

The New England Journal of Medicine

© Copyright, 2000, by the Massachusetts Medical Society

VOLUME 343

OCTOBER 12, 2000

NUMBER 15



LONG-TERM EFFECTS OF BUDESONIDE OR NEDOCROMIL IN CHILDREN WITH ASTHMA

THE CHILDHOOD ASTHMA MANAGEMENT PROGRAM RESEARCH GROUP*

ABSTRACT

Background Antiinflammatory therapies, such as inhaled corticosteroids or nedocromil, are recommended for children with asthma, although there is limited information on their long-term use.

Methods We randomly assigned 1041 children from 5 through 12 years of age with mild-to-moderate asthma to receive 200 μ g of budesonide (311 children), 8 mg of nedocromil (312 children), or placebo (418 children) twice daily. We treated the participants for four to six years. All children used albuterol for asthma symptoms.

Results There was no significant difference between either treatment and placebo in the primary outcome, the degree of change in the forced expiratory volume in one second (FEV₁, expressed as a percentage of the predicted value) after the administration of a bronchodilator. As compared with the children assigned to placebo, the children assigned to receive budesonide had a significantly smaller decline in the ratio of FEV₁ to forced vital capacity (FVC, expressed as a percentage) before the administration of a bronchodilator (decline in FEV₁:FVC, 0.2 percent vs. 1.8 percent). The children given budesonide also had lower airway responsiveness to methacholine, fewer hospitalizations (2.5 vs. 4.4 per 100 person-years), fewer urgent visits to a caregiver (12 vs. 22 per 100 person-years), greater reduction in the need for albuterol for symptoms, fewer courses of prednisone, and a smaller percentage of days on which additional asthma medications were needed. As compared with placebo, nedocromil significantly reduced urgent care visits (16 vs. 22 per 100 person-years) and courses of prednisone. The mean increase in height in the budesonide group was 1.1 cm less than in the placebo group (22.7 vs. 23.8 cm, $P=0.005$); this difference was evident mostly within the first year. The height increase was similar in the nedocromil and placebo groups.

Conclusions In children with mild-to-moderate asthma, neither budesonide nor nedocromil is better than placebo in terms of lung function, but inhaled budesonide improves airway responsiveness and provides better control of asthma than placebo or nedocromil. The side effects of budesonide are limited to a small, transient reduction in growth velocity. (N Engl J Med 2000;343:1054-63.)

©2000, Massachusetts Medical Society.

ASTHMA is a disease of chronic airway inflammation characterized by reversible airway obstruction and increased airway responsiveness.¹⁻³ Recent studies have demonstrated that asthma can be associated with impaired lung growth during childhood and with a progressive decline in pulmonary function in adulthood.⁴⁻¹¹ Clinical practice guidelines recommend antiinflammatory medication for the long-term control of persistent asthma; treatment with inhaled corticosteroids or nedocromil is recommended for children.^{1,2}

The Childhood Asthma Management Program was designed to evaluate whether continuous, long-term treatment (over a period of four to six years) with either an inhaled corticosteroid (budesonide) or an inhaled noncorticosteroid drug (nedocromil) safely produces an improvement in lung growth as compared with treatment for symptoms only (with albuterol and, if necessary, prednisone, administered as needed).¹² The primary outcome in the study was lung growth, as assessed by the change in forced expiratory volume in one second (FEV₁, expressed as a percentage of the predicted value) after the administration of a bronchodilator. Secondary outcomes included the degree of airway responsiveness, morbidity, physical growth, and psychological development.

METHODS

The design and methods of the research program have been described previously.^{7,12-15}

Screening and Schedule of Visits

Between December 1993 and September 1995, we enrolled 1041 children from 5 through 12 years of age at eight clinical cen-

Stanley Szefer, M.D., Scott Weiss, M.D., and James Tonascia, Ph.D., take responsibility for the content of this article. The other members of the writing committee were N. Franklin Adkinson, M.D., Bruce Bender, Ph.D., Reuben Cherniack, M.D., Michele Donithan, M.H.S., H. William Kelly, Pharm.D., Joseph Reisman, M.D., M.B.A., Gail G. Shapiro, M.D., Alice L. Sternberg, Sc.M., Robert Strunk, M.D., Virginia Taggart, M.P.H., Mark Van Natta, M.H.S., Robert Wise, M.D., Margaret Wu, Ph.D., and Robert Zeiger, M.D., Ph.D. Address reprint requests to Dr. Tonascia at the CAMP Coordinating Center, Johns Hopkins University, 615 N. Wolfe St., Rm. 5010, Baltimore, MD 21205.

*The members of the research group are listed in the Appendix.

ters. The children had mild-to-moderate asthma, as defined by the presence of symptoms or by the use of an inhaled bronchodilator at least twice weekly or the use of daily medication for asthma. The children's airway responsiveness to methacholine, as indicated by the concentration of the drug that caused a 20 percent decrease in the FEV₁, was 12.5 mg per milliliter or less. They had no other clinically significant conditions.¹² The children's parents or guardians signed an informed-consent form approved by the local institutional review board. Follow-up visits occurred two and four months after randomization and at four-month intervals thereafter. From March through June 1999 (the end of the treatment period), the children discontinued the study medication and returned two to four months later for spirometry and methacholine challenge. Children who had been using additional medications because of inadequate control of asthma continued to use those medications.

Treatment

Three hundred eleven children were randomly assigned to receive budesonide (Pulmicort, AstraZeneca, Westborough, Mass.) (200 µg twice daily, delivered by two 100-µg actuations of a breath-actuated metered-dose inhaler [Turbohaler, AstraZeneca]), and 208 were assigned to receive a matching placebo. Three hundred twelve children were assigned to receive nedocromil sodium (8 mg twice daily, delivered by four 2-mg actuations of a pressurized metered-dose inhaler [Tilade, Rhone-Poulenc Rorer, Collegeville, Pa.]), and 210 were assigned to receive a matching placebo. Assignments were made by permuted-blocks randomization with stratification according to clinic.¹⁶ The total daily doses of budesonide (400 µg) and nedocromil (16 mg) were administered as two equal daily doses to maximize adherence to the treatment regimen,¹⁷⁻²⁰ and adherence was also promoted by an educational program.¹⁵ Albuterol (Ventolin, Glaxo Wellcome, Research Triangle Park, N.C.), delivered by two 90-µg actuations of a pressurized metered-dose inhaler, was used as needed for symptoms of asthma or to prevent exercise-induced bronchospasm.¹² A written action plan guided rescue treatment.^{12,15} Short courses of oral prednisone were prescribed for exacerbations of asthma.¹² The addition of beclomethasone dipropionate (168 µg twice daily; Vanceril, Schering-Plough, Kenilworth, N.J.) to the study medication was allowed if the control of asthma was inadequate. If control remained unsatisfactory, replacement or addition of medications was allowed. To account for remission, it was permissible to taper the study medication to a dose of zero (by stepwise reductions from 100 percent to 50 percent to zero), according to defined procedures.¹² Algorithms guided the resumption of the full dose of the study medication.¹²

Outcome Measures

Spirometry was performed twice yearly, with measurements obtained both before and after the administration of a bronchodilator.^{7,12} A methacholine challenge was performed annually.¹² Methacholine challenge was not performed within 28 days of an upper respiratory tract infection or the use of prednisone for exacerbations of asthma.

