1938

Multiple sclerosis

Robert M. Heilman
University of Nebraska Medical Center

MULTIPLE SCLEROSIS

By

Robert M. Heilman

Senior Thesis

The University of Nebraska College
of Medicine

Omaha, Nebraska April 1938

INTRODUCTION

Multiple sclerosis, as it is known today is a progressive degenerative disease of the central nervous system characterized by periods of remissions and relapses.

Of unknown etiology and inadequate treatment, this disease, since its discovery a little over one hundred years ago, has been investigated from nearly every angle in an effort to learn the etiological agent.

Many theories have been advanced concerning the etiology of the disease, but unfortunately none of the theories have proved adequate in explaining the many problems that confront the investigator.

This disease has been investigated by many outstanding men in the field of neurology. Among these men, Charcot, perhaps contributed the most valuable information. His descriptions and accurate observations of the disease are still recognized and taught in medical schools throughout the world today.

The purpose of this thesis has been to present to the reader, an analysis of the most important and outstanding facts concerning multiple sclerosis. I have refrained from the discussion of therapy principally because of its inadequacy.

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The History of Multiple Sclerosis

Perhaps the disease, multiple sclerosis, has existed for centuries, as have many other diseases which were not recognized as distinct clinical entities until the nineteenth century.

Men, who have been interested in the historical aspect of multiple sclerosis, agree that the disease was first recognized in 1835. Charcot (18) and Timme (57) both wrote interesting articles on the history of multiple sclerosis. The most complete article on this disease was Timme's Historical Retrospect from which I have obtained the bulk of the history of multiple sclerosis.

Prior to 1835, the ancients, exemplified by Hippocrates, used the term " paraplegia " as connoting a palsy of all parts of the body below the neck following an apoplexy. The nature and cause of paralysis at this time was not definitely understood.

Galen was perhaps the first man to note that a partial paralysis could ensue independent of cerebral apoplexy. By means of animal experimentation he obtained valuable information concerning the correlation between nerve function and paralysis.

In 1835, Carswell, a London medical student, sketched the gross findings of the spinal cord of a

patient who had died of multiple sclerosis. Cruveilhier at this time, was perhaps the first investigator to describe the pathology and clinical manifestations of multiple sclerosis.

Cruveilhier mentioned the gross pathology as being scattered areas of gray degeneration first manifesting itself in superficial taches which later obtained a certain depth in its growing progressive pathology. He also noticed that the sclerose en taches or en iles, appeared at the expense of the normal white matter of the cord.

Since this observation made by Cruveilhier was the first to appear in literature, it would be interesting to quote his observations verbatim.

The patient was a woman, fifty-four years of age, who had been at the Salpetriere for at least ten years, and who had had the disease many years previous to her admission.

" There seems to be a very incomplete controlling of the will over the muscles which seem to obey imperiously some involuntary cause; and this produces a conflict between the will and some involuntary cause resulting in 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." He also described the toes as " being strongly flexed, " and mentions that he found sensibility delayed and diminished.

Frerichs in 1856, more completely described the pathology of the disease. He mentioned the loss of nerve elements, and a poverty of blood vessels in the areas of sclerosis.

In the same year, 1856, Carl Rokitansky published in his Pathological Anatomy, a description of the nervous system and the connective tissue new growth in the central nervous system, especially at the convexity of the brain through the pons and particularly in the medulla and thence through the spinal cord.

Many other investigators added their contribution to the pathological picture of multiple sclerosis, but it remained for Charcot and his workers in the sixth and

seventh decades of the last century, following the close study of many cases, to crystallize the earlier observations and to publish the symptomatology and pathology of the disease as we know it today. He also divided the disease into three categories; the cerebral form, the spinal form and the combination of the cerebral and spinal forms.

Charcot introduced the classic triad of symptoms in multiple sclerosis, namely, intention tremor, nystagmus and scanning speech.

Following Charcot's contribution, Oppenheim laid stress on the sensory findings in this disease, while Strumpell described the nature of reflexes and stressed the importance of the disappearance of abdominal and epigastric responses.

Uthoff published a monograph in 1889 on the eye symptoms, more especially retrobulbar neuritis and the various types of scotomata and contractions in the visual fields found in multiple sclerosis.

