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Review of theories of the possible infectious etiology of multiple sclerosis

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A REVIEW OF THEORIES OF THE POSSIBLE INFECTIOUS ETIOLOGY OF MULTIPLE SCLEROSIS

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Introduction

Multiple sclerosis is a strange perplexing disease of the central nervous system. Once thought to be a rare disease, it is now considered the second most common of the neurological diseases, lues being the most common.

The onset is insidious, the course bizarre, and characterized by remissions and exacerbations, eventually progressing to the classical features of nystagmus, dysarthria, intention tremor, and ataxic paraplegia (1, 2, 3).

There are various theories regarding the etiology of this disease. Five of these theories are prominent in the current literature. They are: (a) the vascular occlusion theory, (4); (b) the toxigenic theory, (5); (c) the metabolic deficiency theory, (6); (d) the infectious agent theory (7, 8); and (e) the allergy theory, (9, 10).

The author is here presenting a review of the literature on the infectious agent theory.

Pierre Marie (7) was the first to suggest that multiple sclerosis was of infectious origin. Since his time, many organisms have been studied as possi-

ble agents of this disease.

This paper approaches the problem by separating the literature into bacterial, viral, spirochetal and protozoal theories of the possible infectious etiology of multiple sclerosis.

BACTERIA AS POSSIBLE ETIOLOGIC AGENTS OF MULTIPLE SCLEROSIS

As early as 1895, Gray (11) felt that febrile diseases, such as scarlet fever, measles, pertussis, diphtheria, smallpox, and typhoid are frequent causes of multiple sclerosis in childhood. Woodbury (12) has emphasized the coexistence of chronic tonsillar infections with patients having the disease.

In 1957, Birkmayer and Neumauer (13) worked from the theory that the demyelinizing agent in multiple sclerosis spreads from the vascular system into the tissue according to physiochemical laws. They incubated the spinal cord of a patient recently dead, with serum from a patient suffering from multiple sclerosis. Demyelinization was found to take place in the spinal cord from the periphery towards the center with preservation of the axis cylinders. They believe that the demyelinating agent is bound to proteins widely distributed in the body, not alone in the central nervous system. They conclude that their work strengthens the belief of some that there is an association between multiple sclerosis and rheumatic diseases.

Barker (14), however, states that in the cases he analyzed, childhood infections were as common but

no commoner than in other patients.

Acid-fast bacilli have been isolated (15) from the spinal fluids of persons suffering from multiple sclerosis.

Shinko and Tschabitscher (16) were concerned with changes in cerebrospinal fluid and serum, particularly those demonstrated by electrophoresis. They concluded that part of the gamma globulin may be formed within the central nervous system. They inferred that in multiple sclerosis, significant immunity reactions are probably concerned. These reactions are supposed to take place within the central nervous system. The conclusion is completed by bacteriologic investigations, and they feel that these immunity reactions are related to the bacilli which the authors have demonstrated in multiple sclerosis patients. The final conclusion of these authors is that multiple sclerosis is due to a mycobacterium and results in immunity reactions.

Attempts by Bauer, Thiemann and Wieding (17) to treat eighty cases of multiple sclerosis with isoniazid revealed no therapeutic effect of the drug. In twenty-eight cases in which the cerebrospinal fluid was examined for acid-fast microorganisms, the examina-

tion was negative.

In 1958, still working on the theory that multiple sclerosis may have a mycobacterial etiology, Bauer, Bonitz and Salchow (18) carried out various bacteriologic and serologic investigations with Koch's bacilli, with cultures and with animals. In no case did they find human and animal pathogenic mycobacteria. In two examinations of the cerebrospinal fluid, acid-fast bacteria were discovered; cultures and tests on animals with these bacteria were negative. The authors felt that their results showed that it is impossible to confirm the mycobacterial etiology of multiple sclerosis on the basis of frequency of positive results of examinations, or comparison of the control tests.

Buchanan (19) also believes that the lesions of multiple sclerosis are not the result of microbic invasion, of the nervous system. In 1959, Tschabitscher (20) emphasized the supposition of a hyperergic reaction. He feels that Mycobacterium tuberculosis causes the sensitization.

VIRUSES AS POSSIBLE ETIOLOGIC AGENTS OF MULTIPLE SCLEROSIS

Since attempts to isolate bacteria as etiologic agents in this disease have been unsuccessful, many investigators think that multiple sclerosis is caused by a virus. Gye (21) assumed that the cause of the disease is either a filterable virus or a water-soluble poison present in cerebrospinal fluid. He based this assumption on the fact that he inoculated cerebrospinal fluid from multiple sclerosis patients by intraperitoneal, intracerebral, intraocular, and intradural routes. None of the fifteen inoculated guinea pigs was affected. Seventeen of the one hundred, twenty-nine inoculated rabbits became "ill and paralyzed". Gye had no control investigation, nor did he do histologic studies.

