Meetings

Demyelinating Diseases

Current research on demyelination was the topic of a recent symposium sponsored by the New York Academy of Sciences and the National Multiple Sclerosis Society, 20–22 January. Scientists from a wide variety of disciplines, ranging in scope from x-ray diffraction and organic chemistry to epidemiology, summarized the most recent advances in biological research directed toward a greater understanding of demyelinative lesions in the central nervous system.

From x-ray diffraction and electron microscopic data, Finean (Birmingham, England) presented his theory of the structure of myelin lipids which was then discussed from the stereochemical viewpoint by Vandenheuvel (Ottawa). He supported the proposal that a bimolecular complex (cholesterol plus polar lipid) was the structural unit of myelin lipid. Phospholipid, sphingomyelin, and cerebroside are considered to be interchangeable in the postulated complex.

Only recently have methods been developed which have provided pure myelin fractions for analysis. Data on the chemical constitution of purified myelin that were presented by Norton (New York City) and Thompson (Bethesda) emphasized important differences between this tissue fraction and proteolipid preparations from white matter. These differences probably stem from the fact that chloroform-methanol extractives are derived from other membrane structures in white matter as well as myelin. Lees (Hanover, N.H.) and Wolfgram (Los Angeles) further emphasized the complexity of proteolipids obtained from whole white matter by chloroform-methanol extraction. Metabolic studies on myelin that involve radioactive tracers in normal animals were discussed by Davison (London).

After a résumé of morphological and chemical data on myelin, the emphasis of the meeting shifted to the role played by this structure in autoimmune phenomena in the nervous system. Experimental allergic encephalomyelitis is readily produced in many animals by a single injection of central nervous system and Freund's "complete" adjuvants (water-in-oil emulsion with heat-killed mycobacteria). Papers presented by Kies (Bethesda), Nakao and Roboz-Einstein (San Francisco), Caspary (Newcastle, England), Honegger (Basel), Kibler (Atlanta), and Wolfgram on the basic proteins of myelin, white matter, and whole tissue provided convincing evidence that the constituent of the nervous system responsible for the induction of experimental allergic encephalomyelitis is a basic protein of low molecular weight derived from myelin, and that encephalitogenicity is related to a specific peptide group rather than to the intact protein molecule. Basic protein preparations from the central nervous system of human beings, guinea pigs, cows, rabbits, and rats are effective in inducing encephalomyelitis in the guinea pig, rabbit, and rat.

Why is a specific fraction of the central nervous system required to produce this disease and what is the role of Freund's adjuvants? As one approach to these fundamental questions, Levine (Jersey City) compared several strains of rats for their susceptibility to encephalomyelitis when nerve tissue was used with or without various adjuvant or enhancing techniques. Within a given strain of rats, the species source of the nerve tissue determines the degree of response; certain heterologous (guinea pig or paca) preparations are more effective than homologous (rat) or other heterologous (human, canine, bovine, or other rodents) preparations.

Stone and Lerner (Bethesda) reported that baby guinea pigs are less susceptible to encephalomyelitis than are the adults of the same strain. The reaction noted in baby guinea pigs was interpreted as being a qualitatively "different" type of encephalitis; it resembled more closely multiple sclerosis. This interpretation was not accepted by other neuropathologists who believe that the differences were merely quantitative; the immature animals are incapable of the same degree of sensitization as adults. Support for this was provided by Stone and Lerner, who noted that the usual form of acute allergic encephalomyelitis could be induced in baby guinea pigs by the passive transfer of fully sensitized adult lymphoid cells.

In his remarks on pathogenesis of experimental allergic encephalomyelitis, Alvord (Seattle) proposed the theory that development of the disease is determined by the balance between specific inductive and protective mechanisms. Both mechanisms appear to involve delayed-type hypersensitivity and circulating antibodies, and the latter at least may require complement. The participation of serum antibody in protective mechanisms was discussed by Paterson (New York) who has demonstrated suppression of disease in rats by passive transfer of encephalomyelitis serum. In seeming contrast to this protective effect, serum containing circulating antibody to whole brain has been shown to induce demyelination of nervous system neurones in tissue culture (Bornstein, New York).

Evidence for the participation of delayed hypersensitivity in encephalomyelitis was presented by Rauch (Palo Alto) who demonstrated the uptake of encephalitogen by specifically sensitized cells. Shaw (Seattle) reported excellent correlation between a delayed skin reaction to homologous encephalitogen and onset of the disease in guinea pigs. Winkler (Boston) observed that demyelination in peripheral nerve culture was induced by sensitized cells obtained soon after sensitization of the host. That sensitized cells were an inadequate explanation of the pathogenesis of encephalomyelitis in mice was discussed by Lee (New York City). Unfortunately all attempts to identify the missing factor in the mouse failed. In the discussion Stone emphasized that sensitized cells were quite sufficient to cause this disease after passive transfer in the guinea pig.

The possible role of complement in experimental demyelination as well as

in the human disease, multiple sclerosis, was discussed by Pette and Kuwert (Hamburg).

