The authors suggest that error could be introduced into their data by studying children as early as 1 year of age, inaccuracy in measuring young children, measurement error due to observer variation over the 18-year span of the study, and technical variation arising from changing hairstyles. They further suggest that the etiology of the delays observed may be multifactorial, with contributions from abnormal endocrine function (including hypogonadism), suboptimal nutrition, and increases in metabolism as the result of a high rate of erythropoiesis. Interestingly, these changes do not affect the final heights of these children.

Singhal A, et al. *Arch Dis Child* 1994;71:404-408.

Editor's comment: *This is a very carefully performed study. The authors are to be congratulated for identifying individuals in the neonatal period and following them through their adolescent growth spurt. It is unfortunate, however, that more information either was not collected or provided regarding the etiology of the retarded growth or the delay in onset of puberty in these children. The pattern observed seems consistent with constitutional delay of growth and adolescence. It is unclear how abnormal endocrine function, suboptimal nutrition, or increased metabolism could have a transient effect on the onset of puberty and yet not affect final height. Interestingly, there is no mention of rates of infection, number of hospitalizations, or numbers of crises, all of which may have temporarily affected growth in enough children to produce the observed delay in growth. Since the SS children achieve a normal final height, one might question the desirability of continuing research into the etiology of their delay. However, these individuals appear to provide a model of constitutional delay of growth and adolescence that might prove useful in better understanding the physiology of the timing of pubertal events in healthy children.*

William L. Clarke, MD

Gene Therapy for Familial Hypercholesterolemia

In theory, diseases caused by genetic deficiency can be treated by the introduction and expression of a normal gene into the affected tissue. Because of the possibility of a noninvasive and accurate monitoring method for familial hypercholesterolemia (FH), and based on previous promising results of gene therapy in animal models (Chowdhury et al[1]), Grossman et al[2] recently reported the first successful ex vivo gene therapy treatment for FH in a human, specifically, in a 29-year-old woman.

FH is an autosomal dominant disorder caused by a deficiency of low density lipoprotein (LDL) receptors. Patients with FH have very high blood levels of cholesterol that deposits in the coronary arteries and leads to premature coronary artery disease (Brown and Goldstein[3]). The homozygous form of FH is a lethal disorder. It is very hard to treat; however, the progress and response to treatment can be easily monitored by measuring serum lipid profiles.

The protocol reported by Grossman and colleagues[2] was as follows: a partial liver resection was performed on the patient (15% of the total mass) and the liver section was perfused with collagenase to obtain hepatocytes, which were then cultured. The cells were exposed to recombinant retroviruses that had a new gene recombined into their DNA that contained the LDL receptor. The genetically-corrected hepatocytes were harvested and infused back into the patient via the inferior mesenteric vein, leading to their deposit in the liver. The patient's serum lipid profile was measured before and after treatment. Two weeks after the procedure, the ratio of LDL to high density lipoprotein (HDL) was noted to drop from 10:13 to 5:8. The patient remained stable for 18 months without further complications. The authors concluded that hepatic reconstitution of LDL receptor expression is sufficient for metabolic correction.

1. Chowdhury JR, et al. Long-term improvement of hypercholesterolemia after ex vivo gene therapy in LDLR deficient rabbits. *Science* 1991;254:1802-1805.
2. Grossman M, et al. Successful ex vivo gene therapy directed to liver in a patient with a familial hypercholesterolaemia. *Nat Genet* 1994;6:325-341.
3. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. *Science* 1986;232:34-37.

Editor's comment: *The use of gene therapy such as that reported here is encouraging. In FH, the liver is an easy organ to target. Successful gene therapy in disorders primarily involving a specific organ may be easier to achieve than gene therapy for disorders that affect many systems. The possibility of removing cells from the affected individual, treating them, and then reinserting them avoids the possibility of rejection and further complications related to immunosuppression. Unfortunately, the same type of approach cannot be easily used in cystic fibrosis.*

Judith G. Hall, MD

Gene Therapy for Cystic Fibrosis

Cystic fibrosis (CF) is a common autosomal recessive disorder. It is characterized by gastrointestinal and respiratory symptoms. The pulmonary complications of CF include mucus plugging and chronic bacterial infections. Ninety percent of CF patients die of respiratory complications. Because the high mortality of CF is related to respiratory symptoms, the lungs have been the logical target for gene therapy, as reported by Cutting.[1]

CF is caused by a mutation of the CF transmembrane conductance regulator (*CFTR*) gene on chromosome 7. The *CFTR* gene codes for a transmembrane channel on the surface of the epithelial cells that affects electrolyte transport and balance. *CFTR* mutations result in the mislocalization of the protein or in reduced function at the membrane that leads to an abnormal electrolyte exchange and, consequently, very thick pulmonary and intestinal secretions.

