The Nature of Multiple Sclerosis

The Nature of Multiple Sclerosis

Papers by
Paavo Riekkinen, Roy L. Swank, John F. Simpson, John F. Kurtzke, Geoffrey Dean, Mariella Fischer-Williams, Hans Link, E. A. Caspary, Oldrich J. Kolar, Bengt Kallen, Helge Hedberg, E. J. Field et al.

MSS Information Corporation
655 Madison Avenue, New York, N.Y. 10021

Library of Congress Cataloging in Publication Data
Main entry under title:

The Nature of multiple sclerosis.

CONTENTS: Riekkinen [and others] Studies on the pathogenesis of multiple sclerosis: basic proteins in the myelin and white matter of multiple sclerosis, subacute sclerosing panencephalitis and postvaccinal leucoencephalitis. [etc.]

1. Multiple sclerosis. I. Riekkinen, Paavo.
[DNLM: 1. Multiple sclerosis--Collected works.
WL 360 N285 1973]
RC377.N38 1972 616.8'34'008 72-13055
ISBN 0-8422-7070-1

TABLE OF CONTENTS

The Nature of Multiple Sclerosis

Papers by
Paavo Riekkinen, Roy L. Swank, John F. Simpson, John F. Kurtzke, Geoffrey Dean, Mariella Fischer-Williams, Hans Link, E. A. Caspary, Oldrich J. Kolar, Bengt Kallen, Helge Hedberg, E. J. Field et al.

MSS Information Corporation
655 Madison Avenue, New York, N. Y. 10021

Library of Congress Cataloging in Publication Data
Main entry under title:

The Nature of multiple sclerosis.

CONTENTS: Riekkinen [and others] Studies on the pathogenesis of multiple sclerosis: basic proteins in the myelin and white matter of multiple sclerosis, subacute sclerosing panencephalitis and postvaccinal leucoencephalitis. [etc.]

1. Multiple sclerosis. I. Riekkinen, Paavo.
[DNLM: 1. Multiple sclerosis--Collected works.
WL 360 N285 1973]
RC377.N38 1972 616.8'34'008 72-13055
ISBN 0-8422-7070-1

TABLE OF CONTENTS

CREDITS AND ACKNOWLEDGMENTS

Caspary, E. A.; and M. E. Chambers, "Antibody to Encephalitogenic Basic Protein in Multiple Sclerosis and other Neurological Diseases as Measured by Immune Adherence," *European Neurology*, 1970, 3:206-210.

Caspary, E. A.; and E. J. Field, "Sensitization of Blood Lymphocytes to Possible Antigens in Neurological Disease," *European Neurology*, 1970, 4:257-266.

Dean, Geoffrey, "Multiple Sclerosis in Migrants to South Africa," *Israel Journal of Medical Sciences*, 1971, 7:1568.

Field, E. J.: and E. A. Caspary, "Lymphocyte Response Depressive Factor in Multiple Sclerosis," *British Medical Journal*, 1971, 4:529-532.

Fischer-Williams, Mariella; and Ronald C. Roberts, "Cerebrospinal Fluid Proteins and Serum Immunoglobulins: Occurrence in Multiple Sclerosis and Other Neurological Diseases: Comparative Measurement of y-Globulin and the IgG Class," *Archives of Neurology*, 1971, 25:526-534.

Hedberg, Helge; B. Kallen; B. Low; and O. Nilsson, "Impaired Mixed Leucocyte Reaction in Some Different Diseases, Notably Multiple Sclerosis and Various Arthritides," *Clinical and Experimental Immunology*, 1971, 9:201-217.

Kallen, Bengt; and Olle Nilsson, "Mixed Leucocyte Reaction in Multiple Sclerosis," *Nature*, 1971, 22:91-92.

Kolar, Oldrich J.; Alexander T. Ross; and Jean T. Herman, "Serum and Cerebrospinal Fluid Immunoglobulins in Multiple Sclerosis," *Neurology*, 1970, 20:1052-1061.

Kurtzke, J. F., "Some Epidemiologic Features Compatible with an Infectious Origin for Multiple Sclerosis," *International Archives of Allergy*, 1969, 36:59-81.

Kurtzke, John F.; Gilbert W. Beebe, Benedict Nagler, M. Dean Nefzger; Thomas L. Auth; and Leonard T. Kurland, "Studies on the Natural History of Multiple Sclerosis," *Archives of Neurology*, 1970, 22:215-225.

Kurtzke, John F.; Leonard T. Kurland; and Irving D. Goldberg, "Mortality and Migration in Multiple Sclerosis," *Neurology*, 1971, 21:1186-1197.

