

Article abstract—We treated 18 clinically definite relapsing-remitting MS patients with recombinant gamma interferon in a pilot study designed to evaluate toxicity and dosage. Patients received low (1 µg), intermediate (30 µg), or high (1,000 µg) doses of interferon by intravenous infusion twice a week for 4 weeks. Serum levels of gamma interferon were proportional to dose and no interferon was detected in CSF. Seven of the 18 patients had exacerbations during treatment, a significant increase compared with the prestudy exacerbation rate ($p < 0.01$). Exacerbations occurred in all three dosage groups and were not precipitated by fever or other dose-dependent side effects. There were significant increases in circulating monocytes bearing class II (HLA-DR) surface antigen, in the proliferative responses of peripheral blood leukocytes, and in natural killer cell activity. These results show that systemic administration of gamma interferon has pronounced effects on cellular immunity in MS and on disease activity within the CNS, suggesting that the attacks induced during treatment were immunologically mediated. Gamma interferon is unsuitable for use as a therapeutic agent in MS. Agents that specifically inhibit gamma interferon production or counteract its effects on immune cells should be investigated as candidates for experimental therapy.

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Treatment of multiple sclerosis with gamma interferon: Exacerbations associated with activation of the immune system

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Clinical trials of alpha and beta interferon (IFN) have been undertaken in patients with MS because of evidence that a viral infection, an immunoregulatory defect, or both, may be implicated in disease activity.¹⁻³ In a double-blind, placebo-controlled crossover trial of natural alpha IFN given systemically,⁴ the number of acute exacerbations in patients with relapsing-remitting MS was reduced, but the study was complicated by the crossover design and a marked placebo effect. Natural beta IFN administered intrathecally to 10 patients⁵ appeared to prevent exacerbations; however, the study lacked a placebo-treated control group. Recently, a multicenter double-blind controlled trial of intrathecal beta IFN⁶ confirmed the favorable results of the earlier study. The first clinical trial of recombinant IFN in MS, in which 2 million units of alpha₂ IFN were given subcutaneously three times per week for 1 year, was recently completed.⁷ There was no therapeutic effect, possibly because the dose was too low. Other studies, using higher systemic doses of recombinant IFN, are in progress.

Gamma or immune IFN has many of the antiviral and immunoregulatory properties of other interferons⁸; in addition, it can activate macrophages and induce class II histocompatibility antigens on monocytes,⁹ endothelial cells,¹⁰ and astrocytes.¹¹ These are properties that could stimulate an autoimmune process. On the other hand, recent reports of deficient gamma IFN pro-

duction in MS patients^{12,13} suggested the possibility of a therapeutic trial. We therefore performed a pilot study of recombinant gamma IFN to determine toxicity and dose, and to judge whether a larger, long-term clinical trial would be feasible. The results have been partially reported elsewhere as a preliminary communication.¹⁴

Methods. Patients and treatment protocol. Eighteen patients with clinically definite relapsing-remitting MS participated. There were 3 men and 15 women ranging in age from 19 to 42 years. All patients had had at least two exacerbations in the preceding 2 years, and were in remission at the time of entry. The study was approved by the University of Maryland Human Volunteers Research Committee. Recombinant gamma IFN (Immuneron, Biogen Research, Cambridge, MA) was given in doses of 1, 30, or 1,000 µg, corresponding approximately to 1.5×10^4 , 4.5×10^5 , and 1.5×10^7 IU of IFN, respectively. Patients were selected at random to receive the low, intermediate, or high doses twice a week for 4 weeks. One half of each dose was administered as an intravenous bolus; the remainder was given as an intravenous infusion over 2 hours. At the beginning and end of the trial, patients were scored according to the Kurtzke Expanded Disability Status Scale (EDSS),¹⁵ and the Scripps Neurological Rating Scale (NRS).¹⁶ Additional examinations were performed and scored for each exacerbation. An exacerbation was defined as the

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occurrence of new or recurrent neurologic symptoms with objective confirmation on examination, lasting at least 48 hours, and followed by complete or partial resolution. Exacerbations were rated as mild, moderate, or severe based on NRS scores.⁴ After completion of treatment, the patients were followed monthly for 12 to 20 months, using the same criteria to define and rate exacerbations. Lumbar punctures were performed before treatment and 1 hour after completion of the last infusion to determine cell count, IgG, albumin, and interferon titer. IgG indexes were calculated and oligoclonal IgG bands were identified by agarose electrophoresis. Myelin basic protein (MBP) in CSF was measured by radioimmunoassay (Metpath Laboratories, Teterboro, NJ).

