The Allergic Aspects of Multiple Sclerosis

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• *For the past ten years there has been an increasing acceptance of the theory that allergenic reaction is a causative factor in multiple sclerosis. In the study of a series of patients the author traced many attacks directly to allergenic insults. When the offending substances were removed, a quiescent period often ensued. The severest symptoms of multiple sclerosis were most often associated with food allergens, the moderately severe with molds and fungi and the least severe with pollens and chemical offenders.*

The earlier the diagnosis and the beginning of treatment, the better the chance of arresting the disease and preventing serious crippling conditions. In cases of longer duration where the patient has become crippled or bedridden, physical therapy with relaxing medication is of great value.

AS BASIS FOR DISCUSSION of the allergic aspects of multiple sclerosis it is necessary first to establish the present day concept of allergy and to define multiple sclerosis. The allergy of von Pirquet and Schick, as described in their monograph of 1906, is far different from the ideas of today as expressed by leading allergists. The classic interpretation of protein sensitivity rather easily forecasts mold and dust insults, but hardly forecasts allergy as it is understood today. As to multiple sclerosis, this designation is unfortunately used frequently for undiagnosed neurological diseases, especially of the demyelinization types. The generally accepted principal diagnostic symptom of this disease is that of remissions and exacerbations, with involvement of more than one portion of the central nervous system.[37, 43, 44, 45, 62, 67] However, in only about 60 per cent of cases diagnosed as multiple sclerosis is this feature present. In the cases in which remissions and exacerbations occur, the first complaints[43] often seem bizarre[24] and only a few objective abnormalities are noted by careful examination. The symptoms frequently disappear spontaneously. A patient may have a number of attacks of transient numbness or paralysis before the development of definite signs of organic disease of the brain or spinal cord.[10, 12, 14, 15, 16, 21]

ETIOLOGIC THEORIES

There are a number of etiologic theories[35] as to the cause of multiple sclerosis, among them being vitamin or mineral deficiencies, viral infections,[38, 50] emotional instability and glandular disturbances. Applying the yardstick of remissions as being needed definitely to establish the diagnosis, most of these etiological theories can be ruled out. It is hard to visualize any of these causes striking at intervals and leaving the patient apparently normal between exacerbations, with remissions lasting up to 20 years. Kennedy,[39, 40, 41] in 1936, directed attention to allergy as a possible basis in the etiologic delineation of multiple sclerosis. He stated: "Its episodes, its remissions, the curability of its most acute crisis, its attack on the optic nerves, its neglect of sensory paths—all these things greatly resemble the happenings of localized allergic edemas after the central nervous system has come under fire. Further, the recent plaques in the rare autopsies of acute cases are not sclerotic; they are infiltrations by fluid of the nerve tissue surrounding blood vessels."

That same year Putnam[46] pointed to the essential similarity between encephalomyelitis and multiple sclerosis. In 1941 he expressed the view that the origin of encephalomyelitis is in some sense an allergic reaction, adding that "it seems not unreasonable to suppose that an instability of the clotting mechanism of the blood might be one aspect of allergy."[47]

Ferraro[20] introduced the concept that demyelinating diseases, especially of the acute form, are the expression of a cerebral allergic reaction. He based his contention on the fact that in these conditions the fundamental histologic features of cerebral allergy are present.

DIAGNOSIS

Before a definite diagnosis of multiple sclerosis is made, at least five of the cardinal symptoms of this disease should be present. These symptoms should also involve more than one part of the central nervous system. The cardinal symptoms are:

1. Nystagmus.
2. Pallor of the temporal halves of the optic disks.
3. Diplopia.

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4. Ocular palsies.
5. Speech disturbance.
6. Ataxic tremor of the upper extremities.
7. Past pointing.
8. Loss of abdominal reflexes.
9. Increase of tendon reflexes.
10. Spasticity of one or both upper or lower extremities.
11. Urinary incontinence.
12. Spastic, ataxic or spastic-ataxic gait and station.
13. Babinski's sign.
14. Remissions leading to disappearance of part or all of the symptoms.

Multiple sclerosis is a disease of adult life, initial attacks occurring usually between 20 and 40 years of age; rarely after 45 and seldom before 15 years.

At the Multiple Sclerosis Clinic, St. Joseph's Hospital, Tacoma, the histories of 2,000 consecutive cases of multiple sclerosis, definitely diagnosed by accredited neurologists or by physicians at well-known general clinics, were reviewed and, on the basis of symptoms, classified in various categories. (Table 1).

For the purposes of this presentation the 1,199 cases (Table 1) in which there was history of complete remissions and the involvement of more than one part of the central nervous system, can be designated as cases to which the theory of allergic cause can be applied. It is to be noted that only about 60 per cent of the 2,000 cases satisfied these requirements. It is quite possible that in others the initial attack may be so severe and so damaging as to prevent the patient from ever becoming symptom-free again.

