CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, Nov. 1997, p. 764–768 Vol. 4, No. 6
1071-412X/97/$04.00+0

Gamma Interferon Prevents Diabetes in the BB Rat

DOUGLAS O. SOBEL[1]* AND JOSEPH NEWSOME[2]

Division of Pediatric Endocrinology and Metabolism[1] and Department of Pathology,[2] Georgetown University Medical Center, Washington, D.C. 20007-2197

Received 1 May 1997/Returned for modification 23 July 1997/Accepted 10 September 1997

The BB rat model of human insulin-dependent diabetes mellitus (IDDM) spontaneously develops diabetes through an autoimmune process. Gamma interferon (IFN-γ) is thought to play an important pathogenic role. This study examined if IFN-γ administration can, paradoxically, prevent diabetes in BB rats. Diabetes-prone BB rats were initially injected intraperitoneally with murine recombinant IFN-γ (rIFN-γ) at doses of 0.5×10^4 to 40×10^4 U three times a week for 6 weeks beginning at 35 days of age. The effects of altering the duration of treatment (2 to 6 weeks) and the age at which injections were initiated (45 through 65 days) were also assessed. rIFN-γ administration prevented the development of diabetes in a dose-dependent manner. The optimal treatment condition resulted in a 9.1% incidence of diabetes versus a 90% incidence in control rats. This diabetes-sparing effect was long lasting and continued to 7 months of age. A 4- to 6-week course resulted in maximal inhibition. Treatment initiated as late as 55 days of age, when insulitis is already present, was effective in preventing diabetes. Islet inflammation was dramatically lower in rIFN-γ- versus saline-injected rats ($P < 0.01$). Total leukocyte count and subpopulations of peripheral mononuclear cells were unaltered by rIFN-γ. In summary, rIFN-γ paradoxically and potently prevents diabetes in BB rats in a dose-dependent fashion by inhibiting islet inflammation. This diabetes-sparing effect occurs even when injections are initiated after evidence of the diabetic process is already present.

The BB rat spontaneously develops diabetes and serves as an animal model to study the pathogenesis of human insulin-dependent diabetes mellitus (IDDM) (15, 17). As in IDDM, the pathogenesis of diabetes is due to a T-cell-mediated autoimmune process associated with specific class II major histocompatibility complex molecules and is characterized by lymphocytic infiltration of islets (2, 13, 15). Gamma interferon (IFN-γ), a cytokine secreted by T lymphocytes in response to antigen stimulation, has important immunomodulatory properties (33) and is thought to play a role in the development of type 1 diabetes mellitus. IFN-γ has been detected in the sera of patients with new-onset IDDM (6, 26). IFN-γ antibody administration has been demonstrated to inhibit diabetes in both the BB rat and NOD mouse models of type 1 diabetes (3, 18). This cytokine not only sensitizes beta cells to T-cell lysis (14) but is beta cell cytotoxic (20). Furthermore, diabetes has been induced in transgenic mice expressing IFN-γ within beta cells (22). However, we hypothesize that IFN-γ can paradoxically inhibit the autoimmune diabetic process since IFN-γ treatment has been shown to suppress and inhibit the course of other autoimmune diseases including human rheumatoid arthritis (11, 12) and autoimmune polyarteritis (19). Thus, IFN-γ administration could also favorably alter the development of IDDM. This report explores the hypothesis that IFN-γ inhibits the development of diabetes in the BB rat model of human IDDM.

MATERIALS AND METHODS

Materials. Diabetes-prone BB rats were obtained from the viral-antigen-free colony at the University of Massachusetts Medical School (Worcester). A viral-pathogen-free environment was maintained by autoclaving food, bedding, and cages, acidifying drinking water, and placing cages covered with filtered bonnets in a laminar flow hood. Murine recombinant IFN-γ (rIFN-γ) was obtained from Genentech (8×10^6 U/mg) and diluted with saline just prior to injection. This rIFN-γ preparation contained 0.067 ng of endotoxin per 10^8 U. The administration of 0.25 pg of endotoxin (Cape Cod Associates), the amount contained in the highest rIFN-γ dose utilized, in a manner similar to that described below for the test animals did not inhibit the development of diabetes (data not shown).

Experimental design. The effect of rIFN-γ on the development of diabetes was initially studied in BB rats randomly placed into saline ($n = 10$) and rIFN-γ ($n = 11$) treatment groups. Beginning at 35 to 40 days of age, 40×10^4 U was administered by the intraperitoneal (IP) route three times a week (TIW) for 6 weeks.