The children (or their parents or guardians) completed a diary card each day that recorded night awakenings due to asthma, morning and evening peak flows as measured by a peak-flow meter (Assess, HealthScan Products, Cedar Grove, N.J.), use of study medication, use of albuterol for symptoms and to prevent exercise-induced bronchospasm, use of prednisone, absences from school due to asthma, visits to a physician's office or hospital because of asthma, and severity of symptoms.¹²

The children's height (measured by Harpenden stadiometer) and weight were recorded at every visit; the total bone mineral density of the spine from L1 to L4 and the Tanner stage of sexual development (assessed on the basis of the development of pubic hair, genitals [in boys] or breasts [in girls], and testicular volume, each scored from 1 [preadolescent characteristics] to 5 [adult characteristics]) were assessed annually.¹² Skeletal maturation (bone age) during the last eight months of follow-up was determined at a

central reading center by evaluation of a radiograph of the left wrist and hand by the method of Greulich and Pyle²¹ and was used to estimate the projected final height.²² Psychological development was assessed with four neurocognitive tests administered at base line and three years later, and by eight psychosocial questionnaires completed at base line and during annual visits.¹² Psychosocial questionnaires included the Children's Depression Inventory,²³ a 27-item questionnaire completed by the child with regard to the symptoms of depression. The total score for this scale ranges from 0 to 54, with higher scores indicating greater depression. Skin-prick testing, with a core battery of 10 allergens and several locally relevant allergens, was performed at base line and four years later.^{12,14}

Anterior and posterior images of the lens of the eye, taken with a digital retroluminescent camera (Neitz Cataract Screener CT-S, Neitz Instruments, Tokyo) during the last eight months of follow-up, were examined for posterior subcapsular cataracts at a central reading center.²⁴

Statistical Analysis

Our study had 90 percent power to detect a difference of 3.5 percent between either treatment group and the placebo group in the mean change in the FEV₁, expressed as a percentage of the predicted value, after the administration of a bronchodilator, after four to six years of treatment.¹² Data from the two placebo groups were pooled after we determined that the children in the two groups were similar with respect to base-line characteristics and outcomes. Each participant was included in his or her assigned study group, regardless of any adjustments of treatment (intention-to-treat analysis). The degree of change in an outcome measure was determined by subtracting the base-line measurement from the measurement obtained at the last follow-up visit during the treatment period. The difference between each treatment group and the placebo group in each measure of change was determined with use of multiple regression,²⁵ with the change in the measure as the response variable, two indicator variables for the treatment groups, and the following eight covariates: the base-line value of the outcome measure, the child's age at randomization, race (two indicator variables), sex, clinic (seven indicator variables), duration of asthma at base line, severity of asthma at base line, and skin-test reactivity at base line (any reactivity vs. none). The adjusted mean change in each outcome measure in each study group was computed from the regression model by the use of mean values for all covariates.²⁶ Kaplan-Meier estimates of cumulative probability and log-rank tests²⁷ were used to evaluate the time to the first course of prednisone and the time to the initiation of therapy with beclomethasone or any other nonassigned medication for asthma in each treatment group. All analyses were performed with SAS software (version 6.12, SAS Institute, Cary, N.C.). The P values presented are two-sided and have not been adjusted for multiple comparisons. Interim monitoring of results by a data and safety monitoring board took place semiannually; statistical guidelines for stopping the study were not used. In the comparisons among the study groups we used regression models to adjust for small imbalances in base-line measures; however, unadjusted analyses for all outcome measures yielded qualitatively similar results.

RESULTS

Study Population

The three study groups were similar at base line, except for a slightly higher proportion of boys in the nedocromil group (Table 1). The duration of follow-up was similar in all the study groups, with a mean of 4.3 years (Table 2).

Measures of Pulmonary Function

Budesonide treatment improved the FEV₁ after the administration of a bronchodilator from a mean of

TABLE 1. CHARACTERISTICS OF THE PATIENTS AT BASE LINE.*

CHARACTERISTIC†	BUDESONIDE (N=311)	NEDOCROMIL (N=312)	PLACEBO (N=418)
Age — yr	9.0±2.1	8.8±2.1	9.0±2.2
Race or ethnic group — no. (%)			
Non-Hispanic white	201 (64.6)	218 (69.9)	292 (69.9)
Non-Hispanic black	44 (14.1)	38 (12.2)	56 (13.4)
Hispanic	32 (10.3)	29 (9.3)	37 (8.9)
Other	34 (10.9)	27 (8.7)	33 (7.9)
Sex — no. (%)‡			
Female	130 (41.8)	106 (34.0)	184 (44.0)
Male	181 (58.2)	206 (66.0)	234 (56.0)
Age at onset of asthma — yr	3.1±2.3	3.1±2.4	3.0±2.6
Time since diagnosis of asthma — yr	5.2±2.6	5.0±2.7	4.9±2.7
Treatments in 6 mo before enrollment — no. of patients (%)			
Cromolyn or nedocromil	133 (42.8)	148 (47.4)	160 (38.3)
Inhaled corticosteroid	126 (40.5)	114 (36.5)	150 (35.9)
Oral corticosteroid	107 (34.4)	94 (30.1)	162 (38.8)
Severity of asthma — no. (%)			
Moderate	166 (53.4)	161 (51.6)	216 (51.7)
Mild	145 (46.6)	151 (48.4)	202 (48.3)
Hospitalizations for asthma in year before enroll- ment — no./100 person-yr	31	29	31
Recordings on daily diary card			
Episode-free days — no./mo§	9.7±7.8	9.9±8.1	9.6±7.6
Use of albuterol for symptoms — puffs/wk	10.4±9.8	10.5±9.8	10.2±9.6
Night awakenings — no./mo	0.9±1.7	1.0±1.7	0.8±1.5
FEV ₁ before bronchodilator use — % of predicted	93.6±14.4	93.4±14.5	94.2±14.0
FEV ₁ after bronchodilator use — % of predicted	103.2±13.2	102.3±12.7	103.3±12.2
Airway responsiveness to methacholine (FEV ₁ PC ₂₀) — mg/ml¶	1.1±3.3	1.2±3.3	1.1±3.3
Height — percentile	56.8±28.0	56.0±28.7	55.3±28.8

*Plus-minus values are means ±SD. Not all percentages add to 100, because of rounding or because some children used more than one treatment before enrollment.

†FEV₁ denotes the forced expiratory volume in one second, and FEV₁ PC₂₀ the concentration of methacholine that caused a 20 percent decrease in FEV₁.

‡P value for homogeneity among groups = 0.02.

§An episode-free day was defined as a day with no night awakenings, morning and evening peak flow ≥80 percent of personal best peak flow (determined by algorithm¹²), no use of albuterol for symptoms, no use of prednisone, no absence from school or contact with a physician because of asthma symptoms, and no episode of wheezing, coughing, chest tightness, or shortness of breath.

