This Month in the *Journal*

This month we feature a series of reviews on the genetics of cardiovascular development and disease. Rudic and Sessa (p. 673) discuss the physiological control of vascular diameter in response to changes in blood flow. This vascular remodeling goes awry in hypertension and atherosclerosis, which appears to be regulated by endothelial nitric oxide synthase. Towbin et al. (p. 678) review cardiovascular development and survey various disorders of vascular morphogenesis, including a number of hereditary defects for which the underlying genes are now available for study. Xiao and Benjamin (p. 685) discuss the significance of stress-response proteins in cardiac health. They indicate that heat-shock proteins may be important tools for reducing damage in ischemic tissues. Furthermore, endogenous proteins of this kind, specifically αB-crystallin, are required in order to maintain the normal function of cardiac and skeletal muscle. Finally, Ring and Cho (p. 691) review the signal-transduction pathways for transforming growth factor (TGF)–β and its relatives. This superfamily of cytokines shapes the development of the vasculature as well as many other tissues and organs, and TGF-β–signaling mediators have been implicated in hereditary hemorrhagic telangiectasia. TGF-β signaling has been extensively studied in the early development of the frog, and Ring and Cho discuss work in this system that begins to explain how this ubiquitous biochemical pathway can induce such a diversity of specific biological responses.

Bicistronic MPT-Synthase Transcript, *by Stallmeyer et al. (p. 698);* ***Molybdenum Cofactor Deficiency Type B,*** *by Reiss et al. (p. 706)*

Molybdopterin, an essential cofactor that is found in all eukaryotic molybdoenzymes, is synthesized in two steps catalyzed by molybdenum cofactor synthases (MOCS) 1 and 2. Deficiency of either of these heterodimeric proteins can lead to molybdenum-cofactor deficiency, a rare but lethal inborn error. The two subunits of MOCS1 are encoded by a single mRNA species, which carries two discontinuous open reading frames (ORFs). Stallmeyer et al. show that, remarkably, the MOCS2 mRNA is also bicistronic. This message contains a short 5′ ORF, which encodes the 10-kD subunit of MOCS2, and an overlapping 3′ ORF, which encodes the 21-kD subunit. Expression of the downstream ORF seems to depend on leaky ribosomal scanning of the mRNA, rather than on internal translational initiation, since an inhibitor of 5′ mRNA end recognition suppresses the in vitro translation of both subunits equally. This leaky scanning mechanism has been found in some viral transcripts but is quite rare in mammalian mRNAs. Reiss et al. have also identified five MOCS2 mutations among seven homozygous or compound heterozygous individuals with molybdenum-cofactor deficiency.

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LEFTY ***and Left-Right Axis Malformations,*** *by Kosaki et al. (p. 712)*

Several vertebrate genes that affect the development of left-right asymmetries have been characterized in recent years, and a few familial or sporadic human cases of abnormal laterality are now beginning to be understood. Kosaki and colleagues have cloned two tandemly repeated genes, *LEFTY-A* and *LEFTY-B,* homologues of *Lefty-1* and *Lefty-2,* which underlie laterality defects in the mouse. *LEFTY-A* encodes a previously identified member of the TGF-β superfamily, TGF-β4, and point mutations in this gene appear to account for the malformations seen in 2 situs individuals, among 126 such cases examined. The detailed cardiac and pulmonary features of these individuals generally match the phenotypes seen in *lefty-1*$^{-/-}$ mice. The mode of transmission of *LEFTY*-related situs defects is complex in both species. Indeed, the probands reported by Kosaki et al. are heterozygotes who had inherited a mutant *LEFTY-A* allele from an unaffected parent; background genotype and stochastic effects probably both influence the laterality phenotype in homozygotes and heterozygous carriers. For more on cardiac laterality and other malformations, see Towbin et al. (p. 678); for more on TGF-β signaling, see Ring and Cho (p. 691).

Cyclic Ichthyosis with Epidermolytic Hyperkeratosis, *by Sybert et al. (p. 732)*

Sybert and coworkers report a novel mutation in the gene for keratin-1 (*KRT1*) that causes a distinctive skin disorder, which they term "cyclic ichthyosis with epidermolytic hyperkeratosis." Presentation of this condition only partly overlaps with bullous congenital ichthyosiform erythroderma, a well-studied disorder in which both of the suprabasal cell keratins, K1 and K10, have been implicated. Sybert et al. noted that individuals from two unrelated families, who were examined 10 years apart, both experienced explosive bouts of erythematous plaques that covered much of their bodies. The presence of cytokeratin aggregates in suprabasal skin cells prompted them to sequence these patients' *KRT1* and *KRT10* genes, and they report here that both families

with this unusual disorder carry missense mutations that affect the identical codon of *KRT1*.

