Another member of the president's council, Fukuyama warns, "New procedures and technologies emerging from research laboratories and hospitals ... can as easily be used to 'enhance' the species as to ease or ameliorate illness."[42] What are Fukuyama's remedies? In terms of the embryo, he sides with Kass: "I believe that human embryos ... are not the moral equivalents of infants, nor are they simply clumps of cells like any other tissue that can be discarded at will."[43] He argues for more regulation, but deems the American government unfit to oversee stem cell research. He cites how our present patchwork of regulations lag behind biomedical science's breakneck pace.[44]

TRUTH-TELLING

Among those who believe that hESC research should wait includes an ethicist who charges the real truth about stem cells has gone missing. The hype about cures — used by the media, stem cell supporters, and scientists alike — obscures the very real possibility that any cures of substance will be a long time coming, if they come at all. This is the sentiment of council member Rebecca Dresser. A professor at Washington University School of Law, Dresser maintains "truth-telling" is an overlooked dimension of stem cell ethics. "Scientists must be clear with patients, egg donors, and the public about the stage of this research. We don't know if it will produce treatments and cures," she says. "Research often surprises, and just as doctors should be honest about a poor prognosis or an uncertain outcome, researchers should be honest about all the things that remain to be looked at and tested."[45]

Dresser cites other, ballyhooed, scientific "revolutions" that have yet come to pass. "My skepticism comes from living through so many examples of excitement, including gene therapy and fetal tissue transplants. A lot of this stuff never works, and it takes a lot longer than people think. If it does produce an incremental benefit, it might only extend their lives for a few years." Dresser's statement might run afoul of critically ill patients, their families, and doctors who regard mere months of extra living as precious commodities. Yet looking deeper into the maw of healthcare reform and the best way to distribute scarce resources, her logic — along with Daniel Callahan's — demands a second thought. Why should we spend all this money at the leading edge of science? Wouldn't it be a much better use of resources to devise, for example, a fair and just means of distributing treatments we currently have to patients who need it? Dresser claims she isn't against hESC research per se. "Look, private funds can be used for stem cell research. And other countries permit it," Dresser states. "There are other exciting areas of research that could benefit from federal funding. It seems to me there ought to be a way to use the funding to benefit patients without violating the strongly held moral views of a large group of people in this country."

Along with nine other members of the president's council, Dresser voted in 2002 for a recommendation to place a four-year moratorium on embryonic stem

cell research. At least in some council members' minds, the moratorium was designed to force scientists and supporters to write guidelines and rules to regulate hESC research. As the first anniversary of the PCBB recommendation nears, would Rebecca Dresser vote the same way again? She hesitates for a moment, and says, "Yes."

THE COSTS OF DELAY

"I don't believe for a second that voting repeatedly for a moratorium is any different than an outright ban."[46] This fiery comment comes from Alta Charo, an outspoken and energetic supporter of embryonic stem cell research. Like scientists who make it their business to know the experimental ins and outs of their competitors, Charo, a professor of law and bioethics at the University of Wisconsin, knows and studies the ethical positions of her peers, including the people she disagrees with. No wonder: as a discipline, bioethics is little bigger than even the youthful guild of stem cell biology.[47]

As some philosophers think "retreat" — that science should withdraw to a simpler, more comfortable time — Charo dares to think ahead. To her, the moral priority is the needs of patients, and she's leery of the government — or presidential advisors — slowing things down. She asks, "How do you balance the patient's demands against the government's role to provide safety?" Charo lists diseases where patient advocacy forced regulators to change (AIDS and cancer come to mind), and predicts the same will happen for stem cell research. "People with degenerative diseases will insist that clinical trials begin. Demand will come from parents with kids suffering from juvenile diabetes — nobody fights harder for a kid than a parent. There will be tremendous pressure on the Food and Drug Administration to quickly approve new treatments." She adds that patients and taxpayers alike will want returns on their political and financial investments in states that have passed legislation favoring stem cell research.

Charo's comments reflect the frustration of scientists who claim that politics, not ethics, stand behind pronouncements from the White House and the [2001] executive order prohibiting government funding of new hESC lines. The criticism is that some government advisory bodies — including one with ethics as its focus — are antiscience. The 18-member PCBE originally had only three scientists: now there are two. Elizabeth Blackburn, a professor of biology and physiology at the University of California, San Francisco, was an outspoken opponent of the Bush administration during her rollercoaster tenure on the council. She was removed from the council in 2005. She firmly expresses her dissatisfaction with their deliberations in a paper entitled *Thoughts of a Former Council Member.*[48] "[A] moratorium is used to gain more information.... But that information can only be gained by performing the same research that the moratorium proposes to halt," she writes. Noting that adult stem cell research alone can't answer important questions about disease, she continues, "But one cannot find answers to

questions about oranges by doing all of one's research on apples. Some research on apples will be useful because it will provide information that applies to fruit in general. Diseases, however, are very specific."

Blackburn, like Charo, regards putting science on ice while calling for more regulations as equivalent to maneuvering for an outright ban. "Such regulations may never emerge, allowing opponents ... to accomplish by administrative delay what they have been unable to accomplish by legislation, that is, a *de facto* ban on SCNT."[49] Along with Michael Gazzaniga, Janet Rowley — a geneticist and cancer specialist at the University of Chicago — is one of the two remaining career scientists on the council. She admitted in 2002 that stem cell treatments were largely based on promise. She asserts the reason that evidence was lacking that hESCs could treat Parkinson's and other problems was due to a decades-long government ban on funding embryo research.[50] Without embryos as a source of embryonic stem cell, knowledge is scarce.

Blackburn, Rowley, Charo, Zoloth, and other ethicists, theologians, and patient rights activists remind us that while the government dithers, people suffer. The reality of suffering is very much on Zoloth's mind. "I worked for 20 years as an intensive care unit nurse, and I know what it is to stand beside the body of a broken, sick child and be desperate for ways to heal the baby," she recounts. "Parents who inject their children over and over with insulin, constantly worried they will get it wrong, kids with sickle cell disease; people suffering from suicidal clinical depression — these are *not* trivial matters!" For Zoloth and other ethics scholars who call themselves "justice theorists," what matters is the priority given to certain kinds of medical research, and how best to distribute the discoveries among those who need it. Zoloth insists that medicine that cuts across class boundaries is the best medicine of all. The philosopher lists spinal cord injuries as one problem that plagues developed and undeveloped countries alike, and she applauds the use of stem cell lines to discover drugs for infectious diseases like malaria and tuberculosis, where pathogens make mincemeat of healthy cells.

Can an argument for longer lives with less suffering be reconciled with the contention that science has become a selfish means to a perfect end? Charo says, "Why would you say, 'all enhancements are bad?' " She uses a compelling object lesson. "If you could use genetic engineering to make your offspring resistant to a deadly virus, wouldn't you? Why wouldn't you?" The heated exchange between those who see biotechnology as out of control and those who don't has, according to Charo, stopped the discussion cold. "We need a nuanced, levelheaded approach about which alterations we are willing to accept," she says. The word "nuanced" however, doesn't occur to Arthur Caplan, chair of the Department of Medical Ethics at University of Pennsylvania, when he writes, "Beating up on the pursuit of perfection is silly."[51] We are already creatures of technology, says Caplan, and have been ever since we've been able to probe nature and question our relations to it. There is nothing in our history, he maintains, "that shows why we should not try to improve upon the biological design with which we are endowed. Augmenting breasts or prolonging erections may

be vain and even a waste of scarce resources, but seeking to use our knowledge to enhance our vision, memory, learning skills, immunity, or metabolism is not obviously either."

Both Charo and Zoloth see the human responsibility to repair what nature has left unfinished, or as Charo puts it, "The point isn't that we play God, it's that we play human." To them, the goal is not to seek perfection. The task is — and always has been — an incremental, painful, and slow approach toward a better life. Zoloth says, "Thank God, we no longer die of smallpox, plague, and horrible infectious diseases. We should stop worrying about a tiny proportion of our society that might use new technology incorrectly. People are sick! Will some abuse science and medicine? Yes. They do already. I would rather let a few of those slip by than have hundreds or thousands of sick people not be treated."

GUIDANCE AND OVERSIGHT

Charo bristles at criticisms that hESC research needs to wait for better guidance — she's one of the principal authors of the National Academy of Science's (NAS) 132-page report, *Guidelines for Human Embryonic Stem Cell Research*. "There is no way a moratorium can be lifted if the conditions for lifting it are that hESC research must have 'adequate regulations,'" she says. "All someone has to do is say, 'hESC research is inadequately regulated by government' to stop it. There is nothing easier for the government than *not* to act." The fact is, a government agency instructed *not* to fund new embryonic stem cell research — the National Institutes of Health — wasn't about to act anyway. So the NAS, a congressionally mandated group of expert scientists and engineers advising the government since 1863, did. The authors say the report is "designed specifically to provide comprehensive coverage of hESC research ... a system with both local and national components that meets the important goals identified by the other advisory bodies, including the President's Council on Bioethics in its report on somatic cell nuclear transfer."[52]

Among other things, the report recommends that each research center form an ESCRO (embryonic stem cell review oversight) committee, similar to committees that oversee and approve human clinical trial research. To garner a wide range of opinion, the NAS suggests an ESCRO should include a mixture of scientists, ethics, legal professionals, and members of the public. The committee's job is to ensure the research has scientific merit and that certain ethical guidelines are followed. If a scientist wants to make an embryonic stem cell line by using an embryo made by *in vitro* fertilization or by nuclear transfer, the ESCRO must be satisfied that the donors have given consent to use their cells or embryos for research and that no payments exchange hands between the donors and research centers. The group also is instructed to ask whether existing lines of hESCs can be used, recognizing that embryos shouldn't be destroyed unnecessarily.

Along with these questions, there are guidelines to protect the donors of cells and embryos. Donors should be assured that their confidentiality will be protected and told clearly that embryos will be destroyed during the process. A statement of risk is required, especially for women who donate eggs for research — a chemical

procedure that stimulates the ovaries to produce extra eggs. Egg donation is an overlooked facet of stem cell ethics. Charo and her colleagues also suggest that both male and female donors be given the option of how they want their cells to be used. For example, some donors may feel fine about their embryo being used to make a cell line for research but uncomfortable if the cells are used to make organs or tissues for transplants.[53] If embryos or gametes come by way of infertility treatments, then the decisions to donate must be free of influence by any researcher interested in using them.

Committees that approve experiments on humans or animals, including hazardous procedures using radiation or infectious agents, have been part of research centers and teaching hospitals for decades. The knock on such groups from critics is that researchers are essentially policing themselves — a fox guarding a henhouse is little protection for the chickens inside. This is a conundrum for any "expert review" process, because often the best people to determine whether a project is scientifically, medically, and ethically sound are the experts themselves. Both Francis Fukuyama and Rebecca Dresser favor broadening oversight of hESC research to include greater participation by the public, although Fukuyama recognizes that members of society at large may not be knowledgeable enough about the science to participate meaningfully.[54] For her part, Dresser proposes something more unconventional. Rather than focus on protecting donors and determining the best medical need, she believes the first task should treat embryos as "moral scarce resources." "If we are serious about giving the embryo some respect, then we should have oversight committees that have an interest in treating them as precious," she states. "We call ourselves a deliberative democracy. Let's engage citizens who feel strongly about protecting an embryo. A real review should have teeth, where people who see the world differently can fight it out and argue about what's best." Both sides of the debate agree that citizen participation is necessary; the question remains what kind of public input will be most effective for ESCRO deliberations.

The NAS report contains other recommendations, including ways to create center-by-center stem cell registries and suggests that lines imported from other laboratories, especially those in other countries, are obtained in ways consistent with the ethical guidelines set down by the NAS. Some of the report follows Britain's lead, where embryo politics aren't so fractious. In the United Kingdom, a centralized agency, the Human Fertilisation and Embryology Authority (HFEA) regulates the research by licensing hESC lines to investigators. The NAS suggests a national authority like the HFEA be organized in the United States. Like the HFEA, the NAS guidelines prohibit researchers from keeping embryos alive past fourteen days, when the neural crest appears.

CAN MICE DO CALCULUS?

Time will tell whether the NAS report will take hold. For now, it represents the only attempt at a national set of hESC guidelines. What surprised many was the report contained a section on a controversial dimension of stem cell research: animal-human chimeras. This [type of] chimera results from human stem cells

transplanted into a lab animal. Animals and humans already share cells and tissues. Heart valves from pigs replace human valves damaged by heart disease. We can do experiments on specially engineered strains of mice with a human immune system that would not be permitted on humans. The ethical equations change, however, when transplanting human embryonic or neural stem cells into animals. If a mouse with a functioning brain made entirely of human neurons can be produced, it could be used as an experimental model for Parkinson's, Alzheimer's, or other dementias. New drugs or other treatments could be first tested for their effects on mice before moving on to human clinical trials. How human neurons are damaged by pathogens could be studied in this mouse without risking harm to a human subject.

Trouble is, a mouse with a functioning brain made from human neural stem cells may no longer be a mouse. It could be partly human.

Such a creature would be vastly more mouse than human, experts contend. A mouse's brain is 1/1,000th the size of a human brain and, as a consequence, organized much differently. Neuroscientists claim the differences in "architecture" among animals as the principal reason that mice are not men — or women.[55] Without proof otherwise, experimental animals made with human stem cells could have an altered form of consciousness. This area of neuroscience is still in its infancy, so experiments to make a neural-mouse model will no doubt be closely monitored by ethicists and neuroscientists who wonder what degree of brain complexity is needed to trigger consciousness or even sentience, the ability to feel pleasure and pain.

The NAS guidelines don't prohibit putting human stem cells into an animal brain; but they do stipulate the degree of caution rises as scientists move up the evolutionary ladder. For example, work with primate embryos raises red flags. Putting a human embryonic stem cell into a monkey blastocyst is forbidden because it will integrate and contribute to the development of the primate — resulting in a human-primate chimera. Such an animal may have heightened consciousness, appear human, or have human characteristics embedded in the genes of eggs and sperm, outcomes unnerving to imagine and of deep concern for most people. Certain human-to-human neural stem cell transplants could be quite controversial; fussing with the human brain could positively or negatively affect the way we process sensory information. "We don't know whether we are on thick or thin ice with neural stem cell transplants," Charo warns.

