- Davison, A. N., Cuzner, M. L., Banik, N. L., and Oxberry, J. M. (1966). *Nature (Lond.)*, **212**, 1373.
- Friede, R. L. (1961). *J. Neurochem.*, **8**, 17.
- Giacobini, E. (1962). *Biochem. Pharmacol.*, **9**, 155.
- Lucy, J. A. (1968). *Brit. med. Bull.*, **24**, 127.
- Maturana, H. R. (1960). *J. biophys. biochem. Cytol.*, **7**, 107.
- Mickel, H. S., and Gilles, F. H. (1968). *J. Neuropath. exp. Neurol.*, **1**, 146.
- Norton, W. T., Davison, A. N., and Spohn, M. (1968). In preparation.
- Peters, A. (1960). *J. biophys. biochem. Cytol.*, **8**, 431.
- Rose, S. P. R. (1968). In *Applied Neurochemistry*, p. 332. Edited by A. N. Davison and J. Dobbing. Blackwell: Oxford.

HISTOCHEMISTRY OF NEUROGLIA AND MYELIN BREAKDOWN

C. W. M. ADAMS and J. F. HALLPIKE (London) In recent years much interest had centred on the rôle of astrocytes in fluid transport in the brain, in their response to trauma, and in their rôle in repair processes. Although oligodendroglia might share some of these functions—and might possibly be one of the precursor cells of astrocytes—their main rôles seemed to be to support symbiotically the neuronal cell-body and to form as well as to maintain CNS myelin.

During CNS myelination, Friede (1962) had demonstrated a marked increase in the oligodendroglial population and in enzyme activity. These observations together with well-substantiated ultrastructural studies showed that the oligodendrocyte was the major cell involved in myelin formation. The question considered here was what happened to the oligodendroglia in demyelinating disease.

Lumsden (1951) reported that the oligodendroglia abruptly disappeared at the edge of plaques of multiple sclerosis. In their experience, however, this situation only applied in those plaques that they regarded as inactive (Ibrahim and Adams, 1963)—and even then a few oligodendroglia persisted in the plaque. Around those plaques that they believed to be active, the oligodendroglia proliferated, hypertrophied, and showed increased oxidative activity; such plaques appeared to be active as judged by the presence of lipid-laden microglia within them and, in occasional cases, as indicated by the clinical history.

It had been suggested that this activity at the edge of certain multiple sclerosis plaques represented a remyelinating process. However, they did not believe this interpretation was correct, because oligodendroglia proliferated and developed increased oxidative activity both in the prodromal stages of experimental cyanide encephalopathy and in very early multiple sclerosis plaques (Ibrahim and Adams, 1965).

In recent further studies of five cases of multiple sclerosis, they had found that proteolytic activity (pH 3.6 and pH 7.4) increased at the edge of active plaques. Trypsin, pepsin, and elastase digested the basic (trypanophilic) protein of myelin and released myelin lipids *in vitro* (Tuqan and Adams, 1961; Adams and Bayliss, 1968). Moreover, they had found that extracts of degenerating peripheral nerves could induce similar changes in CNS myelin—namely, removal of trypanophilic basic protein and acceleration of myelin-bud formation.

Proteolytic activity increased in the early phase of Wallerian degeneration in peripheral nerves. Thus, the

initial disruption of the sheath in the primary stage of myelin breakdown—where Rossiter (Johnson, McNabb, and Rossiter, 1950) had shown that the myelin lipids remained chemically normal—could be attributed to digestion of the myelin basic-protein. In fact, trypanophilic basic protein was abruptly lost at the edge of the multiple sclerosis plaque and, moreover, substantially decreased during the first few days of Wallerian degeneration in the peripheral nerve. Conversely, chemical degradation of the lipids and the formation of Marchi-positive esterified cholesterol were delayed and proceeded in the second stage of myelin breakdown. Therefore, the myelin basic-protein seemed to be a particularly vulnerable part of the myelin sheath in that it was first attacked during myelin-breakdown.

An outstanding problem was where these proteolytic enzymes came from. It would not be unreasonable to suppose that they were derived from lysosomes, as was suggested by the early increase in acid phosphatase in Wallerian degeneration. However, myelin was compacted cell-surface membrane and itself contained leucin aminopeptidase (L-leucyl- β -naphthylamidase) as well as a neutral protease. At present they were further investigating the origin of proteolytic enzymes by analysis of subcellular fractions from both normal and degenerating peripheral nerves.

REFERENCES

- Adams, C. W. M., and Bayliss, O. B. (1968). *J. Histochem. Cytochem.*, **16**, 110.
- Friede, R. L. (1962). *J. Neuropath. exp. Neurol.*, **21**, 645.
- Ibrahim, M. Z. M., and Adams, C. W. M. (1963). *J. Neurol. Neurosurg. Psychiat.*, **26**, 101.
- , — (1965). *J. Path. Bact.*, **90**, 239.
- Johnson, A. C., McNabb, A. R., and Rossiter, R. J. (1950). *Arch. Neurol. Psychiat. (Chic.)*, **64**, 105.
- Lumsden, C. E. (1951). *Brit. med. J.*, **1**, 1035.
- Tuqan, N. A., and Adams, C. W. M. (1961). *J. Histochem. Cytochem.*, **6**, 327.