Separation and analysis of mononuclear cells. Mononuclear cells (MNC) were separated from heparinized whole blood by gradient centrifugation on Ficoll-Paque (Pharmacia Fine Chemicals, Piscataway, NJ). Cells were then washed twice in phosphate-buffered saline (PBS) and resuspended either in PBS with 5% heat-inactivated pooled normal human AB serum for flow cytometry, or in RPMI-1640 medium (Gibco, Grand Island, NY) with 5% fetal bovine serum (FBS, Gibco), 10 mM HEPES buffer, 1% glutamine, and 20 µg/ml gentamicin (complete RPMI) for other assays. One-ml aliquots of MNC containing 1×10^6 cells were centrifuged in 12×75 -mm plastic tubes at $400 \times g$ for 5 minutes. Pellets were resuspended in 50 µl of monoclonal antisera diluted in PBS to insure antibody excess. The antibodies included fluorescein-conjugated OKT3, OKT4, and OKT8 (Ortho Diagnostics, Raritan, NJ), and anti-Leu 11, anti-Leu M3 and anti-HLA-DR (Becton-Dickinson, Mountain View, CA). Activated monocytes were identified by double labeling with fluorescein-conjugated anti-Leu M3 and phycoerythrin-conjugated anti-HLA-DR. After incubation for 30 minutes at 0 °C, cells were washed in cold PBS with 5% AB serum, and fixed in 1% paraformaldehyde. Five thousand cells per sample were analyzed in a Becton-Dickinson FACS IV flow cytometer.

Natural killer cell assay. K562 target cells were maintained in suspension culture in complete RPMI, and labeled with 100 µCi/ 10^6 cells of ^{51}Cr (Amersham, Arlington Heights, IL) on the day of the assay. MNC were added to the target cells in ratios of 20:1, 10:1, and 2:1 in a total volume of 0.2 ml in triplicate wells of 96-well round-bottom microtiter plates, and incubated for 5 hours at 37 °C. Supernatants were harvested using a semiautomatic harvesting press (Skatron Inc., Sterling, VA). Filters containing 0.2 ml of radioactive medium were counted in an LKB model 1282 gamma counter. Specific ^{51}Cr release was calculated as a percent of maximum counts released by treating target cells with 1% sodium dodecylsulfate. To determine whether NK cells retained or lost responsiveness to IFN during treatment of patients, the ability of gamma IFN to enhance NK activity in vitro was tested. Preliminary studies showed maximum enhancement of ^{51}Cr release when 1,500 units per ml of gamma IFN were added to cultures at an effector:target ratio of 20:1. After incubation with IFN for 18 hours at 37 °C, cells were centrifuged, washed,

counted, resuspended in complete RPMI, and tested in the NK assay described above.

IFN assay and gamma IFN synthesis. Production of gamma IFN by cultured cells was assayed by incubation of 2×10^6 MNC in 2 ml of complete RPMI with 3 µg/ml of concanavalin A (Con A, Difco Laboratories, Detroit, MI) or an equivalent volume of PBS, at 37 °C. After three days, supernatant fluids were collected and stored at -70 °C. IFN assays were performed using a solid phase radioimmunoassay kit (Centocor Inc, Malvern, PA) as described previously.¹⁷ Supernatant samples were assayed for 10 of the 18 patients, representing all three dosage levels, before, during (days 3 to 17), and after IFN treatment. Serum and CSF IFN levels were determined by enzymatic immunoassay at Biogen Research Corp.

