This Month in the *Journal*

This month we present a series of reviews on ethical issues that have been raised among human geneticists and the lay public. Reilly (p. 682) recounts the historical abuse of subjects by the medical community and the rise of institutional review boards, and he comments on the proposed guidelines for working with indigenous communities that Foster et al. (p. 696) developed in their work with the Apache Nation. Claims of community rights, which Foster and his colleagues presuppose, have been made only recently, and concern for notions such as the right of a group to prevent the study of its genotype is nearly nonexistent in institutional policy. Juengst (p. 673) argues that the appeal to community rights, which might conflict with or even supersede the rights of individuals, should be rejected, because these rights are based on a biologically naive definition of "community." We (Byers and Ashkenas; p. 678) discuss the issues of privacy that surround the publication of pedigrees in research papers. Finally, Knoppers (p. 686) considers the claims, discussed by Mao (p. 688), that the present-day medical policy in China is tantamount to eugenics.

Mutations in Opitz Syndrome, *by Gaudenz et al. (p. 703)*

Midline defects have been identified in many organisms. Opitz syndrome, one of several recognized midline-defect diseases in humans, is associated with mutations in the X-linked *MID1* gene. The MID1 gene product is a RING-finger protein that is believed to interact with multiple partner proteins to form a large complex, probably within the nucleus. In their article, Gaudenz and colleagues describe the genomic structure of *MID1,* and they report six novel mutations that they have identified by SSCP and direct sequence analysis. All but one of the nine published disease alleles in *MID1* affect the C-terminal domain, which is highly conserved among RING/B-box proteins but which has no known function. The authors note that, although they were able to identify mutations in more than a third of the familial cases of Opitz syndrome, only 1 of 18 apparent sporadic cases carried identifiable mutations.

Parental Origin of the Achondroplasia Mutation, *by Wilkin et al. (p. 711)*

G1138 of the growth-factor–receptor gene *FGFR3* may be the most mutable nucleotide in the human genome. This base occurs in a CpG dinucleotide, but its rate of mutation is at least two orders of magnitude greater than the average value for CpG sequences, and it is subject to both transitions and transversions. These two classes of mutation cause an identical amino acid substitution and lead to a common autosomal dominant growth disorder, achondroplasia. Because the risk of sporadic achondroplasia increases with paternal age, the *FGFR3* defect long has been supposed to arise in the male germ line. Wilkin et al. used a set of novel single–base-pair polymorphisms in this gene to determine the phase of the G1138A mutation in a large set of sporadic cases. They report that the mutation occurred on the paternally derived allele in each of 40 informative cases. Because achondroplasia is seldom seen in more than one child of unaffected parents, germ-line mosaicism seems unlikely, and the authors conclude that de novo mutations occur during spermatogenesis but rarely, if ever, during oogenesis.

Deletions in Epidermolysis Bullosa, *by Sakuntabhai et al. (p. 737)*

Blistering diseases can arise from defects in the extracellular-matrix components that link the dermal and epidermal layers of the skin. One such disorder, dystrophic epidermolysis bullosa, results from mutations in the type VII collagen gene, *COL7A1*. As with other collagen defects, severe, dominantly acting mutations would be expected when in-frame deletions or insertions make it impossible for the product of the mutant allele to align with the wild-type chains, during molecular assembly. Sakuntabhai and coworkers now report two such mutations—namely, short genomic deletions that occur within exons and that, surprisingly, cause the affected exon to be skipped. The deletions, which cause in-frame deletions in the mRNA sequence, may act by removing exonic splicing enhancers or by reducing the length of the exons so that they are recognized inefficiently by the splicing machinery. The products of the improperly spliced mRNAs cause procollagen molecules to accumulate within the cell, and they prevent normal deposition of anchoring fibrils below the dermal-epidermal boundary.

Genetic Testing of Young Colon Cancer Patients, *by Farrington et al. (p. 749)*

hMSH2 and *hMLH1* encode two components of the DNA-mismatch–repair system and commonly are mutated in families with hereditary nonpolyposis colorectal

0002-9297/98/6303-0001$02.00

cancer (HNPPC). Indeed, half of all HNPPC probands who fulfill strict criteria for family history of the disease carry a mutation in one of these two genes. Farrington and coworkers suggest, however, that the carrier frequency for mutations may be higher than that indicated by the frequency of such cancer-prone families. The authors screened for mutations in constitutional tissue from individuals who were diagnosed with colorectal cancer at age <30 years. This stringently selected group displayed microsatellite instability at an unusually high rate, compared with that among other colorectal cancer patients, and more than a third of these individuals carry *hMSH2* or *hMLH1* sequence variants that are likely to be pathogenic. Family history proves to be a poor predictor of germ-line mutation status among these individuals.

Mapping Osteosarcoma and Paget Disease, *by Nellissery et al.* (*p. 817*)

Bone fragility and excess resorption, as well as overgrowth of osteoblasts, are hallmarks of both osteosarcoma and, in a milder form, Paget disease of the bone. Paget disease is a common precursor to osteosarcoma, predicting both which individuals in an affected family and which bones in that individual are at risk for development of osteosarcoma. Both Paget disease and a similar autosomal dominant condition, familial expansile osteolysis, have been mapped to 18q. Nellissery et al. propose that osteosarcomas could arise from pagetic tissue by loss of heterozygosity (LOH) at this same locus. In their article, they report multiple independent osteosarcomas that have undergone mitotic recombination leading to LOH in 18q. The minimal region of LOH defined by these somatic events may help restrict the critical region for Paget disease.

LOD-Score Analyses in Complex Disease, *by Greenberg et al.* (*p. 870*)

Greenberg et al. have argued that linkage analysis can proceed even without an accurate model for the mode of transmission of a trait. In an earlier paper, they recommended analyzing the likelihood of linkage, under just two models—one dominant and the other recessive—and accepting the results of whichever model yields the higher LOD scores. They showed that, even when complex models were used to generate simulated family data, analysis based on one or the other of these simple models could reliably detect linkage with only a modest reduction of the peak LOD score, relative to analysis under the true model that had generated the data. These authors now revisit this approach, to consider the loss of statistical power that results from analysis under the simple, rather than the true, model. In general, power loss is <20%, suggesting that simple models might be useful when the mode of inheritance cannot be specified in advance. However, when power is low even for analysis under the true model, the power loss is proportionally greater, and, so, the simplified models may be inadequate to identify linkage. Thus, for a data set in which the effects of a single locus predominate, the additive effects of a minor locus may not be detected consistently, unless the mode of inheritance is known in advance and can be built into the analytic model.

JOHN ASHKENAS
Editorial Fellow