

Link H & Müller R. Immunoglobulins in multiple sclerosis and infections of the nervous system. *Arch. Neurol.* 25:326-44, 1971.
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This paper shows the value of demonstrating oligoclonal immunoglobulin bands by agar gel electrophoresis of cerebrospinal fluid (CSF) and of the CSF kappa:lambda ratio in the diagnosis of inflammatory nervous system diseases, especially multiple sclerosis. [The SC²® indicates that this paper has been cited in over 255 publications since 1971.]

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The observation by Kabat *et al.*¹ of increased concentrations of immunoglobulin G (IgG) in cerebrospinal fluid (CSF) when expressed as percentage of CSF total protein, mostly in the presence of normal serum IgG levels, suggested a compartmentalized immune response within the central nervous system (CNS) and introduced a new dimension in diagnosis and research into inflammatory CNS diseases, especially multiple sclerosis (MS). In 1964, my coauthor and supervisor, Ragnar Müller, who was heading the Department of Neurology at the University of Lund, encouraged me to examine the humoral immune response as reflected in CSF in greater detail. At that time, several European groups worked on separation of CSF proteins by agar gel electrophoresis. Abnormalities of band patterns were observed in various neurological disorders and summarized by Lowenthal.² Separation of MS CSF revealed extra bands migrating in the gammaglobulin region, and they were claimed to consist of oligoclonal IgG that was secreted by restricted numbers of plasma-cell clones within the CNS.³ The IgG type of the bands was proven by isolation of IgG from MS CSF and subsequent agar gel electrophoresis.⁴ Our finding of an abnormal kappa:lambda light-chain distribution in

CSF compared with serum was further evidence for an oligoclonal reaction within the CNS in MS.⁵

The goal of our 1971 paper was to examine patients with MS, CNS infections, and other neurological disorders. We also examined "healthy controls" for immune abnormalities detectable by CSF studies, i.e., mononuclear pleocytosis; increase of IgG, IgA, and IgM; oligoclonal bands; and abnormal kappa:lambda ratio. In MS, these variables were related to clinical parameters.

Ninety-four percent of our patients with MS had oligoclonal bands in their CSF. Of 17 patients with normal relative CSF IgG concentrations, 13 had oligoclonal bands. Of the patients with CNS infections, 39 percent had oligoclonal bands, including patients with herpes simplex encephalitis and neurosyphilis who also had elevated relative IgM levels in CSF.

This paper showed that demonstration of oligoclonal bands by electrophoresis of CSF was an easily performed and valuable method for detecting an immune response within the CNS in neurological diseases, especially MS. After publication of our paper, separation of CSF and of simultaneously obtained serum for demonstration of oligoclonal bands became a routine procedure in many European neurological centers, which might be one reason for the frequent citation of the paper. In the US, this development has been slower, and CSF studies first gained ground after the oligoclonal reaction was rediscovered,⁶ although there are many prestigious neurological centers in North America where CSF examination for oligoclonal bands is still regarded with suspicion and where other tests, such as registration of evoked potentials, are more eagerly used when, e.g., a diagnosis of MS is suspected. None of these tests, however, has the potential to demonstrate that the lesion present has an immune background, which is another advantage of the variables examined in our paper.

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2. Lowenthal A. *Agar gel electrophoresis in neurology*. Amsterdam: Elsevier, 1964. 204 p.
3. Laterre E C. *Les protéines du liquide céphalo-rachidien à l'état normal et pathologique*. Brussels: Éditions Arscia S.A., 1964. 327 p.
4. Link H. Immunoglobulin G and low molecular weight proteins in human cerebrospinal fluid: chemical and immunological characterisation with special reference to multiple sclerosis. *Acta Neurol. Scand.* 43(Suppl. 28):1-136, 1967. (Cited 135 times.)
5. Link H & Zettervall O. Multiple sclerosis: disturbed kappa:lambda light chain ratio of immunoglobulin G in cerebrospinal fluid. *Clin. Exp. Immunol.* 6:435-8, 1970. (Cited 85 times.)
6. Johnson K P, Arrigo S C, Nelson B J & Ginsberg A. Agarose electrophoresis of cerebrospinal fluid in multiple sclerosis: a simplified method for demonstrating cerebrospinal fluid oligoclonal immunoglobulin bands. *Neurology* 27:273-7, 1977. (Cited 75 times.)