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Disseminated sclerosis

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D I S S E M I N A T E D S C L E R O S I S

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DISSEMINATED SCLEROSIS

Introduction

It is nearly one hundred years since disseminated sclerosis was first recognized as a pathological entity. In 1835 Cruveilher, at the Salpêtrière, and Carswell, a London medical student, described the characteristic sclerotic patches of this disease in the spinal cord (5). The pathology of the disease was further studied by Rokitansky and Rindfleisch in 1863, Leyden emphasized the causal importance of exposure to damp and cold, trauma, mental stress, and antecedent infections. Following this, Charcot (17) made the great contribution to the symptomatology and pathology of the disease. Uthoff analyzed the ocular manifestations and Marie (40) stressed the role of the acute infectious diseases in the etiology of disseminated sclerosis.

The end of the nineteenth century saw the emergence of the view that the underlying disturbance was a neuroglial hyperplasia due to an inborn abnormality of the central nervous system. The new facts brought to light by newer staining methods and new knowledge of neuroglial reactions have relegated the striking neuroglial changes to a secondary place as the reaction to a pathogenic agent, and reestablished disseminated sclerosis as an infective disease.

The purpose of this paper is to give a comprehensive but concise review of the subject as a whole, although it is by no means a complete review of all the material obtainable by the numerous investigators and writers on the subject.

Etiology

Disseminated sclerosis is most commonly found in young persons and is more prevalent in males than in females by a ratio of 3 to 2. The onset of the disease is usually between the ages of 15 and 30 years, although there have been some cases reported in much younger and much older individuals. The distribution and incidence shows that Switzerland reports the greatest number with 360 cases per million population, while England and Wales report 160 cases per million population. The incidence in the United States is much less, being only about one-third that of England and Wales. The disease is quite rare in countries outside of Europe and the United States. In this country statistics show that the disease is far more prevalent in the urban districts as compared to the rural districts, and the regions of the United States in which a large fraction of the Scandinavian peoples are found report the majority of cases, i.e. around the Great Lakes region (5).

Precipitating factors. In the earlier literature of disseminated sclerosis considerable importance was attached to factors which were believed to precipitate the onset of the disease, especially trauma, exposure to cold, and antecedent infections. It is perhaps significant that now days these predisposing causes receive little attention.

Marie (40) not only, at an early date, proclaimed the infective character of disseminated sclerosis, but regarded it as a complication of a large number of infective diseases. Today

the general recognition of the specific character of the disease has reduced such precedent illnesses to precipitating factors only, and even as such their importance is much disputed. The strongest advocates of a causal relationship between such diseases as the exanthemata, acute rheumatism, influenza, enteric fever, and disseminated sclerosis can only claim that such an association occurs in about 25 per cent of cases and if only those cases are included in which an acute infection preceded the onset of the disease by two or three months the statistics of the literature show such a relationship in only 3 to 5 per cent of cases. Some authors contradict tonsillar and dental sepsis, infections so commonplace that they might be regarded as the cause of most diseases.

It is not necessary now to add that syphilis plays no part in the etiology of disseminated sclerosis. The Wassermann reaction and increasing clinical knowledge have permitted the differentiation from the latter of these forms of neurosyphilis which were formerly confused with it.

The etiological role of intoxications, especially metallic poisoning have been stressed by some authors. Brain (5), in his review of the literature of multiple sclerosis states, "However, in a study of occupational incidence it is readily seen that there are no grounds for supposing that the occupational handling of metals is a causative factor, and it has been pointed out that the disease is common in women who are not exposed to metallic intoxications."

Lead as a causative factor has received more attention probably than the other metallic substances. Three months ago,

Boshes (4) in studying the possible relation of lead intoxication to this disease, analyzed specimens of cerebrospinal fluid from twenty-eight patients for lead by the Fairhall hexa-nitrite method. In only one of sixteen cases of multiple sclerosis the fluid showed a positive result, and this one patient had been given sodium iodide which liberates bound-up lead in the body. Lead was also found in the urine of this patient. He concludes, "...there is no adequate proof for, and ample evidence against, the theory that lead is an etiologic agent in cases of multiple sclerosis."

The etiological significance of trauma when it precedes the apparent onset of disseminated sclerosis is a difficult question of some medico-legal importance. According to Brain (5) the following possibilities must be considered: "(1) that the association is a coincidence; (2) that traumatic lesions of the nervous system may be mistaken for disseminated sclerosis; (3) that trauma may induce changes in the neighborhood of pre-existing but hitherto latent plaques of disseminated sclerosis and so lead to the appearance of symptoms; (4) that a patient after spending some time in bed as a result of the trauma may manifest symptoms because he has lost the power to compensate for a defect, such as inco-ordination of the lower limbs, due to previously-acquired disseminated sclerosis; (5) that the trauma (e.g. a fall) may be the result of pre-existing symptoms of disseminated sclerosis (e.g. inco-ordination); (6) that the trauma may produce a lesion of the nervous system (e.g. contusion) which may afford a locus minoris resistentiae for the development of the virus of the disease, hitherto latent. It would be rash to deny the possibility of a causal relationship between trauma and dissem-

inated sclerosis, and perhaps equally rash to assert it."

Exposure to cold, heat, and electric shock have also been invoked as precipitating factors. These ideas antedate the recognition of disseminated sclerosis as a specific disease. Much that has been said concerning trauma applies to these hypothetical factors also, with the addition that the evidence in favor of their importance is even scantier.

Direct cause. A vast amount of investigation has been carried on in recent years in order to establish the nature of the etiological agent in disseminated sclerosis. A good number of theories have grown out of this work some of which are deserving of discussion.

In 1913 Bullock (now Dye) (14) in attempting to prove the transmissability of the disease, injected subcutaneously into rabbits cerebrospinal fluid withdrawn under rigidly aseptic conditions from a case of disseminated sclerosis. He claims to have produced paralysis of the limbs in four out of five rabbits. The fluid was found to be potent after exposure to a temperature of 0° C. for fourteen days, and after being filtered through unglazed porcelain. He states that "Histological examination of the spinal cord reveals a complete reproduction of the appearances found in the human subject--viz.: (1) vascular engorgement and fragmentation of the myelin sheath in the early stages; (2) areas of degeneration throughout the cord, demonstrable by the Marchi and Weigert-Pal methods, in the later stages of the disease." A cat which was inoculated with fluid from this case remained active and healthy for nine weeks. Cerebrospinal fluid from a second case of disseminated

sclerosis failed to produce paralysis when injected into two wild rabbits. He concludes from his work, "If one assumes that disseminated sclerosis is a definite entity and that the first patient from whom cerebrospinal fluid was obtained was an instance of the disease one is bound to conclude that the cause of the disease is either a filterable virus (organism) or a water-soluble poison found in the cerebrospinal fluid. ...the fact that paralysis occurs from 14 to 22 days after the inoculation is fairly strong evidence against a non-living poison." Bullock's explanation of failure in the rabbits injected from the second case was the fact that wild rabbits were used in these experiments, whereas tame ones were employed in the first.

In the following year Steiner repeated Bullock's experiments and in 1917 Kuhn and Steiner (37) carried out further experiments. They injected by various routes a series of rabbits and guinea-pigs with blood, cerebrospinal fluid or a mixture of both, obtained from 13 patients suffering with disseminated sclerosis. A large proportion of animals developed paralytic symptoms following these injections, guinea-pigs proving more susceptible than rabbits, and blood more effective than cerebrospinal fluid. They 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. At the same time Steiner inoculated a monkey, Macacus rhesus, intracerebrally with cerebrospinal fluid from a case of disseminated sclerosis. The animal showed no symptoms for 11 months, when it developed a transitory paresis of the lower limbs. Five months later it was killed and he 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 cylinder--appearances which he considered indistinguishable from those of multiple sclerosis. 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 affected animals. They named this spirochete 'Spirochaeta argentinesis'.

In 1933 Hudson (34) attempted to confirm the findings of Steiner by injecting fresh material aseptically into three monkeys. Then these animals were observed for 10 months, and it was found that the temperature remained normal for over one month. The animals were killed after 10 months by inhalation of ether and grossly and histologically there was not the slightest deviation from normal.

Gye (formerly Bullock) (30), in 1921, repeated his investigation of 1913 on a larger scale. He obtained cerebrospinal fluid from 21 patients with disseminated sclerosis and inoculated by various routes 129 rabbits and 15 guinea-pigs. He concluded that "Disseminated sclerosis is probably an infectious disease and that the virus may sometimes be found in the cerebrospinal fluid."

In 1924 Adams, Blacklock, Dunlop and Scott (1) carried on a similar line of work. They write, "In confirmation and extension of experimental work of others, it has been shown that nervous phenomena (paralysis of limbs and cerebellar symptoms) develop in animals which have received injections of blood or cerebrospinal fluid from cases of disseminated sclerosis. Passage of the condition to a second animal has been successful in several instances. Positive

inoculation results have been obtained with material both from cases and from experimental animals after transmission through culture. The symptoms in animals have developed in about 30 per cent of those inoculated, after very variable latent periods. These authors write, "Spirochete-like organisms have been found in a proportion of inoculated animals in various internal organs. These spirochetes have been seen both in animals affected with, as well as in some free from, nervous symptoms. Cultivation of the spirochetes has not succeeded, and at present their causal relationship to the disease is undecided."

Numerous observers have described negative results experimentally in attempts to confirm the work of those above. Space does not permit an account of all these negative experiments, but mention should be made of the work of Birley and Dudgeon in 1921 and Noguchi in 1923.

Birley and Dudgeon (3) carried on a large series of well-controlled experiments and met with nothing but negative results throughout. In their conclusion they make the following statements: "(6) Cultural and microscopic examination of the cerebrospinal fluid has in our hands thrown no light on the pathogenesis of the disease, and no specific organism has been isolated. (7) Our attempts to transmit disseminated sclerosis from man to animals (rabbits) have been unsuccessful. (8) We regard the transmissibility of the disease from man to animals to be unproved. (9) We are of the opinion that the evidence in favor of the assumption that the pathogenic agent is a spirochete is incomplete and in many respects unsatisfactory, and we consider that the origin and nature of the morbid agent must for the present remain sub judice. (10) We consider that the clinical and histological evidence is overwhelmingly in favor of the view that the morbid process underlying the disease is inflamma-

tory in character."

Two years following the report of Birley and Dudgeon, Noguchi (45) took up the question of the etiology of multiple sclerosis in order to confirm, if possible, the observations of Kuhn and Steiner, and to study the spirochete by means of cultivation. The blood and cerebrospinal fluid in every instance were utilized within a few hours from the time of withdrawal. The blood was citrated, oxalated, defibrinated, or used in the form of clear serum from the clot. The materials were sometimes inoculated separately into rabbits and guinea-pigs, but more frequently a mixture of blood and spinal fluid was employed. In most cases a combination of two or more modes of inoculation was used. Cultures were set up with ascitic fluid tissue medium, such as that employed for the cultivation of the Treponema pallidum and other anaerobic treponemes; also in the medium used for growing relapsing fever spirochetes and in leptospira medium.

