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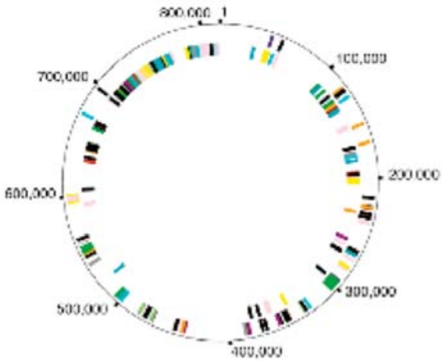
GENETICS:

Ethical Considerations in Synthesizing a Minimal Genome

Mildred K. Cho,* David Magnus, Arthur L. Caplan,* Daniel McGee, and the Ethics of Genomics Group*

The appearance of Dolly, the first cloned mammal made from DNA of an adult cell, set off a flurry of ethical concern about the pace with which cloning technology could be applied to human beings (1-3). Dolly's surprise appearance illustrates the negative consequences of letting ethics and law lag behind scientific advances. Without prior discussion of ethical issues, the general public cannot develop a framework or common language to discuss acceptable uses of a new biomedical technology, or even whether it should be used at all.

Dolly represented a technological progression that was just one in a series of many steps. Singly, these steps may have seemed not to pose any obvious ethical challenges. Indeed, the incremental nature of scientific progress with respect to cloning hindered our ability to recognize that society was about to face an ethical problem. Attention to the direction in which cloning research was headed before Dolly's creation would have better served society than the overreaction that ensued. Cloning is not the only area of scientific research that could merit broad public discussion. Efforts to create a free-living organism with a minimal genome (4-7), such as reported by Hutchison *et al.* on page 2165, provide an opportunity for proactive identification and debate of the associated ethical issues.



A representation of a set of "essential" genes from *M. genitalium* according to Hutchison *et al*. (5) that could represent a step toward creating a minimal genome.

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A minimal genome is generally defined as the smallest set of genes that allows for replication of the organism in a particular environment. The ability to create a new organism with a minimal genome is still a long way off. As with any research, this work will progress in a series of steps that could go in a number of different directions, and that might or might not lead to the intended end points. Some of the intermediate milestones may have more important social, ethical, or commercial implications than others.

To create a novel organism based on a minimal genome, scientists must (i) determine which genes are the minimal set necessary for basic metabolism and replication, (ii) construct this minimal gene set, and (iii) provide or create the necessary nongenetic components for successful gene expression. To achieve step one, some laboratories are developing computer models of the minimal number of biochemical pathways needed for basic metabolic and reproductive functions (8, 9). Others are developing models by comparing the genes of *Mycoplasma genitalium*, which has the smallest known genome of any free-living organism, with the genomes of other bacteria. The assumption is that common genes are important to survival. So far, by this approach, a minimal set of 256 genes has been proposed (4).

Scientists have proposed, and are working on, two different ways of achieving steps two and three. The first, a "top-down" approach, entails removing or inactivating the entire set of genes of *M. genitalium* thought to be unnecessary. The second, and more technically challenging, "bottom-up" approach, entails synthesizing the proposed minimal genome " and inserting it into an environment that allows metabolic activity and replication. The means for synthesizing relatively short pieces of DNA already exists, but assembling the entire genome of an organism and proving that the genome is capable of supporting a free-living life form within that environment has not been done. Recent work by Hutchison *et al*. (5) represents a significant step in the "top-down" approach. These experiments define a "minimal essential set" of genes that, individually, are required for replication under permissive laboratory growth conditions. This minimal essential set does not include redundant genes that are "individually dispensable" (5). Thus, it does not represent a minimal genome, but a subset thereof.

It is important to stress that there is still a large technological gap between what has been achieved to date (defining a portion of a minimal set of genes necessary for an organism to survive under permissive laboratory conditions) and actually "creating life." The latter requires knowledge of what other cellular components (including proteins, lipids, and sugars) are necessary for metabolism and replication, and how to assemble all these components along with DNA. It is not obvious how to achieve this assembly, or even whether we can achieve it. Not all of the issues we raise here apply to current research, but they include concerns about future knowledge and technology that might develop from work being done today.

Applications of a Minimal Genome

Creating a minimal genome would represent an important step forward in genetic engineering as it would permit the creation of organisms (new and existing) simply from knowing the sequence of their genomes. This research may provide insight into the origins of life, bacterial evolution, or the control of bacterial metabolism. In addition, definition of a minimal genome could lead to a better understanding of the genomes of more complex modern organisms.

The first practical benefits might be in microbial engineering. Bacteria are now commonly engineered to produce useful products, ranging from industrial chemicals to insulin. A minimal organism might require less energy or produce fewer waste products that could contaminate the desired product. A minimal organism could be used as the basis for novel "designer" bacteria that are created to perform specific tasks, such as the breakdown of environmental toxins.

