Asthma, Steroids, and Growth

LONG-TERM administration of systemic corticosteroids is a cause of impaired growth. Trials comparing inhaled corticosteroid preparations with other treatment regimens in nearly 600 children with asthma found that inhaled beclomethasone had greater therapeutic effect than did other regimens. In the studies, each of which lasted about one year, children treated with inhaled corticosteroids had less growth in height (1 to 1.6 cm [23 to 27 percent] less) than those assigned to other treatments. The mechanisms by which this delay in growth occurs are unknown. If inhaled corticosteroids are not discontinued, does growth suppression continue, so that children with asthma who are at the 50th percentile for height at the age of six years fall to the 25th percentile by the time they are adults?

Two articles in this issue of the Journal report on growth among children with asthma who were treated for many years with inhaled budesonide in doses of about 400 µg a day. Both report a reduction of about 20 percent in growth velocity during the first year of treatment. Growth velocity subsequently recovered, however, and the children ultimately attained or are expected to attain a normal adult height. Although the results are reassuring to children receiving such treatment, their families, and pediatricians, neither study addressed the mechanism of budesonide's effect on growth in height or the growth of other organs.

A strength of the study by Agertoft and Pedersen is that nearly all subjects were followed until they reached their final adult height. A weakness is that there was no concurrent control group of children with asthma who had been randomly assigned not to receive inhaled budesonide. Although the mean adult height of subjects treated with inhaled corticosteroids was slightly lower than the mean value in a contemporary Scandinavian population, the children treated with budesonide did reach their target adult heights, as calculated from the heights of their parents. The children's height was not influenced by either the duration of treatment or the cumulative lifetime dose of budesonide. Moreover, it did not differ from that of the control subjects, a heterogeneous group of children with asthma who were never treated with inhaled corticosteroids and healthy siblings of the children with asthma who received budesonide. Lung function improved markedly in budesonide-treated patients, who had substantially impaired lung function at the start of therapy.

The second article is a report from the Childhood Asthma Management Program Research Group, which conducted a randomized treatment trial for more than four years in more than 1000 children with mild-to-moderate asthma. The trial demonstrated substantial symptomatic improvement in children treated with budesonide as compared with nedocromil or placebo. The observation period was five years shorter and patients had milder asthma than was the case in the study by Agertoft and Pedersen. Because the age of subjects was 5 to 12 years when they entered the study, their final adult height had to be estimated. Over the duration of the study, the budesonide-treated subjects grew less than those assigned to nedocromil and placebo (mean increase in height, 22.7 cm vs. 23.7 and 23.8 cm, respectively), and most of the difference in growth was evident during the first year of treatment.

It is reassuring that the reductions in growth velocity observed in the first year of budesonide treatment were not sustained during continued treatment. However, a cautionary note is warranted: the Childhood Asthma Management Program Research Group did not report the children's pubertal status at entry or during the study. The level of sexual maturation at onset, if it differed among groups, could have influenced growth, regardless of treatment. Thus, further analysis of the data on growth, with pubertal status and sex taken into account, is warranted. Nonetheless, the differences in measured height among the groups at the conclusion of the study were small — far less than the 4- to 6-cm differences projected from the growth velocity measured in studies of beclomethasone treatment lasting one year or less.

The primary outcome measure, the degree of change in the forced expiratory volume in one second (FEV1) after the administration of a bronchodilator, was not improved by either inhaled budesonide or nedocromil. Otherwise, virtually all measures of relevant symptoms of asthma improved in the budesonide group, and some improved to a lesser extent in the nedocromil group. No measures of lung growth and function improved significantly, except for the ratio of FEV1 to forced vital capacity. In view of the multiple comparisons made, this effect is unlikely to be important. The normality of both the mean values and the degree of variation in measures of lung function in this population of children with asthma can be considered evidence against a progressive decline in lung function when the disease is well treated, and is a tribute to the physicians at the participating centers. This study and that by Agertoft and Pedersen clearly demonstrate that children generally older than six years of age who have asthma with a wide range of severity have improvements with budesonide treatment.

One caveat is that the reassuring message about skeletal growth may not apply to the growth of other organs, such as the brain and the lung. The number and branching structure of airways and conducting vessels are complete in early gestation, whereas alveoli are formed in the last months of gestation and during the
first years of postnatal life. The number of alveoli increases by a factor of about six after birth, mostly in the first two years. Formation of alveoli is complete by the age of five to eight years.10,11 Thereafter, the lung grows by increasing the size of airways and alveoli already present. Glucocorticoids accelerate the development of many features of the lung, particularly the formation of normal lung architecture. These features of lung development have been clarified in a glucocorticoid-deficient mouse model, in which the hormone decreases cell proliferation and increases architectural maturation.12 The administration of corticosteroids during a period of alveolar development results in decreased lung-cell mass13 and in the presence of too few abnormally large alveoli.14

With the exception of assays of amniotic fluid before birth, we lack surrogate markers of accelerated or delayed lung development. We cannot readily detect decreased numbers and surface area of alveoli. For example, total lung capacity, a measure of lung size rather than surface area, is normal in older children who have a marked reduction in the number of alveoli as a result of congenital diaphragmatic hernia, bronchopulmonary dysplasia, or lobar resection.