Material from Case I was inoculated on two occasions, six guinea-pigs and three rabbits being used in the first instance, and four guinea-pigs and four rabbits in the second. Nothing of note developed. In Cases 2, 3, 4, 5, and 6, inoculations were made in each instance into four guinea-pigs and four rabbits, and in Case 8, three rabbits were inoculated, also without any result that could be interpreted as experimental reproduction of multiple sclerosis. Repeated dark-field examinations of the blood and cerebrospinal fluid while perfectly fresh failed to reveal any spirochetes. Most of the culture tubes remained free from ordinary contaminations, but no spirochetes were found in any of them. Injections of the

contents of the culture tubes into guinea-pigs and rabbits produced no symptoms of significance. Dark-field examination of peripheral or heart blood of the inoculated guinea-pigs and rabbits showed no spirochetes. In addition to blood, emulsions of liver, spleen, kidney, suprarenal glands, lymph nodes, and the brain from guinea-pigs or rabbits killed at the height of fever were carefully examined under the dark-field microscope without a single positive finding. He states, "As indicated in the experimental protocols presented, the results were disappointing, being chiefly negative." In addition to this Noguchi draws attention to the ease with which morphological elements in blood and emulsions of organs may be mistaken for spirochetes and infers that some of the observers claiming the presence of spirochetes in the cerebrospinal fluid may have mistaken these elements for them.

In Brain's (5) discussion of experimental and bacteriological results of the foregoing investigators he first discusses the spontaneous infections of experimental animals. He states, "Any claim to have transmitted a neurotropic infection to animals, especially to rabbits, requires to be criticized in the light of modern knowledge of the spontaneous diseases involving the nervous system to which these animals are liable. There are three such infections which have been recognized and studied only in recent years: (1) Encephalitozoon cuniculi, (2) Toxoplasma cuniculi, and (3) Spirochaeta cuniculi. All of these are great sources of error in experimental work since, as in the case of the former, the organism may be present without symptoms in more than half

of a stock of rabbits, which produces inflammatory changes in the brain, and may be roused into activity by intracerebral inoculations." He also makes note of the fact that the symptoms in animals following inoculation of material from cases of disseminated sclerosis, although they have borne some resemblance of the symptoms of the disease in man, have been much more acute, and often rapidly fatal. It is possible that animals should be much more susceptible than man to the infective agent of disseminated sclerosis, but he feels that it is unlikely that a disease would run a markedly different course in man and animals. "Too, if animals are so susceptible to disseminated sclerosis that it may prove fatal in a few days, it is difficult to understand why so many investigators should have failed altogether to transmit it experimentally."

The majority of alleged successful transmissions of disseminated sclerosis to animals are unsupported by histological examination of the nervous system of the inoculated animals. Such histological examinations as have been made have not, with the exception of Steiner's monkey, revealed the pathological features of disseminated sclerosis. In addition control experiments are almost entirely lacking in the reported experimental work, and in instances where controls have been used they have been insufficient to be of any practicable value.

The spirochetal theory of infections is also supported by evidence that is quite inconclusive according to Brain (5). There is considerable variation in the appearance of the spirochetes described by the various investigators. They vary from

fine and delicate organisms resembling the spirochete of spirochaetal jaundice to a spirochete thicker than the Treponema pallidum. Although spirochetes in general are not difficult to cultivate upon appropriate media, all attempts to culture the spirochete of disseminated sclerosis have failed, even when tried by the investigators who claim to have seen the organism.

As is the case with the rest of the experimental work on disseminated sclerosis control experiments are almost completely absent on work dealing with the demonstration of spirochetes. However, Adams, Blacklock, and McCluskie (15), two of whom had previously presented evidence for the existence of spirochetes in inoculated animals demonstrated the presence of spirochete-like bodies in the cerebrospinal fluid obtained from the lateral ventricles of normal monkeys, rabbits, and guinea-pigs. In view of this demonstration and the absence of control experiments, no pathological significance can be attached to similar bodies when found in inoculated animals. Brain (5) says, "Even if, in spite of the objections put forward, the bodies described be accepted as spirochaetes there is still no evidence that they are the aetiological agents of disseminated sclerosis or that they have ever reproduced this disease in animals."

In London in 1930 Miss Chevossut (18), working on the theory that the lesions of disseminated slcerosis pass through an inflammatory stage and that there is an agent, possibly in the form of a toxin which has special affinity for myelin, carried out a series of quite technical observations. By special methods of taking and culturing cerebrospinal fluid she claims to have

grown cultures which bear a striking resemblance to the organism which is regarded as the causative agent of bovine pleuro-pneumonia. The latter is said to appear as a connecting link between ordinary bacteria and those known as filterable viruses. It is a small particulate body of about 0.2_u diameter. The particulate form is accompanied by and is dependent for its reproduction on a larger spheroidal body which develops from the particulate form. Miss Chevossut named this supposed organism Spherula insularis and claims to have cultured it successfully in 176 cases out of 189.

The following year Weil (63) attempted a repetition of the experiments of Chevossut and Purves-Stewart and failed to produce convincing evidence that, in multiple sclerosis, cultures from spinal fluids yield a filterable virus and that this virus is responsible for the production of the disease. In his conclusions he states, "The fact that spheres and colonies of spheres may more readily be seen in agar cultures of spinal fluids that have given a positive globulin reaction suggests the precipitation of colloid protein (or lipid) particles, which become visible in the dark field." During this same time Carmichael (16) was attempting to check this work and arrived at the same conclusion: "No distinctive spherules were found in 19 cultures of cerebrospinal fluid from cases of disseminated sclerosis."

Then in 1932 Dr. B. Halley Stewart (59) gave a report on the work of Miss Chevossut before the Board of the Institute of Hampstead where she was carrying on her work. They had become suspicious that her work might not be truly scientific, so they checked her work and watched her actions for a period of six months.

During this time she never supplied them with evidence when asked, and was seen to destroy cultures of those trying to check her work. She finally resigned under pressure, and following her resignation her method was followed meticulously by Dr. Stewart and an assistant on the cerebrospinal fluid of 32 patients with nothing but negative results. This finally served to discredit all of her work on the theory of a filterable virus.

As will be seen later, the main principles of the definite pathology of disseminated sclerosis are destruction and removal of myelin from around the axis cylinder, and gliosis. While there has been dispute as to whether the myelinolysis or the gliosis is primary, it is now generally believed that the myelinolysis comes first. Nothing is known of the causes of the myelin disintegration and most of the contemporary interest revolves around its being either purely degenerative on the one hand, or the result of inflammation on the other. Working from this angle Brickner (6) studied the effect of blood plasma from patients with multiple sclerosis upon the fresh spinal cords of rats, running parallel controls with normal blood plasma, and also fresh formaldehyde-fixed cords. A consistent myelinolysis is produced in vitro with the oxalated plasma from the patients to a much greater degree than with plasma from normal subjects. He hypothesizes that the blood from such patients contains a myelinolytic factor or condition, and deduces that it is the cause of the destruction of myelin in the disease. He also found consistently that the greatest changes occurred in the sheaths of the white column fibers; next came the fine fibers that stream across the ventral part of the gray matter; and last

the ventral nerve rootlets and nerves themselves. He concluded, therefore, that myelin is varyingly constituted in different parts of the nervous system of the rat, and, if this condition is the same in man, it may have much to do with the evident selectivity of so many diseases of the central nervous system. From these experiments the writer arrived at the hypothesis that the blood factor might turn out to be enzymatic, and, if such was the case, a lipase. Since quinine is known to be an inactivator of certain blood lipases, Brickner started a series of treatments with this drug (to be discussed under treatment).

In 1931 Brickner (7) published the results of further investigation on the hypothesis that there was an abnormal lipase in the blood of patients with multiple sclerosis. In this work he ran a series of well-controlled tests on the plasma of patients with the disease and with normal subjects, using lecithin as the lipoid, and testing the changes in pH (those with the greater destruction of lipoid showing more acid.) He found that more acid if formed in both plain multiple sclerosis serum and lecithinated multiple sclerosis serum than in the corresponding controls, and he concludes that in multiple sclerosis the blood contains a lipase which does not occur normally; this lipase differs from normal blood lipase; and it is probably the same agent as the one which will produce myelinolysis in the spinal cords of rats.

Since Brickner's theory of a lipase as a causative agent in multiple sclerosis has appeared Crandall and Cherry (19 and 20) and Weil and Cleveland (64) have published articles in contradiction. Weil studied the influence of patients' serum on the spinal cords of

rats and agreed with Brickner that a larger number of serums from cases of multiple sclerosis than of normal serums acted destructively on the spinal cords, but he also demonstrated that such action occurred in serums from other diseases, and the difference did not seem to be large enough to warrant the drawing of conclusions as to the importance of increase in lipase in the etiology of multiple sclerosis. Furthermore, experiments with active pancreas lipase on the spinal cords of rats gave a negative result. These authors also showed a definite decrease in the blood phosphorus, it being 3.4 mg/100 cc. in multiple sclerosis as compared with 4 mg. in normal cases, 4.2 mg. in 21 cases of eight different diseases, and 4.4 mg. in cases of syphilis in the central nervous system. They write, "There exists the possibility that the increase in lipase and decrease in phosphorus are only secondary manifestations of a primary lesion of other organs of the body, e.g., the liver, and that such a lesion eliminates a myelinolytic toxin or prepares the way for the passing of toxic metabolic products through the hemato-encephalic barrier. Lesions of this kind may be brought about in infectious diseases. They occur in acute disturbances of the metabolic equilibrium, as in pregnancy or following operations with narcosis of long duration or severe trauma to the nervous system, all of which are conditions that are known to favor the beginning of multiple sclerosis. On the other hand, disturbances of lipase and phosphorus metabolism may also be sequelae to a primary disease of the central nervous system with interference with the normal nervous mechanism of the supervision of this metabolism."

Crandall and Cherry (20) also agree with Brickner that engzymes occur in larger amounts in patients with multiple sclerosis, and they feel that it is logical to suggest that it may be the cause of demyelinization in this disease, but they also find the occurrence of such a lipase in patients with involvement of the liver or pancreas. It occurs in experimental injury of the liver or pancreas. They also followed several dogs with Eck fistulas for more than six months, and in these animals the lipase is more consistently present than in cases of multiple sclerosis. They write, "We believe that at present the best interpretation of the presence of abnormal amounts of lipase and diastase in the serum of patients with multiple sclerosis is that they are evidence of dysfunction of the liver."

Greco (27) in 1935 presented a summary of the work of Brickner and others on a supposed myelinolytic ferment in the cerebrospinal fluid as a causative agent or related to the production of or interpretation of the changes in the myelin sheaths seen in this disease. He also conducted parallel researches and arrived at a negative general conclusion, both as to technical histological and chemical details and as to the conception as a whole.

Putnam, McKenna, and Morrison (49) published their work in 1931 on the formation of experimental sclerotic plaques. From a study of the histology they found that the sclerotic plaques were always surrounding a blood vessel and felt that vascular disturbances such as thromboses or interference with blood supply might explain the formation of plaques in disseminated sclerosis. By injecting minimal doses of tetanus toxin into dogs they found disseminated

areas of myelin loss with perivascular infiltration and reactive gliosis, the cardinal factors in the pathology of this disease. This myelin loss is permanent up to a year from the time of inoculation and the gliosis appeared to be progressive. They also showed areas of myelin destruction with reactive gliosis in dogs by carbon monoxide poisoning, the myelin showing no sign of regeneration within two months. Similar areas of demyelinization and gliosis may be produced by embolism with cod liver oil emulsion. The destroyed myelin in these cases is not regenerated at the end of five months, but gliosis is progressive. Vascular obstruction appears to play a part in the production of lesions of the two latter types; also perhaps in the first. These writers claim that all three types of lesions resemble closely the "early" plaques of multiple sclerosis and quoting, "It is not necessary to postulate a specific virus, toxin or ferment to account for the histologic appearances seen in multiple sclerosis."

