest stages to the final development of the dense sclerotic areas visible to the naked eye and scattered throughout both brain and cord, and he found areas of recent and of old disease in the same patient. Almost every diseased area showed evidence of an advancing process. They are either wholly "early" or show a peripheral advancing zone around a condensed center, giving the impression that the primary process has never quite died down but is gradually extending peripherally.

According to Dawson (36) vascular phenomena are not prominent in the earliest stages, as he states: "in its diffusion through the vessel wall the noxa causes no recognizable primary alteration, but there is probably an abnormal permeability and increased transudation of toxic lymph". The first vascular changes are found at, or just after, the stage which he calls "fat granule cell myelitis", and are
secondary to the resorption of the fatty products of destruction. This in time is followed by a proliferation of all the cell elements of the adventitia, and later by a modified infiltration of small round cells and a few plasma cells. Finally as the tissue condenses the vessel walls become thickened and undergo hyaline degeneration. While not attempting to explain the irregular distribution of the lesions, Dawson considers that the sites of predilection are "probably related to the vessels, to the terminal ramifications of end-arteries, and to areas where much glia is normally present".

After discussing the somewhat different views as to what should be accepted as the histological criteria of inflammation when it affects the central nervous system he concludes by regarding Multiple Sclerosis as subacute inflammatory disease; a localized, disseminated, "subacute encephalomyelitis" which terminates in areas of actual and complete sclerosis, the causal agent being probably a soluble toxin which is conveyed to the nervous system by the blood stream. He further points out that the remissions and relapses so characteristic of the disease "necessitate the assumption of the latent presence of the morbid agent in the body, or, if this is an autogenous toxin, either of its intermittent evolution or of its accumulation from deficient elimination".

Kuhn and Steiner (37) in 1917 injected blood and cerebrospinal fluid from four patients with Multiple Sclerosis into guinea pigs and rabbits. Some of the guinea pigs developed paralytic phenomena. These authors also claim to have transmitted the disease through a series of four guinea pigs and later of two rabbits, using for the first injection material obtained from previously inoculated animals who had developed
paralytic phenomena. The exact nature of the material used and the route employed for the injections are not stated in the article.

All the affected animals showed symptoms in from three days to three months after injection. They moved about less, sat hunched up, the hind legs became stiff and weak, and total paralysis preceded death. Post-mortem examination of the paralyzed animals revealed no naked-eye lesions in the internal viscera or nervous system, and at the time of publication the histological examination had not been completed. Delicate, slender spirochetes, resembling those found in epidemic jaundice, were demonstrated during life and after death in the hearts blood of several of the affected animals, and also in the blood vessels of the liver.

Of course in the absence of any histological examination of the brain and cord of the affected animals there is no reason for assuming that the animals had developed Multiple Sclerosis.

One year later Siemerling (38) published a positive result for finding spirochetes in the brains of patients who died of Multiple Sclerosis. He was the first to do so. In the brain of a patient with Multiple Sclerosis who died of erysipelas, examined two hours after death, numerous focal lesions were present. Minute pieces from the diseased areas were removed and examined by the dark field method. In two preparations living spirochetes were found, similar to those discovered by Kuhn and Steiner (37) but attempts to stain them in sections did not succeed.

In 1919 Marinesco (39) inoculated the cerebrospinal
fluid of two patients with Multiple Sclerosis into six guinea pigs, of which four were unaffected. The other two, who had received one cubic centimeter intracerebrally, presented in three or four days difficulty in moving about. In the fluid obtained by puncture of the fourth ventricle of these animals spirochetes were found similar to those described by Kuhn and Steiner (37).

In the following year Buscher (40) reported the finding of spirochetes by the dark field method in the brain of a chronic case of Multiple Sclerosis. The parasites exhibited undulatory movements from fifteen to thirty-nine hours after death. They could not, however, be detected in hardened sections of the brain in ordinary silver preparations.

During 1921 Birley and Dudgeon (15) published work regarding the experimental transmission of Multiple Sclerosis. They also studied a series of cases proved to be Multiple Sclerosis and found the spinal fluid negative as to its cytology, globulin reaction, Wasserman reaction, and microscopical examination. Bacterial cultures taken from the spinal fluid of these patients were all negative except for proved instances of contamination. These men inoculated their experimental animals with fresh cerebrospinal fluid and blood-serum of patients suffering from Multiple Sclerosis and also with fresh, filtered suspensions of the brain and cord of patients recently dead of the disease. In spite of a variety of routes which these observers used for their injections they failed to produce in rabbits any condition of ill health with the exception of a transient stiffness of the hind legs in two animals. I believe the following statement of the authors requires quotation: "All animal experiments were
conducted under general anesthesia and with strict aseptic precautions. We consider the use of a general anesthetic important in order to obviate the traumatic palsies, especially of the hind limbs, to which rabbits are particularly susceptible; these palsies which occur in animals improperly treated have been a fruitful source of error in the past. The intracerebral, along the sciatic nerve, and intrathecal and intracocular routes were taken." It seems very probable that most of the experimental work which had been done during the previous few years was subject to the error which these authors emphasize, that is, traumatic palsies of the hind limbs of the rabbits used.

