

Regulation of immunoglobulin production in hyperimmunoglobulin E recurrent-infection syndrome by interferon γ

(IgE/lymphocytes/Job syndrome/IgG subclass)

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ABSTRACT The hyperimmunoglobulin E recurrent-infection (Job) syndrome (HIE) is a congenital disorder characterized by high serum IgE, chronic eczematoid dermatitis, and recurrent infections. We examined the effect of interferon γ (IFN- γ) on excessive IgE production in HIE patients. Spontaneous *in vitro* production of IgE by peripheral blood mononuclear cells from HIE patients was elevated compared to normal individuals and correlated with serum IgE. In 9 of 13 patients, IgE production by peripheral blood mononuclear cells was inhibited by 50% by IFN- γ at 100–1000 units/ml, whereas inhibition by IFN- γ at 10^4 units/ml ranged from 67 to 93% for these 9 patients. IFN- γ also inhibited IgG1, IgG3, and IgG4 production by B lymphocytes without inhibiting IgG2 production. IFN- γ was administered subcutaneously to 5 HIE patients. After 2 weeks of treatment with IFN- γ (0.05 mg/m²) at three doses per week given on alternate days, peripheral blood mononuclear cells from all 5 HIE patients decreased spontaneous *in vitro* IgE production (27–62% decrease) with no change in IgG and IgM. One patient had a 58% decrease in serum IgE and another patient had a 50% decrease in serum IgE after the IFN- γ was increased to 0.1 mg/m² for three doses per week for a month. In both patients, serum IgE returned to pre-IFN- γ -challenge levels 1–3 months after completion of treatment, and *in vivo* IFN- γ did not affect serum IgG and IgM, although serum IgG4 decreased with changes in serum IgE. Our studies demonstrate that IFN- γ can regulate production of IgE and some IgG subclasses in humans.

Regulation of IgE production has been studied in rodents and humans (1–3). Regulatory T cells that selectively enhance (4–10) or suppress (11, 12) IgE responses in humans have been identified. Products of regulatory T cells that suppress or enhance IgE production have also been described. Supernatants from T cells derived from patients with severe atopy (13, 14), parasitic diseases (6), and the hyperimmunoglobulin E recurrent-infection (Job) syndrome (HIE) (4) induce IgE production *in vitro*. In contrast, soluble factors from T cells of normal nonatopic individuals suppress the IgE response (15, 16).

In mice, recombinant interleukin (IL) 4 induces IgE and IgG1 synthesis whereas recombinant interferon γ (IFN- γ) suppresses IgE, IgG1, IgG2b, and IgG3 production by lipopolysaccharide-activated B lymphocytes (17–21). It is the balance between these two lymphokines that ultimately determines the concentrations and isotypes of antibody responses (22). Recent studies in human peripheral blood mononuclear cells (PBMCs) support the proposal of IL-4/IFN- γ -mediated regulation of IgE (23). Purified human

recombinant IL-4 induces IgE production in unfractionated human PBMCs, an effect inhibited by IFN- γ (24).

HIE is characterized by recurrent skin and sinopulmonary tract infections and elevated serum IgE (25, 26). A causal relationship between excessive production of IgE and the clinical problems occurring in HIE has not been established. PBMCs from HIE patients spontaneously produce excessive IgE *in vitro* (4) and provide a model to evaluate the role of cytokines in the regulation of immunoglobulin production. Here we demonstrate that IFN- γ added to lymphocyte cultures or administered to patients with HIE suppresses spontaneous production of IgE and specific IgG subclasses.

METHODS

Patient Population. All 13 HIE patients studied were in good health and satisfied the clinical criteria for HIE by having markedly elevated serum IgE, chronic eczematoid dermatitis, a significant fraction of IgE directed to *Staphylococcus aureus*, and a history of deep-seated soft tissue infection. Clinical characteristics of most of the patients have been reported (25, 27). Patients were from 7 to 50 years old and included 3 males and 10 females.

Isolation of Cell Populations. PBMCs from heparinized blood were purified by sedimentation on a Ficoll/diatrizoate gradient. T cells were obtained by collecting the lymphocyte fraction forming rosettes with 2-aminoethylisothiuronium bromide-treated sheep erythrocytes. T-cell depleted PBMCs were enriched for B cells by allowing monocytes to adhere to plastic. Immunofluorescence labeling of B-cell-enriched subpopulations revealed <3% T cells.

