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# Do antibodies to myelin basic protein isolated from multiple sclerosis cross-react with measles and other common virus antigens?

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## SUMMARY

Immunological activity to various antigens, including brain components, measles and other viruses, has been associated with IgG in multiple sclerosis (MS). One possible explanation for the presence of anti-viral antibodies and antibody to myelin basic protein (MBP) in MS patients is that there are antigenic determinants common to certain viruses and MBP. To assess this possibility, IgG from individual brains and sera from patients with MS, subacute sclerosing panencephalitis (SSPE) and controls was isolated by protein A and MBP-Sepharose affinity chromatography. Antibody to MBP was measured with a solid phase radioimmunoassay and antibody to measles and other viruses by immunofluorescence and/or complement fixation. Anti-MBP activity was detected in brain extracts and sera of all MS patients tested. In contrast to the low levels of antibody to MBP in control brains, high levels of anti-MBP antibodies were found in most of the normal sera. There was no correlation between the presence and levels of serum anti-measles antibodies and the anti-MBP activity. None of the anti-MBP antibodies affinity purified from brain and serum of MS patients reacted with any of the viruses tested, including measles. IgG purified from SSPE patients or from a rabbit hyperimmunized with measles antigen had no reactivity to MBP, despite high levels of anti-measles antibody. It is concluded that there is no direct link between the presence of antibody to MBP and antibody to measles and other viruses in MS patients.

## INTRODUCTION

Multiple sclerosis (MS) is characterized by the presence in the patient's cerebrospinal fluid (CSF) of an elevated level of immunoglobulin (Ewan & Lachmann, 1979; Link, 1967). At least some of the IgG in the CSF is produced within the central nervous system (CNS) (Ewan & Lachmann, 1979; Sandberg-Wollheim, 1974) presumably by plasma cells identified within demyelinated plaques in the CNS (Esiri, 1980). Extensive work has been carried out in search of the immunological specificity associated with CSF IgG, in the hope that identification of the antigenic stimulus for its production would help in the understanding of the pathogenesis and aetiology of MS. While most of the IgG in CSF of patients with neurological infections, such as subacute sclerosing panencephalitis (SSPE), represents antibodies directed against the infectious agent (Connolly *et al.*,

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1967), the nature of the antigenic stimulus for increased levels of IgG in MS CSF and CNS is unknown. Normal brain components or a virus may be implicated or there may be random activation of 'irrelevant' B cells in the neuraxis. Part of the increased IgG is directed against measles and other viral antigens (Nordal, Vandvick & Norrby, 1978) and part against MBP (Bernard *et al.*, 1981a; Panitch, Hooper & Johnson, 1980; Ruutiainen *et al.*, 1981), but antibody to the particular antigens does not by any means account for all increased IgG in CSF (Bernard *et al.*, 1981a; Vandvik *et al.*, 1976). Furthermore, as the intrathecal antibody synthesis against particular viruses differs from one MS patient to another (Norrby *et al.*, 1974) it has been impossible to establish a link between a common virus and MS.

One possible explanation for the presence of anti-viral and anti-brain antibody in MS patients is that common antigenic determinants exist between certain viral proteins and CNS antigens. Indeed, Panitch, Swoveland & Johnson (1979) claimed from a preliminary experiment that a cross-reactivity exists between oligoclonal antibody to measles and MBP present in CSF of patients with SSPE. In the present study attempts were made to determine the antibody specificity of immunoglobulins purified from brain and serum of MS patients and to assess if anti-MBP antibodies purified from this material could react with measles and other common viruses. Also included in this report are the results of similar studies performed with SSPE serum and with rabbit anti-measles antibodies.

## MATERIALS AND METHODS

*Brain samples.* Brains were obtained at autopsy from four female and three male patients with a confirmed diagnosis of MS. Their ages ranged from 53 to 70 years (mean = 58 years) and the duration of disease ranged from 8 to 31 years.

Control brains were obtained from three females and two males with non-neurological diseases (age range = 36–80, mean = 66 years). At post mortem, brains were divided into samples of approximately 25 g and stored at −70°C within 8–16 h of death.