Antibodies to the alcohol-soluble brain hapten were described by Niedieck (Hamburg). The hapten itself is cerebroside but requires cholesterol and lecithin as auxiliary factors. Both precipitating (7S γ_2) and complement-fixing (19S γ_1) antibodies were demonstrated. The antibodies paralleled the development of encephalomyelitis induced with whole tissue, but could hardly be the critical antibody since no disease resulted when rabbits were sensitized to cerebroside.

In spite of the fact that experimental studies cannot be translated directly to clinical situations, an optimistic atmosphere was created by papers on specific immunologic prevention, suppression, and therapy of encephalomyelitis (Alvord), and suppression and treatment of this disease with antimetabolites (Brandriss, Bethesda) and steroids (Kibler). The paper presented by Bunge (New York City) on the possibility of remyelination in the central nervous system after certain types of experimentally induced demyelination is also pertinent to the possible reversal of demyelinating processes in human beings.

Although experimental allergic encephalomyelitis is interesting in itself as one of the most extensively studied examples of autoimmune pathology, the fact remains that it is the closest experimental model for the greater neurological enigma, multiple sclerosis. With the recent development of skin tests and serologic reactions to the specific encephalitogenic proteins of the myelin of the central nervous system, it is anticipated that critical tests will soon be made of the hypothesis that encephalomyelitis and multiple sclerosis are in fact related.

In addition to the large amount of new data on the experimental disease, additional information was also provided on the etiology and treatment of multiple sclerosis. Yokoyama (Bethesda) reported β_{2A}- and three new components of γ_2-globulins in the CSF in multiple sclerosis, but the antigen to which these antibodies react remains unknown. Chemical studies on tissue obtained at autopsy from the central nervous system were described by two groups of investigators. Barron (Hines, Illinois) reported that the esterase profile of multiple sclerosis plaques differed from that of normal white matter. Gerstl (Palo Alto) described a chemical abnormality in the lipids of grossly normal samples of white matter from cases of multiple sclerosis and its ultracentrifugally separated myelin. These reports, if substantiated in a large number of cases, should give investigators important leads for metabolic studies. In this regard it is of interest that Smith (Palo Alto) demonstrated an increased uptake of glucose and acetate in certain brain lipids in rats developing encephalomyelitis. The increase coincided in time with clinical and histologic evidence of the disease (12 to 14 days) but persisted into the recovery phase (22 to 26 days).

The status of clinical investigations in multiple sclerosis was reviewed by Scheinberg (New York) as an introduction to the final session of the symposium. Problems that still remain are accurate diagnosis (Poser, Kansas City) and assessment of the patient's physical condition during the variable disease course (Tourtellotte, Ann Arbor). The relation of such problems to experimental trials of therapy was discussed by Schumacher (Burlington, Vt.). Bauer (Göttingen) reviewed the long-term prognosis of 1200 multiple sclerosis patients on the basis of their capacity to carry out remunerative work. Of the patients studied for 20 years or longer, 30 percent were still gainfully employed.

The search for new etiologic leads has continued without much success. A slightly higher titer of measles antibodies has been reported by several laboratories, but Sibley and Foley (Cleveland) could find no correlation between relapses of multiple sclerosis and infections by measles or any of several other viruses and bacteria.

The extent of interest in research on demyelination was evident from the papers presented at the symposium and from the size of the audience. Although the scheduled program left little time for discussion, the combination of experimental and clinical papers in a single large meeting brought together scientists of exceedingly varied research interests and provided opportunity for much discussion after meeting hours.

The symposium proceedings will be published by the New York Academy of Sciences. This publication will complement a similar monograph soon to appear in the *Zeitschrift für Immunitätsforschung*, which resulted from a colloquium on "Experimental Contributions to the Pathogenesis of the Demyelinating Diseases" held in August 1962, at the Institute for Research on Poliomyelitis and Multiple Sclerosis, Hamburg, Germany.

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Cave Ecology

The special interest of the ecologist for life in caves lies not so much in the fact that many obligate cavernicoles (troglobites) are eyeless and depigmented, but rather in the comparative simplicity of the cave community. Relatively few metazoans and a limited selection of microorganisms are able to adapt to an aphotic environment in which food must be imported from the surface or manufactured *in situ* by chemosynthetic autotrophs (sulfur and iron bacteria). The deep cave is an essentially isothermal environment in which food and vapor pressure deficit (for terrestrial cavernicoles, which are usually stenohygrobic) become the principal limiting factors.

Cave ecology was the main theme of a symposium held at the Cleveland meeting of the AAAS on 27 December 1963. The fact that the majority of the participants dealt directly with, or referred frequently to, the Mammoth Cave region of Kentucky is indicative of the significance which this major karst region has assumed in North American biospeleology. There are two reasons for this. (i) The Mammoth Cave fauna is exceptionally rich, incorporating elements from at least four cave regions of the Interior Low plateaus (Thomas Barr, University of Kentucky). (ii) About 90 percent of the species of the fauna have been described. A conservatively estimated 50 percent of the cavernicoles of the United States remain taxonomically unknown, thus complicating or delaying ecological research in most other cave systems.

Biological research in caves of the