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Multiple sclerosis

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MULTIPLE SCLEROSIS

by

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INTRODUCTION

It has been over one hundred years since multiple sclerosis was first described as a separate disease entity. One would think that in that length of time all the details of the disease from the etiology to the treatment would have been worked out. However, this is one disease that has withstood all investigation by thousands of investigators who have tried to determine and prove its true etiology. Because the etiology has not been ascertained the correct type of treatment can only be found by trial and error.

Multiple sclerosis is noted for its remissibility and this further hinders finding an effective treatment. However, there is one form of treatment now being used which offers some promise if used in early cases. It is the purpose of this paper to give a review of some of the literature written on the disease, but giving special attention to the early symptomatology so that a early diagnosis can be made.

HISTORY

Multiple sclerosis was first described by Sir Robert Carswell, a medical student in London. He followed his masters around the hospital, requested and received permission to draw in color, pathological tissues which were exhibited to students. Among these sketches there appeared in 1837 one of the spinal cord with pons and medulla showing superficial colored plaques seemingly indiscriminately placed throughout the parts. This condition he described as "A peculiar diseased state of the cord and pons varolli 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 into the gray substance."

Almost contemporaneously Cruveilhier described a similar condition pathologically as well as clinically. Because this is probably the first description appearing in the literature it may be interesting to quote Cruveilhier verbatim. The patient was a fifty-four year old woman, who had been at Salpêtrière 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 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 incoordinating 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. The 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 toward it; by the sudden combined movements of head and hand the snuff reaches the nostrils." He described the toes as being "strongly flexed". A further statement of interest, because it has been supposed that only more recent authors have stressed this point, is that sensibility be found in places diminished and delayed.

In 1849 Frerichs diagnosed clinically a few cases as examples of spinal sclerosis, although, much adverse comment was made on these diagnoses,

yet in 1856 one of his pupils, Valentiner, was enabled to publish their subsequent history with autopsy reports and pathological findings. This established with certainty the brilliant correctness of the diagnosis. The pathology as described by Frerichs as "an abnormal firmness of leathery consistency in irregular circumscribed parts of the white, rarely involving the gray matter of the cord, with a poverty of the blood vessels. The patches are almost normal in color or milky white, dull and occasionally grayish red. There is loss of nerve elements." Frerichs stated that clinically the following characteristics of the disease had been observed: (1) The condition is produced gradually with exacerbations and remissions; (2) one side of the body is first affected, then the other; (3) paresis of the lower extremities appears early and reaches a high degree; (4) the disturbance of motility outweighs that of sensibility; (5) the chief seat of the disease is in the medulla with disturbances of the ninth, tenth, and eleventh cranial nerves; (6) there are frequent psychic episodes; (7) sclerosis of the nervous system is more frequent in the young; (8)

the general nutrition, for a long period remains undisturbed.

In the same year, 1856, Carl Rokitansky published in his "Pathological Anatomy" a description of the connective tissues 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 cord. "Connective tissue proliferations are found in the cord in the so-called slowly producing paraplegias in normal gray matter. At times the contraction produced thereby is so great that the cord seems a series of knotted strands." He then states, "At times the condition is continuous with the spinal nerves and is then known as tabes dorsalis."

In 1863, Kindfleisch went somewhat further in the pathological description; he recognized the changes that took place in the blood-vessels and nerve elements as being produced by either a constantly recurring or else a long standing inflammatory condition combined with hyperemia. He also recognized the perivascular cell infiltration with the thickened vessel walls and the fatty changes in the neuroglia cells.

In 1868, Jean Marie Charcot (see Hoeber (22)) published a clear concise review of the literature, also a description of a case of a servant girl in his own household suffering from multiple sclerosis. Her symptoms of nystagmus, scanning speech, and intention tremor are familiar as Charcot's triad to every medical student. He definitely fixed the name of the disease "Sclérose en plaques disseminée" or disseminated sclerosis or multiple sclerosis.

Following Charcot, many observers now began to add to our general knowledge of the disease, but always within the framework outlined by the great Frenchman.

In 1889, Uthof (48) published a comprehensive monograph going into the details of the eye symptoms. Since that time the advance has largely been on the clinical side in the addition of minutiae and the nicer points in diagnosis.

DISTRIBUTION AND INCIDENCE

GEOGRAPHIC DISTRIBUTION

Probably the most complete survey ever completed concerning the incidence of multiple sclerosis in the United States was conducted by Davenport (16) based on men drafted for service in the U. S. Army of 1918. The map at the end of this section shows by states the varying density according to the rate of the disease. The maximum rate found was in the states of Michigan and Minnesota, each having 180 per 1,000,000. There were large camps in this area but there were also several camps in other states none of which had such a high incidence. However, it must be remembered that these men drafted for service were of an age at which the incidence of multiple sclerosis is maximum, and the above rates must be considered higher than those for the general population, which includes children and the aged. Taking this into consideration, Davenport thinks the proportion of the whole U. S. population affected is not likely to be more than 50 per 1,000,000, a rate less than one-third or 160 per 1,000,000 the approximate incidence reached by Bromwell (12); of that in England and Wales.

In other countries multiple sclerosis is found to be quite common especially in European countries, with the exception of Italy and Rumania. A survey taken in Northern Switzerland by Bing and Reese (3) has shown that 360 per 1,000,000 of the population are affected. In the town of Basel the morbidity rate is 740 per 1,000,000. Monrad-Krohn states that multiple sclerosis is very common in Norway. Putnam (42) states, "It is common in Baltic countries, Scotland, North Atlantic seaboard, and the Great Lakes region. Rare in Mediterranean countries and our own South, almost unknown in China, Turkey, India, and Japan."

VARIATIONS IN RACIAL SUSCEPTIBILITY

Because the United States is composed of such a heterogeneous population, comprising many races, it offers exceptional opportunities for studying variations in racial susceptibility to the disease. Davenport, in his survey found the highest incidence of the disease among the Finns and the Scandinavians, with rates of 290 and 160 per 1,000,000 men examined. No other section showed a higher rate than 100 per 1,000,000, and he thought the high ratios in the Finn and Scandinavian sections "are probably signif-

icant."

Bailey (see Hoeber (22)) has investigated the incidence of the disease among cases of organic nervous disease and injury in different races of drafted men. Whereas, for the whole group, cases of multiple sclerosis constituted seven and one-half percent of the cases of organic disease, the proportion was above the average in certain races, being highest in the Scandinavians--twelve and one-half percent, and the French--ten percent. The Slavs, Germans, English, and Irish also showed a higher incidence of the disease than others.

Several American observers have pointed out the incidence of multiple sclerosis is higher in the foreign-born than in the native population. Bailey found the proportion of foreign-born men, in the whole group of drafted men with organic nervous disease, was nine percent, while in the group with multiple sclerosis it was nearly thirteen percent. Davenport (16) analyzed the racial incidence of the disease among seventy foreign-born patients in New York, and found that it is low among the Russians and Italians. The English and Germans have twice as many cases as expected,

while the Swedes have a rate two and one-half times, and the Norwegians three and one-half times the expectation.

