

based on animal experiments or indirect evidence derived from studies in which parents of diabetic children tried to recollect when their babies first started drinking milk-based formula.

The Finnish researchers who conducted this study avoided the vagaries of poor recall by studying children from birth. In so doing, they have added to the case against cow's milk. By monitoring infants in diabetes-prone families, namely, those with HLA-DQB1*0302, the scientists found that infants getting cow's milk formula were more likely to develop the immune reactions associated with insulin-dependent diabetes mellitus (IDDM) than infants fed exclusively human milk.

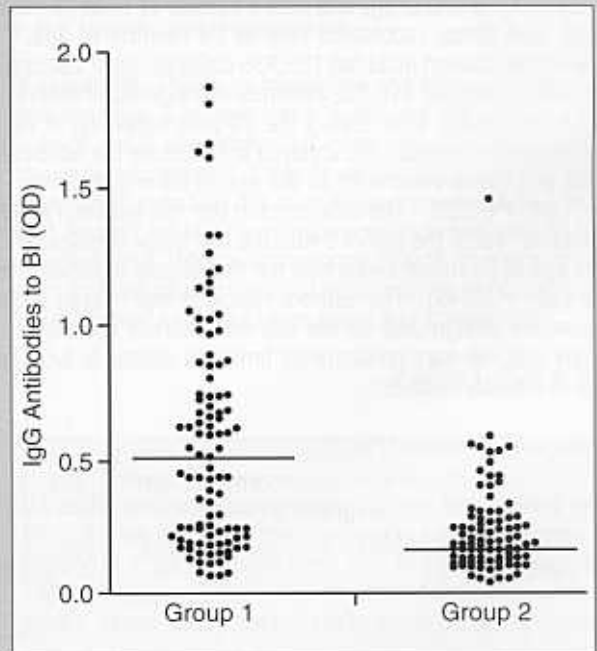
It is known that having one type of autoantibody to insulin indicates that a child has roughly a 40% chance of developing type 1 diabetes within the next decade. Additionally, having more types of these autoantibodies may be a sign of greater risk; having 3 types of autoantibodies imparts an 80% to 90% likelihood of developing type 1 diabetes. However, the precise cause of IDDM remains unclear. The children in the study were genetically predisposed to IDDM, but most will never get the disease. Something in the environment or diet, such as consuming cow's milk during infancy, may be a triggering factor.

This study presents further evidence implicating cow's milk. In Puerto Rico, fewer than 5% of mothers breast-feed their children. Instead, nearly all use formula made from cow's milk. Meanwhile, the IDDM incidence in Puerto Rico is roughly 10 times the rate seen in Cuba, where breast-feeding is nearly universal. Such findings represent circumstantial evidence suggesting that ingestion of cow's milk in the first few months of life plays a very important role in the etiopathogenesis of this disease.

To date, none of the data on cow's milk and IDDM preclude feeding cow's milk formula to infants who do not have the good fortune of being fed human milk.

Fima Lifshitz, MD

Figure
The Levels of IgG Antibodies to Bovine Insulin (BI) at Age 3 Months in Infants Who Received Cow's Milk Formula Before Age 12 Weeks (Group 1) and in Infants Who Were Exclusively Breast-Fed Until Age 12 Weeks (Group 2)



The median is marked with a line. $P < 0.0001$, group 1 versus group 2 (Mann-Whitney U test).

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A Molecular Pathway Revealing a Genetic Basis for Human Cardiac and Craniofacial Defects

The investigators have identified a gene that is deleted or mutated in patients with the DiGeorge association (DGA) of craniofacial and cardiovascular malformations. Specific defects include interruption of the aortic arch, truncus arteriosus, tetralogy of Fallot, defective immunocompetence, and hypoparathyroidism. These widespread anomalies have been attributed to a defect in the function of neural crest cells important for normal structural development. The vast majority of patients with DGA have a monoallelic microdeletion of chromosome 22q11.2. Noting that mice lacking the transcription factor *dHAND*, a factor necessary for survival of neural crest cells in the branchial arches, aortic arch, and right ventricle, have many of the anomalies present in DGA, these workers examined the genes that this protein regulates. They found it to regulate the human homologue of *Ufd1*, a gene that encodes a protease that degrades proteins linked with ubiquitin that is localized to the critical region of 22q11 associated with DGA. The investigators demonstrated that in mice, *Ufd1* was expressed in those tissues that are adversely

affected in patients with DGA. In all 182 patients with DGA and deletion of 22q11, *UFD1L* was absent. In 1 patient with DGA but no apparent chromosomal anomaly, the investigators demonstrated monoallelic deletion of exons 1 through 3 of *UFD1L* with retention of exons 4 through 12 of this gene. In the same patient, there was partial deletion of an adjoining gene, *CDC45*, a cell cycle protein. However, this gene is widely expressed. Therefore, the authors suggest that monoallelic inactivation of *UFD1L*, either by gross deletion or more subtle mutation, may be responsible for DGA. They hypothesize that the failure to degrade an as yet unidentified, ubiquitinated protein adversely affects the development of those neural crest cells necessary for normal formation of craniofacial bones, heart, thymus, and parathyroid glands.