POLICY OR JUST POLITICS?

Ethics isn't limited to street corners, coffee shops, and university corridors. In its most mature form, ethics becomes policy — rules made by society to guide our best attempts to living a good life. More than ever before, positions pounded out by ethicists are being used for political ends, especially in government administrations. The debate has reached every developed country with the capability of biomedical research. What are the consequences of limiting or outlawing

embryonic stem cell research? How does the U.S. compare to other governments facing the same challenges?

The moral divide between philosophers has widened to a chasm between politicians. Our state and federal governments have changed — indeed are now changing — our ability to use embryonic stem cells.

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17

Applications, Benefits, and Risks of Synthetic Biology

PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES

Use of recombinant DNA (rDNA) has become commonplace in many spheres since the techniques of gene-splicing were first developed in the 1970s. Work that at first was done in meticulously isolated laboratories to protect society from unknown risks is now routinely done in high school (and even middle school) biology labs. Entire industries involving such products as genetically engineered foods and medical tests for genetically-linked diseases have grown up around rDNA techniques. What they have in common is that they all start with DNA from existing organisms, take the strands apart, and reassemble them in novel ways. Synthetic biology goes one step further: it involves creating living organisms by assembling DNA from non-living chemical components. This has long been the stuff of science fiction, but it moved closer to reality when, in May 2010, scientists at the J. Craig Venter Institute announced in a paper published in the journal Science *that they had created a self-replicating synthetic genome inside a bacterial cell from non-living chemicals.*

The announcement drew enormous media coverage and stimulated intense discussion of the potential risks and benefits of what many regarded as a step toward the ability to "create life." Reaction from the White House was swift. President Obama called on his recently created Presidential Commission for Study of Bioethical Issues to study, as its first task, the implications of the controversial development and report back within six months. The selection that follows is adapted from Chapter 3 of the Commission's report. It is in written a straightforward — some would say dull — style. But it serves to lay out the basics of synthetic biology and, without going into

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From Presidential Commission for the Study of Bioethical Issues, "Applications, Benefits and Risks of Synthetic Biology," chapter 3 from *New Directions: The Ethics of Synthetic Biology and Emerging Technologies*, December 2010.

great technical detail, describes what its applications might be in several different areas. As such, it is a useful introduction to the subject.

The Presidential Commission for Study of Bioethical Issues is the Obama Administration's version of a White House body that has existed through several administrations to advise on the complex ethical, social, and policy issues raised by developments in modern biology. It consists of 13 members including physicians, lawyers, bioethicists, researchers and patient advocates. It is chaired by Amy Gutmann, President of the University of Pennsylvania, and Christopher H. Browne, Distinguished Professor of Political Science at the University, and supported by a sizable professional staff.

Synthetic biology offers opportunities to apply biological and engineering principles to benefit humankind in unprecedented ways. Clean energy sources, targeted medicines and more efficient vaccine production, new chemicals, environmental cleansers, and hardy crops are some of the potential applications of this burgeoning field of science. While most of the fruits of synthetic biology remain in early stages of development, some applications are expected to come to market within a few years.[1] Success in these research efforts will yield new jobs as novel products and product streams develop. The pace of acceleration of synthetic biology is likely to increase dramatically in the years ahead.

Despite its promise, synthetic biology raises concerns about risks to human health, the environment, and biosecurity. Some of these potential harms include unanticipated adverse human health effects, negative environmental effects (anticipated or unanticipated) from field release and dual-use concerns when research undertaken for "legitimate scientific purpose ... may be misused to pose a biologic threat to public health and/or national security."[2]

This chapter provides an overview of the potential applications, benefits, and risks of synthetic biology. Because renewable energy is expected to yield the first large-scale commercial products of synthetic biology, the Commission discusses this area first. Next, the Commission reviews potential health application and benefits. Many products remain in research and development, but a few are nearing commercialization. Finally, the Commission provides a summary of potential agricultural, environmental, and biosecurity applications of synthetic biology, all of which are in more preliminary stages of development. Within these discussions the potential health, security, and other risks are examined, as well as anticipated technical challenges.

RENEWABLE ENERGY APPLICATIONS OF SYNTHETIC BIOLOGY

In general, biofuels are renewable energy sources derived from biomass, which includes material derived from plants, animals, and organic waste. Several methods can be used to harvest energy from biomass, including burning, chemical treatment, or biodegradation using the metabolic power of microorganisms. Processing

biomass into biofuels or electricity through more complex chemical and biochemical reactions, as opposed to simple combustion, limits environmental impact by minimizing the production of waste and decreasing net greenhouse emissions. Current practices for farming biomass for energy use employ a range of biological sources including grains, grasses, oil seed crops, trees, sugar, and corn.

Ethanol is the most common biofuel worldwide. It is produced mainly from corn or sugar cane. Biodiesel, another currently used biofuel, is made from vegetable oils, animal fats, or recycled restaurant grease. There are challenges to widespread commercial development of either of these fuels. For ethanol production, challenges include inefficiencies and energy costs for production, as well as concerns about the volume of plant sources needed and possible collateral impact on food prices. Biodiesel also involves significant energy costs for production.

Promise and Potential Benefits

Biofuels and related products produced through synthetic biology offer the potential to reduce global dependence on fossil fuel, cut harmful emissions, and minimize economic and political volatility surrounding fossil fuel reserves. Some biofuels produced with synthetic biology processes are expected to be available commercially within the next few years. Other research may not yield commercial products for a decade or more. The various synthetic biology alternatives to current biofuel production methods include producing cellulosic ethanol (derived from cell walls rather than corn) and manufacturing other bioalcohols with synthetically manipulated biomass. Biofuel can also be produced from modified algae that use the natural process of photosynthesis to manufacture bio-oils, such as biodiesel, more easily than current chemical processes.[3]

The biochemical conversion of biomass into energy involves chemical reactions performed by biological systems. Enzymes in microorganisms such as bacteria break down biological materials into their component parts, from which energy can be extracted more easily. Perhaps the simplest example of biochemical conversion is a backyard composting bin, in which microorganisms gradually degrade vegetation in the presence of oxygen. As is apparent from the surge of warm air that emerges upon opening the lid of the bin, this form of bioconversion is an energy-yielding process.

Synthetic biologists aim to improve the speed and efficiency of converting biomass into advanced, second- or third-generation biofuels with cleaner and more favorable energy-usage profiles.[4] This challenge may be met by creating "super-fermenting" yeast and bacteria through synthetic biology. These organisms have the potential to boost the power and potential of current industrially used microorganisms by means of new or altered genes. Synthetic biology also offers new biomass sources, or feedstocks, that are more efficient, reliable, low-cost, and scalable than current sources. These include forest and agriculture residues, some grasses, algae, oilseeds, and potentially sewage.[5]

Aside from biofuels, synthetic biology may also play an important environmental role by harnessing energy in novel, cleaner ways than traditional nonrenewable energy production processes. Large global reserves of hydrocarbons,

such as oil, gas, shale, and oil sands, might be leveraged with synthetic biology tools. Coal bed methane, for example, is a globally available source of natural gas. Its reserves are vast and largely untapped. Synthetic biology research is underway to harvest this methane through microbial digestion and other processes.[6]

BIOALCOHOLS

Unlike ethanol derived from corn or sugar cane, cellulosic ethanol is made from cellulose fibers, a major component in the cell walls of all plants. Processing plant biomass not used for food, for example, waste corn stalks, straws, grass clippings, prairie grasses, and wood chips, could reduce economic and other pressures imposed by relying on corn for ethanol. However, cellulosic ethanol is a relatively low-yield bioalcohol and, like ethanol fuel derived from more conventional chemistries, still tends to corrode storage and transport equipment.

A potentially more promising bioalcohol made by synthetic biology and used for energy production is butanol. Like ethanol, butanol is produced by the fermentation of sugars and starches or through the breakdown of cellulose. The crude product is then refined to make usable fuel. A particular advantage of butanol (and a similar biofuel called isobutanol) is that it can be used directly in a traditional gasoline-powered engine. It also has a relatively high energy density, resulting in better gas mileage than ethanol.[7] Some bacteria have the built-in enzymes to manufacture butanol, but the natural process is not very fast or high-yield. Synthetic biologists have engineered the easy-to-manipulate bacterium *E. coli* to improve this bacterial biochemical reaction to make butanol more industrially useful.[8]

PHOTOSYNTHETIC ALGAE

Another tool for creating biofuels via synthetic biology is through the use of photosynthetic algae. Algae are low-input, high-yield feedstocks that, under experimental conditions, produce substantially more energy per acre than land crops such as corn or soybeans.[9] To create biofuel from algae, the cells are grown, harvested, and treated chemically or thermally to recover the oil content inside algal cells, the so-called "bio-oil." While experimental yields have not yet been duplicated on a commercial scale, an alternative strategy currently under development with synthetic biology is engineering algal cells to secrete oil continuously through their cell walls and thereby increase yield. This time-saving step may support large-scale industrial operations in the near future.[10]

Proponents of farming algae note that it is biodegradable and therefore relatively harmless to the environment if spilled. Algae can also be grown on land and in water that is otherwise unsuitable for crops and food production. Making bio-oils using algae is expected to be less polluting and more efficient than converting vegetable oils or animal fats into biofuel.[11]

Through its capacity to consume carbon dioxide, algae offer the added benefit of mitigating greenhouse gas emissions. Unlike ethanol, algae-derived bio-oils, such as gasoline, diesel, and jet fuels, have been found to have very similar physical and chemical properties in comparison to currently used petroleum-based products, suggesting that these fuels are likely to be compatible with current transportation technologies and infrastructure.

HYDROGEN FUEL

Hydrogen fuel is an additional area of focus for commercial applications of synthetic biology. Hydrogen is a highly desirable fuel source because it is clean-burning, producing water as a by-product. Hydrogen also has the second highest energy density per unit of weight of any known fuel.[12] Several possible routes to generate biohydrogen are under investigation. One method uses engineered *E. coli* as a host organism to produce hydrogen in 62 addition to other biofuels.[13] Engineered algae are also being examined as sources of biohydrogen.[14] Finally, and perhaps most promisingly, researchers are investigating ways to produce high yields of hydrogen using starch and water via a synthetic enzymatic pathway.[15] The latter system is particularly attractive, as it may enable sugar to be converted into hydrogen fuel inside a vehicle itself. This would mitigate the problem of storage that exists today, as hydrogen takes up inordinate amounts of space at regular atmospheric pressure and compression of the gas requires energy and makes storage both difficult and dangerous.[16]

The synthetic processes being explored, if successful, will differ markedly from the current method of producing hydrogen fuel, which involves converting natural gas using steam. Natural gas techniques are costly, inefficient, and heavily reliant on fossil fuels. The synthetic biology-driven process is expected to cost significantly less while providing substantially higher yields, though research remains early in the developmental pipeline.

Risks and Potential Harms

Synthetic biology offers many potential methods to improve energy production and reduce costs, which deservedly generate attention and enthusiasm. A full assessment of these promising activities requires comparable attention to the current limitations, challenges, and anticipated risks or harms. This assessment is particularly important at this time because renewable energy applications may be the first synthetic biology products to come to market. Contamination by accidental or intentional release of organisms developed with synthetic biology is among the principal anticipated risks. Unlike synthetically produced chemicals, which generally have well-defined and predictable qualities, biological organisms may be more difficult to control. Unmanaged release could, in theory, lead to undesired cross-breeding with other organisms, uncontrolled proliferation, crowding out of existing species, and threats to biodiversity.[17]

Consider biofuel production systems that employ synthetic biology and pond grown algae. One hypothetical, worst-case scenario is a newly engineered type of

high-yielding blue-green algae cultivated for biofuel production unintentionally leaking from outdoor ponds and out-competing native algal growth.[18] A durable synthetic biology-derived organism might then spread to natural waterways, where it may thrive, displace other species, and rob the ecosystem of vital nutrients, with negative consequences for the environment.

This scenario is theoretical. Considering it and developing appropriate precautions is nevertheless appropriate because of the rapid development of synthetic biology-generated photosynthetic algae for fuel production and the uncertain nature of the harm that may arise from accidental release. One of the advantages of synthetic biology is that many of the tools being developed include strategies to remediate such risks. Some of the approaches proposed include the engineering of so-called "terminator" genes or "suicide" switches that can be inserted into organisms, precluding them from reproducing or surviving outside of a laboratory or other controlled setting in the absence of unique chemical conditions.[19] Some are clearly sufficient to neutralize the risk of release, and others require further study as synthetic biology progresses.

Another risk in the energy sector is harm to ecosystems from the required dedication of land and other natural resources to production of biomass as feedstock for biofuels. If large areas of land were to be dedicated to biofuel development, this could put new and intense pressures on land, potentially affecting food production, communities, and current ecosystems. Because these applications of synthetic biology are still young, the impact of biofuel production on land use remains unknown. Some argue that efforts to develop and grow additional cellulosic biofuel will dramatically change and adversely impact the way land is used in the United States and abroad.[20] Others suggest that biofuel production can proceed safely with only minor adjustments in current land use practices.[21] Existing biodiverse prairie and meadow grasses may actually enhance the growth of feedstock for second-generation biofuels.[22]

On balance, many anticipate the potential efficiencies and attendant reduction in reliance on fossil fuels offered by energy production using synthetic biology would offset anticipated risks to the environmental ecosystem as it exists today. But considerable uncertainty remains.

HEALTH APPLICATIONS OF SYNTHETIC BIOLOGY

Synthetic biology has the opportunity to advance human health in a variety of ways. Improved production of drugs and vaccines, advanced mechanisms for personalized medicine, and novel, programmable drugs and devices for prevention and healing are among a few of the expected achievements.

