

In vivo effects of glucocorticoids on IgE production

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Recent in vitro investigations have demonstrated that corticosteroids in combination with interleukin-4 induce the synthesis of IgE. Corticosteroids are increasingly being used to treat the inflammatory component of asthma. This has raised concern over the potential in vivo effects of corticosteroids on IgE production and the correlation of IgE-enhancing effects with clinical effects on asthma. In this study 10 patients with asthma were given a 7-day course of 20 mg of prednisone, administered orally two times a day. All of the patients had a rise in serum IgE levels after the course of prednisone ($p = 0.005$). Detection of specific IgE to pollen and perennial allergens demonstrated that the rise in serum IgE was polyclonal. Peripheral blood mononuclear cells from patients treated with prednisone produced increased levels of IgE in vitro when exogenous IL-4 was added to their cultures. Peripheral blood mononuclear cells obtained from patients before and after administration of prednisone revealed a significant decrease in interferon- γ synthesis ($p = 0.005$), but not in interleukin-4 ($p = 0.6$), after the course of prednisone. These findings were paralleled by a significant decrease in the frequency of interferon- γ ($p = 0.03$), but not interleukin-4 ($p = 1.0$) expressing cells. Despite the increase in IgE synthesis, there was a significant increase in forced expiratory volume in 1 second after the course of prednisone ($p = 0.01$). These data suggest that the observed rise in IgE production associated with prednisone treatment is not clinically deleterious but reflects the immunomodulatory effects of corticosteroids on T lymphocytes. (J ALLERGY CLIN IMMUNOL 1994;94:222-30.)

Key words: IgE, asthma, prednisone, corticosteroids

In 1989, Burrows et al.¹ reported that the prevalence of asthma is closely related to serum IgE levels irrespective of skin test reactivity to allergens. This observation was further pursued by Sears et al.² who found a direct correlation between airway hyperresponsiveness and serum IgE levels in children. However, the basis for this association between IgE and asthma remains poorly understood, although it is believed to reflect the central role of IgE in the pathogenesis of allergic inflammation.³

Recent studies have demonstrated that the induction of IgE synthesis requires two signals.⁴ The

Abbreviations used

FEV ₁ :	Forced expiratory volume in 1 second
IFN- γ :	Interferon gamma
IL:	Interleukin
IQ:	Interquartile range (25th and 75th percentiles)
NK:	Natural killer
PBMCs:	Peripheral blood mononuclear cells

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first is delivered by the cytokine, interleukin-4 (IL-4), which induces the expression of ϵ germ line transcripts in B cells.^{5, 6} However, switch recombination and expression of mature ϵ RNA transcripts, resulting in secreted IgE protein, requires a second signal. Several second signals have been identified. These include T cells,⁷ Epstein-Barr virus infection,⁸ monoclonal antibodies to the CD40 B-cell ligand,⁹ and corticosteroids.^{10, 11} A variety of cytokines can modulate IgE synthesis including interferon- γ (IFN- γ), which inhibits IgE synthesis.⁴

Because corticosteroids are commonly used in the treatment of asthma, concern has been raised

TABLE I. Patient characteristics and FEV₁ response to prednisone

Donor No.	Age (yr)	Sex	FEV ₁		% Improvement	Maintenance medications
			Before prednisone (L)	After prednisone (L)		
1	24	M	3.20	3.65	4	*
2	25	M	2.93	3.38	15	*
3	38	M	2.38	3.32	39	*
4	43	M	1.55	2.85	84	*
5	24	M	4.61	ND	ND	*
6	28	F	4.50	ND	ND	Triamcinolone MDI*
7	36	M	3.34	3.64	9	Theophylline, triamcinolone MDI*
8	30	M	2.71	2.76	2	Albuterol tablets*
9	22	F	1.58	3.11	97	Theophylline*
10	28	M	2.98	3.95	33	Triamcinolone MDI*

ND, Not done; MDI, metered dose inhaler.

*All donors used albuterol on an as needed basis. Albuterol was withheld for at least 12 hours before blood was drawn. All patients were receiving a daily dose of less than 1 mg of triamcinolone acetonide from a metered dose inhaler.

over whether potential IgE-enhancing effects of corticosteroids might have "hidden" deleterious effects to the allergic patient undergoing treatment with corticosteroids.¹¹ The purposes of the present investigation were therefore to prospectively study the in vivo effect of corticosteroids on IgE synthesis in the patient with asthma, to examine potential mechanisms for corticosteroid-induced IgE synthesis in vivo, and most importantly to correlate changes in pulmonary function with changes in serum IgE.

