Editorial

Growth Hormone Therapy

Growth hormone (GH) replacement therapy for improving the height of GH deficient children is safe and effective(l). However, the majority of children seeking advice for short stature are not GH deficient. They may carry a diagnosis of familial short stature, constitutional delay, a genetic syndrome, skeletal dysplasia, *etc.* Many of these may be at as much of a psychological or social disadvantage.as GH deficient children. Extrapolating from the pathophysiology of gigantism, we know that high doses of GH given to any child with open epiphyses will increase stature. Efforts have therefore been on to find a regimen of GH therapy which will increase height in some of these causes of short stature, but without morbidity.

Response to GH therapy is influenced by numerous factors(l,2). These include age, height and deviation of height below nor mal at the time of starting therapy, timing of puberty, dose of GH, etiology of short stature, parental height, *etc.* Therefore, the ideal way to evaluate the effectiveness of GH is to prospectively randomize the cohort into a treatment group and a well matched untreated group and follow them both to final height *(i.e.,* until they stop growing). Unfortunately, (a) the majority of studies reported so far have not used a matched control group for comparison, and *(b)* waiting till final height is a very long process. To circumvent these two obstacles, investigators have relied on height predictions. A word about height predictions and their use: There exist normative data of percentage of adult height achieved at various bone ages throughout childhood. Thus, knowing the present bone age of a child, as well as the current height, one can calculate the adult height the child will achieve. If a growth therapy increases height without commensurate bone age advancement, it will be successful in improving adult height. Most studies of GH therapy have reported their results as improvements in "predicted adult height" rather than improved final height in comparison to an untreated cohort. However, height predictions using these tables are prone to inaccuracies(3). Thus, a somewhat confusing volume of literature exists today, regarding guidelines for GH therapy.

Where does the state of the art of GH therapy lie today? Let us consider the following sets of indications:

I. Conditions in Which GH Therapy is Effective Beyond Doubts

Growth Hormone Deficiency (GHD): In children with classic GHD, with subnormal growth velocity, delayed bone age and unequivocally poor response to provocative GH testing, a two to four-fold increase in growth velocity occurs in the first year of therapy. In subsequent years, the growth velocity is usually less than in the first year, but still exceeds pretreatment velocity. Over a number of years of therapy, a majority of patients achieve a height significantly greater than that of untreated GHD patients. In the studies reporting final height in GHD patients who were treated in the years before recombinant GH was available, patients achieved a mean height at the third percentile of normal(4). Of course, doses were half of present recom-

mendations and were given 2 or 3 times a week instead of daily. Current methods of treatment are expected to give better final heights. The best results are obtained in younger children and in those with delayed puberty.

The weekly dose ranges between 0.4 to 0.7 units/kg (12 to 21 units/m^2), given as a daily subcutaneous injection(5). Beneficial effects of GH therapy are seen only with continuous treatment for a number of years, preferably till the completion of puberty and growth. Stopping treatment after 1 or 2 years results in ensuing poor growth velocity, even to below pretreatment levels, detracting from previously obtained benefits.

Side effects in these doses are rare and include decreased insulin sensitivity, pancreatitis, pseudotumor cerebri and slipped capital femoral epiphysis(6). Central hypothyroidism must be monitored for. The greatest concern has been regarding increased chances of malignancy with GH therapy. About 40 cases of leukemia have been reported worldwide among patients receiving GH therapy. However, many of these patients had a setting for malignancy. The consensus to date is that GH therapy does not increase the risk of malignancy^). Nevertheless, physicians as well as the family should be taking an informed decision about this aspect of GH therapy.

Finally, a word about therapy for the GH deficient infant or young child presenting with hypoglycemia. In this situation, GH can be lifesaving, or prevents irreversible brain damage. The indication for GH therapy here is strong indeed. Fortunately, due to the low body weight, therapy is more affordable. Also, hypoglycemia ceases to be a prominent feature in the older child.

II. Conditions for Which GH Therapy May Prove Effective

Turner Syndrome (TS): Given in doses higher than those used for GHD, *i.e.,* 0.7 to 1.0 unit/kg/week (21 to 28 units/m^2/week), GH produces elevated growth velocity for a number of years in girls with TS(7). Since spontaneous puberty does not occur in many girls with TS, this does not become a limiting factor in response to therapy. Most early studies without a concurrent control untreated group showed extremely encouraging results, so much so that in about 25 countries (and most recently by the FDA in the US), TS is one of the approved indications for GH therapy. In the majority of these studies, however, the girls had not yet achieved final height.

A European multicenter trial reported a modest gain in final height, 3 cm over the predicted height(8). Treatment had been started after 10 years of age, GH doses ranged from 0.7 to 1.0 units/kg/week and estrogen had been added at a mean age of 14 years. Twenty five per cent of girls achieved a final height more than 5 cm above predicted height. It is possible that better results will be obtained with an earlier age of onset of therapy or a higher GH dose. Expectations from growth therapy should be cautious until more final height data are in(3). Presently, two large randomized, controlled studies are in progress in patients of TS, the final height results of which are still awaited.

