MULTIPLE sclerosis continues to be a serious medical problem. Despite numerous investigations, no etiological agent has yet been discovered and not one authenticated cure has been reported. It has been estimated that approximately 300,000 cases exist in the United States, as compared with 250,000 cases of chronic poliomyelitis. In 1949 it was reported that 1,379 deaths were due to multiple sclerosis, and yet this is from incomplete data. Furthermore, considering that 90 per cent of the patients who develop multiple sclerosis do so before the age of 45, during the most productive and fruitful years of life, the problem assumes special import for its socioeconomic implications.2

In the search for a specific etiological agent in multiple sclerosis, many causes have been implicated. These include infection (either viral or bacterial); metabolic disorders, such as disturbances in carbohydrate or fat metabolism; psychogenic factors; cerebral vascular disease, such as localized vasoconstriction or scattered thromboses of venules in association with altered coagulability; sludging; and allergy.11

This article is concerned primarily with an analysis of one of the possible factors, allergy. It is my intent to review and evaluate experimental, pathologic, and clinical data implicating allergy and possibly to indicate new avenues of approach in estimating the true etiological relationship, if any, between allergy and multiple sclerosis.

In order to evaluate any possible etiological agent of a specific disease or any therapeutic measure to relieve it, it is necessary that the disease entity be clearly defined clinically. Here we are at once confronted with serious difficulty. Kurland,12 for example, is of the opinion that we may be dealing with two or more disease entities displaying the multiple sclerosis syndrome and that the disease may be etiologically different in northern and southern climates.

The difficulty in clinical definition is reflected in the diagnostic difficulties. Although many procedures and tests have been devised for the diagnosis of multiple sclerosis, none has proved clinically useful.† As yet, the only way,
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according to Schumacher, that the diagnosis of multiple sclerosis can be made is on the basis of (1) clinical evidence indicating widely scattered, discrete lesions in various parts of the central nervous system and (2) a tendency for alleviation or remission. Another difficulty stems from the evolutionary nature of the disease; it may be many years before the clinical picture indicates multiple sclerosis.

Kurland indicates that only post-mortem examination is a reliable method for making the correct diagnosis. In a review of 25,000 autopsies which he analyzed, thirty-three had a clinical diagnosis of multiple sclerosis, of which twenty-three were confirmed and ten had been misdiagnosed. On the other hand, eleven persons were discovered at autopsy to have had multiple sclerosis which had not been clinically diagnosed. Nathanson reports that 15 per cent of 250 patients seen in a large multiple sclerosis clinic were misdiagnosed.

Finally, any evaluation of an etiological agent or therapeutic procedure must also consider the observations already mentioned—that multiple sclerosis occurs only during a limited span of years, sparing the very young and the old; that the colder climates definitely increase the incidence and death rate; and that it has a peculiar evolution and a tendency for remission.

THE STATUS OF ALLERGY IN THE ETIOLOGY OF MULTIPLE SCLEROSIS

To incriminate allergy effectively as a cause of multiple sclerosis, certain criteria must be fulfilled; these have been indicated by Cooke: (1) an allergic constitution, (2) a repetitive history of symptoms, (3) a history of unusual or excessive contact with an allergen, and (4) positive skin reactions which, if not specific as in other atopic diseases, at least indicate the allergic constitution of the patient. To these four, the reviewer believes, should be added a fifth, usually included in Cooke’s postulates: that elimination of a suspected allergen, if extrinsic, should relieve the symptoms, and that deliberate reintroduction of the suspected antigen should reproduce them.

Although this latter criterion is of marked value in clinical allergy (and, in the case of certain food and drug reactions, is the only way of establishing relationship between an allergen and disease), it may not hold in a disease entity in which allergy is not the sole factor but is associated with one or more agents acting simultaneously, or in which the allergen is intrinsic and cannot be eradicated. Were this fifth criterion to be demonstrated conclusively in multiple sclerosis (and this has not occurred under controlled conditions), the case for an allergic role would be markedly enhanced and the search for specific allergens thereby intensified. It is significant that, with all the years of observation of patients by competent investigators, no report has completely fulfilled these criteria.

1. Is There an “Allergic Constitution” Among Patients With Multiple Sclerosis?—Approximately 10 per cent of the general population suffers from recognized allergic diseases. On the other hand, data on the incidence of multiple sclerosis in allergic patients are meager. In my experience during
twenty years of allergy practice, including attendance at several large clinics, I have encountered only one patient with multiple sclerosis who also had hay fever. If allergy, as we commonly use the term, were a substantial etiological factor, the allergist should see a greater number of such cases. The literature reflects, both quantitatively and qualitatively, the rarity of the clinical evidences of allergy's relationship to multiple sclerosis, despite excellent experimental studies implicating allergy. Studies of the association of known allergic disease with multiple sclerosis are discussed further in Part III.

2. Repetitive History.—Here a certain superficial parallelism between allergic diseases and multiple sclerosis can be shown, since one of the chief characteristics of multiple sclerosis is its periods of exacerbation and remission. However, it remains to be demonstrated that these exacerbations are due to exposure to specific allergens and the periods of remission due to lack of contact with such allergens. Furthermore, although multiple sclerosis and allergic disease are both characteristically periodic, the two disorders differ sharply in their patterns of attack. The periodicity of allergic disease is largely predictable, particularly when the allergen is known and extrinsic. Neither the onset of symptoms nor the occurrences of remissions and exacerbations are predictable in multiple sclerosis, however. In addition, while most allergic disorders are completely reversible, leaving no pathologic residues, the characteristic pathologic lesion of multiple sclerosis (scarring of the brain tissue) appears to be irreversible.

Thus, the analogy is not complete, even if it be argued that the parallelism between multiple sclerosis and allergy need not necessarily apply to the so-called atopic diseases (in which heredity and positive skin reactions are dominant factors), but rather to the collagen disorders.

3. History of Unusually Excessive Contacts With an Allergen.—As a precipitating factor, this is not substantiated by any of the observers who have studied multiple sclerosis from the point of view of allergy.

4. Positive Skin Reaction.—Jonez[17] makes no statistical analysis of the results of skin tests performed using such allergens as foods, inhalants, pollens, and molds. Ehrentheil, Shulman, and Alexander[19] who offer the most data on allergy testing but use the conjunctival test rather than the skin test, consider positive reactions to be evidence of specific sensitivity rather than indicators of the hypersensitive state, as implied by Cooke.[16] (They do not necessarily imply that every positive reaction is of clinical importance.) Skin testing, therefore, has not been correlated with multiple sclerosis.

5. Manipulation of the Allergen.—The fifth criterion (namely, the deliberate clinical induction of signs of multiple sclerosis by or with the aid of a specific allergen) also has never been truly demonstrated. Ehrentheil and his co-workers[19] have made this attempt in twelve patients, eliminating and then deliberately introducing specific foods (based upon allergy tests), hoping thereby to obtain induced remissions and exacerbations. This, it is recognized, is
a difficult procedure in a disease characterized by spontaneous remissions and exacerbations. The evidence, although strongly suggestive in some patients, was not conclusive for the group.

Despite the foregoing negative evidence, however, there is a basis for considering allergy as a mechanism for the induction of multiple sclerosis. The available data come from the experimental, pathologic, and clinical studies which are presented in this article.