The effect of rIFN-γ dose on the development of diabetes was assessed in 35- to 40-day-old BB rats utilizing the above-described injection schedule (IP TIW) with rIFN-γ doses of 0.5×10^4 ($n = 7$), 2.5×10^4 ($n = 7$), 10×10^4 ($n = 7$), and 40×10^4 U ($n = 6$). A control group ($n = 8$) received only saline.

The effect of altering the duration of IFN-γ treatment was determined by comparing the rates of diabetes development in BB rats injected with rIFN-γ (40×10^4 U IP TIW) for 2 ($n = 7$), 4 ($n = 7$), or 6 weeks ($n = 6$) or with saline alone ($n = 8$).

To determine the effect of initiating rIFN-γ injections in older animals, BB rats were injected with 20×10^4 U IP TIW for 4 weeks beginning at 45 ($n = 25$), 55 ($n = 18$), and 65 ($n = 18$) days of age.

Blood glucose concentrations were determined TIW. When glucose concentrations reached >250 mg% on two consecutive days, the animals were diagnosed with diabetes and sacrificed. Nondiabetic animals were sacrificed at 130 days unless otherwise stated.

Testing for glucose tolerance. To assess the long-term diabetes-sparing effect of rIFN-γ administration, an oral glucose tolerance test was performed on 150-day-old nondiabetic rats ($n = 5$) previously treated with 40×10^4 U IP TIW for 6 weeks. A 20% dextrose solution (2 mg/g of body weight) was administered by orogastric tube (23). Blood glucose concentrations were then determined just prior to and 60 and 120 min after dextrose administration.

Pancreatic histology. Pancreata were resected from 60-day-old rIFN-γ ($n = 10$)- and saline ($n = 10$)-treated rats, fixed in buffered formalin, and embedded in paraffin. The tissues were later sectioned and stained with hematoxylin and eosin. Under light microscopy, the degree of islet inflammation was blindly scored as follows (and as previously described [25]): 0, no inflammation; 1, 1 to 10% islet infiltration; 2, 10 to 25% islet infiltration; 3, 25 to 75% islet infiltration; and 4, >75% islet infiltration or islet fibrosis.

Analysis of cell surface phenotypes. Peripheral blood mononuclear cells (PBMC) were separated from whole blood by Ficoll-Hypaque centrifugation. A minimum of 10,000 cells were analyzed by flow cytometry with a FACScan (Becton Dickinson). OX19 (pan T-cell phenotype) fluorescein isothiocyanate-conjugated antibody and OX8 phycoerythrin-conjugated antibody (Serotec, Oxford, United Kingdom) were utilized to delineate cytotoxic-suppressor T-cell phenotype ($OX19^+$ $OX8^+$), helper-inducer T-cell phenotype ($OX19^+$ $OX8^-$), and NK cell phenotype ($OX19^-$ $OX8^+$) populations. T cells expressing RT6.1 cells, cells with putative suppressor-like activity (7), were assessed by using

* Corresponding author. Mailing address: Division of Pediatric Endocrinology and Metabolism, Georgetown University Medical Center, 3800 Reservoir Rd., N.W., Washington, D.C. 20007-2197. Phone: (202) 687-8881. Fax: (202) 687-7161.

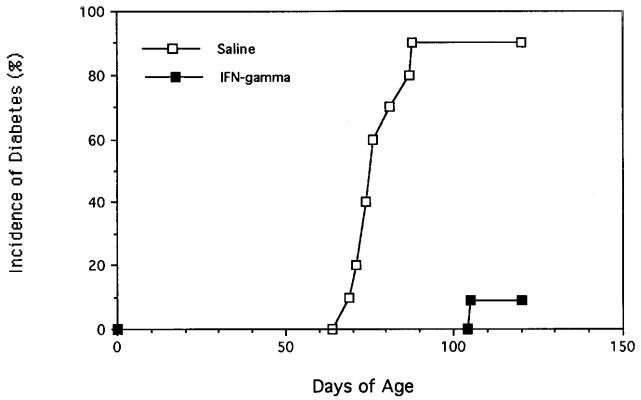

FIG. 1. Effect of rIFN-γ administration on the development of diabetes. Beginning at 35 to 40 days of age, rIFN-γ (40×10^4 U) ($n = 11$) or saline ($n = 10$) was administered IP TIW for 6 weeks. Animals were diagnosed with diabetes when blood glucose concentrations on two consecutive days were greater than 250 mg%.