Earlier work on gene therapy for CF was directed at the respiratory epithelial cells of mice. Human epithelial airway tissue is one site of the expression of the disorder. However, targeting respiratory epithelial cells has been difficult, mainly because the epithelial tissue is composed of a number of different cells at different stages of differentiation, and it is unclear which are the cells that express the defective *CFTR* gene.

Recently, Crystal et al[2] reported their results of gene therapy with a recombinant adenovirus vector (Ad*CFTR*) containing the human *CFTR* cDNA, administered to the respiratory tracts of 4 individuals with CF. All individuals had baseline evaluation of the respiratory epithelium before and after the administration of Ad*CFTR*. The Ad*CFTR* was then inhaled by the patients. The number of "corrected cells" was difficult to assess, but the epithelial cells did express the corrected *CFTR*. The authors concluded that it is feasible to use an adenovirus vector to introduce the gene and to achieve expression of the normal human *CFTR* in the epithelial tissue in a living patient. They point out, however, that their study does not establish whether this therapy will be successful in treating the common respiratory symptoms of CF or whether incorporation will be stable for long periods. No change in respiratory function was noted.

1. Cutting GR. Two steps closer to gene therapy for cystic fibrosis. *Nat Genet* 1992;2:4-5.
2. Crystal RG, et al. Administration of an adenovirus containing the human *CFTR* cDNA to the respiratory tract of individuals with cystic fibrosis. *Nat Genet* 1994;8:42-51.

Editor's comment: *Gene therapy for CF has proven "tricky." Animal studies have been encouraging in that the gene can be incorporated, so the next step was to try gene therapy in humans. However, since CF involves the lung, pancreas, and other organs in humans, the incorporation of the gene is harder to assess. It is unclear whether the respiratory symptoms accessible for monitoring improve after gene therapy, and it may be that the improvement is only temporary. The dosage of gene therapy has been problematic as well. Perhaps the "trick" is to concentrate on targeting only one organ for treatment and involve the stem cells. The question then becomes what organ or which tissue in that one organ should be targeted?*

Judith G. Hall, MD

Body Composition and Spontaneous GH Secretion in Normal Short Stature Children

In adults, the effect of obesity in suppressing growth hormone (GH) release has been well studied over 30 years. In children, only a few studies to determine the effect of obesity on GH release have been published. Abdenur et al attempt to fill that void in the study reported in this article.

Fifteen pubertal and 22 prepubertal short normal children were studied in relation to auxologic parameters, with emphasis on the measurements of body fat (BF) composition and the relationship of BF with spontaneous GH secretion (SGHS) over 12 hours at night.

A significant negative correlation between the degree of adiposity and mean SGHS was reported. A strong negative correlation was demonstrated with %BF as determined by bioelectrical impedance and BF mass index (BFMI), which is calculated as BF in kilograms/height in meters squared (Figure 1). Females required greater adiposity levels than males to decrease SGHS in pubertal subjects. Correlation between SGHS and BF was best with the mean pulse amplitude in pubertal subjects and the number of pulses and the sum of pulse amplitudes in prepubertal subjects.

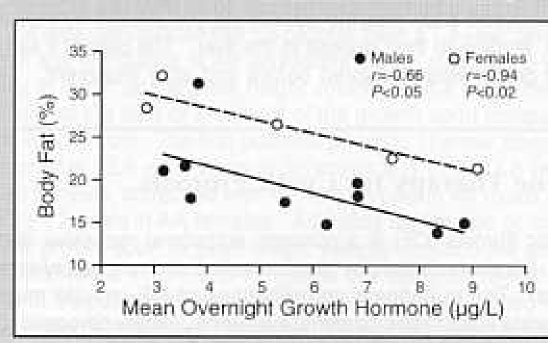
The authors conclude that in normal short-statured children, body composition greatly influences SGHS. Consequently, SGHS levels that appear low may actually be normal for a short child with mildly increased BF, and SGHS values that appear normal may be abnormally low for a lean individual who would be expected to have high SGHS levels because of leanness. This is an extremely important concept for a patient being evaluated for possible relative alterations in GH secretion. These results suggest also that normal values for SGHS must take into account not only pubertal status but also gender and body composition. The use of a mathematical formula that considers SGHS and IGF-1 values has been proposed (Oerter KE et al, *J Clin Endocrinol Metab* 1992;75:1413-1420). However, with a sufficient number of male and female patients, a more practical approach would be the use of confidence intervals to define normal values of SGHS according to body composition and gender.

Abdenur JE, et al. *J Clin Endocrinol Metab* 1994;78:277-282.

Editor's comment: *The authors are to be commended on performing and presenting a much needed study pertaining to the correlations of SGHS and various measurements of BF. Space did not permit an elaboration of the different important ways that BF was assessed.* GGH *readers are encouraged to read this article in its entirety, particularly to attain better comprehension of the various ways that BF can be measured and what those parameters really mean and reflect.*

Robert M. Blizzard, MD

Figure 1
% Body Fat and Mean SGHS: Correlation Analysis



Correlation between the %BF and mean overnight GH secretion in pubertal patients.