¶Values are geometric means ±SD.

103.2 percent of the predicted value to a mean of 106.8 percent within two months, but this measurement gradually diminished to 103.8 percent by the end of the treatment period, at which point the change in the FEV₁ after bronchodilator use in the budesonide group was not significantly different from that in the placebo group (Table 3 and Fig. 1). The nedocromil group was similar to the placebo group in this measure throughout the treatment period (Table 3 and Fig. 1). The ratio of the FEV₁ to the forced vital capacity (FVC, expressed as a percentage of the predicted value) after bronchodilator use was smaller at the end of the treatment period than at the start in all study groups; the decline in the budesonide group was less than that in the placebo group (1.0 percent vs. 1.7 percent, P=0.08) (Table 3 and Fig. 1).

In patients treated with budesonide, FEV₁ before

the administration of a bronchodilator increased within two months and was significantly higher at the end of the treatment period than it was in those receiving placebo (P=0.02); the nedocromil group was similar to the placebo group with respect to this measure throughout the treatment period (Table 3 and Fig. 1). The FVC (expressed as a percentage of the predicted value) before bronchodilator use increased in all study groups. The increase in the nedocromil group was less than that in the placebo group (P=0.02), whereas the increase in the budesonide group was similar to that in the placebo group (Table 3). The FEV₁:FVC ratio before bronchodilator use was smaller at the end of the treatment period than at the start in all three groups; the decline in the budesonide group was less than that in the placebo group (0.2 percent vs. 1.8 percent, P=0.001) (Table 3 and Fig. 1).

TABLE 2. FOLLOW-UP, ASTHMA TREATMENT, AND MORBIDITY DURING THE TRIAL.*

EVENT	BUDESONIDE (N=311)	NEDOCROMIL (N=312)	PLACEBO (N=418)	P VALUE	
				BUDESONIDE VS. PLACEBO	NEDOCROMIL VS. PLACEBO
Follow-up					
Duration of follow-up (yr)	4.3±0.8	4.3±0.7	4.3±0.7	0.35	0.40
Percentage of scheduled visits completed	95.2	95.2	95.1	0.94	0.92
Percentage of days with completed diary card	85.7	85.6	85.7	0.94	0.65
Percentage of patients in whom primary outcome was measured	98.4	98.4	98.3	0.94	0.94
Asthma treatment					
Percentage of days during which treatment was prescribed					
Budesonide, nedocromil, or placebo only					
Full dose	88.9	78.6	78.4	<0.001	0.89
Tapered to half dose	3.4	3.3	2.3	0.05	0.03
Tapered to zero dose	1.1	1.0	0.6	0.10	0.16
Beclomethasone or other asthma medications	6.6	17.1	18.7	<0.001	0.53
Percentage of days child reported to take pre-scribed dose of study medication†	73.7	70.2	76.2	0.34	0.01
Prednisone course (no./100 person-yr)‡	70	102	122	<0.001	0.01
Morbidity					
Urgent care visits due to asthma (no./100 person-yr)‡	12	16	22	<0.001	0.02
Hospitalizations due to asthma (no./100 person-yr)‡	2.5	4.3	4.4	0.04	0.99
Fractures (no./100 person-yr)‡	5.7	4.1	5.1	0.59	0.23
No. of eyes with posterior subcapsular cataracts§	0‡	0	0	1.00	1.00

*Plus-minus values are means ±SD. The primary outcome was the forced expiratory volume in one second after bronchodilator use, expressed as a percentage of the predicted value.

†Results are based on daily diaries.

‡Rates have been adjusted for age at randomization, race or ethnic group, sex, clinic, duration of asthma at base line, severity of asthma at base line, and skin-test reactivity at base line.

§Results are based on photographic evaluations of 1909 eyes in 955 children. In one child in the budesonide group, an area in the right eye was classified as a questionable posterior subcapsular cataract on photographic evaluation; the child was found to have a barely measurable (<0.5 mm) posterior subcapsular cataract on slit-lamp examination five months later. Uncorrected Snellen visual acuity in the eye was 20/25. This child received budesonide as study medication, beclomethasone (for a total of 13 months), and oral prednisone (for a total of 38 days) during the trial, as well as an intranasal corticosteroid.

Airway responsiveness to methacholine, expressed as the concentration that caused a 20 percent decrease in FEV₁, improved throughout the treatment period in all three groups (Fig. 1), with the greatest improvement occurring in the budesonide group. At the end of the treatment period, airway responsiveness to methacholine was significantly improved in the budesonide group as compared with the placebo group ($P<0.001$), whereas the change in the nedocromil group was similar to that in the placebo group (Table 3 and Fig. 1).

Health Outcomes

As compared with the placebo group, the budesonide group had a 43 percent lower rate of hospitalization ($P=0.04$), a 45 percent lower rate of visits for urgent care ($P<0.001$), and a 43 percent lower rate of use of courses of prednisone ($P<0.001$) over the treatment period (Table 2). The nedocromil group had a 27 percent lower rate of urgent care visits ($P=$

0.02) and a 16 percent lower rate of use of courses of prednisone ($P=0.01$) than the placebo group, but there was no significant difference in the rate of hospitalization. One death from asthma occurred in the nedocromil group; the child had been receiving supplemental treatment, including inhaled corticosteroids, for several months before her death. One child in the placebo group required intubation for an exacerbation of asthma.

Control of asthma was best in the budesonide group, as indicated by significantly fewer symptoms ($P=0.005$), less use of albuterol for symptoms ($P<0.001$), and more episode-free days ($P=0.01$) (Table 3). Changes in morning peak flow and the number of night awakenings per month were similar in all groups (Table 3). The times to the first course of prednisone and to the initiation of treatment with beclomethasone or other nonassigned asthma medications were significantly longer in the budesonide group than in the placebo group ($P<0.001$) (Fig. 2).

TABLE 3. SPIROMETRIC MEASURES, AIRWAY RESPONSIVENESS, PHYSICAL GROWTH, PSYCHOLOGICAL DEVELOPMENT, AND DIARY-CARD MEASURES ACCORDING TO TREATMENT GROUP.

