

- general well-being\*
- presence or absence of abdominal mass
- weight
- use of antidiarrhea drugs
- presence or absence of intestinal manifestations
- hematocrit.

Subjects were assessed at baseline, 1 to 2 weeks after initiation of the study, and monthly thereafter. Laboratory studies were extensive. All subjects were instructed to increase their protein intake by at least 2 g/kg/d, which was monitored with 3-day food diaries.

At 30 days, the subjects treated with GH had a significantly greater reduction in the Crohn's Disease Activity Index than the placebo group ( $P=.02$ ), with further decreases during the next 3 months. The 3 variables that most significantly improved were those marked with an asterisk in the above list. The change in the Crohn's Disease Activity Index scores are seen in the Table. In addition, at the end of 4 months the subjects in the GH group reduced their other drug requirements by 56%, compared with a 4% increase in the placebo group. Insulin-like growth factor 1 increased significantly in the GH group, but no other significant differences were observed between the groups in any of the other biomedical studies measured. The most frequent side effect in the GH group was edema, which occurred in 10 of 19, patients and headache which occurred in 5 of 19. These symptoms occurred only during the first 2 weeks of the study. Two subjects in the GH group had tumors detected during the study (renal tumor, benign schwannoma), as did 1 subject in the placebo group (precancerous cells of the esophagus and a benign polyp of the stomach).

Slonim AE, et al. *N Engl J Med* 2000;342:1633-1637.

**Editor's comment:** This is an intriguing and potentially very important study. As pointed out in an accompanying editorial by R. Balfour Sartor of the University of North Carolina, Chapel Hill, the article by Slonim et al is provocative. There are a number of clinical questions about the optimal dose of GH, the frequency of administration, and the length of therapy that need to be considered.

**Table**  
**Changes From Baseline in the Crohn's Disease Activity Index Scores During 4 Months of Treatment With Growth Hormone or Placebo\***

Month	Placebo			Growth Hormone			P Value†
	No. of Patients	Score	Change From Baseline	No. of Patients	Score	Change From Baseline	
0 (Baseline)	15	206±126	—	19	287±134	—	
1	15	202±115	-5±76	19	186±107	-100±135	0.02
2	15	235±109	29±77	18	172±110	-116±139	0.001
3	15	204±140	-3±91	17	148±123	-139±159	0.006
4	15	187±163	-19±63	17	145±124	-143±144	0.004

\*Plus-minus values are means ± SD. Only the 15 patients in the placebo group for whom follow-up data were available were included in the analysis. Higher scores on the Crohn's Disease Activity Index indicate more disease activity.

†P values are for the comparison of the changes in scores between the 2 groups.

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py that need to be considered. Also, whether intestinal fibrosis with possible resultant intestinal strictures might occur is not known. The mechanism of action resulting in improvement also is not known.

Obviously, additional studies in both adults and children are desirable. A review of the literature as of July 2000 reveals only 1 report (Henker J. *Eur J Pediatr* 1996;155:1066-1067) of children with Crohn's disease being studied with GH administration. Three adolescents possibly benefited from GH therapy. Studies such as these are difficult to do but, hopefully, are being pursued.

William L. Clarke, MD

## Risk of Persistent Growth Impairment After Alternate-Day Prednisone Treatment in Children With Cystic Fibrosis

Lai and coworkers report growth data on children with cystic fibrosis who, at 6 to 14 years of age, participated in a trial of alternate-day prednisone (1 to 2 mg/kg body weight) and were followed for approximately 6 to 7 years. Their growth data were obtained from the Cystic Fibrosis Patient Registry. Of the 224 subjects, 151 received prednisone and 73 received placebo. All had mild to moderate lung disease when the trial began. Four years after its initiation, the clinical trial was discontinued when it was determined that the side effects of prednisone outweighed its potential benefits.

Sixty-eight percent of the subjects who were reevaluated were 18 years of age or older. Results were reported 10

years after the trial began. Their Z scores for height declined during prednisone therapy but catch-up growth began 2 years after treatment was discontinued. The mean height for boys 18 years or older was 4 cm years less than that in the placebo group (or 13 percentile points). However, in girls the difference in height between the placebo and treatment groups was no longer present 2 to 3 years after the discontinuation of prednisone (Figure on next page).

The effect of alternate-day prednisone therapy varied depending on the age at which treatment was given. Specifically, boys who started prednisone every other day at 6 to 8 years of age had declines in height Z scores that last-

ed for 10 years. Boys beginning prednisone at 8 to 12 years had catch-up gains beginning about 2 years after stopping therapy. Boys who started prednisone during adolescence (12 to 14 years of age) maintained their baseline Z scores. When indices of pulmonary status were controlled for, the negative association between the use of prednisone and the Z score for height remained strong ( $P < 0.001$ ) in boys after prednisone was discontinued, and none of the 3 indices of pulmonary function correlated significantly with Z scores for height.