Although most authorities believe that the Negros are less subject to the disease than Whites, Kolb (26) at Johns Hopkins' Hospital went over the histories of all patients with the disease who were seen in the dispensary from Jan. 1, 1929 to Dec. 31, 1939. It was decided to consider as definite cases of multiple sclerosis only those in which a predominate number of the following criteria was satisfied: Onset of symptoms between the ages of 15 and 55 years, a history of remissions and exacerbations of the disease, subjective or objective sensory disturbances, objective evidence of disease of the pyramidal tract or cerebellum, nystagmus, slurred speech, loss of abdominal reflexes, retrobulbar neuritis, presence of central scotomas, pallor of the optic discs, and changes in the cerebrospinal fluid. Of the two hundred forty-one cases collected during this period, forty-two were rejected and one hundred and ninty-nine were retained as definite instances of multiple sclerosis. From this group of cases Kolb states, "The disease is as frequent among the Negro

as among either the native or the foreign-born population. The rate for the disease over an eleven year period is 170 per 1,000,000 of the general population and 168 per 1,000,000 of the Negro population.

HEREDITARY, FAMILIAL, AND SEX INCIDENCE

Davenport (16) states it seems most probable that such geographical, ethnological, and familial distribution as multiple sclerosis shows depends in part upon one or more hereditary factors. He sites a most famous case that was first described by Pelizaeus (1885) and continued twenty-four years later by Merzbacker. In this case the parents were not affected but of their eight children (four boys and four girls) one of the boys was affected; of thirty-eight grandchildren (twenty-one boys and seventeen girls) four boys were affected; and of twenty-three great-grandchildren (thirteen boys and ten girls) five boys and two girls were affected. In this series running through four generations there were ten boys and two girls affected.

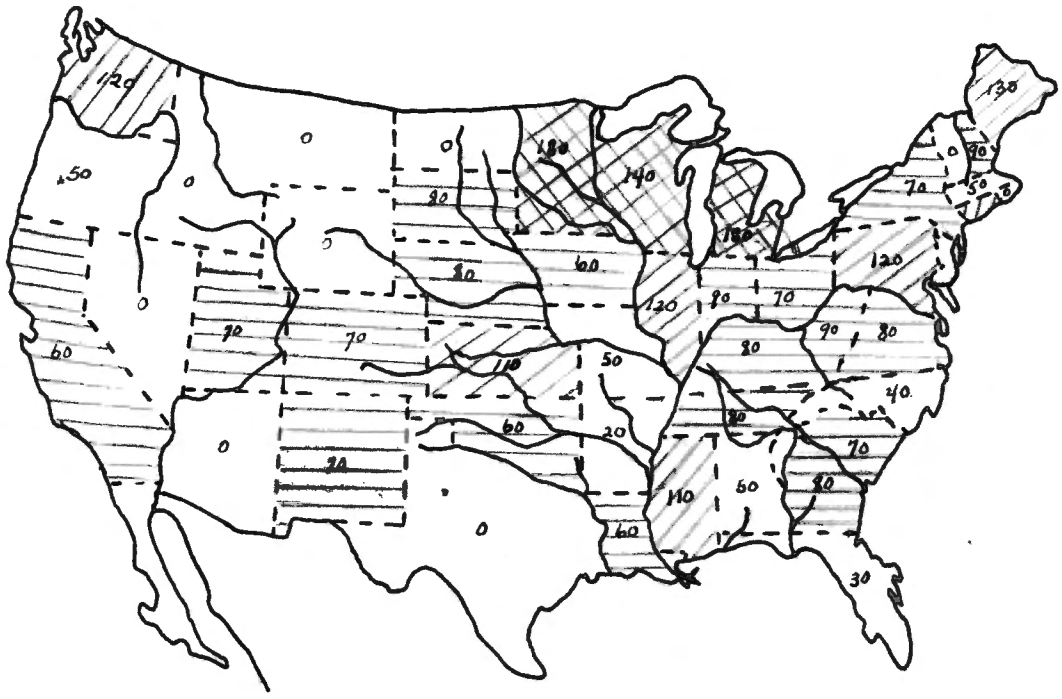
Wechslers' series of cases collected from the literature contained eight hundred seventy-four males to six hundred thirty-one females, or in proportion

of approximately three to two. Outher authors substantiate this proportion with the exception of Bing and Reese (3) whose survey in Northern Switzerland yielded one hundred seventeen males to one hundred sixty-four females. This last series may be due to local environmental conditions, investigation of which might provide a clue to the etiology of the disease. Davenport (16) in closing states, "Whatever may eventually be proven to be the endogenous cause of multiple sclerosis, the factor of heredity cannot be left out of account."

AGE OF ONSET

Multiple sclerosis occurs in all ages, from early childhood to very old age. It has been described in about one hundred cases in children. The literature mentioned is made up of as young as one and one-half, three, and four years old. The youngest recorded by Wechsler was ten years, with the onset of the illness at seven. Olkon (38) gives a case history of a patient twelve years old who was diagnosed as multiple sclerosis. She had had the symptoms then for six years. Jelliffe (25) speaks of a patient of eighty-one years, but in all other records no mention is made of patients above sixty-five. The disease is most common between the ages of twen-

ty and forty, about seventy to seventy-five percent of all cases. Wechsler in one hundred ninty-four cases has thirty-four percent between twenty-one and thirty years of age and thirty-seven percent between thirty-one and forty years of age.



Map of the United States showing by states the varying density rate of multiple sclerosis

SYMPTOMATOLOGY

It is very difficult to describe the symptoms of multiple sclerosis for there are few disease which raise such difficulties of diagnosis. The "classical" clinical picture with which Charcot familiarized us, though highly distinctive, is now recognized as occuring in only ten to twelve percent of cases. In the remainder the manifestations of the disease assume the most varied forms. Brain (7) states the "onset may be acute, subacute, or chronic, its course remittent or steadily progressive." However most authorities divide the disease into the acute fulminating or the more usual chronic type. The acute fulminating begins with the symptoms of headache, vertigo, generalized pain, fever, and gastrointestional disturbances and within a few days characteristic signs of the disease develop. The chronic slowly progressing form is unassociated with any marked bodily reaction. (18)

The course of symptoms is often characteristic. They sometime come on within a few minutes, or overnight. A patient may watch a scotoma develop, or be thrown down by a hemiplegia. Often the onset is subacute, gradually increasing overdays, sometimes with

fever and leukocytosis. Even when symptoms come on insidiously, the patient is able to remember slight variations in progression. Once at their height, symptoms tend to improve or disappear. If relapses occur, they more often consist of an exacerbation of existing symptoms, rather than the appearance of new ones though both may concur. (42)

A single isolated "signal symptom", such as numbness of one extremity, diplopia, or central scotoma, may appear and disappear long before the disease as a whole becomes recognized.

As the symptoms of multiple sclerosis are so protean in their manifestations, it is thought advisable to present them from the view point of various systems.

CRANIAL NERVES

Disturbances of the olfactory nerves are rare. Hallucinations of smell have been described.