THEORY AS TO PATHOLOGIC CHANGES

To understand the major role of allergy in multiple sclerosis, one must have knowledge of the pathologic changes that occur in acute and subacute cases. They can be considered analogous to urticarial wheals, scattered at various times,[29,49,55,58] throughout the entire central nervous system. The skin and the central nervous system originate from the same embryological layer, namely the ectoderm.[34] Because of this, it is reasonable to assume that the entire central nervous system might be susceptible to the same allergic insults that the skin is. When urticarial wheals occur on the skin or along the intestinal tract, there is no serious damage, as there is no pressure exerted. However, in a bony cavity such as the skull or vertebral column there is little room for expansion. Therefore, through pressure the blood supply to certain areas is obliterated; and if this pressure continues long enough,[56] the destruction of tissue in these areas occurs with resulting scar or sclerotic plaques. If the urticarial wheals disappear and the pressure is removed soon enough, the symptoms that have resulted from pressure disappear: a remission occurs. If pressure continues, a demyelinizing effect results, with irreversible changes.

TABLE 1.—*Classification, after review of records, of 2,000 consecutive cases previously diagnosed*

	No. cases	Per cent
Typical multiple sclerosis with remissions	1,199	59.9
Typical multiple sclerosis without remissions	*349*	*17.5*
Familial and atypical	100	5.0
Hereditary ataxia	48	2.4
Amyotrophic lateral sclerosis	51	2.6
Primary and posterior lateral sclerosis	233	11.6
Others	20	1.0
Total	2,000	100.0

For the last ten years there has been an increasing acceptance of the theory that allergenic reaction is a causative factor in multiple sclerosis; and no research project can be complete that does not take this into consideration. Rowe[51,52,53] has many times called attention to the manifestations of neurological allergic disease, stating that in his opinion foods are the worst offenders. The author has used Rowe's elimination diets for many patients with multiple sclerosis, especially those with extreme sensitivity to foods. The results have been very good in many cases.

EOSINOPHIL DETERMINATIONS

In considering the theory of allergenic cause of multiple sclerosis, the question of eosinophil content in the blood arises. Before the advent of the chamber method of counting eosinophils, the author carried on a rather elaborate set of studies of eosinophil content in multiple sclerosis. In a period of two years, eosinophil determinations were made on 5,164 specimens of blood from 271 patients with multiple sclerosis, including 116 just beginning the treatment described in later paragraphs. In these studies it was observed that (1) as formerly reported by other investigators,[9] eosinophil averages in multiple sclerosis are usually normal; (2) under treatment with histamine by any method, eosinophil content typically increases, usually reaching a maximum between the first and third months (range 0 to 29 per cent; average 5.2 per cent); (3) when determined monthly over a year of histamine therapy the eosinophil content was usually within normal range but almost always there was one fluctuation or more to a higher level.

The development of the chamber method of counting eosinophils antiquated older techniques for quantitative work, and the differential count studies were discontinued. In one series of 203 cases, determination of eosinophil content by the modified Randolph technique was carried out at the beginning and end of a two-month standard course of treatment. In this series the average proportion of eosinophils before treatment was 1.58 per cent with a range of 0 to 10.6 per cent. After treatment with histamine for two months the average was 5.52 per cent with a

range of 0 to 17 per cent. Medians for both were almost identical with the averages.

Some question is raised as to the concept of allergic disease as a histamine imbalance of the body that occurs during the state of hypersensitivity. However, the eosinophil continues to be the most baffling of all blood components. There is the factor of temporary storage from the circulation and the factors of production and loss. In the study described above most of the patients were in a state of fair remission when the determinations were made. Where there were increases, they could not be definitely correlated with exacerbations. But where there were temporary increases of the eosinophils, there appeared to be in some cases a connecting link. The content of eosinophils, however, might also be influenced by the rate with which they passed out of the blood stream into the areas of shock tissue.[11, 61]

SCRATCH TESTS

In dermal scratch tests of over 2,200 patients with demyelinating diseases, almost all were noted to be sensitive to some group of allergens, such as foods, molds, epidermal material or pollens. The author uses the scratch test as a gauge in the study of the allergenic background of patients with multiple sclerosis—taking into account the probability that as sensitized persons they may exhibit the allergic phenomena only when they are "triggered" by emotional factors.[7, 18, 48, 60, 65, 66]

EMOTIONAL FACTORS

It is well known that in the majority of patients with multiple sclerosis there are indications of emotional instability. The author is of the opinion that most have neuroses.[42] This resolves itself into the chicken-or-the-egg proposition. Does the neurosis occur first, or do the symptoms of multiple sclerosis come first? That is a question very difficult to answer, as it is hard to state definitely where subjective symptoms of multiple sclerosis begin and neurosis stops. At any rate, after carefully analyzing the cases, the author believes that any allergic insult, including instances in which emotional upset is a factor, can trigger the initial attack. There is no doubt that a great many patients have their first exacerbation as the result of trauma, accidents,[23] fright, worry, great joy, emotional upset or other stress—just as angioneurotic edema will occur as the result of any of these.