Two years later (1933) Putnam (50) found that arterial embolism or thrombosis did not cause the true histopathological picture of multiple sclerosis, and after making careful studies of slides from experimental animals and from humans he found that the blood-vessel in the center of sclerotic plaques were usually if not always veins. He states, "Very recently, I have been able to produce some acute lesions which have both gross and microscopic resemblance to those occurring in human beings by injecting bland oily substances forwards--that it, upstream,--into the ligated longitudinal sinus of dogs. The resulting lesions are confined almost exclusively to the white matter, and consist of gradual

myelin changes, a perivascular infiltration with phagocytes and lymphocytes, and a glial proliferation. There is no destruction of axis cylinders or of connective tissue structures, and only minor changes in ganglion cells." Putnam feels that it is premature to attempt to correlate the pathological processes here outlined with the recognized features of the human disease in any detail. Infections are known to predispose to the production of thromboses in various parts of the body, and also to the onset or exacerbation of multiple sclerosis. The association, both pathological and clinical, between multiple sclerosis and retro-bulbar neuritis, and between the latter and sinus disease is well recognized. Exacerbations of multiple sclerosis are almost constantly produced by pregnancy, in which the coagulability of the blood is increased. He again emphasizes the superfluity of postulating a specific demyelinizing organism, virus, or toxin to account for such lesions. "The ultimate etiological factor should probably be sought in a local vascular abnormality, or in some alteration in coagulability of the blood."

In 1935 Solomon (58) studied the reaction of blood coagulation in 12 cases of multiple sclerosis and in 14 controls. He studied the reaction to (1) intravenous typhoid vaccine and to (2) subcutaneous adrenalin. His control cases comprised 5 patients with epilepsy, 5 with psychoneurosis, and one each of post-encephalitic Parkinsonism, brain tumor, neuro-muscular dystrophy, and syringomyelia. In the typhoid vaccine experiments the degree of the maximum drop in clotting time was not significantly different in the two groups of patients, except in the duration of the drop

in clotting time, the average duration of the drop being 69 hours in the multiple sclerosis group as contrasted with 26 hours in the control group. In the adrenalin experiments there was a marked difference in the two groups, both in regard to degree and duration of the drop in clotting time. The average maximum drop in multiple sclerosis group was 45 per cent as contrasted with 11 per cent in the controls. The average duration of the drop was 3.7 hours in the multiple sclerosis group, and 1.0 hour in the control group. This is an adjunct to the belief of Putnam who emphasizes it in his last article of 1935 (51).

From this survey of the etiology of disseminated sclerosis it appears quite evident that the causative agent or factors are still as obscure as when the disease was first recognized as a clinical entity. All of the theories advanced have been severely attacked with the exception of the last presented, Putnam's belief of a vascular origin, probably a change in the coagulability of the blood. This theory, though appearing quite logical needs much further investigation before conclusions can be properly made.

Pathology and Pathogenesis

Charcot's (17) early description of the pathologic changes, consisting of a patchy loss of myelin, with relatively intact axis cylinders, perivascular infiltration, and dense glial infiltration has not been markedly altered by later investigators.

The pathological unit in disseminated sclerosis 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". 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 (young or old), 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 axones (demyelinated nerve fibers); some are covered with myelin but partially, while others show a destruction of both the myelin and axone, exhibiting a state of Wallerian degeneration (Hassin (32)). These three pathological features occur not only in the patches themselves, but also in parts of the central nervous system which show no visible patches whatever.

Most observers agree that the patch is in many cases perivascular, i.e. placed concentrically around a vessel. Brain (5) gives a pathological description of sclerotic plaques in both the early and the late stages which is the compilation of works of most authors on this subject. Tracing the changes in an 'early

patch' from the center to the periphery one finds: (1) the blood vessels are dilated, but in the early stages there are few changes in the vessel wall; sometimes capillary hemorrhages are observed. Symonds (61) adds that occasionally the lumen of one of these vessels is filled with a thrombus. (2) The perivascular spaces contain cells of several different types. The occurrence of lymphocytes and plasma cells in the perivascular spaces in disseminated sclerosis is now well-recognized and emphasized by such writers as Oppenheim (47), Guccione and Lhermitte (38), Siemerling and Raecke (57), Birley and Dudgeon (3), and Symonds (61), although Dawson (21) failed to observe these ("I have never seen any marked grouping of small round cells analogous to the so-called 'round cell infiltrations.'"). The other type of cell found in the perivascular space is the fat granule cell, a large cell containing globules of fatty substances produced by the breakdown of the myelin of the nerve sheathe. (3) External to the perivascular space is a concentric zone in which the myelin sheaths of the nerve fibers are severely damaged. Some have disappeared; others stain faintly, or appear swollen or granular. This zone contains proliferated glial cells with numerous processes, and fat granule cells lie in the tissue interstices together with a few lymphocytes. The axis cylinders for the most part persist, but may show degenerative changes, such as swelling, inequality in size, twisting, longitudinal splitting, or fragmentation. (4) Peripheral to this last zone is an area transitional to normal tissue in which there is less disintegration.

Later on in the pathological changes the 'late patch' or end result is reached consisting of: (1) The blood vessels show hyalin thickening, and may be infiltrated with embryonal cells;

(2) Fat granule cells disappear from the perivascular space leaving it dilated, and lymphocytic infiltration may persist to some extent, and be associated with proliferation of the cells of the adventitia; (3) demyelinization of the surrounding nerve tissue is complete and the spaces are filled with fibroglia (a condensation of the original glial network). The axis cylinders are reduced in number, and some of those persisting show abnormalities, swelling, spindle enlargements, etc.; (4) the transitional zone is constituted by a narrow ring rich in glial nuclei, the smaller the patch the sharper its differentiation from its surroundings.

The sclerotic patch is believed to be produced by this mechanism passing through a stage called 'fat granule cell myelitis' although Dawson (21) believes that the process may be much more chronic in some instances, and consist of little more than increasing glial hyperplasia with an absence of granular cells and other cellular reactions.

Distribution of patches. A number of writers classify the distribution of patches in disseminated sclerosis as (1) perivascular, (2) subpial, and (3) periventricular.

(1) Perivascular patches: In the spinal cord there are two basal types of patches, wedge-shaped and oval or round, corresponding to the distribution of the transverse and perpendicular branches of the lateral vessels of the cord. Corresponding to the transverse branches, which run in from the vaso-corona, (the arterial wreath which unites the anterior and posterior spinal arteries) are the wedge-shaped areas of sclerosis with their base to the surface. Other arterial branches enter the cord and divide into a perpendicular branch running upwards and downwards. The patches corres-

ponding to these are of an elongated oval shape extending through several segments longitudinally. The cervical and thoracic cord are more affected than the lower segments.

In the brain-stem and cerebellum the same primary forms are to be found, and in addition the cerebellum is often involved by extension from the roof of the fourth ventricle.

In the corona radiata round or oval submiliary foci occur, and in the basal ganglia round areas which appear to begin as perivascular patches around the branches of the lenticulo-striate and strio-thalamic vessels, later fuse to form irregular-shaped areas.

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

(2) Subpial patches: Probably, both in the brain and cord, the subpial patches constitute a variety of perivascular patch related to the distribution of vessels entering from the pial surface.

(3) Periventricular patches: Lhermitte and Guccione (38) and Dawson (21) as well as several other writers have stressed the predilection of disseminated sclerosis for the neighborhood of the cerebral ventricles. The whole of both lateral ventricles may be involved or the process may be limited to a part of one. It is most marked in the horns, particularly the posterior horns. The patches nearest the ventricles have a direct and extensive

relationship with the ventricular surface, and are formed of thick fibrillar bands. From these, finger-like projections extend into the surrounding white matter, e.g. the corpus collosum and corona radiata, or into the grey matter, e.g. the optic thalamus. The histological appearance of these plaques are the same as elsewhere. Some observers believe these periventricular plaques are due to the rich vascular bed in these regions and would classify them under the perivascular types. Others believe they are secondary to abnormalities of the cerebrospinal fluid, while others believe it a combination of the two.

Pathological changes in special situations.

1.) The visual fibers: Disseminated sclerosis may attack the visual fibers at many points, but the optic chiasma is the most frequently affected and most frequently on its anterior border. Patches here and in the optic tracts are in relation to the third ventricle while those of the optic nerves are related to the central vessels. The optic radiations may also be involved by periventricular patches near the posterior horn of the lateral ventricles.

2.) Cranial and spinal nerves: Usually the typical patches of this disease are confined to the glia-bearing parts of the central nervous system, but frequently the spinal roots are involved, particularly those of the lumbar region (21 and 57). Changes in the peripheral nerves are attributed to a toxic neuritis and are not typical of disseminated sclerosis.

3.) Secondary degeneration: The absence of secondary degeneration in the nervous system in disseminated sclerosis was

emphasized by a number of early writers, but is is now generally recognized that such occurs (5).

4.) Meninges: Thickening and blood vessel changes similar to those in sclerotic patches occur, sometimes associated with such patches and other times not. No conclusions have been accepted although Dawson (21) believes they are changes due to "complications".

Pathogenesis

1. The Nature of the Pathological Process.

There has been considerable controversy by investigators as to the primary and secondary changes in the pathological lesions of disseminated sclerosis. Seimerling and Raecke (57) claimed that the presence of plasma cells in particular as being evidence of a true inflammatory process, whereas Dawson (21) claimed he was unable to find any perivascular infiltration with lymphocytes or plasma cells and he considers that the earliest stage in the formation of a sclerotic focus is a subacute degeneration of the myelin sheaths. In response to the presence of the fatty products of this degeneration numbers of mononuclear phagocytes are developed both from the glia cells and the vascular endothelium, and these taking up the fatty droplets become the "fat-granule cells", which make their way towards the small vessels around which they are grouped in dense clusters. He states, "At the stage of abundant fat-granule cell formation, when these cell elements are passing into the lymph spaces of the adventitia, every vessel in the affected zone is marked out by a ring or rings

of such cells. If such an area, with fat-granule cells crowding the vessel sheaths and tissue spaces be looked at with low power, and especially in celloidin sections where it is difficult to analyze the constituent elements, the impression is given of a softened area with cell-infiltrated walls. The possibility that areas at such a stage of development have been taken as illustrating cell-infiltrated areas may explain the great significance that has been ascribed to the vessels and to the inflammatory nature of the process." He concludes that disseminated sclerosis is a subacute disseminated myelitis, probably due to a soluble toxin which is conveyed to the tissues through the blood vessels, and he distinguishes from the disease known as acute disseminated myelo-encephalitis, cases of which have been from time to time reported as acute multiple sclerosis.

According to Brain (5) all the main features of glial hypertrophy and compound granular cell formation which are to be found in this disease have been observed to result from the experimental destruction of brain tissue. These facts assume importance in relation to the theories of the nature of disseminated sclerosis put forward in the early years of this century by a number of foreign writers. These conceptions, though not identical, possess a common feature in the view that the pathological process is essentially a hypertrophy of the glia arising from a congenital abnormality, and the demyelinization is a degeneration secondary to the glial growth. Charcot's conception of a diffuse glial hypertrophy in response to an exogenous irritant, though much more in accord with modern views, takes no account of the early stages of myelin destruction.

Hassin (32), in reviewing the changes which he found in material from thirteen cases, concluded that the primary change is a degeneration of the myelin sheaths and that all the subsequent reactive phenomena, formation of fat-granule cells, and overgrowth of glia cells and fibrils, are purely secondary, the histological picture being exactly comparable with that seen in the secondary degeneration following, for instance, a vascular lesion of the internal capsule. As to the perivascular infiltration, he believed that this consists entirely of fat-granule cells. "Such infiltrated blood-vessels suggest at first glance an inflammatory condition as if the infiltration consists of lymphocytes, plasma cells and similar haematogenous elements. Such an error can easily be corrected by having the specimens stained with osmic acid or scarlet red which will show that the infiltrating cells are fatgranule bodies." He was so certain of the degenerative nature of the lesions that he goes on to say, "Those cases of multiple sclerosis that have been described by many good pathologists as containing or showing inflammatory phenomena have not been cases of multiple sclerosis at all."