Mutations in* MRP2/cMOAT *Gene in DJS, *by Toh et al.* (*p. 739*)

ATP-binding–cassette (ABC) proteins first came to attention with the identification of the multidrug-resistance transporter (MDR1). This family of versatile transmembrane-transport proteins also includes the cystic fibrosis transmembrane-conductance regulator (CFTR) and the canilicular multispecific organic anion transporter (cMOAT). cMOAT is expressed on the apical surface of hepatocytes and appears to shuttle glutathione-conjugated bilirubin into the bile, for excretion. Toh et al. recently implicated cMOAT in Dubin-Johnson syndrome (DJS), an autosomal recessive condition in which bilirubin and various drugs accumulate as glutathione conjugates in the bloodstream. These authors now present the exon structure of this gene, and they identify four probable disease alleles, one of which was known from their previous study. One missense mutation is identical to a mutation found at the corresponding site in a disease allele of *CFTR*.

Localization of a Prostate-Brain Cancer–Susceptibility Locus, *by Gibbs et al.* (*p. 776*)

As Gibbs and colleagues have suggested in the past, the contradictory linkage findings that have bedeviled the search for prostate cancer genes could be explained by locus heterogeneity and subtle differences in ascertainment in different studies. Now, these authors have attempted to turn this heterogeneity to advantage by focusing on a specific subset of probands with prostate cancer—namely, those who have a family history of malignant brain tumors. Initial evidence linked prostate cancer to 1p36, a region that is commonly deleted in brain tumors but that has not been reported previously in prostate cancer studies. Among 141 prostate cancer families, Gibbs et al. found linkage to markers in this region in only the 12 families with a history of malignant brain tumors and of early-manifesting prostate cancer. The suggestion of a prostate and brain cancer gene is consistent with epidemiological work that suggests that tumors in the CNS are increased in frequency in prostate cancer families.

***Homozygous Parent TDT Analysis of* IDDM1,** *by Lie et al.* (*p. 793*)

The portion of 6p that carries the human leukocyte antigen (HLA) major histocompatibility loci has been implicated in numerous autoimmune disorders, but this region often confounds detailed genetic analysis, perhaps because it is relatively rich in genes and is subject to strong transmission disequilibrium. Insulin-dependent diabetes mellitis (IDDM) is among the best studied of these disorders, and specific HLA haplotypes have been defined that promote the disease in humans and mice. Still, it has been difficult to untangle the effects at these loci from those of other, potentially tightly linked genes. Lie et al. have devised a statistical approach, the so-called homozygous parent TDT, that allows them to detect the latter effects. Starting with samples from three large northern European IDDM studies, Lie et al. selected 225 families in which one or both parents were homozygous for an HLA haplotype, and they applied the TDT in order to find alleles at surrounding loci that are preferentially transmitted to affected children. They show that one or more genes, probably located several megabases telomeric to the HLA region, promote IDDM, at least in the context of particular HLA haplotypes. The precise localization of these genes remains a challenge, but a mouse IDDM-related gene, which has been identified in a syntenic region, may prove more tractable.

The Duty to Recontact, *by Fitzpatrick et al.* (*p. 852*)

Individuals and families referred for genetic diagnosis or counseling clearly deserve the most accurate information available at the time of their visit, but what should they expect once they have left the clinic? Do advances in diagnosis, prognosis, or treatment of genetic disorders obligate genetics service providers to reestablish contact with all their former patients? Fitzpatrick and coworkers have surveyed 252 North American members of the American Society of Human Genetics on a number of such questions, and they report here that there is little consensus on the notion of a "duty to recontact." Among respondents who see patients, a clear majority indicated that they had, on some occasions, recontacted one or more individuals with regard to recent advances, but considerably fewer respondents felt that recontact should be the standard of care. The demands on time and resources seem to cause the greatest concern. An alternative approach that might address these problems would be to work through referring physicians. This possibility was not explicitly considered in the questionnaire, but Fitzpatrick et al. conclude by suggesting several such measures that might increase patient or physician involvement and help provide up-to-date information to those at risk of carrying or transmitting a hereditary disorder.

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