

3. Therapy may be justified for children whose height could prevent them from participating in the basic activities of daily living.
4. Pediatricians should be alert to commercial efforts to

stimulate parental interest in GH therapy as an avenue for improving athletic ability and other forms of social "success" for their children.

Fima Lifshitz, MD

Increased Height in Patients With Medulloblastoma

Robertson et al report their surprising findings from chart reviews of 85 patients with medulloblastomas seen at the University of Iowa College of Medicine from 1963 to 1995. These patients (64 children and 21 adults) had their height and weight documented on standardized growth charts before treatment of their tumors. The data show that 22.4% of these patients were above the 95% curve (see Table) in height. In a comparison group of patients with cerebellar astrocytomas, only 7.1% were above the 95% curve for height. Thus, there is a clear difference between linear growth in the 2 different groups. Most of the increased height was in male patients; however, 56 of the 85 patients were male. Interestingly, patients who presented as adults also were taller than expected at diagnosis.

The authors related that medulloblastoma cell lines can express different levels of growth factors, including epidermal growth factor, platelet-derived growth factor, transforming growth factor, and insulin-like growth factor (IGF). They note that since the adults in the study also were above normal height, something must have occurred that predated the development of neoplastic cells.

Robertson SC, et al. *Neurosurgery* 1997;41:561-566.

Editor's comment: These authors have presented some very interesting and intriguing data. Since the study was retrospective, there are no carefully collected hormonal data from the individuals, ie, testosterone, growth hormone, IGF-1, etc. Nor do the authors present any data regarding the pubertal status of the children at the time of diagnosis. It is conceivable that some of the children with medulloblastoma may have had early puberty, which would account for their being taller than expected. Postoperatively, growth failure is the rule rather than the exception in these individuals. Although we have no data on final heights in the children, one would anticipate that those patients diagnosed and treated as children would not end up being tall adults. The data do suggest, however, that it is important for pediatric endocrinologists to continue to encourage their neurosurgical colleagues to evaluate the hormonal status of their patients preoperatively as well as after treatment.

William L. Clarke, MD

Preoperative Height and Weight of Patients With Medulloblastomas^a

Medulloblastoma Preoperative Curves (%)	Height		All Patients Total (%)	Weight		Total (%)
	M	F		M	F	
>95	14	5	19 (22.4)	6	0	6(7.1)
>90	18	8	26 (30.6)	9	1	10(11.8)
>75	36	11	47 (55.3)	15	2	17(20.0)
>50	46	18	68 (80.0)	32	10	42(49.4)
>25	55	25	80 (94.1)	44	14	58(68.2)
>10	55	29	84 (98.8)	50	18	68(80.0)
>5	55	29	84 (98.8)	54	23	77(90.6)
>0	56	29	85 (100)	56	29	85(100)

^aNumbers in each column represent the total number of patients above or equal to the percentile group listed.
From Robertson SC, et al. Increased height in patients with medulloblastomas. *Neurosurgery*. 1997;41:561-566.

Prenatal Diagnosis From Fetal Cells in Maternal Circulation

Detection of fetal aneuploidy by noninvasive means has been a long-term goal of the prenatal diagnostician. Screening procedures based on measuring substances in maternal serum, for example, maternal serum α -fetopro-

tein, detect many instances of aneuploidy. However, many are missed, and this deficit has prompted the search for other strategies, including analyzing fetal cells circulating in maternal serum. Indeed, it has been known for many

