This Month in the *Journal*

Oogenesis and spermatogenesis, fundamental developmental process that make sexual reproduction possible, lie at the heart of genetics. This month we feature three reviews on the molecular genetics of gametogenesis. Bestor (p. 1269) addresses the control of DNA methylase activity and its significance in gametic imprinting. He concludes with a discussion of epigenetic restrictions on developmental potential and the probable difficulty of producing phenotypically similar clones of an adult mammal. Okabe et al. (p. 1274) discuss the stages of spermatogenesis and the various cellular strategies that allow sperm with distinct haploid genomes to be equally efficient at the fertilizing of eggs. They review the various targeted mutations that specifically affect spermatogenesis or sperm activation in the mouse and that thereby lead to male-specific infertility. They discuss both the possible role of similar mutations in human male infertility and the possibility of using the insights from these mutations to devise novel contraceptives. Greenhouse et al. (p. 1282) review oogenesis, focusing on the zona pellucida and the promise of human/mouse chimeric oocytes for the investigation and diagnosis of human infertility.

Mutation in Microsatellites, *by Brinkmann et al.* **(***p. 1408***)**

Instability in numbers of short tandem repeats (STRs) provides the basis for the STR polymorphisms that are seen in all populations. Here, Brinkmann and coworkers address the question of how rapidly new polymorphic variants arise. They have examined >10,000 triads of parents and children from Germany and Austria and have followed the transmission of nine highly polymorphic loci. The overall mutation rate that they observe (0.2/meiosis/locus) agrees with published findings, but Brinkmann et al. also note considerable variation among loci. Alleles with small numbers of uninterrupted repeats are free of mutations, whereas longer repeats are prone to both single-repeat-unit expansions and contractions. A significant majority of such events occur in the paternal germ line, especially in those of older fathers. This last observation agrees with theories of the growing instability of the male genome with increasing age.

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A Possible Predisposing Gene for Prostate Cancer, *by Berthon et al.* **(***p. 1416***);** ***Dominant Inheritance of Prostate Cancer,*** *by Schaid et al.* **(***p. 1425***)**

Two papers this month address the inheritance of prostate cancer, a vexed point in the recent genetic literature. Despite consistent indications that a family history of the disease confers significant risk, both the identification of prostate cancer loci and the rate of phenocopies remain controversial. Here, Schaid et al. revisit the mode of transmission of prostate cancer, using complex segregation analysis on a large cohort of men who have undergone prostatectomy. Schaid et al. report that a genetic model involving a single rare dominantly acting mutation fits their data best. Their model is generally consistent with a previous analysis that used similarly ascertained men. Berthon and colleagues have scanned the genome for prostate cancer loci, starting with a set of 47 families with at least three affected men each. They identify a region on 1q42, considerably distal to the "HPC1" locus on 1q24. Like several other groups, Berthon et al. fail to confirm that 1q24 is associated with the disease. The locus on 1q42 was not identified in earlier linkage studies, but Berthon et al. note that it is deleted in some sporadic prostate tumors, as might be expected of a tumor-suppressor gene.

Hereditary Renal Cancer, *by Bodmer et al.* **(***p. 1475***)**

Bodmer et al. describe a family in which renal-cell carcinoma (RCC) segregates over three generations, along with a balanced 2;3 translocation. The familial form of this cancer is rare, but several putative tumor-suppressor genes have been associated with it, including the von Hippel Lindau (*VHL*) gene on 3p. The authors suggest a modification of the standard two-step model of tumorigenesis, to account for the development of RCC in this family. The initial event, loss of the der(3) chromosome through nondisjunction, is predicted to lead to chromosomal mosaicism; cells lacking this chromosome would then suffer a "second hit" in the form of a random somatic mutation that would initiate tumorigenesis. In support of this model, Bodmer et al. show that *VHL,* which maps to this chromosomal derivative, carries different point mutations in different renal tumors, even in tumors from the same individual.