METHODS

Donors

Ten patients with asthma, eight men and two women with a median age of 28 years (interquartile [IQ] range was 24 to 35 years, which represents 25th to 75th percentile), were enrolled in this study after informed consent was obtained (Table I). The medium serum IgE level at entry into the study was 242.5 IU/ml (IQ, 91-529), and all patients were atopic as determined by positive skin prick allergen test results. All patients fulfilled the American Thoracic Society criteria for asthma,¹² which included a requirement for an increase of 15% or greater in forced expiratory volume in 1 second (FEV₁) after two inhalations of albuterol (90 µg per actuation). Patients were excluded from the study if there was any evidence of other types of lung disease, pregnancy, suspected noncompliance with therapy, or concurrent therapy with medications that would alter glucocorticoid metabolism. Furthermore, none of the patients were receiving systemic corticosteroids for at least 1 month before the beginning of the study, and five of the 10 were receiving no prophylactic asthma medication (see Table I). All medications were withheld for at least 12 hours before blood was drawn.

The study group received 20 mg of prednisone (Deltasone; Upjohn, Kalamazoo, Mich.) orally twice a day for 7 days. There were no alterations in their usual medications during the 1-week course of prednisone. Serum samples and heparinized blood were drawn before and after the course of prednisone. Of the 10 patients, eight had a morning prebronchodilator FEV₁ of less than 70% of predicted value before prednisone therapy. These eight patients performed pulmonary function tests before and after prednisone treatment.

Assay for cytokine synthesis

Peripheral blood mononuclear cells (PBMCs) from 10 patients with asthma were isolated from heparinized venous blood by density gradient centrifugation on Ficoll-Hypaque (Pharmacia Fine Chemicals, Piscataway, N.J.) washed three times in Hanks' balanced salt solution (Gibco, Grand Island, N.Y.), and resuspended at 1.0×10^6 cells/ml in RPMI-1640 (Whittaker Bio-products, Walkersville, Md.) supplemented with 10% fetal calf serum (Hyclone Sterile Systems, Inc., Logan, Utah) supplemented with 2 mmol/L L-glutamine, 2 mmol/L N-2-hydroxyethylpiperazine-N-2-ethanesulfonic acid, 100 µg/ml streptomycin, and 100 U/ml penicillin. Cells were stimulated with 10 µg/ml concanavalin A (Boehringer Mannheim, Indianapolis, Ind.) and cultured at 37° C in a 5% CO₂ humidified atmosphere. After 48 hours, the supernatants were harvested and stored at -20° C.

IL-4 quantitative determinations were measured with a commercial ELISA kit (R&D Systems, Minneapolis, Minn.) with a sensitivity of 3.0 pg/ml. Because of low levels of IL-4, all supernatants were concentrated fivefold by Centricon Concentrators (Amicon, Beverly, Mass.) before assay. IFN-γ was measured by a commercial ELISA kit (Endogen, Boston, Mass.) with a sensitivity of 5.0 pg/ml.

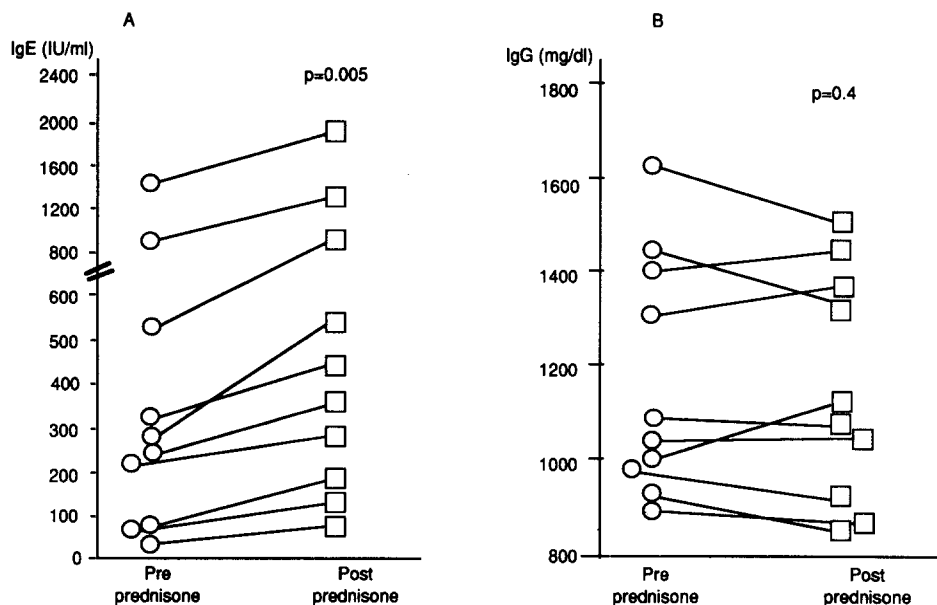


FIG. 1. Effect of prednisone on serum IgE (**A**) and IgG (**B**) levels. Ten patients with asthma were given a course of 20 mg of prednisone two times a day for 7 days. Serum immunoglobulins were drawn before and after prednisone treatment. All patients showed a significant increase in serum IgE levels ($p = 0.005$) but no significant change in serum IgG levels ($p = 0.4$).

