tween closely linked loci (and not distantly linked loci) in populations that have expanded rapidly, if the LD was present at an early stage of the expansion. In mapping disease genes, it is LD due to tight linkage that one wishes to exploit, rather than LD due to genetic drift. Rapidly growing populations, therefore, such as the Finns or the Sardinians, are ideal for this purpose. This is equally true for rare recessive diseases, such as diastrophic dysplaisis in Finland[9], and for common diseases with complex inheritance patterns, such as insulin-dependent diabetes mellitus in Sardinia[10].

It is thus important to emphasize the difference between methods used for quantifying background LD from those that search for LD around a disease locus. In the latter case, individuals affected with a disease phenotype are assumed to have inherited disease susceptibility (and linked marker alleles) that are identical by descent, from one or a few common ancestors (Fig. 1). Factors that affect LD —genetic drift and mutation *versus* linkage—lead to different expectations of haplotype distributions. There is thus no theoretical reason to extrapolate from the results of studies of background LD that rapidly expanding populations will not be useful for mapping genes that contribute to disease susceptibility. Time will tell. □

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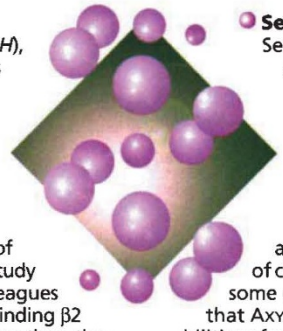
TOUCHING**base**

More on *HFE* mutations

Following the discovery of *HFE* (formerly known as *HLA-H*), the gene responsible for haemochromatosis, the pages of this illustrious organ have lent themselves to some debate regarding the aetiologic and epidemiologic relevance of the putative 'mutation', H63D. Its appearance when associated with the disease is usually in consort with the more prevalent C282Y mutation, and it is only rarely found to be associated with the disorder on its own—at least one family study has failed to detect this mutation at all. The reputation of the C282Y mutation is home and dry, with a functional study published in *J. Biol Sci.* by Randall Schatzman and colleagues demonstrating that the mutant protein is incapable of binding β2 microglobin and fails to appear at the cell surface. Wherefore then, the H63D mutant? The authors could find no aberrant processing there. Nonetheless, a composite analysis by Neil Risch, printed in the correspondence section of this issue, lends firm support to the hypothesis that H63D is a true mutation. Clearly, in comparison with C282Y, its penetrance is much reduced, explaining a more 'sporadic' and less 'familial' pattern—reminiscent of a polygenic paradigm; that sporadic disorders may have genetic contributions from the garden-variety genes responsible for monogenic disease. The way in which the H63D mutation disposes towards haemochromatosis remains to be resolved ... eyes are on the Progenitor group who originally cloned the gene.



The taming of the shrew

The idea of using bacteria in cancer treatment is over 50 years' old, but the findings of some recent experiments—so far only in mice, reported in the 15 October issue of *Cancer Research* (**57**, 4537–4544)—are promising enough to have already been licensed by the pharmaceutical company, Vion. *Salmonella thyphimurium* is not a friendly bug—to either mice or humans. To tame the beast, John Pawelek and colleagues at Yale University used a genetic approach; they put an initially highly virulent *Salmonella* strain through several rounds of mutagenesis and selected for auxotrophic mutants with defects in major biosynthetic pathways, thus rendering the bacteria dependent on their host environment for purines, pyrimidines and amino acids. These mutants, which are much less toxic to the host, congregate at particularly high concentrations in tumours, where actively dividing cells and ongoing necrosis provide a nutritious environment. And hungry *Salmonella* means bad news for tumours: mice harbouring melanomas survive twice as long when inoculated with the auxotrophic bugs. Having achieved reduced virulence with retention of tumour targetting, Pawelek *et al.* used the bugs to deliver therapeutic proteins to the tumour sites; inoculating melanoma-bearing mice with 'transgenic' *Salmonella* expressing the herpes simplex virus thymidine kinase gene led to ganciclovir-mediated suppression of tumour growth. The utility of *Salmonella* as a delivery vector awaits convincing proof, however, and the routine administration of antibiotics to cancer patients receiving radiation therapy also provides a practical obstacle to routine application. For now, *Salmonella* joins the group of 'tamed' pathogens—including HIV—that might be put to good use in cancer and gene therapy.

Sequana plus Arris equals AxyS

Sequana, the Genomics company which describes itself as a "genes-to-lead" company and has interests in finding the genes for a variety of common disorders (asthma, diabetes, osteoporosis, schizophrenia, *et cetera*) has bitten the bullet and sold its stock to Arris, a drug development company, staving off once and for all that pesky stock-share problem, at least in its current incarnation. To house the gene-to-drug process under one roof certainly has advantages, both practical and intellectual, and times of change are times of excitement ... which partly explains some of the more euphoric claims to fame, such as the fact that AxyS is "the first biotechnology company that has capabilities of extending from gene to drug". This elicited some mirth from William Haseltine, who notes that other Genomics companies —Darwin and Mercator, for example—have joined forces with drug companies, and whose maverick endeavours with Human Genome Sciences has launched "dozens if not hundreds of therapeutic discovery products" (without so much as a mention of the words "positional" and "cloning"). His response to gene-finding is a quote from Sophocles: "what availeth knowledge, when knowledge availeth not?". While gene-hunting has yet to pay back, in terms of health, happiness and fortunes, it may yet prove a better investment than the wooden votives bestowed by the ancient Gauls upon the Goddess Sequana. And in the meantime, it keeps some of us in business ...