Ocular manifestations may be divided into seven different symptoms according to Larkin (29). These are seen in forty percent of all cases: (1) Retrobulbar neuritis--first and may be the only symptom for a long time; (2) diplopia; (3) nystagmus; (4) abnormal pupillary reactions; (5) nerve head altera-

tions; (6) alterations in visual fields; and (7) papillitis and papilloedema.

According to Drake (18) the most common ocular disturbance is nystagmus. This occurs in about sixty to seventy percent of his cases and is usually of the horizontal type when it is induced, but when spontaneous it commonly occurs in all directions. The movements are fairly coarse, rhythmical, and rapid.

Failing vision may come on gradually or it may be acute and present transitory attacks of amblyopia. In the most acute cases the symptoms are those of an acute retrobulbar neuritis whether the process comes on insidiously or acutely there is finally an atrophy of the fibers of the macular bundle, recognizable as a temporal pallor of the disc. (7)

The defective fields in multiple sclerosis are of three types: (1) Peripheral contraction; (2) central or paracentral scotoma; and (3) a combination of both peripheral and central defects. The most characteristic defects in the fields are the central and paracentral scotoma. (50)

Changes in the pupils, while not characteristic of this disease, may occur. Pupillary inequalities

are not infrequent. Miosis occurs in the later stages. There has been considerable dispute as to the presence of the Argyl-Robertson pupil.

Trigeminal neuralgia may appear as an initial and predominant symptom in the course of multiple sclerosis but only rarely. Finesilver (19) in reviewing the literature found but twenty-five cases in the seventeen years up to 1935. He gives a report of three of these cases; in one the patient was a 50 year old white married male who developed a typical trigeminal neuralgia. This was treated by surgery and the dorsal sensory root was cut and he received complete relief. However, as time progressed the patient began to notice difficulty in the finer movements of the right hand. There was also gradual difficulty in walking due to the weakness of the right lower extremity. These symptoms continued until at present the patient has a fine persistant nystagmus in all directions; a bitemporal optic pallor is present; the speech somewhat explosive; and there is a bilateral ataxia in the heel to knee and finger to nose tests. There is a marked diminution in the motor power of the right lower extremity. The deep tendon reflexes

are markedly active throughout, greater on the right than on the left. There is a bilateral hypertonic condition of the lower extremities. The abdominal reflexes are absent. There are bilteral Babinskis' and confirmatories. This patient has, therefore, developed a typical case of multiple sclerosis following the initial symptom of trigeminal neuralgia.

Paralysis of the facial nerve occurs more commonly in association with hemiplegia or pontile symptoms and is often transitory.

Transitory deafness occurs in some cases and complete or partial and transitory deafness has been recorded. (18) Rotatory giddiness with a tendency to fall is present in a few of the cases. (7)

The act of swallowing is affected quite frequently in the later stages of the disease. Speech disturbances are present in about one-half of the cases. Easy fatigability and stuttering sometimes occur. Aphonies are rare.

The tongue sometimes shows atrophy and fibrillary tremors which are often unilateral. Ataxic movements of the tongue are common in the later stages.

MOTOR SYSTEM

Weakness of the lower extremities is one of the

earliest symptoms in multiple sclerosis. As this muscle weakness increases, the lower extremities become spastic and eventually paraplegia develops and leads to contractures. Muscular weakness may begin in muscles which are habitually used, as in the arms of carpenters or painters and in the larynx of singers. (18)

Jackson (24) states symptoms referable to the motor system predominate over those of the sensory system. Spastic conditions are common, muscular atrophy is rare, and pain seldom occurs.

Kolb (26) in his studies on multiple sclerosis in the American negro found in thirty cases that weakness and stiffness of the legs was the first symptom in seven cases; weakness of a single extremity was first in five cases; and unsteadiness of the legs was the first symptom in four cases. In his cases, therefore, of thirty cases, sixteen had symptoms referable to the motor system as first symptoms. In following these cases up there were fourteen who showed spastic paraplegias and seven showed ataxic paraplegias when first examined.

Brain (7) in reviewing the literature of various investigators found the following relative frequency which individual symptoms were found by four groups

of investigators: Sachs and Friedman, in the United States, found spastic weakness in eighty-one percent of their cases; Birley and Dudgeon, in England, found abnormal extensor plantar reflexes in ninety-nine percent of their cases; Marquexy, in France, also found abnormal extensor plantar reflexes in ninety-nine percent of his cases; and Bohmig, in Germany, found spastic weakness in seventy-seven percent of his cases. It is shown, the, that even from widely separated investigators symptoms referable to the motor system are usually the first symptom seen and are present in practically all cases sometime during the course of the disease.

Ataxia of the upper extremity may be elicited in a majority of the cases. It also occurs in the lower extremities but less frequently. The ataxic movements often preceed the development of the intention tremor and may or may not be increased on closing the eyes.

The intention tremor is a frequent sign, especially in the later stages-the tremor develops gradually and is usually of equal intensity on each side. It is aggravated by fatigue and emotional disturbances but not greatly altered on closing the eyes. This form of tremor, while usually

present in the upper extremity, may affect the head, trunk, and lower extremities.

REFLEXES

The deep reflexes of the upper and lower extremities are usually increase. Ankle clonus is commonly present while the patellar clonus is rarely found. The loss of palatal reflex has been described. The phenomenon of Babinski is commonly present and the crossed Babinski may be found. Oppenheim, Chaddock, and Rossolimo phenomena are frequently present and there may be a positive Hoffman sign in the upper extremities. The abdominal reflexes are usually absent bilaterally. The cremasteric reflex may be modified on one or both sides. (16)

Hoeber (22) in a study of one hundred forty-one cases and listing in order of frequency of their occurrence listed loss of abdominal reflexes in one hundred eighteen cases or in eighty-three percent. Babinski's sign was present in sixty-seven percent of cases and increased deep reflexes in ninety percent of the cases. It has then been shown that the reaction of various reflexes is quite important in the diagnosis.

Disturbances of gait and station-the most common types of gait are the spastic, the spastic-ataxic,

and spastic-paretic. With the patient in the Romberg position there is usually some degree of swaying with the eyes open which is little affected upon closing the eyes. (18)

SENSORY SYSTEM

Most observers agree that changes in the sensory sphere occur quite frequently. Birley and Dudgeon (4) found occurrence of paraesthisiae in eighty-two percent of their cases. Often the complaint is of formication in one-half of the body which may either persist or occur as sensory Jacksonian attacks.

Among the objective sensory changes the most important from the viewpoint of diagnosis are those affecting the sense of vibration, passive motion, and muscle position sense. When changes in the cutaneous sensibility occur they may be manifested by areas of hypesthesia or anesthesia, hyperesthesia or hypalgesia, or analgesia and hyperalgesia. These changes may be limited to one side of the body or may be segmental in distribution.

Spontaneous pains, though comparatively uncommon, are important, since if their significance is misunderstood they may be misleading. The are sometimes severe and may involve the limbs, e.g. sciatic

pain, pain in the shoulders, or trunk, girdle pains. The pains are said to be "boring" or "neuralgic" but "lancinating." Vertebral tenderness may be present and headache may occur.