Analysis of frequency of cytokine producing cells

To determine the percentage of cells producing specific cytokines, cells were stained for production of intracellular cytokines. PBMCs from six atopic donors were suspended at 3.0×10^6 cells/ml in RPMI-1640 medium supplemented with 10% fetal calf serum. After 20 hours incubation at 37°C in a 5% CO_2 humidified atmosphere, the cells were stimulated with 10 nmol/L phorbol 12-myristate 13-acetate (Sigma Chemical Co., St. Louis, Mo.) plus 0.5 $\mu\text{mol/L}$ ionomycin (Calbiochem, San Diego, Calif.) along with monensin (1 $\mu\text{mol/L}$) (Sigma) for 4 hours before staining.

PBMCs were stained for IL-4 and IFN- γ in the cytoplasm as previously described.¹³ Briefly, cells were fixed for 10 minutes in 4% paraformaldehyde, and after two washes, were "permeabilized" for 5 minutes in 0.1% saponin solution. The PBMCs were then blocked with 10% AB serum (Advanced Biotechnologies, Columbia, Md.) and 100 $\mu\text{g/ml}$ goat immunoglobulin (Jackson Immuno Research Laboratories, West Grove, Pa.) and divided into samples of 2×10^5 cells for individual staining. Samples were incubated with mouse anti-human anti-IL-4 antibody (Immunex Corp., Seattle, Wash.) and mouse anti-human IFN- γ antibody (Genzyme Corp., Cambridge, Mass.) at a concentration of 5 $\mu\text{g/ml}$ at room temperature for 30 minutes in saponin solution. After two washes, cell pellets were resuspended in saponin solution and a phycoerythrin- or fluorescein isothiocyanate-conjugated goat anti-mouse isotype-specific antibody (Southern Biotechnology Associates, Birmingham, Ala.) was added for 30 minutes together either with a phycoerythrin- or fluorescein isothiocyanate-labeled surface marker antibody (anti-

CD3, anti-CD4, anti-CD8, anti-CD16, anti-CD56) (Becton Dickinson, San Jose, Calif.). Samples were washed twice, and two-color flow cytometry was used to analyze the frequency of cytokine-producing cells in different lymphocyte populations.

Cell cultures for IgE synthesis

PBMCs were suspended at 1.0×10^6 cells/ml in Iscove's modification of Dulbecco's medium (Gibco) supplemented with 0.5% bovine serum albumin (Sigma), 1 $\mu\text{g/ml}$ of palmitic acid, oleic acid, and linoleic acid (Sigma), 5 $\mu\text{g/ml}$ bovine insulin (Sigma), 50 $\mu\text{g/ml}$ apotransferrin (Sigma), 10% heat-inactivated fetal calf serum, and 100 $\mu\text{g/ml}$ streptomycin and 100 U/ml penicillin as previously described by Buckley et al.¹⁴ PBMCs were cultured in the presence and absence of IL-4 (400 U/ml) a gift of Dr. Paul Trotta, Schering Research Institute, Bloomfield, N.J.). Cell cultures were maintained at 37°C in a 5% CO_2 humidified atmosphere. Supernatants were harvested after 15 days and frozen at -20°C .

IgE was quantified by ELISA as previously described.¹⁵ Briefly, 96-well microtiter plates were coated with purified mouse monoclonal anti-human IgE no. 4.12 and no. 7.12 (a kind gift of Dr. Andrew Saxon, University of California, Los Angeles) diluted in 0.1 mol NaHCO_3 at a concentration of 10 $\mu\text{g/ml}$. After overnight incubation at 4°C , the wells were blocked with 1% (wt/vol) bovine serum albumin-Tris buffer for 2 hours at 37°C . Supernatants were incubated in duplicate at 4°C overnight along with human IgE standard controls (Pharmacia Diagnostics AB, Uppsala, Sweden). After washing the plates, a 1:100 dilution of biotinylated goat anti-human IgE (Vector, Bur-

