

sible prenatal diagnostic approach for trisomy 21 and potentially other aneuploidies. As pointed out in an accompanying editorial by Goldberg, there are problems that still must be resolved, such as the persistence of fetal cells from previous pregnancies. He notes 2 issues that must be addressed before widespread testing of fetal cells in maternal circulation is undertaken. The first issue is whether it should be offered to all pregnant women. The second issue is whether it should be used for gender selection.

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**Guest Editor's comment:** Advanced maternal age, variably defined as 35 to 40 years of age at the time of delivery, has long been a standard indication for prenatal diagnosis by chorionic villus sampling or amniocentesis. However, because the majority of infants with autosomal trisomies are born to women under 35 years of age, a number of approaches are used to screen for high-risk pregnancies among younger women. Clinical trials currently under way involving analysis of fetal cells in maternal circulation offer prospects for yet an additional approach.

Maternal serum triple screening, ie,  $\alpha$ -fetoprotein, HCG, and estriol, which assist in detecting neural tube defects,

Down syndrome, and trisomy 18, provides a high detection rate for these entities. However, its use at 15 to 20 weeks of gestation, followed by the subsequent requirement for amniocentesis if the screening is suspicious for definitive diagnosis, is too late in pregnancy for use by many women. Transvaginal ultrasonography also is used to detect birth defects. Taipalae et al recently published their experience in detecting increased nuchal translucency in 10,000 unselected pregnancies, reporting a sensitivity of 54% for the detection of trisomy 21.

It is reasonable to assume that for the foreseeable future a combination of maternal serum triple screening, ultrasonography, and very possibly, analysis of fetal cells in maternal circulation will be used for testing pregnancies of younger women. However, none of these techniques is currently sufficiently sensitive or specific enough to obviate standard cytogenetic analysis of the fetus to arrive at a confident prenatal diagnosis of an autosomal aneuploidy.

Taipalae P, et al. *N Engl J Med* 1997;337:1654-1658.

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## Gene Therapy: Promises, Problems, and Prospects

Gene therapy is a concept with which most of us are familiar. We know of its potential and that it has not lived up to this potential. However, few of us understand the biology that underlies gene therapy or appreciate the obstacles that gene therapists face. Fortunately, Verma and Somia have come to the rescue with a timely and concise review of the subject.

First, they point out that despite more than 200 clinical trials currently under way worldwide, there has been no clear success story yet. They consider the primary obstacles to be the lack of an efficient delivery system, the lack of sustained expression, and often a host immune response to therapy.

To Verma and Somia, the Achilles' heel of gene therapy is the delivery system. The properties of currently used gene therapy vectors, including retroviral, lentiviral, adenoviral, and adeno-associated viral vectors, are compared. Each has certain advantages, but each also has disadvantages. For example, retroviral vectors, which have been employed

most widely in clinical trials, integrate well into host genomes and there are few immunologic problems; however, expression of the therapeutic gene is short lived. In contrast, adeno-associated viruses support long-term expression, but the logistics of producing large quantities of virus needed for therapy is difficult. As for adenoviral vectors, many patients have preexisting immunity to adenoviral proteins. Lentiviral vectors, which are related to HIV, show considerable promise. The authors conclude that the ideal vector will be constructed from elements of different viral vectors.

Regarding clinical trials, Verma and Somia note that more than half the trials initiated to date involve cancer; nearly 30 involve monogenetic disorders as listed in the Table (page 13). They also point out that most of the trials are Phase I (safety) studies, and that for the most part, no major toxicity problems have been encountered with the existing delivery systems.

Finally, the authors are optimistic about the future of gene therapy, basing their optimism on the steady progress being made in vector design.

Verma IM, Somia N. *Nature* 1997;389:239-242.

**Editor's comment:** This is a short but informative review of the current status of gene therapy. It is written to be understood by the nongeneticist, yet provides a broad overview of the field.

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## Candidate Diseases for Gene Therapy

Disease	Defect	Incidence	Target Cells
<b>Genetic</b>			
Severe combined immunodeficiency (SCID/ADA)	Adenosine deaminase (ADA) in ~25% of SCID patients	Rare	Bone marrow cells or T cells
A Hemophilia	Factor VII deficiency	1:10,000 males	Liver, muscle, fibroblasts, or bone marrow cells
B	Factor IX deficiency	1:30,000 males	
Familial hypercholesterolemia	Deficiency of low-density lipoprotein (LDL) receptor		Liver
Cystic fibrosis	Faulty transport of salt in lung epithelium. Loss of <i>CFTR</i> gene	1:3,000 whites	Airways in the lungs
Hemoglobinopathies: thalassemias/sickle cell anemia	Structural defects in $\alpha$ - or $\beta$ -globin gene	1:600 in certain ethnic groups	Bone marrow cells, giving rise to red blood cells
Gaucher disease	Defect in the enzyme glucocerebrosidase	1:450 in Ashkenazi Jews	Bone marrow cells, macrophages
$\alpha_1$ -Antitrypsin deficiency: inherited emphysema	Lack of $\alpha_1$ -antitrypsin	1:3,500	Lung or liver cells
<b>Acquired</b>			
Cancer	Many causes, including genetic and environmental	1 million/y in US	Variety of cancer cell types; liver, brain, pancreas, breast, kidney
Neurologic diseases	Parkinson's, Alzheimer's, spinal cord injury	1 million Parkinson's and 4 million Alzheimer's patients in US	Direct injection in the brain, neurons, glial cells, Schwann cells
Cardiovascular	Restenosis arteriosclerosis		Arteries, vascular endothelial cells
Infectious diseases	AIDS, hepatitis B	Increasing numbers	T cells, liver, macrophages

From Verma IM, Somia N. Gene therapy: promises, problems, and prospects. *Nature* 1997;389:240.

## Changes in Bone Mineral Density, Body Composition, and Lipid Metabolism During Growth Hormone (GH) Treatment in Children With GH Deficiency

Adults with childhood-onset growth hormone deficiency (GHD) have reduced bone mass, increased fat mass, and disorders of lipid metabolism. The aim of the present study was to evaluate bone mineral density (BMD), bone metabolism, body composition, and lipid metabolism in GHD children before and during 2 to 3 years of GH treatment. The mean age of the 40 children participating in this study of bone metabolism and body composition was 7.9 years. An additional 17 GHD children participated in the study of lipid metabolism. Lumbar spine BMD, total body BMD, and body composition were all measured with dual energy X-ray absorptiometry. Volumetric BMD (or bone mineral apparent density [BMAD]) was calculated to correct for bone size. Standard deviation scores (SDS) were used to compare with normative data.

Lumbar spine BMD, total body BMD, and BMAD were all decreased at baseline. All these BMD variables increased significantly during treatment. The Table (page 14) presents the effects at various time points. Lean tissue mass SDS

increased continuously. Fat mass SDS decreased markedly during the first 6 months and remained stable thereafter. The chemical parameters of bone formation and resorption at baseline did not differ from those of normals and then increased during the first 6 months of treatment. Serum 1,25 dihydroxyvitamin D increased continuously during treatment, whereas parathyroid hormone and serum calcium remained stable. The lipid profile was normal at baseline.

The authors conclude that children with GHD have decreased bone mass. BMD, together with height and lean tissue mass, increased during treatment, which also had a beneficial effect on lipid metabolism.

Boot A, et al. *J Clin Endocrinol Metab* 1997;82:2423-2428.

**Editor's comment:** This interesting paper adds further data supporting the importance of GH treatment for GHD children, promoting linear growth and regulating different metabolic pathways. All patients presented in this study