Many workers tried to infect animals by inoculating them with spinal fluid, blood, brain, and spinal cord tissue from multiple sclerosis patients (22). All attempts were unsuccessful. One worker was able to cause myelin sheath destruction in experimental animals by infecting them with the virus of canine distemper. However, he has not been able to determine what relation this has to multiple sclerosis (23).

Schaltenbrand (24) thought he had proved a viral etiology for multiple sclerosis. He inoculated cerebro-

spinal fluid and nervous tissue of multiple sclerosis patients into monkeys. Some of these animals showed demyelination and inflammatory changes resembling encephalomyelitis. Suspensions of nervous tissue from these animals were inoculated into other monkeys. The investigator also attempted to reproduce multiple sclerosis in humans by inoculating fifteen patients from a mental asylum with cerebrospinal fluid from "affected" monkeys, which were originally injected with multiple sclerosis material. No abnormalities occurred in the human patients, other than slight pleocytosis and transient fever. The validity of Schaltenbrand's work is doubtful, because spontaneous encephalomyelitis of monkeys was endemic in his animal quarters, and some of his uninoculated animals had become infected with this disease by contact. Also, his use of multiple injections of nerve tissue into monkeys is a method now used to cause an "allergic" encephalitis.

Margulis, Solovieu, and Shubladze (25) reported that they isolated a virus from two patients with "acute disseminated encephalomyelitis". They successfully passed this virus to guinea pigs, puppies, and mice, causing clinical signs of paralysis and

histologic lesions consisting of inflammatory cell infiltrations, demyelination and necrosis. They found that the virus was neutralized by the sera of twenty-five out of fifty multiple sclerosis patients tested. The authors felt that their work was the first in which experimental investigation of acute encephalomyelitis and multiple sclerosis has been successfully carried out, and the "infectious origin of these diseases experimentally and clinically confirmed."

Miller and Schapira (26) feel that the clinical features, natural history, and epidemiology of multiple sclerosis do not favor a direct origin of infection by a specific virus. They do state, however, that the possibility of viral etiology cannot be excluded.

Seiden (27) used human cell tissue cultures and the tissue culture of the central nervous system of monkeys in an attempt to isolate a transmissible cytotoxic agent from the blood and spinal fluid of patients with acute and chronic multiple sclerosis. His attempt was unsuccessful; however, he feels that this does not rule out the viral or infectious etiology of multiple sclerosis because; (a) the human cells used were not of central nervous system origin and thus it is possible that they are not suitable host cells; (b) it is

a well known fact that viruses are difficult to isolate from spinal fluid and blood; (28), (c) it is conceivable that specimens were taken from the patients at improper times during the course of their illness; and (d) the virus may be capable of a latent existence in the cells, both in and out of the body. His attempt to determine the proliferation of antigen by serologic testing of tissue cultures against serum pooled from patients with multiple sclerosis was also unsuccessful.

Lumsden (29) attempted to work out a tissue culture method using human nervous tissue, with neurons, neuroglia, and cerebral mesoblastic cells, and taking fresh plaque material under aseptic conditons within the first few hours. He thought that by this method the plaque tissues would still contain viable tissue cells which he expected to act as temporary vehicles or hosts for the virus until the nerve fibers had had time to merge with the living cells and dead fragments from the plaque tissue under test. His results were completely negative.

SPIROCHETES AS POSSIBLE ETIOLOGIC AGENTS OF MULTIPLE SCLEROSIS

In 1921, Kuhn and Steiner (30) injected spinal fluid, spinal fluid mixed with blood, and blood from patients with multiple sclerosis into guinea pigs and rabbits. They concluded that the disease was due to a spirochete which was found in the blood of the paralyzed rabbits and guinea pigs. Buzzard (31) at the conclusion of his experimental work also felt that spirochetes were the cause of multiple sclerosis.

Teague (32) tried to cultivate spirochetes or other organisms from blood or spinal fluid of patients with multiple sclerosis. He tried to produce recognizable symptoms in animals by inoculating them with blood or spinal fluid from patients with multiple sclerosis. He also attempted to demonstrate spirochetes in blood or organs of the inoculated animals by dark-field examination or culture methods. All of his results were negative.

Rothfield, Freund and Hornowski (33) used blood, spinal fluid, and organ emulsions from patients with multiple sclerosis and injected them into guinea pigs and rabbits. Their results were negative. Reese (34) was also unable to demonstrate spirochetes as the

etiologic agent.

Lumsden (29) feels that the spirochetes that Steiner demonstrated in his work may have been sapraemic in nature from moribund patients with extensive bedsores. Steiner (35) later presented a paper reporting and evaluating the specific spirochete he found in the brain of a subacute case of multiple sclerosis. In 1954, he presented another paper (36) in which he gave a detailed description of these spirochetes, their classification, their reproduction, and disintegration. His conclusion was that he had presented further evidence of the spirochetal nature of specific structures in brains and spinal cords of patients with multiple sclerosis.

