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Etiology of multiple sclerosis

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Preface

I first became interested in multiple sclerosis as a junior clinical clerk. I was privileged during that period to observe such a case. Up until then, I never knew that the disease existed. This patient was in the hospital for the third time; suffering his third remission. The peculiar pattern of recovery and relapse that this disease presents captured my imagination, and I have been interested in it ever since.

Also, the fine diagnostic lines that must be drawn, at times, to make a diagnois appealed to me. Further study, has disclosed its importance as a relatively common neural disease. These considerations and a personal interest in neurology as a possible future speciality aided me in my choice of this study as a subject for a senior thesis.

Multiple sclerosis is the "Will o' the Wisp" of neurological disease. In none of the classical compartments of disease study has it been sharply deliniated or understood. The best one could do in the way of definition is to say it is a condition of envolvement of the white and to a lesser extent the gray matter of the central nervous system by diffusely scattered plaques of demyelinization, glial scaring, and limited destruction of axons and cell bodies, the symptoms are determined by the location of the lesion, the prognosis is unpredictable except that it is characterized by remissions and is invariably fatal; the etiology is unknown.

The disease was first described by Cruvielhier.[1] He included plates taken from the lesions of two cases along with the clinical histories. For the next thirty years it was studied in a confused helter skelter manner. Names such as Leyden, 1867; Zuker, 1867; Roketeisky, 1856, were among those reporting cases. The great Charcot[2] in the 1870's did much to create what organization exists in this field by sketching as accurately as possible the clinical picture and describing the pathology. His famous triad of scanning speech, nystagmus, and intention tremor have lasted through the years. He also mentioned the absence of abdominal reflexes; the frequent retro-bulbar neuritis; the scattered areas of hypasthesia and paralysis; and

the mental changes, euphoria and others. He puzzeled over the spotty history of remissions and exacerbations as have all neurologists since him.

All the great names in neurology since Charcot have added their ideas, Marie, Oppenheim, Babinski just to mention a few. Since their day diagnosis has become surer, the course of the disease is a little more clearly anticipated if not understood, but very little has been produced in the way of an established etiology or a rational treatment outside of empirical groping. This is not because of a lack of interest in the subject, for research has been vigorous and extensive. Practically every neurologist could be said to "suffer" with multiple sclerosis although he doesn't have it personally.

Incidence

The incidence of the disease presents some interesting statistical facts. It is a disease, according to Brain,[3] confined almost exclusively to the white race. It is almost unknown outside of Europe and the United States. Its prevalence is often overlooked by practitioners; for it stands second to neuralsyphillis in patients admitted to hospitals for nervous diseases. In most series males have about a three to two ratio over females. The incidence is slightly higher (12 per 100,000) in urban populations than, in rural areas (8 per 100,000). Its national disturbution is as follows; the highest incidence is in the Finns with a rate of 29 per 100,000; next come the Swedes and Norwegians with a rate of 16 per 100,000; the French have a rate of 10.7 per 100,000; the Slaves, English, and Irish show a higher incidence than average.. The Italians and Roumanians have the lowest European incidence. It is slightly higher among the foreign born Americans. During the last war the highest incidence in draftees was found in those from Michigan, Minnesota, and Wisconsin possibly reflecting their Scandinavian lineage. It is practically unknown in the southern United States. Many attempts have been made to show an industrial distribution. The wood workers, iron

workers, and lead workers being singled out in turn; but none of these studies were extensive enough or had sufficient controls to justify their conclusions.

The disease has a characteristic age pattern. Cases have been reported at ages stretching all the way from nine to eighty years of age, but by far the vast majority is seen in the two decades from twenty to forty.

Thus, from the incidence of the disease we can conclude that there is a definite predilliction for the white race, that it shows slight but definite national tendencies, that males are a little more prone to suffer with it than females, and that it has a definite age distribution.

Clinical Course and Pathology

In general, three different clinical courses are described. There is classical multiple sclerosis, that was pictured so well by Charcot and since appearing in all the text books of neurology. This is the chronic, drawn-out disease, lasting for years with a varying number of remissions. In the later stages the famous triad is frequently found. Then, there is the steady progressive type unblessed by remissions. The paralysis spreads in a crazy patch work fashion over the body and death again is the outcome. Finally there is the acute form with few symptoms; there may be nothing but a "dead" extremity and bi-temporal palor of the fundus. It can go into a sudden transverse myelitis with death resulting in a few weeks, or there can be complete recovery and the case then turns into the classical Charcot type. The course then can vary from a few weeks to half a century. The average duration of life after the initial lesion being seven years.

The classical pathology described by Charcot was confined to advanced long-standing lesions. Grossly, he found grayish disseminated plaques. They were located much more frequently in the white matter than in the gray matter of the central nervous system.. No part of the central nervous system was immune. The cortex, thalamus,

basal ganglia, pons, medulla, pyramidal tracts, and the posterior columns were all mentioned as being involved.

On microscopic analysis, he reported an intense gliosis made up the main substance of the plaque. In the center bothethe reticulum, and some of the axons were shrunken; but here and there an intact axon could be found. Around the periphery of the lesion were signs of more activity. There was beading and breaking down of the myelin sheaths; and phagocytic cells and cells containing fat globules were seen.

Naturally, the post mortem material Charcot drew his conclusions from was little more than old burned out scares. The same thing would be true if one described tuberculoses of the lungs and merely gave the histology of a Gohn tubercle. As more material became available it was possible to study the disease in its acute forms. By doing this, it was found that the first visible signs are picked up in the myelin sheaths. They become beaded and fragment into fat droplets. The axons show edema-like swelling and some necrosis. The blood vessels show a perivascular cuff of cells the source of which is still in hot dispute. One group of neuro-pathologists claiming that they are glial cells, phagocytes whose parents are the microglia of normal neural tissue; and another

group that they are lymphocytes that have been brought in by the blood stream.(Symonds[4]) These phagocytic cells soon become engorged with myelin droplets and beome the glitter cells so often described by the German pathologists. Pathology is vitally important in the question of the etiology of multiple sclerosis and more shall be told about it later.

Since, the scope of this paper is limited to the etiology of the disease; no more general discussion of its symptoms and its clinical course seem necessary. The various theories arranged as near as possible in their chronological order shall be paraded. Pathology, smyptoms, and laboratory study shall be mentioned only as it pertains to these theories.

Infectious Diseases and Trauma

Charcot was first impressed with the number of infectious diseases that were associated with the initial onset of multiple sclerosis. He cited an impressive array of cases to prove his point. Typhoid fever and small pox were among the chief offenders in his series.

In 1895 Marie[5] wrote, "I am quite convinced that another cause exists which is more frequent than any, without which the islets of sclerosis would not be present in the brain or spinal cord. The truly effective cause is the presence of infection or rather the presence of infections."

Among the diseases he indicted most vigorously were: enteric fever; small pox; and the other eruptive fevers; such as, measeales, scarlet fever and scarletina.

Oppenheim[6] in 1900 mentioned the following diseases as showing correlation with the onset of multiple sclerosis, typhoid, variola, scarlitina, morbulli, infulenza, cholera. diptheria, rheumatism and one case which followed the puerperium.

Brain[3] in 1930 pointed out that only in about twenty-five per cent of the cases could an accurate association with infections be demonstrated, and if this were limited to but three months before the onset of the initial attack,

it could be seen in only three to six per cent of the histories.

None of these workers tried to establish a direct causal relationship. None of them stated in so many words that the lesions of multiple sclerosis were actually small pox, typhoid etc. of the central nervous system. Most of them confined themselves to such ideas as resistance lowering factors, preparation of the host, and so forth. Such ideas as this are impossible to refute. It would be silly to assert them or deny them; an open mind is the only treatment of this subject.

Before the infectious disease theory is passed, the diseases or syndromes known as measles encephalomyelitis and post vacinal encephalomyelitis should be mentioned. These are conditions that sometimes occur following these two situations. Clinically and pathologically many neurologists defy anyone to tell them from acute multiple sclerosis.(Putnam[7]) The question shall be considered under a later heading.

