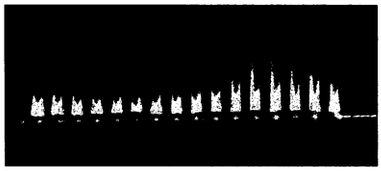
Can this project succeed? The goal of sequencing 5×10^{10} nucleotides can likely be reached, but assembling these raw data is another story. The main problem lies in the presence of regions difficult to sequence—with an increasing load of poor base identification and of the repeat sequences that literally stuff the human genome—that will eventually (and erroneously) associate raw sequences that originate in regions remote from one another. A correcting move would be to sequence both ends of recombinant clones and, at the time of assembly, impose a constraint such that the two sequences are positioned at a given distance calculated from the size of the clones.

These difficulties have not been overlooked by Venter *et al.* Their objective is not to get a perfect human sequence, but to get 99% of the genome sequence in some 5000 fragments—which is adequate for the purpose, namely, the discovery of human genes and their control elements. The strategy is industrial and is intended for economic purposes. In contrast, the motivation of the publicly founded sequencing centers is primarily academic. Only a complete, overall view of the human genome will allow researchers to grasp its complexity, internal consistency, and phylogenic relations.



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Sixteen fast lanes: DNA sequencing

Venter's expertise in the field of sequencing is tremendous. The scientific community should take his proposal seriously and integrate it into the larger strategy. Doubling the financial effort while sticking to present-day technology, as recently advised at a meeting in Warrenton, Virginia ("Sequence, sequence, sequence," ScienceScope, 5 June, p. 1515), would not be enough.

What is really needed is a demarche complementary to that proposed by Venter *et al.* It should be established at the outset is that (i) the number of species for which a sequenced genome is useful is large, (ii) the full significance of a sequence can only be grasped if it can be compared with other sequences, and (iii) a complete sequence of the human genome would be the most useful of all. From these considerations, the following three proposals might appeal to the scientific community and its sponsors.

First, we should strive to analyze complete complementary DNAs. A large number of tags have been described, but complete sequencing of all complementary DNAs is essential. Predicting the location and exon structure of genes from the bare sequence data remains a hard task. Second, we should commit ourselves to finishing up other ongoing efforts to sequence the human genome. Third, we should increase efforts to analyze mouse DNA. Mouse is the model *par excellence* for understanding the significance of the human genome. By comparison with the latter, knowledge of the mouse genome will enable us to spot the genes and their most conserved parts—namely, the exons—and to mutagenize genes at will, to disrupt or simply modify them, and to study their function. Also, knowledge of the mouse genome sequence should facilitate the finishing of the human genome.

Drawing inspiration from the centralized organization of Venter *et al.*, we could combine the energy and competence of many scientists into a decentralized network of laboratories dedicated to performing the sequencing reactions and migrations while bringing back the raw sequences for analysis in a unique information center.

Many in the scientific community are uneasy about the conditions in which the sequences produced by this private consortium are to be released and kept accessible to all. Venter *et al.* advocate collaboration, not confrontation. Their associate, Applied Biosystems of Perkin-Elmer (ABI), is not a pharmaceutical company, but one known for its reagents and sequencing machines. Availability of the mouse and human sequences will provide a fantastic interpretative tool to all, including Venter *et al.* It is my belief that both sound emulation and efficient cooperation can be founded on this ground.

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DRD2 Gene and Alcoholism

The article "New clues to alcoholism risk" by Constance Holden (Research News, 29 May, p. 1348) includes statements attributed to "the COGA [Collaborative Study on The Genetics of Alcoholism] people" with which I disagree. The statement that their study leads to "debunking" the D2 dopamine receptor gene (*DRD2*) as an "alcoholism gene" runs counter to the growing body of evidence implicating this gene not only in alcoholism but in other drug addictions.

A number of studies both in the United States and abroad have ascertained the association of the *DRD2 A1* allele with alcoholism. At least seven independent meta-analyses of ethnically matched (non-Hispanic) Caucasians found the prevalence

(and frequency) of the *A1* allele to be significantly higher in alcoholics than in people serving as controls. The most recent such analysis of about 1000 alcoholics and 1000 controls had a statistical level of significance of $P < 10^{-7}$ (*1*).

DRD2 has also been implicated in the abuse of other drugs [see a review (*2*)] and in nicotine addiction [recently, (*3*)], with about 50% of smokers carrying the *DRD2 A1* allele (*4*). Thus, *DRD2* is not an "alcoholism gene" per se, but is likely a reinforcement or reward gene involved in reactions to a variety of abused substances (*5*).

In any experiment designed to study alcoholism, control subjects should be carefully screened to exclude individuals who use other drugs—and those who show signs of possible alcohol abuse, if not addiction. Otherwise, the inflated A1 allele in the comparative group could obscure significant association with alcoholism in the study group (*6*, *7*). The "unaffecteds" in the COGA study (*8*) did not exclude smokers and other drug abusers, common in families with alcoholics. Furthermore, when alcohol-related problems were examined, only 6% of the "unaffecteds" actually showed no symptoms of alcoholism (*9*). Because of this limited group size, the COGA authors decided to broaden the definition of "unaffecteds" by including subjects with as many as eight (of a total of nine) "sporadic" symptoms of alcoholism. Because three or more symptoms are required for defining alcohol dependence and a minimum of one symptom for that of alcohol abuse, a large majority of these "unaffecteds" could have contained not only smokers and other drug abusers, but also individuals experiencing significant alcohol problems.

Two studies of sibling pairs, one by a British group (*10*) and another by Americans (*11*), found significant linkage of *DRD2* with alcoholism and heavy drinking. In the same journal issue in which the COGA study was published, a quantitative trait loci (QTL) study of mice (*12*) found linkage between the *DRD2* locus and alcohol consumption, replicating two previous QTL studies of animal models of alcoholism. Mutations in *DRD2* also appear to have other measurable behavioral and physiological correlates [see reviews (*1*, *13*)].

In sum, there is strong evidence, derived from association and other types of studies, that the *DRD2* is an important gene in substance use disorders and neural functioning.

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Testing for Alzheimer's

In his article "Allen Roses: From 'street fighter' to corporate insider" (News & Comment, 15 May, p. 1001), Eliot Marshall notes (p. 1004) that Roses disagreed with a group of experts at Stanford who had concluded that widespread