I. EXPERIMENTAL EVIDENCE*

The experimental lesion most closely resembling multiple sclerosis is that encountered in experimental encephalomyelitis (iso-allergic). This is a disorder which produces widespread demyelinating lesions in the central nervous system. Accordingly, many studies of this phenomenon have been made in order to shed light upon the possible etiology of multiple sclerosis.

Several approaches have been used. Most of the studies have been concerned with attempts to induce brain damage through injection of nervous tissue. Serologic studies have also been made in a search for a possible immune mechanism. Other research has dealt with infection, metabolic disorder, and circulatory impairment.

Von Pirquet,24 in 1907, shortly after he had introduced the concept (and the term) of allergy, indicated that an allergic mechanism was probably involved in the production of the papule and areola and in the accelerated reaction following revaccination with vaccine virus. It was logical, therefore, for Glanzmann, in 1927,25 to implicate allergy in the postvaccinal encephalitis then relatively common. Stuart and Krikorian26 extended this concept to include the encephalitis occasionally seen following antirabic treatment, and Finley27 later endorsed it. A series of experimental studies was undertaken, beginning in 1932 with the observation by Hurst28 of paralysis without obvious pathologic findings in the brains of four of forty-three rabbits injected with normal brain tissue.30 During the following years, Rivers and his associates29,30 did a series of studies with monkeys in which prolonged injections with heterologous brain emulsion produced neurologic signs and symptoms owing to marked brain damage. This work was confirmed in 1940 by Ferraro and Jervis,31 who also produced eencephalomyelitis in monkeys with injections of heterologous (rabbit) brain over long periods of time. The pathologic findings, although not exactly typical of multiple sclerosis, resembled it. Freund and McDermott32 subsequently (in 1942) introduced the use of adjuvants to enhance antibody production and, with this new tool in the hands of the researcher, a series of animal experiments was performed in which encephalomyelitis could be induced inexpensively by an exceedingly rapid method. Thus, in 1946 Morgan,33,34 as well as Kabat, Wolf, and Bezer,35-37 independently observed that homologous brain combined with Freund's adjuvants could be injected into monkeys, with demyelination following two or three injections. The histologic picture was not that noted by Rivers and associates29 and by Ferraro and Jervis31 in which giant

*Hurst26 has written an excellent and detailed review of experimental demyelination to which the reader is referred. Only a limited review is presented here.
cells were seen, but was, rather, that of a more acute process. Kabat, Wolf, and Bezer were successful with a single injection and noted that both homologous and heterologous brain tissues were effective. Ferraro and Cazzullo indicated that by modifying the dosage of a specific antigen (using smaller amounts) a picture more suggestive of the chronic condition could be produced. It was soon revealed that this phenomenon could be produced in the guinea pig, rabbit, mouse, and dog.

Although the rat was refractory, Lipton and Freund later succeeded in producing encephalomyelitis by intradermal inoculation of brain emulsion plus adjuvants. Certain strains of both the dog and the mouse were noted to be particularly susceptible; others were more resistant. Olitsky and Yager were successful in inducing experimental encephalomyelitis in mice. Experiments with brain emulsions from different animals indicated that, with the exception of the immature cerebrum of neonatal or fetal origin, brains of guinea pig, rabbit, man, goat, cow, and pig could produce encephalomyelitis. Extracts of frog or fish brain were ineffectual. Lumsden further showed, in 1949, that emulsions of homologous, peripheral nerve could produce the same phenomenon as emulsion of brain tissue. With the exception of organ emulsion, as reported by Kopeloff and Kopeloff, encephalomyelitis could not be produced by investigators using emulsions of any other tissue (for example, muscle, liver, spleen, or lung, heterologous or homologous).

The pathologic findings in experimental encephalomyelitis varied somewhat from animal to animal, and were affected by the amount of antigen injected, the number of injections given, and whether or not an adjuvant was used. Subsequently, Freund, Lipton, and Morrison showed that changing the Mycobacterium butyricum \footnote{Kabat, in a personal communication, states that he and other investigators have failed to confirm Lumsden's observation.} in the adjuvant from one grown in glycerin to one not grown in glycerin modified the type of response and produced a chronic encephalomyelitis which more closely resembled multiple sclerosis.

In the earlier experiments, the induction of encephalomyelitis by injection of nervous tissue with and without adjuvants had been inconstant. With the technique subsequently developed by Lipton and Freund and by Freund and his co-workers—selection of the Hartley strain of guinea pigs and a single intradermal injection of the emulsion of brain and adjuvant—all the animals developed iso-allergic encephalomyelitis. Lee and Olitsky, utilizing pertussis vaccine as an additional adjuvant, have markedly enhanced the experimental production of encephalomyelitis in mice.

The production of acute disseminated encephalomyelitis by injection of brain emulsion immediately raises the question of whether or not a form of autosensitivity may be involved. This was clearly answered by Kabat, Wolf, and Bezer, who induced the phenomenon by injection of monkeys with emulsions from portions of the recipient's own brain previously removed by operation, along with the adjuvants.
The general conclusion was that the mechanism which most probably accounted for the experimental production of encephalomyelitis was an antigen-antibody reaction. According to Kabat, Wolf, and Bezer, antibodies produced by the injected brain tissue passed into the circulation and across the blood brain barrier to react with antigen in the central nervous system, thus producing perivascular lesions resembling those seen in multiple sclerosis. The search for a specific antigen disclosed that this was organ (rather than species) specific, that it was most abundant in the white matter of the brain, and that it was not present in fetal and neonatal cerebrum. Experiments with a variety of fractions obtained from extracts of brain tissue revealed that the proteolipide (a new type of lipoprotein discovered by Folch and Lees in 1951) comprised the encephalitogenic activity of brain. This has been confirmed by Waksman and his associates and by others.

Further immunologic studies have provided another approach to the problem. Bailey and Gardner subjected rabbits to prolonged immunization with a heat-killed vaccine of Pasteurella bovis septica grown in an infusion broth prepared from rat brain. The resultant antiserum contained antibodies against both the bacteria and the brain broth. Guinea pigs passively sensitized with this serum were shocked anaphylactically by a challenging dose of broth of brain or emulsified medullated nerve given intravenously. No other extracts of organs duplicated this phenomenon. This study showed not only that brain tissue can be antigenic, but that the resultant antibodies can be passively transferred.

The possibility that an immune mechanism was involved arose also from the previous observations of Rivers and Schwentker, of Brandt, Guth, and Muller, and of Witebsky and Steinfeld, all of whom had indicated that antibodies against brain tissue could be produced by injections of heterologous brain tissue. Schwentker and Rivers had also reported the presence of such antibodies with the use of homologous brain tissue. Their work antedated the use of Freund’s adjuvants, and antibodies were produced more readily when the brain tissue was combined with pig serum, given with vaccine virus, or after the brain had undergone autolysis. The suggestion was made, therefore, that in postinfectious encephalomyelitides, autogenous antigens, capable of formation of brain antibodies, were liberated and the antigen-antibody union produced further brain damage, that is, demyelination.