Evidently Bullock (34), who was the first to publish the transmission to animals, anticipated that the future trend of thought would not be in agreement with his work because during the same year that Birley and Dudgeon presented their important negative experiments W.E. Gye (formerly Bullock) (41) published in the same Journal an alibi, so to speak, in an attempt to strengthen the foundation of his previous work. In this article he explains he ran experiments through a group of rabbits and guinea pigs and got some to develop paralysis after some time. He continues by saying that the frequency with which this occurs has varied considerably in different laboratories. But, the author states, "there is no doubt that wherever large numbers of rabbits and guinea pigs are kept cases of paralysis are observed from time to time from no apparent cause". He then cites such an example where the animal was killed and a fractured vertebrae was found with transection of the spinal cord. He continues by saying that the reason so few animals injected develop
paralysis is that the organism is not always present just as in tuberculosis of the central nervous system and syphilis.

It is quite evident in Gye's (41) article that he is no longer able to prove his point in view of Birley and Dudgeon's (15) experimental work.

However, it remained for Noguchi (42) in 1923 to firmly disprove the spirochetal theory as the etiological agent in Multiple Sclerosis. Noguchi pointed out that the spirochetes as described by Kuhn and Steiner (37) had inconsistent morphological features. It varied in length from a fraction of the diameter of a red cell of the infected animal to a whole diameter. It was extremely delicate in width. There were often highly refractile balls at both ends. Some specimens even showed a loop at the end or along the course of the body. The movements were somewhat worm like, moderately active, but seldom rotatory as in the case of 'Leptospira Icterohaemorrhagiae'. In stained preparations a small, delicate, straight projection of varying size was observed, resembling a flagellum. In Levaditi sections of the liver of animals, the organisms appeared only in the blood vessels and never in the tissue itself. And only a few isolated blood vessels were involved. Noguchi emphasizes the fact that no spirochetes were ever found in human materials. He continues by saying that in Kuhn and Steiner's animals, the disease lasted from three days to twelve weeks in the guinea pigs from the time of inoculation to death. In rabbits the symptoms consisted of emaciation, inactivity, ruffled fur, paroxysmal drowsiness, increased reflexes, and paralysis before death. No remarkable changes of organs were observed at necropsy and no organisms grew on culture media.
The author continues by saying that in a similar group of experiments conducted by him, in addition to blood, emulsions of liver, spleen, kidney, suprarenal glands, lymph nodes, and the brain from guinea pigs or rabbits killed at the height of fever, were carefully examined under dark field without a single positive finding. The usual morphologic elements were present in the citrated and defibrinated blood, in suspensions of the clot, and in organ emulsions, elements such as frequently deceive even the skilled microscopist when seen by dark field illumination. He points out that errors of this sort have occurred in the past and are particularly apt to occur when the illumination is partial, because the delicate, tremulous, beaded filaments of varying length and width appear as if moderately motile, and behave not unlike the leptospira group of spirochetes. By full central illumination they are shown to be thinner than the leptospiras. These filaments are abundant in blood suspensions kept for a time at room temperature, and there are many swimming forms not attached to erythrocytes. Noguchi concludes by saying they are undoubtedly derived from altered red blood cells. I might add, that all the cases used by Noguchi in his experiments were proved to be Multiple Sclerosis by a competent neurologist.

So, the spirochetal theory, held so strongly by the observers of the second decade of this century, was fairly well not only disproved but the source of error of the former observers was clearly pointed out.

Hassin (43) believed a toxin was responsible for this condition. He was not in agreement with an infectious theory at all as is clearly shown in the following quotation: "The
essential feature of Multiple Sclerosis is a degeneration of the myelin. What causes this degeneration I do not know. It is certainly not an organism, because if the process were due to them, there would be degenerative phenomena, not in the nerve fibers but in the cell bodies. In addition, there would be inflammatory phenomena. Nothing of the kind occurs in Multiple Sclerosis. There would probably be the same thing as one sees in general paresis. Nothing of this kind occurs in Multiple Sclerosis, and those cases of Multiple Sclerosis that have been described by many very good pathologists as containing or showing inflammatory phenomena have not been cases of Multiple Sclerosis at all."

In the year following Noguchi's work, Symonds (44) summarized the various theories as to the nature and distribution of the cellular changes occurring in the initial phase of the disease. He points out one group believes Multiple Sclerosis is infectious in origin on the assumption that there is perivascular infiltration with lymphocytes and plasma cells. Another group hold that the perivascular infiltration depicted consists of fat granule cells and therefore deny the infective origin of the disease. Symonds concludes from his own histological observations that vascular engorgement and perivascular infiltration with lymphocytes and plasma cells, although not a constant feature of the lesions, may occur in the acute phases of the disease, and that the type of cellular reaction is that met with in diseases of the nervous system due to micro-organisms. He deduces, therefore, that the cause of Multiple Sclerosis is probably of a similar nature.
Early in 1930 the infectious theory was revived by a worker in England, Miss Kathleen Chevassut (45). Miss Chevassut first reviews the literature in her article and points out that climate, heredity, trauma and psychical shock have been adduced as etiological factors by the writers of the last century. However, she dismisses such ideas by stating: "It is clearly impossible that any of these can be capable of actually generating the process, although they may act as the means of lighting into activity some dormant, pre-existing, morbid condition. --- It seems that all such factors act as predisposing causes by lowering the resistance of the body, thus allowing the final specific cause to operate".