Culture Conditions for *in Vitro* Antibody Production. Supernatant immunoglobulin production was measured in quadruplicate cultures grown in RPMI 1640 medium containing 10% (vol/vol) fetal calf serum, gentamicin (80 μ g/ml), and 25 mM Hepes (C-RPMI). Unfractionated PBMCs or cell fractions were placed in flat-bottomed wells of microtiter plates at 10^6 cells per ml in C-RPMI (total volume, 220 μ l) alone or containing cycloheximide (100 μ g/ml) and/or various amounts of recombinant IFN- γ or IL-2 and incubated for 10 days. As controls, cells were frozen and thawed four times either at the beginning or at the end of the experiment to determine the amount of unreleased preformed IgE within the cells. The amount of *in vitro* spontaneous immunoglobulin production is defined as the amount produced in the experimental condition after subtracting the amount produced by the identical culture containing cycloheximide.

Abbreviations: PBMC, peripheral blood mononuclear cell; HIE, hyperimmunoglobulin E recurrent-infection system; IFN- γ , interferon γ ; IL, interleukin.

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Assays for IgE, IgM, and IgG Subclasses. IgM, total IgG, and IgE in culture supernatants were measured using ELISAs as described (28, 29). IgG subclasses from cultures were measured using a streptavidin-alkaline phosphatase-biotin-amplified ELISA with IgG subclass-specific monoclonal antibodies (30). Serum IgE was measured using a solid-phase immunofluorescent assay (Whittaker M.A. Bioproducts). Total serum IgG and IgM were measured using nephelometry. Serum IgG subclasses were measured using an immunodiffusion kit (ICN) by following manufacturer's instructions and confirmed by ELISA (30).

Measurement of IFN- γ Production. IFN- γ production was measured in 2- and 5-day culture supernatants of PBMCs incubated in C-RPMI alone or containing Con A ($5 \mu\text{g/ml}$) or phytohemagglutinin ($5 \mu\text{g/ml}$) and cultured at 2×10^6 cells per ml. IFN- γ was measured using a double-sandwich ELISA consisting of a monoclonal anti-human IFN- γ monoclonal antibody (a gift of G. Delespesse, University of Montreal) and a polyclonal rabbit anti-human IFN- γ . Purified recombinant human IFN- γ (Genentech) was used as standards and no antibody binding activity was detected against purified recombinant IL-2, IL-4, granulocyte-macrophage colony-stimulating factor, interferon α , or tumor necrosis factor. The ELISA was standardized using a radioimmunoassay (Centocor, Malvern, PA) and a vesicular stomatitis viral inhibition bioassay. The ELISA was found to reliably detect IFN- γ at levels as low as 50–100 pg/ml.

In Vivo Administration of IFN- γ . Patients 1, 3, 4, 7, and 8 were treated with human recombinant IFN- γ (0.05 mg/m^2) (Genentech) by subcutaneous injection of three doses per week on alternate days for 2 weeks (six doses). The specific activity of the IFN- γ was 2×10^7 units/mg (National Institutes of Health IFN- γ standard). For adult patients with an average surface area of 1.5 m^2 , this corresponds to 1.5×10^6 units per dose. Patients 3 and 7 were treated with a 4-week course of IFN- γ at 0.05 mg/m^2 on alternate days, which was increased to 0.1 mg/m^2 for an additional 4-week period. Dosing schedules were chosen on the basis of previous *in vivo* studies in which these doses of IFN- γ had a measurable effect upon monocyte production of superoxide (31, 32). This dosing was the highest that did not consistently produce side effects (fever, malaise, and headache; refs. 33 and 34). Patients did not take any additional medications that might have immunomodulating effects (antihistamines or topical or systemic steroids).

Statistical Analyses. Data are expressed as the mean \pm SEM and were compared using Student's *t* test. Correlations of groups of ordered data were determined by Spearman's rank correlation.

RESULTS

Correlation of Serum IgE Levels with Spontaneous IgE Production *in Vitro* in Patients with HIE. The 13 patients with HIE had serum IgE levels from 72,000 to 8600 ng/ml (Fig. 1A; normal individuals <350 ng/ml). For patients followed long term, IgE levels were found to remain relatively constant for a specific patient over many years (25) except with severe infection.

