This Month in the *Journal*

We focus this month on apoptosis, the regulated process of cellular suicide. In recent years, apoptosis has emerged as a feature of metazoan life that is no less important in disease and normal development than is cellular proliferation. Travis (p. 503) discusses human retinal-degeneration disorders, a bewilderingly diverse set of conditions that all lead to abnormally high rates of apoptosis in the retina. Travis steps back from the mechanistic details of the apoptotic pathway and considers features of retinal physiology that may make this tissue particularly susceptible to degeneration. Brinkmann (p. 509) discusses CAS, a dual-function protein that renders human cells susceptible to apoptosis and also participates in cell proliferation. Because of the latter function, the *CAS* gene may serve as an oncogene, and CAS is, in fact, commonly overexpressed in tumors. Brinkmann considers the biological significance of the finding that a single protein, such as CAS, p53, or MYC, can drive cells toward either growth or death. Rodriguez et al. (p. 514) review work on apoptosis in *Drosophila* and show that many of the mechanisms, elicitors, and inhibitors of apoptosis defined by genetic analysis of the fly are preserved through evolution and act in human cells as well.

GJA8 *Mutations and CZP1 Cataract,* *by Shiels et al.* **(*p. 526*)**

Connexins are integral plasma membrane proteins that form gap junctions, gated openings that permit flow of cytoplasmic molecules from cell to adjacent cell. These intercellular structures are nearly ubiquitous, but there is significant specialization among the connexins, as shown by the tissue-specific effects of mutations in various human and murine connexin genes. Connexins have been implicated in sensorineural hearing loss, in heart defects, and in a peripheral neuropathy, X-linked Charcot-Marie-Tooth syndrome. Here, Shiels et al. report that congenital cataracts result from a missense mutation in the connexin gene *GJA8,* which encodes an ocular gap-junction protein, one of the major structural proteins that make up the retina. They show that zonular pulverulent cataracts segregate with this point mutation in two branches of an eight-generation pedigree. This association is strengthened by the recent finding that mice with a targeted mutation in the corresponding gene are born with clouded retinas. Also see the invited editorial by Hejtmancik (p. 520) in this issue.

0002-9297/98/6203-0000$02.00

Mutations in the* PMM2 *Gene in CDG1A, *by Matthijs et al.* **(*p. 542*)**

N-linked sugars are found on most secreted and cell-surface proteins and, in many cases, are required for the stability, function, or localization of glycoproteins. Glycosylation requires the coordinated activity of numerous proteins, including the products of at least four human disease genes that are associated with carbohydrate-deficient glycoprotein (CGD) syndromes. CGD1A, an autosomal recessive disorder of the liver and nervous system, arises from mutations in a gene for phosphomannomutase, *PMM2*. This enzyme is required for synthesis of GDP-mannose, which is consumed in the endoplasmic reticulum to make the dolichol glycolipid, the immediate donor of carbohydrates to N-linked sites in nascent glycoproteins. Matthijs and colleagues, who identified the first disease alleles of *PMM2,* now report the genotype of 56 people independently ascertained with CDG1A. They find in this group 24 point mutations, most of which are novel. Only 1 of the 24 is likely to represent a null allele; all the others are missense mutations that are distributed widely across the gene. This dearth of obvious nulls may suggest that PMM2 activity must be at near-normal levels for development to proceed. Matthijs et al. argue that the most common disease allele, R141H, must be a particularly weak hypomorph, since it has never been found in the homozygous state, a condition that might mimic complete deletion of the gene.

Genotype-Phenotype in A-T, *by Gilad et al.* **(*p. 551*)**

In classically defined ataxia-telangiectasia (A-T), the loss of a nuclear kinase, ATM, removes a cell-cycle checkpoint that monitors chromosomal DNA for breaks. A-T individuals are short-lived, with a characteristic set of neuromotor, vascular, and immunological defects. Although these symptoms and their associated cellular phenotypes are relatively uniform, some A-T variant individuals and families have been reported. Gilad and co-workers show here that milder symptoms arise from weak alleles that reduce but do not abolish expression of ATM. DNA synthesis in cells from classic A-T and A-T variant individuals is not suppressed by DNA damage, as it would be in normal cells. However, radiation-induced cell death is more variable in A-T variant cells, and no simple correlation emerges between the residual protein levels, the cellular phenotypes, and the clinical symptoms in the variant group. Possibly, other environ-

mental or genetic factors influence the effects of weak *ATM* alleles.