The author continues by saying that intoxications have been suggested as etiological factors. The endogenous toxins include not only those produced within the body by bacteria, but also those arising through abnormal metabolic processes, or as the result of deficient or abnormal secretions. Thus, it has been urged that a toxin such as indol, skatol, and phenol is elaborated and that this has a selective action on the nervous system. Of course it is assumed that the toxin is continually reformed and that when lowered bodily resistance, by chills or trauma, allows sufficient concentration of the toxin, then a relapse ensues. The exogenous intoxications which this author reviews are those of lead, copper, zinc, and alcohol. She states that these can only act as predisposing factors by the production, perhaps, of a toxic arteritis. She continues by saying "obviously there must be one specific cause, whether organismal or toxic, of Multiple Sclerosis, producing the clearly defined anatomical and clinical features which characterize the disease. All
these predisposing factors merely accentuate the preexisting morbid condition determined by this specific causal agent". Of course, the conclusions stated by the author are merely her ideas and have not been definitely proved.

Miss Chevassut (45) then continues by stating her experimental work whereby she 'definitely demonstrates a filterable virus' as the etiological agent of this disease. Her laboratory procedures are very elaborate and in view of succeeding information which shall be given, I shall not give all of her technical procedures here. She named this virus "Spherula Insularis". The author cultured the spinal fluid of patients with Multiple Sclerosis and she states that out of 189 cases she cultured her virus from 176 patients, a percentage of 93%. However, she found that in cases in which arsenic had been used as therapy she obtained consistent negative results. Cultures of this virus were then inoculated in a small series of seven monkeys by the author. One of these monkeys developed paralytic symptoms and examination of its spinal cord by the Marchi method showed tract degeneration in one posterior column and one direct cerebellar tract. A second monkey showed degenerations in one anteromedian and in both lateral columns.

In the same publication James Purves-Stewart (46) presented results obtained by treating cases of Multiple Sclerosis with a vaccine made from Miss Chevassut's virus. This form of therapy was carried out in 128 cases and the results were: considerable improvement 5.80%, slight improvement 18.85%, no change 36.23%, and worse 39.13%. He then pointed out the fact that care must be taken in interpreting the results because of the normal remissions of the disease.
This work aroused great interest among the medical world. In fact an editorial appeared in the Lancet (47) which lauded the work of Miss Chevassut (45) and Sir Purves-Stewart (46) and states that while the work has not yet been checked by other observers it is a great step forward in the problem of etiology and treatment of Multiple Sclerosis.

A few weeks later Hicks, Hocking, and Purves-Stewart (48), who were all more or less assistants of Miss Chevassut, published that a method had been devised for estimating the strength of the suspension of the virus isolated from cases of Multiple Sclerosis. They stated that the virus is readily killed with carbol-saline and suspensions of it can be used as experimental vaccines and administered intravenously without harm. They found that there was some evidence that after the administration of a virus suspension to patients and to rabbits, inhibitory substances are formed in their sera. No similar evidence was obtained in monkeys. However, they were not able to demonstrate a complement fixation phenomena in patients who had Multiple Sclerosis or who had the vaccine administered. And they conclude that it is highly probable that the best results with the vaccine occurs when the intravenous route of administration is used.

Hocking (49), a biochemist, thought that he would see whether the "Spherula Insularis" was capable of splitting lipoids of nervous tissue in vitro and the degeneration of the myelin sheath occurs in Multiple Sclerosis. By a series of complicated biochemical experiments this author believes that the cerebro-spinal fluids containing this virus exert a specific hydrolytic action not only upon proteins and their disintegration products, but also upon the fatty constituents
which occur in the nervous tissues. He believes a substance is split off from the fatty constituents in vitro, which can be detected in these fluids when organic degenerations of the nervous system are present.

However, while the filterable virus theory was being pushed in England, experimental work from another aspect of the problem was going on in this country.

In 1930 Brickner (50) published his experimental work. He stated that the aim of his investigation was to determine whether the blood of patients with Multiple Sclerosis contains any element that will cause myelin to disintegrate. He said that studies of animals into which such blood has been injected are infinitely complicated and have yielded little information. It was his idea that a more direct means of testing the question would be to place blood in immediate contact with myelin. He believed that myelin is so best procured for such a purpose in parts of the central nervous system removed from freshly killed animals. He immersed pieces of rat's spinal cord in blood from patients with Multiple Sclerosis. Of course the difficulties of securing fresh cords from human beings at the proper moment obviated their use. Only oxalated blood plasma was utilized.

In the author's experiment everything was done with aseptic technique. Blood from both normal and Multiple Sclerotic patients was used, sodium oxalate being used to prevent the blood from clotting. He then immersed the spinal cord of a rat in one set and the cord of a rat fixed in formaldehyde in another set, the rats being killed with ether. These were then incubated 24, 36, or 48 hours. The segment was then fixed with formaldehyde and stained with hematoxylin.
and eosin or by the Marchi or Weigert-Pal methods.