Spontaneous IgE production by 10^6 cultured PBMCs from these same patients ranged from 54,000 to 330 pg/ml in 10-day cultures and was significantly correlated ($r = 0.52$; $P < 0.05$) with simultaneously measured serum IgE (compare Fig. 1A and B). The proportion of B cells in PBMCs was 5.3–11.5% and did not correlate with spontaneous IgE production. Spontaneous IgE production by PBMCs from normal individuals was undetectable.

Effect of *in Vitro* IFN- γ on Spontaneous IgE Production by PBMCs. When HIE patient PBMCs were cultured with human recombinant IFN- γ at 10^4 units/ml, there was a

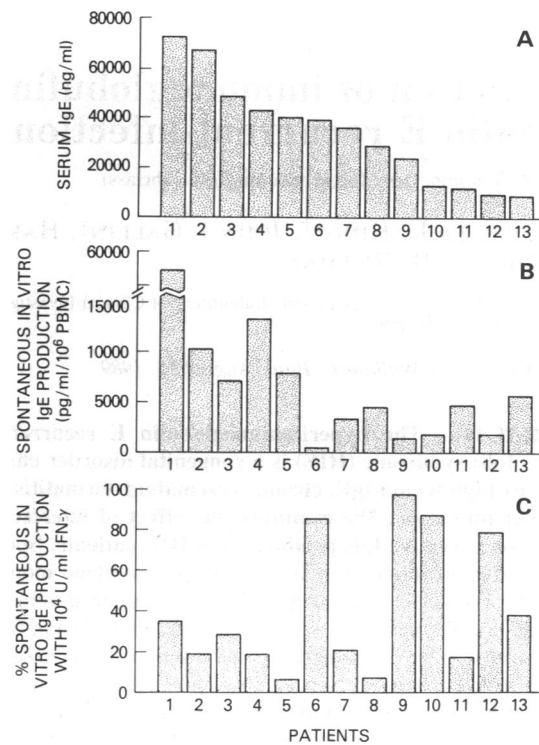


FIG. 1. (A) Analysis of IgE serum levels. (B) Spontaneous *in vitro* IgE production by PBMCs over 10 days. (C) Effect of *in vitro* addition of IFN- γ at 10^4 units/ml on spontaneous IgE production by PBMCs expressed as a percent of the amount seen with the same patient cells in B. Numbers on the abscissa identify the 13 patients with HIE syndrome.

marked decrease in spontaneous IgE production in the 9 of 13 patients (Fig. 1C). These 9 patients as a group decreased IgE production from 7 to 33% of control. However, cells from patients 6, 9, 10, and 12 produced the lowest amount of IgE in control cultures (Fig. 1B) and were the only ones to show no significant decrease with addition of IFN- γ (Fig. 1C). In subsequent studies we focused on the 9 patients with the high spontaneous *in vitro* IgE production that was inhibited by IFN- γ .

We examined the effect of a range of *in vitro* doses of IFN- γ on spontaneous IgE production by PBMCs from all nine HIE patients whose cells had responded to IFN- γ at 10^4 units/ml (Fig. 2). With IFN- γ at 100 units/ml, IgE production was inhibited an average of 48% for the nine patients as a group ($P < 0.001$). With IFN- γ at 1000 units/ml, IgE production was inhibited by $>50\%$ in all nine patients and increased to 81% inhibition with IFN- γ at 10^5 units/ml. No individual showed complete inhibition of spontaneous *in vitro* IgE production, even at the highest doses used. In contrast, another human recombinant lymphokine, IL-2, produced only 22% inhibition of IgE production even at the highest doses tested (10^4 units/ml) (Fig. 2).

To exclude the possibility that IFN- γ might act primarily by inhibiting release of IgE from lymphocytes, cells were washed and lysed at completion of the 10-day culture period and the intracellular IgE was measured. In five patients intracellular IgE, expressed as a percentage of IgE measured in supernatants from the same cultures, was the same in IFN- γ -treated cells as compared to untreated controls (range 5–11%, intracellular).