Promise and Potential Benefits

There is a long tradition of employing plants and other biological organisms to detect and cure human disease. Genetic engineering technology has been used for more than three decades in medicine to engineer bacteria with the ability to produce commercially relevant molecules like insulin and vaccines for hepatitis B

virus and human papillomavirus.[23] Synthetic biology applications related to health build on this history, but most remain early in the research and development pipeline. The quick pace of biomedical research in general, and synthetic biology research in particular, suggests that this could change soon. This research is being conducted at universities and biotechnology or synthetic biology companies in the United States and overseas.[24]

MEDICINES

Synthetic biologists have refined a chemical technique called metabolic engineering to enhance the production of medicines. Through this process, scientists alter an organism's metabolic pathways — the series of chemical reactions that enable the organism to function at the cellular or organism level — in order to better understand and manage how those pathways work. They can redesign these pathways to produce novel products or augment the production of current products, like drugs. Synthetic biology can also be used to engineer molecules and cells that express proteins or pathways responsible for human disease. At some point these products may be used in efficient, large-scale screening methods to identify novel drugs for disease treatment or prevention.

One well-known example of synthetic biology in medicine is the reengineering of a microorganism to make the antimalarial drug artemisinin more cheaply and efficiently. Malaria affects approximately two to three hundred million people each year and results in between 700,000–1,000,000 deaths, largely among young children in sub-Saharan Africa.[25] Artemisinin is a naturally occurring chemical derived from the plant artemesia, or sweet wormwood. It is an effective malaria treatment, but is difficult to obtain due to limitations on plant yield and high production costs. To address this problem, synthetic biologists at the University of California genetically engineered *E. coli* bacteria to produce a high volume precursor that can be chemically converted to artemisinin.[26] This semi-synthetic artemisinin is being developed today by the pharmaceutical company Sanofi-Aventis in collaboration with the California researchers and the Institute for OneWorld Health. If successful, these efforts should substantially reduce the drug's production cost and increase and stabilize world supply. Full-scale production is expected to begin shortly, with marketing expected in 2012.[27]

VACCINES

Synthetic biology techniques are also being studied and used to accelerate the development of vaccines. Influenza vaccine production is among the key areas of focus. To develop a vaccine, one first needs to identify the virus strain, with its unique genetic code, against which the vaccine will be used. Synthetic biology tools, including rapid, inexpensive DNA sequencing combined with computer modeling, may streamline production time by accelerating this first step.

One industry group is developing a "bank" of synthetically created seed viruses for influenza vaccines that it hopes will enable more rapid vaccine production by reducing virus identification time.[28] DNA-based vaccines created "on-the-spot" to match actual, circulating viral genetic material may be a more efficient process for producing vaccine seed stock in the future.[29] However, these strategies are preliminary and may prove no more efficient or effective than conventional reverse engineering techniques. More research and experience are needed.

ADVANCING BASIC BIOLOGY AND PERSONALIZED MEDICINE

Twenty years ago, cloning, or replicating, a single gene was enormously time consuming. Today, such a task can be done in minutes by a machine, a development that has fueled rapid advances in synthetic biology. The ability to easily manufacture and manipulate DNA in the laboratory has enhanced scientists' productivity and opened new directions for scientific exploration. Researchers see great potential for synthetic biology to advance knowledge of fundamental biological principles. Expanding the DNA "alphabet" beyond its traditional four nucleotides — A, C, G, and T — to include non-naturally occurring nucleotides also gives synthetic biologists more flexibility in studying, detecting, and treating disease. For example, scientists recently used polymerase chain reaction (PCR) with novel nucleotides, a process that increases DNA's information potential and thus enables the manufacture of proteins with new properties.[30] To this end, researchers have already developed diagnostic tests using these DNA nucleotides to screen for human immunodeficiency virus, cystic fibrosis, and other diseases.[31]

In general, personalized medicine aims to apply the science of genomics to develop individually tailored, and thereby more effective, approaches to disease prevention and health care.[32] Synthetic biology offers useful strategies for advancing this goal. Many current cancer treatments focus on non-selective cell killing or on delivery to specific tissues. A growing body of knowledge supporting a molecular classification of tumors may facilitate the development of specifically designed detection devices matched to individual tumors. A synthetic biology approach currently under study is a cancer treatment that focuses on up to six cellular identifiers rather than one, effectively enabling the treatment to be targeted more carefully and precisely toward the cells intended to be killed, while sparing healthy ones.[33]

Custom protein and biological circuit design may eventually enable the delivery of "smart proteins" or programmed cells that self-assemble at disease sites. Similarly, synthetic organisms could be developed to create a trigger to deliver or withhold treatment depending upon a local disease environment (such as low levels of oxygen) and provide targeted killing of cancer cells.[34] These and other novel approaches to tailored disease treatment may substantially improve outcomes and reduce the costs and burden of disease across the

population. While the benefits of synthetic biology to health care may prove monumental, significant hurdles remain. With the exception of semi-synthetic artemisinin and potential, near-term improvements in vaccine design, most of the anticipated health benefits of synthetic biology remain in the preliminary research stage. We are unlikely to see commercial applications from much of the biomedically oriented synthetic biology research for many years, although the pace of discovery is unpredictable.

Risks and Potential Harms

In addition to practical challenges, biomedical applications of synthetic biology raise potential risks for humans and the environment that are, in part, similar to those identified in the biofuels discussion and those commonly understood within the biomedical or greater engineering research communities today. Human health risks may arise from adverse effects of intentional or inadvertent release of the organisms engineered using synthetic biology. Infectious diseases may be transmitted to laboratory workers after needle sticks or to family members following airborne transmission of disease agents manipulated using synthetic biology techniques. Risks may also accrue to the wider human community or the environment if organisms proliferate without adequate means to limit reproduction.

Similarly, novel organisms developed with synthetic biology to treat illness may trigger unanticipated adverse effects in patients. The use of cell therapies of bacterial, or potentially, mixed microbial origin may cause infections or unexpected immune responses. New organisms developed with the emerging technology of synthetic biology may pose unusual, if not unprecedented, risks resulting from their potential as biological organisms to reproduce or evolve.

Many of these risks are qualitatively similar to the risks that arise in horticultural biomedical and biotechnology research. There are well-established mechanisms in place to identify and manage future risks. Additionally, as with energy applications, internal mechanisms to reliably contain function and reduce or eliminate these risks are being developed. "Biological isolation," which is also termed "biosafety engineering," aims to build in molecular "brakes" or "seatbelts" that restrain growth or replication of partially or fully synthetic organisms.[35] Synthetic organisms can be engineered to be contained physically or temporally. Additional data are needed to assess how well biologically engineered safeguards, such as "kill switches" that activate after a defined number of generations, will work.

AGRICULTURAL, FOOD, AND ENVIRONMENTAL APPLICATIONS OF SYNTHETIC BIOLOGY

Synthetic biology may also help to shift, if not substantially mitigate, some of the existing threats to our global food supply and environmental health. These potential benefits are in some ways more preliminary than the expectations for energy and health, but research and development in these fields are well underway.

Promise and Potential Benefits

In agriculture, efforts to manipulate crops and breed animals for specific purposes are not new. Many traditional farming practices, from plant breeding to animal husbandry, aim to direct evolution to achieve desired outcomes. Use of recombinant DNA technology, cloning, and other biotechnology tools have enhanced these practices. Taking these activities one step further, synthetic biologists are experimenting with high-yield and disease-resistant plant feedstocks that can be supplemented with efficient and environmentally friendly microorganisms to minimize water use and replace chemical fertilizers.[36] Researchers are altering the properties of plants through methods that combine metabolic components from various organisms in order to gain nutritional benefits, such as higher levels of food-grade protein.[37]

Efforts to remove waste using biological means date to at least 1972, when a researcher at General Electric applied for a patent on a form of *Pseudomonas* bacteria genetically engineered to digest oil slicks.[38] Environmental applications of synthetic biology are generally targeted to pollution control and ecological protection. The impact of naturally occurring oil-devouring microorganisms at the site of the 2010 oil spill off the U.S. Gulf Coast, for example, demonstrated how these organisms could reduce some types of pollution.[39] Synthetic biologists are eager to understand and direct these biological capabilities, or even enhance them, to respond to existing and future waste generated by human activities.

Other environmentally relevant examples of synthetic biology applications include laboratory-constructed microbial consortia, known as synthetic biofilms, which are being developed for use as environmental biosensors. These sensors could be used, for example, to monitor soil for nutrient quality or signs of environmental degradation. The design of biological "wetting agents," or biosurfactants, could increase the efficiency of bioremediation efforts and minimize the extent of damage from pollutants.[40] Biosurfactants are naturally produced by bacteria, yeasts, or fungi and are environmentally friendly in freshwater, marine, and terrestrial ecosystems. Synthetic biology may offer the ability to enhance the features of microbially produced biosurfactants to tailor them to specific spills or otherwise polluted areas.

Risks and Potential Harms

Synthetic biology applications in the context of agriculture, food, and the environment raise concerns broadly similar to those raised about genetic engineering in the past and those discussed above with respect to safety, resource management, and biodiversity. In brief, these risks include harms to humans, plants, or animals from, for example:[41]

- uncontrolled environmental escape or release and attendant disruption to ecosystems,
- new or sturdier pests — animal or plant — that may be difficult to control, and
- increased pesticide resistance and growth of invasive species.

As in the discussion of energy and health applications, the risks may be assessed and managed through existing protections long in use for biomedical and greater engineering research. Synthetic biology applications in the context of agriculture, food, and the environment may require more targeted efforts, however, including use of inbred checks, such as "suicide genes" or "kill switches" to ensure that they cannot propagate unintentionally.

Many potential applications of synthetic biology go well beyond the genetic engineering practiced throughout the biotechnology industry today. In the future, the field may be capable of creating entirely new organisms and systems previously unseen in the world today. Synthetic biology's critics and proponents alike worry that creating new organisms that have uncertain or unpredictable functions, interactions, and properties could affect ecosystems and other species in unknown and adverse ways. The associated risks of escape and contamination may be extremely difficult to assess in advance, as such novel entities may have neither an evolutionary nor an ecological history.[42]

Countering these concerns, at least somewhat, is experience showing that synthetic cells and systems in research settings have tended to be short-lived by comparison to those that have evolved in nature. Scientists have observed that synthetic organisms allowed to develop in the laboratory have consistently evolved toward nonfunctionality.[43] These are encouraging preliminary findings, but they do not eliminate the need for precautions in the event that a future synthetic organism behaves differently than expected outside of the contained laboratory setting.

Another concern related to synthetic biology's impact on natural systems — crops grown for either biofuel or food consumption — is the broader effect on how society views and protects biodiversity. Does a chemically synthesized organism increase or decrease biodiversity, as measured by traditional taxonomy-based classification schemes? This concept becomes important in policy discussions pertaining to the use and potential abuse of land and other natural resources.

BIOSECURITY

Generally, the term "biosecurity" refers to the efforts needed to prevent misuse or mishandling of biological agents and organisms with the intent to do harm. The National Science Advisory Board for Biosecurity (NSABB), an independent federal advisory committee charged with advising the U.S. government on biosecurity issues and "dual use" research — that which may be used for either good or ill — defines the term as follows: "[b]iosecurity refers to the protection, control of, and accountability for high-consequence biological agents and toxins, and critical relevant biological materials and information, to prevent unauthorized possession, loss, theft, misuse, diversion, or intentional release."[44]

Unlike applications and potential applications of synthetic biology in the energy, health, agricultural, and environmental sectors, possible benefits in the biosecurity arena have not garnered significant public attention. Nor have they received comparable investment from academia, industry, or the government. It is nonetheless easy to anticipate some potential benefits.

Synthetic biology may enhance biosecurity by enabling researchers to identify biological agents of concern that may be developed synthetically or semisynthetically. In the same way that the J. Craig Venter Institute "branded" the bacterium it synthesized this year with traceable information in the organism's genetic code, researchers may uniquely tag the genetic code of new organisms that they develop. When combined with other measures to ensure biosecurity, this tagging process may provide an additional and effective deterrent to malicious use.

Similarly, biosecurity may be improved using the techniques discussed above for applications in energy, human health, agriculture, and the environment. As noted, "suicide" genes or terminator technologies built into the genome of a new organism to inhibit growth or survival outside of a contained environment may offer particularly effective means to counter biosecurity threats. Related tools could be crafted to ensure organism death in the face of particular chemicals or contexts. Uncertainties remain, however, with regard to the effectiveness of such strategies.

Concerns about dual use or intentional misuse of synthetic biology to do harm are among the most prominent critiques of this emerging technology. One of the most widely voiced risks attributed to synthetic biology is that it may be used, in the wrong hands, to intentionally create harmful organisms for bioterrorism. Recent examples of virus reconstruction using traditional recombinant DNA techniques fuel these concerns. These examples include the laboratory creation of infectious polio virus, the mycoplasma genome, and the 1918 strain of influenza virus.[45]

Frequently lost in these discussions about synthetic biology risks is recognition that DNA alone is not sufficient to create an independently functioning biological entity, such as a disease-causing virus that could spread. Despite the relative ease of access to known DNA sequences through public databases like GenBank[46] (an annotated collection of all publicly available genetic sequences), and equivalent databases across the globe, most experts in the scientific community agree that mere knowledge of a viral genome is far from sufficient to be able to re-constitute it or create a disease-forming pathogen. Rather, one must have an appropriate host and conditions for a virus to grow. Few individuals or groups today have the financial means or the technical skills to accomplish such ends, even when scientifically feasible. As the many technical challenges in synthetic biology affirm, it is not yet possible to craft functioning biological organisms from synthesized genomic material alone.

Risks and Potential Harms

With regard to biosecurity risks arising from synthetic biology, NSABB has twice issued reports and made recommendations to the federal government — first in 2006 and again in 2010.[47] In 2006, the group focused on synthesis of select agents and toxins, which are defined in law as certain infectious components of identified "select agent viruses," meaning those that the U.S. government has found to pose a severe threat to human health.[48] Following a review of the science at that time, the group made specific recommendations to reduce biosecurity risks, many of which the United States has since implemented, such as the establishment of a screening infrastructure for genetic sequence providers and others.[49]

NSABB's report "Addressing Biosafety Concerns Related to Synthetic Biology," issued in April 2010, offered four specific recommendations to ensure biosecurity in the current field of synthetic biology:

- Synthetic biology should be subject to institutional review and oversight since some aspects of this field pose biosecurity risks.
- Oversight of dual use research should extend beyond the boundaries of life sciences and academia.
- Outreach and education strategies should be developed that address dual use research issues and engage the research communities that are most likely to undertake work under the umbrella of synthetic biology.
- The U.S. government should include advances in synthetic biology and understanding of virulence/pathogenicity in efforts to monitor new scientific findings and technologies.