MEASURE*	MEAN VALUE†			SD‡	P VALUE	
	BUDESONIDE (N=311)	NEDOCROMIL (N=312)	PLACEBO (N=418)		BUDESONIDE VS. PLACEBO	NEDOCROMIL VS. PLACEBO
Changes in spirometric values after broncho- dilator use						
FEV ₁ (% of predicted)	0.6	-0.5	-0.1	9.6	0.36	0.56
FEV ₁ (liters)	1.04	1.06	1.08	0.40	0.30	0.58
FVC (% of predicted)	0.7	-0.1	0.9	9.3	0.74	0.16
FVC (liters)	1.27	1.29	1.33	0.45	0.05	0.25
FEV ₁ :FVC (%)	-1.0	-1.3	-1.7	5.2	0.08	0.26
Changes in spirometric values before broncho- dilator use						
FEV ₁ (% of predicted)	2.9	0.4	0.9	11.2	0.02	0.57
FEV ₁ (liters)	1.02	0.99	1.01	0.43	0.76	0.58
FVC (% of predicted)	2.3	0.6	2.4	10.0	0.89	0.02
FVC (liters)	1.29	1.28	1.35	0.47	0.07	0.06
FEV ₁ :FVC (%)	-0.2	-1.0	-1.8	6.5	0.001	0.10
Airway responsiveness to methacholine (ratio of follow-up to base-line values)	3.0	1.8	1.9	3.3	<0.001	0.97
Change in height (cm)	22.7	23.7	23.8	5.4	0.005	0.65
Height percentile at last follow-up	51.3	55.2	55.7	15.5	<0.001	0.62
Bone age at last follow-up (yr)	13.7	13.6	13.7	2.5	0.84	0.61
Difference between bone age and chronologic age (yr)	0.2	0.4	0.4	1.1	0.18	0.83
Projected final height (cm)§	174.8	174.8	174.8	4.4	0.86	0.87
Tanner genital stage at last follow-up (boys)¶	3.0	2.8	2.9	0.9	0.53	0.10
Tanner breast stage at last follow-up (girls)¶	3.3	3.2	3.4	0.8	0.56	0.17
Change in bone density (g/cm ²)	0.17	0.17	0.18	0.08	0.53	0.15
Change in total score on Children's Depression Inventory	-3.2	-1.8	-2.2	5.1	0.01	0.35
Changes in daily diary-card measures						
Symptom score	-0.44	-0.38	-0.37	0.37	0.005	0.80
Morning peak flow (liters/min)	131	131	132	67	0.86	0.82
Episode-free days (no./mo)	11.3	9.3	9.3	10.2	0.01	0.97
Use of albuterol for symptoms (puffs/wk)	-7.4	-5.7	-5.3	7.1	<0.001	0.42
Night awakenings (no./mo)	-0.7	-0.6	-0.6	1.1	0.14	0.48

*Changes were calculated by subtracting the base-line values from the values at the last follow-up. FEV₁ denotes forced expiratory volume in one second, and FVC forced vital capacity. The primary outcome measure was the FEV₁ after bronchodilator use, expressed as a percentage of the predicted value.

†Means have been adjusted for the average base-line values of the outcome measure, age at randomization, race or ethnic group, sex, clinic, duration of asthma at base line, severity of asthma at base line, and skin-test reactivity at base line. Only measures with both base-line and follow-up values are included in this table.

‡SD is the standard deviation estimated from the regression model.

§Projected final height was calculated from the prediction equations of Tanner et al.,²² which use height, chronologic age, bone age, and (for girls) age at first menses.

¶The Tanner stage is an assessment of sexual development. The possible scores for genital stage and for breast stage range from 1 to 5, where 1 indicates preadolescent characteristics and 5 indicates adult characteristics.

||The Children's Depression Inventory²³ is a 27-item questionnaire completed by the child with regard to the symptoms of depression. The total score ranges from 0 to 54, where higher scores indicate greater depression.

During the treatment period, the percentage of days on which beclomethasone or another asthma medication was prescribed in addition to or instead of the originally assigned treatment was significantly lower ($P<0.001$) for children assigned to budesonide (6.6 percent) than for those assigned to placebo (18.7 percent); there was no significant difference in the measure between the nedocromil group (17.1 percent) and

the placebo group (Table 2). Compliance with treatment, defined as the percentage of days on which a child was reported to have taken the prescribed dose of study medication, was similar in children assigned to budesonide and those assigned to placebo (73.7 percent and 76.2 percent, respectively), but it was lower in children assigned to nedocromil (70.2 percent) ($P=0.01$ for the comparison with placebo) (Table 2).

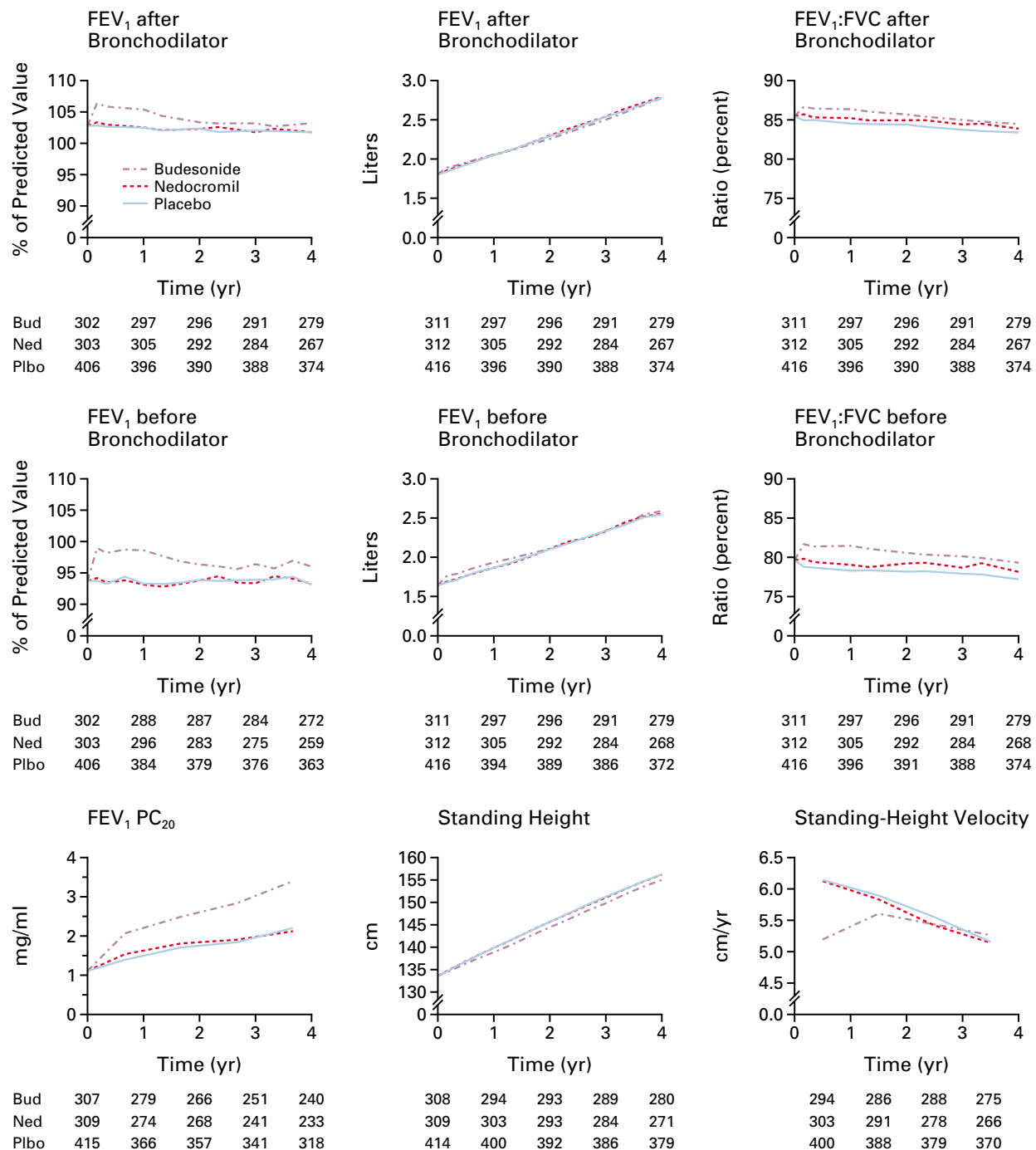


Figure 1. Mean Values for Spirometric Measures before and after the Use of a Bronchodilator, Airway Responsiveness, Standing Height, and Standing-Height Velocity during Four Years of Follow-up in the Budesonide (Bud), Nedocromil (Ned), and Placebo (Plbo) Groups.