Link, Hans; and Ragnar Muller, "Immunoglobulins in Multiple Sclerosis and Infections of the Nervous System," *Archives of Neurology*, 1971, 25:326-344.

Riekkinen, P.J.; J. Clausen; H. J. Frey; T. Fog; and U. K. Rinne, "Acid Proteinase Activity of White Matter and Plaques in Multiple Sclerosis," *Acta Neurologica Scandinavia*, 1970, 46:349-353.

Riekkinen, P. J.; Jorma Palo; Antti U. Arstila; Heikki J. Savolainen; Urpo K. Rinne; Erkki K. Kivalo; and Harry Frey, "Protein Composition of Multiple Sclerosis Myelin," *Archives of Neurology*, 1971, 24:545-49.

Riekkinen, P. J.; U. K. Rinne; A. U. Arstila; T. Kurihara; and T. T. Pelliniemi, "Studies on the Pathogenesis of Multiple Sclerosis: 2', 3'-Cyclic Nucleotide 3-Phosphohydrolase as Marker of Demyelination and Correlation of Findings with Lysosomal Changes," *Journal of the Neurological Sciences*, 1972, 15:113-120.

Riekkinen, P. J.; U. K. Rinne; H. Savolainen; J. Palo; E. Kivalo; and A. Arstila, "Studies on the Pathogenesis of Multiple Sclerosis: Basic Proteins in the Myelin and White Matter of Multiple Sclerosis, Subacute Sclerosing Panencephalitis and Postvaccinal Leucoencephalitis," *European Neurology*, 1971, 5:229-244.

Simpson, John F.; Wallace W. Tourtellotte; Empre Kokmen; Julius A. Parker; and Hideo H. Itabashi, "Flourescent Protein Tracing in Multiple Sclerosis Brain Tissue," *Archives of Neurology*, 1969, 20:373-377.

Swank, Roy L., "Multiple Sclerosis: Twenty Years on Low Fat Diet," Archives of Neurology, 1970, 23:460-474.

PREFACE

A chronic neurological disease, multiple sclerosis (M.S.) affects from 10 to 60 people per 100,000 population in the United States alone. Yet the etiology of M.S. is still unknown. We do know that its incidence varies according to graphical latitude and that its early course is characterized by relapses and remissions. The average duration may exceed 25 years as the patient progresses to a bed-ridden, paralyzed, incoordinate, incontinent dysarthric state before death.

Present evidence suggests the involvement of an infectious agent as well as the immune mechanism. The infectious agent is probably viral, for it has been observed that M.S. patients exposed to such other viruses as measles and mumps often have higher measles or mumps antibody titers than titers in controls. Some M.S. patients have high immunoglobulin levels in the cerebrospinal fluid which also suggests that an infectious agent is associated with the disease. Inclusion bodies and small multi-nucleated giant cells have been found in demyelinating scarred areas of the brain from M.S. patients, thus further implicating viruses.

Immunological processes also play a part in the genesis of M.S. Patients often have cellular responses to nervous tissue antigens, lymphotoxic as well as lymphocyte response depressive factors in their serum, and demonstrate impaired mixed leucocyte reactions. However, at this juncture one cannot determine if M.S. is an autoimmune disease or if the immune mechanism is involved as a consequence of a viral infection. It is clear that the course of the disease is highly complex, thereby taxing the clinician in terms of treatment and prognosis.

This volume surveys the recent developments in the areas of pathology, epidemiology, virology, and immunology. It will serve as a reference tool for both beginners and experienced investigators wishing to update their knowledge on this serious and problematic disease.

Ronald Acton, Ph.D.
November, 1972

Pathogenesis of the Disease

Studies on the Pathogenesis of Multiple Sclerosis

Basic Proteins in the Myelin and White Matter of Multiple Sclerosis, Subacute Sclerosing Panencephalitis and Postvaccinal Leucoencephalitis

P. Riekkinen, U. K. Rinne, H. Savolainen, J. Palo, E. Kivalo and A. Arstila

During recent years there have been 2 main approaches in studies concerning the etiology and pathogenesis of multiple sclerosis (MS). Both of them, slow virus infection and neuroallergy were reviewed recently from a clinical standpoint by Bauer [1970]. World wide epidemiological data and virological studies suggest an early childhood infection as the origin of the disease [Alter, 1968; Sever *et al.,* 1970; Kurtzke, 1970]. Furthermore, there are reports about specific involvement with measles in MS [Mai, 1969; Adams *et al.,* 1970; Panelius *et al.,* 1970]. The role of environmental factors were also stressed by

KURTZKE [1969] and LEIBOWITZ [1971]. Despite this progress there is still no evidence that slow virus infection explains the whole pathogenesis of MS. Although in subacute sclerosing panencephalitis (SSPE) the association of measles is firmly established [HORTA-BARBOSA *et al.*, 1969] there remain many problems concerning the development of the disease.