The results of this experiment were that there was a general disarrangement and disorganization of the pattern made by the myelin sheaths as they appear in cross section. There was a swelling of the myelin sheath, which in cross sections, gave the appearance of large unstained lacunae, by all the methods used. There was a thickening of the sheath, with increased density of stain by the Weigert-Pal method. Also, there was a running together of myelin from different sheaths as well as fragmentation of the sheaths and a great variation in the size of the sheath. There was the formation of scattered globules which stained black by the Weigert-Pal method. In no case was there severe damage to every sheath. The degree of change varied from sheath to sheath and frequently entirely normal ones were encountered. The effects are shown mainly as changes in the form and arrangements of the myelin sheaths and only slightly as differences in stain taking capacity.

The author continues by stating that the modifications are obviously due to the presence of a substance which has come into the cord from the outside, because usually the peripheral half of the white matter was damaged to a far greater extent than the central half. Also, the myelin in close proximity to the ventral fissure or to an occasional accidental gross tear and to nerve roots which course through the white matter, was usually damaged to a greater degree than elsewhere. The author states that this cannot be due to autolysis since in that case the damage should be more uniformly distributed. Also, the post-mortem factor was
excluded by the cords that were utilized after fixation in formaldehyde. In these the distinction between disease and normal specimens was even sharper.

Brickner continues by saying it must not be anticipated that the cords incubated in normal plasma will be entirely free from alteration. They too were damaged but to a less extent and in much smaller areas than those from diseased plasma. But the changes were of the same type in both as might be expected. Therefore, what one must seek is a difference in degree rather than in type of change between normal and diseased plasma. Of course this work is surrounded by implications and complexities because myelin itself is a very intricate mixture.

However, the author observed that the greatest changes occurred in the sheaths of the white column fibers and next came the fine fibers that stream across the ventral part of the grey matter and last the ventral nerve rootlets and nerves themselves. So the author concluded that the myelin is varyingly constituted in different parts of the nervous system of the rat and if this condition is the same in man, it may have much to do with the evident selectivity of locus of so many diseases of the central nervous system.

The author points out that the conditions of the experiment are artificial yet the procedures in both parts of each experiment were identical to the smallest detail of staining. So he believes it is fair to hypothesize that the blood from such patients contains a myelinolytic factor or condition. Whether or not that factor is the cause of the destruction of myelin in the disease cannot be definitely
stated. But, Brickner does think it is a logical deduction. Of course the modifications in the specimens from normal plasma suggest that there may be there, too, a myelinolytic element, possibly the same one that occurs in blood from patients with Multiple Sclerosis, but there is strikingly less of it. He states the nature of this element will demand further study.

The author did consider the possibility that this factor may be enzymatic, a lipase. Quinine is an inactivator of certain blood lipases and this drug has been used with moderate success in the treatment of Multiple Sclerosis for some years.

In the following year Brickner (51) did another series of experiments where he found in plain Multiple Sclerotic serum acid is produced and that this acid production can be entirely inhibited by the addition of sodium oxalate. In lecithinated serum, acid is formed from both normal and Multiple Sclerotic preparations. The acid production is slightly greater in the Multiple Sclerotic preparation. This acid production is partly inhibited by oxalate in normal serum but is markedly inhibited by oxalate in Multiple Sclerotic serum. In the presence of increased alkalinity it is slightly inhibited in normal serum, but strikingly in Multiple Sclerotic serum.

He found in plain Multiple Sclerosis plasma the behavior is similar to that of serum but the differences are less marked. He believes this is probably due to the inhibitory power of the oxalate.
The author also found that in lecithinated plasma acid is formed in about the same quantities in both normal and in Multiple Sclerotic preparations. The oxalation has little or no effect upon this acid production in normal plasma, but inhibits it markedly in Multiple Sclerosis plasma. In the presence of increased alkalinity this acid production is slightly inhibited in normal plasma, just as normal serum, but it is strikingly accentuated in Multiple Sclerotic plasma.

From the above experimental evidence the author believes that there is evidence that in Multiple Sclerosis, the blood contains a lipase which does not occur normally. He believes this lipase differs from normal blood lipase in two of its properties and it is probably the same agent as the one which will produce myelinolysis in the spinal cord of rats described in his previous experiment.

Basing his reasons in the two previous experiments, Brickner (52), in a later article, states he uses quinine in the treatment of Multiple Sclerosis and he believes he obtains fairly good results with it. It is not my purpose to get into a discussion on the therapy used in this disease, but I wish to bring out the fact that the author has attempted to utilize his experimental findings in clinical cases of Multiple Sclerosis.