In treatment, emotional factors should be gone into thoroughly and rationally with the patients, with explanation to them of the degree to which their emotional upsets influenced the course of the disease.

Once urticarial whealing within the central nervous system occurs, whatever the allergenic factor, recurrences may be brought about by any other kind of allergic insult as well as the original one.

Relation of Severity of Disease to Specific Allergens

In correlating results of scratch tests with the multiple sclerotic condition of the patient, it was noted that the vast majority of patients who had particularly severe symptoms of multiple sclerosis had strong sensitivity to foods; those with less severe disease reacted strongly to molds and fungi; those who were least disabled had strong sensitivity to pollens, and in many instances of patients in this latter category it was noted that the episodes of exacerbations were related to the seasons when the pollens to which they were sensitive were afloat.

It is easy to see why patients sensitive to food had the severest cases of multiple sclerosis: They were exposed daily the year round to offending items. Two patients who were strongly sensitive to orange had minor but definite exacerbations whenever oranges were peeled in the same room they were in. There are many reports in the literature both from allergists and neurologists of cases in which persons sensitive to various foods had pronounced neurological symptoms whenever they ate or handled any of them.[32, 51, 52, 53] Many of the patients observed by the author complained of increased nystagmus, spasticity and many other symptoms of multiple sclerosis following the ingestion of certain foods.

It has been noted for years that there seem to be geographic factors in multiple sclerosis: The disease is much more prevalent in the northern parts of Europe and North America than in the southern parts of these continents.[31, 54] The same is true of the regions of Australia and New Zealand farthest from the equator. The disease is practically unknown in southern Asia and in the semitropical and tropical parts of the world. The places of greatest prevalence are those in which milk and cereal products such as wheat and rye—outstanding among allergens—form a high proportion of the food intake.

Swank[59] made a study of the diets of the various peoples of Europe before, during and after World War II with reference to multiple sclerosis. His conclusions were that the highest incidence of new cases of multiple sclerosis was in those countries where the largest amounts of milk and butter were used. Although he attributed the phenomenon to the relatively high consumption of animal fat, the correlation might be better explained on a basis of milk as an allergenic offender.

Ehrentheil, Schulman and Alexander,[20] working at the Boston State Hospital Multiple Sclerosis Research Clinic, reported on 65 cases in which an intensive study of sensitivity to foods was made. They

noted that rye, wheat, oats and orange juice were the worst offenders. (This corresponds with the results of the author's studies, except that chocolate, eggs and milk were found to be greater offenders than orange juice.)

In summarizing the Boston Clinic's study, Ehrentheil and co-workers stated:

"1. Ophthalmic tests with 25 different food proteins in patients suffering from multiple sclerosis showed a very high percentage of positive reactions to rye and wheat. This finding proved statistically to be significantly higher than in the random population.

"2. Allergen-free diets based on a carefully taken allergic history and on the results of ophthalmic tests brought about favorable therapeutic results in 31 per cent of the cases.

"3. In 12 cases the temporary reintroduction of the previously omitted food resulted in temporary exacerbations of symptoms."

TREATMENT

The treatment administered by the author is primarily that which would be used in the general management of a patient with any allergic condition. This includes instruction as to the avoidance of offenders, the use of allergenic extracts and the administration of histamine,[8, 13, 25, 26, 27, 28] at first intravenously and then by iontophoresis,[1, 2, 3, 4, 5, 6] or repository injections.[33, 36, 64] Histamine is the most powerful dilator of intracranial vessels known.[30, 57] Therefore, it covers that need. At the same time, when given properly it is the universal hyposensitizer and the recommended treatment for acute and chronic urticaria. Acute and subacute cases of multiple sclerosis usually respond to histamine therapy. Where there are irreversible changes in the chronic cases, little can be expected from hyposensitization other than eliminating exacerbations or rendering them less severe.

In addition to antiallergic therapy, everything available that has proven efficacious in the care of patients with multiple sclerosis is used, especially physical therapy, curare, vitamins and gonadotropic hormones. For the past six years curare has been used in a repository menstruum, and in that time more than a million doses of the material have been given, most of it injected by the patients themselves in the same manner as insulin. No undesirable reaction has been observed or reported.

The author firmly believes that antiallergic management is the most effective method of dealing with multiple sclerosis, especially acute and subacute cases. A complete, harmonious understanding must exist between the patient and the physician, be he an allergist or a neurologist. The patient must be taught to watch for events of stress, offending foods and other situations that occur in connection with symptoms. When he can himself connect exacerbations with some allergenic offense that he can avoid, fear of the disease and the future subsides.

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