

different treatment options available for patients with this disorder. Unfortunately, in the United States, the major supplier of injectable cortisone acetate has discontinued its production, and pediatric endocrinologists will be forced to become familiar with other glucocorticoid agents or other forms of treatment.

Gasparini et al did not report on any adverse clinical events during times of physiologic stress that may have occurred in patients receiving <25 mg/m²/d. Such information would be important to have prior to making recommendations regarding their proposed therapeutic regimen.

William L. Clarke, MD

2nd Editor's comment: The reader also is referred to an article by Kerrigan et al (J Clin Endocrinol Metab 1993;76:1505-1510), reporting that the production rate of hydrocortisone is less than that calculated by Migeon's group (approximately 6.1 mg/m²/d vs approximately 12 mg/m²/d). It is not surprising, therefore, that a dose less than twice the production rate (25 mg/m²/d), which is the dose previously accepted by endocrinologists as being a suppressive dose in congenital adrenal hyperplasia, may be more than necessary to adequately treat the disorder.

Robert M. Blizzard, MD

Opitz Syndrome Gene Found

Opitz syndrome, which was originally described as G and BBB syndromes, is characterized by midline defects, including hypertelorism, hypospadias, lip/palate/laryngotracheal clefts, and imperforate anus. Clinically indistinguishable forms have been genetically mapped to the X (Xp22) and 22 (22q11.2) chromosomes. A consortium of several groups (see references) headed by Andrea Ballabio in Milan has now found the gene that harbors the mutations responsible for the X-linked form.

After first constructing a physical map of the Xp22 breakpoint region, the investigators next identified expressed sequences from which they were able to assemble a consensus cDNA sequence of 3,452 bp. The predicted protein product is 667 amino acids, which was named MID1. Expression of the MID1 gene was then studied. Transcripts were found in virtually all normal fetal tissues examined, especially kidney, brain, lung, and placenta, and in the heart and brain of adults. No transcripts were detected in samples from an affected male. Studies in the mouse revealed that *mid1* is expressed ubiquitously in early embryos, with the highest levels found in the first and second branchial arches.

The sequence of predicted protein places it in the so-called B-box family of zinc-finger proteins. These proteins contain a "RING-finger" and 2 "B-box" domains, which are thought to mediate protein-protein interactions. Genes belonging to this family encode transcriptional regulators.

Mutation analyses were carried out in patients from 22 independent families; mutations were found in 4 families. The gene was disrupted by the pericentric inversion in the family used for mapping. The other mutations were an in-frame 3-bp deletion, a frameshift that produces a premature stop codon, and a tandem duplication of 24 bp. All are predicted to disrupt the function of the protein.

The authors conclude that the MID1 encodes a protein whose function is important for development of midline structures.

Green EA, et al. *Science* 1997;278:615-630.
Henikoff S, et al. *Science* 1997;278:609-614.
Quaderi NA, et al. *Nature Genet* 1997;17:285-291.
Tatusov RL, et al. *Science* 1997;278:631-637.

Editor's comment: Genes relevant to early human development are being discovered at a rapid pace, primarily from positional cloning of "birth defect syndrome" genes. This is very exciting, but it is difficult to keep track of the different genes and mutations. The situation is analogous to the chondrodysplasia situation in the early 1990s, when there were well over 100 distinct disorders, multiple ways of classifying them, and considerable debate over grouping versus separating conditions with subtly different clinical features. Fortunately, molecular genetics helped to sort out the situation by revealing that a large portion of these disorders fell into a relatively small number of "chondrodysplasia families" that shared common genetic origins.

The situation is more complicated when the entire spectrum of birth defects is considered. However, attempts are now being made to "organize" genes into families, which will likely lead to a reconsideration of how these syndromes are classified and managed nosologically. This move to better organize genetic information into a family context was very evident at the 1997 American Society of Human Genetics meetings in Baltimore, as well as in the 1997 Genomics issue of *Science*. These efforts should eventually help keep clinicians from becoming lost in the maze of molecular genetic information.

William A. Horton, MD

In The Next Issue

Growth Hormone Replacement in Adults

Peter Sönksen, MD,
and J Weissberger, MD