These recommendations reflect an attempt to balance the considerable potential benefits of synthetic biology with the risks resulting from intentional or unintentional misuse of this technology and its products. Noticeably absent were recommendations to restrict access to genetic sequences separate from those components of Select Agents and toxins already limited by the U.S. Select Agent regulations. In large part, this determination appears to reflect the fact, as noted, that sequences alone will not yield, nor often be sufficient to predict, functions.

NSABB's work is not unique. Many experts and interested groups in the United States and abroad have recently devoted considerable time and energy to evaluating the biosecurity risks of advancing synthetic biology practices.[50] This still-young field benefits from a clear consensus among scientists and policy-makers that biosecurity risks, while perhaps overstated by some, nevertheless are serious and warrant ongoing and proactive re-examination as technical capacity evolves. The tools used to mitigate these risks may also be the tools to mitigate environmental, health, and other potential risks. The tools to address risk depend on an expanding scientific knowledge base as much as potential benefits do.

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Five Hard Truths for Synthetic Biology

ROBERTA KWOK

The Presidential Commission report is generally optimistic about the future of synthetic biology. Although the report contains plenty of cautions about the risks and possible harms of the technology, it focuses mainly on the applications and benefits. It also describes developments that are likely to come to fruition in the relatively near future. Roberta Kwok is more skeptical. In the article that follows, which appeared in Nature *a few months before the J. Craig Venter Institute's announcement and nearly a year before the publication of the Presidential Commission's report, she looks at some of the challenges that will need to be overcome if the promise of synthetic biology is to be realized. These challenges "loom at every step in the process," she writes. Concerned with the prospects for scaling up from the laboratory to industrial applications, she quotes a researcher who warns, "There's a lot of biology that gets in the way of the engineering." Nevertheless, Kwok looks for — and finds — ways to overcome these challenges.*

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Roberta Kwok, "Five Hard Truths for Synthetic Biology," *Nature* (Vol. 263), 21 January 2010, pp. 288–290. Reprinted by permission of the author.

To read some accounts of synthetic biology, the ability to manipulate life seems restricted only by the imagination. Researchers might soon program cells to produce vast quantities of biofuel from renewable sources, or to sense the presence of toxins, or to release precise quantities of insulin as a body needs it — all visions inspired by the idea that biologists can extend genetic engineering to be more like the engineering of any hardware. The formula: characterize the genetic sequences that perform needed functions, the 'parts', combine the parts into devices to achieve more complex functions, then insert the devices into cells. As all life is based on roughly the same genetic code, synthetic biology could provide a toolbox of reusable genetic components — biological versions of transistors and switches — to be plugged into circuits at will.

Such analogies don't capture the daunting knowledge gap when it comes to how life works, however. "There are very few molecular operations that you understand in the way that you understand a wrench or a screwdriver or a transistor," says Rob Carlson, a principal at the engineering, consulting and design company Biodesic in Seattle, Washington. And the difficulties multiply as the networks get larger, limiting the ability to design more complex systems. A 2009 review[1] showed that although the number of published synthetic biological circuits has risen over the past few years, the complexity of those circuits — or the number of regulatory parts they use — has begun to flatten out.

Challenges loom at every step in the process, from the characterization of parts to the design and construction of systems. "There's a lot of biology that gets in the way of the engineering," says Christina Agapakis, a graduate student doing synthetic-biology research at Harvard Medical School in Boston, Massachusetts. But difficult biology is not enough to deter the field's practitioners, who are already addressing the five key challenges.

1. Many of the Parts Are Undefined

A biological part can be anything from a DNA sequence that encodes a specific protein to a promoter, a sequence that facilitates the expression of a gene. The problem is that many parts have not been characterized well. They haven't always been tested to show what they do, and even when they have, their performance can change with different cell types or under different laboratory conditions.

The Registry of Standard Biological Parts, which is housed at the Massachusetts Institute of Technology in Cambridge, for example, has more than 5,000 parts available to order, but does not guarantee their quality, says director Randy Rettberg. Most have been sent in by undergraduates participating in the International Genetically Engineered Machine (iGEM) competition, an annual event that started in 2004. In it, students use parts from a 'kit' or develop new ones to design a synthetic biological system. But many competitors do not have the time to characterize the parts thoroughly.

While trying to optimize lactose fermentation in microbes, an iGEM team from the University of Pavia in Italy tested several promoters from the registry by placing them in *Escherichia coli*, a standard laboratory bacterium. Most of the promoters tested by the team worked, but some had little documentation, and one

showed no activity. About 1,500 registry parts have been confirmed as working by someone other than the person who deposited them and 50 have reportedly failed, says Rettberg. 'Issues' have been reported for roughly another 200 parts, and it is unclear how many of the remaining parts have been tested.

The registry has been stepping up efforts to improve the quality by curating the collection, encouraging contributors to include documentation on part function and performance, and sequencing the DNA of samples of parts to make sure they match their descriptions, says Rettberg. Meanwhile, synthetic biologists Adam Arkin and Jay Keasling at the University of California, Berkeley, and Drew Endy at Stanford University in Stanford, California are launching a new effort, tentatively called BIOFAB, to professionally develop and characterize new and existing parts. Late last year, the team was awarded US$1.4 million by the National Science Foundation and is hiring staff, says Arkin. Endy, moreover, has proposed methods to reduce some of the variability in measurements from different labs. By measuring promoter activity relative to a reference promoter, rather than looking at absolute activity, Endy's team found that it could eliminate half the variation arising from experimental conditions and instruments.[2]

Measurements are tricky to standardize, however. In mammalian cells, for example, genes introduced into a cell integrate unpredictably into the cell's genome, and neighboring regions often affect expression, says Martin Fussenegger, a synthetic biologist at the Swiss Federal Institute of Technology (ETH) Zurich. "This is the type of complexity that is very difficult to capture by standardized characterization," he says.

2. The Circuitry Is Unpredictable

Even if the function of each part is known, the parts may not work as expected when put together, says Keasling. Synthetic biologists are often caught in a laborious process of trial-and-error, unlike the more predictable design procedures found in other modern engineering disciplines.

"We are still like the Wright Brothers, putting pieces of wood and paper together," says Luis Serrano, a systems biologist at the Centre for Genomic Regulation in Barcelona, Spain. "You fly one thing and it crashes. You try another thing and maybe it flies a bit better."

Bioengineer Jim Collins and his colleagues at Boston University in Massachusetts crashed a lot when implementing a system called a toggle switch in yeast. His lab built one roughly ten years ago in *E. coli*[3]: the team wanted to make cells express one gene — call it gene A — and then prompt them with a chemical signal to turn off A and express another gene, B. But the cells refused to express B continuously; they always shifted back to expressing A. The problem, says Collins, was that the promoters controlling the two genes were not balanced, so A overpowered B. It took about three years of tweaking the system to make it work, he says.

Computer modelling could help reduce this guesswork. In a 2009 study,[4] Collins and his colleagues created several slightly different versions of two promoters. They used one version of each to create a genetic timer, a system that would cause cells to switch from expressing one gene to another after a certain

lag time. They then tested the timer, fed the results back into a computational model and predicted how timers built from other versions would behave. Using such modeling techniques, researchers could optimize computationally rather than test every version of a network, says Collins.

But designs might not have to work perfectly: imperfect ones can be refined using a process called directed evolution, says Frances Arnold, a chemical engineer at the California Institute of Technology in Pasadena. Directed evolution involves mutating DNA sequences, screening their performance, selecting the best candidates and repeating the process until the system is optimized. Arnold's lab, for instance, is using the technique to evolve enzymes involved in biofuel production.

3. The Complexity Is Unwieldy

As circuits get larger, the process of constructing and testing them becomes more daunting. A system developed by Keasling's team,[5] which uses about a dozen genes to produce a precursor of the antimalarial compound artemisinin in microbes, is perhaps the field's most cited success story. Keasling estimates that it has taken roughly 150 person-years of work including uncovering genes involved in the pathway and developing or refining parts to control their expression. For example, the researchers had to test many part variants before they found a configuration that sufficiently increased production of an enzyme needed to consume a toxic intermediate molecule.

"People don't even think about tackling those projects because it takes too much time and money," says Reshma Shetty, co-founder of the start-up firm Ginkgo BioWorks in Boston, Massachusetts. To relieve similar bottlenecks, Ginkgo is developing an automated process to combine genetic parts. The parts have pre-defined flanking sequences, dictated by a set of rules called the BioBrick standard, and can be assembled by robots.

At Berkeley, synthetic biologist J. Christopher Anderson and his colleagues are developing a system that lets bacteria do the work. Engineered *E. coli* cells, called 'assembler' cells, are being equipped with enzymes that can cut and stitch together DNA parts. Other *E. coli* cells, engineered to act as "selection" cells, will sort out the completed products from the leftover parts. The team plans to use virus-like particles called phagemids to ferry the DNA from the assembler to the selection cells. Anderson says that the system could shorten the time needed for one BioBrick assembly stage from two days to three hours.

4. Many Parts Are Incompatible

Once constructed and placed into cells, synthetic genetic circuits can have unintended effects on their host. Chris Voigt, a synthetic biologist at the University of California, San Francisco, ran into this problem while he was a postdoc at Berkeley in 2003. Voigt had assembled genetic parts, mainly from the bacterium *Bacillus subtilis*, into a switch system that was supposed to turn on expression of certain genes in response to a chemical stimulus. He wanted to study the system

independently of *B. subtilis'* other genetic networks, so he put the circuit into *E. coli* — but it didn't work.

"You looked under the microscope and the cells were sick," says Voigt. "One day it would do one thing, and another day it would do another thing." He eventually saw in the literature that one of the circuit's parts dramatically disrupted *E. coli*'s natural gene expression. "There was nothing wrong with the design of the circuit," he says. "It was just that one part was not compatible."

Synthetic biologist Lingchong You at Duke University in Durham, North Carolina, and his colleagues found that even a simple circuit, comprising a foreign gene that promoted its own expression, could trigger complex behavior in host cells.[6] When activated in *E. coli*, the circuit slowed down the cells' growth, which in turn slowed dilution of the gene's protein product. This led to a phenomenon called bistability: some cells expressed the gene, whereas others did not.

To lessen unexpected interactions, researchers are developing 'orthogonal' systems that operate independently of the cell's natural machinery. Synthetic biologist Jason Chin of the Medical Research Council Laboratory of Molecular Biology in Cambridge, UK, and his colleagues have created a protein-production system in *E. coli* that is separate from the cell's built-in system.[7] To transcribe DNA into RNA, the team uses a polymerase enzyme that recognizes genes only if they have a specific promoter sequence that is not present in the cell's natural genes. Similarly, the system's orthogonal 'O-ribosomes', which translate RNA into protein, can read only 'O-mRNA' that contains a specific sequence, and O-mRNA is unreadable by natural ribosomes.

A parallel system gives biologists the freedom to tweak components without disrupting the machinery needed for the cell to survive, says Chin. For example, his team has stripped down the DNA sequence encoding part of the O-ribosome to speed up production. This allows the cell to boot up protein manufacture more quickly, he says.

Another solution is to physically isolate the synthetic network from the rest of the cell. Wendell Lim, a synthetic biologist at the University of California, San Francisco, is experimenting with the creation of membrane-bound compartments that would insulate the genetic circuits. Lim's team is working in yeast, but similar principles could be applied to bacterial cells, he says.

5. Variability Crashes the System

Synthetic biologists must also ensure that circuits function reliably. Molecular activities inside cells are prone to random fluctuations, or noise. Variation in growth conditions can also affect behavior. And over the long term, randomly arising genetic mutations can kill a circuit's function altogether.

Michael Elowitz, a synthetic biologist at the California Institute of Technology in Pasadena, observed the cell's capacity for randomness about ten years ago when his team built a genetic oscillator.[8] The system contained three genes whose interactions caused the production of a fluorescent protein to go up and down, making cells blink on and off. However, not all cells responded the same way. Some were

brighter, and some were dimmer; some blinked faster, others slower; and some cells skipped a cycle altogether.

Elowitz says that the differences might have arisen for multiple reasons. A cell can express genes in bursts rather than a steady stream. Cells also may contain varying amounts of mRNA and protein-production machinery, such as polymerase enzymes and ribosomes. Furthermore, the number of copies of the genetic circuit in a cell can fluctuate over time.

Jeff Hasty, a synthetic biologist at the University of California, San Diego, and his colleagues described an oscillator with more consistent behavior[9] in 2008. Using a different circuit design and microfluidic devices that allowed fine control of growth conditions, the team made nearly every monitored cell blink at the same rate — though not in sync. And in January 2010, Hasty's team reported the ability to synchronize the blinking by relying on cell-cell communication.[10] But Hasty says that rather than trying to eliminate noise, researchers could use it to their advantage. He notes that in physics, noise can sometimes make a signal easier to detect. "I don't think you can beat it, so I think you ought to try to use it," says Hasty. For example, noise could allow some cells to respond differently to the environment from others, enabling the population to hedge its bets, says Elowitz.

Meanwhile, geneticist George Church at Harvard Medical School in Boston, Massachusetts, is exploring ways to make a bacterial strain more stable. Church says that this might be achieved by introducing more accurate DNA-replication machinery, changing genome sites to make them less prone to mutation and putting extra copies of the genome into cells. Although stability may not be a serious issue for simple systems, it will become important as more components are assembled, he says.

Time to Deliver?

Despite the challenges, synthetic biologists have made progress. Researchers have recently developed devices that allow *E. coli* to count events such as the number of times they have divided and to detect light and dark edges. And some systems have advanced from bacteria to more complex cells. The field is also gaining legitimacy, with a new synthetic-biology centre at Imperial College London and a programme at Harvard University's recently launched Wyss Institute for Biologically Inspired Engineering in Boston. The time has come for synthetic biologists to develop more real-world applications, says Fussenegger. "The field has had its hype phase," he says. "Now it needs to deliver."

Keasling's artemisinin precursor system is approaching commercial reality, with Paris-based pharmaceutical company Sanofi-Aventis aiming to have the product available at an industrial scale by 2012. And several companies are pursuing biofuel production via engineered microbes. But most applications will take time.

