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Challenging genomic integrity

As one wag at the third *Nature Genetics* annual conference last month* put it, the integrity of the genome — unlike that of the presenters at the meeting — is continually under attack. In many instances, such as during DNA replication, errors can be corrected before they become permanent; but on other occasions, the damage incurred may be missed or simply irreparable, leading to a large number of different cancers or genetic disorders.

In some respects, chromosomal integrity begins at the end with the simple nucleotide repeats at the tips of chromosomes known as telomeres. Moreover, expression of the enzyme which adds these repeats, telomerase, is highly correlated with uncontrolled cell growth. C. Greider (Cold Spring Harbor) reported substantial progress in identifying components of telomerase, both in the form of RNAs from the human and mouse enzymes, as well as the protein component of the *Tetrahymena* enzyme. Constructing telomeres is already a feasible target in the design of mammalian artificial chromosomes, which might one day revolutionize genetic therapy. But as C. Huxley (St. Mary's Hospital, London) explained, solving the structure of the centromere is proving a far more taxing problem. However, our overall understanding of chromosomal architecture is improving rapidly, thanks to the definition of domains such as boundary elements, which restrict the influence of gene enhancers, and the proteins which bind to them (U. Laemmli, Geneva).

Model organisms continue to prove invaluable for studying fundamental properties of DNA repair and chromatin organization. E. Friedberg (U. Texas) illustrated the growing complex of yeast proteins involved in nucleotide excision repair and transcription. Six of these polypeptides constitute TFIIH, part of the transcription machinery, which appears to be recruited to areas of the chromosome in need of repair. Using fluorescence hybridization, D. Ward (Yale) showed that another DNA repair protein, RAD51, forms foci in certain cells in response to radiation damage, probably as a result of some sort of unmasking or redistribution rather than new synthesis.

The typical genomic instability in cancers comes in the form of scores of chromosomal translocations found in various haematologial malignancies and solid tumours. While the cause of many of these rearrangements remains unclear, sometimes the therapies themselves are to blame. For example, in therapy-related acute myeloid leukaemia (M. Le Beau, Chicago) and prostate cancer (J. Trent, Bethesda), chemotherapy can lead to specific translocations or gene amplifications, producing new or recurring tumours. As S. Friend (Charlestown) pointed out, most cancer patients do not respond to chemotherapeutic agents, suggesting that chemotherapy could be tailored to each patient depending on certain factors such as p53 status.

According to B. Vogelstein (Johns Hopkins), some five million people may have mutations in one of the four mismatch repair genes known to

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give rise to hereditary non-polyposis colon cancer. But in rare cases where repair activity is not just reduced but abolished, the patients have surprisingly few tumours, posing the provocative question of whether exogenous mutagens do something else apart from just mutating DNA? Insights into the mechanism of microsatellite instability are more likely to emerge from studies in yeast, however. T. Petes (North Carolina) showed that long, inherently unstable dinucleotide tracts are stabilized either by interruptions in the repeating sequence or an intact mismatch repair system.

Triple play: Perhaps the most 'dynamic' instability in the genome to come to light recently is the expansion of trinucleotide repeats in several neurological and neurodegenerative disorders. G. Sutherland (Adelaide) and others have characterized several chromosomal fragile sites which in a few cases have been associated with trinucleotide expansions, most notably in fragile X syndrome. Indeed, a fragile site on chromosome 11 may even lead to the complete breakage of the tip of the long arm in Jacobsen syndrome. While the mechanism underlying such DNA expansions remains elusive, there has been progress in studying those genes encoding polyglutamine (CAG) repeats involved in neurodegeneration. H. Zoghbi (Baylor College of Medicine) showed that transgenic mice containing the expanded spinocerebellar ataxia type 1 gene exhibit the hallmarks of ataxia after about 6 months — the first report of a triplet repeat phenotype in transgenic mice. But with notable differences in the subcellular neuronal distribution of some of these polyglutamine proteins, J-L Mandel (Strasbourg) suggested that toxicity, rather than a gain-of-function, may be the cause of nerve damage (see *News & Views* on page 3 and related articles in this issue).

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Hereditary diseases (and cancer) can also arise when a retrotransposon such as an L1 element actively copies itself and inserts within a gene such as factor VIII or dystrophin. Using a clever *in vitro* yeast assay, H. Kazazian (Philadelphia) finds that about half of the L1 elements examined so far have innate reverse transcriptase activity. Such transposable elements are most amenable to study in *Drosophila*, where there are about 50 different families (B. Charlesworth, Chicago). The accumulation of such elements may be facilitated by chromosome inversions that shelter the genome from recombination.

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Some clues underlying the extraordinary diversity among minisatellite loci are finally beginning to emerge (A. Jeffreys, Leicester). Some loci, such as MS32, exhibit heterozygosity greater than 99%, with an estimated 100 million or more different alleles worldwide. New mutations are germline-specific and directed to one end of the array, and the rate of mutation correlates dramatically with a single nucleotide change in the flanking sequence. Gene conversion also appears to have a role in determining allelic diversity at the HLA locus (H. Erlich, Roche Molecular Systems), where single sperm analysis has revealed the creation of new alleles. Such variations are of powerful forensic value, whereas polymorphisms at microsatellite loci, especially tri- and tetra-nucleotides, are becoming the standard tool in linkage mapping. J. Weber (Marshfield) believes that genotyping of densely spaced polymorphisms, rather than the disease genes themselves, may prove to be the most effective means of genetic screening.

Correction

In last month's editorial (vol. 9, page 331), the picture showing the two plates of bacterial colonies was inadvertantly reversed; the plate with the dense layer of bacterial colonies from *cftr*-deficient mice should have appeared on the right.