Trauma is the next consideration. By trauma exposure to wet, cold, fatique, physical violence and emotional shock is intended. Charcot, Marie, and Oppenheim, all mentioned it as closely allied with infections in the etio-

logy of this condition. Brain was only able to get a ten per cent correlation with trauma.

Here again, the factor of resistance depletion could be argued with the same imponderable indefinitness. My own experience, brief as it is, has convinced me that in any diseased condition, causing any sort of disability such as the paralysis of multiple sclerosis, a history of trauma is almost invariably elicited. The exigencies of life are so interwoven with trauma that a scientific study of its effects and relations to such an obscure an entity as multiple sclerosis would be a task that few would attempt. All have been content with generalizations mentioned above. Now and then, a very striking association is obtained; but these are so isolated that it would be hard to ascribe anything more than coincidental weigh to them. As far as such trauma as falls are concerned it is hard to establish that the disease itself is not often the cause of the fall rather than the result.

Heavy Metal Intoxication

Among the earlier theories of importance was that of heavy metal intoxication. As was mentioned, in the introduction, the iron and lead industries showed higher incidence in some series; but larger more extensive studies have tended to disprove this. After them, little was done. Later, the diagnosis of both lead poisoning and multiple sclerosis were more carefully drawn and the confusion of missed diagnosis largely avoided. Another factor that tended to smother the heavy metal idea was the fact that women who were supposedly more carefully protected from exposure seemed to have almost as high an incidence as men.

Meanwhile the question of lead intoxication was better understood. More recent chemical analysis techniques showed that exposure to lead was much more general than supposed. (Harwood and Russel[8]) Cosmetics, silk hosiery, paint and many other articles of ubiquitous nature were shown to be showering the population with constant lead particles.

Russel and Harwood in 1934 presented a study of six cases of clinical multiple sclerosis all of which showed lead abnormalties. These six patients were all of the

chronic recurrent type. In three of these patients lead could be found in small amounts in the urine, stools, and spinal fluid.

In twenty controls, among which were two cases of multiple sclerosis suffering from the steady non-remittant type of the disease, lead could not be recovered even with the adjunct of acidosis.

These authors also reported an interesting case history of a woman who had first shown signs of multiple sclerosis when she was nursing her first baby. She made a good recovery and then had a recurrance with her next child which she also nursed. This was repeated with her third child after which episode she died.

On post mortem the sclerotic plaques of multiple sclerosis was found. The plaques were analized quantitatively for lead and 0.55 mg. per 100 gm per dry weight was found.

Another case is related of a patient who following an infection had lead in his spinal fluid, urine, and stools. He developed retro-bulbar neuritis and an ascending transverse myelitis and died. The sclerotic plaques were present and again tested positive for lead.

Putnam[9] sites a few cases where women suffer exacerbations regularly with their menses. He also mentioned

six cases that had flare ups after the onset of their seasonal hay fever and asthma.

AAll of this may seem rather confusing and disjointed, but it does tie together in a very intriguing theory. One of the clinical traits of multiple sclerosis has been its tendency to improve suddenly and for considerable periods to remain quiescent, then as suddenly to reappear. A patient can be in sore straits, paralysed and almost blind and in a short period of time be back on the job.

There are not many ways to explain this phenomena. Few infections work that way; endogenous toxins or metabolic deficiencies or perversions that rush off and on the stage like circus clowns are hard to postulate.

However, with this lead intoxication thesis one sees a plausible explanation. It has been shown that chronic exposure to lead brings about slow absorption and storage in the boney skeleton. Lead substitutes for calcium in bone salts. This process can take place upon a subclinical bases without any external signs of an impending toxic condition.

The maintenance of this stored lead in the bones is dependent upon the delicate balance of body calcium and

the hydrogen-ion concentration of the blood. Hence anything that can produce an acidosis (like infections) or the mobilization of calcium as in lactation, will shower the body with lead from the bone reservoirs. Here then is a noxa which can very well supply the varying pattern of attack and retreat which is necessary to explain multiple sclerosis on a chronic toxic basis. The importance of infection has already been stressed. Russel and Harwood's experience as well as the observation of Dr. Putnam lend support. It should be noted that in controls two cases of steady progressive multiple sclerosis were negative to lead. This would almost necessitate a search for another toxin in their case if the authors' thesis is correct.

This work cannot be too highly praised. It certainly is pointed in the correct direction. Unfortunately, there were no follow ups in the subsequent literature; and this left several points still in the air at this writing.

Any real scientific conclusions are difficult to draw from case studies of multiple sclerosis established on clinical diagnosis alone. Neurologists disagree many times in this disease, and even the best of them are sometimes fooled. It is not without the realm of possiblity that some would have diagnosed these cases as lead

poisoning; this condition is a notorious imitator.

A gain, not enough is known about the significance of finding small traces of lead in the body fluids. The authors agree that large proportions of the apparently normal population will test positive for lead. They contend that these people are merely subclinical, hidden cases of potential poisening.

Finally, if their contribution is correct, why should some lead poisening produce the classic picture, and others produce multiple sclerosis of the remittant type? Is it just low grade intoxication of a chronic nature that produces sclerosis, while a massive exposure produces the classical form of lead poisening? Much more work is obviously needed upon this question.

Familial Tendencies

The next phase of etiology to be examined is the familial tendency. It is not surprising that the genetic question came up early in the study of the disease; for the early work was done at the same time that such definite heriditary diseases as Friedrick's ataxia and the various muscle distrophies were worked out. A lso the ease with which some of the forms of multiple sclerosis can be mistaken for these conditions confuses the picture. In fact, it should be stated now that no history of familial multiple sclerosis should be excepted without a post mortem examination because of its close resemblance to the inherited degenerative diseases of the cord and brain.

Baily[10] in 1922 after a statistical analysis of the World War draftees reported that the histories of thirty per cent of the patients with multiple sclerosis gave a family story of other nervous diseases. This is significant when compared to the same factor in draftees suffering from syphilis of the central nervous system, for only seven per cent of that group gave a family story of other nervous diseases. Baily further stated that among all the inductees, a family history of nervous diseases could be obtained in but ten per cent.

Then, one runs into occasional histories similar to this one reported by Brown and Davis.[11] It concerned a family in which a man of forty was dying of multiple sclerosis plus mental symptoms. His brother died at the age of thirty-one of multiple sclerosis plus mental symptoms. (This was confirmed by autopsy.) His sister was then in the Islip state hospital suffering from a case diagnosed as multiple sclerosis plus a psychosis.

Wilson[12] in 1940 collected twenty cases of the disease in siblings from the literature. He added two examples from his own experience. He mentioned a Swiss national health survey containing 891 cases, of which, herdofamilial envolvement was present twelve times. There were six sibling pairs, two father and daughter relationships, one mother and son, one mother, daughter and son, and two cousins.

Brain agrees that two generation transmission is very unusual.

The trouble is that most of these cases lack post-mortem confirmation, and even overlooking that one should agree with Wilson when he states, "Though due weight be attacked to such occurances they are nevertheless entirely exceptional when contrasted with the sporadic types; at

most, they allow for a very occasional inherited disposition; and they do not formerly exclude the chance of mere accident."

It seems that the true importance of the heredity factor can be weighed accurately when one listens to Putnam[13] who reported fourteen pairs of identical twins gathered from the literature and one such set from his own experience; one of each pair was suffering from multiple sclerosis and the other was normal.

The Spirochete Question

The spirochete theory now appears. This was one of the stormiest periods in the study of this disease. It convinced many before its initial impetus was lost; and in complete fairness, it cannot be said to be settled yet.

Perhaps, one should start with the work of Bullock[14] back in 1913. He achieved what appeared to be the first recorded transmission of the disease. Using a rabbit and the spinal fluid of a patient with clinical multiple sclerosis, he made two injections, one intra-durally and the other along the sciatic nerve. In fourteen days, the rabbit showed spastic quadraplegia. He killed and autopsied it and found areas of demyelinization, edema and congestion in the central nervous system. He then took spinal fluid from the same patient and used two rabbits. Into one, he injected fluid filtered through unglazed porcelain and into the other he injected unfiltered spinal fluid. The injection was made subcutaneously.. In twenty four days both rabbits showed paralysis of their hind limbs, from which they quickly recovered, only to have reoccurrences in six weeks. He then performed autopsies and found what he described as typical areas of multiple sclerosis in both spinal cords. There was demyelinization, gliosis, and fat laden cells.