The lungs of young children have relatively thick airway walls, diminished elastic recoil, and increased airway compliance—all features that contribute to the amplification of airway responsiveness. Smooth muscle may not respond to stretching, an important feature of prenatal dexamethasone. With the exception of assays of amniotic fluid before birth, we lack surrogate markers of accelerated or delayed lung development. We cannot readily detect decreased numbers and surface area of alveoli. For example, total lung capacity, a measure of lung size rather than surface area, is normal in older children who have a marked reduction in the number of alveoli as a result of congenital diaphragmatic hernia, bronchopulmonary dysplasia, or lobar resection.

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rhythm of its own production and of other circadian variables. In this issue of the Journal, Sack et al. take advantage of this action of melatonin to restore a more normal pattern of sleep in totally blind persons with free-running circadian rhythms and associated sleep disorders.

Normally, melatonin is produced during the night. In most species, including humans, its secretion is related to the length of the night: the longer the night, the longer the duration of secretion. In many species, this pattern of production serves as a time cue for seasonal rhythms. Whether melatonin has an essential role in mammalian circadian rhythms has been much debated. Certainly, the evening increase in melatonin secretion is associated with an increase in the propensity for sleep. Secretion of melatonin during the day, as occurs in diverse pathologic or occupational health situations, is strongly associated with daytime sleepiness or napping, and the administration of melatonin during the day induces sleepiness. In the early 1980s, the results of two independent studies (one in rats and one in humans) showed that daily timed administration of melatonin could shift the phase of the internal clock and (in rats) entrain it to a normal cycle.

These observations led directly to the current interest in melatonin and its analogues for the treatment of circadian-rhythm disorders. A sleep–wake cycle that is not synchronized to the 24-hour day is a disorder associated with blindness and may well represent the most important application of melatonin treatment, since in most other circumstances, timed treatment with sufficiently bright light can (at least in theory) re-establish a normal rhythm. In studies of many blind people, my colleagues and I have found that the presence of a free-running rhythm is directly related to a greater degree of visual loss. In addition, the incidence of this disorder increases with decreases in the perception of light; it occurred in all of our subjects who had no eyes. Treatment with light for synchronization to the 24-hour day is, of course, impossible for persons with no light perception (unless extracocular light proves to be effective). The properties of melatonin thus make it the optimal treatment, if indeed it can entrain free-running circadian rhythms in humans.

Melatonin (in a dose of 5 mg daily, timed to advance the phase of the internal clock) can maintain synchronization of the circadian rhythm to a 24-hour cycle in sighted persons who are living in conditions likely to induce a free-running rhythm, and it appears to synchronize the rhythm in some persons after a short period of free-running. In blind persons with free-running rhythms, it has been possible to stabilize, or entrain, the sleep–wake cycle to a 24-hour period, with resulting improvements in sleep and mood. However, it has proved difficult to show that the clock itself could be entrained. Two groups have recently reported that complete synchronization can be achieved in some, but not all, blind persons. Sack et al. attribute their success to the use of a higher dose of melatonin (10 mg daily, as compared with the 5 mg daily used in most previous studies) and to careful timing of the treatment to start an hour before the preferred bedtime, as the subjects’ free-running rhythms approached a normal phase. Previous, unsuccessful studies in which the 5-mg dose was used took this approach to timing, and thus perhaps the use of the higher daily dose was the key to success. However, earlier this year, Lockley et al. reported complete synchronization in three totally blind men with only 5 mg of melatonin, timed to advance the phase of the internal clock (as in the current study, but with a more precise definition of phase). Sensitivity to melatonin varies among individual people, as do the pharmacokinetics of the drug. This variation may explain the discrepancies among the results of these studies, especially because the number of subjects in whom synchronization has been achieved to date is very small.

The timing of the start of melatonin treatment may be critical. In theory, if melatonin is given daily at the same clock time to a person with a free-running circadian rhythm for a treatment period lasting longer than a complete cycle (i.e., the time taken for the circadian rhythm to become delayed, or very rarely advanced by 24 hours), at some point in the cycle the timing will be optimal for synchronization to occur. This happens in rats, but some people treated for years with melatonin continue to have a free-running rhythm, albeit with subjective improvement in sleep. These observations underline the importance of assessing the circadian phase before treatment of a circadian-rhythm disorder begins (whether the treatment consists of light, melatonin, or another method). The rhythm of melatonin secretion can be determined by measurements of plasma or salivary melatonin or urinary 6-hydroxymelatonin sulfate (a particularly practical method in field studies).

The most noteworthy observation in the study by Sack et al. is the maintenance of synchronization with a reduction in the dose of melatonin to 0.5 mg daily. Maintenance of synchronization with melatonin at physiologic concentrations supports the view that melatonin is an important component of the human circadian system. Sleep–wake disorders involving a circadian cycle longer than 24 hours are a lifetime problem for blind persons, and it is of the utmost importance that the lowest possible dose of melatonin be used and that long-term safety be evaluated.

The hype and the claims of the so-called miraculous powers of melatonin several years ago did a great dis-service to a scientific field of real importance to human health. With these recent careful and precise observations in blind persons, the true potential of melatonin is becoming evident, and the importance of the timing of treatment is becoming clear. Our 24-hour...
society, with its chaotic time cues and lack of natural light, may yet reap substantial benefits.

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