Exacerbations of multiple sclerosis (MS) are triggered by exogenous events, the best documented being viral upper respiratory infections (URIs), which can stimulate secretion of cytokines such as interferon-γ (IFN-γ) by immune cells. In conjunction with a recent clinical trial of systemic interferon-β (IFN-β) in relapsing-remitting MS, we studied the occurrence of viral infections and their correlation with MS attacks. Thirty patients kept daily logs, noting URI symptoms in themselves, family members, and co-workers. Patients were examined every 3 months, or whenever an attack of MS occurred, and were tested for antibodies to common upper respiratory pathogens. A strong correlation was found between MS attacks and URIs. There were 168 URIs in 2,792 patient-weeks, including 996 weeks at risk (the interval beginning 1 week before and ending 5 weeks after onset of URI symptoms) and 1,796 weeks not at risk. Nearly two-thirds of attacks occurred in periods at risk. Attack rates were 2.92 per year in weeks at risk compared to 1.16 per year in weeks not at risk, a significant difference (p < 0.001). High-dose interferon reduced the frequency of MS attacks, but had no effect on the number of URIs. Although a specific virus could not be incriminated, we concluded that URIs of presumed viral origin are an important trigger of MS attacks, and that treatment with IFN-β reduces the attack rate, but not by preventing URIs. Rather, it may modulate responses to viral infection that would otherwise lead to immune activation and clinical symptoms.

Panitch HS. Influence of infection on exacerbations of multiple sclerosis. Ann Neurol 1994;36:S25–S28

Numerous exogenous events have been proposed as triggering factors for exacerbations of multiple sclerosis (MS), e.g., "stress," trauma, infection, immunization, pregnancy, climatic changes, and physical exertion. The only ones that have been well documented are infection, delivery after pregnancy, and trauma in the form of electrical shock or direct penetrating injury to the central nervous system (CNS) [1].

In 1985 Sibley and colleagues [2] published a landmark prospective study showing that minor infectious illnesses, presumably viral in origin, were a potent trigger of MS attacks (Table 1). Twenty-seven percent of documented attacks were preceded or accompanied by such infections, and more than 8% of infections were associated with attacks. These were usually upper respiratory or gastrointestinal in nature. Interestingly, bacterial infections, especially urinary tract infections (UTIs), were not a significant trigger.

At about the same time, we were conducting a clinical trial of interferon-γ (IFN-γ) in a small number of patients with relapsing-remitting MS, and in 1987 [3] published the disappointing but interesting result that administration of IFN-γ seemed to precipitate exacerbations of MS. This led to the hypothesis that infections might trigger attacks via release of cytokines such as IFN-γ which then acted on the immune system to induce or enhance an autoreactive response to CNS antigens. Since then other investigators [4] have noted a connection with viral infections. No specific virus has been consistently implicated, although adeno- and herpesviruses such as Epstein-Barr virus (EBV) have been suggested. In addition, cytokines, especially IFN-γ and tumor necrosis factor (TNF), seem to be produced in increased amounts just before acute attacks, or in conjunction with progression of MS [5].

The data presented here were collected prospectively during the first 2 years of the recently completed trial of IFN-β 1b (Betaseron) in MS at the University of Maryland, where we followed 30 of the 372 patients. The study design called for three groups treated systemically with either high dose (8 MIU), low dose (1.6 MIU), or placebo by subcutaneous injection every other day. The results [6] showed that the high dose of IFN-β significantly reduced the frequency of MS attacks. The question we asked at the outset was whether this would simply be a trivial phenomenon (i.e., IFN prevented attacks by preventing the viral infections that induced them) or did it have an immunological basis that did not involve prevention of viral infections but somehow blocked their triggering effect on the immune system.

We developed a questionnaire that the patients filled...
Table 1. Clinical Viral Infections and Multiple Sclerosis*

| Status  | Weeks (%) | Attacks (%) | Attack Rate |
|---------|-----------|-------------|-------------|
| At risk | 12        | 27          | 0.64        |
| Not at risk | 88        | 73          | 0.23        |

*Adapted from [2].

Information on upper respiratory infections (URIs) and multiple sclerosis (MS) exacerbations was collected over 8 years in 170 patients with MS. The period “at risk” extended from 2 weeks before to 5 weeks after onset of URI symptoms. All other periods were considered “not at risk.” Attack rate = exacerbations per patient per year.

out with each injection and submitted every 3 months. They recorded their oral temperature prior to the injection and noted any symptoms of infection in themselves, family members, and co-workers. Almost all the infections recorded turned out to be upper respiratory (URIs). To analyze the data, we followed the procedure published by Sibley and colleagues of dividing the time on study into periods “at risk” and “not at risk.” The periods at risk extended from 1 week prior to the onset of infection to 5 weeks after onset. Any MS attack occurring in that time period was considered temporally related to the infection. In addition, we drew blood before the study began and every 3 months

Fig 1. Exacerbation rates in at-risk (AR) versus not at-risk (NAR) periods.

Table 2. Panel of Antibodies to Common Respiratory Pathogens (Performed at 0, 3, 6, 9, and 12 Months)

| Pathogen                  | Method                  |
|---------------------------|-------------------------|
| Influenza A, B, and C     | Coxackievirus B1–6     |
| Parainfluenza 1, 2, and 3 | Mycoplasma pneumoniae  |
| RSV                      | EBV viral capsid antigen|
| Adenovirus               | HSV-1 and 2 (IgG and IgM)|
| Reovirus                 | HIV-1 (done only at entry)|

Most tests done initially by complement fixation or immunofluorescent assay, later by enzyme-linked immunosorbent assay (Metpath).

