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EDITORIAL

Pushing at the Envelope

Before the sound barrier was broken, test pilots taking their experimental planes to the limit would talk about how far they had been able to "poke holes in the envelope." Similarly, the Human Genome Project is stretching the limits of the technology and the limits of our ability to ethically and rationally apply genetic information to our lives. This issue of *Science* features a wall chart and an accompanying article, a policy forum, perspectives, and reports that show different aspects of the progress that has been achieved and the challenges that remain in this endeavor.

The same sense of exhilaration and purpose that characterized the pilots can be seen in the policy forum written by F. Collins and D. Galas, which sets out goals for the Genome Project through 1998. Unequivocally, exciting progress has been made in generating genetic and physical maps and in the identification of disease genes. Included in the new plan is a firm commitment to sequencing the entire genome and an explicit statement of the importance of identifying all of the genes. However, the technology for whole-genome sequencing is not currently in place and development and innovation will be costly. The authors estimate that sequencing alone will require the immediate outlay of $100 million per year if we hope to have a complete human sequence by the year 2005. Further discussion of the ramifications of these goals can be found in the news story by L. Roberts.

Progress in mapping genes in model systems has been a source of gratification for the genome-mapping community. Efforts to map the mouse genome are being propelled by the value of this animal as a model system for human disorders. Significant portions of the mouse genome have been conserved in humans, and the mouse has the added advantages of a short gestation time, the availability of inbred strains, and the ability to control breeding. A major goal is to maximize these advantages in combination with the rapidly growing maps to dissect out complex multifactorial disorders such as diabetes, opiate addiction, and hypertension. A chart at the center of this issue of *Science* represents the integration of two different maps of the mouse genome; one based on simple sequence polymorphisms and the other based on identified genes. Rather than attempting to show all of the genes that have been mapped, the authors have focused specifically on mouse-human homologies, which are also described in the accompanying article by N.G. Copeland and collaborators.

Medical advances that would not have been posssible without knowledge of the genome and imaginative approaches that are being applied to mapping and analysis are exemplified in the reports section this week. The possibility of gene therapy for hemophilia B in humans has been made more likely by the results of M.A. Kay *et al.*, who were able to partially correct Factor IX deficiency in hemophilic dogs by gene transfer into the liver. The ability to visualize restriction endonuclease digestion of DNA fragments as a dynamic process in the light microscope, as shown by D. C. Schwartz and colleagues, may provide an easier way to build maps. Finally, in an advance that outflanks some of the limitations of DNA sequencing, a new approach to protein sequencing is reported by B.T. Chait *et al.* that could be rapid, inexpensive, and useful for directly locating sites of posttranslational modification.

There is a tendency, at least on the part of the uninitiated, to take for granted the ability of our computer systems to incorporate and manipulate data. However, as described by A. J. Cuticchia *et al.*, a fundamental challenge to the Human Genome Project is the provision of "one-stop shopping" to investigators who require the integration of a flood of diverse information. There are scientific and political barriers to providing this kind of user-friendly system.

The concept of trying to break through barriers again comes to mind when one considers C. T. Caskey's perspective on presymptomatic diagnosis and the challenges it poses to a society that has not demonstrated a clear ability to evaluate risks and make reasoned choices. The potential of the "crystal ball" of genetic analysis is enormous and public education should be developed so that there is a better understanding of the power of genetics and the concept of predisposition. The full potential of the technology can certainly not be realized until therapies for the diagnosed genetic disorders are available. In this time of intense discussion of health care reform, Caskey's recommendation for the inclusion of heritable disease care into our national policy deserves serious attention.

Barbara R. Jasny