The same technology could, however, harm our health or the environment. The development of recombinant DNA techniques in the 1970s raised concern about the introduction of "alien" species into the wild. Initial fears of cancer being spread by bacteria-carrying oncogenes have, fortunately, not been realized. Nevertheless, novel species, however derived or introduced, are still cause for concern because they can wreak ecological havoc. Even small genetic alterations to organisms can have far-reaching, unintended consequences (10). These results point to the need for broader research on potential environmental and health impacts of genetically altered organisms. Although organisms developed from minimal genomes would not necessarily pose more of a risk than organisms engineered by current genetic engineering techniques, this technology could accelerate the pace at which genetically modified organisms are developed.

The building of new organisms also raises intellectual property and commercialization issues that will affect the conduct of research and the ability of both industry and academia to continue developing the technology for public good. The precedent for patents for altered organisms was set by the Chakrabarty case, which ruled that genetically altered organisms were not products of nature and thus were patentable (9). However, it is not clear how far-reaching patents on any newer methods to create genetically altered organisms will be, or how patents on individual genes will be reconciled if many of the genes are used in a newly assembled genome. Current patenting practices may already be restricting development of and access to clinical applications of genomics, as well as academic and industry researchers' access to genetic information and reagents. Large-scale gene identification efforts such as that involved in minimal genome research, as well as other technologies that require use of large numbers of genes simultaneously (such as gene arrays) have great potential to exacerbate these problems. A new regulatory framework for intellectual property pertaining to genes and organisms is needed to ensure that public and commercial interests are protected.

Finally, the combination of large-scale sequencing of human pathogens, determination of function of disease-associated gene products, and development of technologies to assemble large pieces of DNA could lead to creation or release of organisms that could be used as biological weapons. The dangers of knowing the sequences of extremely deadly pathogens could pose threats to public health and safety that might outweigh the benefits. It is disturbing that current regulatory methods provide little if any oversight of these technologies. To ensure responsible use of knowledge that could be applied to the construction of biological weapons, we need to give serious thought to monitoring and regulation at the level of national and international public policy. Should we regulate the science, and if so, at the level of specifying which genomes will be sequenced or at the level of access to the sequence information? Or will we regulate the application of the science?

Defining Life: Realizing Reductionism

The attempt to model and create a minimal genome represents the culmination of a reductionist research agenda about the meaning and origin of life that has spanned the 20th century. Most contemporary scientific discussions of what constitutes being alive focus either on metabolic properties, the ability to respond to the environment, or on the ability to replicate. Those who focus on replication as the key feature of life have seen genes (or their molecular analogs) as the source of both the origin and nature of life. According to this view, genes are what make all living things alive. The search for minimal genomes builds on and refines this idea (7). It attempts to point not just to DNA generally as the stuff that determines an organism's characteristics, but to a specific set of sequences that defines the difference between life and nonlife. (Scientists do acknowledge, however, that there could actually be multiple minimal genomes depending on what the organism is expected to do and under what environmental circumstances the organism is placed).

This approach to understanding life is apparent in the language used to describe minimal genome research (5). In the words of Craig Venter, "What is life? I don't think there are that many biologists trying to answer that one.... We're...working on a reductionist view of trying to take the smallest genome that we have...and see if we can't understand how those...[genes] work together to create life...(11).

There are important concerns raised by a reductionist approach to understanding life. First, a reductionist approach can limit our scientific understanding of living organisms. Focusing on a reductionist approach has had some historical value in helping scientists produce a better understanding of cellular function. Indeed, Fraser *et* *al*. (4), remains one of the most widely cited articles in science over the past several years, because it provides information on some of the crucial functions necessary for cellular function, as well as insight into the evolutionary process. In spite of its usefulness, however, reductionism has also led to erroneous thinking, for example, that viruses were the phylogenetic precursors to cellular life. Similarly, by devoting far greater effort to understanding the role of the nucleus in the functioning of the cell compared with other cellular elements, which have their own causal roles to play, we can bias our understanding of how cells operate (12).

Second, a reductionist understanding of life, especially human life, is not satisfying to those who believe that dimensions of the human experience cannot be explained by an exclusively physiological analysis. What are the ultimate implications of defining life in terms of DNA? Should we allow the definition of life to be treated as a narrow scientific issue, one that assumes that there is nothing in the world that is not physical? Can or should those in the natural sciences decide the meaning of life without input from theologians, philosophers, social scientists, and the general public? There is a serious danger that the identification and synthesis of minimal genomes will be presented by scientists, depicted in the press (13), or perceived by the public as proving that life is reducible to or nothing more than DNA. But life need not be understood solely in terms of what technology permits natural scientists to discover. This may threaten the view that life is special. At least since Aristotle, there has been a tradition that sees life as something more than merely physical. This provides the basis for belief in the interconnectedness of all living things and the sense that living things are, in some important way, more than organized matter (14-16). The special status of living things and the value that we ascribe to life may therefore be undermined by reductionism.

Reducing life to genes has profound implications for several critical societal debates, including what constitutes human life and when life begins. It is important that scientists and the general public understand the implications and limits of the claims being made by the scientific community about minimal genomes in order to participate effectively in the debates. As an example, scientists have suggested application of the minimal genome approach to higher organisms. If we extend the reductionism implicit in minimal genome research to a definition of human life, this has implications for the debate about whether stem cells, early embryos, or hybrid embryos combining human DNA with the cellular components of other species are human. Likewise, a genetic definition of when life begins would have implications for the abortion debate. We would argue that the complex metaphysical issues about the status of human beings cannot be discussed in terms of the presence or absence of a particular set of genes.