RSV = respiratory syncytial virus; EBV = Epstein-Barr virus; HSV-1 = herpes simplex virus type 1; HIV-1 = human immunodeficiency virus type 1.

Fig 2. Attacks in at-risk period (weeks -1–5) in patients followed for 104 weeks.

Fig 3. Upper respiratory infections (URIs) in study patients versus household members and co-workers.

Fig 4. Seasonal variation in upper respiratory infections (URIs) and multiple sclerosis attacks (weeks 0–104).
in the first year and tested the serum for a panel of antibodies to common respiratory pathogens (Table 2).

The results are shown in Figures 1 through 6 and in Table 3. A strong correlation was found between MS attacks and URIs. Nearly two-thirds of exacerbations occurred in periods at risk, and one-third of infections were accompanied or followed by exacerbations. Attack rates for the entire group, irrespective of treatment, were 2.92 per year in weeks at risk compared with 1.16 per year in weeks not at risk (see Fig 1). The difference is significant at the 0.001 level. These figures are much higher than those found in previous studies, probably because the data were collected prospectively and noted daily by the patients. Figure 2 shows the temporal relationship to exacerbations, with a peak at 1 week after the onset of clinical symptoms of infections. The exacerbations are divided into documented attacks and minor or nonreported attacks. The latter were considered to be genuine attacks, but either the patient was not examined at the time or the findings did not fulfill the criteria for documentation as a definite attack (i.e., they consisted of sensory symptoms alone or other symptoms without objective findings on neurological examination, which lasted a week or less and resolved completely with no treatment).

When URIs and other infectious illnesses were compared between study subjects and family members or co-workers, there was no difference in seasonal incidence (see Fig 3). The same spring and fall peaks were seen in both groups, phenomena also found by other investigators [1]. There were also no significant differences between the incidence of or seasonal pattern of URIs in the three treatment groups, indicating that systemic IFN treatment had no effect on the occurrence of infections. In contrast, we did not find a seasonal pattern for exacerbations of MS, suggesting that IFN treatment prevented at least some of the URIs from triggering attacks (see Fig 4).

Figure 5 shows the pattern of attacks in periods at risk and not at risk by treatment group. In this figure, only documented attacks are shown, with the highest attack rate in the placebo group and a lower rate in the 8 MIU group, irrespective of whether the patients were in the critical at risk periods surrounding URIs. Finally, the number of attack-free patients was greatest in the 8 MIU group throughout the study (see Fig 6).

Serum antibody titers to a variety of common, predominately viral, respiratory pathogens did not implicate a specific agent as being more likely to precipitate an attack (Table 3). Although titers of IgG antibody to

![Fig 5. Attack rates for documented exacerbations in at-risk (AR) and not-at-risk (NAR) periods by treatment group.](image)

![Fig 6. Attack-free patients by treatment group.](image)

### Table 3. Summary of Viral Serology

| Antibody   | No. of Positive Patients (30 Total) | Relative Titer | Comments                      |
|------------|------------------------------------|----------------|-------------------------------|
| EBV-VCA    | 28                                 | High           | Increase with attacks         |
| HSV-1      | 16                                 | High           | Flutuate independently of attacks |
| HSV-2      | 11                                 | High           | Flutuate independently of attacks |
| Flu A      | 12                                 | Low            | Flutuate independently of attacks |
| Flu B      | 7                                  | Low            | Flutuate independently of attacks |
| Paraflu    | 9                                  | Low            | Flutuate independently of attacks |
| Adeno      | 17                                 | Low            | Flutuate independently of attacks |
| Other      | 13                                 | Low            | Flutuate independently of attacks |

EBV = Epstein-Barr virus; VCA = viral capsid antigen; HSV = herpes simplex virus; Flu A and B = influenza A and B; Paraflu = paramunfluenza; Adeno = adenovirus.
EBV generally fluctuated in parallel with attacks, we feel this is likely to result from nonspecific activation of the immune system. Herpes virus types I and II and adenovirus antibodies were found in the majority of patients, but titers fluctuated independently of clinical changes in neurological function. Titers of coronavirus and rhinovirus antibodies were not performed. IFN-γ production by peripheral blood mononuclear cells was tested, but the results are not available at this time.

The attacks in periods at risk were not qualitatively different from those that occurred in periods not at risk. They were of approximately the same severity and duration and responded equally well to corticosteroids. There were also no obvious differences in proportions of new and recurrent symptoms in the two groups. It would have been useful to perform gadolinium-enhanced MRI scans at the time of each URI in selected patients to determine if changes in blood-brain barrier permeability heralded the development of clinical attacks; however, the resources to do this were not available.

We conclude that mild infectious illnesses, largely of nonspecific viral origin, are responsible for the majority of exacerbations in a population of patients with early relapsing-remitting MS. They probably act via systemic release of cytokines such as IFN-γ and TNF that then activate the immune system and facilitate the entry of activated T cells into the CNS, leading to exacerbations. Treatment with IFN-β reduces the attack rate but not by preventing infections. Rather, its immunoregulatory effects probably tend to inhibit responses to viral infection that would otherwise lead to immune activation and clinical neurological symptoms.

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