Since 1889, little has been added to complete the picture of multiple sclerosis. The advance has been chiefly on the clinical side in the addition of minutiae and the nicer points of diagnosis.

The Etiology of Multiple Sclerosis

There has been a great deal of scientific literature published on the etiology of multiple sclerosis. Many investigators have felt confident that they had discovered the etiological agent, only to have other men disprove their findings.

Barker's (10) paper on the etiology of multiple sclerosis, deals with the exogenous factors which may contribute to the etiology.

Barker considered the exogenous causes to be: (1) The influence of earlier infections; (2) the influence of intoxications; (3) thermal and electrical influences, and (4) trauma. He based his considerations on the fact that many of the cases he studied had a history of at least one of the above exogenous etiological factors. He found that in a number of cases, trauma of some nature such as a fall or severe blow was followed by the active symptoms of multiple sclerosis. In other instances a predisposing upper respiratory infection seemed to be followed by active neurological findings. Poisons, thermal and electrical influences all have been paramount outstanding points in the patients histories prior to the active form of the disease.

It is quite easy to understand how such a wide range of etiological factors were considered. No case

of multiple sclerosis seemed to have a definite history, prior to diagnosis.

Woodberry (1919) strongly emphasized the co-existence of chronic tonsillar infections with multiple sclerosis. Gill and Bassoe at the same time supported Woodberry's theory and added that long standing dental infections played an obviously important part in the etiology.

Oppenheim was at first staunch in his belief that the etiology of multiple sclerosis was due strictly and primarily to mineral poisonings.

However, his theory was proved to be false, when other investigators found that the pathological findings in metallic poisonings, didn't correlate with the pathological findings in multiple sclerosis.

A history of exposure to cold and wet or heat stroke have often been considered compatable with the onset of the disease. Most observers feel however, that sudden thermal changes are not the cause of multiple sclerosis, but, at most are influencing factors that cause an exacerbation of an already existing disease.

One of the considerations observers often overlooked in regard to trauma as an etiological agent, was that injuries often occur in multiple sclerosis as a result of

rather than as a cause of the disease. It is agreed by most men that a latent multiple sclerosis may suddenly be manifested in active form. It is also agreed that trauma may cause exacerbations in an already existing active form of the disease and cause a definite increase in the signs and symptoms of the disease.

As far as the exogenous factors are concerned in the etiology of multiple sclerosis, all one can definitely state is that they must act either as predisposing influences for the true cause, or as aggravators of a disease already started by the true cause.

Putnam (46) summarizing his work on the etiology of multiple sclerosis discloses the following information: (1) He found the histological features in multiple sclerosis could be produced in two ways in animals, first, by the injection of minute doses of tetanus toxin and secondly by the obstruction of cerebral vessels; (2) he also noticed that the thrombosis and obstruction of vessels in multiple sclerosis were similar to those in post infectious encephalitis; (3) he lastly found that patients suffering from multiple sclerosis had increased coagulability of the blood when injected with adrenalin or typhoid vaccine.

Therefore there is probably a fundamental abnormality in blood in multiple sclerosis which interacts with endogenous or exogenous factors to cause thrombi in cerebral venules.

Potts (43) feels that a toxemia of some sort is probably the etiological factor in this disease. Ranney (48) on the other hand thinks that chronic cerebral congestion and morbid changes in the walls of the capillary vessels are predisposing factors. He associates these changes with epilepsy, insanity, idiocy, bulbar paralysis, tremor, destructive lesions of the brain and old age.

Cone (19) discovered that in a number of cases at autopsy, lead was found in the spinal cord and spinal fluid. Six cases of multiple sclerosis had lead in the urine and feces. His enthusiasm about his discovery was never experienced by others, for it seemed that only Cone's series had lead which might have been introduced at autopsy or during the course of the disease.

Perhaps one of the outstanding bits of research on the etiology was done by Bullock, as cited by McAlpine (39) in his address on disseminated sclerosis. In this instance, Bullock seeking to prove his theory of an infectious agent, injected cerebro-spinal fluid from a 19 year old patient suffering from multiple sclerosis,

into the sciatic nerve area of a rabbit. On the 13th day after the injection, paralysis ensued in the hind quarters of the rabbit. Post mortem examination revealed broken down myelin sheaths. Other investigators had negative results with the same type of experiment. Sufficient experimental proof of the infective nature of the disease is lacking.