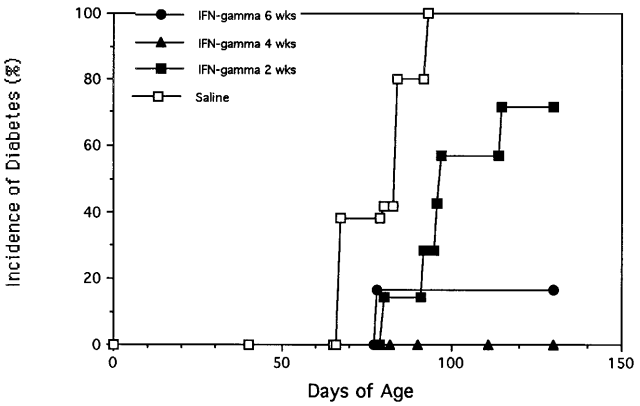

FIG. 3. Effects of altering the duration of rIFN-γ administration on the development of diabetes. BB rats were administered 40×10^4 U of rIFN-γ IP TIW for 2 weeks ($n = 7$), 4 weeks ($n = 7$), or 6 weeks ($n = 6$) or were given saline ($n = 8$).

DS4.23 (a rat monoclonal antibody obtained from D. Lubaroff [4]) and goat anti-rat immunoglobulin G conjugated to phycoerythrin (Serotec).

Statistical analysis. The product limit method of Kaplan and Meier was used to estimate survival from diabetes. Log-rank tests were used to compare the product limit functions. Group means were compared by Student's *t* test.

RESULTS

Development of diabetes. The effect of rIFN-γ administration on the development of diabetes is depicted in Fig. 1. By survival curve analysis, rIFN-γ (40×10^4 U IP TIW) decreased the development of diabetes compared to control animals ($P < 0.001$). In addition, the incidence of diabetes by 130 days was significantly lower in the rIFN-γ-treated rats (9.1%) than in the control group (90%) (chi square = 11.6, $P < 0.001$). Only one animal within the IFN-γ group developed diabetes. No behavioral side effects were observed in rIFN-γ-treated animals. The weights of nondiabetic rIFN-γ-treated and control animals were similar over time.

The effect of rIFN-γ dose on diabetes development was assessed by administering 0.5×10^4, 2.5×10^4, 10×10^4, and 40×10^4 U IP TIW for 6 weeks (Fig. 2). The diabetes-sparing effect of rIFN-γ was dose dependent overall. Doses of 10×10^4 and 40×10^4 U maximally inhibited the development of diabetes ($P < 0.03$ and $P < 0.01$, respectively) while a dose of 2.5×10^4 U also tended to slow the diabetic process ($P < 0.06$).

Effect of duration of treatment. The effect of duration of rIFN-γ treatment was explored utilizing 2-, 4-, and 6-week courses of 40×10^4 U of rIFN-γ IP TIW (Fig. 3). By 100 days of age, all durations of rIFN-γ treatment, even as short as 2 weeks, slowed the development of diabetes compared to control animals ($P < 0.01$ for all groups). Rats treated with IFN-γ for 4 or 6 weeks that did not develop diabetes by 80 days remained nondiabetic until the end of the experiment at 130 days of age. However, animals treated for only 2 weeks continued to develop diabetes. Animals receiving the 4- or 6-week course of rIFN-γ had a slower development of diabetes than those administered the 2-week course by the end of the observation time ($P < 0.03$).

Effect of age of initiation of treatment. The ability of rIFN-γ to prevent diabetes in older rats was examined by initiating treatment at 45, 55, and 65 days of age (Fig. 4). The diabetes-sparing effect was inversely age dependent. Diabetes was inhibited when rIFN-γ treatment was initiated at 45 days of age ($P < 0.005$) and 55 days of age ($P < 0.04$). Even when rIFN-γ was initiated at 65 days of age, there tended to be a delay in diabetes development.

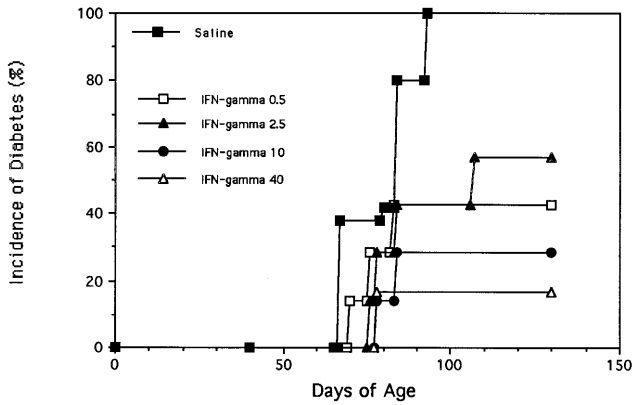

FIG. 2. Dose effects on the diabetes-sparing effect of rIFN-γ. rIFN-γ at doses of 0.5×10^4 (0.5; $n = 7$), 2.5×10^4 (2.5; $n = 7$), 10×10^4 (10; $n = 7$), and 40×10^4 (40; $n = 8$) U or saline ($n = 8$) was injected IP TIW for 6 weeks.