In 1957, Ichelson (37) devised a new culture medium in which she claims it is possible to grow spirochetes from spinal fluid of fifty-nine out of seventy-six cases of multiple sclerosis. Newman, Purdy, Rantz and Hill (38) attempted to repeat Ichelson's work. Although their series was small, they found some form of what seemed to be a living organism. No such forms were found in a series of patients without the disease. The authors found these organisms in only 18.5% of multiple sclerosis patients, whereas

Ichelson found them in 78%. Although they do not know the nature of the organism, they feel that further experiments in this field should be done.

Roach, Rosenberg, and Ichelson (39) prepared an antigen from spirochetes cultured from spinal fluids of multiple sclerosis patients, and used it in a complement fixation technique to diagnose multiple sclerosis. They found that fixation occurred in 77% of all cases with histories of multiple sclerosis, and 26% of cases with normal or other pathologic findings.

PROTOZOA AS POSSIBLE ETIOLOGIC AGENTS OF MULTIPLE SCLEROSIS

Bequignon (40) reported that Toxoplasma gondii had been passed to mice and rabbits by inoculating the animals with cerebrospinal fluid and blood from five patients with multiple sclerosis.

Burrows (41) feels that infection with Toxoplasma gondii is very common in man, and that it very rarely gives rise to acute disease. Most cases occur in newborn infants. Infection in the adult is usually subclinical.

Craig (42) and Calkins (43) do not mention any protozoa associated with multiple sclerosis. They do, however, mention that protozoan infections are common in man.

In evaluating Bequignon's report, it must be kept in mind that infections with Toxoplasma gondii are common in man. It is very possible that these patients with multiple sclerosis were also infected with Toxoplasma gondii; each being a separate entity.

STUDIES THAT BROADLY INVESTIGATE THE INFECTIOUS DISEASE THEORY

Dekaben (15), in his investigation into the possible infective etiology of multiple sclerosis, used 667 animals of various species. Five-hundred and nineteen received cerebrospinal fluid or brain suspension from multiple sclerosis patients and 148 received control material. The investigator used various procedures such as injection of cortisone and total body X-irradiation in an attempt to lower the resistance of the inoculated animals to infection. He also ran careful histologic studies on all inoculated species. of his results were negative. His conclusion was that it is unlikely that multiple sclerosis is caused by a transmittable agent.

Harding and co-workers (44), using several inoculation techniques, passed tissues and fluid from a group of thirty-eight patients with a clinical diagnosis of multiple sclerosis and from two patients who died during the course of their illness, into monkeys, adult mice, suckling mice, hamsters, chick embryos, and rabbits in an effort to establish the presence of an infectious agent for multiple sclerosis. Passages were also tried in 448 tubes of culture media designed to

support the growth of members of the genus Borrelia and of the genus Leptospira. Attempts were made to infect 500 tubes of HeLa cell and monkey kidney cell tissue cultures. They also ran a serology survey of sixty-eight persons with a clinical diagnosis of multiple sclerosis, using viral, rickettsial, spirochetal, Wasserman, Kahn, heterophile antibody, and cold agglutinin antigens. The authors concluded by saying that none of their results tend to support the infectious concept of the etiology of multiple sclerosis.

Diamond (45) feels that clinical evidence and pathologic studies have not yielded valid arguments that the disease is due to a virus or bacteria.

CONCLUSIONS

Many theories exist on the possible etiology of multiple sclerosis. One of the prevalent theories is the infectious etiology theory. Studies on bacteria, spirochetes, viruses, and protozoa have been carried out in an attempt to ascertain an infectious agent.

Among the bacterial etiology theories, acid-fast bacilli are the organisms which are thought to be the infectious agent. All attempts to definitely incriminate this organism have failed. Attempts to isolate a virus from various tissues of multiple sclerosis patients have also failed.

At present, the spirochetal theory is probably one of the most prevalent theories. A spirochetal-like organism has been demonstrated and cultured. No one has actually disproved that this organism is not the cause of multiple sclerosis, however neither has it been definitely proved that this organism is the etiologic agent of the disease.

The protozoal theory is presented merely for the sake of completeness. Most workers feel that a protozoal agent as the causative factor is quite unlikely.

Several workers have recently attempted studies

using the most modern methods of inoculation, culture, transfer, and histologic examination in an attempt to prove or disprove all of the previous experimental work that has been done on the infectious agent theory. The results of their work was negative. The author, after having reviewed the literature on the possible infectious etiology of multiple sclerosis, feels that no one has been able to prove definitely the existence of an infectious agent as the etiologic factor in multiple sclerosis.

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