*Brain extracts.* Brain white matter samples were thinly sliced, homogenized, centrifuged and concentrated as previously reported (Bernard *et al.*, 1981a).

*Human serum samples.* Sera were obtained from three female and three male clinically diagnosed MS patients. Their ages ranged from 25 to 64 years (mean = 45 years), and the duration of disease ranged from 1 to 11 years. SSPE serum specimens were obtained from three females and two males. Their ages ranged from 5 to 17 years (mean = 14 years). Control sera were obtained from two females and four males. Their ages ranged from 15 to 67 years (mean = 31 years).

*Human MBP (H-MBP).* H-MBP was prepared, from the brain of a patient who had MS, as described by Dunkley & Carnegie (1974).

*Immunoglobulin determination.* The concentration of immunoglobulin in human samples and purified eluates was determined by radial immunodiffusion using 'LC-Antigen' plates and Protein Standard Serum LC-V (Behringwerke, Marburg).

*Affinity chromatography.* IgG from brain eluates and serum were affinity purified on protein A–Sepharose CL-4B (Pharmacia, Uppsala, Sweden) columns and further purified on a H-MBP–Sepharose column to obtain specific anti-MBP antibodies (Bernard *et al.*, 1981a). Four millilitres of concentrated brain extract or 2 ml of serum were used for each purification.

*Assay for antibody to H-MBP.* Antibody to H-MBP was detected using a solid phase radioimmunoassay as previously described (Bernard *et al.*, 1981a).

*Detection of antibody to viruses.* Viral antibodies were determined by the immunofluorescence technique as previously described (Donaldson *et al.*, 1978). Ten microlitres of human coded specimens, adjusted to a protein concentration of 0·1 mg/ml were placed on each of 10 wells of a glass microscopic slide. Eight of the wells contained fixed cells infected with each of the following viruses: influenza A and B, parainfluenza types 1, 2 and 3, respiratory syncytial virus, measles and adenovirus. The other wells contained fixed *Bordetella pertussis* and fixed uninfected cells (negative control). Rabbit antisera (10 μl) to the appropriate micro-organism was added to each well of the positive control slide, normal rabbit serum being added to the negative control well. Each coded slide was read by two observers independently and scored on a scale from − to + + + according to

the degree of fluorescence present. Anti-measles antibodies were also tested on selected samples and in whole serum using the complement fixation test previously described (Donaldson *et al.*, 1978). The measles antigens used were prepared from a local isolate, grown in a continuous cell line of monkey embryo kidney (F.A. Lewis, personal communication).

*Immunization of rabbits and antisera.* Antisera to H-MBP was raised in rabbits by procedures similar to those previously described (Bernard *et al.*, 1981b). Antisera against measles virus (Edmonston strain) was produced and kindly provided by Ms M. Kennett and Dr J. White, Fairfield Hospital, Melbourne.

*Statistical analysis.* Calculation of arithmetic means and standard errors were done as previously described (Bernard *et al.*, 1981a). The significance of differences between the anti-MBP antibody activities were tested by the Student's *t*-test.

## RESULTS

Since previous studies from this laboratory and others (Bernard *et al.*, 1981a; Glynn *et al.*, 1982; Vandvik *et al.*, 1976) have indicated that the majority of antibody activity detected in MS brain and CSF was mediated by immunoglobulin G, brain extracts and serum were first fractionated on a protein A-Sepharose column, before being applied to an MBP-Sepharose column. Immunoglobulins bound to brain tissue were not examined as previous studies have indicated that only small amounts of additional IgG could be recovered after MS brain tissues were treated with dilute acid following successive washes with PBS (Bernard *et al*, 1981a; Mehta *et al*, 1981). As indicated in Table 1 most, if not all, the anti-MBP activity present in MS brain was recovered from the immunoglobulins bound to the MBP column (fraction B). The specific binding of $^{125}$I-protein A (% bound/10 mg of brain tissue $\pm$s.e. (mean)) for the MBP affinity purified IgG of seven MS brains was $32{\cdot}2 \pm 6{\cdot}6$, as compared to $3{\cdot}57 \pm 1{\cdot}1$ for the IgG recovered in the PBS effluent. There was also a low degree of binding with some of the non-MS brains, but the mean for this group of $11{\cdot}6 \pm 3{\cdot}7$ was significantly lower ($P < 0{\cdot}02$) than that for the MS group. Immunoelectrophoresis and radial immunodiffusion analysis showed that the majority of the immunoglobulins eluted from this MBP column were of the IgG1 isotype.