Another theory was advanced by Da Fano (22) who supported Bullock's work. Da Fano felt that spirochetes may be the etiological agent.

Jellifee and White (33) mention in their discussion of multiple sclerosis, that Strumpell was definitely convinced that heredity played an important role. Strumpell also cites his belief that there is an essential abnormal congenital factor present, predisposing to the disease.

Gowers (25) attributed small pox and typhoid fever to be the two most common acute diseases predisposing to multiple sclerosis.

In Charcot's (17) lectures, he mentions the fact that Rindfleisch believes that the disease starts as a vascular phenomena with inflammation, usually initiated by moist cold, trauma, grief and infections.

Vulpian (58) says that heredity is uncontestible in considering the etiology of multiple sclerosis.

Perhaps one of the most widely accepted theories of today is that originating with Stevenson (49) who felt that multiple sclerosis was caused by a spirochete. Using Jahnels spirochetal stain, in a study of 37 sections from 4 cases of multiple sclerosis, he failed to find any evidence of spirochetes although some men since have stated that they have found the presence of the spirochete in their sections. The consensus of opinion in this matter hinges on the fact that spirochetes may be present in the lesions of multiple sclerosis, but until better and more adequate spirochetal stains are invented, the question of spirochetes as being the etiological agent of multiple sclerosis will remain in doubt.

There are many men who still feel that toxemias are the underlying causes of the disease and they have good reasons to support their view, but unfortunately can't prove their points by experimentation.

Gye (28) concludes from his experimental studies of disseminated sclerosis that the etiology is probably due to an infectious agent and that the virus may sometimes be found in the cerebro-spinal fluid.

Weil's (61) serological studies of patients suffering from multiple sclerosis states, " that in 26

cases of multiple sclerosis, the influence of the patients serum on the spinal cord of the rat was studied. In agreement with Brickner's experiments with plasma of patients with multiple sclerosis it was found that a larger number of serums from cases of multiple sclerosis than of normal serums acted destructively on the spinal cord of rats, and the difference did not seem to be large enough to warrant the drawing of conclusions as to the importance of lipase increase in the etiology of multiple sclerosis.

The possibility that the etiology was due to a spirochete was studied by Adams (2). He attacked the etiology on the supposition that if the disease were caused by spirochetes, anti-spirochetal drugs should bring about a cure. Therefore, treatment was carried out with spirocheticidal drugs. In practically every case under treatment, modifications towards a negative result of the colloidal gold reaction were noted. The clinical symptoms of the disease were only slightly ameliorated in a few cases.

Brickner (4) (5) in studying the blood esterase changes in multiple sclerosis, concludes that there is some lipolytic agent in the blood which causes a demyelinization of the myelin sheaths. This etiological

possibility certainly should receive further study and investigation.

Stieglitz (52) in his discussion of multiple sclerosis, feels that previous attacks of infectious diseases such as cold, flu and grippe are predisposing etiological factors. He also states that these diseases being extremely common in adults, might bear some relation to the etiology of multiple sclerosis in adults.

Oppenheim, in his discussion of children afflicted with multiple sclerosis states that, " the beginning of multiple sclerosis in adults can not infrequently be traced to very earliest childhood " and " that proof of the existence of infantile multiple sclerosis is still missing but it may trace its beginning to childhood" and " the development of the process on the basis of congenital predisposition is most likely.

There is nothing concerning the geographic distribution of multiple sclerosis, to add light on the etiology of this disease. Davenport (24) reports that the geographic distribution of this disease in the United States is somewhat similar to the distribution of goiter. In other words, the Great Lakes area seems to claim the bulk of the cases in this country, although it is by no means uncommon in other sections of this country.

In Europe, the disease tends to occur in greatest numbers in the northern countries. The British Isles claim a great percentage of the cases in Europe. Countries bordering the Mediterranean sea are relatively free from the disease as compared with the northern countries.

Bramwell (12) cites that multiple sclerosis would appear to be commoner in Scotland than in the United States. The disease is world wide in its distribution, but tends to be concentrated within the north temperate zone.

Davenport further states that the urban incidence is one half greater than the rural incidence. This observation has been endorsed by other investigators.

The disease may appear at nearly any age, but tends to occur in individuals between twenty and forty years of age.