Unfortunately, this experimental transmission work was then taken up by German research workers. Not that German work is automatically ruled out because of its source, but rather that the original pieces of work are unintelligible to this monolinguist. A good second hand outline however, is obtainable from Brain,[3] and he is largely followed in this account.

In 1914 Steiner[15] repeated Bullock's work with a rabbit, and then in 1917 working with Kuhn[16] he injected by various routes a series of rabbits and guinea pigs with blood, cerebrospinal fluid, or a mixture of both obtained from thirteen patients suffering from multiple sclerosis. A large proportion of the animals developed paralytic symptoms, guinea pigs being the more susceptable. It was also seen that blood was more potent than the cerebrospinal fluid.

He also claimed to have transferred this paralytic condition from one animal to another. He had one series of four guinea pigs and another of two rabbits.

On doing autopsies, he made a most important discovery. In the heart and in the blood vessels of the liver he observed spirochetes resembling those of icterohemorrhagica; but with the addition of a frequent terminal

nodule or cilia. He called this spirochete, Spirocheta argentinensis.

Next Steiner[17] inocculated a Macacus rhesus intra-cerebrally with some spinal fluid from a case of multiple sclerosis. Nothing happened for eleven months. Then a transitory paresis of the lower limbs developed. He autopsied it five months later finding plaques in the cerebral hemispheres. Histologically, they exhibited demyelinization, infiltration iwth granular cells, glial over growth, and a relative survival of the axons. He described this as indistinguishable from human multiple sclerosis.

In 1919 Marinesco[18] produced motor weakness in two guinea pigs injected intra-cerebrally with cerebrospinal fluid taken from a multiple sclerosis patient. This produced no ill effect on other animals when injected by any other route. By puncturing the ventricles of the guinea pigs, spirochetes were obtained. Attempts to further transmit this condition failed.

In 1921 Kalberlah[19] found spirochetes in the blood and tissues of rabbits which had received inocculations of cerbrospinal fluid and blood from patients with the disease. He described a plumper heavier spirochete than

Steiner's. It was even larger than that of Treponema pallidum.

Bullock[20] in 1921 repeated his original work on a wider scale using twenty cases of multiple sclerosis as sources for his cerebrospinal fluid, and a 129 rabbits plus fifteen guinea pigs as the test animals. The guinia pigs all stayed healthy as did 112 of the rabbits. However, seventeen of the rabbits showed paralysis. Grossly, he found slight congestion of the brain upon autopsy and several small hemorrhages in the brain and spinal cord. It is regretable that he did no sectioning or microscopic examinations.

In 1922 Pettit[21] reported the observation of spirochetes in the cerebrospinal fluid of two patients with multiple sclerosis. He inocculated a monkey intra-spinally with cerebrospinal fluid from a case, and six days later spirochaetoid bodies were recovered from its spinal fluid. It died in a coma on the twelveth day. He also claimed to have found spirochetes in the cerebrospinal fluid of inocculated rabbits.

In 1925, Adams, Blacklock, and McCluskie[22] found spirochetes in the cerebrospinal fluid of two monkeys inocculated with material from a case of multiple sclerosis.

One of the monkies was killed because it was dying of coliform peritonitus, and in the other monkey only one spirochete was found.

It is not surprising that with evidence such as this, many concluded that the etiology of multiple sclerosis had at last been established. Nevertheless, this theory was soon open to bitter attack.

Noguchi[23] observed that finding a spirochete in a patient with multiple sclerosis was not too significant for three reasons. First, the close resemblance that multiple sclerosis has to tabes in some cases. Second, the fact that neural syphilis can very possible be superimposed upon a case of multiple sclerosis. Finally, disintegrated blood elements especially red blood cells can closely resemble spirochetes. It should be added that none of the alleged sources of cerebrospinal fluid were ever reported to be established cases upon post mortem examination. This casts doubt upon any of the experiments validity at the outset.

Stevenson[24] in 1923 stained thirty seven sections from four cases of multiple sclerosis and found no trace of spirochetes. He took paretic sections as controls and was able to demonstrate spirochetes in every section.

Baily and Dudgen[25] in 1921 inocculated a large number of rabbits with all the body fluids of thirty three clinical cases of multiple sclerosis. They produced no ill effects except a transient paralysis in two rabbits inocculated intra-occularly. They also pointed out that finding spirochetes in the livers and spleens of animals like guinea pigs and rabbits has little meaning, for no one knows to what extent these animals harbor spirochetes in health. Without doubt, they are found there at times.

Brain[3] summed up the objections to the spirochete theory in 1930 on this basis. Rabbits used in the study of nervous disease are untrustworthy. They are peculiarly liable to nervous diseases of their own. When trying to study spirochetal diseases in rabbits, one is particuliarly off base because they carry a spirochetal infection of their own called Spirochaeti cuniculi.

What histological work on these supposed rabbit cases of multiple sclerosis that was done showed rather than the picture of multiple sclerosis, the inflamatory changes of Encephalitozoon cuniculi, a protozoan disease of rabbits found in over one-half of normal rabbits.

Furthermore, there was gross variance in the several spirochetes that were described. Kuhn and Steiner's

spirochete was fine and delicate, while that of Adams, Blacklock, and McCluskie was plumper than the spirochete of syphilis. In addition, Adams and Blacklock, two of the spirochetal adherents, demonstrated the spirochetal bodies in the spinal fluid obtained from the lateral ventricles of normal monkeys, rabbits, and guinea pigs. This was tantamount to the destruction of all the controls of these experiments.

The German workers and backers of the spirochetal theory had been answered rather extensively. Reasonable doubt was thrown upon their work, and the etiology of multiple sclerosis was as far from solution as ever. Steiner has not however abandoned his efforts. He has worked assiduously through the twenties and thierties in defense of his doctrine. Writing in 1941 he sums up the spirochetal case as follows. First, it is undeniably an infectious disease. In his ninty-three cases he has never failed to find lymphocytes and frequently finds polymorphonuclear leucocytes in the vascular adventia of the central nervous system. He states further that he has worked out a complement fixation test that was positive in 41.5 per cent of 289 of his cases. In 1,340 controls, it was positive in only three per cent. The

exact nature of this reaction was not known. He admits that animal inocculation has never been successfully established. Working on a patient in 1931 that died of an acute attack he found innumerable spirochetes which he called Spirocheta myelopthora. He find it in 22.4 per cent of his cases. He refuted other investigators' failures in attempts to find the spirochetes by stating that they haven't followed his methods or that they didn't work long enough.

The silver cells which all have agreed can be found in cases of multiple sclerosis are results of degeneration of spirochetes. There is an inverse ratio between the number of spirochetes found and the number of silver cells present.

Perhaps the most devastating attack of all upon the spirochete theory is the complete failure to culture spirochetes from the spinal fluid of multiple sclerosis patients or animal claimed to have been infected with the disease. Naguchi and others have tried with complete failure. Spirochetes are not by nature hard to culture.

Primary Gliosis

Another early concept of the etiology of multiple sclerosis was the principle of primary gliosis. It was argued by its followers that the fundamental fault was in the glial tissue of the central nervous system. It was thought to go through a hyperplasia destroying the other nervous tissue and producting the characteristic scar. It is easy to see how they formed this idea when one considers that the early work on the pathology of the disease was done on the old burned out scars of chronic cases. For a long time, a clinical diagnosis was not made unless Charcot's triad was present. Naturally, all that met the observer's eye was a plaque of wavey glial fibers. Muller[26] was the leader of this school.

However, as late as 1923 one find Weil[27] defending this theory by pointing out that plaques are only found in that portion of the nervous system that has glial fibers as its support. Wherever one finds connective tissue as a supporting tissue i.e. peripheral nerves, one does not find these plaques.

As the more acute stages of the disease were studied pathogically, it came to be generally accepted that in a

case of early sclerosis demyelinization can be seen long before there are any signs of glial activity. Most agree that demyelinization is the primary lesion.