To exclude the possibility that HIE PBMCs are deficient in their capacity to produce IFN- γ , cells from five patients were mitogen-stimulated. With Con A stimulation for 2 days, HIE PBMCs produced a mean of 7.4 ng of IFN- γ per 10^6 PBMCs,

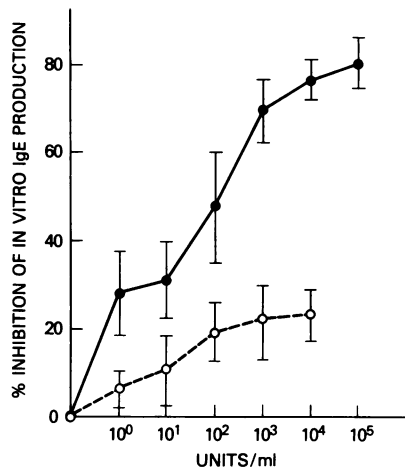


FIG. 2. Effect of *in vitro* addition of various concentrations of IFN- γ (solid line) or IL-2 (dotted line) on spontaneous IgE production by PBMCs from the 9 HIE patients who responded to IFN- γ at 10^4 units/ml in the study shown in Fig. 1C. The data are expressed as percent inhibition (mean \pm SEM) of control IgE production without lymphokine.

whereas for eight normal individuals the mean was 6.5 ng of IFN- γ per 10^6 PBMCs. With phytohemagglutinin stimulation, HIE PBMCs produced an average of 7.8 ng of IFN- γ per 10^6 PBMCs, whereas for normal individuals the average was 7.0 ng of IFN- γ per 10^6 PBMCs. Data were similar for 5-day cultures, and there was also no difference in the amount of spontaneous production of IFN- γ by PBMCs from HIE patients and normal individuals. Studies of the same supernatants using a viral bioassay for IFN- γ yielded identical results (data not shown).

Effect of *in Vitro* IFN- γ on Spontaneous IgE, IgM, and IgG Subclass Production by a B-Cell-Enriched Fraction of PBMCs. We examined the effect of T lymphocytes on spontaneous *in vitro* IgE production by B-lymphocyte-enriched preparations from HIE patients 1, 4, and 8. For the three patients as a group, the amount of IgE produced by B-cell-enriched populations (24.9 ± 12 ng/ml) was not different from the same number of B cells within the unfractionated PBMCs (18.4 ± 5.9 ng/ml) and was not altered by addition of T lymphocytes (18.6 ± 7.5 ng/ml at a T/B-lymphocyte ratio of 2:1).

We next studied the effect of IFN- γ at 10^4 units/ml on spontaneous *in vitro* production of IgE, IgM, and all IgG subclasses by B-lymphocyte-enriched preparations from four HIE patients (Fig. 3). At baseline, spontaneous *in vitro* IgM and IgG subclass production by HIE B-lymphocyte-enriched fractions was not different from three normal individuals (data not shown), while IgE production was elevated. As shown in Fig. 1 with unfractionated PBMCs, IFN- γ at 10^4 units/ml significantly inhibited IgE production by B-lymphocyte-enriched fractions from HIE patients as shown in Fig. 3 (range, 62–95% inhibition). Addition of T lymphocytes to B-lymphocyte-enriched preparations did not alter this response to IFN- γ (data not shown). In the same cultures of B-lymphocyte-enriched fractions, there was slight inhibition of IgM production by IFN- γ (range, 17–30% inhibition). In the same cultures IgG1, IgG3, and IgG4 production was inhibited by IFN- γ in all four patients studied (range, for IgG1 71–92% inhibition; for IgG3 60–80% inhibition; for IgG4 63–100%). However, IgG2 production in the presence of IFN- γ at 10^4 units/ml slightly increased in two patients (4% and 8% increase) and decreased in two other patients (26% and 36% decrease).

Effect of *in Vivo* Administration of IFN- γ on Spontaneous *In Vitro* Production of Immunoglobulins by PBMCs from HIE Patients. IFN- γ (0.05 mg/m²) was administered subcutane-