The numbers of observations used to calculate means at annual intervals are shown below each panel. When comparisons were made over the total follow-up time, the budesonide group differed significantly ($P < 0.001$) from the placebo group in all measures, even though these differences may not be apparent in every panel, and there were no significant differences between the nedocromil group and the placebo group in any measure. FEV₁ denotes forced expiratory volume in one second, FVC forced vital capacity, and FEV₁ PC₂₀ airway responsiveness measured by the concentration of methacholine that caused a 20 percent decrease in FEV₁. For FEV₁ PC₂₀, values were obtained at 0, 8, 20, 32, and 44 months. P values for the comparisons between study groups of the changes from base line to last follow-up are shown in Table 3.

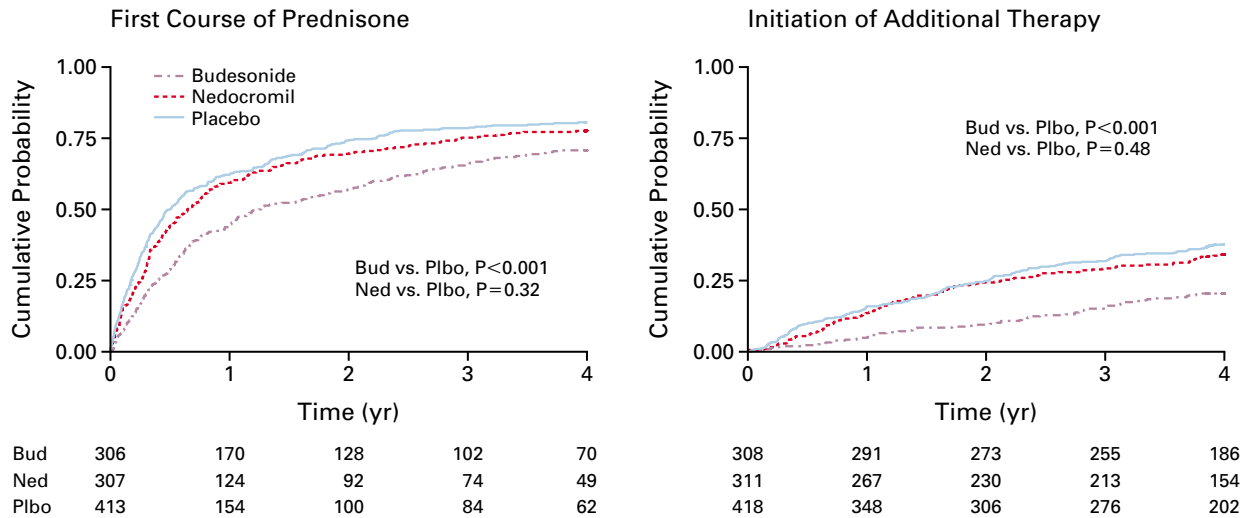


Figure 2. Kaplan–Meier Estimates of the Cumulative Probability of a First Course of Prednisone and Initiation of Additional Therapy (Beclomethasone or Other Nonassigned Asthma Medications) during Four Years of Follow-up in the Budesonide (Bud), Nedocromil (Ned), and Placebo (Plbo) Groups.

The numbers of children at risk at annual intervals are shown below each graph.

Measures of Growth and Assessment for Cataracts

At the end of the treatment period, the mean increase in height in the budesonide group was 1.1 cm less than the mean increase in the placebo group (22.7 vs. 23.8 cm, $P = 0.005$); the height increase was similar in the nedocromil and the placebo groups (Table 3). The difference between the budesonide and placebo groups in the rate of growth was evident primarily within the first year of treatment and did not increase later: all groups had similar growth velocity by the end of the treatment period (Fig. 1), as well as similar changes in bone density (Table 3). At the end of treatment, the bone age, projected final height, and Tanner stage in the budesonide and nedocromil groups were similar to those in the placebo group (Table 3). The only difference with respect to changes in any of the psychosocial measures was a greater improvement in the total score on the Children's Depression Inventory,²³ indicating less depression, in the budesonide group as compared with the placebo group (a decline of 3.2 vs. 2.2, $P = 0.01$) (Table 3). None of the children had posterior subcapsular cataracts according to lens-photography criteria (Table 2). However, one child in the budesonide group was classified as having a questionable posterior subcapsular cataract. A barely measurable (<0.5 mm) posterior subcapsular cataract was found in this child on slit-lamp examination by an ophthalmologist five months after the photographs were taken. The uncorrected Snellen visual acuity in the eye was 20/25. This child received budesonide as study medication, beclomethasone (for 13 months), and oral prednisone (for 38

days) during the study, as well as an intranasal corticosteroid.

Discontinuation of Study Medication

Four months after discontinuation of the study medication, the children assigned to nedocromil had a smaller reduction from base line in the $FEV_1:FVC$ ratio after bronchodilator use than did those assigned to placebo (a decline of 1.2 percent vs. 2.2 percent, $P = 0.03$). Also at this time, children assigned to budesonide or nedocromil had a smaller reduction in $FEV_1:FVC$ before bronchodilator use than did those assigned to placebo (budesonide vs. placebo: a decline of 0.9 percent vs. 2.5 percent, $P = 0.005$; nedocromil vs. placebo: a decline of 1.1 percent vs. 2.5 percent, $P = 0.01$). The groups were similar in all other measures, including airway responsiveness, which worsened in the budesonide group during the four-month period after discontinuation of budesonide and became similar to that in the placebo group (data are available elsewhere*).

DISCUSSION

The finding that neither budesonide nor nedocromil improved lung function, as measured by the percentage of the predicted value for FEV_1 after the administration of a bronchodilator, was unexpected. FEV_1 was chosen as the primary outcome measure because it is widely accepted as the most clinically

*See NAPS document no. 05569 for 16 pages of supplementary material. To order, contact NAPS, c/o Microfiche Publications, 248 Hempstead Tpke., West Hempstead, NY 11552.

useful and predictive measure of lung function. It is highly reproducible and correlates well with the progression of disease,^{28,29} use of health care,³⁰ and severity of asthma^{1-3,31} and accurately describes the natural history of childhood asthma. The value after bronchodilator use was chosen as the outcome measure because it minimizes the effects of airway constriction and has less variability over time in individual patients than the value before bronchodilator use.