The principal alternative to the hypothesis that disseminated sclerosis is an endogenous glial hypertrophy implies the existence of an exogenous noxa brought to the nervous system from without. According to Brain (5) this pathogenic agent must be such as to produce circumscribed lesions, mainly if not exclusively perivascular in distribution, and attended by perivascular infiltration with plasma cells and lymphocytes. There are two explanations of these facts that have been proposed: (1) that an infective

agent is present in the nervous system, and (2) that the lesions are the reaction to a toxin, brought by the blood stream or by some other route. Many recent workers have stressed the perivascular and meningeal infiltration as almost conclusive evidence of the infective nature of the disease. Brain believes that apart from the nature of the cellular reaction, it is difficult to ascribe to a toxin, changes at the same time so widespread and yet so focal. He gives the cardinal features of the effects of toxins, whether endogenous or exogenous, upon the nervous system as (1) diffuseness, limited by (2) certain selectivity, and (3) symmetry both in distribution and chronology. The patches in disseminated slcerosis are circumscribed, involve all parts of the central nervous system with little discrimination, are only superficially symmetrical in distribution, and highly irregular in their chronological development. He sums up by saying, "The hypothesis of a toxic origin has weighty support, but the evidence appears to be more in favour of the view that disseminated sclerosis is due to a neurotropic infection and is an encephalo-myelitis, characterized pathologically by perivascular demyelinization and clinically by its relapsing tendency."

Symonds'(61) conclusion is practically the same: "The type of cellular reaction is that met with in all diseases of the central nervous system which are known to be due to microorganisms, and it may be deduced that the cause of disseminated sclerosis is in all probability of a similar nature."

2. Which Tissue is Primarily Affected.

There has been much discussion as to which tissue element

is primarily affected by the pathogenic agent. One group of observers believe that it is the nerve fiber, and Dawson states that "the most constant and uniform change is the absence of the myelin sheath". Another group of observers, however, consider that the blood vessels or the perivascular spaces are the first involved and that changes in the neural elements are secondary. On the other hand, there are some that believe that the glia reaction is the primary change and others secondary. Brain (5) believes that these attempts to find a locus minoris resistentiae to the noxa of disseminated sclerosis are somewhat academic, for it seems impossible to do more than speculate whether the reaction of a certain tissue element is to the hypothetical infection or to the products of the destruction of other cells. He believes that probably both factors operate. Dawson (21) also believes that the response is in part to the pathogenic agent, and in part to tissue damage. The constancy of degeneration of the myelin sheaths indicates their high susceptibility to the noxa.

3. The Route of Infection of the Nervous System.

Siemerling and Raecke (57) found that the foci of disease, especially within the brain, were grouped around the terminal branches of the blood vessels. On these grounds they concluded that the disease was infective or toxic in origin, and that the virus or toxin was conveyed to the nervous tissues through the blood vessels and there set up an inflammatory reaction with destruction of nerve elements and secondary overgrowth of neuroglia.

At first sight the perivascular distribution of many of the patches in the nervous system suggests a hematogenous origin

of the infection, just as periventricular sclerosis suggests the cerebrospinal fluid as the source. However, according to Brain (5), there is an alternative explanation in either case. Recent studies of the perivascular spaces have shown them to be extensions of the subarachnoid space surrounding all vessels entering the nervous system and subdividing to clothe their branches in a similar fashion, thus reaching the pericellular spaces in the grey matter and the interfibrous spaces in the white. It is probable that no pathogenic agent brought to the nervous system by the blood stream can avoid passing through the perivascular space. But a perivascular distribution would also be attained by a noxa which ascended the perivascular space from the cerebrospinal fluid of the subarachnoid space. He says that this is difficult to accept as a likely explanation of isolated patches deeply situated in the central portions of the cerebral hemispheres, but it is probable that once a particulate virus has been brought to any situation by the blood stream the perivascular spaces play an important part in the diffusion either of the virus itself or of its toxins. "It is indeed probable that both blood-stream and cerebrospinal fluid play a part in the spread of the disease. Haematogenous infection probably leads to invasion of the perivascular spaces and hence of the subarachnoid space. On the other hand, if the periventricular sclerosis is secondary to the presence of the virus in the ventricular fluid the latter has probably been infected by way of the blood-vessels of the choroid plexuses."

We see from this review that even the pathology and the pathogenesis of disseminated sclerosis are not entirely settled

questions, but the most modern and most widely-accepted views seem to be that the disease is of an infectious nature due to some living organism, or at least some exogenous agent, that is carried to the nervous tissues by way of the blood stream.

Symptomotology and Diagnosis

There are few diseases which raise such difficulties of diagnosis as disseminated sclerosis. The classical clinical picture with which Charcot familiarized us, though highly distinctive, is now recognized as occurring in only 10 to 12 per cent of cases. In the remainder the manifestations of the disease assume the most varied forms. Its onset may be acute, subacute, or chronic, its course remittent or steadily progressive. Evidence of multiple foci may be present from the outset, or the physical signs may, even for years, point only to a single lesion. Whichever be the case there are few regions of the nervous system, from the optic nerves to the conus medullaris, which may not be involved.

Birley and Dudgeon (3) feel that it is useful to recognize two clinical types of disseminated sclerosis: (a) the remittent type characterized by acute exacerbations at widely varying intervals alternating with quiescent periods, and (b) the chronic progressive type. In their series of thirty-five patients the proportion of remittent to chronic progressive cases if 6:1, and they concluded that in early cases of the remittent type, once the acute disturbance has subsided, the patient may present no clinical evidence of organic disease over prolonged periods. The possibility of spontaneous cure cannot therefore be entirely denied. The remittent type in its later stages tends to assume the characteristics of the chronic progressive type. They further say that the great bulk of clinical and histological evidence is opposed to the view that these two types correspond to two different pathological pro-

cesses. On the contrary, they are to be regarded as manifestations of one and the same disease.

Following the plan of Brain (5) it is convenient and helpful to consider the symptomatology of disseminated sclerosis from three aspects: (1) its clinical course, that is, its mode of onset, development, duration, and termination, (2) the significance and frequency of individual symptoms, and (3) 'symptom-groups' or clinical varieties arising from the predominant involvement of a particular region.

I. Clinical course. (a) Mode of onset. Adams, Blacklock, Dunlop, and Scott (1) in studying the pathogenesis and symptomatology of disseminated sclerosis, feel that the disease would appear to be a disease of more common incidence than has been recognized in the past, and they say an outstanding feature of the cases considered in their series is the frequency with which the significance of the earliest symptoms have been overlooked. A disease in which the morbid pathology consists of plaques of sclerosis distributed in an irregular and apparently haphazard fashion throughout the brain and spinal cord must of necessity vary widely in its clinical manifestations, and yet the almost constant presence of a combination of the so-called cardinal signs is a striking phenomenon. In this respect the disease resembles syphilis from the fact that certain parts of the nervous systems seem to be specially prone to be attacked. These authors, too, divide the cases into two types. First is the more acute type in which the victim is usually a young and otherwise healthy adult under 30 years of age. There is usually a preceding history of trauma or acute exanthem, so frequent in fact

that they cannot be totally disregarded. The second type of case attacks, as a rule, older patients, and has more of a spinal than of a cerebral distribution: its onset is more gradual and its clinical course more slowly progressive. It is this group which presents the greatest difficulty in diagnosis, as syphilis and arterio-sclerosis have to be excluded. "These cases do not, in our experience, tend to develop the established picture of classical disseminated sclerosis."

In considering the onset of the disease, Wetherell (66) writes, "It is now well-known that the old triad of Charcot--nystagmus, scanning speech and intention tremor--manifests itself late in the disease. Many of the earlier symptoms are often overlooked and, because of the sudden remissions so characteristic in its beginning, are put down as hysterical attacks or mild apoplexies, or "rheumatism". Among these early manifestations are ocular palsies; transitory diplopias; muscular weaknesses, which are associated with giddiness, nausea and headache; stumbling and tripping; stiffness of the legs and difficulty in climbing stairs; urinary frequency of sudden onset and cessation equally sudden; slight difficulties in speech and the like. Very often these disturbances follow or occur at periods of distress such as pregnancy, etc."

The sudden onset of symptoms in disseminated sclerosis is well recognized. The modern tendency has been to emphasize the frequency with which the onset is insidious, the figures varying considerable from 45 per cent of cases by Birley and Dudgeon (3) to 73 per cent of cases. W. Bohmig (quoted from Brain (5)) has analyzed the histories of 163 cases and found the following fre-

quency of early symptoms: disturbances of gait in 64 per cent, paresthesiae in 26 per cent, sphincter disturbances in 24 per cent, giddiness in 19 per cent, diplopia in 18 per cent, pain and weakness of the back in 13 per cent, disturbances of speech in 6 per cent, abnormalities in the upper extremities in 4 per cent, and facial weakness in 1 per cent.

Cadwalader and McConnell (15) in presenting the symptoms of disseminated sclerosis write that in the earliest stages of the disease many of the symptoms are so mild as to escape detection. It must be remembered, however, that these symptoms may subside without leaving any trace, and yet recur later and become progressively more intense. If, in a given case, spastic paraplegia, intention tremor, scanning speech, optic atrophy, and nystagmus are present, the diagnosis presents little difficulty, since these symptoms point to an advanced stage of the disease. But in the earliest stages of multiple sclerosis, before any of these signs have developed fully, the diagnosis is exceedingly difficult. "The point that we wish to emphasize and discuss at this time is that a knowledge of the mode of succession of the symptoms may constitute sufficient evidence on which to base a positive diagnosis in the early and undeveloped stages. Isolated objective signs, such as impairment of vision, ocular paralyses, weakness of one or more of the extremities, associated with paresthesia are exceedingly common. These phenomena are, however, transitory and are frequently so fleeting as to be overlooked."

Remission of the onset symptoms is far more common than is generally believed, and is prone to occur in the majority of cases. Birley and Dudgeon (3) have shown that most cases run an intermittent course, accompanied by a haphazard series of relatively acute disturbances due to focal lesions. In one case of the cases of Cadwalader and McConnell (15), the earliest evidence of the disease--dating back to 1907--was a paralysis of the left leg that lasted one month, disappeared, and returned within two months. It was absent again for a prolonged period, but in 1909 it recurred, and remained as an intermittent feature up to and for some time after the full development of marked bilateral spastic paraplegia and other symptoms of multiple sclerosis--about eight years later. In another one of their cases the only complaint was of intermittent diplopia over a period of three years before other characteristic signs developed. In another case there were irregular attacks of sudden but transient blindness preceding the development of optic atrophy; and in still another case there developed very rapidly bilateral oculomotor paralysis that persisted for eighteen months, no other symptoms, either objective or subjective, being present. Tremor, scanning speech, and weakness of the extremities developed later.

For diagnostic purposes isolated symptoms of the disease under consideration are of little value, but the knowledge that paralytic phenomena are at first isolated and later become permanent and are combined with nystagmus, scanning speech, tremor, or other manifestations, may be of considerable importance.

It has been the experience of these authors that the classic symptoms, i.e., nystagmus, scanning speech, and intention tremor, differ from the other signs of this disease in that they are not so frequently remittent in character, although occasionally they appear as isolated signs. Once established, they tend to become permanent and to progress. Each of these symptoms seems to point to a more or less widespread distribution of the inflammatory lesions, and for this reason they are of far greater importance than almost any other single sign of the disease. Scanning speech or other dysarthria indicates disturbance in the combined motor function of the respiratory, laryngeal, palatal, lingual, and lip muscles that are supplied by different cranial nerves; and each one of these cranial nerves has its origin at a different level within the brain stem. One lesion sufficiently severe to have destroyed all of these must, therefore, be very diffuse.