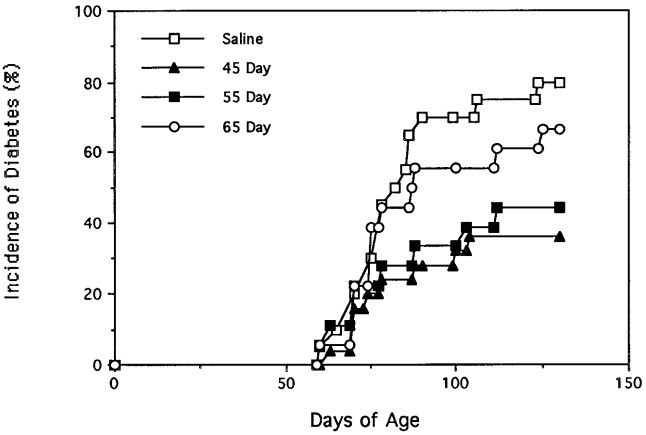

FIG. 4. Effects of initiating rIFN-γ in older rats on the development of diabetes. BB rats were injected with 20×10^4 U of rIFN-γ IP TIW for 4 weeks beginning at 45 ($n = 25$), 55 ($n = 18$), and 65 ($n = 18$) days of age.

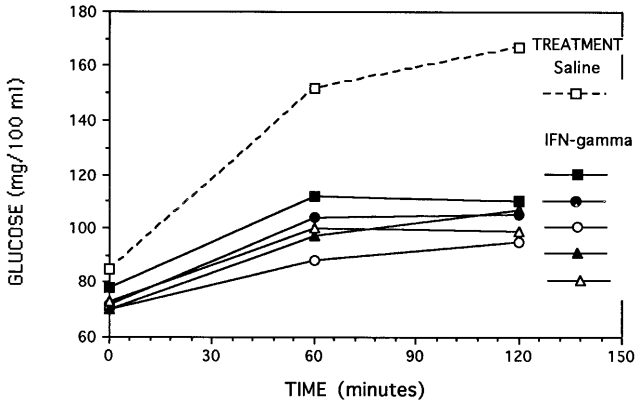

FIG. 5. Glucose tolerance testing of 150-day-old BB rats previously treated with rIFN-γ. A total of 40×10^4 U of rIFN-γ ($n = 5$) or saline ($n = 1$) was administered IP TIW for 6 weeks. A 20% dextrose solution (2 mg/g of body weight) was administered by orogastric tube. Blood samples for glucose determination were obtained prior to and 60 and 120 min after dextrose administration.

Glucose tolerance testing of rIFN-γ-treated rats. To assess the very-long-term disease-sparing activity of rIFN-γ, oral glucose tolerance tests were performed with 150-day-old nondiabetic BB rats previously treated with a 40×10^4 U dose of rIFN-γ for 6 weeks. Glucose excursions were normal in all rIFN-γ-treated rats (Fig. 5). The single saline-treated 150-day-old nondiabetic rat had an elevated blood glucose level at 120 min. To further assess the long-lasting effect of rIFN-γ, rIFN-γ-injected rats found nondiabetic by 130 days of age were monitored for another 80 days. All animals remained nondiabetic.

Histopathology of pancreata. The histopathology of pancreata from rIFN-γ (dose, 40×10^4 U)-treated ($n = 10$) and saline-treated ($n = 10$) nondiabetic 60-day-old BB rats was assessed. An inflammatory response consisting of predominantly mononuclear cells was found in the islets and only very rarely in the exocrine tissue in both treatment groups. However, the degree of islet inflammation was far lower in rIFN-γ-injected rats (Fig. 6) as determined by the lower inflammatory scores ($P < 0.01$) (Fig. 7).