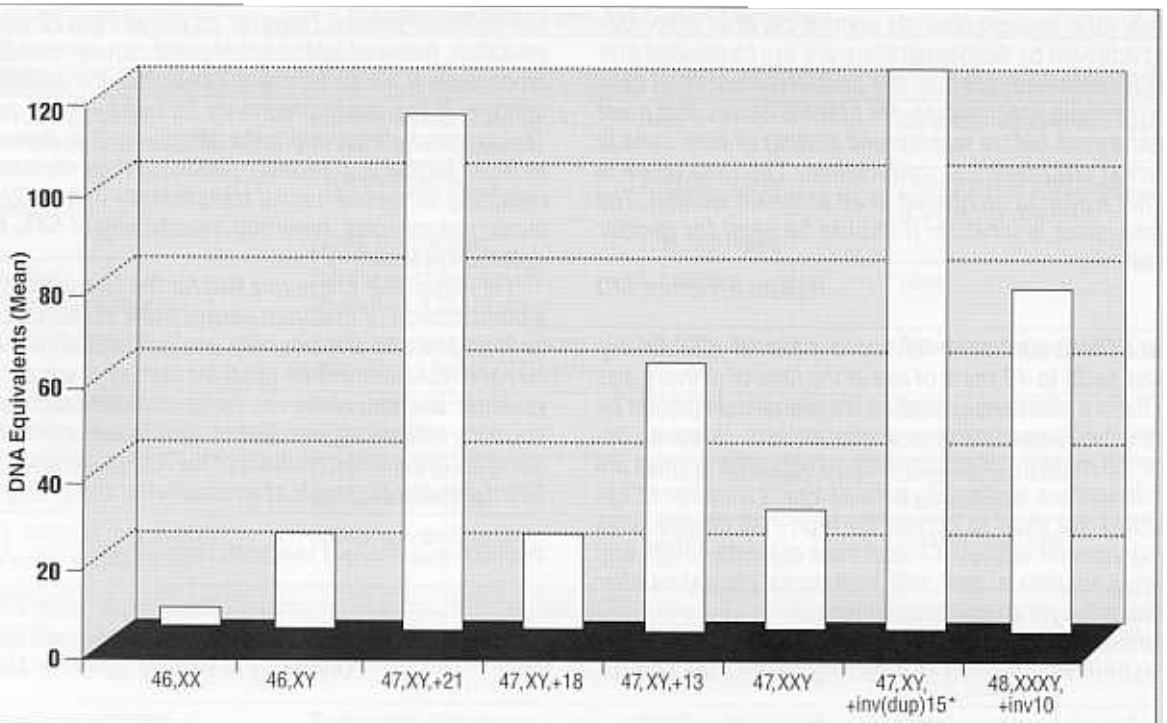


Figure. Bar graph demonstrating mean number of male fetal-cell DNA equivalents detected in maternal samples, stratified by fetal karyotype. Note that the highest number of male fetal-cell DNA equivalents is detected when the fetus has 47,XY,+21 or 47,XY,+inv(dup)15. The asterisk (*) indicates that the values for 47,XY,+inv(dup)15 are off the scale, with a mean value of 230.

From Bianchi DW, et al. PCR quantitation of fetal cells in maternal blood in normal and aneuploid pregnancies. *Am J Hum Genet* 1997;61:822-829. Published by University of Chicago. ©1997 by the American Society of Human Genetics.

years that a limited number of fetal trophoblasts, lymphocytes, granulocytes, nucleated erythrocytes, and platelets reach the maternal circulation. Several studies have explored various aspects of this issue, but differences in patient populations, cells studied, and methods used to enrich and analyze the cells have made it difficult to draw definite conclusions about the efficacy of this approach for prenatal diagnosis.

An article by Bianchi et al sheds light on the issue. In a large, multicenter clinical trial, PCR-amplified Y-chromosome sequences were obtained from 16-mL peripheral blood samples of 199 women carrying chromosomally normal fetuses and from 31 women with male aneuploid fetuses. They sought to determine the number of male cells, or their equivalent, that could be detected in maternal serum under different clinical conditions. Results were expressed as male fetal-cell DNA equivalents. There was no enrichment of cells so that values reflected the number of cells in the original sample and were not artifacts of enrichment; no distinction was made between the different cell types.

The mean number of male fetal-cell DNA equivalents from 90 women bearing 46,XY fetuses was 19, and more than 80% had values over 2 cell equivalents. There was no difference if the specimen was taken before or after amniocentesis. Surprisingly, Y-specific DNA sequences were found in about one fourth of women carrying female fetuses, although the values were lower than when male fetuses

were being carried. Possible explanations for the presence of male cells in the maternal circulation were that the male cells had come from a male twin who had been lost early in the current pregnancy, or were from a previous transfusion from a male donor, or were from a previous pregnancy with a male fetus.

Most remarkable, Bianchi et al found a substantial increase in the number of male fetal-cell DNA equivalents if the fetus was aneuploid. There was a 6-fold increase in fetal cells detected in the maternal circulation when the fetus had trisomy 21 (see Figure). Lesser increases were observed for trisomy 13 and 18, but fewer cases were assessed. The authors pointed out that this finding is consistent with pathologic observations of placental abnormalities in trisomies.

The authors concluded that a small but consistent number of fetal cells are normally transfused across the placenta into the maternal circulation. The number is increased substantially for aneuploid fetuses, especially for trisomy 21, which should make feasible detection of at least trisomy 21 from maternally circulating fetal cells.

Bianchi DW, et al. *Am J Hum Genet* 1997;61:822-829.
Goldberg JD. *Am J Hum Genet* 1997;61:806-809. Invited Editorial.

Editor's comment: This technology has evolved from little more than wishful thinking 2 decades ago to an almost fea-

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.

William A. Horton, MD

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, α -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. Taiplae 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.

Taiplae 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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