Salmon (43) describes a condition which was at one time thought to be diagnostic. When the head is flexed strongly there is a sensation originating in the nape of the neck and like a flash traverses the whole length of the spinal cord and the four extremities. This is known as Lhermittle syndrome but is only found in a few of the cases.

Birely and Dudgeon (4) found an impairment of postural sensibility in sixty-six percent, of appreciation of vibration is sixty-one percent, and of cutaneous sensibility in thirty-two percent of their cases.

SPHINCTERS

The urinary bladder is affected in a majority of cases. This may be an initial symptom or a transitory phenomenon occuring during the course of the disease. The patient may complain of urgency of urination or a feeling of having to strain to pass urine. In the later stages marked retention and incontinence may occur. Constipation is frequent and rectal incontinence less commonly encountered.

MENTAL SYMPTOMS

Seiffer in 1905 first used the term "polysclerotic dementia" in describing a psychotic state occuring in multiple sclerosis, characterized by a morbidly expansive mood, euphoria, or a marked lability and sudden change of mood. (48)

Ambredane and Saethre have recently classified the psychic disturbances into three types: (1) The usual polysclerotic psychic disturbances affecting about seventy-five percent of the cases in which there were both emotional and intellectual changes, such as excessive affectivity, often associated with diminution in intelligence and inability to perceive and remember new stimuli; (2) the picture of dementia, either severe as in general paresis, or partial dementia characterized by intellectual dullness and marked impairment of memory; (3) frank psychoses accompanied by hallucinations, delusions, and suicidal tendencies. Ambredane stresses the fact that anxiety is often the main symptom in the initial stages of multiple sclerosis which later develop psychoses.

Cottrell and Wilson (15) studied twenty-eight patients with multiple sclerosis of more than ten years duration. They observed these cases from six

to eight months and studied them with special emphasis on their emotional affective symptomatology. They found in general: (1) The emotionally content or prevailing mood most often in the direction of increased cheerfulness; (2) a marked sense of well being out of proportion to their physical condition; and (3) a tendency toward an increased expression, which at times was incongruous with the underlying mood.

Arbuse (1) states, "Mental symptoms do not always occur in multiple sclerosis, although they probably appear in a large proportion of cases. While they are not usually prominent, they may be of wide variety. One of the most frequent manifestations is a certain amount of mental deterioration shown by impairment of memory, slowness in stream of thought, and emotional indifference. When multiple sclerosis begans early in life, it usually has particular serious results psychically and may jeopardize further mental development. On the other hand, where hallucinations and deliriums have been described there is certainly a combination with a psychoses. Psychic alterations often occur after a long period of an apparently normal mental condition. Late in the disease, in a fairly large number of cases, we are apt to find mental aberrations."

CONVULSIONS

Wilson and MacBride (see Brain (7)) in 1925 were able to find eight cases in the literature and added seven more from their own experiences. These authors described Jacksonian attacks which may or may not be followed by hemiparesis, generalized epileptic attacks, one doubtful case of petit mal, and one case of epilepsia partialis continua.

Brain and Kiddoch (7) have reported a case in which the fits led to an erroneous diagnosis of intracranial tumor. This patient, "after suffering for several years from occasional generalized epileptiform convulsions, developed a progressive weakness of the right lower limb with increase tendon reflexes, an extensor plantar response on the right side, and some loss of postural sensibility in the toes of the right foot. These were the only signs of nervous disease, but autopsy showed the case to be one of disseminated sclerosis with a particularly large plaque in the upper part of the precentral and post central convolutions on the left side."

THE CEREBROSPINAL FLUID

Although there are no true symptoms referable to the cerebrospinal fluid it was thought advisable

to add this section because of its aid in the diagnosis of the disease.

Brain (7) in reviewing the work done on the cerebrospinal fluid by various investigators found the following: the pressure is sometimes slightly raised, the naked-eye appearances are normal, and in at least half the cases the cell count is normal. More than ten cells per cu. mm. were found in five out of forty-seven counts by one investigator and eleven out of fifty-one counts by another, with maximal counts of two hundred thirty-one and forty-two respectively. The cells are mononuclear in type. The total protein is usually just below the upper limit of normal, 40 mg. per 100 cc. It is somewhat above normal in fifteen to twenty percent of cases, but never very high. The Nonne-Apelt and Pandy tests for globulin occasionally yield a positive response, the former in about one-third of cases. The Wassermann reaction is negative.

According to Merritt (34) the cells are increased beyond five in twenty-eight percent of cases but rarely above one hundred. Protein was increased in twenty-four cases, abnormal gold curves in seventy-one percent, slight increased pressure in most cases, and in seventeen percent the fluid was normal.

Ayer and Foster (see Hoeber (22)) carried out the colloidal gold test on forty-two specimens obtained from thirty-three patients, with the following results: So-called "paretic" type--twenty-one fluids in sixteen patients; so-called "luetic" type in seven fluids in seven patients; other positive reactions--three fluids in three patients; and negative reactions--eleven fluids in ten patients. There was thus a "paretic" curve in about half the cases and some other abnormality in a further quarter. These investigators believe that the "paretic" type of gold curve often indicates a progressive phase of the disease and that a negative results is more often obtained from stationary cases.

PATHOLOGY

The early investigators of the disease such as Cruveihier (1835), Frerichs (1849), Rokitansky (1856), and Kinfleisch (1863) did a great deal of study on the disease and recognized some of the salient features of the pathological process which have not been improved on greatly even by our present day pathologists.

However, from Charcot in naming the disease "Sclerose en plaques disseminee" we get the main pathological "unit" in the disease. This is a circumscribed patch of nervous tissue in which the pathological process runs a fairly well-defined course, terminating in the formation of a "sclerotic plaque".

These so-called patches of sclerosis are also the best known and most notable characteristic features of multiple sclerosis. Scattered throughout the central nervous system and varying in size and form they preferably affect the white substance, its long or short nerve fibers. They may be symmetrical or asymmetrical and may invade even the peripheral nerves. Wherever located, whatever the size or age, there can be discerned in a patch many nerve fibers

in fairly good condition. A great many are merely deprived of myelin, appearing as naked axons; some are covered with myelin but partially, while others show a destruction of both the myelin and axon, exhibiting a state of Wallerian degeneration. (22)

According to Schinker (44) in a histological study of twenty-two cases the loss of myelin was the cardinal feature. The majority of the small areas of demyelinization were perivascular--these appeared as light staining circular or oval zones surrounding small veins and capillaries. These areas revealed the following characteristic changes in myelin: (1) In the central part of the plaque the destruction of myelin was generally complete, practically no or very few fragments being discernible; and (2) at the periphery a transitional zone was often observed characterized by swelling, fragmentation, and beading of myelin sheaths. This zone was sometimes very small or imperceptible, so that the transition was rather abrupt.