Comment on similar investigative work with the kidney is appropriate here. Masugi, in 1934 (later confirmed by Smadel), produced glomerulonephritis in rats by injecting them with antikidney serum obtained by injection of rabbits with kidney emulsion of the rat. It was concluded that specific tissue sensitivity of the kidney was responsible for the glomerulonephritis. Schick had postulated in 1907, on purely clinical grounds, that nephritis resulted from an antigen-antibody mechanism; this was indirectly confirmed by Masugi and Smadel. Direct confirmation came from Cavelti and Cavelti, who produced a form of glomerulonephritis in rabbits by injection of homologous kidney extracts inoculated with hemolytic streptococci.
This awaits confirmation. Lange and his co-workers have further developed this concept by the clinical application of a complement fixation test as an expression of autosensitivity.

The Burky phenomenon is another suggestive observation of autosensitivity. In the rabbit, Burky succeeded in inducing sensitivity to its own muscle and lens tissues by the simultaneous injection of tissue and staphylococcus toxin. Swift and Schultz confirmed Burky’s results and also were able to produce identical sensitivity by modifying Burky’s procedure, either by previously sensitizing to horse serum or by inducing infection with a streptococcus organism.

In view of such demonstrations of autosensitivity (that is, with the kidney as antigen as well as the Burky phenomenon), it might be postulated that nervous tissue also may act as an antigen and produce an autosensitivity capable of producing demyelination. The possibility of such a mechanism in encephalomyelitis was considered by Kolb and Bolton, Freund, Stern, and Pisani, Kopeloff and Kopeloff, Morgan and Kabat, Wolf, and Bezer. Their attempts, however, to produce demyelination by the injection of antisera to brain tissue were unsuccessful. What Masugi and Smadel were able to do with kidney tissue these workers could not do with tissue of the brain.

Not only were complement-fixing brain antibodies demonstrated in experimental encephalomyelitis, but further studies indicated the presence, not of a single antibody, but of a variety of antibodies resulting from injections of brain tissue. These antibodies were not species specific, since brain tissue derived from many sources produced the same results. Lumsden, Kabat, Wolf, and Bezer, working with experimental encephalomyelitis, noted multiple complement-fixing antibodies (to brain and placental tissue) in some animals, but none in others, or present only as anticomplementary to one tissue. Since the antigen was complex, multiple antibodies were produced. Thomas, Paterson, and Smithwick not only observed the presence of complement-fixing antibodies, but reported the presence of flocculating antibodies which they equated with the complement-fixing antibodies. There is, however, no apparent relationship between the concentration of antibodies with the production of symptoms and pathologic lesions. Antibodies may be present without disease, or disease without antibodies. It has been suggested, therefore, that the presence of antibody may be only coincidental to the disease and unrelated to its pathologic manifestations. This view does not seem compatible with a more positive role for an antigen-antibody mechanism in view of the remarkable role that the adjuvants play in experimental encephalomyelitis. Since the use of adjuvants in less complex studies enhances antibody production remarkably, the same mechanism is presumably applied here. Indeed, a logical explanation for the mechanism of experimental encephalomyelitis is that of an antigen-antibody reaction.

In addition to the circulation of antibodies against brain tissue previously demonstrated, several investigators, including Lipton and Freund and Kope-
loff and Kopeloff, demonstrated the presence of tissue-sensitizing antibodies by skin testing. These positive skin reactions, however, were produced only with heterologous brain and were not clearly correlated with the production of nervous disease. Waksman and Morrison, however, later induced tuberculin-like skin reactions (delayed type) which were said to correspond in degree and time to the production of encephalomyelitis.

Where antibody production was demonstrable, unsuccessful attempts were made to produce the disease in the untreated animal by means of passive transference. This included the passive transfer not only of serum but also of peritoneal exudates and spleen or lymph node washings as originally described by Chase in the passive transfer of tuberculin sensitivity. Kabat and his associates explain this failure of passive transference by assuming a continuous fixation of antibody by the antigen present in the nervous tissue of the donor.

Ferraro, Roizin, and Cazzullo, utilizing this principle of the fixation of antibody, reduced the morbidity and mortality of encephalomyelitis by injecting brain emulsion without adjuvant simultaneously with an injection of brain emulsion combined with adjuvant. Their explanation was that antibody produced by means of the adjuvant presumably was neutralized by the antigen without the adjuvant. Freund, however, observed that antigens injected without the complete adjuvants result in a hyperimmune response; with the complete adjuvants, the response is hyperergic. His explanation is that some subtle, unexplained, qualitative change is brought about by use of the complete adjuvant. This theory is discounted by Fischel, Kabat, Stoerk, and Bezer, who regard the differences as only quantitative; that is, the adjuvant merely provides a localized inflammatory area which enhances the production of the same antibodies as those obtained by injection of the antigen without adjuvants. The assumption of Ferraro and his associates that injection of brain emulsion merely introduces antigen, is therefore not adequate, since the condition is not static and antibody can be produced even without adjuvants. Are two types of antibodies produced (one immune and one hyperergic), and do they interfere with each other? It is acknowledged that prolonged use of brain tissue can also produce a hyperergic state.

Further evidence of an antigen-antibody mechanism in experimental encephalomyelitis is seen in the prevention of this phenomenon by the use of sodium salicylate and ACTH presumably by interference with an allergic reaction. Kabat, Wolf, and Bezer believe that cortisone inhibits antibody formation by inhibiting tissue reaction to the adjuvant (including tubercle bacilli) but that, once antibody is formed, it does not affect the subsequent reactions with brain antigen. This accounts for the equivocal clinical results of cortisone and ACTH as reported by Glaser and Merritt. Garcia-Reyes and co-workers, in Thorn's laboratory, observed no impairment of the hypothalamus-pituitary-adrenal cortex function in multiple sclerosis.

It is possible for the brain to react through a variety of allergic mechanisms. Thus, Davidoff and Kopeloff and Davidoff, Seegal, and Seegal pro-
duced sensitivity in the brain by initially sensitizing animals with horse serum and subsequently injecting horse serum intracerebrally to elicit an Arthus reaction in the brain.

The pathologic pattern of the acute Arthus phenomenon in the brain, while not that typically produced in experimental encephalomyelitis, is nevertheless closer histologically to it than to multiple sclerosis. Repeated injections of specific antigen (egg or horse serum) into the sensitized monkey brain produced some lesions which took the form of demyelination and exhibited giant cells and other features similar to those following multiple injections of brain suspensions. The investigators, Jervis, Ferraro, Kopeloff, and Kopeloff, concluded that these changes were due to the action of brain-specific antibodies which were formed in response to a complex antigen composed of foreign protein united to a hapten derived from the myelin damaged by repeated intracerebral inoculations. This explanation of the changes produced by the Arthus reaction in the brain is thus brought somewhat closer to the observations which follow the use of adjuvants and emulsions. Further substantiation comes from Koprowski and Jervis, who found that guinea pigs which were treated with heterologous brain emulsion and adjuvants and failed to develop encephalomyelitis reacted violently to intracerebral injections of a suspension of heterologous brain. Those which succumbed quickly revealed a typical Arthus phenomenon with hemorrhage and necrosis; those which survived over a long period of time showed areas of demyelination which were noted not only at the site of injection, but scattered throughout the central nervous system.