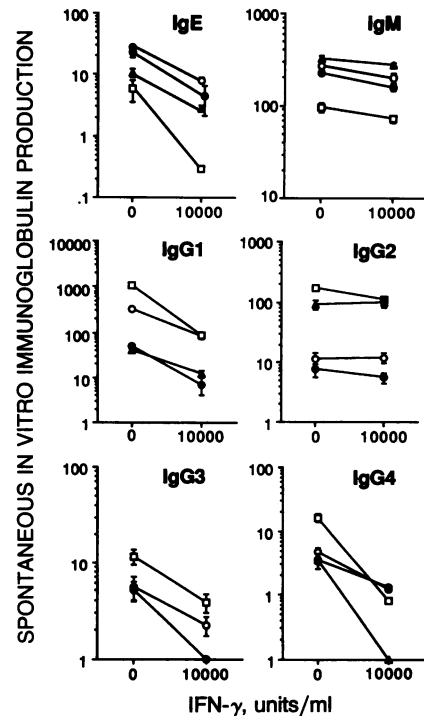


FIG. 3. Effect of *in vitro* addition of IFN- γ on spontaneous immunoglobulin production by B-lymphocyte-enriched fractions from HIE patients. For each experiment the amount of immunoglobulin isotype and subclass were determined from the same culture supernatants. The ordinate shows the amount of the indicated immunoglobulin produced over 10 days by 10^6 cells; the scale for IgM is in μ g/ml, whereas all the other immunoglobulins are expressed in ng/ml. Patients 1, 4, 7, and 8 are represented by an open circle, solid circle, solid triangle, and open square, respectively.

ously to five HIE patients at three doses per week on alternate days for 2 weeks. Fig. 4 shows that there was a fall in spontaneous IgE production by PBMCs in all patients at 2

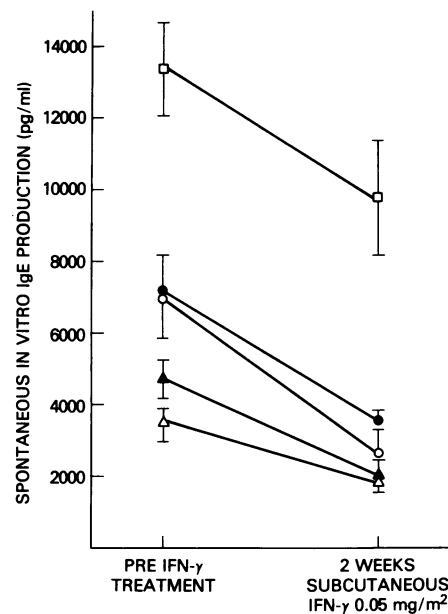


FIG. 4. Effect of 2 weeks of subcutaneously administered IFN- γ on spontaneous *in vitro* IgE production by PBMCs from five responder HIE patients. Each data point represents IgE produced by PBMCs over 10 days in culture. Patients 1, 3, 4, 7, and 8 are represented by an open square, solid circle, open circle, solid triangle, and open triangle, respectively.

weeks of treatment with IFN- γ at this dosage. The decrease ranged from 27 to 65% of pretreatment IgE production and was highly significant ($P < 0.002$) for the group. This dose of IFN- γ had no effect on spontaneous *in vitro* production of total IgG or IgM (pretreatment production of total IgG of 450 ± 138 ng/ml (mean \pm SEM) and IgM of 532 ± 70 ng/ml; 2-week treatment production of total IgG of 464 ± 166 ng/ml and IgM of 562 ± 62 ng/ml).

In patients 3 and 8, IFN- γ was increased to 0.1 mg/m^2 and given for an additional 2 weeks at which time a greater decrease in spontaneous *in vitro* IgE production from pretreatment values occurred in both patients (from a 51% decrease at 0.05 mg/m^2 to a 67% decrease at 0.1 mg/m^2 for patient 3 and from a 42% to a 47% decrease with the same dose change for patient 8).

Effect of *in Vivo* Administration of IFN- γ on Serum Immunoglobulin Levels in HIE Patients. In one of five patients receiving IFN- γ at 0.05 mg/m^2 for 2 weeks (patient 1), there was a marked decrease in serum IgE at 2 weeks (Fig. 5 *Left*). This decrease persisted and was 58% below pretreatment levels 2 weeks after termination of therapy. Serum IgE levels slowly returned to baseline by 10 weeks after termination of therapy. Seven additional serum samples from this patient (from 1977 through 1988) were assayed for IgE levels simultaneously with serum samples obtained during the IFN- γ study period. Prestudy levels ranged between 60,700 ng/ml and 80,700 ng/ml over that 11-year interval. When compared to the prestudy levels over the previous decade, the drop in serum IgE from 72,000 ng/ml to a low of 29,900 ng/ml in this patient is highly significant ($P < 0.001$). Because this significant drop occurred in the context of administration of IFN- γ , it is likely that it represents a response to the IFN- γ .