In contrast to normal brain material, five out of the six normal serum immunoglobulins tested displayed relatively high levels of anti-MBP activity. However, as indicated by the mean percentage of $^{125}$I-protein A bound (Table 2), there was significantly ($P < 0{\cdot}01$) more anti-MBP activity in MS than in non-MS samples ($93{\cdot}0 \pm 3{\cdot}21$ and $48{\cdot}0 \pm 12{\cdot}7$ respectively). While most of the anti-MBP activity detected was associated with the immunoglobulin bound to the MBP column, a lower but nevertheless significant level of anti-MBP activity was detected in the PBS effluent. Analysis of the protein present in the PBS and acetic acid eluates revealed that in contrast to the brain material, two out of the six MS sera (patients La and C) and two of the control sera (patients D and M) had IgM binding MBP in addition to IgG.

As indicated in Table 2 no correlation was observed between the presence and levels of serum complement fixing anti-measles antibody and the presence or level of anti-MBP activity. Such a dichotomy between the levels of anti-measles and anti-MBP antibodies was further confirmed when the immunoglobulins purified from SSPE were analysed. It can be seen from Table 2 that despite the high titres of complement fixing anti-measles activity, these immunoglobulins had very low levels of anti-MBP activity.

In order to assess the possibility that cross-reactive determinants exist between MBP and viral antigens, MBP affinity purified immunoglobulins from brain and serum of MS and controls were tested against a panel of eight viruses. The immunoglobulins collected in the PBS effluent of the MBP column served as a control. Tables 1 and 2 show that in no instance could any viral antibody activity be detected with the affinity purified anti-MBP antibody, despite their high levels of anti-MBP activity. In contrast, the majority of the immunoglobulins recovered in the PBS effluent were found to react with one or more viruses. Of particular interest was the finding that all MS brain eluates and serum samples reacted against measles virus. A strong reactivity to adenovirus was observed with the majority of the MS serum immunoglobulin and some of the controls tested, but

**Table 1.** Anti-MBP and anti-viral activity of immunoglobulins purified from MS and control brains

| Patient | | | MBP affinity chromato-graphy fraction* | Anti-MBP activity† | Anti-viral activity‡ | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Influenza | | Parainfluenza | | | | |
| Code | Age | Sex | | | Measles | A | B | 1 | 2 | 3 | RSV§ | Adeno-virus |
| *MS brain* | | | | | | | | | | | | |
| T | 53 | M | A | 0 | + | − | − | − | − | − | − | − |
| | | | B | 34 | − | − | − | − | − | − | − | − |
| B | 55 | F | A | 5 | ++ | − | − | − | − | − | + | − |
| | | | B | 18 | − | − | − | − | − | − | − | − |
| E | 57 | F | A | 8 | ++ | − | − | − | − | + | − | − |
| | | | B | 20 | − | − | − | − | − | − | − | − |
| E | 57 | F | A | 3 | + | − | + | − | − | + | + | − |
| | | | B | 12 | − | − | − | − | − | − | − | |
| P | 57 | F | A | 7 | + | − | + | + | − | − | + | − |
| | | | B | 64 | − | − | − | − | − | − | − | − |
| S | 62 | M | A | 1 | ++ | − | − | − | − | − | + | − |
| | | | B | 40 | − | − | − | − | − | − | − | − |
| C | 70 | M | A | 1 | + | + | ++ | − | − | + | + | − |
| | | | B | 38 | − | − | − | − | − | − | − | − |
| *Control brain* | | | | | | | | | | | | |
| P | 80 | F | A | 8 | − | − | − | − | − | − | − | − |
| | | | B | 10 | − | − | − | − | − | − | − | − |
| S | 78 | M | A | 1 | − | − | ++ | − | − | − | − | − |
| | | | B | 13 | − | − | − | − | − | − | − | − |
| F | 53 | M | A | 0 | | | ——— | ND | ——— | | | |
| | | | B | 4 | | | | | | | | |
| A | 36 | F | A | 0 | − | − | − | − | − | − | − | − |
| | | | B | 25 | − | − | − | − | − | − | − | − |
| T | 86 | F | A | 1 | | | ——— | ND | ——— | | | |
| | | | B | 6 | | | | | | | | |

* Fraction A represents the IgG purified by protein A which did not bind to the MBP-Sepharose column (PBS eluate). Fraction B are the IgG purified by protein A which were bound to the MPB column and subsequently eluted with acetic acid.