The possibility of still another antibody mechanism capable of producing encephalomyelitis has been reported by Jervis, who utilized the "carotid syndrome" of Forssman. The tissues of the guinea pig normally contain the Forssman antigen. If a serum containing Forssman antibodies is slowly injected centripetally into a carotid artery, an antigen-antibody reaction is induced in the brain tissue, producing areas of demyelination. Injected intracerebrally, the same serum produces changes characteristic of the Arthus phenomenon. Thus, a variety of antigens, in addition to brain tissue, is capable of producing brain reaction resulting in either the acute hemorrhagic necrosis of the Arthus phenomenon in some properly sensitized animals or demyelination in others.

Evidence has also accumulated to indicate that antigen-antibody mechanisms are not alone in the ability to produce demyelination. For example, enzymes, toxic agents, and production of cerebral anoxia have been implicated by various investigators. Thus, Vogel produced demyelination in animals by injecting a large dose of a lipolytic enzyme. Whether the results were achieved through enzymatic action may be questioned. Since rather large doses of the enzyme were injected, primary toxicity alone can explain the demyelination. Morrison and Zameenik showed that myelin sheaths could be broken down by several different types of enzymes, such as cobra venom
or the alpha toxin of Clostridium welchii. They indicated that the chemical reactions involved differed and that demyelination was therefore not a single, chemical process.

It also has been shown that any agent producing anoxia, such as potassium cyanide, as demonstrated by Ferraro, can induce lesions resembling multiple sclerosis and that these lesions can be modified by altering the dosage of the agent. Likewise, Hurst showed that sodium azide could produce a similar response. Morrison produced demyelination by deliberately subjecting his experimental animals to an atmosphere poor in oxygen. Here no antigen-antibody mechanism could possibly be involved. There is also evidence that, at times, poisoning with carbon monoxide, nitrous oxide, and barbiturates can produce similar lesions.

Alteration of the circulation, another way of producing cerebral anoxia, has been used by Putnam in the experimental production of demyelination. It is his contention that venule thromboses are responsible for the characteristic picture of multiple sclerosis.

Although most authorities believe that viruses produce encephalomyelitis through an allergic mechanism, Hurst suggests that the distemper seen in dogs is specifically due to the neurotropic action of the virus, since inclusion bodies could be demonstrated. Furthermore, preparations of diseased brain, when injected into healthy animals, reproduced symptoms. Here, then, is another distinct mechanism for the production of demyelination.

It is evident, therefore, that demyelination may be a response of nervous tissue to many noxious agents, including infection, disordered metabolism (potassium cyanide, sodium azide, etc.), impaired circulation of the brain, and allergy. To summarize the role of allergy in this process, Hurst may aptly be quoted: "Thus although the postulated antigen and antibody have not finally been identified and the detailed mechanism by which the nervous lesions are produced awaits discovery, a good deal of circumstantial evidence favors the view that the encephalomyelitis following injections of brain tissue is the expression of an allergic reaction."

Assuming the validity of Hurst's statement, we then ask how this applies clinically to multiple sclerosis. Granted that an animal's brain can be sensitized and, as a result of an antigen-antibody reaction, can produce lesions resembling those of multiple sclerosis, must we assume an exclusive allergic mechanism in man when it has been demonstrated that nonallergic mechanisms (infective, anoxic, enzymatic) also may produce demyelination in animals? If what we produce experimentally in animals casts light on a like mechanism in the human being, then we must accept the possibility that demyelination in the latter can also be a nonspecific tissue response to many noxious agents, including allergy. Multiple sclerosis, therefore, may be a syndrome (as suggested by Kurland), rather than a specific disease entity, and demyelination only one of the signs, the extent of which (or even its presence) may vary from case to case.
Pursuing further the possible role that allergy may play in multiple sclerosis, which is strongly suggested by the experiments cited, the question arises: "Allergic to what?" Shall we look for specific brain sensitivity, either homologous or heterologous? How shall we test for such sensitivity? Skin testing with brain antigen may not be of help, since only a few investigators have demonstrated skin-sensitizing antibodies in the experimental animal, and since no specific correlation has been shown between the presence of antibodies (skin-sensitizing, complement-fixing, or flocculating) and encephalomyelitis induced in animals.

Can we test by serologic methods for hypersensitivity to nervous tissue in multiple sclerosis? Studies by Sachs and Steiner were suggestive but not completely affirmative. Those by Kolb in a small series were completely negative. These findings were not surprising since, in the experimental animal, the presence of complement-fixing antibodies was not correlated with the presence of encephalomyelitis. Further advances in this field may result from identification of a purified antigen, so that the precise antibody sought for can be detected. In this connection, the finding of encephalitogenic proteolipids points to a more hopeful goal.

II. PATHOLOGIC EVIDENCE

If multiple sclerosis is an allergic disease, does the pathologic examination support this concept? The answer to this question must be preceded by an analysis of the pathology of allergy which can then be compared with the pathologic changes encountered in both human and experimentally induced demyelination.

To begin with, there is no agreement as to specific pathologic changes induced by allergic disease. The usual allergic disorder leaves no residue for the pathologist to examine. The process, in most instances, is highly kinetic and reversible. It is the unusual allergic reaction which is irreversible and associated with demonstrable pathologic changes. In the past, the lesions of allergy were associated with an inflammatory response, resulting in fibrinoid degeneration in which eosinophils were conspicuous and considered diagnostic; the plasma cell was subsequently implicated along with the eosinophil. Current opinion, however, holds the view that an allergic response may take any of several forms. Allergy may be reflected pathologically by hyperemia and edema (usually reversible); by an acute inflammatory response frequently associated with necrosis (the Arthus phenomenon); by vasculitis damage and fibrinoid degeneration, as seen in periarteritis nodosa and other collagen diseases; by purpuric reactions; and possibly by eosinophilic granulomatosis. Which of these entities, then, may be implicated in multiple sclerosis?

The demyelinating diseases may be compared, in a way, with the collagen diseases. Although each of the collagen diseases, when classic, is distinct and differs from the others, there is enough overlapping in some cases to make specific diagnosis difficult and to show the close relationship that exists among them. Likewise, Adams and Kubik in an excellent review of the pathology
of the demyelinating diseases, indicated the obvious differences between classic multiple sclerosis, acute disseminated encephalomyelitis, Schilder’s disease, and acute necrotizing hemorrhagic encephalopathy, yet noted sufficient overlapping to link them. Indeed, Ferraro and others hold that these diseases are all variants of a single pathologic affection.

The pathologic findings in multiple sclerosis are not static but vary with the duration and severity of the disease, whether acute or chronic. Thus, there is more perivascular infiltration in the acute form and more scarring and involvement of the axis cylinders in the chronic. Further, some cases of multiple sclerosis show findings suggestive of acute disseminated encephalomyelitis. This is of particular importance since the allergic theory is strongly supported by the evidence based on the experimental production of encephalomyelitis, presumably by an allergic mechanism.