Later, in 1931, Crandall and Cherry (53) showed in twelve out of nineteen patients with Multiple Sclerosis the presence of an olive oil splitting lipase in the blood. They also tested 146 normal individuals and of these 140 gave negative results. Special tests were carried out on patients with suspected liver or pancreatic injury, and on animals of known liver and pancreatic injury. These authors
believe that this abnormal serum lipase which appears in Multiple Sclerosis, in experimental hepatic and pancreatic damage, and in clinical cases of hepatic disease may be possibly an etiological factor as suggested by Brickner (51). But, they believe it appears more likely to be merely evidence of pathology in the liver or pancreas.

In the latter part of the same year Weil (54) published his results in attempting to duplicate Miss Chevassut's (45) work on the filterable virus theory. He failed to culture any type of growth and says that it is not necessary to even incubate to get the sphere formation which Chevassut calls the "Spherula Insularis". He states that the "spheres" of Chevassut were colloidal particles, submicrons precipitated in the mixture of agar broth, serum and spinal fluid, and "perhaps to a greater extent in the presence of 'positive' spinal fluids containing globulin." Of course this author's work was a great "blow" to the followers of Miss Chevassut.

However, in the following year Sir Halley Stewart (55), son of Sir James Purves Stewart, published the result of checking Miss Chevassut in her own laboratory. In 1931 Miss Chevassut resented Halley Stewart's presence in the laboratory. So he then started to check all of her experiments. However, during the night, his cultures were killed, the incubator was thrown out of adjustment, and many strange things occurred. He was unable to duplicate any of her work. Several times he caught her secretly taking cultures from tubes hidden on her body. The author had Dr. F.M. Walshe to review the results of treating cases with the vaccine made from her so-called virus and Dr. Walshe replied: "Your
results amount roughly to this, that 25% of cases showed some measure of improvement (trivial in 20%) and 75% showed no improvement or definitely retrogressed. I may say with confidence that these results are markedly worse than hospital records would show for the treatment on other lines of Disseminated Sclerosis and also are not so good as a similar number of wholly untreated cases would probably show. I can only conclude from your figures that the treatment you have been investigating must aggravate the malady, and that patients so treated are worse than if left alone."

So, Miss Chevassut and her virus "theory" have been cut of the medical literature since. Her work was apparently all false.

Weil (54), who first threw doubt on Miss Chevassut's work, brought out the fact that a small minority of research workers have followed the original idea of Marburg (33), that of a lipolytic ferment. Of course this is the idea that Brickner (50,51) followed. However, Weil believed that the ferment Brickner refered to was not a lipolytic ferment because in a former article Weil (56) pointed out that demyelination of nerve fibers can easily be produced in test tube experiments by many toxins which, at the same time, are hemolytic and also by a bile product, sodium taurocholate.

Weil then reviewed Hassin's (43) theory of the action of a toxin acting on the myelin sheaths. He then continues by saying "assuming the presence of a toxin circulating in the blood, there must be another factor present which allows these toxins to penetrate through the 'hemato-encephalic
barrier' and invade the central nervous system, or there
must be a diminished resistance of the myelin sheaths against
the action of such a toxin. Such conditions may be establish­
ed in trauma, infection, and pregnancy—all of them conditions
known to favor the onset of Multiple Sclerosis."

He then attempted to demonstrate the presence of a
myelolytic toxin in the urine of patients with Multiple
Sclerosis and he found that twelve out of fourteen showed
destruction of myelin sheath when using the urine of patients
with Multiple Sclerosis while eighteen out of twenty normal
urines did not show this picture.

During the latter part of the following year Crandall
and Cherry (57) extended their observation on a lipase that
was present in the blood of patients with Multiple Sclerosis,
liver disease and pancreatic disease and in dogs with ex­
perimental damage of the pancreas or liver. They believed
that if this enzyme were of pancreatic origin it would be
accompanied by other enzymes from the pancreas, so they
extended their studies to include diastase.

These observers again obtained abnormally high lipase
tests. The diastase incidence in Multiple Sclerosis was:
47.6% of cases presented abnormally high diastase tests
whereas the controls only showed 8.3% of cases as abnormally
high. These men believe that the best interpretation of
these facts at the present is that they signify a functional
disturbance of liver in Multiple Sclerosis.

At this same period Weil and Cleveland (58) found
that in twenty-six cases of Multiple Sclerosis the influence
of the patient's serum on the spinal cord of the rat was the
same as that observed by Brickner. Weil and Cleveland,
however, found that such action could also be demonstrated in serums from other diseases and the difference did not seem large enough to warrant the drawing of conclusions as to the importance of increase in lipase as the etiological agent in Multiple Sclerosis.

These men also found the amount of inorganic phosphorus in the serum of patients with Multiple Sclerosis was 3.4mg. per 100 cubic centimeters on the average as compared with 4 mg. in normal cases and 4.2 mg. in twenty-one cases of eight different diseases and 4.4 mg. in cases of syphilis of the central nervous system. In 40% of the cases of Multiple Sclerosis the inorganic phosphorus of the serum was below 3.3 mg. and in 65% it was 3.5 mg. or less. They pointed out that this was contrary to the expectation of a high amount in a disease that is associated with a rapid breaking down of nerve substances. In syphilitic cases there was an increase.