Lymphocyte proliferation. MNC were suspended in complete RPMI with addition of Con A at a final concentration of 3 µg/ml, PHA (PHA-P, Difco) at 20 µg/ml, or human myelin basic protein (MBP) at 10 µg/ml. PBS was added to control cultures. Mitogen-stimulated cultures were incubated for 3 days and MBP-stimulated cultures for 5 days in flat-bottom microtiter plates at 37 °C with addition of 1 µCi of ^3H thymidine (specific activity, 40 Ci/mM; Amersham) for the final 18 hours. Cells were harvested on glass fiber filters and five replicates of each sample were counted in a Beckman LS 3100 liquid scintillation counter. Counts per minute (cpm) of unstimulated cultures were subtracted from cpm of stimulated cultures to determine specific proliferative activity (Δcpm). Stimulation indexes (SI) were calculated by dividing cpm of stimulated by cpm of unstimulated cultures.

Statistical methods. Exacerbations before and during treatment were compared by chi-square analysis. Results of experiments involving multiple comparisons over time were tested for significance by an analysis of variance for repeated measures. Means of other data sets were analyzed by two-tailed *t* test.

Results. Clinical findings. Seven of the 18 patients had exacerbations of MS during 18 patient-months of IFN treatment. This differed significantly ($p < 0.01$) from the number of exacerbations during the preceding 2 years (51 attacks in 432 patient-months). The exacerbation rate increased from 1.42 to 4.67 attacks per patient per year (figure 1). Most of the exacerbations involved recurrence of signs and symptoms that the patients had experienced previously. In the seven patients who had exacerbations during treatment, the mean interval from their last exacerbation before administration of IFN was 4.6 months (range, 1 to 12 months); in the 11 patients who did not have attacks during treatment, it was 7.2 months (range, 3 to 19 months). This difference was not statistically significant. Although the number of patients with acute attacks was greatest (3/5) in the 1,000-µg group, attacks of comparable severity occurred in patients receiving 1 µg or 30 µg of IFN. Recovery from exacerbations was complete in all patients, and the attack rate during 12 to 20 months of follow-up was 1.05 per year (figure 1). Neurologic dysfunction as quantitated by the EDSS and NRS scores did not increase.

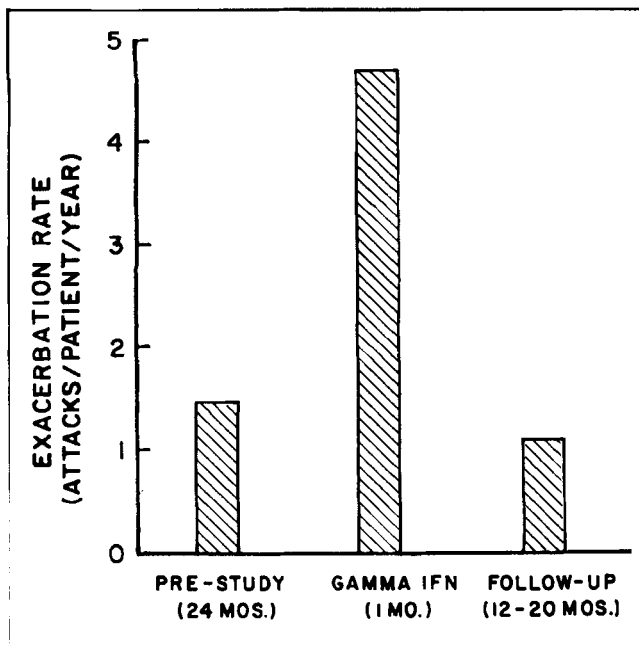


Figure 1. Increase in exacerbation rate during treatment with gamma interferon compared with pretreatment and follow-up periods.