It seems that the prime factor explaining Weil's observation is that multiple sclerosis is a disease of the central nervous system, and therefore, the only possible replacement tissue after an injury to any of its components would be the more durable glial fibers.

In passing, it might be mentioned that several attempts have been made to implicate vectors. The most notable among these was Steiner's[28] incrimination of the tick. His basis was evidence of tick contact in twenty-one out of forty-three cases, while in the control group, only ten per cent reported such contact. The study has never gove any further and seems to remain as an isolated observation in the literature. It could be pointed out that ticks carry a disease that causes a transient spastic paralysis. This is in addition to the various recket-tsial diseases. The confusion might have arisen in this manner.

Wilson[12] also did some work on the rat when it was thought for awhile that the incidence of the disease was higher among ~~people~~ ~~living~~ near water ways. This was also

during the height of the spirochete fever. He dropped this idea however after unpromising results.

Brain[3] speaking of Steiners ticks observed that at most, if his figures were correct, he had only discovered an index of another factor.

Virus Infection

Again, the shadow of suspicion has long been cast upon a hypothetical virus. Where the story should begin it is hard to say. Back when Marie and Charcot were blaming small pox and measles, they were blaming virus disease. When Bullock announced the transmissionsof the disease to rabbits he was apparently proving its infectious nature, a step which is indespensible if a virus is someday to be established as the causal agent. However, work upon this line had to await developement in the techniques of virus study.

Perhaps, the most significant work along this line was reported in 1930 by Chevassut.[29] She was aroused by the characteristic gold curve obtainable in seventy per cent of the patients with multiple sclerosis. A typical curve would run something like this, 0003222000. A lmost without exception, percipitation starts in the fourth tube, and very rarely does the value in any tube go over three or four. The author considers this curve so specific that it cannot be explained by nerve degeneration. If it were merely a high globulin ratio, why isn't it present in a brain tumor? She further reasoned that this is so specific a picture, somewhat analogous

to an aglutination reaction, that a very specific cause would be necessary to produce it. She argued that the only place such a specific agent could be found would be in the person of a micro-organism. She then set about to culture a micro-organism from the spinal fluid of multiple sclerosis. Finally, she produced a hydrogen-ion concentration change in a tube of Hartlay's media, plus human serum and cerebrospinal fluid from a case of multiple sclerosis. The hydrogen-ion concentration remained unaltered in a control tube.

After carefully examining the positive media with dark field illumination and one thousand four hundred magnification, she saw small groups of spherical bodies containing granuals. They first appeared after twelve hours of incubation at thirty seven degrees centigrade. They were most nummerous at twenty-four to thirty-six hours and disappeared in seven days. This, she alleged showed a typical colony growth curve. Subculturing was successful. She concluded that she had demonstrated a virus very similar to the virus of bovine pleural pneumonia. She destroyed these colonies with a temperature of fifty degrees centigrads, and inhibited their growth with a temperature of zero degrees centigrade. A hydrogen-

ion concentration of from 7.6 to 7.5 was necessary for their existence. Acid was produced when glucose, fructose, or manite were added to Hartley's media.

Dr. Chevassut then put her observation to a rather large clinical test. From 188 cases of clinical multiple sclerosis she obtained 176 positive reactions by culturing their spinal fluid using the technique just outlined. She was unable to obtain any sphericals from blood cultures. Her 269 controls were all negative. She further found that positive results could only be obtained while the spinal fluid colloidal gold curve was present. She concluded that she had cultured the virus of multiple sclerosis and named it Spherula insularis.

Weil[30] tried to repeat this work using sixteen patients with multiple sclerosis and eleven normal controls. He reported the same spheres that Dr. Chevassut had found, but he also found it in his controls. He further found that smaller spheres and colonies could be demonstrated in the media without incubation. He took human serum alone and emulsions of egg lecithin and produced similar colonies. He concluded that the granuals were due to an optic reflection phenomena because their

position changed with the direction of his reflecting mirror.

Cleveland[31] claimed that the spheres were colloidal particles percipatated to a greater extent by the postive serum containing globulin.

There has been no more work comparable to Dr. Chevassut's on the virus. Her question arising from the apparent specificity of the colloidal gold curve pointing at a specific causative agent is well put and hard to answer.

On the other hand, what about the failure to satisfactorily transfer the disease: If it is a virus its virulence is certainly lower than that of any known virus. Also, the periods of remissions do not fit into a virus pattern, for viruses characteristically confer immunity. The pathology and clinical picture varies so much in f form that of poliomyelitis and equine encephalitis that doubts are justified. However, the question is not settled; and much more remains to be leared about viruses and multiple sclerosis before it shall be.

Nutritional Deficiencies

Nutritional deficiencies as a possible cause of multiple sclerosis have not been overlooked. Putnam[32] has succeeded in producing demyelinization in the spinal cords of eight dogs fed from sixty to eighty days on vitimin B deficient diets.

Later, Brickner and Brill[33] conducted a rather extensive and careful dietary survey on thirty-four patients suffering from clinical multiple sclerosis. Seventeen of these seemed to be low in requirements, especially butter and cream. They also found a correlation between weight loss and attacks, and weight gains and improvements in the course of the disease. All the patients were able to associate at least one attack with marked dietary change; and all but six of the patients improved on a corrected dietary regime. The six cases failing to improve were the most advanced cases.

They concluded that this association could well be coincidental, secondary to the disease, or possible the primary cause. The old imponderable of resistence lowering factors was again brought up. Their final observation was that it is rare to see a fat person with multiple sclerosis.

Wile[30] found that inorganic serum phosphates were far below normal, in one-third of all cases of multiple sclerosis.

It is hard to take the nutritional factor seriously, for all surveys agree that the incidence of the dise se is the lowest in those parts of the world where diets are the poorest; for instance, southern United States, China, and Japan. However, the racial immunity question which no one has yet tackled interposes itself before the conclusion becomes clear cut. Klob[34] working in Baltimore announced that the incidence of multiple sclerosis is as high among the negros as among the whites. This would seem to settle the racial question as far as Negros go, but the yellow races' apparent immunity should be investigated. Klob reports that all previous surveys were based on flimsy opionins rather than scientific study.

The subject of diet and multiple sclerosis should not be dismissed, because it is well known what vitiman deficiencies can do to peripheral nerves; and the possibility of something similar happening in the central nervous system is not a ridiculous thought. Brickner and Brill conservatively admit the limitations of their

work. The necessity of using clinical diagnosis as a starting basis and the subjective nature of this inquiry are freely acknowledged. However, their results were promising enough to justify further research.

Enzyme Perversion

Closely following the deficiency speculation is a group of ideas centering around enzymatic action. Brickner[35] searching for the chemical cause of demyelinization, the apparent prime lesion of multiple sclerosis, found that oxalated blood plasma of patients with the disease contains something which causes myelin disintergation.

He used the plasma from seventeen patients and the same from seventeen medical students as controls. He incubated this plasma for twenty-four hours at thirty-seven degrees centigrade with sections of freshly collected rat spinal cords. Both the controls and the plasma from the diseased patients showed results of a similar nature, but the plasma from the multiple sclerosis patients produced the results of a much more severe degree; namely, swelling, thickening, lacunization, fragmentation, and a matting together of the mylein. This process became less noticable as one went farther into the center of the section, proving that the changes were not merely post mortem changes. Thirty-seven of the forty-two experimental sections exceeded the controls in damage. One group could be told from the other without labeling. Brickner believed

that the enzyme lipase was at fault. On that basis, he commenced treating eight patients suffering from multiple sclerosis with quinine, which is known lipase inactivator. Of those eight patients, two showed no results, one was slightly improved and five had complete remissions in ten to fourteen days.

Weil and Cleveland[36] checked Brikner's work, reduplicating his original experiment in every aspect. Their results confirmed his altho, they differed in the degree of separation between the experimental and control sections. They concluded from their work that serum and plasma from a patient with multiple sclerosis has greater demyelinizing power than normal serum and plasma. They then attempted to test the lipase of the serum and then titrating it with n/20 sodium hydroxide. It was found that no demyelinization would occur where there was a lipase value less than o.2 cc of sodium hydroxide. However, they found no corrolation existed between the higher lipase values and the degree of rat cord demyelinization. Also, lipase extracted from a feef pancreas produce no effect when incubated with rat cords.