Chronic Renal Failure (CRF): In children with CRF, GH has been found to be effective in markedly improving predicted adult height(9,10). The therapy has not so far resulted in any harm to the renal status. GH is approved by the FDA for use in CRF as a growth therapy, in the USA. However, in none of the studies has final height been reached and therefore the final word is not yet in.

III. Conditions in Which GH Therapy is Experimental

There are several conditions in which the use of GH is under study. The results do not indicate any striking benefit so far, though the studies are not yet complete. These conditions include constitutional delay of growth and puberty(11), non-GH-deficient short stature(12,13), intrauterine growth retardation including genetic syndromes like Russell Silver(14), Down and Prader Willi syndromes, skeletal dysplasias and glucocorticoid-induced growth failure(6). GH therapy for these conditions is carried out only under research protocols, as an experimental therapy. Of these, the first two are common conditions, and deserve some detailed consideration.

Constitutional Delay of Growth and Puberty (CDGP): This condition is not a disease but a variant of normal growth. In CDGP, the child grows at a normal velocity, enters puberty later than normal, has a late pubertal growth spurt, and ultimately achieves full (or nearly full) genetic potential for height. The bone age is typically delayed. The most important therapy for CDGP is to recognize the condition and reassure the family that all will be well in the future. However, some youngsters, due to marked differences between themselves and their peers, are extremely psychologically handicapped. For this reason, and due to the fact that some groups have reported relatively lower secretion of GH in CDGP, GH therapy has been tried for bringing early growth to patients of CDGP. However, this has not been shown to increase adult height. In speeding up the initiation of puberty or pubertal growth, a short course of androgen or estrogen is equally effective and less costly(15).

Non-GH Deficient Short Stature: This includes two categories of children: *(a)* those who have normal growth velocity, bone age and GH secretion, but a predicted adult height significantly (>10 cm) below midparental height as well as national standards, and *(b)* those who have all the above features, but predicted adult height is similar to midparental height, *i.e.,* both the child's predicted adult height as well as midparental height are below the national standards (familial short stature). Numerous investigators have used GH therapy for this condition. Most have reported significantly improved growth velocity in the first 3-4 years of therapy(12). However, growth velocity comes closer to pretreatment values in later years. Some studies have reported earlier onset of puberty. The resultant advance in bone age would then limit the response to therapy. Two recent studies reporting on final height with GH therapy in children with non GH deficient short stature have concluded that it is of no benefit in improving adult height(16,17).

Practical Aspects of GH Therapy in the Indian Setting: Before considering GH therapy, or even testing for GHD, a thorough search must be conducted for all other causes for short stature. One should aim to treat for the present and expected future psychological and social handicaps due to short stature, not just to correct a biochemical deficiency. Since there are no studies from India on the social handicaps of short stature, we have to individually evaluate each patient against the background of his/her social circumstances.

Only a person who is familiar with all the literature and the subtleties of this therapy, for example, a pediatric endocrinologist or an endocrinologist trained in GH therapy, should prescribe GH therapy. The treatment is expensive; for a 20 kg GHD child, the cost per year will be approximately 2.5 lakh rupees. The therapy must be given continuously for many years to be

of any benefit. Therapy is not only costly, but the family must be motivated enough for a long and involved regimen. *It is unethical to prescribe GH for short periods of time like 1 to 2 years.* Since 1985, recombinant GH is available world over, as well as in India. Pituitary extracted human GH was proven in 1985 to cause the slow virus Jacob Creutzfeld disease. Even if some companies claim to make human GH with better purification methods now, there is no place for its use when recombinant GH is available.

On the basis of current information, it would be logical to advocate the following specific indications for the Indian setting:

1. Untreated GHD, especially isolated GHD (in contrast to panhypopituitarism where spontaneous puberty is delayed or absent), has a dismal prognosis for height, and is the ideal indication for GH therapy.
2. Patients of TS have a similarly poor height prognosis. As per the literature available today, TS patients in India should not be denied GH, though, until the reports of randomized controlled trials are available, a cautious prognosis should be given.
3. Though the same considerations stated above for TS hold true for CRF also, there are many other problems in caring for a child with CRF which do not apply to TS. Even if cost is not a factor, family resources of time, patience and energy must first be earmarked for good quality medical care, dialysis, the transplant, and post transplant care. To carry out all this successfully in our country is an uphill task even for the most motivated of families. For these reasons, CRF will not form an indication for GH therapy under the circumstances prevalent today in most of the centers for advanced care in our country.

Other etiologies of short stature do not form clinical indications for GH therapy at the present time.

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