These authors believe that there exists the possibility that the increase in lipase and decrease in phosphorus are only secondary manifestations of a primary lesion of other organs of the body and that such a lesion eliminates a myelolytic toxin or prepares the way for the passing of toxic metabolic products through the "hemato-encephalic barrier". Lesions of this kind, they state, may be brought about in infectious diseases. They occur in acute disturbances of the metabolic equilibrium, as in pregnancy or following operations with narcosis of long duration or severe trauma to the central nervous system, all of which are conditions known to favor the beginning of Multiple Sclerosis. But, they state, disturbances of lipase and phosphorus metabolism may also be sequelae to a primary disease of the central
nervous system with interference with the normal nervous mechanism of the supervision of this metabolism.

Brickner (59) published another article in 1932 to prove his lipolytic theory. By using esters as substances to be acted upon, he again proved the presence of abnormal lipolytic activity in the blood of patients with Multiple Sclerosis. The author states that the lipolytic activity of Multiple Sclerotic serum has now been tested by three methods, two of these tests being done by him and one was carried out independently by Crandall and Cherry (53). The author then quoted Weil's criticism (56) and for the sake of clearness I shall quote Weil. "The supposed ferment in the lecithin experiments is suppressed by the addition of sodium oxalate, while, on the other hand, such oxalated plasma has a demyelinating effect on rat's spinal cords, speaks against the action of a lipolytic ferment". Brickner states that if it were possible to establish a ready relationship between the appearances of chemical and biological phenomena, Weil's conclusion might be correct. However, the author believes that the differences between the two types of experiments are so great that it seems too venturesome to try to make direct analogies between them.

As to Weil's remark, in his later publication (58), that pancreas lipase does not affect the rat's spinal cords the author replies: "This is interesting, but it does not seem to have a bearing on the question at issue, since there is no reason to believe that pancreas lipase is related to abnormal lipolytic activity of Multiple Sclerosis blood".

During the same year Brickner (60,61) published two
more articles on quinine therapy in Multiple Sclerosis basing his reasoning on the lipolytic theory. Two years later, 1934, Max Weinberg (62) published an article stating he believes that the difficulty in Multiple Sclerosis is due to the inability of the myelin sheaths, in their ordinary wear and tear, to regenerate because of a destruction of the lipid, and that lecithin injected intraspinally neutralizes the lipase or toxin, thus enabling the myelin sheaths to undergo the ordinary repair and bring about the replacement of used up material. This author offers no experimental data upon which to base his views, it is a hypothesis so to speak.

In June of 1935 Brickner (63) submitted a paper of the treatment of Multiple Sclerosis with quinine over a five year period. I mention this work here merely for what information may be gained as to the author's lipolytic theory. During this period Brickner was not able to show as definite improvement in cases of this disease as one would like to see if his theory was absolutely correct. As to this thought, the author states "there is still no basis for expecting quinine to do more than inhibit the activity of the disease, and the drug should have nothing to do with the rebuilding of myelin. Any aid to this process might be valuable". No doubt Brickner has not as yet tried Weinberg's theory of intraspinal injection of lecithin.

In the mean time, Putnam, McKenner, and Morrison (64), in 1931, were experimenting with Hassin's (43) idea that a toxin was responsible for the lesions of Multiple Sclerosis. These authors found that by injecting minimal doses of tetanus toxin in dogs disseminated areas of myelin loss with peri-
vascular infiltration and reactive gliosis could be produced. The lesions so formed resembled those seen in some cases of human encephalomyelitis. The myelin loss so produced was permanent up to a year from the time of inoculation and the gliosis appeared to be progressive.

These authors were also able to produce areas of myelin destruction with reactive gliosis in dogs by carbon monoxide poisoning. The myelin in this case showed no sign of regeneration within a period of two months. In addition, similar areas of demyelination and gliosis were produced by embolism with cod-liver oil emulsion. The destroyed myelin was not regenerated at the end of five months, but the gliosis was progressive. In all three incidences the lesions closely resembled those of early plaques of Multiple Sclerosis. It was the author's idea that vascular obstruction seemed to play a part in the production of the lesions and they concluded that it was not necessary to postulate a specific virus, toxin or ferment to account for the histologic appearances seen in Multiple Sclerosis.

Two years later Ferraro (65) thought that in order to elucidate the etiology of some degenerative pathologic conditions of the central nervous system that he would try the action of potassium cyanide on the central nervous system. He believed that cyanide was a product of intermediary metabolism and a precursor of urea and even perhaps of creatine. According to Warburg, the author states, it affects the respiratory enzymes and therefore inhibits the respiration of tissue. So Ferraro thought that interference with the supply of oxygen might, through inappropriate metabolism,
lead to the destruction of elements, with consequent pro-
duction of either Multiple Sclerosis or Diffuse Sclerosis.

The author injected 35 mg. into each of fourteen cats
and four monkeys. Following each injection he observed an
increase in respiration, vomiting, bowel movement, twitching,
occasionally tremors of the head, occasionally nystagmus,
spasms, and a spasticity of the legs. With repeated injections
he obtained a spastic paralysis of the hind legs but it was
only transitory. Post-mortem examination of the eighteen
animals revealed a process of demyelinization involving all
areas of white substance. In sixteen of the animals there
was a purely degenerative process and in two an inflammatory
process. However, there were some areas of softening, thus
differing from Multiple Sclerosis and resembling Diffuse
Sclerosis. Nevertheless, he obtained demyelinization and
this is an important point, as it is a possible endogenous
toxic cause of this neurological disorder.

