Allergy in the Nervous System*

*A Review of the Literature

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In recent years an increasing tendency has been noted in neurologic clinics and meetings to ascribe to allergy an important rôle in the etiology of measles encephalitis, scarlet fever encephalitis, multiple sclerosis and some other nervous diseases. Especially in those forms of encephalitis in which there is loss of myelin, an allergic reaction of some kind has been suspected as the common factor producing the break-up of the myelin sheaths.

CLINICO-PATHOLOGIC STUDIES

Osler,2 in 1889, added the third case of hemiplegia following vaccination, giving credit to Heine1 in 1860 and Wuillamie in 1882 for reporting the first two. In addition, Osler noted that cerebral palsies “may follow any of the specific fevers.” According to Pollet,9 Englemann3 in 1897 noted peripheral neuritis following the use of serum and Gardere and Gangolphe4 noted neuritis during the treatment of a case of tetanus by serum therapy in 1908. Optic neuritis during serum sickness was observed by Mason5 in 1922. May6 in 1923 noted attacks of unnatural somnolence of anaphylactic origin. Sternberg27 also drew attention to seasonal somnolence as a possible form of pollen allergy.

In 1926, Kennedy7 suggested that acute perivascular edema of the brain may play a part in some of the malignant types of insular sclerosis. In 1926, Duke8 suggested that peripheral nerve lesions may result from food allergy. Hurst29 gave credit to Glanzman10 as the first to suggest, in 1927, that allergy might be a factor in causing demyelination of the nervous system.

Kennedy11 in 1928 reported meningeal and focal brain disease causing hemiplegia, aphasia, hemianopsia and severe papilledema during the course of serum sickness. Allergic headache due to food was reported by Eyermann12 in 1930. A case of polyneuritis due to typhoid vaccine was reported by Dr. Geo. H. Hyslop and was described by Kennedy11 in 1928. Typhoid vaccine and staphylococcus vaccine were also reported by Young13 in 1932 to cause peripheral neuritis. Winkelman and Gotten15 reported two cases, one with autopsy findings of encephalomyelitis following the use of serum or vaccine. The autopsied patient had received horse serum seventy-two days previously but had also had symptoms of an upper respiratory infection three weeks later. At autopsy there was inflammation with lymphocytes in the meninges and about blood vessels, especially in the spinal cord, with obliteration of the gray and white matter, congestion and an increase in astrocytes. There also was degeneration with focal necrosis and Gitter cells especially in the cerebrum. Gayle and Bowen16 reported the case of an eighteen year old boy who developed an acute ascending polyneuritis following the administration of typhoid vaccine and condensed the available autopsy reports in the literature suggesting the following fundamental lesions: peripheral neuritis, destruction of anterior horn cells and focal destruction throughout the brain.

A case of encephalomyelitis following vaccination against yellow fever was described by Lhermitte and Fribourg-Blanc16 in 1936. This case came to autopsy fifteen
months after the illness in the nervous system began and so resembled multiple sclerosis clinically and in the pathologic lesions that it strongly suggested to one of us that allergy might be a cause of, or a mechanism in, the production of multiple sclerosis and that allergy might be the common factor underlying the breaking up of myelin in all demyelinating diseases of the nervous system.

In 1936, Kennedy suggested that multiple sclerosis should be studied from the standpoint of allergy. The most interesting case that he reported was that of a physician who was sensitive to pork, suffered from recurring eczema and retrobulbar neuritis with a cerebellar seizure and a slight hemiplegia with homolateral severe thalamic sensations after "inadvertently crossing the pork-line," as the patient himself stated.

In 1938, Pardeel reported a case of violent convulsions due to ingestion of chocolate. Clark described cases of convulsions from foods in 1939.

Finley in 1938 wrote a paper of great interest dealing with encephalitis occurring with vaccination, variola and measles. This paper, coupled with the case of encephalomyelitis described by Lhermitte and Fribourg-Blanc, suggested further the idea that "allergy . . . is . . . an important factor in the pathogenesis of encephalitis associated with vaccination, variola, and measles." Ross in 1939 described allergic response to honeybee stings. Baer and Sulzberger in 1939 studied a group of forty cases of multiple sclerosis from the point of view of atopy. Their comment and conclusions in part follow: "In our opinion and experience the incidence of atopic sensitivity found in this group of cases of multiple sclerosis is little higher than that which is to be expected in any equivalent unselected group studied by the same methods." This, of course, has been the experience of most neurologists but such a conclusion, as they themselves admit, adds nothing for or against the hypothesis that some sort of antibody-antigen reaction may be the factor responsible for the initial breakup of myelin in this disease.