The use of budesonide was associated with improvement in the FEV₁ before bronchodilator use, when measured as a percentage of the predicted value, but not when measured in liters (Table 3). The use of nedocromil was not associated with improvement in either measure of FEV₁. Since predicted values depend on height,^{32,33} the statistical significance of the change in the FEV₁ as a percentage of the predicted value is mostly attributable to the slightly smaller stature of the children in the budesonide group.

As a consequence of normal lung growth,³⁴ the FEV₁:FVC ratio before bronchodilator use decreased over time in all three groups (Fig. 1). The decrease was minimized by budesonide (before bronchodilator use, $P=0.001$; after bronchodilator use, $P=0.08$). The minimization of the decrease was not due to improvement in FEV₁ and might have been due to lower FVC or improved bronchodilation in the budesonide group.

During the trial, there was a lack of decline in the FEV₁ before and after bronchodilator use in the placebo group and a lack of long-term improvement in the budesonide and nedocromil groups as compared with the placebo group. An irreversible deterioration in lung function might have occurred in the patients before their enrollment, and the treatment might therefore have been too late to effect a change. Eighty percent of all childhood asthma is diagnosed by the age of six years,³⁵ and normal proliferation of the alveoli and airway development occur predominantly before the age of five years.³⁶ We enrolled children from 5 through 12 years of age, who had had asthma for a mean of five years. Some studies recommend initiating treatment within two to three years after the onset of disease.⁹

In contrast to the results of lung-function measurements, our findings on airway responsiveness and health outcomes clearly favor budesonide. As expected,³⁷ improvement in airway responsiveness to methacholine occurred during the treatment period in all three study groups (Fig. 1) but was substantially and significantly greater in the budesonide group (Table 3); this finding is consistent with the results of shorter trials in children.^{38,39} The relative improvement in the budesonide group suggests additional improvement as a consequence of lower bronchomotor tone or diminished airway inflammation.

The rates of hospitalization and of urgent care visits and the need for additional therapy and oral prednisone were lowest in the budesonide group (Table 2).

Budesonide was also associated with a greater reduction in symptoms and in the use of albuterol for symptoms and with an increase in the number of episode-free days as compared with placebo (Table 3).

We also evaluated the long-term effects of inhaled nedocromil in children. Overall, the results in the nedocromil group were similar to those in the placebo group, except that nedocromil was associated with fewer exacerbations, as evidenced by a lower rate of prednisone use and a lower rate of urgent care visits.

The current literature indicates that treatment of children with inhaled or nasal corticosteroids, specifically beclomethasone dipropionate, results in a loss of 0.7 to 1.4 cm in linear growth over a one-year period.³⁸⁻⁴⁶ Our four-to-six-year trial provides evidence that the effect of budesonide on growth velocity is not sustained and that extrapolations from one-year studies to projected loss in subsequent years are not appropriate. Calculations of projected final height²² suggest that the children in the study groups will achieve similar final heights.

There were no significant differences among the three groups in the change in bone density. Several recent studies have suggested that the use of high doses of inhaled corticosteroids in adults can lead to the development of cataracts.^{47,48} In one child in the budesonide group, an area of one eye was classified as a questionable posterior subcapsular cataract on photographic assessment. However, interpretation of this finding was complicated by the child's use of oral corticosteroids and the lack of base-line photographic assessment.

After discontinuation of the study medication, no differences were observed among the study groups in lung function or growth from base line (the beginning of the study) to the final measurement, except for the FEV₁:FVC ratio before bronchodilator use. The increase in responsiveness to methacholine seen in the budesonide group after discontinuation of the study medication suggests that the beneficial effect of budesonide on airway responsiveness to methacholine is due to changes in bronchomotor tone or airway inflammation, and not to the prevention or resolution of remodeling of the airway wall.

The percentage of days on which only the full dose of the assigned study medication was prescribed was greater in the budesonide group than in the placebo group (88.9 percent vs. 78.4 percent, $P<0.001$) (Table 2). However, it is unlikely that this difference substantially influenced the findings. Four post hoc analyses confirmed the results of the intention-to-treat analysis. These analyses excluded any outcome measures obtained after departure from full-dose study medication, were restricted to children who used only full-dose study medication throughout the follow-up, included only children who had reported compliance with full-dose study medication on at least 80 percent of days, and categorized children according to their

prescribed treatment at the end of the treatment period (data are available elsewhere*).

Our study demonstrates the importance of long-term, controlled trials of treatment for asthma. A benefit of budesonide in terms of lung function, as measured by the FEV₁ after bronchodilator use, was evident at one year, but not at four years; a reduction in linear growth velocity in children treated with budesonide was evident at one year but was absent by the second year. Airway responsiveness to methacholine improved in all study groups over the four to six years of treatment. The improvement was substantially and significantly greater with budesonide than with placebo, but this advantage disappeared after the discontinuation of treatment with budesonide.

In summary, we found that in children five or more years of age with mild-to-moderate asthma, continuous daily treatment with inhaled budesonide or nedocromil had no therapeutic benefit in terms of lung function, as measured by the FEV₁ after bronchodilator use, as compared with therapy given as needed for the control of symptoms (as in the placebo group). Intervention with antiinflammatory medications earlier in childhood, earlier after the onset of disease, or in patients selected because of a decline in pulmonary function might still be beneficial and should be evaluated. Continuous daily treatment with inhaled budesonide leads to better control of asthma than symptomatic treatment (as in our placebo group) or treatment with nedocromil, and its side effects are limited to a small, transient reduction in growth velocity. Inhaled corticosteroids are safe and effective for long-term use in children with asthma.

Supported by contracts with the National Heart, Lung, and Blood Institute (NO1-HR-16044, NO1-HR-16045, NO1-HR-16046, NO1-HR-16047, NO1-HR-16048, NO1-HR-16049, NO1-HR-16050, NO1-HR-16051, and NO1-HR-16052) and by General Clinical Research Center grants from the National Center for Research Resources (M01RR00051, M01RR0099718-24, M01RR02719-14, and RR00036).

Pharmaceuticals were supplied by AstraZeneca, Westborough, Mass.; Glaxo Research Institute, Research Triangle Park, N.C.; Rhone-Poulenc Rorer, Collegeville, Pa.; and Schering-Plough, Kenilworth, N.J.

Dr. Szefer has served as a consultant or advisory panel member for Astra USA, Glaxo Wellcome, Merck, 3M Pharmaceuticals, and Sepracor.