In these authors' conclusions they write, "we would emphasize that the sequence, mode of development, and the combination of signs are more important than the individual symptoms themselves. In addition, the occurrence of cerebral symptoms, most particularly scanning speech and nystagmus, either alone or after spinal symptoms have developed, or the reverse, spinal symptoms following the cerebral manifestations, is strongly indicative of the dissemination of the pathologic process. If there is a history of earlier remissions or of a discontinuance of the process in the early stages, followed by a progressive course, the nature of the disease can be determined with confidence."

Many observers in this country and Europe, more particularly in France, will not make the diagnosis of multiple sclerosis unless there be present the classical triad of symptoms, namely nystagmus, intention tremor and scanning speech; while others, like Sachs and Friedman (53), venture to diagnosticate the disease in the presence of another series of symptoms, although one or two of the famous Charcot triad, developed and emphasized by Charcot and his followers, may be absent. As in tabes dorsalis the earlier concepts of multiple sclerosis were based upon the full-fledged chronic forms of the disease, and as such the older clinical studies were keen and discriminating. The present-day views are based upon the attempt to recognize the disease in its earliest stages.

(b) Age of onset. The occurrence of disseminated sclerosis in children has been reported not infrequently in the past, and it is perhaps significant that such reports have been much less common of recent years. Many diseases which in some ways resemble disseminated sclerosis are now recognized, and in the past confusion has probably arisen with Schilder's disease, neuromyelitis optica, acute disseminated encephalo-myelitis, hepatolenticular degeneration, tuberose sclerosis, and other conditions. The occurrence of disseminated sclerosis before the age of ten is, to judge from the literature, probably even rarer than its familial incidence.

Brain (5) composed a table from the series of a number of authors, English, French and German concerning the age incidence:

Age of patient	11-20	21-30	31-40	41-50	51-60	Over 60
Percentage of total	12.0	35.5	32.4	13.3	6.1	1.0

It will be seen that the incidence in the third and fourth decades is approximately equal, and that 67.9 per cent of patients are between 20 and 40 years of age.

(c) Duration. The duration of the disease is notoriously variable, and ranges from a few months to twenty or thirty years. Wechsler's (62) figures show that only 5 per cent out of 192 patients gave a history of more than five years. The extremes of Brain's experience are represented by a patient who died within three months of his first recognized symptoms and one who is still able to carry on his occupation of serving behind a counter more than 26 years after the onset of his illness.

(d) Termination. The ordinary termination of disseminated sclerosis is quite familiar and heeds little description. Increasing paralysis and ataxia cause the patient to become bedridden, and spastic paraplegia or pseudobulbar palsy leads to urinary, cutaneous, or pulmonary infections as terminal complications. Rare, but of considerable importance, is the terminal occurrence of what appears to be an extremely acute exacerbation of the disease. The termination of disseminated sclerosis by 'acute myelitis' has been described by some of the early authors. Such endings have been described with the pathological picture of an acute myelitis characterized by marked perivascular infiltration and demyelinization.

II. Individual Symptoms.

First, it is of special interest to note the gradual development of the weakness, as a rule in the lower extremities, in association with the increase of the deep reflexes (Sachs and Friedman (53) found that the chief complaint was weakness and stiffness of one or

both lower extremities in 115 cases in their series of 141 cases.) The upper extremities are less frequently involved in the general loss of power, while a very slight ataxic tremor often precedes by months the development of weakness or paralysis of the upper extremities and the upper extremity reflexes are increased at a very early day. It is also noted that in both the upper and lower extremities weakness or paralysis is associated with a very moderate degree of spasticity; not infrequently there is also in the early stages of the disease a very slight though distinct disturbance of sensation.

The loss of the abdominal reflex is one symptom of importance that has been added to the symptomatology of multiple sclerosis in the last 30 years, although there are some authors who are inclined to disregard the value of this reflex. Sachs and Friedman (53) state, "In any number of instances the absence of abdominal reflexes has helped us to suspect the presence of disseminated sclerosis early in the disease, the suspicion of the diagnosis having been confirmed by the subsequent course of the disease." Except at the beginning of the disease, all abdominal reflexes seem to be equally affected. The authors find no other explanation for this frequent loss of cutaneous reflex except that in view of the extensive character of the disease, the reflex pathways with their cerebral connections, are certain to be hit somewhere by one or more of the sclerotic patches.

So far as speech disturbances are concerned, "scanning speech" does not tell the whole story. In addition to or instead of syllabic utterances we may have other forms of dysarthria.

Speech may be purely tremulous or bulbar or cerebellar in character.

For some time, the pallor of the temporal halves of the optic discs (11 of Sachs and Friedman's cases) has had great diagnostic value, and last but not least the unusual remissions of the disease often afford great difficulty in diagnosis. Every now and then, men of experience begin to doubt the diagnosis because of the disappearance of many signs. The gait improves, the speech becomes less scanning, the contractures are partially relaxed, the ataxic tremor of the upper extremities may be far less pronounced. There is great subjective improvement reported by the patient, and the general progress is so marked that not infrequently hysteria or some functional form of disease is suspected.

Brain (5) composes a table showing the relative frequence with which individual symptoms were found in four groups of cases in different countries; those of Birley and Dudgeon with a series of 35 cases, Sachs and Friedman with a series of 141 cases, Marquezy (France), and Bohmig (Germany):

Individual symptoms.	Percentage of cases in series			
	Birley and Dudgeon	Sachs and Friedman	Marquezy	Bohmig
Mental symptoms	-	15.6	-	4.7
Lack of emotional control	51.4	17.0	-	-
Scanning or ataxic speech	28.6	36.0	21	16.3
Pallor of optic discs	57.6	32.6	54	33.0
Nystagmus	74.3	70.0	70	56.2
Diplopia	34.3	29.0	34	-
Vertigo	51.4	8.25	39	-
Intention tremor	42.6	55.3	34	41.5
Signs of cerebellar defect	42.6	-	50	-
Spastic weakness of lower limbs	45.7	81.7	-	77.6
Ataxic or spastic ataxic gait	51.4	43.2	83	-
Absent abdominal reflexes	77.1	-	68	64.1
Extensor plantar reflexes	91.4	78.3	99	-
Sphincter disturbances	71.4	40.0	40	26.0
Parasthesiae	82.6	30.0	75	13.2
Objective sensory loss				
Postural sensibility	65.7	17.0	-	-
Vibration sensibility	60.8	-	32	-
Cutaneous sensibility	31.4	16.3	-	-

Individual symptoms--Special symptomatology.

(1) Mental symptoms. Until recently the mental symptomatology of disseminated sclerosis has received very inadequate attention. Numerous isolated cases have been reported in which psychoses resembling general paralysis or schizophrenia have been attributed to disseminated sclerosis, but these publications were made before the days of diagnostic lumbar puncture and the Wassermann reaction.

In 1926 Wilson and Cotrell (69) found that the 'vast majority' of 100 patients with disseminated sclerosis showed certain well-defined changes in prevailing emotional disposition, emotional expression and control, and sense of physical well-being. While the majority showed an increased sense of mental and physical well-being--called by Wilson and Cotrell 'euphoria' and 'eutonia sclerotica'--some were depressed and pessimistic. Associated with euphoria and eutonia there was often a persistent optimism as to the prognosis, described as 'spes sclerotica' by analogy with spes phthisica. They found that intellectual disorders were minimal and negligible and attribute the disorders of feeling-tone to invasion of the palaeothalamus by periventricular sclerosis.

Brain (5) feels that Willson and Cotrell omitted one mental symptom of importance, namely, the predisposition to hysteria which clinical experience has long associated with this disease. Hysterical symptoms such as pareses and ataxia, seem to occur more often in association with disseminated sclerosis than with any other organic disease of the nervous system.

Brown and Davis (13) feel that despite the descriptions of mental symptoms in multiple sclerosis which are found in the literature, it is difficult to get in this way a comprehensive idea of their character. This is because the mental symptoms are of several patterns and writers vary in regard to what symptom they stress. A cursory view of the subject shows that there is not in multiple sclerosis a group of symptoms as consistent as the fairly consistent symptoms seen, for example, in general paresis. However, counting the euphoria, probably in 90 per cent of cases there are mental alterations which warrant the meaning commonly granted to the term "mental symptoms". These authors also describe cases with euphoria, states of mental depression, mental deterioration, hallucinations, and they say that an interesting characteristic of the mental symptoms is their marked tendency toward change and progression. Very often the paranoid trends and delusional states are of but a few months duration. The brevity of their stay may be quite unexplained. Or again they may disappear as the deteriorating factors advance. With the subsidence of trends, there is a tendency for the euphoria to assume greater intensity and grandiose elaboration of the euphoria may be a very late development.

Brown and Davis divide mental symptoms of multiple sclerosis into two groups: first, those which are primary and directly the result of the organic lesions; second, those which are incidental and secondary. In the first group they place euphoria, the mental defect symptoms, the occasional hallucinations of

organic origin, and the very rare confused states and the Korsakoff clinical pictures. They also include here the occasional terminal states with delusions of grandeur.

In the secondary group of symptoms these authors place transitory delusional states and depressions which appear to arise as a result of the handicapped and incapacitated condition in which the patient finds himself. Here may be suicidal attempts, delusional trends accompanied by hallucinations often of only a few months' duration. They say, "It is reasonable to suppose that the secondary symptoms such as depressed states, and the paranoid symptoms, depend to a considerable extent upon the mental make-up of the patient before the disease developed; but with the primary symptoms of the disease this is not the case."

(2) Convulsions. The occurrence of convulsions as a symptom of disseminated sclerosis has been reported a few times in the literature. Wilson and MacBride (68) in 1925 were able to find eight cases in the literature and added seven more from their own experience. These authors describe 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. Epilepsy is admittedly an infrequent symptom of this disease, but its occurrence may be misleading unless such a cause is borne in mind.

(3) Ocular symptoms. (a) Disturbance of the ocular movements. Nystagmus is present in some 70 per cent of cases according to Brain (5). Paresis of single ocular muscles is not very common and usually transitory, while diplopia is commoner (30 - 40 per

cent of cases). Paresis of conjugate ocular movement is comparatively rare.

According to Friesner (24), "The usual type of spontaneous nystagmus (namely, rhythmic) combined with the fact that it is frequently not amenable to influences aroused by vestibular stimulation suggest that the origin of the nystagmus is a lesion in the vestibulo-ocular mechanism", and he states that about 50 per cnet of cases show nystagmus, although 7 of the 10 cases examined by him showed spontaneous nystagmus in all directions, in some cases several directions being combined.

Holden (33) believes that the incidence of palsies of the ocular muscles are found in but 20 per cent of the cases, are of nuclear origin, are frequently transitory and have no features which are characteristic.

(b) Disturbances in the optic nerve. The following discussion of optic nerve changes was taken mainly from the work of Grinker (28). The optic nerve seems to be a site of predilection for the disease process. Almost all patients develop some ocular manifestations some time during the course of the disease. When the patient, with the fully developed syndrome of multiple sclerosis, sees the neurologist, a history of preceding visual disturbances is often obtainable. The optic nerve is attacked behind the orbit in the form of retrobulbar neuritis. The disturbance is most commonly unilateral although it may appear in both eyes. The patients complain of a blurring of vision as if a mist were before them, gradually increasing in intensity, but rarely producing complete blindness. Some patients may notice that

only a portion of the central vision of one or both eyes is defective.