As the cost of DNA synthesis continues to drop and more people begin to tinker with biological parts, the field could progress faster, says Carlson. "It's a question of whether the complexity of biology yields to that kind of an effort."

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The Case against Perfection

MICHAEL J. SANDEL

Advances in biotechnology have begun to make possible a range of interventions in human development that, until recently, could only be dreamed of. Some of these possibilities, as Michael Sandel says, "present us with a promise and a predicament." The promise is the ability to treat and prevent a range of diseases and alleviate a great deal of human suffering. The predicament is that the same knowledge may enable us to change our very nature — to enhance or choose such specific traits in our children as their height, athletic or musical talents, intelligence, or gender — in other words, to design our offspring. Related technologies may make possible the safe and reliable cloning of individual human beings. Most people would say there is something not quite right about designing a child to certain specifications or, through cloning, creating a child who is genetically identical to a parent or, perhaps, to a sibling who has died.

These prospects are unsettling for many of us. But why? Sandel explores various possible reasons for our discomfort. What is the difference between using medicine to cure and using the same technologies to design or enhance? In exploring these questions, Sandel helps us to articulate the reasons for our unease and, in the process, to explore the ethical dilemmas that face us and the choices that technology may require us to make in the near future.

Michael J. Sandel is the Anne T. and Robert M. Bass Professor of Government at Harvard University; he has taught political philosophy at Harvard since 1980. His highly popular courses include "Justice" and "Ethics, Biotechnology, and the Future of Human Nature." Sandel is the author of several books, including The Case against Perfection: Ethics in the Age of Genetic Engineering, *of which this chapter is the introduction. He served as a member of President George W. Bush's Council on Bioethics. Sandel's*

"The Ethics of Enhancement," reprinted by permission of the publisher from *The Case Against Perfection: Ethics in the Age of Genetic Engineering*, by Michael J. Sandel, pp. 1–24, Cambridge, Mass: The Belknap Press of Harvard University Press, Adapted and expanded from an original essay published in the Atlantic Monthly, 2004.

undergraduate degree is from Brandeis University; his doctorate is from Oxford University, where he was a Rhodes Scholar. He holds three honorary degrees.

A few years ago, a couple decided they wanted to have a child, preferably a deaf one. Both partners were deaf, and proudly so. Like others in the deaf-pride community, Sharon Duchesneau and Candy McCullough considered deafness a cultural identity, not a disability to be cured. "Being deaf is just a way of life," said Duchesneau. "We feel whole as deaf people and we want to share the wonderful aspects of our deaf community — a sense of belonging and connectedness — with children. We truly feel we live rich lives as deaf people."[1]

In hopes of conceiving a deaf child, they sought out a sperm donor with five generations of deafness in his family. And they succeeded. Their son Gauvin was born deaf.

The new parents were surprised when their story, which was reported in the *Washington Post*, brought widespread condemnation. Most of the outrage focused on the charge that they had deliberately inflicted a disability on their child. Duchesneau and McCullough (who are lesbian partners) denied that deafness is a disability and argued that they had simply wanted a child like themselves. "We do not view what we did as very different from what many straight couples do when they have children," said Duchesneau.[2]

Is it wrong to make a child deaf by design? If so, what makes it wrong — the deafness or the design? Suppose, for the sake of argument, that deafness is not a disability but a distinctive identity. Is there still something wrong with the idea of parents picking and choosing the kind of child they will have? Or do parents do that all the time, in their choice of mate and, these days, in their use of new reproductive technologies?

Not long before the controversy over the deaf child, an ad appeared in the *Harvard Crimson* and other Ivy League student newspapers. An infertile couple was seeking an egg donor, but not just any egg donor. She had to be five feet, ten inches tall, athletic, without major family medical problems, and to have a combined SAT score of 1400 or above. In exchange for an egg from a donor meeting this description, the ad offered payment of $50,000.[3]

Perhaps the parents who offered the hefty sum for a premium egg simply wanted a child who resembled them. Or perhaps they were hoping to trade up, trying for a child who would be taller or smarter than they. Whatever the case, their extraordinary offer did not prompt the public outcry that met the parents who wanted a deaf child. No one objected that height, intelligence, and athletic prowess are disabilities that children should be spared. And yet something about the ad leaves a lingering moral qualm. Even if no harm is involved, isn't there something troubling about parents ordering up a child with certain genetic traits?

Some defend the attempt to conceive a deaf child, or one who will have high SAT scores, as similar to natural procreation in one crucial respect: whatever these parents did to increase the odds, they were not guaranteed the outcome they sought. Both attempts were still subject to the vagaries of the genetic lottery. This defense raises an intriguing question. Why does some element of

unpredictability seem to make a moral difference? Suppose biotechnology could remove the uncertainty and allow us to design the genetic traits of our children?

While pondering this question, put aside children for a moment and consider pets. About a year after the furor over the deliberately deaf child, a Texas woman named Julie (she declined to give her last name) was mourning the death of her beloved cat Nick. "He was very beautiful," Julie said. "He was exceptionally intelligent. He knew eleven commands." She had read of a company in California that offered a cat cloning service — Genetic Savings & Clone. In 2001 the company had succeeded in creating the first cloned cat (named CC, for Carbon Copy). Julie sent the company a genetic sample of Nicky, along with the required fee of $50,000. A few months later, to her great delight, she received Little Nicky, a genetically identical cat. "He is identical," Julie proclaimed. "I have not been able to see one difference."[4]

The company's Web site has since announced a price reduction for cat cloning, which now costs a mere $32,000. If the price still seems steep, it comes with a money-back guarantee: "If you feel that your kitten doesn't sufficiently resemble the genetic donor, we'll refund your money in full with no questions asked." Meanwhile, the company's scientists are working to develop a new product line — cloned dogs. Since dogs are harder to clone than cats, the company plans to charge $100,000 or more.[5]

Many people find something odd about the commercial cloning of cats and dogs. Some complain that, with thousands of strays in need of good homes, it is unconscionable to spend a small fortune to create a custom-made pet. Others worry about the number of animals lost during pregnancy in the attempt to create a successful clone. But suppose these problems could be overcome. Would the cloning of cats and dogs still give us pause? What about the cloning of human beings?

ARTICULATING OUR UNEASE

Breakthroughs in genetics present us with a promise and a predicament. The promise is that we may soon be able to treat and prevent a host of debilitating diseases. The predicament is that our newfound genetic knowledge may also enable us to manipulate our own nature — to enhance our muscles, memories, and moods; to choose the sex, height, and other genetic traits of our children; to improve our physical and cognitive capacities; to make ourselves "better than well."[6] Most people find at least some forms of genetic engineering disquieting. But it is not easy to articulate the source of our unease. The familiar terms of moral and political discourse make it difficult to say what is wrong with reengineering our nature.

Consider again the question of cloning. The birth of Dolly the cloned sheep in 1997 brought a torrent of worry about the prospect of cloned human beings. There are good medical reasons to worry. Most scientists agree that cloning is unsafe and likely to produce offspring with serious abnormalities and birth defects. (Dolly died a premature death.) But suppose cloning technology

improves to the point where the risks are no greater than with natural pregnancy. Would human cloning still be objectionable? What exactly is wrong with creating a child who is a genetic twin of his or her parent, or of an older sibling who has tragically died, or, for that matter, of an admired scientist, sports star, or celebrity?

Some say cloning is wrong because it violates the child's right to autonomy. By choosing in advance the genetic makeup of the child, the parents consign her to a life in the shadow of someone who has gone before, and so deprive the child of her right to an open future. The autonomy objection can be raised not only against cloning but also against any form of bioengineering that allows parents to choose their child's genetic characteristics. According to this objection, the problem with genetic engineering is that "designer children" are not fully free; even favorable genetic enhancements (for musical talent, say, or athletic prowess) would point children toward particular life choices, impairing their autonomy and violating their right to choose their life plan for themselves.

At first glance, the autonomy argument seems to capture what is troubling about human cloning and other forms of genetic engineering. But it is not persuasive, for two reasons. First, it wrongly implies that, absent a designing parent, children are free to choose their physical characteristics for themselves. But none of us chooses our own genetic inheritance. The alternative to a cloned or genetically enhanced child is not one whose future is unbiased and unbound by particular talents, but a child at the mercy of the genetic lottery.

Second, even if a concern for autonomy explains some of our worries about made-to-order children, it cannot explain our moral hesitation about people who seek genetic enhancements for themselves. Not all genetic interventions are passed down the generations. Gene therapy on nonreproductive (or somatic) cells, such as muscle cells or brain cells, works by repairing or replacing defective genes. The moral quandary arises when people use such therapy not to cure a disease but to reach beyond health, to enhance their physical or cognitive capacities, to lift themselves above the norm.

This moral quandary has nothing to do with impairing autonomy. Only germline genetic interventions, which target eggs, sperm, or embryos, affect subsequent generations. An athlete who genetically enhances his muscles does not confer on his progeny his added speed and strength; he cannot be charged with foisting talents on his children that may push them toward an athletic career. And yet there is still something unsettling about the prospect of genetically altered athletes.

Like cosmetic surgery, genetic enhancement employs medical means for nonmedical ends — ends unrelated to curing or preventing disease, repairing injury, or restoring health. But unlike cosmetic surgery, genetic enhancement is not merely cosmetic. It is more than skin deep. Even somatic enhancements, which would not reach our children and grandchildren, raise hard moral questions. If we are ambivalent about plastic surgery and Botox injections for sagging chins and furrowed brows, we are all the more troubled by genetic engineering for stronger bodies, sharper memories, greater intelligence, and happier moods. The question is whether we are right to be troubled — and if so, on what grounds?

When science moves faster than moral understanding, as it does today, men and women struggle to articulate their unease. In liberal societies, they reach first for the language of autonomy, fairness, and individual rights. But this part of our moral vocabulary does not equip us to address the hardest questions posed by cloning, designer children, and genetic engineering. That is why the genomic revolution has induced a kind of moral vertigo. To grapple with the ethics of enhancement, we need to confront questions largely lost from view in the modern world — questions about the moral status of nature, and about the proper stance of human beings toward the given world. Since these questions verge on theology, modern philosophers and political theorists tend to shrink from them. But our new powers of biotechnology make them unavoidable.

GENETIC ENGINEERING

To see how this is so, consider four examples of bioengineering already on the horizon: muscle enhancement, memory enhancement, height enhancement, and sex selection. In each case, what began as an attempt to treat a disease or prevent a genetic disorder now beckons as an instrument of improvement and consumer choice.

Muscles

Everyone would welcome a gene therapy to alleviate muscular dystrophy and to reverse the debilitating muscle loss that comes with old age. But what if the same therapy were used to produce genetically altered athletes? Researchers have developed a synthetic gene that, when injected into the muscle cells of mice, makes muscles grow and prevents them from deteriorating with age. The success bodes well for human applications. Dr. H. Lee Sweeney, who leads the research, hopes his discovery will cure the immobility that afflicts the elderly. But Dr. Sweeney's bulked-up mice have already attracted the attention of athletes seeking a competitive edge.[7] The gene not only repairs injured muscles but also strengthens healthy ones. Although the therapy is not yet approved for human use, the prospect of genetically enhanced weight lifters, home-run sluggers, linebackers, and sprinters is easy to imagine. The widespread use of steroids and other performance-enhancing drugs in professional sports suggests that many athletes will be eager to avail themselves of genetic enhancement. The International Olympic Committee has already begun to worry about the fact that, unlike drugs, altered genes cannot be detected in urine or blood tests.[8]

The prospect of genetically altered athletes offers a good illustration of the ethical quandaries surrounding enhancement. Should the IOC and professional sports leagues ban genetically enhanced athletes, and if so, on what grounds?

The two most obvious reasons for banning drugs in sports are safety and fairness: Steroids have harmful side effects, and to allow some to boost their performance by incurring serious health risks would put their competitors at an unfair disadvantage. But suppose, for the sake of argument, that muscle-enhancing gene therapy turned out to be safe, or at least no riskier than a rigorous weight-training regime. Would there still be a reason to ban its use in sports? There is something unsettling about the specter of genetically altered athletes lifting SUVs or hitting 650-foot home runs or running a three-minute mile. But what exactly is troubling about these scenarios? Is it simply that we find such superhuman spectacles too bizarre to contemplate, or does our unease point to something of ethical significance?

The distinction between curing and improving seems to make a moral difference, but it is not obvious what the difference consists in. Consider: If it is all right for an injured athlete to repair a muscle tear with the help of genetic therapy, why is it wrong for him to extend the therapy to improve the muscle, and then to return to the lineup better than before? It might be argued that a genetically enhanced athlete would have an unfair advantage over his unenhanced competitors. But the fairness argument against enhancement has a fatal flaw. It has always been the case that some athletes are better endowed, genetically, than others. And yet we do not consider the natural inequality of genetic endowments to undermine the fairness of competitive sports. From the standpoint of fairness, enhanced genetic differences are no worse than natural ones. Moreover, assuming they are safe, genetic enhancements could be made available to all. If genetic enhancement in sports is morally objectionable, it must be for reasons other than fairness.

Memory

Genetic enhancement is possible for brains as well as brawn. In the mid-1990s scientists managed to manipulate a memory-linked gene in fruit flies, creating flies with photographic memories. More recently researchers produced smart mice by inserting extra copies of a memory-related gene into mouse embryos. The altered mice learn more quickly and remember things longer than normal mice. For example, they are better able to recognize objects they have seen before, and to remember that a certain sound leads to an electric shock. The gene the scientists tweaked in mouse embryos is present in human beings as well, and becomes less active as people age. The extra copies installed in the mice were programmed to remain active even in old age, and the improvement was passed on to their offspring.[9]

Of course human memory is more complicated than recalling simple associations. But biotech companies with names like Memory Pharmaceuticals are in hot pursuit of memory-enhancing drugs, or "cognition enhancers," for human beings. One obvious market for such drugs consists of those who suffer from serious memory disorders, such as Alzheimer's and dementia. But the companies also have their sights on a bigger market: the 76 million baby boomers over fifty who are beginning to encounter the natural memory loss that comes with age.[10]

A drug that reversed age-related memory loss would be a bonanza for the pharmaceuticals industry, a "Viagra for the brain."