The disease may occur as early as the tenth or as late as the sixtieth year. It occurs more often in males than females in about a 3:2 ratio.

Multiple sclerosis makes up about 2 to 4 % of the organic diseases of the nervous system including neuro-syphilis. With the nicer points in the differential diagnosis of multiple sclerosis, now known, the incidence

of multiple sclerosis should increase as more and more cases will be unearthed from the realm of nervous disorders.

Of course, nearly every investigator had his ideas concerning the etiology of this disease, therefore I've cited what I consider the most important discussions to avoid repetition.

There hasn't been any definite convincing evidence to support any theory on the etiology. Some men feel that dietary dyscrasies and states of avitaminosis are predisposing factors, but there is nothing to support the theories.

In reviewing the possible etiological factors of this disease, one thing is quite apparent, and that is; whatever the etiological agent may be, states of stress and strain either endogenous or exogenous, are apparently the precipitating factors which are first associated with the active recognized case of multiple sclerosis.

The Symptomatology of Multiple Sclerosis

One striking feature of the study of multiple sclerosis has been the uniformity of opinions by investigators regarding the symptomatology of this disease.

Sachs and Friedman (56) wrote a very complete paper on the symptomatology of multiple sclerosis and gave the percentages of the findings in each case as based on a study of 141 cases. The following information is an analysis of the signs and symptoms of multiple sclerosis in the order of their diagnostic importance:

1. Easy fatigue, weakness and stiffness of one or both upper or lower extremities culminating in spastic paraplegia--81.7%, associated with, (a) increase of deep reflexes--90.0% and (b), positive Babinski--78.3%.

2. Nystagmus, generally horizontal, slight at the beginning, gradually becoming more marked--79.0%.

3. Ataxic tremor of upper extremities and tremor of the head--55.3%.

4. Marked diminution or loss of abdominal reflexes and sensations--83.7%

5. Spastic ataxic or ataxic gait and station--43.2%.

6. Scanning speech or some form of dysarthria-36%.

7. Pallor of optic discs, especially of the temporal halves--32.6%.

8. Disturbance in facial innervation--32.6%

9. Deviation of the tongue-- 10.0%.

10. Disturbances in deglutition-- 3.5%

11. Explosive laughter and emotional instability-17%.

12. Unusual remissions often leading to disappearance of all symptoms--42.0%.

13. Transitory ocular palsies with diplopia--29.0%.

14. Vague objective and subjective sensory findings. (a) Objective-- 1. Posterior column disturbance--17%; 2. Pain, touch and temperature disturbance--16.3%; (b) Subjective-- Numbness, tingling and pain--30.0%.

15. Disturbance in vesical reflexes--40.0%.

16. Tenderness of the spine, chiefly mid-dorsal-14%.

17. Dizziness (vestibular vertigo)-- 8.25%.

18. Mental Changes--15.6%.

Bramwell (12) found that the knee jerks are almost always exaggerated, the knee jerk generally being more exaggerated on one side. In some cases a patellar clonus was elicited. The tendon reflexes in the upper extremities as a rule are abnormally active. In some cases, absence of the knee jerk has occurred, but this is quite rare.

Birley and Dudgeon (11), in studying 35 cases mention the paresthesias as being the most common symptom. These symptoms included tingling, numbness, aching, tightness and hot and cold flashes.

Oppenheim described the "useless arm" a rapid paresthesia occurring within a few days after the first evidence of paresthesia. This condition was as a rule unilateral. The pyramidal tract was involved in 91.4% of the cases and the abdominal reflexes were lost in 77.0% of the cases. Incoordination was present in 51.4% and the same percentage in regard to vertigo. Mystagmus was found in 74.3% of the cases and pallor of the optic disc was found in 45.5%. There was evidence of disturbance in deep sensibility in 65.7% of the 35 cases.

Cottrell's (21) conclusions in 100 cases were that the vast majority of the cases showed changes in (a) prevailing emotional disposition; (b) emotional express and control; (c) sense of physical well being.

Sittig (51) concludes that every case of multiple sclerosis has sensory changes and fugitive rapid paresthesias which shift as a rule. He also mentions that sensory changes may be bilateral or unilateral and that pains do occur in the disease, but are quite rare.

Adie (1) found that 52% of all his patients presented eye findings these being: Poor vision--42%; field defects--3%; and diplopia--22%.