Brain (7) divides the plaques into an "early patch" and a "late patch". In the early patch the blood vessels are dilated, but in the early stages there are few changes in the vessel walls. Capillary hemorrhages have been observed. The perivas-

cular spaces play a important part in the pathology and in the early stages contain cells of several different types. The occurence of lymphocytes and plasma cells in the perivascular spaces in multiple sclerosis have been observed by many observers. (4) The other type of cell found in the perivascular spaces is the fat granule cell, a large cell containing globules of a fatty sybstance produced by the breakdown of myelin of the nerve sheaths. External to the perivascular space is a concentric zone in which the myelin sheaths of the nerve fibers are severly damaged. Scheinker (44) divides this into three types: (1) Those in which the axis cylinders were completely destroyed and practically absent; (2) those in which the axis cylinders were severly damaged and reduced in numbers; and (3) those in which the axis cylinders were fairly well preserved or substantially intact. The glia changes may also be divided into three types: (1) Pronounced rarefaction and a spongy appearance of the glial reticulum with loss of affinity for the stain; (2) in some patches Hortega preparation reveals numerous microglia cells of most bizarre nuclei, mainly bean and kidney shaped; and (3) glial fibrosis in formation of scars was frequently observed. Peripheral

to the zone in which much myelin is lost is an area transitional to normal tissue in which it is less completely dissentegrated.

The "late patch" as described by Brain (7) exhibits the end results of the changes just described. The blood vessels show hyalin thickening and may be infiltrated with embryonal cells. The perivascular spaces show disappearance of the fat granules leaving the perivascular space dilated. The lymphocytic infiltration may persist to some extent and may be associated with proliferation of cells of the adventia. Demyelinization of the surrounding nerve tissue is complete and the spaces are filled with fibroglia, a condensation of the original glial meshwork. The axis cylinders are reduced in number and some of those persisting show abnormalities, swelling and spindle enlargements.

The distribution of the plaques is widespread. Marburg (31) believes the favorite site is the outer and inner surfaces of the brain and the areas bordering upon the walls of the ventricles. The outer surface is preferred in the spinal cord and brain stem, but not in the hemisperes, so that the role of the cerebrospinal fluid in the production of foci may be ignored. Dow and Berglund (17) found twenty-

nine plaques in the white matter, twenty-eight in mixed white and gray, and only three in the gray alone. Size was an average of 3 mm. in sixty cases. As to shape they found thirty-one ellipsoid, eleven cylindric, ten spherical, five irregular, and three crescentic. Of the above sixty cases twenty had no central vein, in eleven no veins could be found, twenty oriented about a normal-appearing vein, and only in nine cases was a vein in which thrombus could be found.

Marburg (31) believes that phlebothrombosis is the probable cause of the swelling of the axons in this morbid condition. He thinks the predilection of the white matter may be explained by the blood circulation being slower there, and by the assumption that the possibilities of a collateral circulation are not as favorable in the white matter as they are in the gray. The prevelance of the patches on the inner and outer surfaces of the neuraxis may be explained by the fact that in these regions the veins emerge from the parenchyma and therefore the circulation here is very slow.

Several writers have described the distribution of the patches in multiple sclerosis as: (1) Perivascular; (2) subpial; and (3) periventricular.

An analysis of this classification would be of benefit.

Perivascular patches

The close relationship of the patches to the blood vessels has been emphasized by many writers, even as far back as Kindfleisch in 1863. Dawson points out that "The changes appear within, but do not coincide with the area of distribution of the arteries." In the spinal cord there are two basal types, wedge-shaped and oval or round. These correspond to the distribution of the transverse and perpendicular branches of the lateral vessels of the cord. The transverse branches run in from the vaso-corna, the arterial wreath which unites the anterior and posterior spinal arteries. Corresponding to these branches are the subpial wedge-shaped areas of sclerosis with their base to the surface. Other arterial branches enter the cord and divide into a perpendicular branches running upward and downward. The patches corresponding to these are of an elongated oval shape and extend over several segments longitudinally. They appear circular or oval when cut transversely. The cervical and dorsal cord are more affected than the lower segments.

In the corna radiata round or oval submiliary

foci occur. In the basal ganglia are found round areas which appear to begin as perivascular patches around the branches of the lenticulo-striae and strio-thalamic vessels, and later fuse to form areas of irregular shape.

The cerebral cortex may be involved by patches of subcortical origin, or by surface patches, wedge or oval shaped, which coalesce to yield a moth-eaten appearance. In these cortical areas demyelinization often corresponds to the area of supply of the superficial plexuses of the cortex. Similar changes are found in the cerebral cortex.

Subpial patches

It is probable that in both the brain and cord the subpial patches constitute a variety of perivascular patches related to the distribution of the blood vessels entering from the pial surface.

Periventricular patches

The predilection of disseminated sclerosis for the neighborhood of the cerebral ventricles has been stressed by a number of observers. (44)(41) The whole of both lateral ventricles may be involved in periventricular sclerosis or the process may be limited to a part of one ventricle. It is most marked in the horns. The patches nearest the ventricles have a

direct and extensive relationship with the ventricular surface and are formed by thick fibrillar bands. From these bands finger-like extensions project into the surrounding gray matter, e.g. the optic thalamus. In this way some periventricular plaques appear to be connected in the neighborhood of the ventricle by a pedicle.

Two views have been put forward to explain the periventricular sclerosis. Dawson appears to accept Borst's suggestion, that it is related to the rich vascularity of the region which would bring periventricular sclerosis into the category of the perivascular lesions; Merel and Pastine believe that it is secondary to abnormalities in the cerebrospinal fluid; and Lhermeth and Guecione regard both factors as playing a part.

The pathological process as seen in special situations may be gone over briefly. Multiple sclerosis may involve the visual fibers at many points. Larkin (29) states that the optic chiasma is most frequently affected, especially its anterior border. Brain (7) notes that patches in the optic nerves are related to the central vessels, while in the chiasma and optic tracts they may be either subpial or subependymal in relation to the chiasmatic

recess of the third ventricle. Dawson points out that there is a marked reaction of the connective tissue as well as of the glia in the optic nerves. The whole intracranial course of both optic nerves may be devoid of myelin. The visual fibers may also be involved in the optic radiations by extensions from the periventricular sclerosis around the posterior horns.

It is generally accepted that, as a rule, the typical patches of disseminated sclerosis are confined to the glial-bearing parts of the nervous system. However, especially in the posterior roots of the lumbar cord, this limit appears to be overstepped and glial proliferation appeared to have extended far into the non-glial portions of the roots.

Peripheral nerves are rarely affected. Inflammatory changes in the meninges have been remarked upon by a number of workers. (7)

ETIOLOGY

There is probably no other neurological disease, at present, which has been such a thorn in the investigators' and pathologists' ego as multiple sclerosis when it comes to explaining the etiology of the disease. Although it has been thirty-one years since Bullock, an Englishman, first attempted to throw some light on the etiology, we are but little more advanced now than he was then on the subject. A review of the early literature will show the reason for this lack of advancement.