Later in the same year Putnam (66) published some
later findings. He said as the myelin was destroyed in his
previous experiments it was taken up by phagocytes and the
axis cylinder was left intact. There was then a perivascular
infiltration of fat cells, lymphocytes, and plasma cells,
and in lesions lasting for some months there was a gliosis.

He continued by saying that in all instances the lesions
had a predominantly perivascular distribution, and in some
of them thrombi could be demonstrated. However, the histolog-
ical picture was entirely different from that seen in throm-
bosis or embolism of a cerebral artery as this leads to a
destruction of axis cylinders, glia and all nervous elements
in the anemic area followed by a cyst with connective tissue wall. Whereas in Multiple Sclerosis the lesion is much milder and there is little, if any, stimulus for mesodermal proliferation.

However, the author pointed out that Pfeifer showed that around many small vessels of the brain there is a zone almost devoid of capillaries which may be three or four times the diameter of the vessel itself. He, Pfeifer, believed this tissue was nourished by transudation and that an obstruction of any length of the vessel might cause a relative anemia of the surrounding tissues without necrosis because of supply from neighboring branches.

With this idea in mind Putnam (66) injected emulsified cod-liver oil in the carotid arteries of cats. His results were disappointing as far as producing lesions similar to those found in Multiple Sclerosis but cysts were formed. The lesions formed were more like those in acute post-infectious encephalitides which come to autopsy within a few weeks of onset. By investigating the choroid plexus of living cats microscopically the author was able to check Pfeifer's anatomical observation that the "perivascular capillary free space" existed. In Pfeifer's article he also pointed out that such a vessel was usually a vein and Putnam, on reviewing his slides of his own experimental work, found in all cases where typical lesions were produced the vessel was a vein.

Putnam (66) then found by injecting bland oily substances forwards in the longitudinal sinus of a dog he obtained "lesions confined almost exclusively to the white
matter, and consist of gradual myelin changes, a perivascular infiltration with phagocytes and lymphocytes, and a glial proliferation". There was no destruction of axis cylinders or of connective tissue structures and only minor changes occurred in the ganglion cells. So, it may be readily seen that these changes closely resemble those found in Multiple Sclerosis. Of course, the idea that the plaques in this disease were due to venous thrombosis was suggested, as pointed out by the author, in 1882 by Ribbert but he offered no proof for his statement.

Putnam believes, with this information, most of the other theories on the etiology of this disease must be abandoned. It does seem foolish to believe that an infectious agent is present in the lesions since similar lesions can be produced by mechanical means.

Many older authors considered pregnancy as an etiological factor in Multiple Sclerosis. Beck (68), in 1913, made a review of the literature on this aspect of the subject and pointed out this fact. Just ten years ago Gobermann (69) reported a case in which the first manifestation of Multiple Sclerosis appeared during the first pregnancy; yet, disappeared after the puerperium. The pathologic symptoms reappeared with each pregnancy. At the end of each pregnancy and occasionally during the first few days of the puerperium there was observed an aggravation of the condition of the nervous system. The author points out that the periodicity in the exacerbations of the disease strictly corresponds with the period of pregnancy in this case. And he believes that on this basis one should advise against pregnancy or marriage in the presence of Multiple Sclerosis.
When one considers the fact that during pregnancy the blood of the patient coagulates more rapidly there does seem to be a close connection between Bobermann's and Putnam's observations.

Just a few months ago Simon and Solmon (19), with Putnam's findings in mind, conducted experiments to see the effect of typhoid vaccine and epinephrine on the coagulation of blood in patients with Multiple Sclerosis and control cases. They desired to see if there was a relation between psychic trauma and infections of the older writers and the venous thrombi theory of Putnam.

In the experiments with typhoid vaccine the degree of the drop in the clotting time was not significantly different in the two groups of patients. However, in their work with epinephrine a marked difference was observed. The maximum drop in the group of patients with Multiple Sclerosis was nineteen minutes as contrasted with four minutes for the controls. The average duration of the drop was three hours and forty minutes for the Multiple Sclerotic group, yet only one hour for the control group.

With this work in mind, one cannot but wonder if patients with Multiple Sclerosis do not have a constitutional make-up so that the clotting ability of their blood is more sensitive to various physiological and pathological systemic manifestations.

N.D. Royle (70), a surgeon, was apparently the first to utilize Putnam's findings in the role of therapy for patients with Multiple Sclerosis. Royle presented four cases
of Multiple Sclerosis which were all greatly improved by doing a division of the thoracic sympathetics, the idea being to allow a vascular dilatation. The author believed that the direct concomitant of the remissions in the cases he presented was due to an improvement in the cerebral circulation and it is his opinion that venous congestion is an antecedent to sclerosis in causing the symptoms of this disease. Royle also pointed out that "the hyperactivity of the vasomotor center, as a result of cerebral venous congestion, must not be forgotten as a factor leading to bulbar and spinal vasoconstriction and thus to altered reflex activity. It is possible, and in fact probable, that the delay in relaxation and absence of oscillations in the knee jerk are signs of increased tone due indirectly to hyperactivity of the vasomotor center."