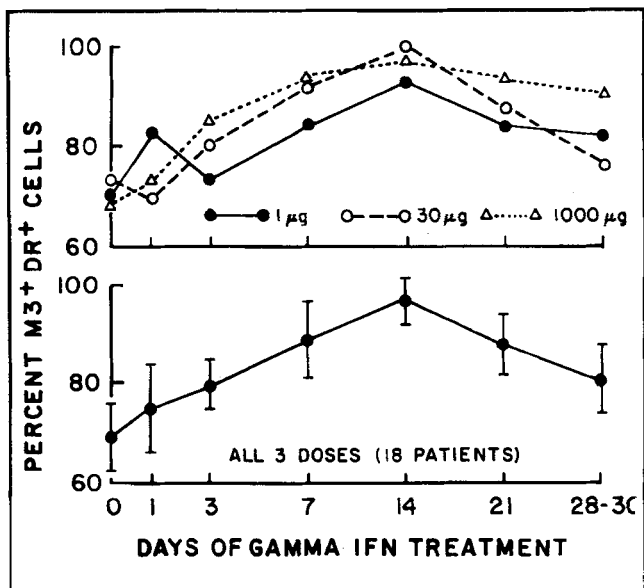


Figure 2. M3⁺/HLA-DR⁺ cells (activated monocytes) expressed as percent of M3⁺ cells in peripheral blood for each dosage group (top) and for all patients combined (bottom). The combined values (means $\pm$ SE) were significantly increased at days 7 and 21 ($p < 0.05$) and day 14 ($p < 0.01$).

Table 1. Side effects of systemic gamma interferon

Symptom	Dose		
	1 µg	30 µg	1,000 µg
Fever/Chills	1/6	4/7	5/5
Fatigue	0/6	3/7	4/5
Myalgias/Arthralgias	0/6	3/7	5/5
Headache	3/6	3/7	4/5
Nausea	0/6	3/7	1/5
Other	2/6	3/7	1/5

The mean pre- and post-treatment EDSS scores were each 3.7, and mean NRS scores before and after treatment were also nearly identical (73.9 versus 72.0). CSF cell counts, IgG indexes, MBP levels, and oligoclonal IgG bands were not significantly affected by IFN treatment.

Interferon levels and side effects. Serum levels of gamma IFN were detected only in those patients receiving the 1,000 µg dose. The mean peak titer of serial samples drawn after beginning the first infusion was 128.8 IU/ml at 2 hours. No IFN could be measured in the CSF of any subject. Systemic side effects (table 1) included fever up to 104 °F, chills, headache, fatigue, and myalgia. Symptoms generally began 3 to 4 hours after each 1,000-µg infusion, lasted 6 to 8 hours, were most severe with the initial treatment, and diminished in severity with subsequent infusions. Subjects who received 30 µg had symptoms only after the first few doses, and those receiving 1 µg had minor symptoms or none at all. Exacerbations were not directly precipitated by fever or other side effects.

Analysis of MNC by flow cytometry. No significant changes were found in percentages or absolute numbers of cells reacting with OKT3, OKT4, or OKT8 monoclonal antibodies, or in T4/T8 ratios. The Leu 11 marker, specific for NK cells, increased on day 21, long after the early increase seen in functional NK activity on days 1 and 3. The percentages of Leu M3⁺ and HLA-DR⁺ cells were only slightly elevated, but cells positive for both markers by the double-labeling technique increased significantly in percentage (figure 2) and absolute number (data not shown). The increase was apparent in all three dosage groups, and in patients who had exacerbations the mean increase was greater than in patients without attacks (28.2% versus 14.3%, $p < 0.05$).

Lymphocyte proliferation. There was a progressive increase in spontaneous proliferation of unstimulated MNC cultures during IFN treatment from 5,000 to 6,000 cpm to over 15,000 cpm. This occurred in both 3-day and 5-day cultures, and was statistically significant at days 21 ($p < 0.05$) and 28 ($p < 0.01$). Responses to Con A and PHA of cultured MNC increased slightly during the study, with maximum proliferation for most subjects on day 21 (table 2); however, the SI did not increase significantly. In contrast, the proliferative response to MBP, which was suppressed below that of unstimulated cultures before treatment, increased in both cpm and SI, and was most pronounced in the seven patients with exacerbations (table 3). Dates of maximum response to MBP varied from day 7 to day 28, but because all time points were not studied in all patients, it was not possible to determine whether the peak proliferative response coincided with the onset of attacks.