The reports on pathologic findings from the various workers who produced experimental encephalomyelitis probably differed because of the differences in technique employed. Freund, Lipton, and Morrison, for example, observed that incorporation in the adjuvant of an organism (Mycobacterium butyricum) not grown in glycerin (one would think a relatively slight modification) produced remarkable differences in the pathologic picture; the resulting, more chronic condition more closely resembled multiple sclerosis. The same effect was produced by Ferraro and Cazzullo by reduction of the dosage of antigen. The pathologic findings produced originally by Rivers and his associates resembled those of Schilder’s disease. Morgan and her coworkers and Kabat and his group, on the other hand, produced pathologic changes closer to those of acute disseminated encephalomyelitis. In the more acute allergic type of reaction, as seen in the induction of the Arthus phenomenon in sensitized nervous tissue, hemorrhagic edema and necrosis are dominant in the pathologic picture, while demyelination is minor. Thus, experimentally produced pathologic reactions overlap in a manner similar to that noted in man by Adams and Kubik.

In considering the possible etiological agents capable of producing demyelination, Adams and Kubik indicate that the pathologic findings eliminate infection, disordered metabolism, and thrombosis. They state: “The most common cause of perivascular infiltration is infection, but the other pathologic findings do not resemble those of any known infectious disease. Allergy is another recognized cause. In both infectious and allergic diseases, lymphocytes, plasma cells and histiocytes are believed to play a role in the formation of antibodies. . . . It may be stated that the morbid anatomy of the demyelinating diseases favors the allergic theory.”

The pathologist and immunologist appear to agree, therefore, that allergy may be important in the production of demyelinating diseases, including multiple sclerosis. Now, what has the clinician to offer?

III. CLINICAL EVIDENCE

In sharp contrast to the numerous excellent experimental studies concerning cerebral allergy, clinical reports, particularly on the relationship of
allergy to multiple sclerosis, have been few. This is surprising, indeed, since as early as 1936 Kennedy had implied such a relationship. Although he enthusiastically endorsed a relationship between allergy and diseases of the central nervous system, writing about it extensively, he was careful to point out that it is easy to throw into the category of allergy any disease entity which defies diagnosis. He stated: "Many allergic encephalopathies are constantly being diagnosed as multiple sclerosis. However, encephalopathies and scleroses en plaque are like two baskets flung over the back of an ass owned by a lazy man. Into them every trouble maker is thrust, disposed of and hidden away." The implication is that there are many truly allergic conditions of the brain, particularly retrobulbar neuritis, which have, understandably, been mistaken for multiple sclerosis, since multiple sclerosis frequently begins with disturbances which cannot be differentiated from retrobulbar neuritis, per se. But, as Kennedy points out, one can have recurrent retrobulbar neuritis on an allergic basis over many years without the manifestation of multiple sclerosis. He has implicated allergy primarily because of "the periods of remissions and the remarkable reversibility of the acute crisis, the attack on the optic nerve, and the neglect of sensory pathways: all of these much resemble the phenomena produced by localized allergic edema which has come to attack the central nervous system." This, of course, refers to the superficial parallelism discussed earlier. But if we apply such reasoning to the acute phase, which might resemble allergic edema, does the same parallelism extend to chronic forms of multiple sclerosis? It is possible, of course, for the acute phenomenon to be on an allergic basis and the chronic symptoms and signs to be due to damage to the nervous system resulting from such an allergic reaction. This was proposed by Jones and Cooke, who considered the underlying mechanism to be urticarial in nature.

Kennedy notes that in the rare cases of acute multiple sclerosis seen at autopsy, the pathologic finding is one of perivascular infiltration. "These fluid areas are usually well absorbed coinciding, no doubt, with improvement of symptoms. Only later do some of these edematous sites become sclerotic like the scar tissue of an old wound." It should be stated, however, that evidence would indicate that many kinds of inflammatory reactions in the brain ultimately lead to the kind of phenomena observed in multiple sclerosis, namely, perivascular infiltration and demyelination. No one will disagree with Kennedy when he implies that, clinically, the central nervous system can react on an allergic basis. His observations on paralysis resulting from allergy to horse serum are classical. But he was never able to demonstrate a typical case of multiple sclerosis which could be specifically labeled as due to allergy. Cooke, who collaborated with Kennedy for many years, does not, in his text, report any case of multiple sclerosis as specifically due to allergy. (Indeed, none of the recent texts on allergy mentions multiple sclerosis.)

Davison, in a comprehensive review of allergy of the nervous system, lists but two references suggesting a possible relationship between allergy and multiple sclerosis. He reports no case of his own.
One of the earliest clinical investigations of the possible role of allergy in multiple sclerosis was conducted by Baer and Sulzberger. They studied forty institutionalized patients under the care of neurologists, thereby reducing doubt as to the correctness of the diagnosis. These patients were scratch-tested with approximately 100 allergens (foods, inhalants, pollens, etc.), and careful histories of thirty patients were obtained. The authors concluded that 33 per cent of the patients presented evidence of personal or familial atopic disease or positive wheal reactions to skin tests, or both. This was not a higher incidence of atopy than that seen in normal persons investigated by others in a similar fashion. Baer and Sulzberger suggested that a non-atopic type of allergy might conceivably be implicated. An interesting aspect of this study was the attempt to demonstrate antibodies in the spinal fluid of one patient with marked skin reactions by the use of the passive transfer technique of Prausnitz and Kustner. Although no reagins comparable to those obtained from the serum of the patient were demonstrable, very weak positive reactions were obtained only within twenty-four hours after inoculation of fresh spinal fluid. This was suggestive of a very unstable antibody.

Jonez was possibly the most enthusiastic of the investigators who implicated allergy as an etiological factor in multiple sclerosis. He stated: “The allergic theory is based on edema. The pathologic change is one of edema or urticarial wheals scattered throughout the entire central nervous system at various times. The skin and central nervous system have the same origin—ectoderm. It is therefore reasonable to assume that the central nervous system is subject to the same type of reaction.” Presumably, these urticarial wheals create internal pressures upon nervous tissue, causing its destruction, since the reaction occurs within an enclosed bony cavity and no expansion is possible.

It should also be pointed out that urticaria of the viscera, including the central nervous system, has usually been associated with urticaria of a generalized nature, involving the cutis and subcutis. No such association between generalized urticaria and multiple sclerosis has been reported by any observer. Urticaria may rarely be limited to a single wheal, but it is usually generalized rather than localized and evanescent rather than persistent to the point of causing pressure necrosis. The edema theory suffers also from the fact that, even during an acute attack of multiple sclerosis, examination of neither the eyegrounds nor the spinal fluid has been suggestive of increased intracranial pressure. Although edema can produce compression of a nerve to the point of paralysis, it can do so only within the confines of the narrow spaces through which the nerves enter or leave the skull or spinal cord. It is doubtful that edematous pressure within the brain can produce multiple sclerosis in a similar manner.

Jonez also advocated the theory that in multiple sclerosis the allergic reaction is mediated primarily through an antigen-antibody mechanism in which histamine is released. For this reason, he treated his patients with histamine. This use of histamine was originally initiated in 1944 by
Horton, who stated, however, that this use of the drug in no way implicated allergy. Histamine, according to Horton, was useful for physiologic reasons in that it produced an increase in the cerebral circulation, sometimes as high as 750 per cent, but Jonez considered it to have a twofold function, pharmacologic and antiallergic. Jonez is practically alone in the idea that histamine therapy is antiallergic therapy. If we assume the validity of the histamine release theory in multiple sclerosis, it should be anticipated that patients should show improvement with an antihistaminic agent, none of which has proved to be useful in the treatment of the disease. These various reasons, then, would seem to dictate the conclusion that no histamine, and possibly no allergy, is involved in multiple sclerosis.