In regard to the eye findings in this disease, Marshall (40) cites a case in which a diagnosis of multiple sclerosis was made entirely on visual field changes.

Parsons (45) states that ocular muscle paralysis occurs in about 10% of the cases. The lateral rectus muscle being involved in the majority of the cases.

Brain (7) differs somewhat with Parsons work. He finds that although diplopia occurs in 30-40% of the cases, paresis of single muscles is not common and of conjugate movements, rare. He also mentions that he found nystagmus present in 70% of his cases. He stresses the value in visual field changes, as a means of diagnosing the disease. In his series, 23% showed visual field defects.

A new symptom of the disease has been recently discussed by Brickner (6) who reveals that oscillopsia, which is literally oscillatory vision, is present in a great many cases. Patients in which this finding is present, complain of objects moving back and forth, usually during walking, although it may also occur at rest. There is motion of the eyes in any direction, but the lateral component seems to be the most frequent.

Church and Petersen (20) found that the papilla may show optic neuritis or atrophy, but the atrophy is very seldom extreme and the disc is pale.

It was observed by Bristowe (8) that rhythmical tremors of the head and arms occurred when unsupported or in use.

He also mentions that impediment of speech comes earlier in multiple sclerosis, than in tabes dorsalis and dementia.

Gowers (25) found that in his series of cases, loss of muscular power in the limbs was the most common symptom.

Hirt (29) lists in order of frequency the following symptoms: Headache, vertigo, digestive disturbances, sensory weakness and general tremor.

The most common symptoms occurring in multiple sclerosis in Danas (23) opinion are: (1) Bladder weakness; (2) absence of abdominal reflexes; (3) spastic paraplegia; (4) optic atrophy; (5) sensory defects; (6) sphincter trouble and (7) speech defects.

The most common symptom according to Peterson and Frederich (42) is the loss of motor power in the limbs.

The foremost symptom in Pott's (43) opinion is motor weakness, especially in the upper and lower extremities.

A recent publication by Salmon (54) on the sensation of electrical shock in multiple sclerosis yielded no conclusive evidence as to the electric shock as being a definite symptoms in multiple sclerosis. This is in direct contradiction to Lhermitte (38) who described a peculiar sensory discharge as being an electrical shock like discharge.

Patrick (44) substantiated Lhermittes findings and cited a case in which electrical discharges were felt by the patient when his neck was flexed. A patient of Wechslers (60) was able to light an incandescent light bulb, by the electricity generated in his own body. This patient constantly complained of electrical flashes and sensations in his body.

Some cases of multiple sclerosis of course are hard to classify according to the symptoms they exhibit. For instance, Hackney (32) cites a case which simulated apoplexy and had an absence of nystagmus. Another case, that of a sub-acute form of the disease as reviewed by Spiller (50) in which the lesions were similar, but differed in the brain and cord.

Although the majority of cases run true to form in symptomatology, it is not uncommon to run across an atypical or subacute form of the disease which complicates the diagnosis.

The later aspects of the course of the disease often manifest mental symptoms. In Sangers, Brown and Davis (9) review of the mental symptoms in multiple sclerosis, the most important fact they disclosed, was that there is no demonstrable predisposition to mental disease in the make-up of the multiple sclerosis patients. The mental symptoms seem more dependent upon the organic brain disease.

Many patients suffering from multiple sclerosis have mental states of euphoria. In this euphoristic state, the patients do not consider their illness to be of a serious nature, nor are they deeply concerned about it.

The cause of this state of euphoria is not definitely known, although involvement of the basal ganglion has been considered.

A number of cases have been reported in which there were states of mental depression with attempts at suicide. In a progressive organic brain disease such as multiple sclerosis, marked mental deterioration occurs in nearly all patients.

Auditory hallucinations without insight and occurring as a feature of a delusional trend are not unusual. The patient afflicted with multiple sclerosis as a rule, does not show marked moral ethical or personality changes.

Cohen (15) maintains that mental deterioration occurs due to the distention of the pathological plaque through the cortex as well as the corpus callosum and the non-cerebral regions of the brain.

In twelve out of twenty cases, Goodhard (26) found atrophy of the hand muscles.

Irregularities in menses,was noted by Vulpian (58).