† Percentage of protein A bound/10 mg of brain tissue.

‡ Anti-viral activity—as assessed by immunofluorescence.

§ Respiratory syncytial virus.

ND = Not done.

not with the MS and non-MS brain samples. It can also be seen from Tables 1 & 2 that no correlation could be found between the residual anti-MBP activity present in some of the PBS effluent samples and the anti-viral antibodies.

Further evidence for an absence of cross-reactivity between viral antigens and MBP was obtained by analysing SSPE and rabbit anti-measles immunoglobulins before and after passage on the MBP column. As shown in Table 2, SSPE serum had little or no anti-MBP activity despite the high levels of anti-measles activity detected by both complement fixing and immunofluorescent techniques. The absence of anti-MBP antibodies was further established by the fact that only minimal amounts of SSPE immunoglobulins were bound to the MBP column (Fig. 1c). There was little or no anti-MBP activity in this material (Table 2) and no anti-viral antibody could be detected. Also, and in contrast to the other serum samples (MS and non-MS) SSPE immunoglobulins recovered in the PBS effluent reacted only against measles virus antigen. Fig. 1 illustrates the results

**Table 2.** Anti-MBP and anti-viral activity of immunoglobulins purified from MS, SSPE and control serum

| Patient | | | Serum anti-measles antibody | MBP affinity chroma-graphy | Anti-MBP | Anti-viral activity‡ | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Influenza | | Para-influenza | | | | |
| Code | Age | Sex | (CF titre) | fraction* | activity† | Measles | | A | B | 1 | 2 | 3 | RSV§ | Adeno-virus |
| *MS patient* | | | | | | | | | | | | | | |
| H | 35 | F | 64 | A | 14 | + | | − | ++ | − | − | + | − | +++ |
| | | | | B | 90 | − | | − | − | − | − | − | − | − |
| L | 37 | F | 128 | A | 13 | ++ | | − | + | − | − | + | ++ | − |
| | | | | B | 90 | − | | − | − | − | − | − | − | − |
| La | 64 | M | 32 | A | 46 | ++ | | + | + | − | − | − | + | + |
| | | | | B | 100 | − | | − | − | − | − | − | − | − |
| C | 64 | M | 64 | A | 27 | ++ | | − | + | − | − | + | + | ++ |
| | | | | B | 80 | − | | − | − | − | − | − | − | − |
| Ct | 25 | F | 8 | A | 0 | + | | + | + | − | − | − | + | ++ |
| | | | | B | 98 | − | | − | − | − | − | − | − | − |
| F | 49 | M | 32 | A | 10 | + | | − | + | − | − | − | + | ++ |
| | | | | B | 100 | − | | − | − | − | − | − | − | − |
| *SSPE patient* | | | | | | | | | | | | | | |
| P | 17 | F | 512 | A | 5 | ++ | (40)¶ | − | − | − | − | − | − | − |
| | | | | B | 2 | − | (0) | − | − | − | − | − | − | − |
| B | 17 | F | 2048 | A | 0 | +++ | (80) | − | − | − | − | − | − | − |
| | | | | B | 6 | − | (0) | − | − | − | − | − | − | − |
| D | 17 | F | 256 | A | 1 | ++++ | (160) | − | − | − | − | − | − | − |
| | | | | B | 2 | − | (0) | − | − | − | − | − | − | − |
| A | 12 | M | 512 | A | 2 | ++++ | (160) | − | − | − | − | − | − | − |
| | | | | B | 0 | − | (0) | − | − | − | − | − | − | − |
| Mc | 5 | M | 128 | A | 1 | + | (0) | − | − | − | − | − | − | − |
| | | | | B | 2 | − | (0) | − | − | − | − | − | − | − |
| *Control* | | | | | | | | | | | | | | |
| D | 23 | M | 128 | A | 29 | ++ | | − | − | − | − | − | ++ | − |
| | | | | B | 68 | − | | − | − | − | − | − | − | − |
| A | 14 | F | 128 | A | 17 | ++ | | − | − | − | − | − | − | − |
| | | | | B | 31 | − | | − | − | − | − | − | − | − |
| R | 25 | F | ND | A | 8 | + | | − | + | − | + | − | + | + |
| | | | | B | 85 | − | | − | − | − | − | − | − | − |
| M | 47 | M | 3 | A | 30 | + | | − | − | − | + | − | + | ++ |
| | | | | B | 69 | − | | − | − | − | − | − | − | − |
| W | 15 | M | 128 | A | 2 | − | | − | − | − | − | − | − | − |
| | | | | B | 2 | − | | − | − | − | − | − | − | − |
| S | 67 | M | 0 | A | 12 | − | | − | − | − | − | − | − | − |
| | | | | B | 33 | − | | − | − | − | − | − | − | − |