Because the other four patients failed to show any change in serum IgE with IFN- γ at 0.05 mg/m^2 , two of those patients received IFN- γ at 0.1 mg/m^2 on alternate days for an additional 4 weeks. One patient receiving this higher dose (patient 3) demonstrated a significant decrease ($P < 0.01$) in serum IgE by 2 weeks and the serum IgE remained below baseline during therapy (Fig. 5 *Right*). However, by 1 week after therapy ended, their serum IgE level had returned to baseline.

Serum total IgG and IgM levels were unaltered in any patients by either dose of IFN- γ (shown in Fig. 5 *Left* for patients 1 and *Right* for patient 3). When serum IgG subclasses were examined, there was no change in IgG1, IgG2, or IgG3 subclasses in any of the five patients receiving IFN- γ (data not shown). However, with patients 1 and 3, serum IgG4 decreased with IFN- γ administration in parallel with decreases in serum IgE levels. For patient 1 pretreatment

serum levels of IgG4 were 1 mg/ml and after 2 weeks of treatment with IFN- γ at 0.05 mg/m^2 , the IgG4 decreased by 50% to 0.5 mg/ml. For patient 3 pretreatment serum levels of IgG4 were 2.2 mg/ml and, after 2 weeks of treatment with IFN- γ at 0.1 mg/m^2 , the IgG4 decreased by 55% to 1 mg/ml. At times when serum IgE levels were unaffected in these and the other HIE patients, there was also no change in serum IgG4.

We did not see any adverse effects of administration of IFN- γ to any of our five patients at either dose level. No serious infections occurred during administration of IFN- γ . We did not see any obvious change in clinical status.

DISCUSSION

The present study demonstrates that the excessive spontaneous IgE production by PBMCs from the majority of HIE patients can be significantly inhibited by IFN- γ . This inhibition occurs when IFN- γ is added to PBMCs in culture or when IFN- γ is administered subcutaneously to HIE patients. Since at least a 50% reduction of *in vitro* IgE production was seen in all nine responsive patients when IFN- γ at 1000 units/ml was added to cultures of PBMCs, it is likely that this effect is physiologically important. Because this inhibition of IgE production by exogenous IFN- γ occurs with T-cell-depleted PBMCs and is not affected by repletion of T cells, it suggests a direct effect of IFN- γ on human B lymphocytes. HIE PBMCs stimulated with mitogens produce normal amounts of IFN- γ , indicating that the baseline excessive IgE production is not a result of a deficiency in production of IFN- γ . Whether the excessive IgE synthesis is related to overproduction of IL-4, as has been suggested (24), has not been addressed in the present studies.

PBMCs from 4 of 13 patients with HIE failed to show a decrease in spontaneous *in vitro* IgE production with addition of IFN- γ at 10^5 units/ml to cultures. This failure to respond to even very high concentrations of IFN- γ correlated absolutely with lower spontaneous IgE production by untreated cultures (these 4 individuals have the four lowest values for spontaneous *in vitro* IgE production) but did not correlate with serum IgE levels. The failure of IFN- γ to inhibit spontaneous *in vitro* IgE production by PBMCs from these 4 patients may not be a consequence of the lower baseline *in vitro* IgE production. For example, patients with filariasis whose PBMCs in culture produce spontaneous IgE in amounts similar to PBMCs from these 4 HIE patients nonetheless show significant inhibition of IgE production by IFN- γ (unpublished observations). This suggests that the spontaneous *in vitro* production of IgE by PBMCs is a more