Early in the process, examination of the discs may reveal no change from normal even though the process is active. The pupil is dilated and reacts poorly to light, but the process is usually invisible ophthalmoscopically because it lies behind the disc head. Occasionally hyperemia or, it is said, even swelling of the disc head may be observed. The neuritis and visual defect may disappear completely and leave no sequela except a reduction in visual acuity. Or, a more severe lesion causes an atrophy of some of the optic fibers. The most susceptible fibers are those of the maculopapillar bundle; hence atrophic changes are visible on the temporal side of the discs as the so-called temporal pallor. Care should be observed that the normal temporal paleness of the disc, or a physiological cupping should not be interpreted as pathological. The disc is rarely completely atrophic so that complete blindness is not to be expected.

Since the maculopapillar bundle supplies central vision, the effect of acute retrobulbar neuritis, aside from decrease in visual acuity, will be central and paracentral scotomata. Patients suspected of having multiple sclerosis should have their central fields plotted, since the scotomata cannot be discerned by gross tests and these defects are so characteristic of the disease.

Grinker feels that double vision attacks are very common, although they are rarely seen by the physician, for even when the

patient has diplopia, it is not a marked type and can be demonstrated only by the candle test. He says, "In a young individual, transient attacks of double vision are extremely suggestive of multiple sclerosis."

(4) Auditory and vestibular disturbances. Auditory disturbances are apparently rare in disseminated sclerosis, but transitory deafness has been described by some writers. Vestibular disturbances have received some attentions, especially from French authors, but it is by no means certain that all symptoms which have been attributed to lesions of the vestibular tracts have really been so produced according to Brain (5). Vertigo may justly be regarded as frequently vestibular in origin, and its frequency, especially in the early stages of the disease, has already been noted. In the majority of cases the responses to caloric, rotatory, and galvanic tests of vestibular excitability are normal, but both hyper-and hypo-excitability have been observed in a small proportion of cases. Brain writes, "The 'vestibular' and 'vestibulo-pyramidal' forms of the disease are rare, and we cannot follow the authors in giving to labyrinthine disorders the preponderating place hitherto attributed to the cerebellar disturbances in disseminated sclerosis."

(5) Sensory disturbances. The variety and frequency of sensory disturbances in disseminated sclerosis has been recognized only comparatively recently.

Paresthesiae: The frequent occurrence of paresthesiae, especially as early symptoms, has already been noted. Birley and Dudgeon (3) found them in 82.6 per cent of cases, Marquezy in 75

per cent of cases, while Sachs and Friedman (53) and Bohmig gave lower figures, but, according to Brain (5) the higher are probably correct. There are a number of varieties of paresthesiae. Numbness or formication may involve one-half of the body, one limb or a part of a limb, or occupy a segmental distribution, e.g., preaxial or postaxial in the upper limb. They are transient and constantly changing. A few cases have been reported in which sensations resembling electric shocks radiated through the body when the patient flexed the cervical spine. Pruritis has also been observed.

Pain: Spontaneous pains, though comparatively uncommon, are important, since if their significance is misunderstood they may be misleading. They are sometimes severe and may involve the limbs, e.g. sciatic pain, pain in the shoulders, or trunk, girdle pains, etc. The pains are said to be 'boring' or 'neuralgic' but not lacinating. Vertebral tenderness may be present. Headache may occur. Trigeminal pain, simulating the tic douloureux, may afflict the patient. Meredith and Horrax (41) report two cases of trigeminal neuralgia in patients having multiple sclerosis and find twenty-five more in the literature of the last 17 years. They say, "No explanation of the facial pain is known, but they respond to ordinary treatment of this condition which refutes the theory of its cause being due to plaques in the pons, medulla, or descending spinal root of the Fifth nerve."

Harris (from Brain (5)) has observed twenty-three cases in which trigeminal neuralgia, often bilateral, was associated with spastic paraplegia. He considers that the majority of these were cases of disseminated sclerosis, and states that the neuralgia is

unassociated with objective sensory loss and responds to alcoholic injection in the same way as tic douloureux.

Objective sensory loss: Objective sensory loss has been found quite frequently in most of the series, Birley and Dudgeon placing it as frequent as 65 per cent of cases, (impairment of postural sensibility 65.7 per cent, vibration 60.8 and cutaneous 31.4). This symptom complex is attributable to the development of a lesion in the lateral portion of one posterior column in the upper cervical cord, with resulting gross loss of postural sensibility and tactile discrimination in the ipsilateral upper limb which exhibits astereognosis and sensory ataxia. Brain (5) has observed a case in which there was loss of all forms of sensibility below a well-defined zone of hyperalgesia in the upper dorsal region, associated with progressive paraplegia of nine months' duration. In this case exploratory laminectomy was performed. The diagnosis of disseminated sclerosis was established at autopsy.

(6) Muscular wasting. Localized muscular wasting due to involvement of the anterior horns of the spinal grey matter in a plaque is one of the rarest symptoms of disseminated sclerosis. It is said to be sometimes sufficiently widespread to simulate amyotrophic lateral sclerosis. Localized wasting may involve one half of the tongue, the small muscles of the hands, one upper limb, the shoulder girdle, quadriceps, or peronei (from Brain (5)).

(7) The cerebrospinal fluid. Examination of the cerebrospinal fluid forms an important part of the investigation of a case of disseminated sclerosis, since in approximately half of the fluids

there are pathological changes which cannot be overlooked. Many papers on the subject have been published and there appears to be general agreement as to the nature and frequency of the abnormalities found. Brain (5) summarizes the reports of a number of observers as follows: The pressure is sometimes slightly raised. The naked-eye appearances are normal. In at least half of the cases the cell count is normal. More than 10 cells per c.mm. were found in from 10 to 20 per cent of counts. The cells are mononuclear in type. The total protein is usually just below the upper limit of normal, 40 mg. per 100 c.c. It is somewhat above normal in 15 to 20 per cent 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 in negative.

Ayer and Foster (2) carried out the colloidal gold test on 42 specimens obtained from 33 patients, with the following results:

So-called 'paretic' type	21 fluids in 16 patients.
So-called 'luetic' type	7 fluids in 7 patients.
Other positive reactions	3 fluids in 3 patients.
Negative reactions.	11 fluids in 10 patients.

These writers believe that the 'paretic' type of gold curve often indicates a progressive phase of the disease and that a negative result is more often obtained from stationary cases. Adams, Dunlop, and Scott(1) have observed a diminution in the colloidal gold curve in response to treatment with salvarsan.

The sugar and chlorides of the fluids show no characteristic changes.

(8) Blood changes. Hansen and Munch-Petersen (31) working on the hypothesis of an essential difference in the genesis of disseminated sclerosis and disseminated encephalo-myelitis, examined the blood with special view to the Arneth blood picture in a number of cases which are classified clinically prior to the blood examination. They found that the cases designated as encephalo-myelitis show a distinct tendency to shift to the left in the Arneth blood picture, whereas the rather typical cases of disseminated sclerosis in their material unmistakeably show blood pictures which come much nearer the normal conditions. There work was controlled and suggests that the results are not influenced by accidental conditions.

III. Symptom groups.

The predominant involvement of different regions of the nervous system leads in the early stages of the disease to widely differing clinical pictures. These need be only briefly described here as their symptoms have in most cases been considered earlier in this review. The following classification and figures were taken from Brain (5).

(1) The classical form. The classical triad of symptoms described by Charcot--nystagmus, intention tremor, and scanning speech--occurs in about 10 to 12 per cent of cases only.

(2) The generalized form. This is the 'common form' which constitutes 37 per cent of cases. Pallor of the optic disks, nystagmus, slight intention tremor, ataxia, spasticity, and weakness of the lower limbs indicate the wide dissemination of the lesions.

This form is especially common among younger patients, and as a rule is fairly rapidly progressive.

(3) Onset with ocular symptoms. In this important group ocular symptoms, especially retrobulbar neuritis, may be the only manifestation of the disease for many years.

(4) Onset with hemiplegia. Hemiplegia appears in only about 2 per cent of cases, and recovery is often rapid and strikingly complete.

(5) Spinal forms. (a) Progressive spastic paraplegia. Paraplegia is the predominant symptom in nearly 25 to 50 per cent of cases. Some cases of Erb's spastic paraplegia are due to this disease. This form is common in older patients. Sensory loss is a variable concomitant.

(b) Brown-Sequard lesions: Lesions which predominantly involve one-half of the cord are most common in the cervical cord. The posterior column may suffer severely.

(c) Sacral form. Incontinence of urine and feces, impotence, and anesthesia in the region of the sacral cutaneous supply have all been noted. These symptoms are attributable to a plaque in the conus medullaris.

(6) Cerebellar, (7) vestibular, (8) pontine, and (9) bulbar forms are sufficiently described by their titles.

(10) Acute forms. The rare occurrence of acute forms seems to be established. Their duration is frequently about 3 or 4 months. The onset is exceptionally rapid. Headache and vomiting may occur and optic neuritis may develop. Cranial nerve palsies are commoner than in more slowly progressive forms.

Treatment

After beginning a review of the methods of treatment in disseminated sclerosis, one is immediately impressed with the large variety of remedies used with varying degrees of optimism as to their efficacy. Since, as has already been seen, the etiology of the disease is not established, it is understandable that theories of treatment would arise to correspond to the many theories of the causative agent. Again, one is confronted with the remissive character of this disease which makes it difficult to evaluate the effect of treatment. As Brain (5) states, "It is notoriously difficult to assess the value of therapeutic measures in disseminated sclerosis, and most advocates of some particular line of treatment qualify their optimism by alluding to the natural tendency of the disease to spontaneous 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 than might have occurred spontaneously." Wetherell (66) also gives us some idea of the vagueness of the situation when he states, "The therapeusis of multiple sclerosis has been a baffling problem since the time of recognition of the disease as a clinical entity, and the multiplicity of agents employed in attempts of relief of the condition signify their lack of specificity."

Concerning general measures, it is most important that rest and avoidance of fatigue be stressed, but permanent confinement to bed should be deferred as long as possible. The suscepti-

bility of the patient to hysterical embroidery of his symptoms demands psychological insight on the part of the attending physician, whose encouragement and optimism are often of greater value than any more specific type of therapy.

As a specific treatment for the supporters of the theory of a spirochete and for treatment on general principles, arsphenamins and other drugs used in the treatment of known spirochetal diseases have been used. Adams, Blacklock, Dunlop and Scott (1) published the results of their treatment with mercury, potassium iodide and Novarsenobillon. The patient received a preliminary course of 10 days' mercurial inunctions combined with the oral administration of potassium iodide. 0.3 grams novarsenobillon is then given intravenously, and if no reaction is noted the dosage is increased to 0.45 grams. Three initial courses of four injections each are given, the administration of mercury and iodide being carried on at the same time. The patient is then given arsenic by mouth for several months, after which a second series of salvarsan injections is administered. Intermittent treatment on these lines is continued over a minimum period of two years.

This type of treatment with drugs of the salvarsan class has given very promising results in the hands of these men, which exceed those obtained by similar treatment in cases of neurosyphilis symptomatically similar. They emphasize the fact that in a disease which normally runs a progressive downward course, any remedy which tends to arrest this progress at the stage at which the disease is first encountered is extremely valuable and should not be withheld, because it cannot confer upon a tissue regenerative power which it

does not posses. "It is, therefore, a logical conclusion that no remedy can ever be expected to 'cure' advanced cases of this disease when the whole nervous system is riddled with plaques of sclerosis. The supreme object of treatment must be towards eradication of the infective agent in the earliest stages of the disease."

Sodium cacodylate has been used and silver-salvarsan is said to yield better results than novarsenobillon and is advocated by a number of foreign writers. The intravenous injection of colloidal silver is recommended by Ohnsorge and Fischer (46) who employed electro-collargol in doses of 2 cc. of 0.06 per cent suspension, increasing to 5 cc. Injections are given two or three times weekly until 40 to 50 cc. have been given. Inunctions of silver in the form of Crede's ointment have also been used by Fischer.