* Fraction A represents the IgG purified by protein A which did not bind to the MBP-Sepharose column (PBS eluate). Fraction B are the IgG purified by protein A which were bound to the MBP column and subsequently eluted with acetic acid.

† Percentage of protein A bound/10 mg of brain tissue.

‡ Anti-viral activity—as assessed by immunofluorescence.

§ Respiratory syncytial virus.

¶ Complement fixing antibody titres.

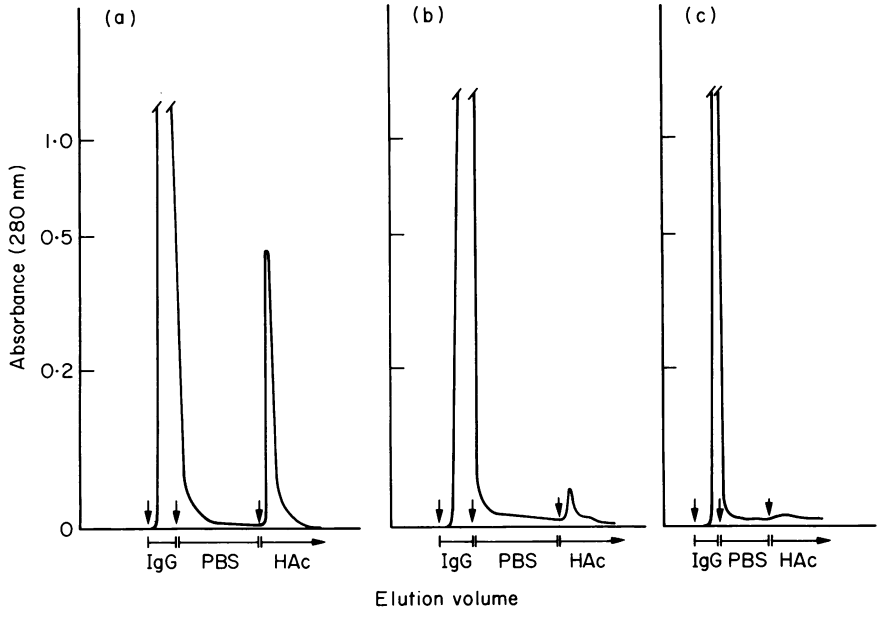


**Fig. 1.** Isolation of serum anti-MBP antibody by affinity chromatography. Immunoglobulin isolated by chromatography on protein A from 2 ml of a rabbit anti-human MBP serum (a), a rabbit anti-measles serum (b) and from the serum of an SSPE patient (patient B, Table 2) (c), were applied to a H-MBP Sepharose column. The unbound protein was washed with PBS and bound immunoglobulins eluted with acetic acid (HAc). The vertical arrows indicate application to the columns. The absorbance was monitored at 280 nm using a single path UV-1, Pharmacia, continuous flow cell.

of a typical MBP affinity purification obtained with rabbit anti-MBP (Fig. 1a) and rabbit anti-measles (Fig. 1b) immunoglobulins. Whereas a large proportion of immunoglobulins purified from the MBP injected rabbit were absorbed on the MBP column and upon elution showed high levels of anti-MBP activity (92% binding at 1/125 dilution), only trace amounts of binding were obtained with the rabbit anti-measles immunoglobulins and no anti-MBP activity could be demonstrated in this material.

