On the Sequencing of the Human Genome

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Philosophy is the product of wonder... the romance of human thought."

Two papers in the current issue of Hypertension, “Evidence for a Gene Influencing Blood Pressure on Chromosome 17: Genome Scan Linkage Results for Longitudinal Blood Pressure Phenotypes in Subjects from the Framingham Heart Study” by Levy et al and “Possible Locus on Chromosome 18q Influencing Postural Systolic Blood Pressure Changes” by Pankow et al use genomic markers and epidemiological studies to identify candidate loci for involvement in human hypertension. This work is representative of the current state of genetic research into polygenic conditions. Although neither study conclusively identifies a gene that plays a role in hypertension, these studies, in combination with many similar efforts, presage an important new chapter in the investigation and treatment of human disease. Progress in this area will probably come rapidly in large part because of the methodological and technical advances that are now occurring, including those in genome sequencing. Indeed, the successful sequencing of a prototypical human genome was recently announced. Finishing touches, perhaps more laborious than some may think, are now being applied. What are the implications of this achievement? Is it more than simply the next logical step in a process of scientific discovery that began in earnest almost 50 years ago? Is it, as some have implied, as much hype as achievement given the complex nature of polygenic traits?

With increasing frequency over the last half millennium, science has produced theories and results that manifestly changed the way humankind thinks. The discovery of the heliocentric solar system, the development of Newtonian mechanics, the invention of the microscope, the demonstration that species evolve, and the creation of modern physics are examples that readily come to mind. The feat of determining the ordered nucleotides that comprise the human genome is widely recognized to represent a monumental technical achievement in its own right. But, it arguably assumes an almost mythological importance when combined with the full repertoire of molecular biological techniques that have developed over the last 2 decades. That is, the genome project must not be viewed in isolation but rather as an enabling achievement for modern biology. Modern molecular genetics, whether or not directed by the knowledge of specific genomic sequences, has become part of our daily experience. A certain comfort has developed with the many safety, technical, economic, and even philosophical issues that have been spawned by the advent of this new science. The idea that genetically engineered food stuffs should be permitted entry into the human food chain is contentious, dispute rages over stem cell technology and research, and genetic early diagnosis and its’ consequences have raised many questions. Nonetheless, many have argued that if relatively simple rules and algorithms are followed, it is in principle possible to not only use molecular genetics safely but to meld it seamlessly, if not painlessly, into the human condition. Does the sequencing of the human genome change this analysis in any meaningful way and, if so, how?

Life can be viewed as a persistent island of negative entropy. It is at heart information based. Some of this information is contained in the genome, some in the structural organization of the cell and organelles, some in the arrangement of cells, and some in the configuration of the biosphere. There is a great deal of information resident in life. It is perhaps fortuitous that, at this time of the emergence of molecular biology, digital electronic computation, the so-called computer revolution, has also burst on the scene. Computer technology is complementary to biology. In fact, modern computer technology is essential to provide the computational power needed to properly arrange and orient the myriad fragments of human DNA that have been sequenced in the effort to determine the entire code of the human genome. Computer technology is, and will increasingly be, essential to genomic research in which drugs and other interventions are aimed at specific portions of the newly sequenced genome. Because of the success of the human genome sequencing project, as well as other successes in molecular genetics and computer science, the molecular biologist may soon be able to model molecular processes and interventions much as a modern draftsman designs a machine with CAD (computer-aided design) software. Moreover, computer technology is itself evolving to higher levels of complexity (with some evolutionary branches ending in degradation or catastrophe) much as life has evolved. Indeed, this sense of an isomorphism between computer technology and biology is made even more palpable by the use of biological systems to actually perform computations such as solving chess problems.

Thus, a synergy between life science and computer science is rapidly developing, and genomics is one of its first beneficiaries. This will increasingly provide the scientist and physician the opportunity to manipulate the genome and its living hosts in unanticipated ways. This will not be easy. Learning to use the emerging science, either for the creation

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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(Hypertension. 2000;36:469-470.)
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of research models or for medical therapy, will be difficult. But it will happen. Processes such as aging, cancer, cardiovascular disease, and many in-heritable diseases may become amenable to effective therapeutic intervention on the basis of genomic research sooner than many suspect. Crops, animals, and plant life will be manipulated in ways never before considered. Although 15 years ago the cloning of animals was considered science fiction and therapy of the human embryo was deemed far off, the first has already been achieved and few doubt that gene therapy (eventually including embryo and germ line therapy) will soon be technically feasible. Stem cell technology is developing rapidly. It is even possible that genetic intervention to relieve relatively minor cosmetic deviations in individual persons could in time become commonplace—a not very welcome prospect.

At the same time, it is important to understand that as life science becomes more powerful and sophisticated, it increasingly bumps into fundamental limits of the physical sciences; not even the most robust computational technology can prevent this. It is interesting to recall that many of the pioneers of the molecular biological revolution of today, including Watson and Crick, were motivated by the work of Erwin Schrödinger, one of the fathers of the quantum physics revolution. Schrödinger, in his book *What Is Life*, gave a physical face to the gene and predicted, on the basis of his quantum principles and the insights of fellow physicist-turned-biologist Max Delbrück, that the gene must be a code-bearing nonrepeating crystal; a material that was eventually identified as a sequence of double-stranded DNA. But just as physical science is at the heart of the new biology and empowers the new biology, it also imposes certain limits. And not only the uncertainty/complementarity of quantum chemistry will provide a limit to biological intervention. As taught us by Gödel, so too will the uncertainty/unknowability intrinsic in any complex mathematical system limit how truly directed or “designer” any biological intervention can actually be. Biology is ultimately never going to be fully knowable, and this has implications for how we deal with (or chose not to undertake) human germ line therapy, genetic testing, interventions in the thought process, “cosmetic” uses of genetic intervention, and the release of engineered organisms into the environment.

Thus, while the sequencing of the human genome and the genomes of other living things will clearly usher in a new world of opportunity for biological and medical intervention, it also will provide challenges. These will include issues of safety (including potentially adverse effects of germ line intervention on the species), the provision of genetic confidentiality to patients, the free release of engineered animals and plants, and the unexpected outcomes of the interaction of genetically engineered entities. As mentioned above, rational principles including those involved with monitoring the dose of intervention at any given time in any given environment or species could provide a way to begin safely regulating this burgeoning technology. But more will be required. And that is not to say that catastrophes will not, or cannot, happen. It is to say that with prudent oversight they need not happen. But prudent oversight can only be provided by a society that is sufficiently educated in this new technology to provide rational input, control, and restraint. Oversight cannot safely be left solely to technical experts who often are parochial in their outlook. Thus the first challenge posed by the new biology is the need to enhance the biological understanding and sophistication of the public at large, which must, after all, make the final choices. Science is a product of society, and society must responsibly oversee it.

An even bigger issue is how to blend this new technology with the human spirit. At first glance, the new biology appears to be reductionist in the extreme, reducing human beings to a blueprint of 3 billion characters. However, as discussed above, this is far from the case in that the nature of any given human, much less all humans, and their interactions with the environment will never be fully known. The new biology will provide a richer and more complex picture of life, including human life. It arguably will increase, not reduce, the wonder. But it will be important that scientists and laymen alike appreciate the emotional, intellectual, and sociological implications of this new science so that, similar to other formidable technologies of the past, it can be blended productively and stably into the human experience. In short, we will all have to become practicing philosophers to a degree never before required. In the end, that may turn out to be the real lesson of the human genome project.

References


Key Words: Editorials ■ genetics ■ genes