

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 al¹), Grossman et al² 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 Goldstein³). 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 colleagues² 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.