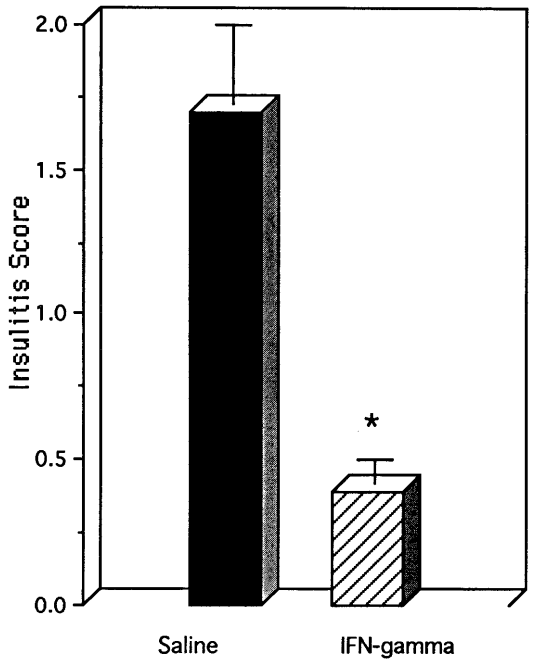

FIG. 7. Mean histopathologic scores of pancreata from 60-day-old BB rats administered saline ($n = 10$) or rIFN-γ (40×10^4 U IP TIW) ($n = 10$). Islets were blindly scored as follows: 0, no inflammation; 1, 1 to 10% islet infiltration; 2, 10 to 25% islet infiltration; 3, 25 to 75% islet infiltration; and 4, >75% islet infiltration or islet fibrosis. Error bars indicate standard errors of the means. *, $P < 0.01$ versus control rats.

Phenotypes of PBMC from IFN-γ (dose, 40×10^4 U)-treated nondiabetic BB rats ($n = 5$) and saline-treated control BB rats ($n = 5$) were assessed. The percentage of cells which were RT6 positive was <2% in each group. The proportions of all other subpopulations of PBMC from each group were also similar (Table 1). Mean total leukocyte counts (± standard

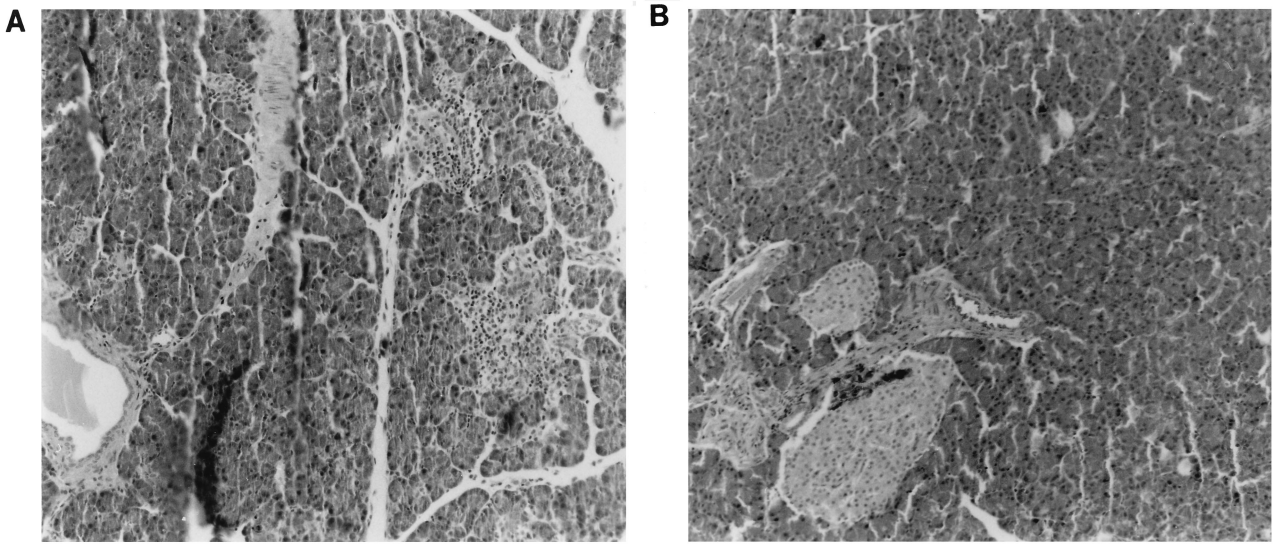

FIG. 6. Photomicrographs of hematoxylin- and eosin-stained pancreatic tissue (magnification, ×60) from 60-day-old BB rats administered rIFN-γ (40×10^4 U IP TIW) (A) or saline (B).

TABLE 1. Percent mononuclear leukocytes from control and treated rats reacting with OX19 and OX8 antibodies[a]

Phenotype	% Cells reacting with antibodies in rats administered:	
	Saline	rIFN-γ
$OX19^-$ $OX8^+$	17.2 ± 9.4	10.1 ± 8.4
$OX19^+$ $OX8^+$	0.5 ± 0.3	0.2 ± 0.2
$OX19^-$ $OX8^-$	80.4 ± 10.0	88.1 ± 9.9
$OX19^+$ $OX8^-$, $OX19^+$	1.8 ± 0.6	1.6 ± 1.3

[a] Rats were treated with 40×10^4 U of rIFN-γ IP TIW for 3 weeks or were given saline. Results were determined by flow cytometric analysis as discussed in Materials and Methods.

errors of the means) were also similar in the saline and IFN-γ groups (7,083 ± 8,141 versus 7,552 ± 1,264 cells/μl of blood).