## DISCUSSION

Although immunological responses to various antigens have been related to the increased IgG in MS CSF, the antigenic specificity of the majority of these intrathecally synthesized immunoglobulins remains unknown. Only a small proportion of oligoclonal IgG reacts with measles and other common viruses (Vandvik *et al.*, 1976). Antibody to purified neural antigens such as myelin, MBP and oligodendrocytes have been demonstrated in MS CSF, but so far results have been inconsistent (Paterson & Whitacre, 1981). The existence of raised levels of IgG in CSF of MS takes on added relevance from recent studies on immunoglobulin extracted from the brains of patients with MS at autopsy. Such brains contained greatly increased amounts of IgG (Bernard *et al.*, 1981a; Mehta *et al.*, 1981) with limited and discrete patterns of immunoglobulin binding as seen in CSF (Bernard & Townsend, unpublished observations; Matteson, Roos & Arnason, 1980; Mehta *et al.*, 1981) of which a substantial proportion (5–20%) was antibody to MBP (Bernard *et al.*, 1981a).

The present study provides further evidence that substantial levels of anti-MBP antibodies are present in brains of patients with MS. There was some anti-MBP activity in the control brains, but these levels were significantly less than those observed with MS brains. This contrasts with the

results obtained with sera, where high levels of anti-MBP antibodies were found in both MS and healthy subjects.

Although there is some controversy as to whether binding of immunoglobulin to myelin antigen represents genuine antibody activity (Sindic *et al.*, 1980), it is unlikely that our results reflect a purely ionic interaction between IgG and MBP, since little or no binding was observed when column eluates were tested against other charged proteins such as histone or lysozyme (Bernard *et al.*, 1981a). Likewise, our findings cannot readily be accounted for by a non-specific binding of MBP by the Fc region of human IgG (Sindic *et al.*, 1980), since no correlation could be found between the amount of IgG binding MBP and the total amount of IgG recovered from the protein A column (see Fig. 1b & c, Table 2, and Bernard *et al.*, 1981a).

The detection of anti-MBP antibodies in healthy subjects is of interest and supports previous reports that naturally occurring antibodies to a variety of antigens, including self, are not only present in humans, but also in various animal species (Guilbert, Dighiero & Avrameas, 1982). The biological role, if any, played by these naturally occurring autoantibodies is not known. Their presence in brain, CSF and serum may be relevant to the much discussed question of self tolerance, and whether this depends on clonal deletion (Burnet, 1959) or some other homeostatic controls (Gershon, 1977; Wigzell, 1977).

A major objective of the present study was to determine if myelin and viral antigens share common antigenic determinants. Such a possibility, which could bring together the viral and autoimmune aetiology theories of MS and possibly explain the increased level of anti-viral and anti-brain antibodies seen in such patients, was taken into consideration following the report of Panitch *et al.* (1979) that cross-reactivity exists between MBP and measles antigens. We have addressed this important issue by testing the anti-MBP and anti-viral antibody activities of immunoglobulins purified from brain and serum of MS and healthy subjects and the serum of SSPE patients, and assessed if the anti-MBP antibodies affinity purified from these samples would react against a panel of viruses. Measles, influenza A and B, parainfluenza 1, 2, 3, respiratory syncytial virus and adenovirus were selected since some of these viruses have been incriminated in MS and because intrathecal antibodies to one or more of them have been demonstrated (Nordal *et al.*, 1978; Rostrom *et al.*, 1981). The results presented in this report clearly indicate that in no instance could any shared antigenic determinants be detected between MBP and viral antigens, including measles. Firstly, there was no correlation between the presence and levels of serum anti-measles antibodies and the levels of anti-MBP activity (Table 2). Secondly, none of the anti-MBP antibodies affinity purified from brain or serum of MS patients or controls reacted with any of the viruses tested, the anti-viral activity being detected only in IgG recovered from the PBS eluate of the MBP column. Thirdly, IgG purified from SSPE patients or from a rabbit hyperimmunized with measles antigen had little or no reactivity to MBP (Table 2). Finally, no difference was found in the amount of protein bound to the column or the level of anti-MBP activity when MBP was prepared from myelin of either MS or normal brain (Bernard *et al*, 1981a).