Gamma IFN production. Peripheral blood MNC

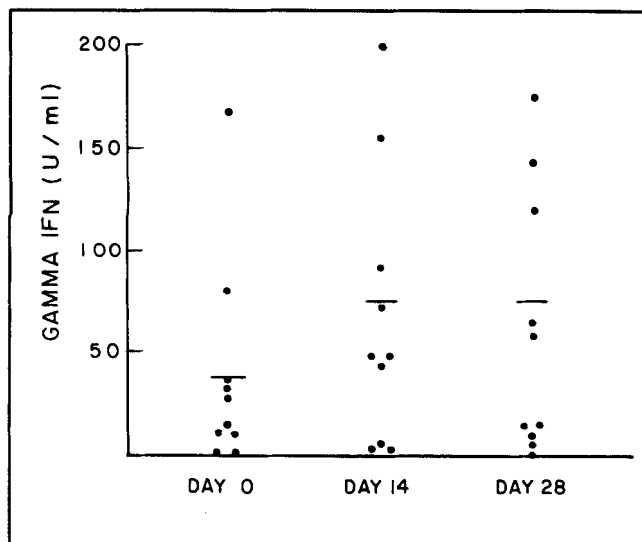


Figure 3. Production of gamma IFN by Con A-stimulated peripheral blood MNC. The mean increases at days 14 and 28 were not statistically significant.

Table 2. Responses to T cell mitogens during gamma IFN study

Mitogen	Day 0	Maximum response*	Significance†
PHA			
ΔCPM ± SD	225,195 ± 43,534	266,469 ± 29,017	$p < 0.05$
SI ± SD	65.4 ± 18.2	69.8 ± 21.6	NS
Con A			
ΔCPM ± SD	148,988 ± 30,142	209,785 ± 27,357	$p < 0.05$
SI ± SD	48.5 ± 12.6	57.5 ± 15.6	NS

* Maximum response occurred on day 21 for most patients.
† Two-tailed t test.
ΔCPM CPM of stimulated minus CPM of unstimulated cultures.
NS Not significant.
SI Stimulation index.

stimulated by Con A produced gamma IFN in 8 of 10 patients tested (figure 3). The mean pretreatment level (38 U/ml) was comparable to levels produced by cells from normal controls, but was less than that previously reported for MS patients by this laboratory.¹⁷ Production was not suppressed by IFN treatment, but increased to a mean of 75 U/ml. Of the seven patients with normal or increased gamma IFN production, five had exacerbations. Of the three patients whose gamma IFN production remained low (less than 10 U/ml) throughout treatment, one had a mild exacerbation. The remaining exacerbation occurred in a patient whose IFN production was not tested.

Natural killer cell activity. Mean pretreatment levels of NK cytotoxicity in the MS patients (18.5%) were lower than in normal laboratory controls (35%, data not shown). With IFN treatment there was an early peak of activity at 1 to 3 days, followed by a return to levels slightly above baseline by day 7 (figure 4). The same pattern was observed with all three doses. Addition of gamma IFN to the cultures in vitro consistently aug-

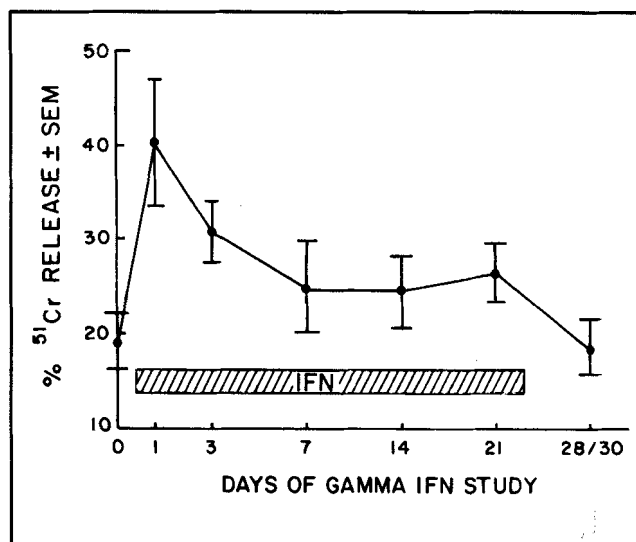


Figure 4. Spontaneous NK cytolytic activity in the 18 patients during gamma IFN treatment. Effector:target ratio = 20:1. Significant differences from prestudy level were found on day 1 and day 3 ($p < 0.05$).