DISCUSSION

This is the first report of rIFN-γ administration preventing diabetes. This effect was very powerful in that as few as 9.1% of BB rats, compared to 90% of control animals, developed diabetes. At optimal conditions, this rIFN-γ effect appears to prevent and not just delay the development of diabetes, since by 150 days of age, nondiabetic rIFN-γ-injected BB rats displayed normal oral glucose tolerance tests and clearly were not going to develop diabetes imminently. Further, similarly rIFN-γ-treated BB rats not developing diabetes by 130 days remained diabetes free by 210 days of age, more than 4 months after the last dose of IFN-γ. Although very potent in preventing diabetes, IFN-γ treatment did not alter animal growth or cause abnormal behavior.

The diabetes-sparing effect of rIFN-γ appeared to be dose dependent. Doses of 10×10^4 and 40×10^4 U induced maximal diabetes inhibition. Treatment for 4 weeks was as effective as treatment for 6 weeks in inhibiting diabetes. A 2-week course was sufficient to initially inhibit disease, but this course of treatment was not as effective as longer courses.

The administration of rIFN-γ was effective in inhibiting diabetes when injections were given as late as 55 days of age. This documents that rIFN-γ inhibits the diabetes process in animals even after the process has begun, since insulitis is already present even in 45-day-old BB rats (5).

The ability of rIFN-γ to successfully inhibit the diabetic process may appear surprising since IFN-γ is thought to upregulate the immune system and play a role in the pathogenesis of diabetes. In fact, it has been demonstrated that IFN-γ is cytotoxic to islets (20), IFN-γ antibody administration prevents diabetes in BB rat and NOD mouse models of IDDM (3, 18), and transgenic mice expressing IFN-γ on beta cells develop insulitis and diabetes (22). Very little data suggest the potential usefulness of IFN-γ to inhibit any autoimmune process. However, IFN-γ administration inhibits the development of experimental arthritis in rats (16) and decreases disease activity in humans with rheumatoid arthritis (11) and polyarteritis (19). The paradoxically positive effect of rIFN-γ on the development of diabetes may be explained by the different levels of IFN-γ generated in the tissues of rIFN-γ-treated rats and transgenic mice since the administration of different doses of cytokine may result in opposite effects (31). But it is interesting to note that over a very wide range of rIFN-γ doses (0.5×10^4 to 40×10^4 U), none accelerated the development of diabetes. The different times at which tissue IFN-γ levels are altered in the course of the disease in the different diabetes models may also explain the paradox. For example, IFN-γ can suppress or augment experimental autoimmune arthritis in rats depending upon the time in the course of disease that rIFN-γ is administered (10).

The lower degree of islet inflammation in rIFN-γ-injected rats suggests that IFN-γ inhibits the diabetic process by preventing islet inflammation and not by protecting the islet from the inflammatory response (8, 29). Although rIFN-γ can induce leukopenia (1), which could depress effector cells to prevent insulitis, leukopenia was not observed. T cells and NK cells have been thought to play a role in the pathogenesis of diabetes in the BB rat (13, 32). Analysis of mononuclear cell phenotypes of PBMC from IFN-γ-treated animals demonstrated no differences in phenotype subpopulations of peripheral mononuclear cells that could account for the effect of rIFN-γ. The prevention of insulitis could be mediated by the property of IFN-γ to induce suppressor cells (9, 27). If present, $RT6.1^+$ cells (putative suppressor cells [4]) do not appear to play a role since their numbers were not augmented by IFN-γ administration. Alternatively, rIFN-γ may be directly inhibiting inflammatory cell recruitment to islets, a mechanism thought to be important in rIFN-γ-mediated inhibition of experimental arthritis in rats (28).

rIFN-γ could be inhibiting insulitis and in turn diabetes by altering other cytokine responses from T cells and macrophages. For example, since IFN-γ augments tumor necrosis factor (TNF) secretion from macrophages (30) and since TNF administration has been demonstrated to inhibit the diabetic process in BB rats (24), rIFN-γ could inhibit diabetes through the augmentation of TNF. Alternatively, IFN-γ, a cytokine produced in Th-1 helper cells, could be inhibiting diabetes by its ability to promote the development of Th-1 lymphocyte subsets and their cytokine production (e.g., interleukin 2 [IL-2] and IFN-γ) or to inhibit the development of Th-2 lymphocyte subsets and their cytokine production (e.g., IL-4 and IL-10).

Freund's adjuvant is an immunopotentiator which prevents the development of diabetes in BB rats (21). It has been hypothesized to act by inducing cytokines. The data presented herein go against the possibility that rIFN-γ and Freund's adjuvant have similar mechanisms of action since, in contrast to the data presented herein, Freund's adjuvant administration can prevent diabetes without inhibiting insulitis and is not effective if administered as late as 45 days of age.