By 1936, Brickner[37] had a series of forty nine cases treated with quinine, for which he claimed considerable

success. He regretted his lack of controls however. He classified 308 symptoms presented by his forty-nine patients. Thirty-eight symptoms, or 11.3 per cent had grown worse since the start of the quinine therapy. All told, only eight of his forty-nine patients are in a worse condition than at the start of his treatment. Seventy-three per cent of the improvement was seen in symptoms of less than two years standing. Most of the improvements started between four and five weeks after the onset of therapy. Only seventeen new symptoms appeared in the group, and only nine of these became permanent. Three of the forty nine have died. As to the question of effective therapy or coincidental remission, he states that from his general experience and from the literature, these are amazingly good results; but he admits the shortcomings of such evidence.

Testing a large group of controls and clinical cases of multiple sclerosis for serum esterase values, he found without exception that their serum esterase was lower than the average during a period of clinical inactivity, and higher than average during clinical activity. By placing some quinine hydrochloride in the flask, he was able to

increase the action of the esterase. He wasn't sure what to make of his results, but hypothesized that esterase is necessary in high values to repair myelin. He now proposes to further study esterase levels during attacks and remissions of the disease.

Brickner[38] concludes this whole complicated study by stating in 1936, "Further study is required for the elucidation of these points. Granted that a difference exists between the ability of the blood from control, and that from the multiple sclerosis patients to split various lipids, of what does that difference exist? There are a number of possibilities, but the profession is not yet in a position to choose between them. The alternatives are:

1. That the action is that of an enzyme. If it is an enzyme it may be,
   a. An abnormal enzyme,
   b. A normal enzyme in abnormal quantity,
   c. A normal enzyme in a normal quantity, but in an abnormal milieu which makes it act in an abnormal fashion.
2. If it is not an enzyme it may be,
   a. A foreign substance with lipolytic power,
   b. A normal lipolytic substance in abnormal quantity,
   c. A normal lipolytic substance in an abnormal milieu which causes it to act abnormally.

In addition, it has not been proved that this abnormal lypolytic activity is actually of primary importance in the

pathogenisis of multiple sclerosis. It accompanies multiple sclerosis, but it still may be a by-product of some other process."

Little more can be added to that comment. It seems that the serum from patients with multiple sclerosis has abnormal lipolytic powers. This has been established. What this is, where it comes from, and the exact part it plays in the disease needs further study.

Liver Damage

The enzyme theory leads closely into the next postulate, the basis of which it forms. It was argued that if there is a difference in the metabolism of the serum of patients with multiple sclerosis and that of the serum of normal persons, could not that difference be explained by altered liver functions? The liver, after all, is the great metabolic gland of the body.

Weil and Cleveland[36] were the first to concieve this new angle of attack. Accordingly, they ligated the cystic and pancreatic ducts of dogs. This produced plaques of demyelinization. They argued that this result could not be explained by an enzyme because it survived the effects of heat, and since its appearance seemed to be independent of the other lipases in the blood.

Chevassut[29] found that sixty-four out of eighty-six of her cases showed a negative glycouric acid test. She also found indicanuria in all of her patients, the average being ten to twelve times the normal amount. Levulose tolerance curves in sixty out of the eighty-six patients were abnormal. She concluded that the liver of multiple sclerosis showed deficiency in its anti-toxic and metabolic functions in a high percentage of her cases.

Weil found that the urine in twelve out of fourteen cases of multiple sclerosis demonstrated lypolytic activity. He first evaporated the urine in vacuo. He redissolved it in a solution buffered to a hydrogen-ion concentration of 7.6. He incubated this with sections of rat cord for twenty-four hours. Upon miscropic examination, he saw distruction of myelin. Eighteen out of twenty normal urines did not produce this altho there was some swelling, but no fragmentation. With urine from cases of Fredrick's ataxia he got normal results. With a case of post encephalitis Parkinson's disease, he got vague traces of demyelinization.

Putnum[39] working on his venous thrombosis theory (to be explained later) did comprehensive autopsy's on five cases of multiple sclerosis, finding central necrosis of the liver present, to a greater or less degree, in all of them.

Crandell and Cherry[40] worked with three groups. Twenty-seven cases of multiple sclerosis, eleven cases of liver disease, and a large series of normal controls; they found that seventy-eight per cent of their cases of multiple sclerosis gave a high lipase value, based on its reaction

with olive oil; eighty per cent of their liver patients gave a similar high lipase value; while only 7.6 per cent of the normal group showed this phenomena. They repeated the experiment testing for diastase, and again, 47.6 per cent of the multiple sclerosis patients were above normal. Seventy five per cent of the liver cases were in this class, while only 8.3 per cent of the controls were out of line. They concluded that the liver in the multiple sclerosis is definately damaged. They explained their results by the following physiological approach. Lipase and diastase is secreted into the small intestine by the pancreas. It is absorbed into the portal system where normally it is destroyed by the liver. In cases of liver damage, these enzymes get by.

The next step in their reasoning would be to blame these enzymes for the demyelinization as Bricknar does. However, they were not ready to go quite that far, for the simple reason that they could not explain why the same thing did not happen with such conditions as cirrhosis of the liver or toxic hepatitis which also gave high lipase and diastase values in their experiments.

As with most of these subjects relating to the etiology of multiple sclerosis, a hopeful beginning is soon

cluttered up with a mass of confusing sidetracks. It seems fairly certain that these workers have established that the blood of patients with multiple sclerosis is d different. Whether it is primary or secondary to the disease, or whether the whole syndrome is a result of a peculiar form of liver disfunction in which perverted enzymes digest the myelin of the central nervous system remains to be worked out in future studies.

Acute Disseminated Encephalomyelitis

It is now proper to turn to another consideration of multiple sclerosis; namely, its relation to another disease, acute disseminated encephalomyelitis. This disease is characterized by a pathology that closely resembles multiple sclerosis. There is diffuse demyelinization of the central nervous system followed by glial scarring. As shall be seen, these are those that claim that it is merely an aberrant form of the great mother disease, multiple sclerosis. Others insist that it is a separate clinical entity.

Putnum [39,41] is one of those who claims that there is no difference. He presents an elaborate clinical and pathological survey of cases of both encephalomyelitis and multiple sclerosis, and shows how the two diseases shade into one another from both aspects. Clinically, he claims that at the height of an attack it is impossible to distinguish the two. Clinitions usually follow the general rule that if a patient recovers and suffers no further reoccurrences, he had encephalomyelitis; but if he suffers from further attacks, it was multiple sclerosis. Putnum counters that relapses and persistent sequela are so common that no such rule is justified. He presents two

cases of suppossed encephalomyelitis, following measels. The patient s suffered from paraplagia and ataxia. They made apparently complete recoveries, but within a year had reoccurrences with a classical signs of multiple sclerosis. Autopsy showed the characteristic plaques of multiple sclerosis.

Steiner[17] disagrees sharply with this conclusion. He maintains that there is a difference between the two clinically and pathologically. Clinically, encephalomyelitis produces a temperature, one does not find retrobulbar neuritus, shooting pains are much more frequent, deep reflexes are more commonly lost, and the Lange gold curve is less often positive. Pathologically, the lesions of encephalomyelitis are less clearly defined, there is more destruction of axis cylinders, and all lesions show a uniform stage of evolution.

Putnum has a rebuttal for each of these points, but the arguments get lost in the trees. It seems that little is to be gained by comparing and drawing generalizations from anything as variable as the pathology and the symptomology of the two diseases. If they are separate entities, a more specific method of diagnosis needed before that truth can be established. Meanwhile this topic opens up into the latest query into the cause of multiple sclerosis.

Venous Thrombosis

The real question is, what are these areas of myelin loss? Do they represent a disease with a specific etiology or are they signs of degeneration? As has already been shown, Cleveland and Weil produced them in dogs by the simple process of damaging the pancreas and liver. Other workers have been equally successful in reproducing the lesions. Putnam[42] reported in 1930 the production of demyelinization and secondary glisosis by the use of tetnus toxin. He injected eighty dogs, each three times; with 0.015 of a cc of standard toxin. Of this group two dogs showed nervous symptoms. One became ataxic and developed a paralysis of posteriour limbs, a month after the last injection. On autopsy, areas of perivascular demyelinization, infiltration with round cells and glial cells, and the beginning of a plaque formation,,were found. The other dog lived a year with only mild ataxic symptoms. It was then killed and disseminated areas of gliosis were found in the central nervous system.