The Pathology of Multiple Sclerosis

The pathology of the disease as reviewed by Charcot (18) was first described quite accurately by Cruveilhier in his " Atlas d' Anatomie Pathologique," in 1835. In 1855 Ludwig Turk (1855) published a description of multiple sclerosis with illustrations of the pathology. Since that time many reports of both gross and microscopic findings have been published. One striking feature of the pathological investigations has been the variance of opinions among noted histologists concerning the histopathology of the disease. The opinions concerning the gross findings in multiple sclerosis have been uniform.

Hassin (31) in his observations of the pathology of multiple sclerosis noted first that the most characteristic feature of the pathology, was the so-called patch of sclerosis. Stewart, in his Lancet article drew attention to what he termed spherioles. Hassin found these plaque like areas of sclerosis scattered throughout the central nervous system appearing in various forms and sizes. The areas of sclerosis seemed to favor the white substance and its long and short nerve fibers. The lesions were found to be either symmetrical or asymmetrical and often invaded the peripheral nerves. Many of these nerves appeared to be deprived of their myelin sheaths and appeared as naked axons, while other nerves suffered both destruction of myelin and axon.

His summary of his findings were that there was regressive and progressive ectodermogenic (neuronal degeneration and glia proliferation) associated with pronounced proliferative mesodermogenic changes, namely hyperplasia and thickening of the vessel walls, of the pia and the septa and dilitation of the adventitial spaces and their infiltration with gitter cells. He also found an absence of significant ganglion cell changes of inflammatory phenomena and of any relationship of the ectodermogenic changes of the territorial blood supply. His last finding was an abundance of lipoids in the pia-arachnoid and the choroid plexus.

Hassin's conclusions of the subject of pathology in multiple sclerosis, embraced the following:

1. In multiple sclerosis there are definite early changes in the form of widespread swelling of the myelin substance.

2. The myelin alteration is an acute and early manifestation with the formation of a waxy patch.

3. The glia undergoes changes later.

4. The pathological changes are primarily ectodermogenic the mesodermogenic tissue participating in the alterations of the disease secondarily.

5. Vascular and septal changes are present, but are accidental phenomena.

6. Theoretically it is impossible to produce the changes of multiple sclerosis without concomitant changes in the connective tissue elements.

7. The patches of sclerosis are not representative of territorial areas in relation to either the arterioles, the venules, or the perivascular lymph drainage.

8. The lesions of multiple sclerosis cannot be produced experimentally either by interference with, or irritation of the spinal cord or the vascular supply.

In an investigation of the axis cylinder in its relation to multiple sclerosis, Leiner (37) concludes the following: (1) The axis cylinder is damaged and may be destroyed; (2) frequently the axis cylinders survive the lesion and primary edema is followed by a subsidance of the same; (3) the medullary sheath is more seriously involved than the axis cylinder. It may be completely destroyed while comparatively well preserved axis cylinders remain and (4) the medullary sheath may be preserved at least in part.

Sachs (58) in his article on special reference to the pathology of multiple sclerosis quotes Goldscheider's description of the pathology: "Blood vessels are dilated, adventitia infiltrated with small cells and detritus. In the vicinity of these blood vessels, the nerve fibers are swollen, the sheath and the axis cylinder participating in the swelling. The medullary sheath suffers more than

the axis cylinder at least with cross section exhibits a number of naked and well preserved axis cylinders are noted."

Goldscheider supposes that the enlarged nerve fibers crowd against each other causing disintegration and absorption of the myelin of some fibers, thus leaving room for other fibers to persist in their enlarged condition.

In a respect, the etiology of multiple sclerosis has hinged somewhat on the findings of the histologists.

For instance in 1863, Rindfleisch stressed the importance of the disease as related to blood vessels. According to him, each plaque contained in its center a blood vessel with changed walls, denoting a condition of chronic inflammation. Taylor is of the opinion that we are not warranted in connecting the vascular changes directly with the sclerotic process, for the patches are not always related to the diseased vessels, and in many plaques, the blood vessels are entirely normal and other portions of the vascular system show no tendency to disease.

Now if histologists could agree on their findings as being an inflammatory condition it might be assumed that the etiology could be limited to either toxins or infectious agents.

The results of histological studies on sections compiled by Klingman (35) are the following: (1) Edema and mononuclear cell infiltration; (2) fat granular cell myelitis; (3) neuroglia fiber formation; (4) sclerosis and (5) retrogression of neuroglia cells and fat granular cells.

