This Month in the *Journal*

Do our bodies age as iron rusts—passively, with the accumulation of damage due to external insults? Or, are the physiological changes of aging better conceived as an intrinsic developmental process, similar to those of our early histories? Bérubé et al. (p. 1015) review the recent evidence from cell-culture studies in favor of the latter model. As Bérubé et al. demonstrate, cells must continue to express several "mortality factors" if they are to retain their normal capacity to senesce, that is, to stop proliferating after a characteristic number of divisions. The accumulation of senescent cells in various tissues may explain many of the conspicuous features of aging. In a similar vein, Effros (p. 1003) discusses the molecular basis of mortality among T lymphocytes. She argues that we need to develop a measure of "immunological age" if we are to understand the variable loss of immunological competence in the elderly. Schächter (p. 1008) considers the evolutionary biology of aging. He focuses on the surprising physiological features of the very old and on the promise of genetic analysis of this group. Normal homeostatic mechanisms go awry, he suggests, because of the absence of selection for continued vitality among postreproductive individuals.

Sequencing the HNPP Deletion Hot Spot, *by Reiter et al. (p. 1023)*

Reiter and colleagues have previously identified a hot spot for meiotic recombination, on 17p, mapping close to a sequence related to the *mariner* family of insect transposable elements. Although this element is not observed to be mobile within human cells, it may influence the local rate of recombination by acting as a substrate for some endogenous transposase: such an enzyme might create recombinogenic double-strand breaks at this site. The *mariner*-like element occurs within a tandemly repeated element, the CMT1A-REP sequence. Misalignment between the two REP sequences should lead, in reciprocal meiotic recombinants, to a duplication and a deletion. Both of these chromosomal structures occur sporadically, but relatively frequently, in people with congenital neuropathies. Now, Reiter et al. have sequenced through the region of exchange in 28 independent disease chromosomes that carry such deletions. Their data allowed them to identify more precisely the hot spots where recombination is resolved. They report that a 456-bp region of exact sequence identity is the favored region for recombination, which may help define the minimal region of identity needed to allow strand exchange in human germ cells.

Sporadic X-Linked Agammaglobinemia, *by Conley et al. (p. 1034)*

Bruton tyrosine kinase (BTK) is a cytoplasmic molecule that is required for differentiation of B cells. Deficiency for this enzyme, which is usually found in X-linked agammaglobulinemia (XLA), leads to B cytopenia and critically low levels of IgGs. Most cases of XLA occur sporadically or are shared by multiple sons of carrier mothers. Conley and coworkers have studied 101 families with at least one immunodeficient boy with low IgG levels. They report here that the mutations within this group are of diverse origins. Unique *BTK* mutations occur in 83 of the families, and, even among the 10 mutations that were found in more than a single family, haplotype analysis showed that only one represents a shared ancestral allele. Five of the families have normal expression of BTK, and, of these, at least two have no defect in the *BTK* gene but carry autosomal recessive defects in genes that encode immunoglobulin heavy or light chains. Mutations occur throughout the *BTK* gene, including the promoter; no correlation is evident between the type of genetic lesion and the severity of symptoms, although one missense allele that had been studied in a mouse model of X-linked immunodeficiency seems to be associated with mild symptoms in both mouse and man.

A New Common Mutation in the MTHFR Gene, *by van der Put et al. (p. 1044)*

Tetrahydrofolate (THF) derivatives are versatile cofactors in multiple biosynthetic pathways. Deficiency in these cofactors during pregnancy may lead to profound defects in fetal neural tube formation, an outcome that depends not only on maternal nutrition and dietary supplements but also on maternal and fetal genotypes. One polymorphic variant, 677T, in the methylenetetrahydrofolate reductase gene (*MTHFR*) is common in the general population but is particularly prevalent in infants with spina bifida or with other malformations, as well as in the mothers of these children. The MTHFR enzyme, which is required for interconversion of THF derivatives, is destabilized by this mutation, creating a greater need for dietary folate supplements. van der Put and colleagues have now identified another common variant, 1298C. This mutation has a less profound effect on MTHFR activity and on circulating folate levels than

0002-9297/98/6205-0001$02.00

does the 677T allele, but the two lesions, which are not found in *cis* to each other, appear to act additively. The biochemical defect caused by the 1298C allele has not been studied, and it will be important to learn whether this genetic defect is equally as responsive to dietary supplements as is 677T.

Paleolithic Expansion from Southwestern Europe, *by Torroni et al. (p. 1137); and* ***mtDNA Variation in the Ancient Oneota,*** *by Stone and Stoneking (p. 1153)*

Two papers in this issue use mtDNA analysis to address large-scale patterns of human migrations. Stone and Stoneking reconsider the peopling of the Americas, drawing on previously published sequences and on a novel set of pre-Columbian DNAs recovered from a 700-year-old cemetery used by the Oneota people of the Illinois River Valley. They argue that mitochondrial haplogroup distributions in these ancient populations, as well as in modern populations, are so similar to those of Mongolians and some other Asian peoples that they appear to represent a single, divided population. This finding contradicts other analyses that suggest that immigration occurred in several waves of genetically and linguistically distinct groups crossing the Bering Strait to North America. Torroni et al. have used haplogroup analysis to reconstruct human expansion into northern Europe, at the end of the last Ice Age, 10,000–15,000 years ago. They focus, in particular, on two haplogroups: H, which is widely distributed in present-day Europe, and V, which is most variable (and, hence, presumably most ancient) around the Iberian Peninsula. Haplogroup H is believed to be of Near Eastern origin, and the coalescence time of variability in this haplogroup suggests that populations with H haplotypes arose, and may have inhabited Europe, prior to the last Ice Age. People with the V haplotypes arose much later and expanded from Iberia to Finland, where haplogroup V is now most prevalent. This result may seem surprising in light of theories of an Asian origin of the Finns, but it appears consistent with another report in this issue on the origins of this intensively studied population.

Dual Origins of Finns, *by Kittles et al. (p. 1171)*

The origin of the Finns is also the concern of Kittles and colleagues, who follow patrilineal inheritance by analyzing Y chromosome haplotypes. They identify two clusters of haplotypes among 280 Finnish men from throughout the country. On the basis of the geographic distribution of these haplogroups and the calculated coalescence time within each cluster, Kittles et al. indicate that two separate waves of immigrants entered Finland: one, from Asia, settling in the central eastern area and the other, a European group, entering from the south and west and populating the rest of Finland. Archeological evidence—such as differences in styles of architecture and in traditions of toolmaking, between eastern and western Finland—is compatible with this dual-origin model.

Allele Image Patterns from DNA Pools, *by Daniels et al. (p. 1189)*

The pooling of DNA samples from an affected group and from a control group should simplify association studies, provided that pooled samples can be analyzed easily and reliably. Unfortunately, because amplification of VNTR markers is subject to PCR artifacts such as "stutter," quantitative analysis of heterogeneous DNA samples may be ambiguous. Daniels et al. have noted, however, that even from such pools the overall electrophoretic pattern of amplified PCR products is highly reproducible, suggesting that this pattern might be used to detect differences, whether or not the origin of each amplified PCR product is certain. Daniels et al. have developed a metric to describe these differences, the allele image pattern difference (ΔAIP). They show here that they can distinguish the effects on ΔAIP of 10% differences in the proportions of different VNTR alleles. As a further test of the utility of the method, they use DNA from pools of people with hemochromatosis and from an ethnically matched control group. Markers known to be in disequilibrium with that disease locus are evident from their effects on ΔAIP, leading the authors to suggest that this method could provide a means of rapid genomic screening with a minimal number of DNA samples.

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