In 1933 Ferraro[43] impressed by Putnum's work, produced areas of demyelinization in cats and monkeys with subcutaneous doses of potassium cyanide. He started with a minimum of two miligrams and increased the dose daily

by one-half miligram, until he reached a maximum dose of from twenty to thirty-five miligrams. This produced avvaried symptomology, including nystagmus, spastic paraplegia, blindness, and convulsions. He described the lesions as very similar to those of human multiple sclerosis.

He reasoned that the mechanism of this reaction was potassium cyanide's ability to interfere with tissue oxidizing power. He then hypothesized that the basis of the lesions of multiple sclerosis was probably tissue anoxemia. As a source of this anoxemia he suggested faulty metabolism; pointing out that cyanide is produced in the body in the metabolism of urea. He admitted that this was only a possiblity.

Again, 1935, Rivers and Schwentker[44] produced demyelinization in seven out eight monkeys by injecting aqueous emulsions and alcohol ether extracts of sterile rabbit brain. Eight control monkeys remained well. There was a definite perivascular arrangement to the lesion. Large central nervous system giant cells and eosinophils were described. Demyelinization was noted in all parts but was heaviest around the ventricles. No conclusions were drawn; only the results were reported.

Putnum[39] in studying demyelinated plaques of multiple sclerosis and comparing them to those of disseminated encephalomyelitis; and to those produced in experimental animals by tetnus, cyanides and alcoholic extractions of rabbits brains was struck by a factor that all of these seemed to have in common. This factor was certain abnormalities in the venous circulation of the central nervous system. More specifically, he described thrombi formed of blood platelets and various degrees of distention of the venous walls.

Practically any worker that ever studied sections of multiple sclerosis has mentioned the relationship of vessels to the lesion. Charcot[2] described the thickening of the intima; Marie[5] mentioned how frequently vessels were found in the center of the islets. Marie further observed that the most advanced portions of the lesions are found in those areas directly adjacent to the blood vessels. Most of the workers decided that the vascular changes were merely the expression of the mechanisms by which the noxa had reached the nervous tissue, or else they were secondary to the sclerotic plaque itself.

Putnum deciding that these observations had been dismissed too hastily set out to study the vascular

relationship extensively. He first made many sections of the central nervous systems of all the cases of multiple sclerosis available to him. In fourteen out of seventeen cases he was able to observe the small veins were occluded by fibrinous plugs of platlets. Sometimes in the older regions all that remained of the vessel was a small chain of connective tissue; the rest had been by obliterated by the secondary gliosis. He stated that the process seemed to start with an accumulation of platelets. He found just such thrombi in three cases of acute encephalomyelitis. In acute multiple sclerosis the same thing was true. In older cases, the veins were harder to find. Often, the thrombi were not found in any direct relation to the plaque, but rather, distal to it. The closer the clot lay to the lesion, the more acute the lesion seemed. He noted that there was little in the way of inflammation around the clot; thus ruling out secondary coagulation to his own satisfaction. In addition, he saw engorgement and proliferation of the vessels. In the three cases of encephalomyelitis, he saw marked perivascular hemorrhages with the accumulation of blood pigments in the surrounding tissue. In the more chronic cases, he saw yellow pigment in the

vessels, which by micro-incineration methods was proved to contain iron. These areas of hemorrhage were ante mortem because there was phagocytosis of the red blood cells.

Shenker[45] confirmed his conclusion. He studied fifteen spinal cords and brains from multiple sclerosis patients. He concentrated on the hearlthy tissue, trying to pick up the earliest lesions by this method. Almost all the tiny lesions that were found were perivascular. They surrounded small veins or capillaries. Most of the veins were markedly dialated and engorged with blood. They showed tortuosity and bead like dilation. The presence of thrombi was not always easy to make out. Agglutinated red blood cells clumped together in amorphous masses were frequently seen. In some areas, they completely obliterated the lumen. He again noticed that in older plaques the interveing gliosis tended to hide the thrombosed vein.

In 1935 P utnum[46] attempted to produce the lesions expirimentally in dogs by an ingenious method of obliterating the veins. He trephine fourteen dogs, located the longitudinal sinus and ligated it at both ends. He then injected a heavy mixture of lard and oil under pressure; so that the fluid flowed back into the cortical veins.

He carefully repaired the wounds and observed the dogs for a year.

Twelve of the fourteen dogs presented lesions at autopsy. Five of the dogs were examined at the end of five weeks; in them he found a small amount of gliosis and demyelinization. The dogs that were killed six to eleven weeks after injection showed approximately the same signs. He autopsied one dog six months after the operation finding wide spread destruction in the myelin. There was beading and thinning over diffuse ill defined areas. It looked much like the shadow plaque often encountered in cases of multiple sclerosis. The last three dogs were killed between ten and twelve months after operation; they showed the same signs only slightly advanced. He concluded that demyelinization can be caused by a disturbance in venous circulation.

Later, Putnum [47] along with Hoefer and Gray produced areas of demyelinization and gliosis in cats, dogs, and rabbits by the intra-venous injection of such coagulants as lung extract, homologous serum, hetrologous serum, and typhoid vaccine. The animals developed blindness, ataxia, spastic paraplegia, and paresthesias. Invariably a clot was located in the cerebral veins.

The adherents of this new approach now felt that they had established that venous occlusion is commonly associated with the early plaques of multiple sclerosis. They further believed that they could explain that pathogenisis of the lesion upon the basis of venous occlusion. It remained to be established that there was something peculiar about a person's venous circulation causing them to contract multiple sclerosis. In other words, something that made them susceptible to venous thrombi in the central nervous system.

Simon and Solomon[48] supplied the missing link. They first studied the clotting and bleeding times of multiple sclerosis patients. They attempted to establish that the abnormality lay there. However, they could not succeed in finding the slightest variation from normal. They then got to thinking about the frequent correclations that are made between the onset of an attack and exposure to such factors as cold, dampness, trauma, infection, pregnacy and emotional excitement. These have all been considered earlier in this paper and dismissed as resistance lowering factors. This was in agreement with earlier workers on the disease. However, Simon and Solomon coupled these factors with the venous thrombi theory, upon a new basis. It is well known that the coagulation time of the blood

drops, and the tendency to intravascular clotting is thus increased, after epinephrine is either injected or liberated into the blood stream. Emotional excitement, fever, trauma, and surgery all tend to liberate epinephrine. Now, if it could be established that multiple sclerosis patients had a greater response to epinephrine the final link would be forged.

Accordingly, it was decided to inject typhoid vaccine to produce a febrile state, thus touching off the secretion of epinephrine. Also it was decided to inject epinephrine itself; and then to measure the degree of fall of the clotting time and the duration of time that it was depressed below normal. Fourteen clinical cases of multiple sclerosis were compared with fourteen normal controls. First, the original clotting time was determined by the Howell method. It was found to vary between twenty-four and forty-five minutes in both groups. Then each patient and control received 200,000,000 typhoid bacili. The clotting times were read at two hours, five hours, eight hours, twenty-four hours, forty-eight hours, and seventy-two hours, after injection. It was found that the clotting time in both groups was depressed. The average time of depression was twenty-three minutes or fifty-four

per cent of the base reading with multiple sclerosis patients. In the controls the average was seventeen minutes or forty-seven per cent of the base readings. In the patients with multiple sclerosis the period of depression lasted sixty-nine hours on the average, against twenty-six hours for the controls.

When the experiment was repeated with epinephrine more striking results were obtained. The average drop was nineteen minutes or forty-five per cent of the base reading for the experimental group with an average depression duration of 3.7 hours. In the control group, the average drop was four minutes or eleven per cent of the base reading. The duration of the drop averaged but one hour.