Winkelman and Moore in 1941 reviewed the literature on "Allergy and Nervous Diseases" and showed the increasing importance placed on allergy in the etiology of many nervous and mental diseases. They presented cases of migraine, epilepsy and focal lesions of the brain in which the clinical picture has been best explained on an allergic basis. Rich in 1942 discussed the rôle of hypersensitivity in periarteritis nodosa. Scarletinal encephalomyelitis has been described by Winkelman. One case showed a diffuse inflammation with perivascular necrosis which he interpreted as possibly due to a virus which was dormant in the central nervous system and which was stimulated by the streptococcal infection. Ferraro reported two other cases and interpreted the perivascular inflammation with microglia proliferation and vascular changes as an allergic response.

Hurst in 1944 wrote a comprehensive review of demyelinating diseases of the nervous system but seemed to doubt that a relation exists between allergy or anaphylaxis and demyelination. In summary, he said in part, " . . . The known antecedents of demyelination and the means by which it may be produced experimentally are very diverse, and appear to include no common determinant more narrowly specific than injury to the white matter of one type or other . . . . Demyelination appears to be the response of the white matter to injuries short of those immediately lethal to the tissues." Cooke has recently summarized most of the knowledge pertaining to allergic neuropathies.

Although the numbers involved are small, the development of a "multiple-sclerosis-like" disease in four of seven workers engaged in research on the disease "swayback" in lambs, hitherto regarded generally as due to copper deficiency, is very suggestive that there is some common factor between the two diseases. Whether this factor is a virus, a toxin, a deficiency or an antigen is, of course, not known.
STUDIES ON EXPERIMENTAL ANIMALS

The experimental analysis of allergy in the nervous system may conveniently be divided into two parts: (1) encephalomyelitis produced by vaccination or immunization with nervous tissue and (2) diseases of the nervous system produced by other mechanisms, such as the Arthus phenomenon and passive immunization with anti-brain or Forssman antibodies.

Hurst in 1932 reviewed the literature concerning paralytic accidents occurring in man following anti-rabies therapy and in experimental animals following injections of brain. Numerous experiments had been performed beginning in 1898 using rabbits, rats and dogs which were given injections of aqueous suspensions of ox, rabbit, human and monkey brain and various types of anti-rabies vaccine. Paralyses were relatively infrequent but the best of these experiments provide interesting data, notably the reports by Miyagawa and Ishii, Koritschoner and Schweinburg, Stuart and Krikorian and Hurst. In general, the pathologic picture was constant, varying from nothing to explain the paralysis to moderate perivascular inflammation throughout the brain and leptomeninges. Additional changes in neurones, myelin sheaths, axis cylinders and glia were described by Miyagawa and Ishii but the lack of correlation of so many changes prohibits adequate interpretation of their findings. However, concerning the nature of the antigen, it was found that rabies virus or toxin was not necessary but that the active paralyzing agent was present in aqueous suspensions of normal brain.

Although the opinions of various workers analyzing the experimental and clinical aspects of the problem differed somewhat, it was also found that the antigen probably could be partially destroyed by phenol and heat. Concerning the mode of action of the antigen, it is also of interest to note the following hypotheses: There was an inherent predisposition of the individual to the disease; the injections of brain were not directly toxic but were one of several means of activating some unidentified latent factor or factors.

Rivers and Schwentker extended the experiments of Rivers, Sprunt and Berry by producing paralysis in monkeys more regularly with more prolonged courses of injection and by finding demyelinization on microscopic examination of the central nervous system. Ferraro and Jervis repeated these experiments almost exactly and thus established the disease on more precise neuropathologic grounds. Concerning the antigen, it is to be noted that its nature had been complicated by the addition of an alcoholic extract to the aqueous suspension. Concerning the mode of action of the antigen, only the allergic theory had come into ascendency. Thus, there was a pause important in consolidating the findings into a coherent picture although at the expense of a complicated and prolonged technic.

By no means have all experiments along these lines been successful. Hurst injected suspensions of human brain and alcoholic extracts of rabbit brain into monkeys and suspensions of pig brain into sheep and lambs repeatedly over a period of one year without producing any disease. Innes and Shearer injected suspensions of rabbit brain into sheep and lambs three times a week for one year also without producing any disease.