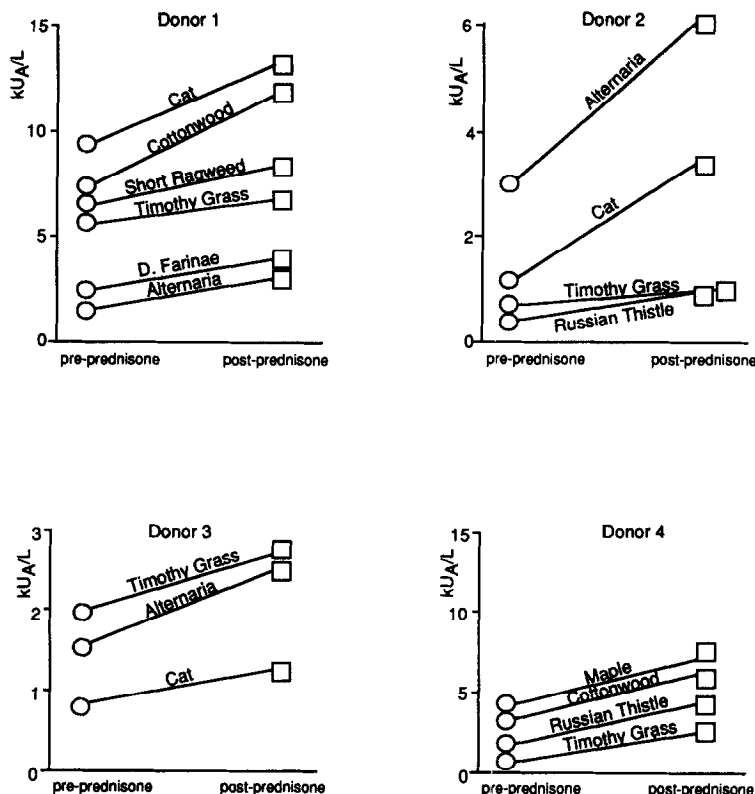


FIG. 2. Effect of prednisone on serum allergen-specific IgE levels. Allergen-specific IgE was measured in 10 patients with asthma. The polyclonal IgE responses of four representative patients to the different allergens tested are shown ($p = 0.0002$).

lingame, Calif.) was added and incubated for 1 hour at 37° C. After a subsequent wash, a 1:1500 dilution of streptavidin alkaline phosphatase was added to the plates and incubated for 2 hours at 37° C. After development with 2 mmol/L p-nitrophenyl phosphate substrate (Sigma), the optical density was read at 405 nm on an Emax Microplate reader (Molecular Devices; Menlo Park, Calif.). The lower limit of sensitivity of the assay was 0.5 ng/ml.

Determination of serum immunoglobulin levels

Serum IgE levels were measured by the IMx Total IgE assay system, which is a microparticle enzyme immunoassay for the quantitative measurement of IgE (Abbott Laboratories, Abbott Park, Ill.). Sensitivity of the IMx Total IgE assay is below 0.048 IU IgE per milliliter. Serum IgG levels were quantitated by nephelometry with the Behring nephelometer (Behring Diagnostics Inc., Somerville, N.J.). The sensitivity of the assay is 170 mg/dl.

Patients' sera were tested against specific allergens, which were previously documented to produce significant immediate wheal-and-flare reaction by skin prick testing in the respective patients. Allergens tested included timothy grass, short ragweed, Russian thistle, *Alternaria* species, cat dander, maple tree, cottonwood tree, and *Dermatophagoides farinae* mite. The Phar-

macia CAP system is an in vitro test system for the determination of circulating specific IgE antibodies (Pharmacia Diagnostics AB, Uppsala, Sweden). The system uses solid-phase-bound allergens ("immunoCAP") that react with antibodies in the serum samples. Units are expressed as kilounits of antibody per liter (kU_A/L) where A represents allergen-specific antibody. Values less than 0.35 kU_A/L represent absent or undetectable levels of allergen-specific antibody. There is no cross-reactivity with IgA, IgD, IgM, or IgG.

Statistical methods

Because of the skewness of the distributions of the variables, the data are described with medians and interquartile (IQ) ranges (25th and 75th percentiles). Tests comparing two measurements on the same subject were made with the Wilcoxon signed rank test, and those comparing measurements between subjects were made with the Wilcoxon rank sum test.¹⁶

RESULTS

Serum IgE but not IgG levels increase after a course of prednisone

To investigate the effect of a 7-day course of high-dose prednisone on in vivo IgE production, serum samples were drawn before and after a

TABLE II. PBMC synthesis of IgE before and after a course of prednisone

Donor No.	Net IgE synthesis (ng/ml)			
	Before prednisone		After prednisone	
	Nil	IL-4	Nil	IL-4
1	0.9	1.65	3.5	7.04
2	2.9	26.0	5.7	88.0
3	1.1	115.0	2.2	352.0
4	1.5	4.4	1.5	11.0
5	0.22	0.44	0.44	1.32
Median	1.1*	4.4*	2.2†	11.0†

PBMCs were cultured at 1×10^6 cells/ml before and after a course of prednisone, in the presence and absence of IL-4, for 15 days.

The data represent the values obtained from five different donors.

* $p = 0.08$.