APPENDIX

The members of the Childhood Asthma Management Program (CAMP) Research Group are as follows: *Asthma, Inc., Seattle*: G.G. Shapiro, L.C. Altman, J.W. Becker, C.W. Bierman, T. Chinn, D. Crawford, T.R. DuHamel, H. Eliassen, C.T. Furukawa, B. Hammond, M.S. Kennedy, M.V. Lasley, D.A. Minotti, C. Reagan, M. Sharpe, F.S. Virant, G. White, T.G. Wighton, and P.V. Williams; *Brigham and Women's Hospital, Boston*: S. Weiss, S. Babigian, P. Barrant, L. Benson, J. Caicedo, T. Calder, A. DeFilippo, C. Dorsainvil, J. Erickson, P. Fulton, J. Gilbert, M. Grace, D. Greineder, S. Haynes, M. Higham, D. Jakubowski, S. Kelleher, J. Koslof, N. Madden, D. Mandel, A. Martinez, J. McAuliffe, P. Pacella, P. Parks, A. Plunkett, J. Sagarin, K. Seligsohn, M. Syring, M. Tata, W. Torda, J. Traylor, M. Van Horn, C. Wells, and A. Whitman; *Hospital for Sick Children, Toronto*: J. Reisman, Y. Benedet, S. Carpenter, J. Chay, M. Collinson, J. Finlayson-Kulchin,

*See NAPS document no. 05569 for 16 pages of supplementary material. To order, contact NAPS, c/o Microfiche Publications, 248 Hempstead Tpke., West Hempstead, NY 11552.

K. Gore, A. Hall, N. Holmes, S. Klassen, H. Levison, I. MacLusky, M. Miki, J. Quenneville, R. Sananes, and C. Wasson; *Johns Hopkins Asthma and Allergy Center, Baltimore*: N.F. Adkinson, Jr., N. Bollers, P. Eggleston, K. Huss, K. Hyatt, B. Leritz, M. Pessaro, S. Phillips, L. Plotnick, M. Pulsifer, C. Rand, and B. Wheeler; *National Jewish Medical and Research Center, Denver*: S. Szefer, B. Bender, K. Brelsford, J. Bridges, J. Ciacco, R. Covar, M. Eltz, M. Flynn, M. Gleason, J. Hassell, M. Hefner, C. Hendrickson, D. Hettelman, C.G. Irvin, J. Jacobs, T. Junk-Blanchard, A. Kamada, A. Liu, H.S. Nelson, S. Nimmagadda, K. Sandoval, J. Sheridan, J. Spahn, D. Sundström, T. Washington, M.P. White, and E. Willcutt; *University of California, San Diego, and Kaiser Permanente Southern California Region, San Diego*: R. Zeiger, J.G. Easton, N. Friedman, L.L. Galbreath, E. Hanson, K. Harden, A. Horner, A. Jalowayski, E.M. Jensen, S. King, A. Lincoln, B. Lopez, M. Magiari, M.H. Mellon, A. Moscona, K. Mostafa, C.A. Nelle, S. Pizzo, E. Rodriguez, K. Sandoval, M. Schatz, and N.W. Wilson; *University of New Mexico, Albuquerque*: H.W. Kelly, R. Annett, T. Archibeque, N. Bashir, H.S. Bereket, M. Braun, S. Bush, M. Clayton, A. Colon-Semidey, S. Devault, R. Grad, D. Hunt, J. Larsson, S. McClelland, B. McWilliams, E. Montoya, M. Moreshead, S. Murphy, B. Ortega, H.H. Raisy, M. Spicher, D. Weers, and J. Zayas; *Washington University, St. Louis*: R.C. Strunk, E. Albers, L. Bacharier, G. Belle, G.R. Bloomberg, W.P. Buchanan, M. Caesar, J.M. Corry, M. Dolinsky, E.B. Fisher, S.J. Gaioni, E. Glynn, B.D. Heckman, C. Hermann, D. Kemp, C. Lawhon, C. Moseid, T. Oliver-Welker, D.S. Richardson, D. Rodgers, E. Ryan, S. Sagel, T.F. Smith, S.C. Sylvia, C. Turner, and D.K. White; *Bone Age Reading Center, Washington University, St. Louis*: W. McAlister, K. Kronemer, and P. Suntrup; *Chair's Office, National Jewish Medical and Research Center, Denver*: R. Cherniack; *Coordinating Center, Johns Hopkins University, Baltimore*: J. Tonascia, D. Amend-Libercci, M. Bacsafra, P. Belt, K. Collins, B. Collison, C. Dawson, D. Dawson, J. Dodge, M. Donithan, V. Edmonds, C. Ewing, J. Harle, R. Huffman, R. Jackson, K.-Y. Liang, C. Meinert, J. Meinert, J. Meyers, D. Nowakowski, L. Oelberg, B. Piantadosi, M. Smith, A. Sternberg, M. Van Natta, and R. Wise; *Dermatology, Allergy, and Clinical Immunology Reference Laboratory, Johns Hopkins Asthma and Allergy Center, Baltimore*: R.G. Hamilton, C. Schatz, and J. Wisenauer; *Drug Distribution Center, McKesson BioServices Corporation, Rockville, Md.*: R. Rice, K. Farris, B. Hughes, J. Lee, and T. Lynch; *Fundus Photography Reading Center, University of Wisconsin, Madison*: B. Klein, L. Hubbard, M. Neider, K. Osterby, N. Robinson, and H. Wabers; *Immunology and Complement Laboratory, National Jewish Medical and Research Center, Denver*: R.J. Harbeck, R. Emeric, and B. Watson; *Patient Education Center, National Jewish Medical and Research Center, Denver*: S. Szefer, B. Bender, C. Culkin, J. Feeley, C. Lumlung, A. Mullen, H. Nelson, S. Oliver, C. Szefer, and A. Walker; *PDS Instrumentation, Louisville, Colo.*: A. Lehman; *Project Office, National Heart, Lung, and Blood Institute, Bethesda, Md.*: V. Taggart, P. Albert, S. Hurd, J. Kiley, P. Lew, S. Parker, and M. Wu; *University of Iowa, College of Pharmacy, Division of Pharmaceutical Services, Iowa City*: R. Poust, D. Elbert, and D. Herold; *Data and Safety Monitoring Board*: H. Eigen, M. Cloutier, J. Connett, L. Cuttler, C.E. Davis, D. Evans, M. Kattan, S. Leikin, R. Menendez, and E.E.R. Simons.

REFERENCES

1. Global strategy for asthma management and prevention: NHLBI/WHO workshop report. Bethesda, Md.: National Heart, Lung, and Blood Institute, 1995. (NIH publication no. 95-3659.)
2. National Asthma Education and Prevention Program. Expert panel report 2: guidelines for the diagnosis and management of asthma. Bethesda, Md.: National Heart, Lung, and Blood Institute, 1997. (NIH publication no. 97-4051.)
3. Warner JO, Naspitz CK. Third International Pediatric Consensus statement on the management of childhood asthma. *Pediatr Pulmonol* 1998; 25:1-17.
4. Peat JK. Asthma: a longitudinal perspective. *J Asthma* 1998;35:235-41.
5. Weiss ST. Early life predictors of adult chronic obstructive lung disease. *Eur Respir Rev* 1995;5:303-9.
6. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998; 339:1194-200.
7. Zeiger RS, Dawson C, Weiss S. Relationships between duration of asthma and asthma severity among children in the Childhood Asthma Management Program. *J Allergy Clin Immunol* 1999;103:376-87.
8. Haahtela T, Järvinen M, Kava T, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994;331:700-5.
9. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;88:373-81.
10. Selroos O, Pietinalho A, Lofroos AB, Riska H. Effect of early vs late