It was in 1913 that Bullock, now Gye (20), first claimed to have transmitted multiple sclerosis to animals. He injected cerebrospinal fluid from a case of multiple sclerosis subdurally into a cat and subcutaneously into a rabbit. The cat was unaffected, but the rabbit became completely paralysed and was killed on the sixteenth day after injection. This animal is said to have shown edema, congestion, and fragmentation of myelin sheaths in the spinal cord. The same specimen of cerebrospinal fluid after being kept on ice for fourteen days was used to inject three more rabbits, two of which remained

unaffected, while the third became paralysed but recovered. A further specimen of spinal fluid from the same patient was divided into two parts, one of which was passed through a porcelain filter; both filtered and unfiltered fluids produced paralysis after injection into two more rabbits. The spinal cord of one of these is stated to have shown extensive degeneration when stained by Weigart-Pal and Marchi's methods. In fact "histological examination of the spinal cord reveals a complete reproduction of the appearances found in the human subject". From these experiments Bullock concluded that either a filterable virus or a water-soluble poison was present in the cerebrospinal fluid in multiple sclerosis.

In the following year Steiner (19) attempted to repeat Bullock's experiments. Following his intradural injection of cerebrospinal fluid into a rabbit the animal became ill and died in six weeks. Kuhn and Steiner carried out further experiments in 1917. They injected by various routes a series of rabbits and guinea-pigs with blood, cerebrospinal fluid, or a mixture of both obtained from thirteen patients suffering from the disease. A large proportion of the animals developed paralytic symptoms following these injections, guinea-pigs proving more

susceptible than rabbits, and blood more effective than cerebrospinal fluid. Kuhn and Steiner claimed to have transmitted the disease from one animal to another in a series of four guinea-pigs and two rabbits. Control experiments were negative. The most important result of this investigation was the authors' observation of spirochetes in the heart's blood and the vessels of the liver of the affected animals. They described these organisms as delicate and slender, resembling those of spirochetosis ictero-hemorrhagica, and often possessing a terminal nodule or cilia. Kuhn and Steiner named this spirochete, Spirocheta argentinensis.

Steiner at the same time inoculated a monkey, Macacus rhesus, intracerebrally with the cerebrospinal fluid from a case of multiple sclerosis. The animal showed no symptoms for eleven months then it developed a transitory paresis of the lower extremities. Five months later it was killed, and Steiner found in the cerebral hemispheres plaques visible to the naked eye which histologically exhibited demyelinization, infiltration with compound granular cells, glial overgrowth, and relative survival of the axis cylinders--appearances which he considered indistinguishable from those of multiple sclerosis in man.

Following this Marinesco in 1919 and Kalberlah in 1921 in their experiments claimed to have found spirochetes in the cerebrospinal fluid, tissues, and blood of rabbits and guinea-pigs which had received inoculations of cerebrospinal fluid and blood from patients with disseminated sclerosis.

Gye (20) in 1921 repeated his investigation of 1913 on a larger scale. He obtained cerebrospinal fluid from twenty-one patients with disseminated sclerosis and inoculated by various routes one hundred and twenty-nine rabbits and fifteen guinea-pigs. The latter were unaffected, but seventeen rabbits became ill and paralysed, usually, in a few days. Similar symptoms were produced in a few instances by passage of material from affected to normal animals. No control experiments were carried out and no histological examinations of the nervous systems of affected animals was made. Gye concluded that "disseminated sclerosis is probably an infectious disease and that the virus may sometimes be found in the cerebrospinal fluid". He found no evidence that the pathological agent was a spirochete.

About 1928 Chevassut and Purves-Stewart came forth with a claim of having isolated minute spherical bodies on a special media from the cerebrospinal fluid

of patients with multiple sclerosis. They gave these bodies the name Sperula insularis. They claimed to have cultured these from the cerebrospinal fluid of one hundred seventy-six out of one hundred eighty-eight cases of multiple sclerosis and absent in two hundred sixty-nine controls.

In 1930 Weil (50) following his study of multiple sclerosis concluded the different theories dealing with the origin of the disease could be divided into five groups according to the etiological agent that is thought responsible for the disease: spirochetes, filterable virus, myelolytic ferments, endotoxin, or primary disease of the glia. In this study, experiments are described in which an attempt was made to demonstrate the presence of a filterable virus in cultures from the spinal fluid. He also repeated the experiment of Chevassut and Purves-Stewart and failed to produce convincing evidence that in multiple sclerosis cultures from the spinal fluids yielded a filterable virus and that this virus is responsible for the production of the disease.

In 1931 Steiner (47) examined the brain and spinal cord of a patient who succumbed from an acute attack of multiple sclerosis. He found numerous extracellular spirochetes; he named these

Spirochete myelophthora. In eleven out of forty-nine cases, in twenty-two percent, extracellular myelophthoric spirochetes were found. The spirochete apparently belongs to the genus Borellia which has regular semispherical spires. The radius from, the center of the half-circle to the deepest point of the spire, is smaller than in the treponema type. There are three to twelve single spires.

In 1935 Kopeloff and Blackman (27) gave a summary of their investigation concerning the presence of silver cells in multiple sclerosis compared with their presence in other disease. Silver cells were seen in the brains of ten of eleven patients. In five of the brains showing silver cells, stained bodies were observed which were suggestive of spirochetes. In fifty brains studied as controls only one revealed silver cells, the brain of a child with congenital syphilis.

In 1938 Blackman and Putnam reported their results concerning the nature of the silver cells occurring in multiple sclerosis and other diseases. According to Putnam, the lesions are due to local stasis in the smaller blood vessels and to venular obstruction. To prove this view, thrombotic and hemorrhagic lesions of well-known origin were

selected as control material. The brains of two cases of multiple sclerosis and of eight control cases (five cases with arteriosclerotic brain lesions, two with traumatic lesions, and one with hemorrhagic encephalitis lesions) were examined. In three of these eight control cases, silver cells were found. Blackman and Putnam (5) conclude that these cells are characteristic for multiple sclerosis, but occur also in vascular lesions under conditions which exclude the possibility of local phagocytosis of microorganisms.

Hassin and Diamond (21) in 1939, reported the results of their study of silver cells and spirochete-like formations in multiple sclerosis and other diseases of the central nervous system. The cells should be called granules for silver cells are probably not definite formations. They found them present in many degenerative diseases of the cord and think their presence in multiple sclerosis confirms the view that the disease is one of degeneration and not imflammation.

This about brings the spirochete theory up to present. It is interesting to note that Steiner found spirochetes in eleven out of forty-nine cases during twelve years of study; Scheinker found spiro-

chetes in four out of eight cases during a nine year search; and Roger found them in one out of eleven cases during nine months of investigation--there seems to be a direct ratio between the length of time spent examining and the amount of findings. Steiner (47) states in closing, "It will be a long time before the spirochetal origin of multiple sclerosis is commonly accepted. The spirocheta myelophthora has to be demonstrated in more cases, with less difficulty, and by the use of other methods which have to be developed in the future.