Religious Issues

Religious voices and opinions strongly influenced by religious points of view have figured prominently in many recent debates about such topics as cloning, research involving the use of fetal tissues, research on human embryos, and stem-cell research. In the deliberations of our group we presumed that the involvement of religious perspectives in thinking through ethical and social concerns would mean having to wrestle with critical or even hostile perspectives. This was not the case. It is important that the scientific and public policy communities stop placing religion and science in opposite camps when it comes to advances in science.

In part, the supposition that religion will oppose efforts to move the borders of science comes from the prominence of many historical instances where religion and science have been in conflict. Some of the presumption of hostility is a function of the lack of contact and communication between these two communities. It is also a function of which voices speak with the greatest heat and passion, a role that is more fascinating to the media and the public when the voices are raised in opposition rather than endorsement.

We chose to limit our discussion to major Western religions because these religions have commented more than others on issues in bioethics. We found nothing inherent in the major Western religious traditions that requires religion to stand in moral opposition to scientific research. There are powerful components of the major Western religious traditions that see inquiry in science, in general, and research into genomics, in particular, as laudatory and exemplary of human nature and the highest human values. By drawing a broad spectrum of religious voices into the dialog about minimal genomes and synthetic life forms early in the evolution of this work it was very clear that the theological response to work in this area need not be hostile. Indeed there are powerful religious traditions that would maintain that, because of its empowering and ennobling goals, this work is exemplary of the highest human values.

Surprisingly, there has been little inclination within major Western religious communities to devise a definition of life or to describe the essence of life. However, these communities have expressed concerns about the limits of a purely scientific definition of life. Perhaps the most pressing question raised by attempts to identify or create minimal genomes is whether such research constitutes an unwarranted intrusion into matters best left to nature; that is, whether work on minimal genomes constitutes "playing God." This is essentially a debate about the extent to which humans should attempt to understand, control, and use life forms (17). Too often, concern about "playing God" has become a way of forestalling rather than fostering discussion about morally responsible manipulation of life.

Within Judeo-Christian religious communities and Western society, in general, there are polar opposite views on the proper extent of human control or manipulation of ourselves and our environment. On one end of the spectrum are those who take a humble stance that brands all new efforts to understand and manipulate life as hubris. Based on a pessimistic assessment of human nature, they fear that such efforts will inevitably lead to catastrophe. At the other end of the spectrum is the heroic stance based on an optimistic view of humanity that assumes that scientific advances always mean human progress. Another view, based on the concept of humans as stewards, is that humans have remarkable abilities and significant limitations (18, 19). This understanding of human capacities rejects both the passivity of the humble stance, with its tendency to avoid responsibility, and the arrogance of the heroic stance, with its tendency to take any risk if it promises to advance human knowledge. A "good steward" would move forward with caution into genomic research and with insights from value traditions as to the proper purposes and uses of new knowledge.

Although there is vigorous debate in some religious circles about the limits of human initiative in the new life sciences, the dominant view is that while there are reasons for caution, there is nothing in the research agenda for creating a minimal genome that is automatically prohibited by legitimate religious considerations. Moving forward with caution requires that the scientific communities be in continual conversation with the entire society, working together to address key ethical and religious concerns.

Conclusions

Long-established techniques for manipulating DNA are continually being refined, extended, and combined in new ways for new ends (5). The prospect of constructing minimal and new genomes does not violate any fundamental moral precepts or boundaries, but does raise questions that are essential to consider before the technology advances further. How does work on minimal genomes and the creation of new free-living organisms change how we frame ideas of life and our relationship to it? How can the technology be used for the benefit of all, and what can be done in law and social policy to ensure that outcome? The temptation to demonize this fundamental research may be irresistible. However, the scientific community and the public can begin to understand what is at stake if efforts are made now to identify the nature of the science involved and to pinpoint key ethical, religious, and metaphysical questions so that debate can proceed apace with the science. The only reason for ethics to lag behind this line of research is if we choose to allow it to do so.

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M. K. Cho is at the Stanford University Center for Biomedical Ethics, Stanford, CA 94304, USA. M. K. Cho, D. Magnus, and A. L. Caplan are at the University of Pennsylvania Center for Bioethics, Philadelphia, PA 19104, USA. D. McGee is in the Department of Religion, Baylor University, Waco, TX 76798, USA. The Ethics of Genomics Group: Robert Aronowitz, Charles Bosk, A. L. Caplan, M. K. Cho, Mary Lynn Dell, M. Susan Lindee, D. Magnus, D. McGee, Glenn McGee, Jon F. Merz, Michael Orsi, Claire Pouncey, Pamela Sankar, Gerald I. Wolpe, and Paul R. Wolpe.

*To whom correspondence should be addressed. E-mail: micho@leland.stanford.edu and caplan@mail.med.upenn.edu

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