† $p = 0.0002$.

course of 20 mg of prednisone administered orally twice a day in 10 patients with asthma. As shown in Fig. 1, A, serum IgE levels increased in all patients after prednisone treatment. The median increase was 46% (IQ, 30-57) above pretreatment values ($p = 0.005$). The median preprednisone IgE level was 242.5 IU/ml (IQ, 91.0-529.0) and median postprednisone IgE level was 384.5 IU/ml (IQ, 174-811).

In contrast to serum IgE levels, there was no significant change in serum IgG levels (Fig. 1, B). The median preprednisone IgG level was 1080 mg/dl (IQ, 995-1400) and the median postprednisone IgG level was 1130 mg/dl (IQ, 916-1380). The overall median change was 1% ($p = 0.4$).

Prednisone induces a polyclonal IgE response

To determine whether this rise in serum IgE was monoclonal or polyclonal in nature, IgE reactivity against various allergens was determined. These were selected on the basis of the previous demonstration of a significant wheal (>3 mm) and flare response by skin prick testing in the respective patients with asthma. All of the patients tested showed that specific IgE levels to multiple perennials and seasonal allergens increased after prednisone treatment. The median preprednisone allergen-specific IgE value was 2.90 kU_A/L (IQ, 1.82-5.48), and the postprednisone allergen-specific IgE value was 4.93 kU_A/L (IQ, 2.66-6.90) ($p = 0.0002$). Fig. 2 presents data from four representative patients, showing the rise in serum IgE directed to multiple allergens (see Appendix).

Effect of prednisone on IgE synthesis

To investigate the potential mechanisms by which prednisone induces a rise in serum IgE, we cultured PBMCs before and after a course of prednisone, in the presence and absence of IL-4. As shown in Table II, the median baseline spontaneous IgE production by PBMCs was 1.10 ng/ml (IQ, 0.73-1.88 ng IgE/ml) and median production after prednisone treatment was 2.20 ng/ml (IQ, 1.27-4.05 ng IgE/ml; $p = 0.08$). This increased in vitro production of IgE, associated with prednisone treatment, was significantly increased when IL-4 was added to the cultures: median baseline IgE production, in the presence of IL-4, was 4.40 ng/ml (IQ, 1.35-48.30 ng IgE/ml) and median production after prednisone treatment was 11.0 ng/ml (IQ, 5.6-154.0 ng IgE/ml; $p = 0.0002$).

Effect of prednisone on cytokine synthesis

It has been established that net IgE synthesis is determined in large part by the balance of IFN- γ and IL-4 production.⁴ Therefore to determine a potential mechanism for the stimulation and in vivo and in vitro IgE synthesis after prednisone treatment, IL-4 and IFN- γ production by PBMCs was examined. Spontaneous production of IFN- γ and IL-4 by PBMCs from all patients, before and after prednisone treatment, was undetectable. However, after concanavalin A stimulation, significant levels of IFN- γ and IL-4 were generated. As can be seen in Fig. 3, A, PBMCs from all 10 patients with asthma had a significant decrease in Con A-induced IFN- γ synthesis after a course of prednisone ($p = 0.005$). The median preprednisone IFN- γ synthesis was 6.9 ng/ml (IQ, 5.0-15.5