Arylsulfatase E Mutations in Chondrodysplasia Punctata, *by Daniele et al.* **(***p. 562***)**

Daniele and colleagues report here on the biochemical effects of mutations in arylsulfatase E (*ARSE*), a gene implicated in the X-linked form of the hypoplastic bone disease, chondrodysplasia punctata (CDPX). The same authors previously described multiple missense mutations in CDPX pedigrees; now, they have expressed five of these, as well as the wild-type cDNA, in cultured cells. They find that, unlike other arylsulfatases, mature ARSE is found solely in the Golgi apparatus, a site of biosynthetic protein sulfation. None of the mutations studied alter this localization or destabilize the protein, but four of the five result in a dramatic loss of in vitro activity. The fifth may be a neutral polymorphism, or its defect might only be apparent when it is assayed with its still-unknown physiological substrate.

Mapping of Normal-Tension Glaucoma to 10p15-p14, *by Sarfarazi et al.* **(***p. 641***)**

Chronic open-angle glaucoma (COAG), a common eye disorder in African American and Caucasian populations, presents with progressive loss of visual field, a result of distortion and degeneration of the optic nerve. High intraocular pressure (IOP) is often used to diagnose preclinical cases of glaucoma, but, in some forms of hereditary glaucoma, loss of vision may occur in some family members with normal IOP, demonstrating that chronic high IOP is not the only factor that can distort the optic nerve. The four-generation pedigree described here by Sarfarazi and colleagues is unusual in that all affected members exhibit IOP values in the normal range. The authors link COAG in this family to GLC1E, a novel dominantly segregating locus on 10p. They suggest a number of candidate genes in this region. Identification of the relevant gene(s) may help explain the origins of normal-tension glaucoma.

Obesity Genome Scan in Pima Indians, *by Norman et al.* **(***p. 659***)**

Norman and colleagues have conducted a genomewide search for factors that lead to obesity among Pima Indians. This group is subject to both obesity and diabetes mellitus (a condition similar to the phenotype of the widely studied *db* mouse strain), but variability in obesity and in measures of respiratory activity is similar among the Pima and among other populations in North America. Norman et al. have followed biometric and metabolic traits in a set of 39 previously unreported Pima families. Here, they report multiple loci with suggestive linkage to each of these quantitative traits, but they find that none of these candidate loci can account for more than one such trait. Furthermore, neither the candidate genes proposed from physiological studies nor the candidate loci suggested by earlier linkage analyses could be confirmed by the present data.

Genome Search in Celiac Disease, *by Greco et al.* **(***p. 669***)**

Celiac disease (CD) is a heritable dietary intolerance in which gluten proteins from certain grains provoke an autoimmune reaction against the absorptive tissue of the small intestine. Several known HLA haplotypes predispose to CD, but these are not sufficient to explain its incidence. One puzzling feature of this condition is the presence in CD families of a "silent" form of the condition, in which autoimmunity and intestinal atrophy occur but do not lead to the clinical effects of malabsorption. Greco et al. employed a two-step strategy to search for linkage to CD. Their initial scan in 39 sib pairs affected with the clinical form of CD identified two putative susceptibility loci (at 5qter and at 11qter), as well as the HLA region. They then confirmed the linkage of 5qter in a set of 71 sib pairs in which CD was "silent" in one sib but "clinical" in the other. The locus at 11qter showed no linkage in this second test, and it may have arisen simply as a type I error. However, the authors suggest, the locus at 11qter might also represent an interacting gene that controls the clinical presentation of CD.

JOHN ASHKENAS
EDITORIAL FELLOW