Yamagishi H, et al. *Science* 1999;283:1158-1161.

Editor's comment: Although it remains possible and perhaps even probable that DGA and associated disorders found in

patients with deletion of chromosome 22q11 are the result of loss of contiguous genes, the current report strongly implicates UFD1L as a key gene in DGA. Examination of this gene in additional patients with DGA without visible microdeletions of 22q11 will be important. Ubiquitin is a 76 amino acid peptide that links to and apparently "tags" proteins before they are degraded by proteases associated with the nonlysosomal 20S proteasome.

Recently, the gene that is mutated in Angelman syndrome (UBE3A) has been found to encode a protein (E6-AP) that is a ubiquitin-protein ligase. (Interestingly, E6-AP also is a coacti-

vator for the transcriptional activity of the human progesterone receptor, but this metabolic function of E6-AP is intact in patients with Angelman syndrome.) Thus, Angelman syndrome is likely to be another example of a disease resulting from accumulation of a toxic protein that escapes degradation by the ubiquitin-proteasome pathway of protein degradation. Thus is identified another class of disorders, the "ubiquitinopathies," a name suggested by Dr. A. diGeorge.

Allen W. Root, MD

Fang P, et al. *Hum Molec Genet* 1999;8:129-135.

Nawaz Z, et al. *Molec Cell Biol* 1999;19:1182-1189.

The Molecular Genetics of Growth Hormone Deficiency

Proctor et al have written an excellent review of growth hormone deficiency (GHD) from a molecular genetic perspective. It is both comprehensive and extremely useful. The GH synthetic pathway is relatively well worked out, as is its relationship to pituitary releasing factors and insulin-like growth factor 1 (IGF-1). Between 5% and 30% of "idiopathic" GHD individuals have a first-degree relative who also is affected, suggesting that there is a genetic etiology for many cases of GHD. The known mutations and genetic forms of GHD are reviewed, including the pituitary-expressed genes that have an effect on GH synthesis and release. In addition, of course, there are primary GH mutations.

The molecular basis of GHD is now being defined in multiple families. More than 30 specific deletions are known. Deletions seem to be particularly predisposed to anti-GH antibody production. At least 10 specific mutations have been described in different parts of the *GH1* gene. Until now, no correlations between mutant genotype and clinical phenotype have been reported.

The GH gene lies in a family of GH-type genes. Their closeness provides potential mechanisms for mutagenesis through slippage. There are a series of *GH1* gene mutations, including deletions, autosomal recessive mutations, and autosomal dominant splice site and intronic mutations. The human GH (*hGH*) gene cluster includes 2 chorionic somatotropin hormone genes, a chorionic somatotropin pseudogene, and 2 GH genes; *GH1* is

the important functional gene. Evolutionarily in nonprimate mammals, GH is encoded by a single gene.

There are several familial forms of combined pituitary hormone deficiency (CPHD). The *PIT1* gene (*POU1F1*) is associated with autosomal recessive and autosomal dominant inheritance. In addition, *PROP1* gene mutations lead to autosomal recessive CPHD. GH-releasing hormone receptor mutations also have been identified.

Proctor AM, et al. *Hum Genet* 1998;103:255-272.

Editor's comment: This is an excellent review. There are 5 pages of references for those individuals trying to research the problem. The delineation of the mutations is complete. As the authors point out, the development of specific mouse models should lead to a better understanding of genotype-phenotype correlation, as well as mechanisms to avoid anti-GH antibody production.

Judith G. Hall, MD

2nd Editor's comment: This article is an absolute must to read and digest for both clinicians and researchers involved in the origin of GHD and/or GHD-like syndromes. Drs. Proctor and Cooper of the University of Wales and Dr. Phillips of Vanderbilt University are eminently qualified as world experts on this topic.

Robert M. Blizzard, MD

Metabolic Effects of Discontinuing Growth Hormone Treatment

The authors serially determined the resting metabolic rate (RMR), fat mass, percent body fat, and total body bone mineral content (BMC) by skinfold measurements and/or dual X-ray absorptiometry after discontinuing the administration of human growth hormone (hGH). The treatment periods ranged from 1.7 to 11.8 years in 11 (4 female) adolescent patients (aged 14.5 to 18.5 years) with isolated GH deficiency (GHD) or multiple anterior pituitary hormone deficiencies (N=8). They found that these measurements were stable during the last year of hGH therapy but that RMR declined within 2 weeks after stopping hGH and remained low through the next year. In GHD patients, fat mass increased within 6 months after cessation of hGH therapy. (In 15

non-GHD control subjects, 5 of whom had been treated with hGH, these measurements did not change appreciably over 1 year.) Six months after hGH administration was halted, there was an inverse relationship between the changes in RMR and fat mass. BMC was normal in the GHD subjects upon completion of hGH treatment and did not change in the ensuing year. The investigators suggest that the short-term decline in RMR after discontinuation of hGH in subjects with childhood-onset GHD may identify those patients with persistent adult GHD who would benefit by reinitiation of hGH therapy.

Cowan FJ, et al. *Arch Dis Child* 1999;80:517-523.