Bramwell (12) feels that the primary change is in the parenchyma, the neuroglial increase being a compensatory process. The strongest argument in support of this view is the circumstance that very profound changes are sometimes found in the myelin sheaths with little or no increase of the neuroglia in the same region. Toward the periphery of a patch, for instance, degenerative changes are sometimes found in nerve fibers which are lying in the midst of perfectly healthy neuroglia. Others think that the myelin sheath and neuroglia suffer primarily as a result of a common cause.

The earlier lesions, according to Boyd (13) may present quite a cellular appearance, the cells being collected in a ring around the vessels. There is a marked difference of opinion as to the nature of these cells. One set of observers, of whom Hassin is a representative hold that they are fat granule or scavenger cells. Others state that the cells are inflammatory in nature, mainly lymphocytes with a few plasma cells.

The distinction is a fundamental one. If the former

view is correct, then the disease is a primary degeneration of the myelin sheaths, purely secondary. If the latter view is true, then multiple sclerosis becomes one of the inflammatory diseases of the nervous system, due probably to some exogenous infection.

Birley (11) reviews the findings of Siemerling and Raecke (1914) who differed with Hassin, Dawson, et el.

According to Siermerling and Raecke; " the essential and primary feature of the histopathology is a localized destruction of the nervous tissue, the process being closely related to changes in the vessels which show definite inflammatory phenomena, viz., congestion, perivascular infiltration with small lymphocytes, polymorphs and plasma cells, and in many cases capillary hemorrhage. Focal destruction of axis cylinder fibers with which is associated considerable destruction of the medullary sheaths. The foci tend to coalesce and the medullary sheath destruction becomes more complete. In the cerebral cortex and periventricular region, the lesions are grouped according to the destruction of terminal arteries and their center. Immediately consequent on the destruction of nervous tissues, a marked proliferation of the glia occurs, which acts as scar tissue and helps to protect the tissues from further damage. The early stages of the glia reaction are characterized by richness of glia nuclei which later on are reduced in number to be

replaced by a thick network of glial fibers. Associated with the myelin sheath mainly from the neuroglia and to a less extent from the blood products of destruction, are chiefly compound granular cells and are most numerous in fresh lesions and in the lymphatic spaces outside the vessels. They are as never 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 former as compared with the latter. Owing to the excessive glia reaction, neighboring foci tend to bound together in a common sclerotic patch. "

Symonds (53) in his discussion of the histopathology stresses the importance of the variations between the findings and conclusions of the two different schools of thought on the subject as subsequently related to the etiology.

In every one of 13 cases, reviewed by King (36) networks of argyrophil connective tissue fibers were found growing diffusely into the parenchyma. Extent varied from case to case and plaque to plaque. In part, the reticulum nets grew from blood vessels of small caliber predominantly capillaries and precapillaries; in part they appeared to grow independently of pre-existing reticulum. Diffuse reticulum invasion may be one of the early pathologic reactions in multiple sclerosis and is

found not only in white matter, but in the cerebral cortex and other gray masses. The growth appears to be very definitely related to the disintegration of myelin, with the intensity of the process playing some role. Such reticulin nets bear no correlation with the degree of gliosis, of axis cylinder destruction or perivascular infiltration. This type of connective tissue proliferation takes place independent of fibroblasts.

Putnam (47) in a recent article, draws attention to the existence of vascular obstruction dilitation and proliferation and of perivascular hemorrhages and deposits of blood pigment in the lesions of multiple sclerosis. He goes on further to indicate that by the use of refined technique, the existence of thrombi in various stages may be demonstrated. The frequent occurrence of vascular engorgement and perivascular hemorrhage in the acute lesions and vascular obliterations in chronic lesions has been confirmed.

In patients suffering from multiple sclerosis, Putnam found that thrombi are occasionally found in organs other than the nervous system.

In conclusion, he feels that the primary abnormality is probably associated with the clotting mechanism of the blood.

Hassin (30) in his discussion of neuroptic myelitis

versus multiple sclerosis, draws attention to the histological picture on which the differentiation of the disease is made. The microscopic differentiation of neuroptic myelitis and multiple sclerosis lies in the fact that in the former a scarcity of glia fibers is the point of differentiation.