Simon[49] repeated the experiment with ten central nervous system diseases, patients as controls, to establish if a disease of the central nervous system, in itself, caused this abnormal reaction to epinephrine. The diseases were, traumatic paraplegia, syphilitic amyotrophic lateral sclerosis, neuro-fibroma of the spinal cord, chronic myelitis, spinal arachnoidits, syringomyelia, Freidrick's ataxia, post encephalitic paralysis agitans, Post pneumonia unilateral paralysis agitans, and a psychoneurosis. With the typhoid the multiple sclerosis patients had a coagulation time drop of seventy-two to

to nint y-six hours duration, against twenty-four hours for the control. The intensity of the change averaged twenty-five per cent greater in the multiple sclerosis group than in the controls. With epinephrine the difference in intensity was fory per cent, while the period of depression was not quite so clear cut. The controls varied. Three of the patients showed a prolonged reaction, two of them were above the average for multiple sclerosis. The psycho-neurosis, the chronic myelitis, and the traumatic paraplegia made up this group.

To complete this pattern these workers have yet to establish that the abnormal clotting reaction to epinephrine is not secondary to the disease itself. An experiment proving this would be hard to conduct for obvious reasons. At any rate, the case is well presented. First, it has been shown that the patient with multiple sclerosis shows as abnormal reaction to epinephrine; the clotting time dropping greater than most people's and staying depressed for a longer time. The blood during this time is rendered much more susceptible to intravascular clotting. Second, the lesions of the disease are frequently associated with venous thrombi. Finally when artificial emboli are introduced into the central nervous system of

dogs, lesions very simialr to those of multiple sclerosis are produced. This is as complete an attack upon the problem as has been worked out yet. However, it has been under severe scrutiny and is not universally accepted. Weil[30] raises several objections. First, he admits it is occasionally possible to see venous thrombi in the acute conditions, but he claims they are secondary. He asks why they cannot uniformally find the remains of the old thrombosed veins in the form of scars. The adventitial connective tissue should not disappear without a trace. Second, there is no constant uniform relation of the plaques to the small vein. Third, if the lesion can be explained by vascular occulsion, more cell bodies should be destroyed, for they are more susceptible than myelin.

Putnam[41] answers that with correct methods and careful study he can find scars of old venules in almost all plaques, and that meylin is much more susceptible to chronic long standing restricted metabolism than the cell bodies are.

Dow and Berglund[42] made complete reconstructions of brains and spinal cords of five cases of multiple sclerosis. Of the total of sixty lesions reconstructed, twenty showed

and central lobular necrosis in all five. In addition, three showed thrombosis in their cardiac veins. Four had signs of venous thrombosis in the kidneys. This series is very small and leaves the question still unanswered.

The issue is clouded. Putnum and his followers have such an ingenious theory and the evidence although not conclusive is enough to support strong hope that these investigations have come much closer to the solution of this mystery than ever before. At any rate, the new therapeutic methods show that some clinitions take them seriously. For instance, the use of hystamine and dicumoral.

an absence of the central vein, twenty showed a normal appearing central vein, and two a collapsed central vein. As controls, twenty-five veins were reconstructed from areas of normal appearing nervous tissue. The control reconstructions produced no venous thrombi, 22.5 per cent of the veins near the sclerotic plaques showed thrombi. Distended veins were very rarely seen in the normal tissues.

They concluded thrombi are not the causative agent because they are not present in a high enough percentage. The thrombi that are found are probably due to the absorption of thromboplastin from diseased sites. This would explain the fact that in every case the thrombus was located central to the lesion and that the thrombi were found in areas of intense perivascular cellular reaction. The vascular changes seemed associative rather than causative.

Perhaps the best argument against P utnam's theory is the failure to find evidence of envolvement in the other organs of the body. By all rights, the thrombosis should be general. Actually the study of the rest of the body's organs in relation to this disease has been sadly neglected, at least in English medical literature. P utnam[39] tried to remedy this, but all he had to work with was five cases. A s has already been reported, he did find liver thrombosis

Summary

The surviving theories of the etiology of multiple sclerosis can be divided into two groups; the infectious and the toxic. The supporters of infection have dwindled, and the spirochete which was once condemned by all has been forgotten by everyone but Steiner. He, almost alone, indicts it today. He presents a well prepared series of slides showing the spirochetes in the tissues of multiple sclerosis; but no one else has been able to duplicate his findings. Foremost against the infectious theory has been the complete inability of anyone to transmit it to animal or man. No one has ever presented a single instance where one man infected anouther. No attempts have ever been made to isolate patients with the disease. In addition, all alleged successful attempts to transmit it to animals have not stood the test of analysis. The smae may be said of all claims of successful culturing of bacteria, spirochetes, or viruses.

Because of this, more and more workers have swung toward the toxic theory. Gratifying results have been produced, especially in the last fifteen years. Among the exogenous toxin theories of promise is the revival of the old lead poisoning theory of Charcot and Oppenheim by Russel and Harwood. They have it up in new

clinical and physiological importance. In addition Putnam has produced what looks like the disease in dogs by the injection of tetnus toxins, Farraro has done the same in monkeys and cats with pottassium cyanide, Rivers and Schwentker have produced similar results with alcoholic extracts of rabbit brains, and finally, Putnam has done it again in dogs with the injection of coagulants.

On the side of endogenous toxins, there is the work of Weil and Cleveland pointing at liver damage and the liver's inability to handle lipase. Lastly, there is Putnam, Simon, and Solomen who believe that the victems of multiple sclerosis have a tendency toward venous thrombi which cause the plaque.

What can one produce in the way of finished pattern from these various pieces? Perhaps, the best that one can say is that multiple sclerosis appears to be a toxic condition rather than a disease of infectious origin. Its areas of demyelinization and gliosis are not a specific lesion resulting from a single cause; but rather the general response of the white matter and to a lesser extent the gray matter to various chronic low grade intoxications of the central nervous system. The clinical picture varies with the source of the toxin. If it is only temporary and clears up a case of ensephalomyelitis is produced with

no reoccurrence. If the toxin is caused by something of relative permanence like liver damage there follows the characteristic picture of remissions and relapses of a classical multiple sclerosis.

It seems established that the toxins capable of producing these lesions are manifold. For that reason, it would seem that the treatment of the disease should be just as comprehensive. Attempts to stimulate the circulation and combat thrombosis are to be applauded. In addition, the general health of the patient demands more attention than it has received in the past. Diet, metabolism, liver function, exposure to toxins, and focal infections should all be considered and any deficiencies should be corrected and guarded against in the patients future years.

Bibliography

1. Cruvelhier, J. 'Atlas d' Anatomie Pathologiquie, Bruxelles, Meline, 1835.

2. Charcot, J. Lectures on the Diseases of the Nervous System, New Sydenham Society, London, 1877.

3. Brain, W. Critical Review of Disseminated Sclerosis, Quart. Jr. of Med., 23: 343-375, 1930.

4. Symonds, C. Pathological Anatomy of Disseminated Sclerosis, Brain, 16:36-57, 1924.

5. Marie, P. Lectures on Diseases of the Spinal Cord, New Sydenham Society, London, 1895.

6. Oppenheim, H. Diseases of the Nervous System, Lippincott Co., Philadelphia and London, 1900.

7. Putnam, T. Multiple Sclerosis and Encephalomyelitis, Bul of N.Y. Acad. of Med., 19:311-322, 1943.

8. Russel, C. and Harwood, R. Lead as a Possible Cause Multiple Sclerosis, Arch. of Neurol. and P sych., 31:237-247, 1934.

9. P utnam, T. Remissions in Multiple Sclerosis, Arch. of Neurol. and Psych., 41:913-918, 1939.

10. Baily, P..Incidence of Multiple Sclerosis in the United States Troops During the First World War, Arch. of Neurol. and Psych., 7:583-588, 1922.