Meiotic Recombination in Humans, *by Brown et al.* **(***p. 1484***)**

Unlike pericentric inversions, which resolve in meiotic recombination to form unstable chromosomal frag-

ments, paracentric inversions are usually transmitted through families, typically without overt effects. However, such inversions may lead to aneuploidy and fetal loss, suggesting that meiotic recombination is affected by this karyotypic abnormality. Brown et al. have followed patterns of recombination around and within an autosomal paracentric inversion. Single-sperm typing allows them to follow large numbers of meioses from three men, one of whom is a heterozygote who carries such an inversion on 9p. The authors find that male meiotic recombination occurs normally in the distal part of the chromosome (where synapsis initiates) but that it is strongly suppressed in the inversion. The only recombinations observed in this region are found in double recombinants; a second recombination in this short domain would normally be a rare event, but it appears to be favored because it restores the topology of the nonrecombinant chromosome. Brown et al. suggest that the first recombination might create a hot spot for a second such event. Alternatively, singly recombinant chromosomes could be lost at some later stage in spermatogenesis.

X-Chromosome TRD among Males, *by Naumova et al.* **(***p. 1493***)**

Transmission distortion (TRD), the unequal transmission of parental alleles, is well known to occur in mice and has been suggested to occur in human disease as well, at least in isolated families. Naumova et al. now document an unusual form of TRD that acts on X-chromosomal loci, even in families that are free of any known X-linked genetic lesions. In healthy families, they find, an 11-cM region of the maternal grandfather's X chromosome is preferentially inherited by boys, although the maternal grandmother's and maternal grandfather's alleles are equally transmitted to girls. This biased transmission occurs uniformly in the 47-family cohort studied, so it is unlikely to arise from mutations that might be common in a subset of the population; more likely, Naumova et al. indicate, it occurs through some epigenetic effect on the grandmaternal chromosome, which reduces the viability of male embryos. Such an effect might be analogous to gametic imprinting, but, unlike imprinting, the effects of this putative epigenetic modification persist to influence the development of the subsequent generation, instead of being erased by passage through the maternal germ line. Unexplained in this model is the birth, in normal populations, of nearly equal numbers of boys and girls. For more on imprinting and methylation, see reviews (in this issue) by Bestor and by Okabe et al.

Age of CCR5-Δ32, *by Stephens et al.* **(***p. 1507***)**

Stephens et al. have previously identified a number of variant alleles of the *CCR5* gene, whose product is a receptor for inflammatory modulators. The CCR5 protein also serves as a coreceptor for HIV, and it is required for infection of macrophages by this virus. *CCR5* mutations, which confer a significant protection against viral progression in individuals who have been exposed to HIV, are prevalent among long-term survivors of HIV infection. Now, these authors have examined the historical origins of the most common AIDS-resistance allele, Δ32. They find that *CCR5*-Δ32 is widely distributed among northern European populations and is likely to have arisen ~700 years ago. They speculate that this allele might have been under selection because of some influence on a carrier's resistance to other infectious agents; hence the selection that is seen among men at risk for AIDS may recapitulate events in a historical epidemic. Whether cells from Δ32 homozygotes are resistant to bubonic plague or tuberculosis bacteria or other pathogens remains unknown.

Longevity and Antagonistic Pleiotropy, *by Toupance et al.* **(***p. 1525***)**

"Antagonistic pleiotropy" refers to opposing effects of a single genotype on an individual's probability of survival when that probability is considered at different times of life. This notion, derived from evolutionary theory, is not easily accommodated by standard demographic models, which assume that a given genotype contributes to a person's overall "frailty," or susceptibility to dying. Toupance et al. now provide a mathematical analysis that describes the changing genetic composition of a population as it enters extreme old age. By fitting their model to data from the French mortality tables, they demonstrate that antagonistic pleiotropy emerges as a general feature of genetic differences between aged and control adult groups. In particular, their model accounts for the genotype data available for the angiotensin-converting enzyme gene, one allele of which is found commonly among centenarians, despite the fact that it is a known risk factor for heart disease in adult populations. When the best-fitting parameters are assumed, the model also predicts that alleles of a gene that are rare in the general population may come to predominate in a cohort as it ages; this provides a mathematical basis for the hope that specific genotypes may be identified that are associated with increased life span.

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