It is noteworthy that absence of cross-reactivities between neural and viral antigens has also been observed in various animal diseases, using different experimental systems (see Carnegie, Lim & Bernard, 1982).

With the exception of anti-measles antibodies which were present in brain and serum of all MS patients studied, no common pattern of anti-viral reactivity could be observed. This is in agreement with previous studies that in MS the intrathecal antibody production against certain viruses differs from one patient to another (Norrby *et al.*, 1974). Of particular interest was the finding that in SSPE patients the levels of anti-MBP activity was significantly less ($P < 0{\cdot}01$) than that found in control serum, and no anti-viral activity other than that directed to measles antigen could be detected. The reason for this is not known but could reflect measles induced immunosuppression (Kauffman, Bergman & O'Connor, 1982).

The significance of increased levels of intrathecally synthesized immunoglobulins in MS remains to be determined. It could be argued that the presence of anti-MBP antibody in brain and CSF of MS patients is merely the result of myelin damage, but a recent study from our laboratory renders this possibility unlikely. It was shown that lambs or sheep treated with cycloleucine, an analogue of methionine causing extensive damage to myelin (Carnegie *et al.*, 1982) had no increased levels of

anti-MBP activity above background. Similarly, no increased levels of anti-MBP or myelin antibodies could be observed in lambs with myelin damage resulting from either thyroid deficiency or genetic abnormality (Carnegie *et al.*, 1982).

As demonstrated for IgG isolated from MS CSF (Stendahl-Brodin, Kristensson & Link, 1981), anti-MBP antibody present in brain could be directly myelinotoxic. Alternatively, since the majority of immunoglobulins in CSF and brain of MS patients belong mainly to the IgG subclass, anti-brain antibodies could be cytophilic for the effectors of antibody-dependent cell-mediated cytotoxicity (ADCC), a mechanism known to cause demyelination (Brosnan *et al.*, 1977). Evidence for specific ADCC against MBP and encephalitogenic peptides has recently been reported in MS (Frick & Stickl, 1982). Such cytophilic antibody could also bind to macrophages present in MS brain (Prineas & Graham, 1981) and induce these to either phagocytose myelin and/or to release proteolytic enzymes, such as neutral proteinases, known to be extremely myelinolytic (Norton *et al.*, 1981). In this context it is particularly relevant to note that in active MS lesions, macrophages contacting myelin sheaths stain for both surface and cytoplasmic IgG (Prineas & Graham, 1981) and that myelin appears to 'melt' in contact with macrophages (Prineas, 1975).

Although further work is needed to elucidate the nature and specificity of intrathecally synthetized immunoglobulins, and to understand the mechanisms by which such autoantibodies could produce an immune-mediated myelinosis, consideration must be given to recent developments concerning the involvement of genetic factors in the predisposition to MS. Recent studies from our (Propert, Bernard & Simons, 1982) and another laboratory (Pandey *et al.*, 1981) have shown that in addition to an HLA linked gene, a distinct genetic marker, Gm allotype, expressed on the heavy chain variable region of immunoglobulins, may also influence the pathogenesis of MS. These findings take on added relevance from increasing evidence that genes from the MHC and those coding for Gm allotypes somehow interact to produce an immune response and also influence the susceptibility to various autoimmune diseases such as thyrotoxicosis, myasthenia gravis and chronic hepatitis (Mackay *et al.*, 1980; Nakao *et al.*, 1980). Since a given immunoglobulin allotype may favor certain antibody activity and/or its biological function (Schanfield, 1980), the expression of a distinct Gm allotype on the anti-MBP antibodies present in MS brain (Bernard, Propert & Townsend, unpublished observations) could be of particular pathogenic significance. This in fact may explain why no evidence of neuronal dysfunction can be observed in control patients, despite the presence in blood and brain of a significant level of anti-MBP activity (Table 1).

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