In addition to the above drugs and methods several men have used antimony in various forms intramuscularly and intravenously, sodium salicylate, intramuscular injections of urotropin, mercury, mercury inunctions combined with iodides by mouth, and many others.

De Nicola (44) has tried the use of arsphenamine and states that early there seems to be a slight improvement, as demonstrated in about 30 per cent of his cases, but he has always felt that it was during the remission of the disease, as later the symptoms became aggravated and the end result showed no definite improvement. He believes that strychnine pushed to its physiological limits is as satisfactory as any treatment, and he also believes that potassium iodide by mammoth doses also seemed to be of benefit. He cites one case in which the disease had been in progress for two years when

he gave the iodide. It has been apparently arrested for the last four years and the patient has been able to attend his occupation daily.

Purves-Stewart (48) attempted to use a specific vaccine made from cultures which were allegedly grown by Miss Chevassut (18). He claimed that this treatment lead to clinical arrest of the disease, improvement in the colloidal gold curve, and globulin reaction of the cerebrospinal fluid, and disappearances of the organism from the fluid. However, at the same time that the younger Dr. Stewart discarded the work of Miss Chevassut, a report was made on the results of treatment with the vaccine showing definitely poor results. Dr. Walshe (see Stewart (59)) wrote, "Your results amount roughly to this, that 25 per cent of cases showed some improvement (trivial in 20 per cent) and 75 per cent showed no improvement or definitely retrogressed. I may say with confidence these results are markedly worse than hospital records would show for the treatment on other lines of disseminated sclerosis, and also are not so good as a similar number of wholly untreated cases would probably show. I can only conclude from your figures that the treatment you have been investigating must aggravate the malady, and that the patients so treated are worse off than if they had been left alone."

A short discussion of Brickner's (6-12) theory of an abnormal lipase demonstrable in disseminated sclerosis was given under etiology. It was also mentioned there that he started treating these cases with quinine since it was known to be an inactivator of certain blood lipases. In 1930 he first administered

this drug to eight badly crippled patients. In two of them there was no result. Five entered fairly complete remissions within from ten to fourteen days, and one was somewhat improved. In 1931 Brickner (8) published an article giving the technique of administering quinine hydrochloride orally, and in July of 1932 he wrote his experiences with the use of the drug in the treatment of 16 cases of multiple sclerosis over a period of one year. In this article he studied the effects of the therapy symptom by symptom and concluded that forty symptoms, most of them of short duration, had shown marked improvement. Thirty-three symptoms had not improved, most of which were old. Three of the unimproved symptoms had regressed.

Then in November of 1932, Brickner (11) gave another report of treatment with quinine over a period of two and one-half years with more than forty patients. According to his chart there are 108 symptoms improved; 61 unimproved; and 4-8 regressions. Again he stresses the fact that the greatest number of improvements are seen in the symptoms of short duration (up to three years), while those of longer duration show a greater number with no improvement. In the discussion of Dr. A. Riley at the end of the article he says, "The results of treatment with quinine must be applied in a large number of cases with an adequate group of control patients and over a considerable period of time before any definite judgment can be reached in regard to its efficacy. Insofar as my own personal experience is concerned with the use of quinine on my service at the Neurological Institute and in private practice, I can state that remissions have occurred

more frequently after the institution of quinine therapy and improvement has been better sustained and more satisfactory than with any other form of therapy which I have followed."

Brickner's (12) last article of 1935 gives his results after the use of quinine hydrochloride over a 5-year period. There were 49 patients in this series with a total of 308 symptoms. The majority (about 73 per cent) of the symptoms of two years' duration or less have improved. There was improvement in about 44 per cent of the symptoms of longer standing. 35 symptoms have regressed during treatment. Only 17 new symptoms have appeared in the whole group, and of these only 9 were permanent. In his conclusions he writes, "The statement seems justified that quinine is really beneficial in the treatment of multiple sclerosis. When improvement cannot be obtained, it is worth while to try to arrest the process. The best responses have occurred in patients the total length of whose illness has been short, in patients who are in their initial attack, in those in whom the progress of the disease has not been rapid and in those whose symptoms are not far advanced when treatment is begun."

In 1934 Weinberg (65) also used quinine hydrochloride in conjunction with intra-spinal injections of lecithin and the administration of cod liver oil on a series of twelve cases of multiple sclerosis. In ten of these carefully studied before and after treatment, nine showed greater or lesser improvement and among these were several severe cases. The theoretical grounds for the success of the treatment from the author's standpoint

are that the lecithin neutralizes the lipolytic substance present in the spinal fluid. He believes the results are sufficiently good to justify further use of this method.

In 1928 Kubie (36) used 'forced drainage' of the cerebrospinal fluid in a wide variety of infections of the nervous system in man, and found that the different types of cells are not homogeneously distributed throughout all fractions of the cerebrospinal fluid; in a significant number of cases the last fractions that appear on lumbar puncture contain a much higher percentage of lymphocytes than the fluid which drains out first. He also showed that the administration of hypotonic fluids orally, subcutaneously or intravenously during lumbar puncture causes an abundant additional flow of cerebrospinal fluid without subjective distress, respiratory difficulties or evidence of diffuse swelling of the brain tissues. He concludes that it is both safe and rational to combine a maximal forcing of fluids with the principle of continuous or frequent drainage of the cerebrospinal fluid in the treatment of patients with infectious diseases of the central nervous system.

Freemont-Smith, Putnam and Cobb (23) also used spinal drainage with forced fluids. They attempted dilution of the cerebrospinal fluid by making the blood hypotonic and by spinal drainage. Hypotonicity was obtained by ingestion of large quantities of water (500-1000 cc. per hour) after the subcutaneous administration of posterior lobe pituitary extract (0.5 cc. vasopressin or 1.0 cc. of solution of pituitary) which prevents diuresis for three to six hours. These authors used this procedure

in eleven cases of multiple sclerosis. In all instances both the blood and spinal fluid were rendered hypotonic, the necessary requisite to the theoretical soundness of their method. They do not present this as a satisfactory method of treatment of the disease, but offer it as grounds for further study by those accustomed to the method and envisage some of its dangers, and state "we know of nothing which is more effective in this disease". They also go on to say, "In the work which we have been doing in the past three years, we have been able to show that in the therapeutic fever of typhoid vaccine and of malaria there is a situation closely analogous to that which we get when we give a solution of pituitary. That is, water which is drunk is not put out, and we are able to show that it is not just a question of sweating to compensate for it, but that there is an actual and marked retention of water in the body. The urine output is almost nil, in spite of the large intake of water. The diuresis is delayed several hours, and a prompt and marked dilution of the blood occurs which is followed by a dilution of the cerebrospinal fluid. This mechanism occurs in various acute infections."

A line of treatment has been established in keeping with the theory of etiology of Putnam (49, 50, 51), i.e. some type of vascular disturbance. Wetherell (66) used a cervicodorsal sympathectomy in 1934 which consisted of removing the inferior cervical and the first thoracic ganglion by the posterior approach. The transverse processes of the first thoracic vertebra and about one inch of the first rib were removed. The ganglia are picked up, and the cords above and below are sectioned, as are all the rami,

and the structures thus sectioned were removed. He proposes this operation as a measure of relief in cases of multiple sclerosis and attempts to rationalize the procedure on a basis of betterment of cerebral circulation, which may relieve irritation and allow a more normal blood supply and more normal conduction of nerve impulses. In this paper he reports one case of eight years' duration with marked symptoms and disability (bedridden for several months). A right sided cervicodorsal sympathectomy was done with marked improvement in speech and eyesight, and muscular power increased. Twenty-one days later the left side was operated and the patient was dismissed sixteen days later in a much improved condition--better eyesight, no constipation, ability to feed himself, able to write legibally, walk several hundred feet with little help, etc., none of which he had been able to do for years.

Later, in 1935, Wetherell (67) published an article presenting six cases in which there was improvement in various symptoms that had been present before operation. He states, "The effect of spinal drainage and of fever therapy, whether it is effected by vaccine or by some other means, is evanescent in nature. With cervicodorsal sympathectomy one causes vasodilatation which is permanent. There I shall leave the gauntlet."

Royle (52) of Australia also used cervicodorsal sympathectomy in 1933 on four patients suffering from advanced disseminated sclerosis. He says that the results of treatment by altering the cerebral circulation are striking, progressive and lasting. "It is nearly 18 months since the first patient was subjected to opera-

tion. It is well known that disseminated sclerosis is characterized by remissions, but is hardly likely that remissions should immediately follow operation in four consecutive cases without having some relationship to the measures adopted." He also says that the earlier the patient is subjected to operation the greater the hope of complete relief.

Mention should be made of liver therapy although little has been done along this line of treatment. Goodall and Slater (25), in 1931, recorded five consecutive cases of disseminated slcerosis of varying duration and severety, treated with whole liver, and in which the authors claim remarkable improvement. Two of these patients, previously totally unfit have returned to work; one man unable to stand is able to walk now; and one young woman who had given up games for two years can now play hockey. They suggest from their therapeutic results that this disease may form an addition to the list of deficiency diseases.

Although it is not determined whether multiple sclerosis is to be considered as a systemic infection with focal lesions in the nervous system, fever therapy has received the greatest attention, and it is being investigated more widely than any other proposed form of treatment. The history and advancement of this type of treatment is very interesting, but space does not permit of a review here. Induction of fever by giving the patient malaria has been quite extensively tried, but discarded now for more effective methods. (Brain (5) reviews the work of Dreyfus and Hanou who claimed improvement in eleven out of twelve cases,

and Grosz who claimed improvement in twenty-nine out of forty-two cases.)

Later Grosz (29) has obtained benefit from the subcutaneous injections of vaccines which produced no general reaction. He treated twenty-six cases with polyvalent staphylococcal vaccines and twenty cases with typhoid vaccine. Eighteen of the latter also had neo-arsphenamine. He concluded here that typhoid vaccine with neo-arsphenamine gives the best results, there being marked improvement in 30 per cent of cases. He considers this better than malarial treatment.

The idea of typhoid vaccine in the treatment of disseminated sclerosis was originated in Vienna, where it was thought the disease was the result of some intestinal infection. Vaccines of various intestinal bacilli were tried and the most suitable was found to be typhoid. MacBride and Carmichael (39) in 1924, used eight to twelve injections intravenously at intervals of one, two, or three days. They usually obtained a rise in temperature to 100° F. within a few hours which returned to normal within twelve hours. They also used it in conjunction with silver salvarsan which they believed brought about 'fairly good remissions'. They wrote, "As a result of our observations we are of the opinion that this method of treatment offers more satisfactory results than any other recognized method. The usual massage, passive movements, and remedial exercises are combined with this form of treatment."

In the same year, (1924) Schackerl (54) reported an extensive study in the treatment of multiple sclerosis by the combined use of calcium, neo-arsphenamin, and typhoid vaccine injec-

tions. He used calcium chloride because of its anti-spasmodic effect in hypertonic muscular conditions. Although he used the typhoid vaccine for the development of a febrile reaction he did not believe high fever reactions were essential, but that subfebrile or low fever reactions were preferable. He concluded that prompt remission can be produced by the therapy in suitable cases with at times astonishing results. He finds that the cranial nerve palsies and cerebellar symptoms quickly disappear, but the spastic findings are more difficult to improve. He believes that duration of illness and age influence the results of the treatment unfavorably and that young cerebellar cases appeared to be of the more favorable prognostic type, (taken from Young and Bennett (70)).