In a study of 13 cases of multiple sclerosis, Greenfield (27) found that the process of myelin destruction involved first a "wall formation" of gitter cells densely packed against the nerve myelin. This was next followed by the perivascular accumulation of lipoids. Lastly, there was a gradual disappearance of fat, first from tissue between the blood vessels, and finally from the blood vessel sheaths themselves.

The Cerebro-Spinal Fluid in Multiple Sclerosis

The cerebro-spinal fluid examination plays an important role in the diagnosis of multiple sclerosis.

Boyd (13) finds that in the disease, the spinal fluid shows an increase in the lymphocytes in about one half of the cases, the count reaching sometimes a high of 100 cells. The number of lymphocytes, of course, depends on

the acuteness of the process. The globulin reaction is often weakly positive. The Wassermann reaction is often weakly positive in encephalitis and in about 50% of the cases a paretic gold curve occurs.

Epidemic encephalitis is the only other disease giving a paretic gold curve with the exception of neurosyphilis. A positive Wassermann rarely occurs in multiple sclerosis

Adams (2) agrees with Boyd's views but finds that a normal cell count is more common than a slight increase.

Kaplan (34) is of the opinion, that, a positive spinal Wassermann, with normal cell count and minimal globulin, should be considered a technical error.

In a study of the spinal fluid of 38 cases of multiple sclerosis, Ayer (3) concludes that there isn't any single fluid test of paramount value in the diagnosis of multiple sclerosis. His findings in the spinal fluid were essentially the same as other investigators have mentioned. The greatest role that the spinal fluid plays in neurological disorders is that of a means of differentiating the many diseases which have similar symptoms and findings.

The Course and Prognosis of Multiple Sclerosis

Wechsler (62) in discussing the course of the disease expresses the opinions of most investigators when he states that, " the course of the disease is chronic, progressive, with numerous exacerbations and remissions."

This is true of most cases, although there may be variations in the course of the disease depending on the age of the patient and any intervention by some intercurrent infection.

The duration of the disease may vary from one to twenty years or more, however, the average is usually about seven or eight years.

Jellifee and White (33) cite a case of Marburg's in which the course of the disease was short, acute and fatal, lasting only six months.

Symonds (53) draws attention to the fact that the disease is characterized chiefly by its relapses and remissions.

The acute, short duration types of multiple sclerosis usually can be attributed to early bulbar involvement. Thus the disease, although chiefly chronic, may be an acute affair.

The course and type of the disease in the opinion of Marie as quoted by Sachs (55) is:

1. "The chronic progressive type--a very gradual increase in all the symptoms and covering a period of years.

2. The chronic type with exacerbations, marked by the occurrence of hemorrhage, sudden amblyopia and the like.

3. The chronic remitting type--the progressive is very slow with only slight exacerbations from time to time."

Many men have tried to pigeon hole a set type of course for multiple sclerosis, but no two cases are similar and the only deduction to make on the course of the disease is that the disease may be acute or chronic, usually the latter which is manifested by a series of remissions and relapses lasting over a period of years.

The prognosis as a rule is unfavorable in multiple sclerosis. Stieglitz (52) cites that although unfavorable the prognosis is better in children than adults.

Gowers (25) believes that the most common cause of death is interference with the vital centers in the medulla, principally the impairment of deglutition with its various consequences.

According to Wechsler (62) the prognosis as to life is not bad, but as to morbidity, it is unfavorable.

He feels that infections, such as nephritis, pneumonia and other intercurrent diseases are the chief cause of death.

Most investigators are of the opinion that patients with multiple sclerosis do not as a rule die of the

disease, but of some intercurrent infection which easily overcomes the bed-ridden weakened patients.

Remissions may last for a long time, but rarely remain stationary. It is the period of remission that has now drawn the attention of investigators who are seeking the etiology of the disease. A great deal of scientific research into the human body chemistry during periods of remissions as yet hasn't revealed anything definite, but is our sincerest hope that the future will yield gratifying results in this field of medicine and science.

At the present time there hasn't been any satisfactory treatment for the disease. The reason for this condition is best expressed by Wechsler who says, " In view of the fact that remissions occur spontaneously in multiple sclerosis, any treatment is apt to be followed by " good results " if it happens to coincide with the remission. Not knowing the etiology or pathogenesis we have no special treatment and can not expect a cure.

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