What, actually, are the results achieved by "allergic management" and histamine therapy as advocated by Jonez? Two reports are available. In the first, in which 152 cases were reported, eighteen of the nineteen listed as acute responded to treatment. If this is compared with the chart tabulating the results of treatment, we find that the best results were obtained in twenty-five subjects. It can be presumed, therefore, that only seven cases, other than the acute ones, showed unusually good results. This follows the general pattern, regardless of type of treatment; the acute cases do well even if untreated. In sharp contrast, a group of twenty-nine patients were listed as showing only slight improvement objectively, which would make it exceedingly difficult to indicate whether or not any type of treatment was efficacious. In addition, twenty-eight cases showed only subjective improvement. Thus fifty-seven patients (approximately one-third of the total) represent cases in which improvement is doubtful or difficult to assess and yet are cited as showing some kind of "improvement." If to this is added the balance of twenty patients who either showed no improvement, became worse, or died, the results are then not striking. Totaling the patients who are listed in the first three categories as improved, we have eighty-two patients, or approximately 50 per cent. This would not seem to compare favorably with the 40 to 60 per cent of patients who ordinarily do just as well without treatment.

As a matter of fact, it is not easy to analyze Jonez's work, since he did not outline criteria, as advocated by Alexander and associates, for the measurement of improvement. In a second report, covering 1,500 patients who were treated by "allergic management" along with histamine, curare, psychotherapy, and physiotherapy, no results of treatment were recorded and, therefore, no positive conclusions as to the merit of the "total push" treatment can be drawn. Furthermore, other reports of Jonez confirm the impression that psychological support and suggestion contributed greatly.

In the report of Horton and his co-workers 102 patients were treated intravenously with 2.75 mg. of histamine in 250 c.c. of isotonic sodium chloride given daily. A minimum of 13 and a maximum of 300 treatments per patient were administered. Of the twenty-four acutely ill patients, eighteen showed clinical improvement estimated at 40 to 70 per cent. In contrast, the chronically ill patients responded poorly; only thirty-six of seventy-eight
showed improvement ranging from 20 to 95 per cent. No objective improvement was seen in forty-two patients, although they were subjectively improved.

A more thorough investigation of the possible role of food allergy in sixty-five cases of multiple sclerosis is that of Ehrentheil, Shulman, and Alexander. The possibility that inhalant allergy or allergy to bacteria or viruses might be equally responsible is disregarded. The ophthalmic reaction was used since, according to the observations of the participating allergist (Shulman), skin testing with foods gives notoriously poor diagnostic results. A delayed type of reaction was observed and reported by the patient to the physician. However well instructed and conscientious patients may be, it is hard to evaluate material so assembled. As a control, fifty normal persons were also eye-tested with four selected antigens frequently found to produce reactions in multiple sclerosis patients. According to these authors, oranges and the cereals (oats, wheat, and particularly rye) were unusually potent allergens, as revealed by positive ophthalmic tests; 77.8 per cent of their multiple sclerosis patients reacted to rye. It should be noted, however, that in one of the control groups allergic patients without multiple sclerosis, 69.6 per cent, reacted to rye. This is an unusually high incidence of reaction to an allergen and one wonders whether or not the allergen, despite precautions, was not unusually irritating. Only 38 per cent in a second control group of nonallergic patients showed positive reactions. With such a relatively high incidence of positive reaction in control allergic patients without multiple sclerosis, it is difficult to assess the significance of these positive ophthalmic reactions. In addition to the ophthalmic test, skin tests were performed by the scratch method. A comparison, however, between the positive reactions obtained by skin tests and by eye tests revealed low parallelism. This is inexplicable and throws further doubt on the validity of either form of testing in multiple sclerosis patients. The investigation, however, was not limited to ophthalmic testing but included a thorough allergic history on a standardized form, a complete dietary analysis of each patient's food intake on a standardized form, an examination of each patient's nasal mucosa, and skin testing (scratch) with common foods as well as pollens. The ophthalmic tests were performed with twenty-five common foods. Among forty-nine cases of multiple sclerosis, adequately studied, a personal history of allergy was obtained in fourteen cases and a family history of allergy was reported in nine additional cases; 24.5 per cent of these patients showed positive reactions by scratch tests. Taking all these factors into consideration, 38.8 per cent of these cases could be labeled as being atopic, based on history and skin testing.

The evaluation of improvement by Ehrentheil, Shulman, and Alexander was based on a rigid classification originally devised by Alexander and associates. This permitted, with some degree of accuracy, a measurement of the results of the therapeutic procedure, including the elimination of specific foods, based upon the ophthalmic reaction. In twelve instances, the deliberate, temporary introduction of these foods resulted in temporary exacerbations of symptoms. Although the results following the elimination of specific allergens
were startling in some instances, the over-all results were disappointing. Of the forty-five patients placed on presumably allergen-free diets (based on testing), full remissions occurred in only three patients (6.7 per cent). In one of these, egg sensitivity may have had some relationship to the symptoms. Two patients (4.4 per cent) reported clinically significant remissions. Nine other patients (20 per cent) were classified as having shown clinically significant improvement. In one of these patients there was strong correlation between ingestion of rye and neurological symptoms. A total of 31.1 per cent of these patients showed improvement through allergic management, as compared with 68.9 per cent who showed no improvement on such a regimen. When the suspected foods were deliberately ingested (the crucial test for evaluating whether a given food is an allergen), reactions were obtained in only twelve instances. Furthermore, there is no indication that the feeding tests were repeated.

The authors suggest that allergy may possibly be a nonspecific stress factor similar to that noted following intercurrent infections, trauma, or emotional upsets which also are considered to aggravate the course of multiple sclerosis. In their estimation, therefore, the role of allergy may be nonspecific. This view is supported in large part by the observations of Squier, who states: "It has been my belief that inhalant or food allergy is not of primary importance in the etiology of multiple sclerosis. I think it is possible and even probable that a patient who does have multiple sclerosis and also has clinical manifestations of allergy may have an aggravation of symptoms or may have a period of remissions broken by an acute upset. I think, however, that such an untoward reaction is entirely secondary and any influence exerted on the course of the disease probably is the result of general rather than specific effect." Dr. Squier cites case reports, one in particular, where a patient who suffered from ragweed hay fever noted exacerbations of symptoms referable to multiple sclerosis during the hay fever season.