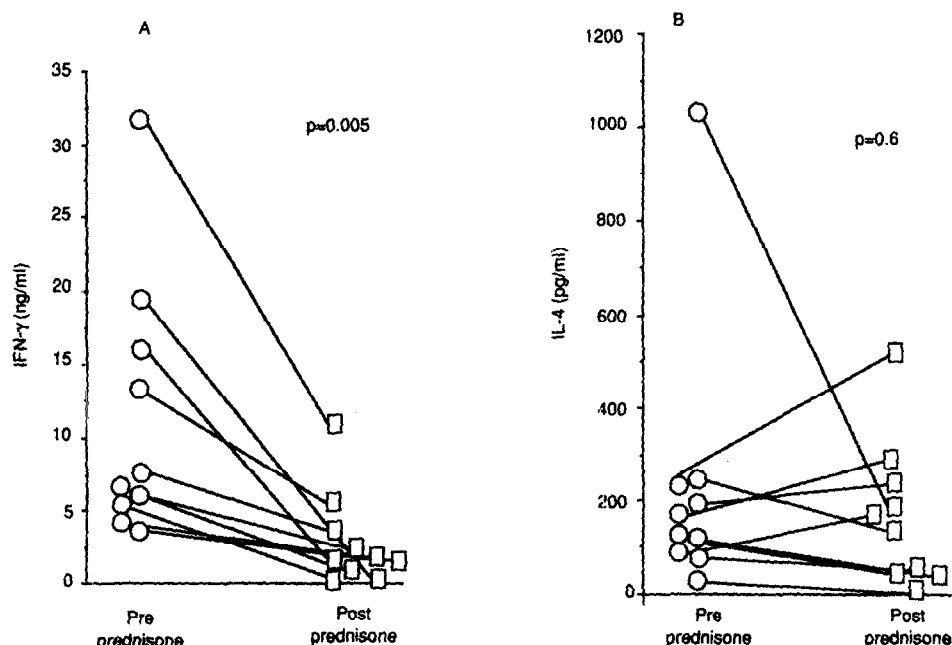


FIG. 3. Effect of prednisone on IFN- γ (A) and IL-4 (B) synthesis. PBMCs (1×10^6 cells/ml) from 10 patients with asthma were cultured before and after a course of prednisone in the presence of concanavalin A ($10 \mu\text{g/ml}$) for 48 hours, after which supernatants were analyzed for IFN- γ and IL-4 levels by ELISA. IFN- γ , but not IL-4 ($p = 0.6$), synthesis was decreased in all patients ($p = 0.005$).

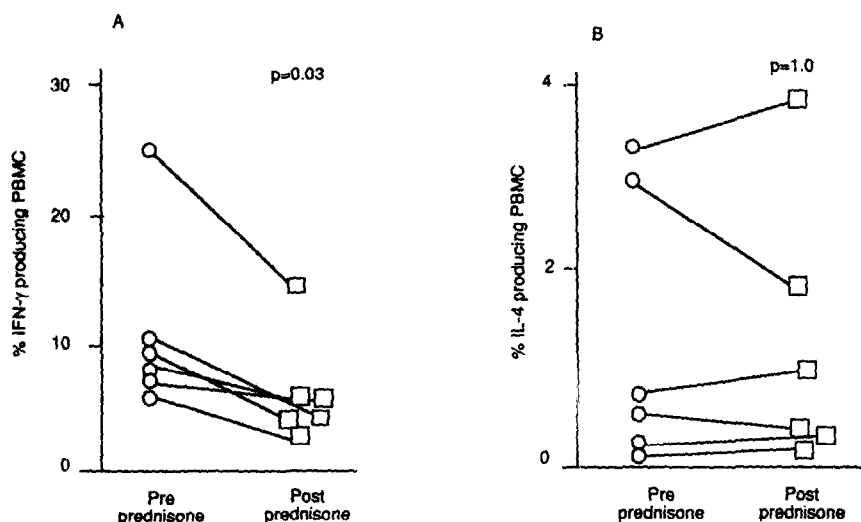


FIG. 4. Effect of prednisone on the frequency of IFN- γ (A) and IL-4 (B) producing PBMCs. Intracellular staining for cytokine production was performed on serum samples from six patients. After prednisone treatment, the frequency of PBMCs producing IFN- γ , but not IL-4 ($p = 1.0$), was decreased ($p = 0.03$).

ng IFN- γ /ml) at baseline. This decreased to a postprednisone treatment level of 1.5 ng/ml (IQ, 1.0-4.1 ng IFN- γ /ml).

To determine whether the decreased IFN- γ production reflected a decreased number of IFN- γ -producing cells, the percentage of cells express-

ing IFN- γ was determined by intracellular cytokine staining. As can be seen in Fig. 4, A, the median frequency of PBMC IFN- γ -producing cells decreased 39% from a median preprednisone frequency of 10% (IQ, 9.4-11.0) to a postprednisone frequency of 6.1% (IQ, 5.0-6.7;

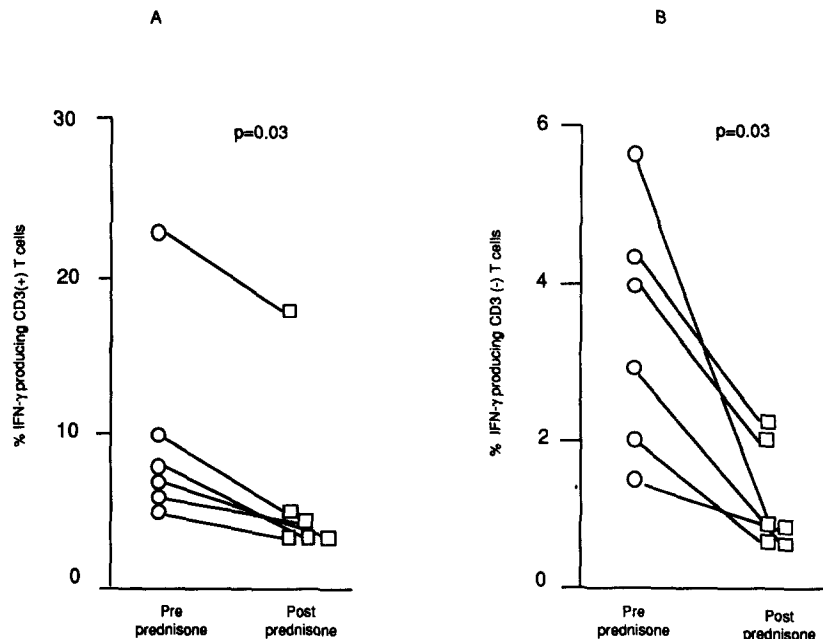


FIG. 5. Effect of prednisone on frequency of IFN- γ on different lymphocyte subpopulations. Intracellular staining for IFN- γ production was performed on serum samples from six patients. After prednisone treatment, the frequency of CD3(+) (A) and CD3(-) (B) IFN- γ -producing cells was decreased ($p = 0.03$).

