The human genome project: mediocre science, terrible science policy.

Few scientific proposals have been greeted with as much media coverage as the human genome project. This is understandable since humans are a narcissistic species, and the thought of knowing their molecular blueprints in detail might appear exciting to many. Unfortunately, the human genome project (HGP) is not a sound scientific undertaking. Moreover, in a period of severe budget restraint at the National Institutes of Health, it is foolish to invest three billion dollars (or more) to sequence the entire human genome. Below, I briefly discuss five reasons for thinking the HGP is an ill-conceived idea. Despite an abundance of articles on the HGP and ample reference to its critics, the basis for their opposition has not found its way into print. I hope this letter contributes to an increasingly vocal opposition to the project.

The HGP has questionable origins.

This statement may sound like back-fence gossip, but it is meant to convey the fact that the HGP did not arise from a broad consensus that the sequence information was badly needed. Rather the idea seems to have emanated from somewhere at the Department of Energy; most evidence points to the deserts of New Mexico. Formally, the idea was presented by Charles DeLisi (1); a bill to fund the HGP was subsequently introduced by New Mexico Senator Domenici (2). This led to a squabble over which government agency, DOE or NIH, should direct the project. Sadly, the NIH won adding an air of medical legitimacy to the venture. Had DOE prevailed, I believe we would see much more vigorous opposition from the biomedical and biological community. As it is, I believe an overwhelming majority of the latter consider the HGP a bad idea.

The HGP has questionable goals.

The original aim of the HGP was simple enough. Determine the sequence of all the base pairs in the human genome. Never mind that 95% of the DNA doesn't code for proteins and is thought by many, including some of its advocates, to be "junk" (1). The goal has shifted recently to include sequencing of plant, worm, yeast and bacterial genomes as well (3,4). This move, reminiscent of political maneuvers by defense contractors to spread manufacturing among several states, has generated a few more enthusiasts for the project. But as noted above, I believe that most U.S. bioscientists do not support brute force sequencing of genomes.

What is the justification for all of this sequencing? We are told that the resulting information will have great impact on major human diseases. This is a specious argument for several reasons. First, significant advances in understanding the two major diseases in the U.S., heart disease and cancer, were made independent of the HGP. The seminal work of Brown and Goldstein on cholesterol metabolism did not require their knowing the map positions of HMG Co A reductase or the LDL receptor. Likewise, most oncogenes have revealed themselves by their dominant effects, not by sequence analysis of human genomes (5).

Second, even the two stunning successes of the human mapping approach, discovery of the genes responsible for cystic fibrosis and muscular dystrophy, did not require detailed sequence information. To be sure, a reasonable linkage map was needed to identify the CF and MD genes, and I support continued refinement of the human genome map. But a map was available and was being refined in the absence of the HGP. It would be far better to target specific diseases using a better human genetic map than to sequence yards of DNA on the chance that a medically important locus is present.

Third, knowing the map location or amino acid sequence of a mutant gene product does not ensure the development of rational therapies. The amino acid sequence and even the detailed X-ray structure of the RAS product have been known for several years (6). Yet, treatments based on these advances remain to be developed. The recent finding that inhibitors of mevalonate production may block the tumor-promoting actions of RAS may be such an advance (7), but all of these results came without

a human genome sequence! Clearly, structural information is important, but it must be accompanied by insights into the physiology and cellular functions of the various gene products. This requires national support for many scientific approaches, which brings me to the next point.

The HGP is a costly, wasteful and inappropriate allocation of research funds.

Its boosters say that the HGP will cost $200 million per year for 15 years. This three billion dollar total assumes, of course, no delays and no cost overruns. But already we are apprised of delays in the project (8). How do we know it will only take 15 years? And what response could be raised at that time to a claim that "we're only half-finished?" The open-ended nature of the venture is disturbing. The HGP may become the first NIH project to compete with defense's C5A transport as a drain on federal coffers.

Of this projected three billion dollar outlay, Cantor estimates that 20% will be used for computer databases alone (9). Imagine that! Six hundred million dollars to computer-warehouse junk DNA sequences. Apparently, the rest of the money will be disbursed to several sequencing centers, to companies for developing sequencing equipment and perhaps to a few individual labs. The thrust is big science, not small science, so no doubt most of the cash will go to centers and/or industry.

Watson is quoted in Science as saying "Two hundred million dollars is not all that much money" (10). Clearly, that is a matter of opinion. Granted, it is not a lot of money by defense department standards. Perhaps that was Watson's frame of reference since so much about the HGP smacks of defense department mentality. As one of a large number of PI's with a current NIH priority score between 10 and 15%, I can assure Watson that 200 million dollars seems like a lot of money to me. For a struggling young assistant professor facing tenure, it might appear to be all the money in the world. However, the key issue is not one's perception of wealth, but whether $200 million should be disbursed as 1000 RO1 grants, thereby funding laboratories in universities, or as 10 or so block grants to sequencing centers. For me, there is simply no doubt the proper choice is the former.

The HGP will provide little useful training and no intellectual stimulation to young scientists.

Headline in the January 8 issue of The Scientist--"Researchers, discouraged by mapping's drudgery, doubt that a five-year plan to finish high resolution image is now feasible." If mapping is drudgery, what word applies to sequencing? Because the HGP provides so little intellectual excitement for graduate students or post-doctoral fellows, it will be accomplished by technicians. Two hundred million dollars translates into 1,000 RO1s that support a diverse collection of undergrads, graduate students and post-doctoral fellows at various universities. Besides the actual scientific product from these grants, there is a tremendous educational benefit to the nation. By contrast, diversion of the same funds to the HGP will result in armies of technicians skilled only in obtaining DNA sequences and entering the results into data bases. At a time when a scientific career looks bleak enough, it makes no sense to compound the problem of recruiting scientists by restricting university grants. Since the future of U.S. biomedical research depends upon vigorous training programs, it is bad science policy to fund cadres of technicians at the expense of university laboratories.

The HGP is divisive.

The concept of big science versus little science, new to biology, is frankly quite distasteful. The words conjure up big leagues versus little leagues, serious versus trivial, important versus unimportant. True, these terms have long been applied to physics where they apparently do not cause rancor. The same cannot be said of their recent introduction into biology. It has been proposed that big science is bad science (11). The spirited debate that followed on whether big science, defined as 20-30 post-docs per lab, is anywhere near as efficient as the typical smaller research group takes on a whole new dimension when applied to the HGP.

The HGP can be curtailed.

Those in power always promote the idea that you cannot beat city hall. I do not believe that. The demise of Mohole, a similar grandiose, costly and ill-conceived project to drill deep into the earth, proves that bad ideas are not inevitably implemented. If there are enough concerned biologists willing to write letters to key congressmen and administrators, we can curtail the HGP to a more reasonable and useful mapping project. If you agree with the arguments presented, then write Science Advisor Allan Bromley, NIH Acting Director William Raub, Senator Gore or Senator Kennedy and express your reservations, concerns or opposition to the HGP. Their addresses are:

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Senator Ted Kennedy
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In short, the HGP is a waste of national resources and is detrimental to the training of young scientists. I urge you to take the time to voice your opposition--5,000 letters would have a significant impact.

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