- intervention with inhaled corticosteroids in asthma. *Chest* 1995;108:1228-34.
11. Overbeek SE, Kerstjens HAM, Bogaard JM, Mulder PG, Postma DS. Is delayed introduction of inhaled corticosteroids harmful in patients with obstructive airways disease (asthma and COPD)? *Chest* 1996;110:35-41.
 12. Childhood Asthma Management Program Research Group. The Childhood Asthma Management Program (CAMP): design, rationale, and methods. *Control Clin Trials* 1999;20:91-120.
 13. *Idem*. Recruitment of participants in the Childhood Asthma Management Program (CAMP). I. Description of methods. *J Asthma* 1999;36:217-37.
 14. Nelson HS, Szefer SJ, Jacobs J, Huss K, Shapiro G, Sternberg AL. The relationships among environmental allergen sensitization, allergen exposure, pulmonary function, and bronchial hyperresponsiveness in the Childhood Asthma Management Program. *J Allergy Clin Immunol* 1999;104:775-85.
 15. Childhood Asthma Management Program Research Group. Design and implementation of a patient education center for the Childhood Asthma Management Program. *Ann Allergy Asthma Immunol* 1998;81:571-81.
 16. Meinert CL. Clinical trials: design, conduct, and analysis. Vol. 8 of Monographs in epidemiology and biostatistics. New York: Oxford University Press, 1986.
 17. Brogden RN, McTavish D. Budesonide: an updated review of its pharmacological properties, and therapeutic efficacy in asthma and rhinitis. *Drugs* 1992;44:375-407. [Errata, *Drugs* 1992;44:1012, 1993;45:130.]
 18. Nyholm E, Frame MH, Cayton RM. Therapeutic advantages of twice-daily over four-times daily inhalation budesonide in the treatment of chronic asthma. *Eur J Respir Dis* 1984;65:339-45.
 19. Callaghan B, Teo NC, Clancy L. Effects of the addition of nedocromil sodium to maintenance bronchodilator therapy in the management of chronic asthma. *Chest* 1992;101:787-92.
 20. Schwartz HJ, Kemp JP, Bianco S, et al. Highlights of the nedocromil sodium clinical study presentations. *J Allergy Clin Immunol* 1993;92:204-9.
 21. Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Stanford, Calif.: Stanford University Press, 1959.
 22. Tanner JM, Whitehouse RH, Cameron N, Marshall WA, Healy MJR, Goldstein H. Assessment of skeletal maturity and prediction of adult height (TW2 method). New York: Academic Press, 1983.
 23. Kovacs M. Rating scales to assess depression in school-aged children. *Acta Paedopsychiatr* 1981;46:305-15.
 24. Klein BEK, Magli YL, Neider MW, Klein R. Wisconsin system for classification of cataracts from photographs. Madison: University of Wisconsin, 1990. (NTIS Accession no. PB 90-138306.)
 25. McCullagh P, Nelder JA. Generalized linear models. 2nd ed. New York: Chapman & Hall, 1989.
 26. Searle SR, Speed FM, Milliken GA. Population marginal means in the linear model: an alternative to least squares means. *Am Stat* 1980;34:216-21.
 27. Hosmer DW Jr, Lemeshow S. Applied survival analysis: regression modeling of time to event data. New York: John Wiley, 1999.
 28. Martin AJ, McLennan LA, Landau LI, Phelan PD. The natural history of childhood asthma to adult life. *BMJ* 1980;280:1397-400.
 29. Martin AJ, Landau LI, Phelan PD. Lung function in young adults who had asthma in childhood. *Am Rev Respir Dis* 1980;122:609-16.
 30. Maier WC, Arrighi HM, Morray B, Llewellyn C, Redding GJ. The impact of asthma and asthma-like illness in Seattle school children. *J Clin Epidemiol* 1998;51:557-68.
 31. Oswald H, Phelan PD, Lanigan A, et al. Childhood asthma and lung function in mid-adult life. *Pediatr Pulmonol* 1997;23:14-20.
 32. Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 1983;127:725-34.
 33. Coultas DB, Howard CA, Skipper BJ, Samet JM. Spirometric prediction equations for Hispanic children and adults in New Mexico. *Am Rev Respir Dis* 1988;138:1386-92.
 34. Mead J. Dysanapsis in normal lungs assessed by the relationship between maximal flow, static recoil, and vital capacity. *Am Rev Respir Dis* 1980;121:339-42.
 35. Yunginger JW, Reed CE, O'Connell EJ, Melton LJ III, O'Fallon WM, Silverstein MD. A community-based study of the epidemiology of asthma: incidence rates, 1964-1983. *Am Rev Respir Dis* 1992;146:888-94.
 36. Thurlbeck WM. Lung growth and alveolar multiplication. *Pathobiol Annu* 1975;5:1-34.
 37. Le Souef PN, Sears MR, Sherrill D. The effect of size and age of subject on airway responsiveness in children. *Am J Respir Crit Care Med* 1995;152:576-9.
 38. Simons FER, Canadian Beclomethasone Dipropionate-Salmeterol Xinafoate Study Group. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. *N Engl J Med* 1997;337:1659-65.
 39. Verberne AA, Frost C, Roorda RJ, van der Laag H, Kerrebijn KF, Dutch Paediatric Asthma Study Group. One year treatment with salmeterol compared with beclomethasone in children with asthma. *Am J Respir Crit Care Med* 1997;156:688-95.
 40. Tinkelman DG, Reed CE, Nelson HS, Offord KP. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. *Pediatrics* 1993;92:64-77.
 41. Merkus PJRM, van Essen-Zandvliet EEM, Duiverman EJ, van Houwelingen HC, Kerrebijn KF, Quanjer PH. Long-term effect of inhaled corticosteroids on growth rate in adolescents with asthma. *Pediatrics* 1993;91:1121-6.
 42. Doull IJ, Freezer NJ, Holgate ST. Growth of prepubertal children with mild asthma treated with inhaled beclomethasone dipropionate. *Am J Respir Crit Care Med* 1995;151:1715-9.
 43. Rachelefsky GS, Chervinsky P, Meltzer EO, et al. An evaluation of the effects of beclomethasone dipropionate aqueous nasal spray [Vancenase AQ (VNS)] on long-term growth in children. *J Allergy Clin Immunol* 1998;101:Suppl:S236. abstract.
 44. Allen DB, Mullen M, Mullen B. A meta-analysis of the effect of oral and inhaled corticosteroids on growth. *J Allergy Clin Immunol* 1994;93:967-76.
 45. Silverstein MD, Yunginger JW, Reed CE, et al. Attained adult height after childhood asthma: effect of glucocorticoid therapy. *J Allergy Clin Immunol* 1997;99:466-74.
 46. Doull IJM, Campbell MJ, Holgate ST. Duration of growth suppressive effects of regular inhaled corticosteroids. *Arch Dis Child* 1998;78:172-3.
 47. Garbe E, Suissa S, LeLorier J. Association of inhaled corticosteroid use with cataract extraction in elderly patients. *JAMA* 1998;280:539-43. [Erratum, *JAMA* 1998;280:1830.]
 48. Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. *N Engl J Med* 1997;337:8-14.