The second approach in the search for the pathogenesis has been experimental allergic encephalomyelitis (EAE). Both immunochemical and morphological studies have provided important results as far as oligodendroglia cells and myelin are concerned as targets of immunological attact. Earlier many differences were stressed between lesions of MS and EAE. From the clinical standpoint the most difficult task has been the explanation of the monophasic course of EAE [LAMPERT, 1967; RAINE *et al.*, 1969; BORNSTEIN, 1968; ADAMS and LIEBOVITZ, 1969; LEVINE, 1970]. Although a chronic course for EAE was claimed by STONE and LERNER [1965] only the most recent studies by RAINE and BORNSTEIN [1970] have demonstrated clearly the fact that long-term treatment of tissue cultures with EAE serum causes changes typical of sclerotic plaques. Moreover they demonstrated changes in synaptic membranes before demyelination was apparent.

The main reason for immunochemical studies has been the unique nature of myelin because it contains basic protein which is also called encephalitogen. This protein has been characterised in detail [EINSTEIN and CHAO, 1970; CHAO and EINSTEIN, 1970; ADAMS and CASPARY, 1970; MEHL and HALARIS, 1970; WESTALL *et al.*, 1971; CARNEGIE, 1971]. Antibodies to encephalitogenic protein have also been much studied especially in sera of MS patients, but the results are conflicting [LISAK *et al.*, 1968; CASPARY and CHAMBERS, 1970; LUMSDEN and JENNINGS, 1970]. It has been proposed that demyelinating antibodies are merely a response to demyelination and have little to do with the origin of a demyelination process. However, it has been demonstrated recently by numerous authors [HALLPIKE *et al.*, 1970; EINSTEIN *et al.*, 1970; RIEKKINEN *et al.*, 1971] that basic protein was lost in MS plaques and decreased in many areas outside them. This finding may simply be related to early myelin breakdown because the basic protein is susceptible to proteolysis.

The encephalitogenic protein is not normally exposed to immunocompetent cells and its liberation can cause 2 immunological responses, namely the production of myelin antibodies or the transformation of

lymphocytes which can later attack myelin and cause demyelination. This point of view has been expressed [BARTFELD and ATOYNATAN, 1970; DAU and PETERSON, 1970]. However, the specificity of this reaction was questioned by FIELD and CASPARY [1970].

Our previous studies have shown that basic protein decreased in MS myelin samples [RIEKKINEN *et al.*, 1971a] and in SSPE myelin [RIEKKINEN *et al.*, 1971b] our study showed normal content of basic protein. In order to exclude the possibility that the loss of basic protein was due to preparative artefacts during successive gradient centrifugation we went on to study homogenates. In the present study we report the results of further study of MS myelin samples and special emphasis will be paid to the analysis of proteolipids and basic protein in MS white matter homogenates. A comparison is made between MS, SSPE and postvaccinal leucoencephalitis, because it has been suggested that the latter condition is based on immunological responses.

Material and Methods

MS patients

Case 1: A 65-year-old woman, who had suffered from multiple sclerosis for 17 years. The diagnosis was based both on clinical follow-up and on CSF findings. The patient died of respiratory infection and at autopsy several plaques and microscopic features typical of MS were found. The sample for the present study was taken from the temporal area.

Case 2: A 38-year-old man who had had the disease actively for 9 years with typical course and pathology in CSF γ-globulins. The clinical picture was dominated mainly by paraparesis and profuse cerebellar symptoms. At autopsy macroscopic dilatation of ventricles was found and extensive demyelination in many areas. Also in this case the sample was taken from the left temporal white matter.

Case 3: A 47-year-old man, who had had multiple sclerosis for 20 years. The diagnosis was based both on the clinical course and repeated CSF findings. The patient died of a heart attack. At autopsy numerous small periventricular plaques were found and histopathological findings confirmed the diagnosis. The sample for chemical analysis was taken from the left temporo-occipital area outside visible plaque.

Case 4: A 39-year-old woman, in whom the disease had startet at the age of 19 years. Her condition declined continuously and typical CSF for MS was found. At autopsy it was confirmed that the patient had been suffering from multiple sclerosis.

Case 5: A 38-year-old woman who had had the disease for 15 years and had had numerous active attacks and a gradual progression of the disease. Both the clinical picture and CFS findings were in accord with multiple sclerosis. At autop-