IMMUNOLOGICAL FACTORS IN EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS AND MULTIPLE SCLEROSIS AS REVEALED BY CULTURES OF MAMMALIAN NERVE TISSUE

MURRAY B. BORNSTEIN (New York) Organized cultures of mammalian central nerve tissues characteristically developed and maintained myelin and polysynaptic relationships. These cultures were used as a model system to examine the blood of animals with experimental allergic encephalomyelitis (EAE) and patients with multiple sclerosis (MS) for the presence of immunological factors which might be involved in these disease processes. The serum of EAE-affected animals and a majority of MS patients experiencing an active phase of their illness contained factors which produced a characteristic pattern of demyelination in the cultured CNS tissues. Their potency had been demonstrated to be complement dependent in both the human and the animal serum. Those in the animal serum had been shown to be localized in the 7-S component of the gamma globulins and to be removed by exposure to brain tissue, but not by liver, kidney, or red blood cells. Immunofluorescence examinations of exposed cultures revealed the globulins concentrated on the neuroglial cell membranes and the

myelin sheaths which in culture, as in the animal, were composed of modified neuroglial cell membrane. On removal of the EAE or MS serum, cultures of mammalian CNS tissue were observed to remyelinate.

In addition to those factors directed against the neuroglial cell membrane, the tissue culture model system had also revealed the presence of others which might be directed against the neuronal cell membrane. The evidence consisted of a rapid decrease and finally abolition of bioelectric activity representative of the propagation and transmission of the nervous impulse. In polysynaptic neuronal networks, the block in transmission and the decrease in propagation was also rapidly reversible once the offending serum was removed from the tissue culture environment. The action of these factors was also dependent upon the presence of complement.

Recently, a series of EAE-inoculated animals had been killed serially from day 3 to day 16 after their exposure and their serum and lymph node cells tested for demyelinating activity. Both possessed the ability to demyelinate cultures beginning at approximately the fourth day after exposure to the inoculum.

These findings were discussed in relationship to the experimentally produced disorder and the naturally occurring disease.

PATHOGENESIS OF MULTIPLE SCLEROSIS

E. J. FIELD (Newcastle upon Tyne) The idea that MS might be infective in origin went back to Pierre Marie (1884) and received powerful impetus from the report by Campbell, Daniel, Porter, Russell, Smith, and Innes (1947) that four of seven research workers investigating swayback of lambs had developed multiple sclerosis. While attempts to transfer the disease had been unsuccessful, the work of Sigurdsson and his school in Iceland (1954) showed that, among sheep at least, some transmissible diseases, such as visna, maedi, and rida might take as long as a quarter or a third of an animal's lifetime to appear. With this possibility in mind, transmission attempts had been made both in sheep (Palsson, Pattison, and Field, 1965) and mice (Field, 1966) over prolonged periods and involving blind passage. Recently a more rapid passage coupled with whole body radiation of the

final recipient had succeeded in producing a neurological illness in mice from kuru material (Field, 1968) and the same technique had been successful in one further case of MS. In all these instances the disease known as scrapie had emerged. A fundamental feature in its pathogenesis was early and marked hypertrophy of astrocytes. The same had been reported by Charcot (1876), Müller (1904), Anton and Wohlwill (1912), and Jakob (1967) to be the earliest change in multiple sclerosis. The hypothesis might be put forward that the pathogenetic mechanism at work in kuru, scrapie, and Jacob-Creutzfeldt disease which leads to marked astroglial hypertrophy (with the character of a benign neoplasia) was also operative in multiple sclerosis. In the latter the process was focalized around small veins and when it went on to extreme degree resulted in the well-known, attention-drawing plaques so readily demonstrable; while in the other conditions mentioned the process was more diffuse. The seemingly normal parts of the brain might be more rewarding to study in MS than actual lesions (cf. Herpes encephalitis).

The suggestion that a 'slow' infection (with no pre-suppositions as to the nature of the agent, cf. Adams and Field, 1968) might be operative in multiple sclerosis did not preclude some other mechanism also being at work—for example, an immunological one—which might account for the continued recurrent activity of the disease in some cases.

REFERENCES

- Adams, D. H., and Field, E. J. (1968). *Lancet*, 2, 714.
- Anton, G., and Wohlwill, R. (1912). *Z. ges. Neurol. Psychiat.*, 12, 1.
- Campbell, A. M. G., Daniel, P., Porter, R. J., Russell, W. R., Smith, H. V., and Innes, J. R. M. (1947). *Brain*, 70, 50.
- Charcot, J. M. (1876). *Maladies du Système Nerveux*, p. 239. Delahaye, Paris.
- Field, E. J. (1966). *Brit. med. J.*, 2, 564.
- (1968). *Lancet*, 1, 981.
- Jakob, A. (1967). *Symposium on Multiple Sclerosis*, held at Locarno. (Auspices German Multiple Sclerosis Society.)
- Marie, P. (1884). *Progr. méd. (Paris)*, 12, 287; 305; 349, and 365.
- Müller, E. (1904). *Die Multiple Sklerose des Gehirns und Rückenmarks*. Fischer: Jena.
- Palsson, P. A., Pattison, I. H., and Field, E. J. (1965). *Slow Latent and Temperate Virus Infections*, p. 49. Edited by D. C. Gajdusek, C. J. Gibbs, Jr., and M. Alpers. U.S. Government Printing Offices: Washington, D.C.
- Sigurdsson, B. (1954). *Brit. vet. J.*, 110 (Nos. 7, 8, 9), 255, 307, and 341.