In conclusion, rIFN-γ administration potently prevents the development of diabetes in the BB rat model of human IDDM in a dose-dependent manner. This diabetes-sparing effect is due to the inhibition of the immune response that causes insulitis. These seemingly paradoxical findings may lead to further investigations on how cytokines modulate autoimmune disease and give us insight into potential ways to inhibit the diabetic process in the future.

ACKNOWLEDGMENTS

This work was, in part, supported by the Diabetes Research and Education Program of Georgetown University and the Diabetes Action Research and Education Foundation.

We thank Barbara M. Runner for her secretarial support and acknowledge the expert technical assistance of Wen Hui Pohlster.

REFERENCES

1. **Brown, T. D., J. Koeller, K. Beougher, J. Golando, E. M. Bonnem, R. J. Spiegel, and D. D. Von Hoff.** 1987. A phase I clinical trial of recombinant DNA gamma interferon. J. Clin. Oncol. **5:**790–798.
2. **Colle, E., R. D. Guttmann, and T. Seemayer.** 1981. Spontaneous diabetes mellitus syndrome in the rat. I. Association with the major histocompatibility complex. J. Exp. Med. **154:**1237–1242.
3. **Debray-Sachs, M., C. Carnaud, C. Boitard, H. Cohen, I. Gresser, P. Bedossa, and J.-F. Bach.** 1991. Prevention of diabetes in NOD mice treated with