More recently Morgan, and independently Kabat, Wolf, and Bezer, using special adjuvants have produced paralyses in monkeys regularly and rapidly following a single or only a few injections. Several antigens have been used, in general the effectiveness paralleling the myelin content, except for peripheral nerves which failed to produce the disease.

There has been much speculation as to what portion of brain is the antigenic material responsible for allergic encephalomyelitis. From the evidence at hand, it is suggested that the following materials extractable from brain are antigenic (really hapten in nature in that they react with specific antibodies but do not stimulate the
production of antibodies unless combined with a suitable adjuvant):

1. Purified but as yet unidentified material soluble in cold alcohol.\(^{37,39,40,44}\)

2. "Protagon," soluble in hot alcohol but insoluble in cold alcohol;\(^ {44}\) composed of a mixture of sphingomyelin and galactolipins.\(^ {45}\)

3. "Sphingomyelin."\(^ {44}\)

4. "Neurokeratin," soluble in water but insoluble in all common solvents, and present in bacterial cultures on brain-broth.\(^ {52}\)

5. Material present in aqueous suspensions of gray matter but as yet not further identified.\(^ {49,44}\)

There is, unfortunately, no evidence that allergic encephalomyelitis is caused by any of these five fractions, although the "alcohol-soluble hapten," "protagon" and "neurokeratin" are more concentrated in the white than in the gray matter as apparently is the paralytic antigen.

Some experiments on allergy in the nervous system have utilized the Arthus phenomenon in which the injection of antigen into sensitized animals intrathecally produced an acute meningitis,\(^ {36,42}\) or intracerebrally produced a focal hemorrhagic necrosis\(^ {35,43,46,50}\) and disseminated secondary foci of inflammation and demyelination.\(^ {51}\) Alexander and Campbell\(^ {46}\) examined the local reaction in guinea pigs and observed a large central zone of hemorrhagic necrosis without patent blood vessels. This was infiltrated with neutrophiles, microglia and oligodendroglia and later by astrocytes. It was surrounded by an anemic zone although the blood vessels were patent. They interpreted their findings as demonstrating a primarily vascular hypersensitivity, possibly even primarily endothelial, with secondary thrombosis of vessels. They believed with Gerlach that there was a quantitative difference only between their allergic and control animals; and they disagreed with Rössle, who thought that there were many eosinophiles as well as the quantitative difference. Jervis, Ferraro, Kopeloff and Kopeloff\(^ {61}\) observed not only a local necrosis typical of an Arthus phenomenon but also scattered cellular reactions with giant cells and demyelinization at other points throughout the brain. These, they believed, were indicative of a secondary allergic response, perhaps to the broken-down brain tissue which then became antigenic. These secondary reactions consisted of demyelinization, a perivascular inflammatory reaction with giant cells, hemorrhage, thrombosis and fibrosis of blood vessels, necrosis and gliosis.

A type of passive immunization was used by Hurst and Atkinson\(^ {29}\) who injected sheep or rabbit anti-pig-brain-serum intrathecally into pigs to produce a widespread meningitis, choroiditis and encephalitis but no demyelinization. Hurst\(^ {29}\) injected rabbit or goat anti-monkey-brain-serum intrathecally into monkeys with the same results. Jervis\(^ {21}\) injected Forssman antibodies (rabbit anti-guinea-pig-kidney-serum or anti-sheep-red-blood-cells-serum) into the carotid artery of guinea pigs and observed ataxia and nystagmus. Pathologically, the blood vessels were dilated and congested and there were hemorrhages. There was a diffuse degeneration of neurones and a mild glial reaction; moreover, there were disseminated foci of softening consisting of areas of demyelinization with compound granular corpuscles. There were no giant cells and blood cells were thought to be more rare than in the other types of anaphylactic experiments using brain vaccines. Jervis thought that the Forssman antibody passed through an impaired blood-brain barrier. One would expect guinea pig tissue, including brain (although it apparently has not been tested\(^ {37}\)), to contain Forssman antigen with which the injected antibody might react.