Such use would straddle the distinction between remedy and enhancement. Unlike a treatment for Alzheimer's it would cure no disease. But insofar as it restored capacities a person once possessed, it would have a remedial aspect. It could also have purely nonmedical uses: for example, by a lawyer cramming to memorize facts for an upcoming trial, or by a business executive eager to learn Mandarin on the eve of his departure for Shanghai.

It might be argued, against the project of memory enhancement, that there are some things we would rather forget. For the drug companies, however, the desire to forget represents not an objection to the memory business but another market segment. Those who want to blunt the impact of traumatic or painful memories may soon be able to take a drug that prevents horrific events from being etched too vividly in memory. Victims of a sexual assault, soldiers exposed to the carnage of war, or rescue workers forced to face the aftermath of a terrorist attack would be able to take a memory-suppressing drug to dull the trauma that might otherwise plague them for a lifetime. If the use of such drugs became widely accepted, they might one day be administered routinely in emergency rooms and military field hospitals.[11]

Some who worry about the ethics of cognitive enhancement point to the danger of creating two classes of human beings — those with access to enhancement technologies, and those who must make do with an unaltered memory that fades with age. And if the enhancements can be passed down the generations, the two classes may eventually become subspecies of human beings — the enhanced and the merely natural. But the worry about access begs the question of the moral status of enhancement itself. Is the scenario troubling because the unenhanced poor are denied the benefits of bioengineering, or because the enhanced affluent are somehow dehumanized? As with muscles, so with memory: The fundamental question is not how to assure equal access to enhancement but whether we should aspire to it. Should we devote our biotechnological ingenuity to curing disease and restoring the injured to health, or should we also seek to improve our lot by reengineering our bodies and minds?

Height

Pediatricians already struggle with the ethics of enhancement when confronted by parents who want to make their children taller. Since the 1980s, human growth hormone has been approved for children with a hormone deficiency that makes them much shorter than average.[12] But the treatment also increases the height of healthy children. Some parents of healthy children who are unhappy with their stature (typically boys) ask for the hormone treatments on the grounds that it should not matter whether a child is short because of a hormone deficiency or because his parents happen to be short. Whatever the cause, the social consequences of shortness are the same in both cases.

In the face of this argument, some doctors began prescribing hormone treatments for children whose short stature was unrelated to any medical problem. By

1996 such "off-label" use accounted for 40 percent of human growth hormone prescriptions.[13] Although it is not illegal to prescribe drugs for purposes the Food and Drug Administration (FDA) has not approved, the pharmaceutical companies cannot promote such use. Seeking to expand its market, one company, Eli Lilly, recently persuaded the FDA to approve its human growth hormone for healthy children whose projected adult height is in the bottom first percentile — under five feet, three inches for boys; four feet, eleven inches for girls.[14] This small concession raises a large question about the ethics of enhancement: If hormone treatments need not be limited to those with hormone deficiencies, why should they be available only to very short children? Why shouldn't all shorter-than-average children be able to seek treatment? And what about a child of average height who wants to be taller so he can make the basketball team?

Critics call the elective use of human growth hormone "cosmetic endocrinology." Health insurance is unlikely to cover it, and the treatments are expensive. Injections are administered up to six times a week, for two to five years, at an annual cost of about $20,000 — all for a potential height gain of two or three inches.[15] Some oppose height enhancement on the grounds that it is collectively self-defeating; as some become taller, others will become shorter relative to the norm. Except in Lake Wobegon, every child cannot be above average in height. As the unenhanced begin to feel shorter, they too might seek treatment, leading to a hormonal arms race that will leave everyone worse off, especially those who cannot afford to buy their way up from shortness.

But the arms-race objection is not decisive on its own. Like the fairness objection to bioengineered muscles and memory, it leaves unexamined the attitudes and dispositions that prompt the drive for enhancement. If we were bothered only by the injustice of adding shortness to the problems of the poor, we could remedy that unfairness by providing publicly subsidized height enhancement. As for the collective-action problem, the innocent bystanders who suffer relative height deprivation could be financially compensated by a tax imposed on those who buy their way to greater height. The real question is whether we want to live in a society where parents feel compelled to spend a fortune to make perfectly healthy kids a few inches taller.

Sex Selection

Perhaps the most alluring nonmedical use of bioengineering is sex selection. For centuries parents have been trying to choose the sex of their children. Aristotle advised men who wanted a boy to tie off their left testicle before intercourse. The Talmud teaches that men who restrain themselves and allow their wives to achieve sexual climax first will be blessed with a son. Other recommended methods have involved timing conception in relation to ovulation, or to the phases of the moon. Today, biotech succeeds where folk remedies failed.[16]

One technique for sex selection arose with prenatal tests using amniocentesis and ultrasound. These medical technologies were developed to detect genetic abnormalities, such as spina bifida and Down syndrome. But they can

also reveal the sex of a fetus, allowing for the abortion of a fetus of the undesired sex. Even among those who favor abortion rights, few advocate abortion simply because the mother (or father) does not want a girl. But in societies with powerful cultural preferences for boys, ultrasound sex determination followed by the abortion of female fetuses has become a familiar practice. In India, the number of girls per 1,000 boys has dropped from 962 to 927 in the past two decades. India has banned the use of prenatal diagnosis for sex selection, but the law is rarely enforced. Itinerant radiologists with portable ultrasound machines travel from village to village, plying their trade. One Bombay clinic reported that, of 8,000 abortions it performed, all but one were for purposes of sex selection.[17]

But sex selection need not involve abortion. For couples undergoing in vitro fertilization (IVF), it is possible to choose the sex of the child before the fertilized egg is implanted in the womb. The procedure, known as preimplantation genetic diagnosis (PGD), works like this: Several eggs are fertilized in a petri dish and allowed to grow to the eight-cell stage (for about three days). At that point, the early embryos are tested to determine their sex. Those of the desired sex are implanted; the others are typically discarded. Although few couples are likely to undergo the difficulty and expense of IVF simply to choose the sex of their child, embryo screening is a highly reliable means of sex selection. And as our genetic knowledge increases, it may be possible to use PGD to cull embryos carrying other undesired genetic traits, such as those associated with obesity, height, and skin color. The 1997 science fiction movie *Gattaca* depicts a future in which parents routinely screen embryos for sex, height, immunity to disease, and even IQ. There is something troubling about the *Gattaca* scenario, but it is not easy to identify what exactly is wrong with screening embryos to choose the sex of our children.

One line of objection draws on arguments familiar from the abortion debate. Those who believe that an embryo is a person reject embryo screening on the same grounds that they reject abortion. If an eight-cell embryo growing in a petri dish is morally equivalent to a fully developed human being, then discarding it is no better than aborting a fetus, and both practices are equivalent to infanticide. Whatever its merits, however, this "pro-life" objection is not an argument against sex selection as such. It is an argument against all forms of embryo screening, including PGD carried out to screen for genetic diseases. Because the pro-life objection finds an overriding moral wrong in the means (namely, the discarding of unwanted embryos), it leaves open the question of whether there is anything wrong with sex selection itself.

The latest sex selection technology poses this question on its own unclouded by the matter of an embryo's moral status. The Genetics & IVF Institute, a for-profit infertility clinic in Fairfax, Virginia, now offers a sperm sorting technique that makes it possible for clients to choose the sex of their child before it is conceived. The X-bearing sperm (which produce girls) carry more DNA than Y-bearing sperm (which produce boys); a device called a flow cytometer can separate them. The trademarked process, called MicroSort, has a high rate of success — 91 percent for producing girls, 76 percent for boys. The Genetics & IVF Institute

licensed the technology from the U.S. Department of Agriculture, which had developed the process for breeding cattle.[18]

If sex selection by sperm sorting is objectionable it must be for reasons that go beyond the debate about the moral status of the embryo. One such reason is that sex selection is an instrument of sex discrimination, typically against girls, as illustrated by the chilling sex ratios in India and China. And some speculate that societies with substantially more men than women will be less stable, more violent, more prone to crime or war than societies with normal distributions.[19] These are legitimate worries, but the sperm-sorting company has a clever way of addressing them. It offers MicroSort only to couples who want to choose the sex of their child for purposes of family balancing. Those with more sons than daughters can choose a girl, and vice versa. But customers may not use the technology to stock up on children of the same sex, or even to choose the sex of their first-born child. So far, the majority of MicroSort clients have chosen girls.[20]

The case of MicroSort helps us isolate the moral question posed by technologies of enhancement. Put aside familiar debates about safety, embryo loss, and sex discrimination. Imagine that sperm-sorting technologies were employed in a society that did not favor boys over girls, and that wound up with a balanced sex ratio. Would sex selection under those conditions be unobjectionable? What if it became possible to select not only for sex but also for height, eye color, and skin color? What about sexual orientation, IQ, musical ability, and athletic prowess? Or suppose that muscle-enhancement, memory-enhancement, and height-enhancement technologies were perfected to the point where they were safe and available to all. Would they cease to be objectionable?

Not necessarily. In each of these cases, something morally troubling persists. The trouble resides not only in the means but also in the ends being aimed at. It is commonly said that enhancement, cloning, and genetic engineering pose a threat to human dignity. This is true enough. But the challenge is to say *how* these practices diminish our humanity. What aspects of human freedom or human flourishing do they threaten?

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Some Possible Legal and Social Implications of Advances in Neuroscience

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A technology that would allow one to know what other people are really thinking — not what they are saying but what is actually going on in their minds — would be an incredibly powerful tool with enormous social and legal consequences. While such a tool does not yet exist, the field of neuroscience is moving rapidly in a direction that suggests that someday it might be a possibility. Henry Greely considers some of the potential implications, principally from the standpoint of the legal system. Knowing whether an individual is telling the truth, whether that person's memory of an event is real and accurate, whether he or she is biased against certain groups — all of these notions are central to many legal disputes. Neuroscience, one of the fastest-growing fields in the life sciences, offers the prospect of being able to determine some of these things. But how certain must the science be for judges and juries to base life-and-death decisions on its findings? The situations in which neuroscience might be used in legal proceedings and the issues that such uses might raise are discussed in this chapter.

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From "Prediction, Litigation, Privacy, and Property: Some Possible Legal and Social Implications of Advances," from *Neuroscience and the Law: Brain, Mind, and the Scales of Justice*," pp. 114–142, by Henry T. Greely.

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"There's no art/To find the mind's construction in the face:/He was a gentleman on whom I built/An absolute trust."[2]

The lament of Duncan, King of Scotland, for the treason of the Thane of Cawdor, his trusted nobleman, echoes through time as we continue to feel the sting of not *knowing* the minds of those people with whom we deal. From "We have a deal" to "Will you still love me tomorrow?" we continue to live in fundamental uncertainty about the minds of others. Duncan himself emphasized this by immediately giving his trust to Cawdor's conqueror, one Macbeth, with fatal consequences. But at least some of this uncertainty may be about to lift, for better or for worse.

Neuroscience is rapidly increasing our knowledge of the functioning, and malfunctioning, of that intricate three-pound organ, the human brain. In expanding our understanding of something so central to human existence, science is necessarily provoking changes in both our society and its laws. This paper seeks to forecast and explore the social and legal changes that neuroscience might bring in four areas: prediction, litigation, confidentiality and privacy, and patents....

Two notes of caution are in order. First, this paper may appear to paint a gloomy picture of future threats and abuses. In fact, the technologies discussed seem likely to have benefits far outweighing their harms. It is the job of people looking for ethical, legal, and social consequences of new technologies to look disproportionately for troublesome consequences — or, at least, that's the convention. Second, as Niels Bohr (probably) said, "It is always hard to predict things, especially the future."[3] This paper builds on experience gained in studying the ethical, legal, and social implications of human genetics over the last decade. That experience, for me and for the whole field, has included both successes and failures. In neuroscience, as in genetics, accurately envisioning the future is particularly difficult, as one must foresee successfully both what changes will occur in the science and how they will affect society. I am confident about only two things concerning this paper: first, it discusses at length some things that will never happen; and second, it ignores what will prove to be some of the most important social and legal implications of neuroscience. Nonetheless, I hope the paper will be useful as a guide to beginning to think about these issues.

PREDICTION

Advances in neuroscience may well improve our ability to make predictions about an individual's future. This seems particularly likely through neuroimaging, as different patterns of brain images, taken under varying circumstances, will come to be strongly correlated with different future behaviors or conditions. The images may reveal the *structure* of the living brain, through technologies such as computed axial tomography (CAT) scans or magnetic resonance imaging (MRI), or they may show how different parts of the brain *function*, through positron-emission tomography (PET) scans, single-photon-emission computed tomography (SPECT) scans, or functional magnetic resonance imaging (fMRI).

Neuroscience might make many different kinds of predictions about people. It might predict, or reveal, mental illness, behavioral traits, and cognitive abilities, among other things. For the purposes of this paper, I have organized these predictive areas not by the nature of the prediction but by who might use the predictions: the health care system, the criminal justice system, schools, businesses, and parents.

That new neuroscience methods are used to make predictions is not necessarily good or bad. Our society makes predictions about people all the time: when a doctor determines a patient's prognosis, when a judge (or a legislature) sentences a criminal, when colleges use the Scholastic Aptitude Test, and when automobile liability insurers set rates. But although prediction is common, it is not always uncontroversial.

The Analogy to Genetic Predictions

The issues raised by predictions based on neuroscience are often similar to those raised by genetic predictions. Indeed, in some cases the two areas are the same — genetic analysis can powerfully predict several diseases of the brain, including Huntington's disease and some cases of early-onset Alzheimer's disease. Experience of genetic predictions teaches at least three important lessons.

First, a claimed ability to predict may not, in fact, exist. Many associations between genetic variations and various diseases have been claimed, only to fail the test of replication. Interestingly, many of these failures have involved two mental illnesses, schizophrenia and bipolar disorder.