In 1929 Young and Bennett (70) published their method and result of treatment with typhoid vaccine. They began treatment with the use of subcutaneous injection of typhoid vaccine (typhobacterin) for two doses, giving 250 and 500 million bacteria in the first and second doses respectively, two days apart. On the fourth day twenty-five million bacteria are given intravenously and on each succeeding fourth day intravenous injections are given of sufficient strength to raise the temperature to 101° or 102° F. From eight to sixteen injections are given according to the condition of the patient. They defer drug treatment until some time after the cessation of the protein shocks. In addition they kept their patients in bed during the treatment and removed what foci of infection were present. They say, "This latter step does not interfere with the vaccine therapy and may

be of benefit to the general health of the patient."

In reporting the results of treatment, these authors divided the cases into three groups, remission, partial remission and no improvement. By remission they meant marked improvement with resumption of work or of social activity. There may be residual organic signs such as increased spasticity or a slight paresthesia, but the patient subjectively feels well and strong. Under partial remission is included a gain in subjective sense of well-being with a definite and persistent improvement in the objective signs such as nystagmus, ataxia or paralysis. No improvement means no change or progressive increase of the symptoms. Of the four acute cases in their series of twenty, one showed a complete remission, one showed no improvement, and two partial remission. Of the eight remitting cases, five showed prompt remission and three partial remission. Of the eight chronic progressive cases, seven showed no improvement and one remission.

Schroeder (56) in 1929 reports the use of Sulfosin (sulphurated oil) in disseminated sclerosis. In the human organism the administration of sulphur in this form sets up a febrile condition of short duration. He felt that this treatment was preferable to infection treatment because it offered the same therapeutic effect without the dangers and drawbacks of infection treatment. His use of sulfosin in three unquestioned cases of disseminated sclerosis showed no recognizable therapeutic effect, but he quotes Gerog Stiefler who had treated twelve cases with sulfosin with encouraging results. "'...it has served me well in several cases which did not respond enough to typhoid vaccine. Sulfosin is also preferable to treatment with typhoid vaccine when the patient is markedly debilitated or suffers from circulatory disturbances.'"

As we have already seen De Nicola (44) was unsuccessful with specific treatment with arsenicals, etc. He writes further that he has had no results with malaria or with typhoid vaccine. He also attempted the use of forced drainage. He writes, "Forced drainage of the spinal fluid has been found of value in the relief of symptoms as amblyopia, Babinski and clonus. I have tried this on two or three cases, but the reaction was so great that severe headache, nausea, vomiting, loss of weight, and even symptoms of collapse followed, that I immediately discontinued it." He also tried specific protein therapy and liver therapy with no results. He does find, however, that the use of sodium amytal, hyoscin hydrobromide, veronal, and luminal are of value in cases with tremor. Hydrotherapy and massage of the affected limbs with heat, offer some relief from sensory disturbances. "And finally, good nutrition and elimination are imperative. Removal of questionable foci of infection, such as teeth, tonsils, etc., is always advisable."

Newer methods of inducing hyperpyrexia are being used which include the use of ultra-violet rays, deep x-ray therapy, diathermy, radiothermy, and lastly air conditioned chambers. In 1934 Neymann and Osborne (43) published their results of twenty-five cases of multiple sclerosis which had been treated by hyperpyrexia produced by diathermy, radiothermy and the electric blanket. After diagnosis was made and established by the Staff of the Neurological Department of Cook County Hospital, 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. The diathermic technique was used in 95 per cent of the cases. They write, "At present radiothermy is an expensive and cumbersome method which is inferior to diathermy for producing temperatures. The electric blanket is generally too exhausting for patients suffering from multiple sclerosis, because a therapeutically active fever cannot be produced fast enough. We believe that a temperature curve with a quick rise to 103.5° F., and a high plateau ranging between 105° and 105.5° F., is the optimum from the therapeutic standpoint. ...The temperature is maintained at the level of 105° F. for from eight to ten hours. The treatments are given biweekly. No other form of therapy was employed in this series."

As a result of this treatment 44 per cent of the cases were much improved and an additional 40 per cent were improved to a lesser degree. During the time interval in which these cases were observed after treatment, all remained stationary, the interval varying from a few weeks to eighteen months. One case returned to the hospital with an exacerbation of symptoms and two patients died, one as the result of treatment.

These authors believe that it is impossible to evaluate this treatment before many years have elapsed, but they do feel that they 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. They go on to say, "We further know 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

dosis of the amount of fever, and have none of the disadvantages of introducing chemicals or infections into the body. They are very safe."

Schmidt and Weiss (55) are also of the opinion that diathermy is of very practical value in producing hyperpyrexia, and they say that such symptoms as spastic paraplegia, intentional tremors, ataxia, and vesical disturbances have shown remarkable improvement in their experience. Other common signs, such as scanning speech, nystagmus, and optic atrophy were not markedly benefited by diathermy. They write, "We have been impressed with the adaptability of diathermy as the only present logical form of treatment at our disposal."

One of the latest methods used for producing fever is the air-conditioned fever chamber (Kettering Hypertherm) which is now in the experimental stage and not on the market. It was conceived and perfected at the Miami Valley Hospital and at the Research Laboratories of the Frigidaire Division of the General Motors Corporation by Dr. Walter M. Simpson, Mr. Charles F. Kettering and Mr. Edwin C. Sittler. A complete description of the cabinets is given by Desjardins, Stuhler, and Popp (22) of the Mayo Clinic at Rochester, Minnesota which may be found in the Journal of the American Medical Association for Febraury 29, 1936. Such a description would be too lengthy and superfluous for this report, but it is felt by those using these cabinets that it is a very satisfactory method of raising the temperature to the required level and holding it there with practically no variations as long as desired.

I have been unable to find any report in the literature of the effects obtained with the Kettering Hypertherm upon this particular disease, probably because the time has been so short since they were first used and most of the operators feel that they do not have sufficient data, either in number of patients or length of time treated, to warrant a report. However, I have had the opportunity to see three of these cabinets in use at the Lutheran Hospital of Omaha, Nebraska, and have had access to the case records of the patients with disseminated sclerosis that are under treatment. To date they have had a total of twenty-two such patients, and the object is to give them one hundred hours of fever above 104° or 105° F. in three series of treatments, six treatments in each series. The apparatus here has been in use for only about 18 months, but it is the object of the Staff to continue over a five-year period before they will have sufficient data on which to make a report. However, they feel, at present, that the results are somewhat promising particularly in the acute and in the remissive types of the disease. After it has reached the chronic progressive stage their results are less promising, but often a marked subjective improvement is noted. Following are two case reports from the present series of patients:

Case I. Patient E.R., age 27, entered 8-20-34 complaining:

1. Incomplete control of left arm and left leg.
2. Double vision.
3. "When bladder is full--if he doesn't urinate right away--it will dribble."
4. "Choking sensations in windpipe while eating"--especially liquids.
5. When under emotional stress and strain, facial muscles will pull to the right.
6. Difficulty in speech of a duration of 14 months.

First noticed about 14 months ago while walking down between rows of corn. He found he "couldn't keep his balance", would swagger from one side to another. He seemed to be bothered with this staggering when his arms were loaded. Later on staggering was evident without arms being loaded.

Patient saw three doctors and started to work again when his complaints returned, the incomplete control of left arm and left leg being most marked. History of seeing double at times.

Neurological:

Cranial nerves: Facial muscles show greater tone on left side with pulling to the right.

Upper extremities: Definite lessed motor effect on left side. Adiodokokinesis - early fatigue of left arm. Point-passing positive bilaterally. Reflexes exaggerated.

Trunk: Dermographia transient. Abdominal reflexes equal. Cremasteric reflex diminished on left.

Lower Extremities: Definite motor weakness on left side. No tremor. Tone good. Left foot held in position of partial T. equinus varus, large toe dorsi-flexed. Babiniski positive bilaterally, more marked on left. Positive Oppenheim's on left. Slight positive Rhomberg.

Sphincters: Normal.

Diagnosis: Chronic progressive multiple sclerosis.

Treatment: Two treatments with inductotherm--temperature to 106° F. Discharged 9-5-34.

Series I. 11-8-34 to 1-17-35. Six treatments with 29 hours above 105° F. Gained 6 3/4 pounds.

Patient still shows a staggering gait but it has definitely improved onver 3 months ago. Reflexes are hyperactive and there is ataxia in both left extremities. Left Babinski and ankle clonus persist. Patient can now drive a car, milk cows, and his general health has improved. Moderate left foot drop persists.

Series II. 6-12-35 to 8-21-35. Six treatments with 30 hours above 104° (1° less than Series I). Lost 2½ pounds.

Patient showed active reflexes with positive Babinski and ankle clonus bilaterally. Gait staggering. Strength good. No nystagmus. Patient is about the same to slightly improved.

Series III. 12-17-35 to present. Four treatments with 4 hours above 105° and 16 hours above 104° F. Lost 10 pounds.

When patient started this series he felt somewhat stronger, but his gait has remained unchanged. He has moderate dysphasia particularly when excited. Otherwise condition is unchanged.

Comment: There is definite subjective improvement, but no objective improvement.

Case II. Patient C.E., age 37, entered 4-22-35 complaining:

1. Sudden numbness in the left small finger.
2. Difficulty in walking.
3. Tendency to lean to the left while walking.
4. Severe left sided and occipital headaches.

Five years ago last December, the patient lost her eyesight during the course of one week. She was in a hospital for one week receiving sweat baths after which her eyesight returned. She then noticied color blindness. Two years later a friend called her attention to her eyes saying she was "cross-eyed". One year ago, the patient, after trying to get out of bed, suddenly became very dizzy. A week later she noticed diplopia and then the right side of her face became paralyzed. This paralysis lasted for three weeks and then started to recede. Her gait became very difficult and she had to have help walking.

Two weeks ago she began to have dizzy spells, inability to turn over on the right side, difficulty in walking and noticed a staggering gait and leaning toward the left. She also noticed a paresthesia from the pelvis to both shoulders. She has noticed a roaring sensation in the right ear. Inability to perceive sensation in both legs and inability to walk.

Diagnosis: Chronic advanced multiple sclerosis.

Neurological: Horizontal nystagmus, temporal pallor, positive bilateral Hoffman and Babinski, right facial weakness, adiodokokinesis, all reflexes except abdominals are active. Abdominals absent. Touch diminshed on right side.

Treatment:

Series I. 4-23-35 to 5-31-35. Six treatments with 5 hours above 103°, but with none above 104° F.

Series II. 10-3-35 to 11-7-35. Six treatments with 27 hours above 104° F.

The patient feels that she has gained in strength, and is gaining steadily in weight. She is able to take a few steps without support. Eye symptoms are less marked. Nystagmus can still be elicited. The patient has a very severe and persistent vertigo, particularly noted when she first gets up.

Comment: Improvement both subjectively and objectively. She has not started her third series of treatments as yet.

The multiplication of remedies is eloquent of their inefficacy. The organic compounds of arsenic have been the most popular therapeutic agents, but there is no general agreement as to their value. This fact, in contrast with the status of these drugs in the therapy of neurosyphilis, suggests that they probably have no specific action upon the cause of disseminated sclerosis. The various forms of pyrexial treatment appear to be the most

effective therapeutic measures at present available, but they cannot be expected to do more than retard the progress of the disease. They can accomplish nothing in the advanced cases, and would seem to be indicated especially in early but apparently rapidly progressive cases. The cure of disseminated sclerosis awaits an increase in our knowledge of the causal organism, or the nature of immunity, and of the factors upon which depend the remarkable variations in the course of the disease.

Dr. Charles H. Dolloff (see De Nicola (44)) sums the disease up in an interesting way in the following two sentences: "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, the etiology so obscure, the symptoms so vague, and treatment so hopeless."

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