Another theory which gained some recognition was that of Cone, Russel and Harwood (14). They found lead in the spinal cord at necropsy. In six cases of the type progressing by exacerbations and and undergoing remissions they have shown lead in the stools. They conceived the ingenious idea that the periods of exacerbation and of remission in multiple sclerosis might be associated with the mobilization into the circulation, and the removal from it, of lead. Their studies yielded some evidence that such may indeed be the case. However, until the amount of lead present in body fluids and normal amount present are arrived at this theory cannot be accepted. About one year after these results were published,

Boshes (6) reported that in twenty-eight cases only one showed any lead in the spinal cord and he could find no proof of it being the etiologic agent of multiple sclerosis.

Brichner (10) has described very much in detail an abnormal lipolytic activity in the serum of patients suffering from multiple sclerosis and he believes this lipolytic material is active not only on the myelin sheath but also on the erythrocytes and that perhaps such erythrocytic alteration could lead to the formation of Putnam's thrombi. This however has never been proven but the solution may be close at hand.

TREATMENT

Dr. Charles H. Dalloff (see Nicola (37)) once stated, "I do not find that there is any treatment yet which offers any real hope for this disease. It is an interesting disease because the pathology is so definite, etiology so obscure, the symptoms so vague, and the treatment so helpless." Since then there has probably been thousands of different forms of treatment tried but it is notoriously difficult to assess the value of therapeutic measures in multiple sclerosis. Most advocates of some particular line of treatment qualify their optimism by alluding to the natural tendency of the disease to spontaneously remissions. That such a qualification is necessary seems to indicate that no mode of treatment is successful enough to achieve, at the most, a greater improvement then might have occurred spontaneously. Also along this line Putnam (40) believes that on the basis of the statistical evidence and also on the microscopic examination of plaques studied at various stages of development, there is good reason for believing that the maximum extent of the future recovery from acute lesions is determined at the time the lesions are formed, and

that reparative processes run their course irrespective of treatment, aside from attention to hygiene and nutrition. Because there has been such a multitude of treatments advocated for this condition the writer will attempt to limit his discussion to those types of treatment which, from a statistical standpoint, gives a slightly better prognosis.

Concerning general measures Putnam (42) believes there are several steps which are always worth considering. In the first place possible precipitating causes should be avoided when possible. The patient should be protected against overexertion and accidents, as far as possible. Female patients should avoid pregnancy. In the second place, advantage should be taken of the regional differences in incidence of the disorder when circumstances permit. Life in a warm, dry climate seems to have a beneficial effect on many cases--possibly because the common infections of the nose and throat are less prevalent there. In the third place, a constant search should be made for means of correcting the instability of the plasma. The use of anticoagulants naturally suggests itself; and actually they can be shown to have an effect on some experimental forms of the disease. By far the most promising substance seems to be dicumerol.

Meanwhile, symptomatic treatment should not be forgotten. The patient's health and strength must be maintained in every possible way. If spasticity is annoying small doses of bromides are sometimes useful. Alcohol in moderations may help the patient's spirits, and paradoxically, his balance if ataxia and tremor are present. The use of sandalwood oil and tincture of belladonna is often helpful in cases of urgency.

Brain (7) believes rest and avoidance of fatigue are of great importance, but permanent confinement to bed should be deferred as long as possible. He believes further that the high susceptibility of the patient to hysterical embroidery of his symptoms demands psychological insight on the part of the physician, whose encouragement and optimism are often of greater value then his pharmacological essays. Along this line of non-chemical treatment mention may be made of the case of Dr. Marshall (32). His method of treatment consisted mainly of psychotherapy, relaxation, and reeducation with the aid of such adjuncts as physical therapy and occupational therapy. He gives a very interesting case history of a patient suffering from multiple sclerosis. The observations on this patient after eleven treat-

ments consisting of routine exercises and psychotherapy, would suggest that there seems to be evidence of improvement when such therapeutic measures are employed.

Brichner (9)(11) has treated several cases with quinine hydrochloride; as much was given as the patient could tolerate without developing cinchonism--usual dose of five grains three times a day taken indefinitely. He had improvement in one hundred six of one hundred seventy-three symptoms with no improvement in sixty-one and regression if four. The theory of using this drug was that the lesions are caused by abnormal lipases activity in the blood, and that this activity may be due to presence of abnormal lipases which are counteracted by the use of quinine.

Weinberg (51) is a firm believer in the use of lecithin in treatment of multiple sclerosis. He gives intraspinous injections of 0.2 cc. of lecithin mixed with 4cc. of warm normal saline diluted with equal amounts of the patients spinal fluid. This is repeated every ten to twelve days and four injections are given. His conclusions based on twelve cases treated of which ten were carefully studied afterwards and nine showed greater or lesser

improvement, is that the results are sufficiently good to justify further use of the method. The method is harmless and based on the theory that lecithin neutralizes the lipolytic substances present in the spinal fluid.

Purves-Stewart (39) used a specific vaccine prepared from cultures from the cerebrospinal fluid which had been inoculated into monkeys. He used this in seventy cases with the following results: Of ten early cases nine showed improvement and one remain stationary; of twenty-seven moderate cases twenty-two showed improvement and five remain stationary; and of thirty-three advanced cases nine showed improvement and twenty-four remained unchanged. Results on serological observations; Of the ten early cases four developed negatives cultures and eight showed improvement of gold and globulin reactions; of twenty-seven moderate cases four developed negative cultures and twenty-one showed improvement of gold and globulin reactions; and of the thirty-three advanced cases none developed negative cultures and twenty showed improvement of gold and globulin reactions. He concludes this form of therapy is of definite value in early cases.

That the disease is not caused by an avitaminosis

is shown by Meller's (33) experimental treatment with vitamin E. Of twelve cases treated this way only three experienced varying degrees of remission, two became worse in spite of treatment, and the rest were unchanged. They believe that their series is too small for definite conclusions but indicate vitamin E as administered by them is of no value in the treatment of multiple sclerosis.

McIntire and McIntire (35) in attempting to determine the prognosis of multiple sclerosis used three forms of therapy: Thirty-two patients received vitamin B, liver extract, and quinine; eight received hyperpyrexia--four by typhoid and four by hypertherm; and fifteen received no treatment. The life charts of all these fifty-five patients recorded comparable progress of the disease over years, regardless of treatment used. They state in conclusion, "The prognosis of multiple sclerosis varies with the type of disease. Obviously, the prognosis with respect to life is poor for the rapidly progressive form and good for the other types. The rapidly progressive form usually proceeds to fatal termination within seven to eighteen months after onset. Many with remittant types remain well and active for ten to fifteen years. However, one is faced with

the somber fact that the lutimate prognosis is unfavorable in all cases."

The induction of pyrexia is at present one of the most important methods of treatment and with this in mind some of the methods of producing this will be discussed.

Typhoid vaccine has been given intravenously by a number of workers, MacBride and Carmichael (30) treated seventy cases in this way, beginning with doses of twenty-five million and increasing in a course of eight to ten injections up to four hundred million. These were given at one, two, or three day intervals and obtained a temperature of about 100°F. They believed this gave satisfactory results and when combined with treatment with silver salvarsan in early cases brought about good results.