The authors point out that it is well known that long-term treatment with pharmacologic doses of prednisone correlates with significant reductions in final height. The differences between the sexes and the degrees of growth suppression seen in this study also have been seen in other studies, including those of children with asthma. They speculate that this may be due to the more pronounced deceleration of normal growth rate in boys prior to puberty, which might make them more susceptible to additional slowing of growth, or perhaps the higher secretion of GH in girls prepubertally. They *conclude* that the benefits of prednisone therapy in terms of pulmonary function are not prolonged once therapy is discontinued and do not outweigh the deleterious effect on final growth.

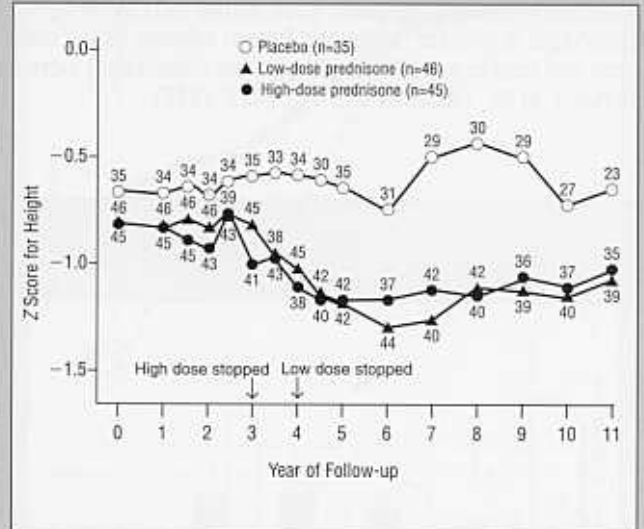
The authors summarized the results as follows: The growth impairment caused by prolonged alternate-day therapy with prednisone in prepubertal boys with CF persisted posttreatment and significantly reduced adult height. Although children gained substantial weight with treatment, this weight did not persist posttherapy. Because of these findings and the failure of therapy to benefit CF symptoms long term, one must conclude that *prolonged therapy is not beneficial* in CF children. If used in the treatment of any disease, glucocorticoid therapy must be monitored and individualized carefully to achieve the lowest effective dose and the shortest duration of therapy possible in order to minimize the risk of permanent growth impairment, particularly in boys.

Lai H, et al. *N Engl J Med* 2000;342:851-888.

**Editor's comment:** This important study demonstrates the significant negative impact of glucocorticoids on linear growth even when prescribed only every other day. It also is important because it stratifies and analyzes the response with regard to different ages at the onset of treatment. Of utmost importance, treatment caused diabetes and cataracts at a rate sufficiently high enough to warrant stopping this trial in 1991, 4 years after its initiation. Thus, the effects of glucocorticoids on other systems is potentially more significant medically than just its effect on height.

Pamela Davis and Carolyn Kercksmar from Cleveland have an excellent editorial in the same issue of the New England Journal of Medicine (2000;342:887-888), entitled "Growth in Children With Chronic Lung Disease." Readers are encouraged to review the thoughtful and useful comments pertaining to the causes of growth retardation in CF and the alterna-

Figure  
Relation of Z Scores for Height to Years of Follow-up in Boys With Cystic Fibrosis Who Received Placebo, Low-Dose Prednisone, or High-Dose Prednisone



The low dose of prednisone was 1 mg/kg, and the high dose was 2 mg/kg. The number of subjects at each point of follow-up is indicated. Among the boys, Z scores for height remained significantly lower after 10 years in those who received prednisone than in those who received placebo ( $P = 0.03$ ). A Z score of zero corresponds to the 50th percentile of the reference population. A Z score of  $-1.0$  indicates 1 SD below the mean, which corresponds approximately to the 15th percentile.

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tives for therapy. The authors emphasize that there are multiple reasons for growth failure in CF patients, that glucocorticoids have multiple toxic effects beyond those reported in the article by Lai et al, and that ibuprofen is a less toxic and more proficient anti-inflammatory agent than glucocorticoids. They add that there is a dearth of evidence concerning the efficacy or adverse effects of inhaled glucocorticoids, although 12% of patients with CF in the United States are treated with these. Davis and Kercksmar recommend that with the increased risk of diabetes, cataracts, osteoporosis, and the reduction in height, the price may be too high to pay to use glucocorticoids in CF, especially since the benefits of anti-inflammatory therapy can be achieved in other ways in children with this disease.

The attention of readers interested in this topic is called to the lead article in GGH (2000;16[2]:21-26) written by Drs. O. Mehls and B. Tönshoff of Heidelberg. The title is "Effects of Glucocorticoids on Growth."

William L. Clarke, MD