Table 3. Enhancement of response to MBP during gamma IFN study

	Day 0	Maximum response*	Significance†
All patients			
ΔCPM ± SD	-4,092 ± 7,487	7,141 ± 5,030	$p < 0.01$
SI ± SD	0.80 ± 0.66	1.69 ± 0.78	$p < 0.01$
7 patients with exacerbations			
ΔCPM ± SD	-3,610 ± 7,159	10,490 ± 3,105	$p < 0.01$
SI ± SD	0.74 ± 0.45	2.16 ± 0.98	$p < 0.05$

* Date of maximum response varied from day 7 to day 28 of treatment.
† Two-tailed t test.
ΔCPM CPM of MBP-stimulated minus CPM of unstimulated cultures.
SI Stimulation index.

mented NK activity two- to threefold. The increase was least on days 1 and 3 when spontaneous NK activity was greatest, but it was significant ($p < 0.001$) at all time points by paired t test.

Discussion. The clinical results of this study contrast with the favorable responses to alpha and beta IFN reported by Knobler et al⁴ and Jacobs et al.^{5,6} Our study also calls into question the reports of Vervliet et al^{13,18} describing defective gamma IFN production in active MS patients. While the present study was in progress, we tested IFN levels in another group of untreated MS patients using a sensitive solid phase radioimmunoassay, and found that their cells produced more gamma IFN than normal controls.¹⁷ This observation has now been confirmed by others.¹⁹ It is consistent with our clinical findings, and similarly implies that gamma IFN is not suitable for use as a therapeutic agent in MS.

Although the effect of gamma IFN we observed was not the one we anticipated or desired, it was consistent with the ability of gamma IFN to augment immune responses and with the hypothesis that exacerbations of MS are mediated by an autoimmune process. It also showed that systemic treatment with gamma IFN can have a profound effect on disease activity within the CNS, even though interferons cross the intact blood-brain barrier poorly.²⁰ The observation that exacerbations precipitated by gamma IFN were clinically similar or identical to earlier exacerbations suggests that gamma IFN or activated cells may cross a recently damaged blood-brain barrier more readily than a normal barrier. The interval between the most recent previous attack and administration of gamma IFN was somewhat shorter in those patients who had exacerbations during treatment than in those who did not; but because of the small number of patients and the broad range of time intervals in each group, the difference was not statistically significant. This remains an intriguing topic for speculation.

During this study, NK cell activity remained at or above normal levels, enhancement of NK activity by IFN *in vitro* was maintained, and the ability of the patients' cells to produce gamma IFN *in vitro* was not suppressed. Nevertheless, disease activity increased in a significant number of treated patients. These results suggest that some of the so-called immunoregulatory defects in MS, in particular reduced IFN production and NK activity, do not bear a causal relationship to the pathogenesis of acute exacerbations. Several other measures of immunologic function similarly did not correlate with treatment or with disease activity. Analysis of T4 and T8 subsets and their ratios by monoclonal antibody surface staining has not been a reliable measure of disease activity in relapsing-remitting patients,²¹ and this study confirms that impression. CSF immunoglobulins are useful diagnostically in MS, and may be quantitatively reduced by certain types of treatment such as ACTH and corticosteroids, but this and previous studies^{4,22} have shown that they cannot be used as disease markers in therapeutic trials. CSF MBP was not increased in any of the patients with acute exacerbations; but because the attacks were relatively mild and lumbar punctures were not done at the onset of attacks, we could draw no conclusions about MBP levels in this small sample of patients.