Neymann and Osborne (36) treated cases of multiple sclerosis by electropyrexia. After the diagnosis was established, the patient was given a series of artifical fever treatments varying from six to fifty-one in number, according to the requirements of each individual case. They had twenty-five cases and treatment consisted of a quick rise to 103.5°F. and a high plateau ranging between 105°F. and 105.5°F. The temperature was maintained at this

high plateau for from eight to ten hours. The treatments were given biweekly. No other form of therapy was employed. The authors state, "The results presented are not to be considered as claims for the positive effectiveness of this therapy. It is manifestly impossible to evaluate the treatment of this syndrome before many years have elapsed. However, it is known that one can produce and maintain hyperpyrexia at will by means of these modalities, and that this can be done with the minimum amount of risk to the patient. Also that if hyperpyrexia per se is to prove of benefit in 'multiple sclerosis', these physiotherapeutic procedures are at present the most practical that can be employed. 'They allow an accurate dosage of the amount of fever, and have none of the disadvantages of introducing chemicals or infections into the body. They are very safe.'" The authors believe remissions after electropyrexia seem to be more frequent than could ordinarily be expected in a similar time interval. In conclusion they state, "It is also striking that these remissions should be coupled directly with treatment. Sixteen of twenty-five cases were chronically progressive over a number of years before treatment was instituted. Two were more or less

chronic or stationary. Excellent remissions were observed in ten. Eleven others showed distinct improvement. This includes three of the more acute type." After treatment, all these remained clinically stationary for the period during which they were observed from a few weeks to eighteen months.

Bennett, Lewis, and Murray (2) have used artifical fever therapy in fifty-one cases of multiple sclerosis and followed these cases for an average of thirty-one months after treatment. Their patients were classified as early, intermediate, and advanced, the first group being of short duration and ambulatory without assistance, the last bedridden and usually of long duration. Of the ten classified as early cases, eight experienced and maintained worthwhile improvement. The results in these ten early cases seem better than what might have been expected with no treatment at all. The twenty-five intermediate cases showed slight to marked improvement in thirteen, of whom eleven are still engaged in full or part time occupation. Although these results appear rather good, it is pointed out that in a group of fifty-three patients with multiple sclerosis of all types, followed four years with no treatment whatever, at least twenty-two are still

ambulatory, many of them working. The results in this intermediate group are therefore, not very different from the probable results without treatment. In the sixteen advanced cases only two showed any definite halting of the progress of their disease, and a few seemed to made at least temporarily worse by the treatments. On the whole these writers think, except in the early group of cases and tose having signs of infection, there is little evidence that fever therapy has any markedly beneficial results in the disease. It should be noted particularly that these writer's results do not bear out the previous report of Neymann and his collaborators of marked and sustained improvement from fever therapy. Their experiments indicate it should be tried in early cases, of short duration and ambulatory without assistance. In the intermediate types requiring assistance to be ambulatory but not completely disabled, the benefits derived from fever therapy are doubtful. Other less vigorous methods of therapy are indicated. In the bedridden group, in which the completely disabling symptoms are of long duration, fever therapy does no good and may do harm.

Horton, Wagener, Aita, and Woltman (23) are at

present observing the treatment of multiple sclerosis by the intravenous administration of histamine. This is the latest form of therapy that has been advocated for the disease and shows promising results. Treatment consisted of the daily intravenous administration of 2.75 mg. of histamine diphosphate in 250 cc. of physiological saline solution at the rate of thirty to ninety minims (2 to 6 cc.) per minute, depending upon the tolerance of the patient. The average patient received forty to fifty such injections; the minimal number was thirteen and the maximal number was two hundred fifty-five. The prompt improvement that follows histamine therapy probably results from vasodilation in the central nervous system. Of the nineteen patients who had an acute form of the disease, fourteen are essentially clinically well, one has shown seventy percent improvement, one, fifty percent improvement, one, forty percent improvement, and two have shown no improvement. The latter two are still receiving treatment. Of the sixty-three who had an advanced or chronic form of the disease, twenty-seven have shown varying degrees of improvement, ranging from ten to ninety-five percent. The remaining thirty-six patients have shown no objective improvement,

although many were subjectively improved. These writers feel that the use of histamine is a safe and efficient form of therapy. They have given a total of five thousand injections without any ill effects, except in one case, that of a young man aged twenty years. In his case a acute gastric ulcer developed after thirteen injections had been administered. It healed completely within twelve days. Symptoms of multiple sclerosis disappeared in this case. The patient had previously received twenty-four injections of typhoid vaccine in three months without any apparent improvement. These writers feel that no type of therapy will be wholly effective in cases of advanced multiple sclerosis in which gliosis has occurred. They are aware that spontaneous remissions occur in many instances so that it is difficult, at the present time, to evaluate fully this type of therapy. It is their impression that the early diagnosis is important and that if treat ment is carried out before irreversible changes occur in the central nervous system, on may accomplish a great deal in the handling of this type of disease.

CONCLUSIONS

One is greatly impressed as they read the early literature written on multiple sclerosis by the fact that many of the early investigators had nearly as complete knowledge concerning this disease as our present-day neurologists. However, after tracing through the literature up to the present one can safely say it is not because there has not been adequate investigation. The disease has been studied from every angle but its true etiology and definitive treatment are still unknown. Therefore, in concluding this paper the writer can but give a concise review of the facts he had culled from a small part of the literature written on the subject.

The Finnish and Scandinavian races seem to be most susceptible to this disease. However, the negro race cannot be ignored for it is found in a surprisingly large number of them. There may be a hereditary factor but it seems very improbable.

The onset may be at any age but seventy-five percent have their onset between the ages of twenty-one and forty-one years of age. The disease I believe can be divided into but two forms, the acute fulminating or the chronic form with remissions.

Charcot's triad of nystagmus, scanning speech,

and intention tremor occur only in a small proportion of the cases. Weakness of the lower extremities appears to be the earliest symptom seen in the majority of cases. However, as shown in this thesis, eye symptoms are commonly the first symptom, especially retrobulbar neuritis. The sudden developing of a scotoma or a history of a sudden transitory blindness should make one very suspicious of multiple sclerosis. Later on hyperactive deep reflexes and loss of abdominal reflexes become prevelant. Late in the course of the disease the mental symptoms are mainly of a euphoric nature.

The pathology is quite distinctive and Putnam's statement that he believes the maximum extent of future recovery from acute lesions is determined at the time the lesions are formed has to the present been quite true and I believe that this will still hold true after the etiological agent has been discovered.

As to the etiology, from the pathology of the disease one would be suspicious of a blood carrying toxin and I think that Brichners theory of abnormal lipolytic substances in the blood seems to be the most likely answer. However Steiner's Spirocheta myelophthora cannot be passed over lightly.

Treatment without knowing the etiology is usually always inadequate. Although treatment with histamine at present seems to be giving promising results, it will take years to evaluate these results. Probably no treatment will ever be entirely satisfactorily because the primary lesions will still be present which no form of therapy will alleviate.

In closing, I believe that it will not be in the too distant future that the etiological agent of this disease will be discovered and then perhaps adequate treatment can be instituted. Until then the early diagnosis and early treatment in an attempt to retard the progress of the disease seems to be the only answer.

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