$p = 0.03$). Because IFN- γ can be produced by T cells, as well as by natural killer (NK) cells, we further assessed the effect of prednisone on the frequency of IFN- γ -producing cells in different lymphocyte subpopulations. CD3(+) T cells showed a 40% decrease in the frequency of IFN- γ -producing cells from a median preprednisone frequency of 8.4% (IQ, 7.0-11.0) to a postprednisone frequency of 5.1% (IQ, 4.8-6.0; $p = 0.03$) (Fig. 5, A). The frequency of IFN- γ -producing cells decreased in both the CD4(+) and the CD8(+) T-cell subpopulations. In the case of IFN- γ -producing CD4(+) T cells, there was a median preprednisone frequency of 5.8% (IQ, 5.0-8.4), which decreased to a postprednisone frequency of 4.3% (IQ, 1.7-5.8; $p = 0.03$). Similarly, IFN- γ -producing CD8(+) T cells showed a preprednisone frequency of 17.4% (IQ, 14.4-21.4) and decreased to a postprednisone frequency of 11.95% (IQ, 7.60-16.90; $p = 0.03$). Interestingly, we also found a 74% decrease in the number of CD3(-) IFN- γ negative producing cells (Fig. 5, B) with a preprednisone median frequency of 3.5% (IQ, 2.0-4.6) and a postprednisone frequency of 0.9% (IQ, 0.7-2.1; $p = 0.03$). These CD3(-) T cells were shown to be NK cells to direct analysis of CD16/CD56(+) IFN- γ -producing cells in two of the patients (data not shown). Therefore it appears that corticosteroids cause a significant decrease in the frequency of

IFN- γ -producing NK cells, as well as the CD3(+), CD4(+), and CD3(+), CD8(+) T cells.

In contrast, treatment with prednisone did not have a significant effect on PBMC synthesis of IL-4 (Fig. 3, B). The median preprednisone IL-4 level was 139 pg/ml (IQ, 90-224), and the median postprednisone IL-4 level was 165 pg/ml (IQ, 30-240; $p = 0.6$). These observations were paralleled by the data obtained for the frequency of IL-4-producing cells. As shown in Fig. 4, B, there was no difference in the percentage of IL-4-producing cells before and after prednisone treatment ($p = 1.0$).

Effect of prednisone on pulmonary function testing

Pulmonary function tests were obtained in the eight patients with asthma who had a baseline FEV₁ of less than 70% of predicted value (Table I). Their median FEV₁ before prednisone was 2.82 L (IQ, 1.99-3.09), and their median FEV₁ after prednisone was 3.35 L (IQ, 2.81-3.65). This was a significant increase in FEV₁ ($p = 0.01$). Next, we attempted to determine whether there was a correlation between the rise in serum IgE levels and the change in pulmonary function studies that was observed. As shown in Fig. 6, the regression analysis provided a correlation coefficient (r) between the increase in serum IgE levels

and the increase in FEV_1 of 0.76 ($p = 0.03$). Thus there was a direct correlation between increased serum IgE levels and improvement in FEV_1 .

DISCUSSION

Our current findings demonstrate that administration of prednisone to atopic patients with asthma causes a significant rise in their serum IgE levels. These data are consistent with the previous observations by Settupane et al.¹⁷ and Posey et al.¹⁸ who also reported that serum IgE levels rise after a course of prednisone. This study extends these previous findings by demonstrating that this rise in serum IgE is due to a polyclonal activation of IgE synthesis. Of greater importance, we have also demonstrated that this rise in serum IgE had no clinically adverse effects on the results of patients' pulmonary function studies.

The induction of IgE synthesis requires two signals: the first is IL-4, and the second is a B-cell activation signal.^{3, 4} Of particular interest is the discovery that corticosteroids can act as a second signal.^{10, 11} This was initially discovered in CD5+ leukemia B cells¹⁰ but subsequently extended to include unfractionated PBMCs in vitro.¹¹ The exact mechanism by which corticosteroids act in concert with IL-4 to increase IgE synthesis is not completely understood but may be of considerable interest to the practice of allergy because corticosteroids are commonly used to treat the inflammatory component of asthma.