In addition to its antiviral, antiproliferative, and immunomodulatory functions, gamma IFN may strongly potentiate immune responses through activation of macrophages and T lymphocytes.⁸ All interferons can induce class I histocompatibility antigens on a variety of cell types; however, gamma IFN is unique in its ability to induce class II (Ia or HLA-DR) antigens.^{9,23} The presence of these determinants on monocytes and macrophages permits them to function as antigen-presenting cells in the induction or enhancement of immune responses. In addition, gamma IFN has recently been reported to induce Ia determinants on endothelial cells¹⁰ and astrocytes.¹¹ Endothelial cell Ia antigen has been implicated in the pathogenesis of experimental allergic encephalomyelitis,²⁴ an animal

model of MS. Astrocytes¹¹ and endothelial cells²⁵ develop the capacity to present MBP to T cells, a process that may play a central role in generation of an autoimmune response to CNS myelin. Because Ia⁺ macrophages, endothelial cells, and astrocytes are prominent in MS plaques,^{26,27} gamma IFN could be intimately involved in the pathogenesis of disease activity.

Although the increased percentage of HLA-DR⁺ monocytes we detected in peripheral blood did not correspond exactly with the onset of exacerbations in all patients, the greatest increase occurred in the 30- μ g and 1,000- μ g dose groups, and patients who had exacerbations showed a greater increase in double-labeled cells than those who remained clinically stable. Studies of specific antigen-presenting activity of these cells were not done; however, the proliferative response of peripheral blood MNC to MBP was studied as a possible correlate of antigen-presenting activity. Increased proliferation to MBP in the face of relatively slight augmentation of the Con A and PHA responses suggests immunologic specificity for MBP. In the present study, although proliferative responses to other soluble protein antigens were not measured, the elevated response to MBP and its association with acute exacerbations are consistent with the interpretation that MBP-specific T cells or other unidentified autoreactive antigen-specific T cells may have been activated by gamma IFN. The progressive increase in spontaneous proliferation in control cell cultures suggests that nonspecific activation also occurred during gamma IFN treatment. Although we did not identify the proliferating cell type in this study, activated T lymphocytes have been reported previously in the peripheral blood and CSF of patients with active MS.^{28,29}

In view of these findings, a possible role for gamma IFN in naturally occurring exacerbations of MS is suggested. Sibley et al³⁰ have documented the frequent relationship of acute exacerbations to common viral infections. Viral infections can activate immune T cells to produce gamma IFN, which may then induce a myelin-specific autoimmune response in the CNS.³¹ If disease activity is mediated by gamma IFN, either through induction of HLA-DR antigen or another mechanism, it is obvious that further clinical trials of gamma IFN in MS should not be attempted. Substances that neutralize gamma IFN, inhibit its production, block its receptors, or react with gamma-induced class II determinants might be considered for therapeutic study. Monoclonal anti-Ia antibodies have already shown promise in the prevention and treatment of experimental allergic encephalomyelitis.³² However, extension of these studies to humans may be hampered by the polymorphism of class II antigens, development of neutralizing antibodies to monoclonal mouse immunoglobulins, or by toxic side effects.

Alpha and beta interferons, in contrast, are relatively nontoxic human gene products. In addition to their antiviral, antiproliferative, and other immunomodulatory effects, they have been shown to counteract the Ia-inducing effect of gamma IFN *in vitro*,³³ and may, therefore, have therapeutic value *in vivo* as

gamma IFN antagonists. Because early clinical trials of natural alpha⁴ and beta^{5,6} interferons in MS have been promising, they should be investigated further with appropriate pilot studies to determine maximum tolerated doses and optimum frequency of administration. In view of the ability of gamma IFN to activate MS via the systemic route, it is likely that agents that counteract gamma IFN could be given systemically, and that intrathecal or intraventricular administration, which are cumbersome and potentially hazardous, can be avoided. In the conduct of such clinical trials, gamma IFN production and activity should be monitored as correlates of disease activity and immunotherapeutic effect.

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