Wetherell (71), in 1934, and other authors, have all reported favorable results in patients with Multiple Sclerosis by doing a cervico-dorsal sympathectomy. All of this work only goes to strengthen Putnam's etiological theory.

However, just two years ago another etiological theory was revived by Cone, Russel, and Harwood (72) of Toronto, namely, lead as a possible cause of Multiple Sclerosis. This theory was previously held by Oppenheim (24) and J.J. Putnam (26). In 1925 a case entered the clinic of Cone, Russel and Harwood with a retrobulbar neuritis following a severe throat infection. Lead was found in the stool and urine. When these authors attempted to promote the secretion of lead an "ascending myelitis" developed and then lead was demonstrated in the cerebrospinal fluid. They found by giving calcium
they were able to stop the progression of the neurological signs and at this time no lead was found in the spinal fluid and less was present in the excreta.

So, these authors then investigated nineteen cases of known Multiple Sclerosis with this thought in mind. They were able to show in some of the cases lead in the excreta and spinal fluid on admission. When throwing the cases into an acidosis they were able to show an increased output of lead in the excreta in those cases already having lead present, and in those in which there was no lead present in the excreta on admission there was demonstrable amounts following the acidosis. One must remember one of the manifestations of ordinary lead intoxication is the retrobulbar neuritis produced. So when one considers the associated retrobulbar neuritis in Multiple Sclerosis there does seem to be some connection suggested.

In only a few instances of these authors cases did the case history indicate the possibility of a previous exposure to undue amounts of lead. Hence, they reasoned, there had probably occurred a slow chronic absorption of amounts too small to produce the ordinary lead toxic symptoms. In several instances the appearance of the acute symptoms of Multiple Sclerosis was preceded by some metabolic change caused by severe infections or by pregnancy and lactation. This was explained by the assumption that the lead which had been absorbed in earlier life had been stored and the subsequent metabolic changes caused its release in toxic amounts.

Of course when we consider the total number of cases
of Multiple Sclerosis met with a history of poisoning by metals is rare among them. Multiple Sclerosis is just as common in women as in men, or nearly so, and women are not exposed to metal poisoning nearly as frequently as men. Also, the majority of cases begins in early life often at a period before the patients could have been subjected to metal poisoning from their occupations. It does not seem conceivable that the successive exacerbations that are characteristic of the disease can be explained on the ground of a succession of metal poisonings.

Yet, as the editor of the Journal of the American Medical Association has pointed out (73), recent analysis show many common foods, particularly fruits and vegetables which have been sprayed with insecticides containing lead, may contain small amounts of lead. In view of this fact, the committee on foods of the American Medical Association (74) has placed a limit of two parts per million as the permissible maximum lead content of foods. Small amounts of lead may also be introduced into the body from drinking water, cooking utensils, fumes, soot, dust and paint, to say nothing of a few cases where one is able to obtain a history of constant painting, mining and plumbing which necessitate the constant handling or manipulation of material containing lead. So it is fairly evident that exposure to lead in varying quantities is inevitable under the average modern living conditions.

Of course lead may be absorbed readily from the respiratory and gastro-intestinal tracts and after absorption it is apparently converted into a colloidal lead phosphate,
transported as such in the general circulation to all parts of the body and finally excreted or stored. According to Kehoe (75) and his followers the amount of lead appearing in the excreta varies directly with the degree of exposure and he points out that Americans excrete normally twice as much lead as the Mexicans who live under more primitive conditions. So, one must remember that while generally no history of acute lead poisoning or exposure can be obtained in cases of Multiple Sclerosis the possibility of exposure of small amounts over long periods of time certainly exists.

A few months ago Boshes (76) published his results after investigating the lead content of the cerebrospinal fluid. He examined specimens of spinal fluid from twenty-eight patients for lead by the Fairhall hexa-nitrite method. Sixteen of these patients had Multiple Sclerosis. Only one case of the sixteen with the disease under discussion showed a positive result. This patient had been given sodium iodide and the urine also showed lead.

Of twelve other cases of various conditions, in only one, a case of lead intoxication, were abundant crystals found in the cerebrospinal fluid. In this case there was 0.2 mg. of lead per liter of urine. And this author believes that there is no adequate proof for and ample evidence against, the theory that lead is an etiological agent in cases of Multiple Sclerosis.

And so, we find after scanning the history of the etiology of Multiple Sclerosis we conclude with merely one theory which seems to withstand criticism. I am referring to Putnam's work. In the one case which the writer of this
paper has observed daily, the initial attack was associated with the patient's first pregnancy and a slight exacerbation a few months ago was associated with an upper respiratory infection—both of which increase the coagubility of the blood.

Whether this theory is correct or not, the field of research of this disease is still but merely started. Much work remains to be done, and it will be extremely interesting to note the progress that shall be made.
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