DISCUSSION

In reviewing the data presented by the allergist, immunologist, and pathologist, it must be concluded that allergy may be an important factor in the production of multiple sclerosis and possibly in other demyelinative diseases. The strongest evidence comes from the immunologists, who have produced a variety of encephalopathies which, under controlled conditions, show clinical and pathologic pictures resembling multiple sclerosis. This was done, under conditions favorable to the production of a hypersensitive state, to mature brain tissue, to peripheral nerve containing myelin, or to both. It must be recalled that the results were achieved under unusual circumstances (prolonged courses of injections with antigens of nervous tissue or by use of such antigens with adjuvants) unencountered in clinical experience. While the fact that sensitization to nervous tissue was produced in the experimental animal does not necessarily indicate that the same may be achieved in man, it strongly suggests such a possibility. More evidence for human sensitization is presented
by the occasional case of encephalomyelitis encountered during the Pasteur treat-
ment against rabies, in which phenolized virus is injected along with rabbit
cord.26 Here, too, we have unusual circumstances under which pathologic
changes are produced in the central nervous system by exposure to nervous
tissue. These untoward reactions occur too infrequently to explain the relative
frequency of multiple sclerosis. We can merely conclude that an allergic
mechanism is capable of producing demyelinating disease.

Immunologists have definitely implicated hypersensitivity to nervous tissue,
heterologous or homologous, intimately associated with myelin, in the demyelina-
tive process. The allergists, however, on rather tenuous grounds, have been
looking for sensitivity in other areas—for example, to foods, inhalants, and
molds. There seems to be no rationale for this belief, however, since the
allergists have not shown that the ingestion of food produces anything resembling
multiple sclerosis. It is agreed that the brain can become sensitized and that
common foods such as eggs, wheat, chocolate, milk, and pork can produce a
variety of cerebral disorders, such as retrobulbar neuritis, migraine, Menière’s
syndrome, epilepsy, angioedema, narcolepsy, paralysis, and disturbances in
cerebration.96, 98 These phenomena are encountered rather infrequently in
practice as true expressions of allergy and are reversible. Except for retro-
bulbar neuritis, they can in no way be linked to multiple sclerosis other than
as evidence that the brain can be an allergic shock organ.

The search for clinical evidence to incriminate allergy in multiple sclerosis
is, therefore, vexing because it is doubtful that the relevant allergen would be
of an extrinsic nature (except perhaps the ingestion of nervous tissue in the
form of food). Since the experimental evidence suggests sensitivity to nervous
tissue itself in the demyelinating diseases, it would be more logical to test with
antigens derived from this source rather than from foods, inhalants, etc. As
a corollary, more suspicion should be directed toward sensitivity to ingested
brain and possibly to nervous tissue containing myelin when meat is eaten.
(Fish may not concern us, since its brain tissue fails to produce encephalo-
myelitis experimentally.) Even if such sensitivity were to be demonstrated
clinically, skin testing probably would be negative, since in experimental animals
the presence of complement-fixing antibodies, rather than demonstrable reagins,
has been shown.54, 67

A delayed tuberculin type of reaction to brain tissue possibly has been
demonstrated by Waksman and Morrison.66 Most investigators,33-37, 44, 65 how-
ever, have reported no antibodies capable of passive transfer in either the
serum or washings of lymph nodes or spleen and, therefore, positive skin test
reactions are improbable.

Allergy may play several roles in multiple sclerosis, but probably not as
envisioned by the clinician who equates multiple sclerosis with known allergic
disorders such as asthma, hay fever, etc. The usual allergic diseases, as sug-
gested by Squier119 and by Ehrentheil, Shulman, and Alexander,19 possibly
modify or aggravate the symptoms of multiple sclerosis in those patients who
are unfortunate enough to have both diseases. It is possible that allergy to foods and inhalants may be one of several components which together may produce demyelination; this, however, has not been established.

This view is based upon the observations of Burky,59 who showed that under certain circumstances autosensitivity can be induced by the injection of staphylococcus toxin. Swift and Schultz60, 61 also showed that, although the staphylococcus toxin produced autosensitivity readily, infection and sensitization with nonhemolytic streptococci deliberately induced in the animal, or the induction of allergy to horse serum, evoked the same response. The observations of Rivers and Schwentker39 on the induction of sensitivity to brain tissue by simultaneous injection of such tissue with pig serum or with vaccine virus, or after brain had undergone autolysis, may be another manifestation of the Burky phenomenon. Is it possible that multiple sclerosis is a form of autosensitivity induced in the human being by a pre-existing allergic state such as the Swift-Schultz modification of the Burky phenomenon? The clinical evidence, as yet, is insufficient to associate multiple sclerosis with usual allergic diseases. It is difficult to assume the development of autosensitivity on the basis suggested in the absence of pre-existing and well-recognized allergic states, such as hay fever, asthma, etc.

If we are to consider further the possible role of autosensitivity as an explanation for an allergic mechanism in multiple sclerosis, then it would seem pertinent to consider the role that infection may play in autosensitivity. Hypersensitivity has been shown to be developed after vaccine virus infection, as evinced by revaccination skin reaction; also after lymphogranuloma venereum infection, similarly detected by skin test. Influenza, measles, and herpes simplex viruses have also been implicated in inducing allergic states. Raffell11 indicates, in addition, that “continued investigation will reveal a widespread occurrence of this form of reactivity, probably in all infections caused by viruses.” Nor has multiple sclerosis been associated with recognized viral diseases.

Störtebecker,4 on the other hand, has implicated common bacterial infections with staphylococci, streptococci, and coliform bacilli. He noted that such infections frequently preceded multiple sclerosis and that evidence of infection was suggested by studies of antistreptolysin and antistaphylolysin titers and coli agglutination reactions. Störtebecker considered infection to be a precipitating factor and suggested that bacterial sensitivity possibly is involved in the etiology of multiple sclerosis.

Infection, bacterial or viral, may be implicated in other ways. It can induce autosensitivity (Burky phenomenon), which presumably could affect supposedly nonallergic persons. This may cause damage to myelin either by direct infection of nervous tissue or, indirectly, by toxin action which might release antigens capable of producing autosensitivity (following the pattern suggested by Rivers’ studies with autolysates of brain tissue). Jervis, Ferraro, Kopeloff, and Kopeloff,56 who gave intracerebral injections of brain antigen,
postulated that damaged brain (from trauma induced by the injection) acted as a hapten to produce lesions in areas of the nervous system distant from the sites of injection.

Kolb attempted to induce sensitivity to brain tissue by Burky's method, employing staphylococcus toxin with rabbit brain emulsion. None of the thirty-five rabbits thus treated showed the dermal hypersensitivity to lens protein demonstrated by Burky, nor were precipitins to brain tissue demonstrable. Needling of the brain of sixteen of the rabbits did not cause demyelination.

Despite these negative results, the possible role of autosensitivity in the production of demyelination needs further study. Autosensitivity has been so implicated in the experimental induction of encephalomyelitis that it cannot be ignored. The overwhelming evidence from experimental studies suggests going beyond the question of whether autosensitivity to nervous tissue can produce demyelination to a consideration of whether this phenomenon occurs in man without the use of adjuvants.

Although the Arthus phenomenon, when experimentally produced in the brain, causes damage which might explain, in part, the demyelinative process, the mechanism involved (initial sensitization followed by direct intracerebral inoculation of the antigen) obviously cannot be reproduced clinically. Knowing that sensitization to myelin and to its degenerative products has been induced, we can assume that nervous tissue contains the antigen and, therefore, no intracerebral inoculation is necessary. The antigen awaits a mechanism for its release. The experimentally induced Arthus phenomenon in the brain may be considered a highly exaggerated reaction of what may possibly proceed, clinically and pathologically, at a much slower pace. The type of antibody commonly associated with the Arthus phenomenon is the precipitin which has not been constantly demonstrable, however, in experimentally induced encephalomyelitis. To incriminate the Arthus phenomenon, we must first discover the initial cause of the sensitization. Does it follow infection or damage to the central nervous system from other sources?