Ferraro\(^ {56}\) discussed the pathology of demyelinating diseases, correlating studies on man and experimental animals, as an allergic reaction of the brain with emphasis on the vascular changes. The vascular reaction consisted of a perivascular exudate which he stated to be always present in acute cases and almost always in chronic cases, which contained lymphocytes and
Gitter cells and other elements, and which itself varied in intensity but was not related to the intensity of the demyelinization. The blood vessels were also thickened and frequently thrombosed and there were areas of necrosis and hemorrhages occasionally in the acute cases. Ferraro believed that the term “reactive allergic inflammation” should be added as a new term to explain this vascular reaction. He thought that it coordinated Putnam's views that the thrombi might be allergic or that there might be an allergic instability of the blood-clotting mechanisms which would also produce a vascular type of lesion. He also stated that giant cells up to now had been underemphasized and that these were sometimes glioblastic tumor nodules such as Scherer described. Ferraro thought that the antigen might be derived from an infectious agent, as either an exo- or endo-toxin, or from products of metabolism and diet; that there might be precipitating factors such as fatigue, hyperventilation, trauma, heat, cold or endocrine disturbances; and that later the antigen might be developed from the gray or white matter of the brain. The difficulties in the past, Ferraro believed, have been (1) a tendency to create new clinical or pathologic diseases easily, (2) a lack of discrimination between the chronic and acute pathologic changes, (3) a tendency to be dogmatic in labelling a disease as inflammatory or degenerative and (4) a lack of experimental support for the establishment of a link between the acute and chronic diseases on the basis of a vascular reaction. Parenthetically, we might add that not only do these objections still remain valid, but other objections are at hand, namely, the assumption that processes which look alike pathologically are otherwise alike and the disregarding of important clinical data in the tendency to lump all the demyelinating diseases together. Ferraro believed that hemorrhages and neutrophiles were seen only in acute cases and that the processes of edema, lymph stasis, necrosis, lymphocytic, histiocytic and giant-cell reactions and repair were fundamental to the disease process. He agreed with Klinge that the time-dose relationship was very important, a large dose producing a typical Arthus phenomenon with a hemorrhagic phlegmonous reaction, whereas smaller repeated doses over a period of weeks produced leukocytic and mononuclear inflammation or repeated over several months produced monocytic and histiocytic and giant-cell reaction without neutrophiles.

By contrast, Hurst, summarizing his experiments on demyelinization produced by cyanide, azide or other chemicals, observed that “nevertheless, demyelination must be mediated by enzymatic processes and must ultimately be explained on a biochemical basis.” Later, however, in commenting upon his own experiments with cyanide, Hurst said: “Massive single or repeated doses usually damaged chiefly the cerebral or cerebellar cortex. Repeated (less often single), rather smaller doses led to bilateral necrosis in the basal ganglia, especially the globus pallidus, or in the cerebral white matter or in both. In a remarkable manner, necrosis often developed suddenly or simultaneously over wide tracts of the white matter after a dose of the poison tolerated previously on many occasions.” Again, concerning azide, he stated: “Necrosis in the optic connections followed single or repeated large doses leading to lengthy unconsciousness or developed abruptly from summation of the effects of many small doses each insufficient to evoke marked nervous symptoms. . . . These sudden marked effects could not be explained on the basis of mere accumulation of the poison in the system; it seemed probable that repeated small insults brought the nervous tissues to a state in which a further small dose of the poison, one normally tolerated, produced the most serious consequences.” We believe that these statements, especially the last, virtually define the term “hypersensitivity” or “allergy.”

SUMMARY

Clinically, allergic manifestations in the nervous system may be produced by the
ingestion of food, inhalation of pollen, injection of serum or vaccination against bacterial or virus diseases or as complications of various diseases. These manifestations include headache, somnolence, convulsions and signs of focal or general central or peripheral nervous system disease. Pathologically, peripheral neuritis, myelitis, meningitis and encephalitis may be found, sometimes with disseminated foci of demyelination or periarteritis nodosa. Whether classical chronic multiple sclerosis falls into this group is not known.

Experimentally, a meningoencephalomyelitis, sometimes with disseminated foci of demyelination, can be produced in ways strongly suggestive that allergy is important: by immunization or vaccination with a presumably normal brain, the antigen apparently being concentrated in the white matter of the central nervous system; by the intracerebral injection of antigen into animals immunized against the antigen, a local hemorrhagic necrosis similar to the Arthus phenomenon also occurring and by the injection of Forssman antibodies into the carotid artery of guinea pigs. Although this condition is comparable to acute disseminated encephalomyelitis or acute multiple sclerosis in human beings, there is no evidence that a picture comparable to classical chronic multiple sclerosis has been reproduced experimentally.

REFERENCES

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