antibody to murine IFN-γ. J. Autoimmun. **4:**237–248.
4. **Ely, J. M., D. L. Greiner, D. M. Lubaroff, and F. W. Fitch.** 1983. Characterization of monoclonal antibodies that define rat T-cell alloantigens. J. Immunol. **130:**2798–2803.
5. **Ewel, C. H., D. O. Sobel, B. J. Zeligs, and J. A. Bellanti.** 1992. Poly I:C accelerates development of diabetes mellitus in diabetes-prone BB rat. Diabetes **41:**1016–1021.
6. **Foulis, A. K., M. McGill, and M. A. Farquharson.** 1991. Insulitis in type 1 (insulin-dependent) diabetes mellitus in man—macrophages, lymphocytes, and interferon-γ containing cells. J. Pathol. **165:**97–103.
7. **Greiner, D. L., T. P. Mordes, E. S. Handler, M. Angelillo, N. Nakamura, and A. A. Rossini.** 1987. Depletion of RT6.1$^+$ T lymphocytes induces diabetes in resistant Biobreeding/Worcester (BB/W) rats. J. Exp. Med. **166:**461–475.
8. **Gronberg, A., M. T. Ferm, J. Ng, C. W. Reynolds, and J. R. Ortaldo.** 1988. IFN-gamma treatment of K562 cells inhibits natural killer cell triggering and decreases the susceptibility to lysis by cytoplasmic granules from granular lymphocytes. J. Immunol. **140:**4397–4402.
9. **Holda, J. H., T. Maier, and H. N. Claman.** 1988. Evidence that IFN-γ is responsible for natural suppressor activity in GVHD spleen and normal bone marrow. Transplantation **45:**772–777.
10. **Jacob, C. O., J. Holoshitz, P. Van der Meide, S. Strober, and H. O. McDevitt.** 1989. Heterogeneous effects of interferon gamma in adjuvant arthritis. J. Immunol. **142:**1500–1505.
11. **Lemmel, E. M., D. Brackertz, M. Franke, W. Gaus, P. W. Hartl, et al.** 1988. Results of a multicenter placebo-controlled double-blind randomized phase III clinical study of treatment of rheumatoid arthritis with recombinant interferon-gamma. Rheumatol. Int. **8:**87–96.
12. **Lemmel, E. M., H. J. Obert, and P. H. Hofschneider.** 1988. Low-dose gamma interferon in treatment of rheumatoid arthritis. Lancet **i:**598.
13. **Like, A. A., C. A. Biron, E. S. Weringer, K. S. Byman, E. Sroczynski, and D. L. Guberski.** 1986. Prevention of diabetes in Biobreeding/Worcester rats with monoclonal antibodies that recognize T lymphocytes or natural killer cells. J. Exp. Med. **164:**1145–1159.
14. **Markmann, J. F., J. Jacobson, J. Roza, I. J. Fox, P. Strome, and A. Naji.** 1987. Increased cytotoxic T lymphocytic killing of isolated islet cells after interferon treatment. Surg. Forum **38:**354–356.
15. **Mordes, J. P., J. Desemone, and A. Rossini.** 1987. The BB rat. Diabetes Metab. Rev. **3:**725–750.
16. **Nakajima, H., H. Takamori, Y. Hiyama, and W. Tsukada.** 1990. The effect of treatment with interferon-gamma on type II collagen-induced arthritis. Clin. Exp. Immunol. **81:**441–445.
17. **Nakhooda, A. F., A. A. Like, C. L. Chappel, F. T. Murray, and E. B. Marlis.** 1976. The spontaneously diabetic Wistar rat: metabolic and morphologic studies. Diabetes **26:**100–112.
18. **Nicoletti, F., P. L. Meroni, S. Landolfo, M. Gariglio, S. Guzzardi, W. Barcellini, M. Lunetta, L. Mughini, and C. Zanussi.** 1990. Prevention of diabetes in BB/Wor rats treated with monoclonal antibodies to interferon-γ. Lancet **336:**319.
19. **Obert, H. J., and J. F. Brzoska.** 1989. Interferon gamma in der Therapie der chronischen Polyarteritis. Arzneim. Forsch. **39:**819–822.
20. **Pukel, C., H. Baquerizo, and A. Rabinovitch.** 1988. Destruction of rat islet cell monolayers by cytokines. Synergistic interactions of interferon-γ, tumor necrosis factor, lymphotoxin and interleukin-1. Diabetes **37:**133–136.
21. **Sadelain, M. W., H. Y. Qin, W. Sumoski, N. Parfrey, B. Singh, and A. Rabinovitch.** 1990. Prevention of diabetes in the BB rat by early immunotherapy using Freund's adjuvant. J. Autoimmun. **3:**671–680.
22. **Sarvetnick, N., D. Liggitt, S. L. Pitts, S. E. Hansen, and T. A. Stewart.** 1988. Insulin-dependent diabetes mellitus induced in transgenic mice by ectopic expression of class II MHC and interferon-gamma. Cell **52:**773–782.
23. **Satoh, J., S. Shintani, K. Oya, S.-I. Tanaka, T. Nobunaga, T. Toyota, and Y. Goto.** 1988. Treatment with streptococcal preparation (OK-432) suppresses anti-islet autoimmunity and prevents diabetes in BB rats. Diabetes **37:**1188–1194.
24. **Satoh, J., H. Seino, S. Shintani, S. Tanaka, T. Ohteki, T. Masuda, T. Nobunga, and T. Toyota.** 1990. Inhibition of type 1 diabetes in BB rats with recombinant human tumor necrosis factor-alpha. J. Immunol. **145:**1359.
25. **Sobel, D. O., N. Azumi, K. Creswell, D. Holterman, O. C. Blair, J. A. Bellanti, V. Abbassi, and J. C. Hiserodt.** 1995. The role of NK cell activity in the pathogenesis of poly I:C accelerated and spontaneous diabetes in the diabetes prone BB rat. J. Autoimmun. **8:**843–847.
26. **Tovo, P. A., F. Cerutti, E. Palomba, C. Salomone, and A. Pugliese.** 1984. Evidence of circulating interferon-γ in newly diagnosed diabetic children. Acta Pediatr. Scand. **73:**785–788.
27. **Uchida, A., E. Yanagawa, E. M. Kokoschka, M. Micksche, and H. S. Koren.** 1984. In vitro modulation of human natural killer cell activity by interferon. Generation of adherent suppressor cells. Br. J. Cancer **50:**483–492.
28. **Wahl, S. M., J. B. Allen, K. Ohura, D. E. Chenoweth, and A. R. Hand.** 1991. IFN-γ inhibits inflammatory cell recruitment and the evolution of bacterial cell wall-induced arthritis. J. Immunol. **146:**95–100.
29. **Wallach, D.** 1983. Interferon-induced resistance to the killing by NK cells: a preferential effect of IFN-γ. Cell Immunol. **75:**390–395.
30. **Williams, J. G., G. J. Jurkovich, G. B. Hahnel, and R. V. Maier.** 1992. Macrophage priming by interferon gamma: a selective process with potential harmful effects. J. Leukocyte Biol. **52:**579–584.
31. **Wilson, C. A., C. Jacobs, P. Baker, D. G. Baskin, S. Dower, A. Lernmark, B. Toivola, S. Vertrees, and D. Wilson.** 1990. IL-1β modulation of spontaneous autoimmune diabetes and thyroiditis in the BB rat. J. Immunol. **144:**3784–3788.
32. **Woda, B. A., and C. A. Biorn.** 1986. Natural killer cell number and function in the spontaneously diabetic BB/W rat. J. Immunol. **137:**1860–1866.
33. **Young, H. A., and K. J. Hardy.** 1995. Role of interferon-gamma in immune cell regulation. J. Leukocyte Biol. **58:**373–381.