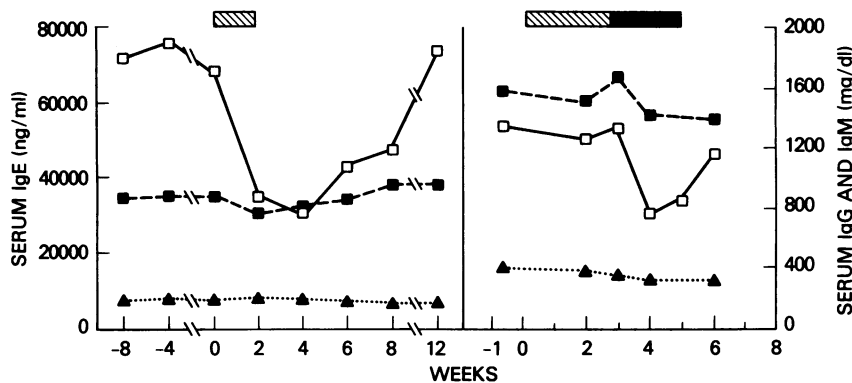


FIG. 5. Effect of subcutaneously administered IFN- γ on serum immunoglobulin in the two of five HIE patients showing a change in serum IgE during the *in vivo* administration. (*Left*) Patient 1. (*Right*) Patient 3. The abscissa shows the study period in weeks with time 0 referring to the start of IFN- γ administration. The solid lines represent serum IgE; the dashed lines represent total serum IgG; and the dotted lines represent serum IgM. At the top of each panel the duration of IFN- γ administration at 0.05 mg/m^2 is represented by the hatched bar and at 0.1 mg/m^2 by the solid bar. Both dose levels were administered as a single daily injection on alternate days for a total of three doses per week.

valid indicator of the unknown but important physiologic differences among HIE patients than serum IgE levels.

This study also demonstrates that IFN- γ at 10^4 units/ml added to cultures of B-lymphocyte-enriched fractions from HIE patients strongly inhibited production of IgE, IgG1, IgG3, and IgG4 (average inhibition of 74%, 81%, 69%, and 85%, respectively). Although part of this inhibition may reflect an antiproliferative effect of IFN- γ , there is a significant differential effect on immunoglobulin isotypes and subclasses, in that IgG2 was decreased by an average of only 13%, and IgM production was inhibited by an average of only 25%. This is similar to results seen in the murine system (17–21) in that production of most, but not all, subclasses of murine IgG is inhibited by IFN- γ . Whereas murine IgG2a production is actually stimulated by IFN- γ (21), IFN- γ *in vitro* did not stimulate production of any the human IgG subclasses.

All five patients given subcutaneous IFN- γ at 0.05 mg/m² for 2 weeks showed suppression of spontaneous *in vitro* IgE production by PBMCs after 2 weeks of therapy. Note that in the two patients whose dose of IFN- γ was increased to 0.1 mg/m² for 2 weeks, there was a further inhibition of spontaneous *in vitro* IgE production.

With IFN- γ 0.05 mg/m², one of the five HIE patients showed a large drop in serum IgE. Although spontaneous changes in serum IgE levels do occur in these patients, the 58% decrease seen in patient 1 after IFN- γ administration is likely to be significant because no similar change of serum IgE level was observed with serum samples obtained during an 11-year period prior to this study or during a year after treatment with IFN- γ . Furthermore, the rapid decrease in serum IgE during and immediately after administration of IFN- γ and a slow return to baseline serum IgE levels also support a causal effect of IFN- γ administration in these changes. When the dose of IFN- γ was increased to 0.1 mg/m² in two other patients who had not shown a decrease in serum IgE with IFN- γ at 0.05 mg/m², one patient (patient 3) showed a significant decrease in serum IgE.

Serum IgG4 decreased in parallel with the decreases in serum IgE in two patients and this decrease only occurred where there was a change in serum IgE. In preliminary studies of spontaneous *in vitro* production of IgG subclasses by PBMCs from two of the patients treated with IFN- γ , IFN- γ completely inhibited IgG4 production but did not change IgG1 and IgG2 and only slightly decreased IgG3 (data not shown). These observations suggest that the immunoregulatory mechanisms for IgE and IgG4 are similar (35).

The doses of IFN- γ administered were 10–20 times less than the maximum doses that have been administered to humans but were chosen on the basis of attaining some physiologic effect while minimizing side effects. The *in vitro* data and the clinical studies suggest that higher doses of IFN- γ might produce a drop in serum IgE in a larger proportion of HIE patients than demonstrated in this study. However, our studies were not designed to address the question of whether IFN- γ may be clinically useful in the treatment of HIE. Not only has a causal relationship between excessive IgE production and the dermatitis and infections seen in HIE not been established, but also none of our patients showed any improvements in dermatitis with IFN- γ administration.

This study extends to humans the observations in mice that IFN- γ is involved in regulation of IgE and IgG subclass production. The study also shows that the excessive production of IgE by HIE PBMCs is responsive to inhibition by IFN- γ *in vitro* and *in vivo*.

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