11. Brown, S. and Davis, T. The Mental Symptoms of Multiple Sclerosis, Arch. of Neurol. and Psych., 7:628-635, 1922.

12. Wilson, S. Neurology, Williams and Wilkens Co., Baltimore, 1940.

13. P utnam, T. Differential Diagnosis of Multiple Sclerosis, Arc. of Neurol. and Psych., 7:551-559, 1922.

14. Bullock, W. Experimental Transmission of Disseminated Sclerosis, Lancet, 41:1185-1188, 1913.

15. Steiner, G. Uber die atiologische Erforschung der Multiplier Sklerose, Neurol. Centralbl. Referabe, 37:535-537, 1918. Quoted by Brain.[3]

16. Kuhn, P. and Steiner, G. Uber die Ursache der M ultiplier Sklerose, Med. Klin., 13:1007-1009, 1917. Quoted by Brain.[3]

17. Steiner, G. Uber die Atiologische der Multiplier Sklerose, Deutsche. Med. Wchnschr., 47:102-109, 1921. Quoted by Brain.[3]

18. Marinesco, G. 'Etude sur l'origine et la Nature de la Sclerose en Plaques., Rev. Neurol., 26:481-488, 1919. Quoted by Brain.[3]

19. Kalberlah, F. Sebiologie der Multiplier Sklerose, Deutsche. Med. Wchnschr., 47:102-114, 1921. Quoted by Brain.[3]

20. Bullock, W. Experimental Study of Disseminated Sclerosis, Brain, 44:293-297. 1921.

21. Pettit, A. A propos dela Nature infectiense de la Sclerose en Plaques, Compl. rend. Soc. de biol., 86:824-826, 1922. Quoted by Brain.[3]

22. Adams, J. Blacklock, T., and McCluckie, R. An Experimental Study of the Spirochete in Disseminated Sclerosis, Brain, 48:476-484, 1925.

23. Naguchi, H. Failure to Find a Spirochete in Multiple Sclerosis, Jr. Amer. Med. Assoc., 99:2108-2119, 1923.

24. Stevenson, G. Spirochete Stain in Multiple Sclerosis, Arch. of Neurol. and Psych., 9:88-90, 1923.

25. Baily, C. and Dudgeon, R. Pathogenesis of Disseminated Sclerosis, Brain, 44:150-163, 1921.

26. Muller, H. Die Multiplier Sklerose des Geherins und Ruckenmarks, Jena, 1909. Quoted by Brain.[3]

27. Weil, A. Etiology of Multiple Sclerosis, Jr. of Amer. Med. Assoc., 97:1587-1590, 1921.

28. Steiner, G. Uber die atiologische Erforschened der Multiplier Sklerose, Neurol. Centralbl., 38:562-568, 1919. Quoted by Brain.[3]

29. Chevassut, K. A Report on Attempts to Culture the Virus of Disseminated Sclerosis, Lancet, 58:552-556, 1930.

30. Weil, A. Further Research on the Etiology of Multiple Sclerosis, Jr. of Amer. Med. Assoc., 97:643-650, 1930.

31. Weil, A. and Clevland, S. Sereologic Studies of Multiple Sclerosis, Tr. of Amer. Neurol. Assoc., 13:400-408, 1931.

32. Putnam, T. Multiple Sclerosis in Dogs, Arch. of Neurol. and Psych., 24:640-655, 1930.

33. Brickner, R. and Brill, N. Diets and Related Studies in Multiple Sclerosis, Arch. of Neurol. and Psych., 46:16-38, 1941.

34. Klob, L. Multiple Sclerosis in the Negro, Arch. of Neurol. and Psych., 47:418-424, 1942.

35. Brickner, R. Studies in the P athogenesis of Multiple Sclerosis., Arch. of Neurol. and Psych., 23: 715-721, 1930.

36. Weil, A. and Clevland, S. Liver Damage and Demyelinization, Tr. of Amer. Neurol. Assoc. 14:154-161, 1932.

37. Brickner, R. Quinine Therapy in Cases of Multiple Sclerosis over a Five Year Period, Arc. of Neurol. and Psych., 33:1235-1248, 1935.

38. Brickner, R. Recent Experimental Work on the Pathogenesis of Multiple Sclerosis, Jr. of Amer. Med. Assoc., 101:2120-2132, 1935.

39. Putnum, T. Evidence of Vascular Occlusion in Multiple Sclerosis and Encephalomyelitis, Arc. of Neurol. and Psych., 32:1298-1312, 1937.

40. Crandell, L. and Cherry, I. Blood Lipase, Diastase and Esterase in Multiple Sclerosis a Possible Index of Liver Damage, Arc. of Neurol. and Psych., 27:376-390, 1932.

41. P utnam, T. Similiarities Between Some Forms of Encephalomyelitis and Multiple Sclerosis, Arc. of Neurol. and Psych., 35:1209-1219, 1936.

42. Putnam, T. Studies in Multiple Sclerosis, Jr. of Amer. Med. Assoc., 97:1591-1598, 1931.

43. Ferraro, A. Experimental Toxic Encephlomyelopthy, Psych. Quart., 7:267-274, 1933.

44. River, T. Encephalomyelistis Accompied by Melin Distruction Experimentally P roduced in Monkeys, Jr. of Exp. Med., 61:689-702, 1935.

45. Shenker, M. Histogenesis of the Early Lesions of Multiple Sclerosis, Arc. of Neurol. and Psych., 49:178-185, 1943.

46. Putnam, T. Studies of Multiple Sclerosis, Arc. of Neurol, and Psych., 33:929-940, 1935.

47. Putnam, T., Hoefer, F. and Gray, M. Experimental D emyelinization in Cats and Dogs, Arc. of Neurol and Psych., 39:742-759, 1938.

48. Simon, B. and Solomon, P. Multiple Sclerosis Effective typhoid and Vaccine and of Epinephrine on the Coagulation of the Blood, Arc. of Neurol, and Psych. 34: 1287-1299, 1935.

49. Simon, B. Blood Coagulation in Multiple Sclerosis and other D iseases of the Brain Stem and Cord, Arc. of Neurol. and Psych., 48:514-526, 1942.

50. Grinker, R. and Bassoe, P. Disseminated Encephalomyelitis, Arc. of Neurol. and Psych., 25:723-738, 1931.

51. Spiller, W. Encephalomyelitis Disseminata, Arc. of Neurol. and Psych., 23:647-650, 1929.

52. Hiller, F. and Grinker, R. Functional Circulatory Disturbaces and Organic Obstruction of the Cerebral Blood Vessels, Arc. of Neurol. and Psych., 24:635-641, 1930.

53. McAlpine, D. Encephalomyelistis and its Relation to Disseminated Sclerosis, Lancet, 59:846-848, 1931.

54. Taylor, E. Multiple Sclerosis Location of Lesions with Respect to Symptoms, Arc. of Neurol. and Psych., 7:561-573, 1922.

55. Hassin, G. Studies in the Pathogenesis of Multiple Sclerosis, Arc. of Neurol. and Psych., 7:589-607, 1922.

56. Leiner, J. An Investigation of the Axis Cylinder in its Relation to Multiple Sclerosis, Arc. of Neurol. and Psych., 7:609-612, 1922.

57. Hassin, G. Multiple Degenerative Softening Versus Multiple Sclerosis, Arc. of Neurol. and Psych, 7:613-621, 1922.

58. MacEwen, W. Diseases of the Brain and Spinal Cord, MacWilliam and Co., New York, 1893.

59. Branwell, B. Diseases of the Spinal Cord, William Wood and Co., New York, 1917.

60. Growers, W. Diagnosis of Diseases of the Brain and of the Spinal Cord, William Wood and Co., New York, 1922.

61. Spiegel, L. Familial Multiple Sclerosis, Arc. of Neurol. and Psych., 50:706-709, 1943.

62. Goodbat, P. and Davidson, C. Multiple Sclerosis and the Amyoprophies, Arc. of Neurol. and Psych., 31: 271-276, 1934.

63. Echer, A. and Jones, W. Arsenic as a Possible Cause of Subacute Encephalomyelitis, Arc. of Neurol. and Psych., 45:25-33, 1941

64. Steiner, G. Is Multiple Sclerosis and Etiologically Uniform Infectious Disease?, Detroit Med. News, 32:7-23, 1941.

65. Steiner, G. Chronic Perivascular Demyelinization, Arc. of Neurol. and Psych., 41:167-181, 1939.

66. Wilson, S. Modern Problems in Neurology, William Wood and Co., New York, 1929.

67. Jellife, C. Diseases of the Nervous System, Lea and Feberger, Philadelphia, and New York, 1917.