Second, and more important, the strength of the predictions can vary enormously. For some genetic diseases, prediction is overwhelmingly powerful. As far as we know, the only way a person with the genetic variation that causes Huntington's disease can avoid dying of that disease is to die first from something else. On the other hand, the widely heralded "breast cancer genes," BRCA 1 and BRCA 2, though they substantially increase the likelihood that a woman will be diagnosed with breast or ovarian cancer, are not close to determinative. Somewhere between 50 and 85 percent of women born with a pathogenic mutation in either of those genes will get breast cancer; 20 to 30 percent (well under half) will get ovarian cancer. Men with a mutation in BRCA 2 have a hundredfold greater risk of breast cancer than average men — but their chances are still under

5 percent. A prediction based on an association between a genetic variation and a disease, even when true, can be very strong, very weak, or somewhere in between. The popular perception of genes as extremely powerful is probably a result of ascertainment bias: the diseases first found to be caused by genetic variations were examples of very powerful associations *because* powerful associations were the easiest to find. If, as seems likely, the same holds true for predictions from neuroscience, such predictions will need to be used very carefully.

Finally, the use of genetic predictions has proven controversial, both in medical practice and in social settings. Much of the debate about the uses of human genetics has concerned its use in predicting the health or traits of patients, insureds, employees, fetuses, and embryos. Neuroscience seems likely to raise many similar issues.

Health Care

Much of health care is about prediction — predicting the outcome of a disease, predicting the results of a treatment for a disease, predicting the risk of getting a disease. When medicine, through neuroscience, genetics, or other methods, makes an accurate prediction that leads to a useful intervention, the prediction is clearly valuable. But predictions also can cause problems when they are inaccurate (or are perceived inaccurately by patients). Even if the predictions are accurate, they still have uncertain value if no useful interventions are possible. These problems may justify regulation of predictive neuroscientific medical testing.

Some predictive tests are inaccurate, either because the scientific understanding behind them is wrong or because the test is poorly performed. In other cases the test may be accurate in the sense that it gives an accurate assessment of the probability of a certain result, but any individual patient may not have the most likely outcome. In addition, patients or others may misinterpret the test results. In genetic testing, for example, a woman who tests positive for a BRCA 1 mutation may believe that a fatal breast cancer is inevitable, when, in fact, her lifetime risk of breast cancer is between 50 and 85 percent, and her chance of dying from a breast cancer is roughly one-third of the risk of diagnosis. Alternatively, a woman who tests negative for the mutation may falsely believe that she has *no* risk for breast cancer and might stop breast self-examinations or mammograms to her harm. Even very accurate tests may not be very useful. Genetic testing to predict Huntington's disease is quite accurate, yet, with no useful medical interventions, a person may find foreknowledge of Huntington's disease not only unhelpful but psychologically or socially harmful. These concerns have led to widespread calls for regulation of genetic testing.[4]

The same issues can easily arise in neuroscience. Neuroimaging, for example, might easily lead to predictions, with greater or lesser accuracy, that an individual will be diagnosed with one of a variety of neurodegenerative diseases. Such imaging tests may be inaccurate, may present information patients find difficult to evaluate, and may provide information of dubious value and some harm. One might want to regulate some such tests along the lines proposed for genetic tests:

proof that the test was effective at predicting the condition in question, assessment of the competency of those performing the test, required informed consent so that patients appreciate the test's possible consequences, and mandatory post-test counseling to ensure that patients understand the results.

The Food and Drug Administration (FDA) has statutory jurisdiction over the use of drugs, biologicals, and medical devices. It requires proof that covered products are both safe and effective. The FDA has asserted that it has jurisdiction over genetic tests as medical devices, but it has chosen to impose significant regulation only on genetic tests sold by manufacturers as kits to clinical laboratories, physicians, or consumers. Tests done as "home brews" by clinical laboratories have been subject only to very limited regulation, which does not include proof of safety or efficacy. Neuroscience tests might well be subject to even less FDA regulation. If the test used an existing, approved medical device, such as an MRI machine, no FDA approval of this additional use would be necessary. The test would be part of the "practice of medicine," expressly not regulated by the FDA.

The FDA also implements the Clinical Laboratory Improvement Amendments Act (CLIA), along with the Centers for Disease Control and Prevention and the Centers for Medicare and Medicaid Services. CLIA sets standards for the training and working conditions of clinical laboratory personnel and requires periodic testing of laboratories' proficiency at different tests. Unless the tests were done in a clinical laboratory — through, for example, pathological examination of brain tissue samples or analysis of chemicals from the brain — neuroscience testing would also seem to avoid regulation under CLIA.

At present, neuroscience-based testing, particularly through neuroimaging using existing (approved) devices, seems to be entirely unregulated except, to a very limited extent, by malpractice law. One important policy question should be whether to regulate such tests, through government action or by professional self-regulation.

Criminal Justice

The criminal justice system makes predictions about individuals' future behavior in sentencing, parole, and other decisions, such as civil commitment for sex offenders.[5] The trend in recent years has been to limit the discretion of judges and parole boards in using predictions by setting stronger sentencing guidelines and mandatory sentences. Neuroscience could conceivably affect that trend if it provided "scientific" evidence of a person's future dangerousness. Such evidence might be used to increase sentencing discretion — or it might provide yet another way to limit such discretion.[6]

One can imagine neuroscience tests that could predict a convicted defendant was particularly likely to commit dangerous future crimes by showing that he has, for example, poor control over his anger, his aggressiveness, or his sexual urges. This kind of evidence has been used in the past; neuroscience may come up with ways that either are more accurate or that *appear* more accurate (or more impressive). For example, two papers[7] have already linked criminality to

variations in the gene for monoamine oxidase A, a protein that plays an important role in the brain. Genetic tests may seem more scientific and more impressive to a judge, jury, or parole board than a psychologist's report. The use of neuroscience to make these predictions raises at least two issues: Are neuroscience tests for future dangerousness or lack of self-control valid at all? If so, how accurate do they need to be before they should be used?

The law has had experience with claims that inherent violent tendencies can be tested for. The XYY syndrome was widely discussed and accepted, in the literature though not by the courts,[8] in the late 1960s and early 1970s. Men born with an additional copy of the Y chromosome were said to be much more likely to become violent criminals. Further research revealed, about a decade later, that XYY men were somewhat more likely to have low intelligence and to have long arrest records, typically for petty or property offenses. They did not have a higher than average predisposition to violence.

If, unlike XYY syndrome, a tested condition were shown to predict reliably future dangerousness or lack of control, the question would then become how accurate the test must be in order for it to be used. A test of dangerousness or lack of control that was only slightly better than flipping coins should not be given much weight; a perfect test could be. At what accuracy level should the line be set?

The Supreme Court has recently spoken twice on the civil commitment of sexual offenders, both times reviewing a Kansas statute.[9] The Kansas act authorizes civil commitment of a "sexually violent predator," defined as "any person who has been convicted of or charged with a sexually violent offense and who suffers from a mental abnormality or personality disorder which makes the person likely to engage in repeat acts of sexual violence."[10] In *Kansas v. Hendricks*, the Court held the state law constitutional against a substantive due process claim because it required, in addition to proof of dangerousness, proof of the defendant's lack of control. "This admitted lack of volitional control, coupled with a prediction of future dangerousness, adequately distinguishes Hendricks from other dangerous persons who are perhaps more properly dealt with exclusively through criminal proceedings."[11] It held that Hendricks's commitment survived attack on ex post facto and double jeopardy grounds because the commitment procedure was neither criminal nor punitive.[12]

Five years later, the Court revisited this statute in *Kansas v. Crane*.[13] It held that the Kansas statue could be applied constitutionally only if there were a determination of the defendant's lack of control and not just proof of the existence of a relevant "mental abnormality or personality disorder":

> It is enough to say that there must be proof of serious difficulty in controlling behavior. And this, when viewed in light of such features of the case as the nature of the psychiatric diagnosis, and the severity of the mental abnormality itself, must be sufficient to distinguish the dangerous sexual offender whose serious mental illness, abnormality, or disorder subjects him to civil commitment from the dangerous but typical recidivist convicted in an ordinary criminal case.[14]

We know then that, at least in civil commitment cases related to prior sexually violent criminal offenses, proof that the particular defendant had limited power to control his actions is constitutionally necessary. There is no requirement that this evidence, or proof adduced in sentencing or parole hearings, convince the trier of fact beyond a reasonable doubt. The Court gives no indication of how strong that evidence must be or how its scientific basis would be established. Would any evidence that passed *Daubert* or *Frye* hearings be sufficient for civil commitment (or for enhancing sentencing or denying parole), or would some higher standard be required?*

It is also interesting to speculate on how evidence of the accuracy of such tests would be collected. It is unlikely that a state or federal criminal justice system would allow a randomized double-blind trial, performing the neuroscientific dangerousness or volition tests on all convicted defendants at the time of their conviction and then releasing them to see which ones would commit future crimes. That judges, parole boards, or legislatures would insist on rigorous scientific proof of connections between neuroscience evidence and future mental states seems doubtful.

Schools

Schools commonly use predictions of individual cognitive abilities. Undergraduate and graduate admissions are powerfully influenced by applicants' scores on an alphabet's worth of tests: ACT, SAT, LSAT, MCAT, and GRE, among others. Even those tests, such as the MCAT, that claim to test knowledge rather than aptitude, use the applicant's tested knowledge as a predictor of her ability to function well in school, either because she has that background knowledge or because her acquisition of the knowledge demonstrates her abilities. American primary and secondary education uses aptitude tests less frequently, although some tracking does go on. And almost all of those schools use grading (after a certain level), which the school or others — such as other schools, employers, and parents — can use to make predictions.

It is conceivable that neuroscience could provide other methods of testing ability or aptitude. Of course, the standard questions of the accuracy of those tests would apply. Tests that are highly inaccurate usually should not be used. But even assuming the tests are accurate, they would raise concerns. While they might be used only positively — as Dr. Alfred Binet intended his early intelligence test to be used, to identify children who need special help — to

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**Daubert v. Merrell Dow Pharmaceuticals* is a 1993 decision of the U.S. Supreme Court that set a new standard for the admissibility of scientific evidence in a trial. The court ruled that the trial judge must act as a "gatekeeper" and determine whether the evidence is relevant to the case at hand and whether it is scientifically valid, for example whether it was arrived at using the scientific method and whether it was subject to peer review. Under the previous standard, *Frye v. United States* (a decision of the D.C. Circuit Court dating from 1923), scientific evidence was admissible if "the thing from which the deduction is made" was "sufficiently established to have gained general acceptance in the particular field in which it belongs." The *Daubert* decision applies only to U.S. federal courts. State courts do not have a uniform standard; some use *Daubert*, others use *Frye*. – Ed.

the extent that they were used to deny students, especially young children, opportunities, they would seem more troubling.

It is not clear why a society that uses aptitude tests so commonly for admission into elite schools should worry about the tests' neuroscience equivalents. The SAT and similar aptitude tests claim that student preparation or effort will not substantially affect the tests' results, just as, presumably, preparation (at least in the short term) seems unlikely to alter neuroscience tests of aptitude. The existing aptitude tests, though widely used, remain controversial. Neuroscience tests, particularly if given and acted upon at an early age, are likely to exacerbate the discomfort we already feel with predictive uses of aptitude tests in education.

Businesses

Perhaps the most discussed social issue in human genetics has been the possible use — or abuse — of genetic data by businesses, particularly insurers and employers. Most, but not all, commentators have favored restrictions on the use of genetic information by health insurers and employers.[15] And legislators have largely agreed. Over 45 states and, to some extent, the federal government restrict the use of genetic information in health insurance. Eleven states impose limits on the use of genetic information by life insurers, but those constraints are typically weak. About 30 states limit employer-ordered genetic testing or the use of genetic information in employment decisions, as does, to some very unclear extent, the federal government, through the Americans with Disabilities Act.[16] And 2004 might be the year when broad federal legislation against "genetic discrimination" is finally passed.[17] [In fact, the Genetic Information Nondiscrimination Act — GINA — did not pass both houses of Congress until 2008. It was signed into law by President George W. Bush on May 21, 2008. — Ed.] Should similar legislation be passed to protect people against "neuroscience" discrimination?

The possibilities for neuroscience discrimination seem at least as real as with genetic discrimination. A predictive test showing that a person has a high likelihood of developing schizophrenia, bipolar disorder, early-onset Alzheimer's disease, early-onset Parkinson's disease, or Huntington's disease could certainly provide insurers or employers with an incentive to avoid that person. To the extent one believes that health coverage should be universal or that employment should be denied or terminated only for good cause, banning "neuroscientific discrimination" might be justified as an incremental step toward this good end. Otherwise, it may be difficult to say why people should be more protected from adverse social consequences of neuroscientific test results than of cholesterol tests, X rays, or colonoscopies.

Special protection for genetic tests has been urged on the ground that genes are more fundamental, more deterministic, and less the result of personal actions or chance than other influences on health. Others have argued against such "genetic exceptionalism," denying special power to genes and contending that special legislation about genetics only confirms in the public a false view of genetic determinism. Still others, including me, have argued that the public's particularly strong fear of genetic test results, even though exaggerated, justifies

regulation in order to gain concrete benefits from reducing that fear. The same arguments could be played out with respect to predictive neuroscience tests. Although this is an open empirical question, it does seem likely that the public's perception of the fundamental or deterministic nature of genes does not exist with respect to neuroscience.

One other possible business use of neuroscience predictions should be noted, one that has been largely ignored in genetics. Neuroscience might be used in marketing. Firms might use neuroscience techniques on test subjects to enhance the appeal of their products or the effectiveness of their advertising. Individuals or focus groups could, in the future, be examined under fMRI. At least one firm, Brighthouse Institute for Thought Sciences, has embraced this technology and, in a press release from 2002, announced "its intentions of revolutionizing the marketing industry."[18]

More alarmingly, if neuromonitoring devices were perfected that could study a person's mental function without his or her knowledge, information intended to predict a consumer's preferences might be collected for marketing purposes. Privacy regulation seems appropriate for the undisclosed monitoring in the latter example. Regulating the former seems less likely, although it might prove attractive if such neuroscience-enhanced market research proved too effective an aid to selling.