Still another allergic mechanism experimentally capable of producing an Arthuslike reaction in the brain is the carotid syndrome of Forssman, which is based on the normal presence of antibodies in the organism, including the central nervous system, and the introduction of specific antigen which would have to be directed particularly toward the brain. For this mechanism there is no clinical parallel or explanation, and its relation to multiple sclerosis is exceedingly doubtful.

As yet there is no one explanation which encompasses all the facets of multiple sclerosis. We must go back, therefore, to the questions raised earlier: Why the difference in incidence associated with climate? Why the exacerbations and remissions? Why does the disease apparently spare the very young and the aged?

Allergic mechanisms cannot explain the first question, since the incidence of the recognized allergic disorders has no relation to climate. If, however,
Störtebecker's theory of the role of infection is valid, it might account for the greater incidence of multiple sclerosis in the northern climates because of the increased incidence of infections with streptococci and staphylococci.

The allergic theory can explain the exacerbation and remission phenomena seen in multiple sclerosis (although there are other possible explanations, such as repeated infections or repeated exposures to anoxic or toxic agents). It might be presumed that it takes a certain period of time for antibody formation, during which interval no symptoms may be present (latency). Then, when sufficient antibody is produced to combine with antigen, an explosive-like reaction occurs (exacerbation), in which the antigen is neutralized by the antibody. This might be followed by a period of remission, during which antigen, liberated as a result of damage to nervous tissue, produces more antibodies and the cycle is repeated and self-perpetuated. This is seen in experimental animals, in which, after an injection with brain tissue, explosive-like reactions seem to occur, with paralysis, blindness, or other symptoms suddenly appearing and then abating and recurring.

Can allergy suggest why multiple sclerosis spares the young and the very old? The young may be spared since it has been demonstrated experimentally that only mature brain is capable of inducing encephalomyelitis. Here it may be added that very young mouse brain also fails to reveal proteolipide and this substance was shown by Olitsky and Tal, and Waksman and associates to be the encephalitogenic moiety of the central nervous tissue. Another possible factor is an incubation period, the exact duration of which cannot be estimated, which may be so long as to spare the very young. Both factors may be involved—time for maturation of the brain and time for development of antibodies. As for the aged, they are known, judging by the clinical diseases of allergy, to have a lessened tendency to hypersensitivity. The possibility of sex hormone influence is not to be overlooked, since multiple sclerosis rarely occurs before puberty and after menopause.

Since experimental evidence indicates that most animals can become sensitized to homologous nervous tissue, and since Rivers and Schwentker have shown that autolyzed nervous tissue may act as an antigen without the use of adjuvants, it is possible, therefore, that any damage to the control nervous system may initiate a self-perpetuating autosensitivity. This postulates the possibility that anoxia, lipolytic action of enzymes, impairment of circulation, infection, or possible allergic cerebral or cerebrovascular reactions even to such common antigens as foods may be the first step in the initiation of a chain reaction involving autosensitivity. One minor reversible allergic reaction, theoretically, might damage the nervous system sufficiently to release antigen capable of inducing a self-perpetuating irreversible allergy—autosensitivity. Assuming the presence of two allergic mechanisms working in sequence, skin testing with the common antigens might, therefore, be of some value only in elucidating the first mechanism. The over-all implication of this theory, therefore, may be, as suggested by Kurland, that multiple sclerosis is not a specific disease but rather a syndrome in which many etiological agents may be concerned and in which
several mechanisms may be involved—an initial damaging of the central nervous system with release of antigen associated with myelin, followed by autosensitization to nervous tissue.

**SUMMARY AND CONCLUSIONS**

Evidence presented by the allergist, immunologist, and pathologist has implicated allergy as a cause for multiple sclerosis. This evidence has been reviewed and the following conclusions seem justified:

1. It is possible to produce in animals a clinical and pathologic condition resembling multiple sclerosis, by injections with extracts or emulsions of homologous or heterologous brain or cord tissue, with or without adjuvants.

2. An allergic mechanism is apparently involved in the experimental production of encephalomyelitis. The antigen, not yet specifically identified, is intimately associated with myelin tissue. Homologous or heterologous nervous tissue may be antigenic. The use of Freund's adjuvants, pertussis vaccine, and selections of strains of animals accelerate the development of experimental encephalomyelitis.

3. The antibodies involved in experimental encephalomyelitis apparently are not capable of passive transfer. Thus far antibrain antibodies have been demonstrated repeatedly by complement fixation, and by precipitation or flocculation against brain antigen. No direct correlation has been shown between the appearance and concentration of these antibodies and the appearance of symptoms in the animal. It may be that the specific antibody still awaits disclosure.

4. Results of skin testing with the antigen from heterologous or homologous nervous tissue are inconclusive.

5. There is no complete correlation between experimentally induced encephalomyelitis and multiple sclerosis, which it resembles. Presumably, they both may be mediated through an allergic mechanism. In experimental encephalomyelitis the allergen is ordinarily extrinsic and is introduced by injection. In multiple sclerosis the mechanism remains obscure. Some evidence suggests autosensitivity, implying the release of a latent intrinsic allergen from brain tissue.

6. The central nervous system is subject to a variety of allergic clinical disorders, traceable, as a rule, to extrinsic allergens and producing, ordinarily, reversible symptoms. In contrast, multiple sclerosis, as suggested by experimental studies, would be an irreversible allergic reaction.

7. Experimentally, allergic reactions within the brain, such as the Arthus phenomenon or the carotid syndrome of Forssman, can produce demyelination, but these have no clinical correlation and indicate merely that allergy in the central nervous system may be a factor in demyelination.

8. The development of specific tissue sensitivity (autosensitivity) as an explanation for multiple sclerosis has been considered. No mechanism for the clinical development of such an autosensitivity has been elucidated, however.
9. Infection (viral and bacterial) has been suggested as a factor in the liberation of the antigen from nervous tissue and the induction of autoimmunity which is self-perpetuating. Possibly, cerebral allergy, due to an extrinsic cause, may initiate a similar mechanism.

10. Demyelination may be produced experimentally by mechanisms other than an antigen-antibody reaction. These include inflammatory reactions, cerebral anoxia, demyelinating enzymes, circulatory disturbances, and metabolic poisons (potassium cyanide, barbiturates). Multiple sclerosis, therefore, may be a syndrome due to a variety of causes, including an intrinsic type of allergy.

11. The pathology of multiple sclerosis is compatible with, but not specific for, an underlying allergic mechanism.

12. Clinical studies of the allergic aspect of multiple sclerosis have been few and inconclusive. An approach limited to a narrow concept of allergy (atopy, involving sensitivity to foods and inhalants, and giving immediate positive skin test reactions) has not been fruitful and is contrary to the evidence presented experimentally, which indicates that demyelination induced on an allergic basis is nonatopic and probably is a form of autoimmunity.

REFERENCES