To further examine the potential mechanism(s) by which prednisone enhances IgE synthesis in vivo, we studied cytokine production by PBMCs from patients with asthma before and after treatment with prednisone. We found that in vivo prednisone treatment causes a significant net decrease in IFN- γ production by PBMCs. These findings are in agreement with findings of previous in vitro studies that corticosteroids, even at nanomolar concentrations, potentially inhibit mitogen-induced IFN- γ synthesis.¹⁹ Furthermore, this study demonstrates that treatment with prednisone causes a significant decrease in the frequency of IFN- γ -producing cells, which include both CD3(+) T cells and NK cells.

In contrast, we did not find a decrease in IL-4 production after prednisone treatment. Although previous in vitro studies have shown suppression of IL-4 production by steroids, it is important to note that the corticosteroid dosage required to achieve this effect was 1 $\mu\text{mol/L}$,²⁰ which is 10 times higher than the physiologic concentration of prednisone reached in vivo.²¹ In this regard, previous studies have shown that corticosteroids have differential dose-dependent effects on synthesis

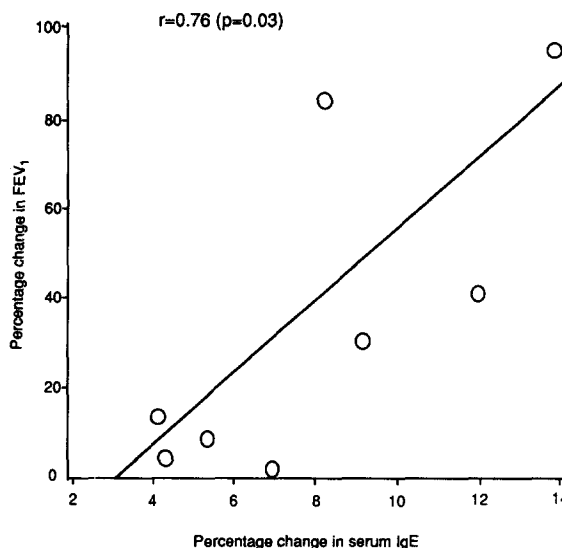


FIG. 6. Regression analysis comparing the change in FEV_1 with the rise in serum IgE. Eight patients with asthma performed pulmonary function studies before and after a course of prednisone. Regression analysis was performed to determine whether the rise in serum IgE had an effect on the results of pulmonary function studies. There was a direct correlation between these two variables ($r = 0.76$, $p = 0.03$).

of various cytokines.²² Thus the relatively greater sensitivity of IFN- γ , compared with IL-4, to the immunosuppressive effects of corticosteroids may account for the imbalance of IL-4 and IFN- γ production after in vivo treatment with prednisone.

Despite the fact that previous epidemiologic studies have demonstrated a correlation between serum IgE levels and the occurrence of asthma,^{1, 2} our present observations do not demonstrate that a short-term rise in serum IgE induced by a 1-week course of prednisone is clinically deleterious. Indeed, there was a direct correlation between the rise in serum IgE and the improvement in results of pulmonary function studies. Clinically significant IgE-dependent asthmatic responses are generally associated with biphasic reactions involving acute and late-phase responses. The acute phase is mediated primarily by IgE through the cross-linking of high-affinity receptors on mast cells. The late-phase reactions is characterized by bronchial inflammation, with a preponderance of eosinophils and T-lymphocyte infiltration. These two cell types play a key role in orchestrating and mediating asthmatic airway inflammation.³ Inhaled corticosteroids have become the therapy of choice for treating chronic asthmatic inflammation. Their effects are broad, suppressing cytokine production and the infiltration of a variety of inflammatory cells.²³

IgE is uniquely important in the acute allergic response but represents only one component of the ongoing, chronic allergic inflammatory response. Asthma represents the end product of a complex interaction of many cell types. This study suggests that the increased production of IgE per se after treatment with prednisone does not cause a worsening of asthma. More importantly, the short-term effect of prednisone on IgE synthesis may not be as important as its antiinflammatory effects on airway inflammation. As more is learned about the antiinflammatory and immunomodulatory effects of corticosteroids, this is likely to provide important new insights into the pathogenic basis of chronic asthma.

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APPENDIX. Cap testing results for allergen-specific IgE (kU_A/L)*

Donor number	Before prednisone	After prednisone
5	Short ragweed: 3 Timothy grass: 22	Short ragweed: 4 Timothy grass: 27
6	Timothy grass: 18	Timothy grass: 24
7	Short ragweed: 12	Short ragweed: 18
8	Timothy grass: 4 Short ragweed: 5	Timothy grass: 7 Short ragweed: 8
9	Cat: <0.35 Timothy grass: 4	Cat: 0.7 Timothy grass: 6
10	Timothy grass: <0.35	Timothy grass: 1

*Data from donors 1 to 4 are shown in Fig. 2.