Parents

The prenatal use of genetic tests to predict the future characteristics of fetuses, embryos, or as-yet-unconceived offspring is one of the most controversial and interesting issues in human genetics. Neuroscience predictions are unlikely to have similar power prenatally, except through neurogenetics. It is possible that neuroimaging or other nongenetic neuroscience tests might be performed on a fetus during pregnancy. Structural MRI has been used as early as about 24 weeks to look for major brain malformations, following up on earlier suspicious sonograms. At this point, no one appears to have done fMRI on the brain of a fetus; the classic method of stimulating the subject and watching which brain regions react would be challenging in utero, though not necessarily impossible. In any event, fetal neuroimaging seems likely to give meaningful results only for serious brain problems and even then at a fairly late stage of fetal development so that the most plausible intervention, abortion, would be rarely used and only in the most extreme cases.[19]

Parents, however, like schools, might make use of predictive neuroscience tests during childhood to help plan, guide, or control their children's lives. Of course, parents already try to guide their children's lives, based on everything from good data to wishful thinking about a child's abilities. Would neuroscience change anything? It might be argued that parents would take neuroscience testing more seriously than other evidence of a child's abilities because of its scientific nature, and thus perhaps exaggerate its accuracy. More fundamentally, it could be argued that, even if the test predictions were powerfully accurate, too extreme parental control over a child's life is a bad thing. From this perspective, any procedures that are likely to add strength to parents' desire or ability to

exercise that control should be discouraged. On the other hand, society vests parents with enormous control over their children's upbringing, intervening only in strong cases of abuse. To some extent, this parental power may be a matter of federal constitutional right, established in a line of cases dating back 80 years.[20]

This issue is perhaps too difficult to be tackled. It is worth noting, though, that government regulation is not the only way to approach it. Professional self-regulation, insurance coverage policies, and parental education might all be methods to discourage any perceived overuse of children's neuroscience tests by their parents.

LITIGATION USES

Predictions may themselves be relevant in some litigation, particularly the criminal cases discussed above, but other, nonpredictive uses of neuroscience might also become central to litigated cases. Neuroscience *might* be able to provide relevant, and possibly determinative, evidence of a witness's mental state at the time of testimony, ways of eliciting or evaluating a witness's memories, or other evidence relevant to a litigant's claims. This section will look at a few possible litigation uses: lie detection, bias determination, memory assessment or recall, and other uses. Whether any of these uses is scientifically possible remains to be seen. It is also worth noting that the extent of the use of any of these methods will also depend on their cost and intrusiveness. A method of, for example, truth determination that required an intravenous infusion or examination inside a full-scale MRI machine would be used much less than a simple and portable headset.

The implications of any of these technologies for litigation seem to depend largely on four evidentiary issues. First, will the technologies pass the *Daubert*[21] or *Frye*[22] tests for the admissibility of scientific evidence? Second, if they are held sufficiently scientifically reliable to pass *Daubert* or *Frye*, are there other reasons to forbid or to compel the admissibility of the results of such technologies when used voluntarily by a witness? Third, would the refusal — or the agreement — of a witness to use one of these technologies itself be admissible in evidence? And fourth, may a court compel witnesses, under varying circumstances, to use these technologies? The answers to these questions will vary with the setting (especially criminal or civil), with the technology, and with other circumstances of the case, but they provide a useful framework for analysis.

Detecting Lies or Compelling Truth

The concept behind current polygraph machines dates back to the early twentieth century.[23] They seek to measure various physiological reactions associated with anxiety, such as sweating, breathing rate, and blood pressure, in the expectation that those signs of nervousness correlate with the speaker's knowledge that what he is saying is false. American courts have generally, but not universally, rejected them, although they are commonly used by the federal government

for various security clearances and investigations.[24] It has been estimated that their accuracy is about 85 to 90 percent.[25]

Now imagine that neuroscience leads to new ways to determine whether or not a witness is telling a lie or even to compel a witness to tell the truth. A brain-imaging device might, for example, be able to detect patterns or locations of brain activity known from experiments to be highly correlated with the subject's consciousness of falsehood. (I will refer to this as "lie detection.") Alternatively, drugs or other stimuli might be administered that made it impossible for a witness to do anything but tell the truth — an effective truth serum. (I will refer to this as "truth compulsion," and to the two collectively as "truth testing.") Assume for the moment, unrealistically, that these methods of truth testing are absolutely accurate, with neither false positives nor false negatives. How would, and should, courts treat the results of such truth testing? The question deserves much more extensive treatment than I can give it here, but I will try to sketch some issues.

Consider first the nonscientific issues of admissibility. One argument against admissibility was made by four justices of the Supreme Court in *United States v. Scheffer*,[26] a case involving a blanket ban on the admissibility of polygraph evidence. Scheffer, an enlisted man in the Air Force working with military police as an informant in drug investigations, wanted to introduce the results of a polygraph examination at his court-martial for illegal drug use.[27] The polygraph examination, performed by the military as a routine part of his work as an informant, showed that Scheffer denied illegal drug use during the same period that a urine test detected the presence of methamphetamine.[28] Military Rule of Evidence 707, promulgated by President George H. W. Bush in 1991, provides that "notwithstanding any other provision of law, the results of a polygraph examination, the opinion of a polygraph examiner, or any reference to an offer to take, failure to take, or taking of a polygraph examination, shall not be admitted into evidence."

The court-martial refused to admit Scheffer's evidence on the basis of Rule 707. His conviction was overturned by the Court of Appeals for the Armed Forces, which held that this per se exclusion of all polygraph evidence violated the Sixth Amendment.[29] The Supreme Court reversed in turn, upholding Rule 707, but in a fractured opinion. Justice Thomas wrote the opinion announcing the decision of the Court, which found the rule constitutional on three grounds: continued question about the reliability of polygraph evidence, the need to "preserve the jury's core function of making credibility determinations in criminal trials," and the avoidance of collateral litigation.[30] Justices Rehnquist, Scalia, and Souter joined the Thomas opinion in full. Justice Kennedy, joined by Justices O'Connor, Ginsburg, and Breyer, concurred in the section of the Thomas opinion based on reliability of polygraph evidence. Those four justices did not agree with the other two grounds.[31] Justice Stevens dissented, finding that the reliability of polygraph testing was already sufficiently well established to invalidate any per se exclusion.[32]

Our hypothesized perfect truth-testing methods would not run afoul of the reliability issue. Nor, assuming the rules for admitted "truth-tested" evidence were sufficiently clear, would collateral litigation appear to be a major concern. Such testing would seem, however, even more than the polygraph, to evoke the

concerns of the four justices about invading the sphere of the jury even when the witness had agreed to the use. Although at this point Justice Thomas's concern lacks the fifth vote it needs to become a binding precedent, the preservation of the jury's role might be seen by some courts as rising to a constitutional level under a federal or state constitutional right to a jury trial in criminal or civil cases. This issue could certainly be used as a policy argument against allowing such evidence, and, as an underlying concern of the judiciary, it might influence judicial findings under *Daubert* or *Frye* about the reliability of the methods.[33] Assuming robust proof of reliability, it is hard to see any other strong argument against the admission of this kind of evidence. (Whether Justice Thomas's rationale, either as a constitutional or a policy matter, would apply to nonjury trials seems more doubtful.)

On the other hand, some defendants might have strong arguments *for* the admission of such evidence, at least in criminal cases. Courts have found in the Sixth Amendment, perhaps in combination with the Fifth Amendment, a constitutional right for criminal defendants to present evidence in their own defense. Scheffer made this very claim, that Rule 707, in the context of his case, violated his constitutional right to present a defense. The Supreme Court has two lines of cases dealing with this right. In *Chambers v. Mississippi*, the Court resolved the defendant's claim by balancing the importance of the evidence to the defendant's case with the reliability of the evidence.[34] In *Rock v. Arkansas*, a criminal defendant alleged that she could remember the events only after having her memory "hypnotically refreshed."[35] The Court struck down Arkansas's per se rule against hypnotically refreshed testimony on the ground that the rule, as a per se rule, was arbitrary and therefore violated the Sixth Amendment rights of a defendant to present a defense and to testify in her own defense. The *Rock* opinion also stressed that the Arkansas rule prevented the defendant from telling her own story in any meaningful way. That might argue in favor of the admissibility of a criminal defendant's own testimony, under truth compulsion, as opposed to an examiner giving his or her expert opinion about the truthfulness of the witness's statements based on the truth detector results. These constitutional arguments for the admission of such evidence would not seem to arise with the prosecution's case or with either the plaintiff's or the defendant's case in a civil matter (unless some state constitutional provisions were relevant).[36]

Assuming "truth-tested" testimony were admissible, should either a party's, or a witness's, offer or refusal to undergo truth testing be admissible in evidence as relevant to his or her honesty? Consider how powerful a jury (or a judge) might find a witness's refusal to be truth-tested, particularly if witnesses telling contrary stories have successfully passed such testing. Such a refusal could well prove fatal to the witness's credibility.

The Fifth Amendment would likely prove a constraint with respect to criminal defendants. The fact that a defendant has invoked the Fifth Amendment's privilege against self-incrimination cannot normally be admitted into evidence or considered by the trier of fact. Otherwise, the courts have held, the defendant would be penalized for having invoked the privilege. A defendant who takes the stand might well be held to have waived that right and so might be impeached

by his refusal to undergo truth testing. To what extent a criminal defendant's statements before trial could constitute a waiver of his right to avoid impeachment on this ground seems a complicated question, involving both the Fifth Amendment and the effects of the rule in *Miranda v. Arizona*.[37] These complex issues would require a paper of their own; I will not discuss them further here.

Apart from a defendant in a criminal trial, it would seem that any other witnesses should be impeachable for their refusal to be truth-tested; they might invoke the privilege against self-incrimination, but the trier of fact, in weighing their credibility in this trial, would not be using that information against them. And this should be true for prosecution witnesses as well as defense witnesses. Both parties and nonparty witnesses at civil trials would seem generally to be impeachable for their refusal to be truth-tested, except in some jurisdictions that hold that a civil party's invocation of the Fifth Amendment may not be commented upon even in a civil trial.

It seems unlikely that a witness's *willingness* to undergo truth testing would add anything to the results of a test in most cases. It might, however, be relevant, and presumably admissible, if for some reason the test did not work on that witness or, unbeknownst to the witness at the time she made the offer, the test results turned out to be inadmissible.

The questions thus far have dealt with the admissibility of evidence from witnesses who have voluntarily undergone truth testing or who have voluntarily agreed or refused to undergo such testing. Could, or should, either side have the power to compel a witness to undergo either method of truth testing? At its simplest, this might be a right to retest a witness tested by the other side, a claim that could be quite compelling if the results of these methods, like the results of polygraphy, were believed to be significantly affected by the means by which the test was administered — not just the scientific process but the substance and style of the questioning. More broadly, could either side compel a witness, in a criminal or a civil case, to undergo such truth testing either as part of a courtroom examination or in pretrial discovery?

Witnesses certainly can be compelled to testify, at trial or in deposition. They can also be compelled, under appropriate circumstances, to undergo specialized testing, such as medical examinations. (The latter procedures typically require express authorization from the court rather than being available as of right to the other side.) Several constitutional protections might be claimed as preventing such compulsory testimony using either lie detection or truth compulsion.

A witness might argue that the method of truth testing involved was so great an intrusion into the person's bodily (or mental) integrity as to "shock the conscience" and violate the Fifth or Fourteenth Amendment, as did the stomach pumping in *Rochin v. California*.[38] A test method involving something like the wearing of headphones might seem quite different from one involving an intravenous infusion of a drug or envelopment in the coffinlike confines of a fullsized MRI machine. The strength of such a claim might vary according to whether the process was lie detection and merely verified (or undercut) the witness's voluntarily chosen words, or whether it was truth compulsion and interfered with the witness's ability to choose her own words.

The Fifth Amendment's privilege against self-incrimination would usually protect those who choose to invoke it (and who have not been granted immunity). As noted above, that would not necessarily protect either a party in a civil case or a nondefendant witness in a criminal case from impeachment for invoking the privilege.

Would a witness have a possible Fourth Amendment claim that such testing, compelled by court order, was an unreasonable search and seizure by the government? I know of no precedent for considering questioning itself as a search or seizure, but this form of questioning could be seen as close to searching the confines of the witness's mind. In that case, would a search warrant or other court order suffice to authorize the test against a Fourth Amendment claim? And, if it were seen in that light, could a search warrant be issued for the interrogation of a person under truth testing outside the context of any pending criminal or civil litigation — and possibly even outside the context of an arrest and Miranda rights that follow it? If this seems implausible, consider what an attractive addition statutory authorization of such "mental searches" might seem to the Bush administration or to Congress in the next version of the USA PATRIOT Act.[39]

In some circumstances, First Amendment claims might be plausible. Truth compulsion might be held to violate in some respects the right not to speak, although the precedents on this point are quite distant, involving a right not to be forced to say, or to publish, specific statements. It also seems conceivable that some religious groups could object to these practices and might be able to make a free exercise clause argument against such compelled speech.

These constitutional questions are many and knotty. Equally difficult is the question whether some or all of them might be held to be waived by witnesses who either had undergone truth testing themselves or had claimed their own truthfulness, thus "putting it in question." And, of course, even if parties or witnesses have no constitutional rights against being ordered to undergo truth testing, that does not resolve the policy issue of whether such rights should exist as a matter of statute, rule, or judicial decision.

Parties and witnesses are not the only relevant actors in trials. Truth testing might also be used in voir dire. Prospective jurors are routinely asked about their knowledge of the parties or of the case or about their relevant biases. Could a defendant claim that his right to an unbiased juror was infringed if such methods were not used and hence compel prospective jurors to undergo truth testing? Could one side or the other challenge for cause a prospective juror who was unwilling to undergo such testing? In capital cases, jurors are asked whether they could vote to convict in light of a possible death penalty; truth testing might be demanded by the prosecution to make sure the prospective jurors are being honest.

It is also worth considering how the existence of such methods might change the pretrial maneuvers of the parties. Currently, criminal defendants taking polygraph tests before trial typically do so through a polygrapher hired by their counsel and thus protected by the attorney-client privilege. That may change. Whatever rules are adopted concerning the admissibility of evidence from truth testing will undoubtedly affect the incentives of the parties, in civil

and criminal cases, to undergo truth testing. This may, in turn, have substantial, and perhaps unexpected, repercussions for the practices of criminal plea bargaining and civil settlement. As the vast majority of criminal and civil cases are resolved before trial, the effects of truth testing could be substantial.

Even more broadly, consider the possible effects of truth testing on judicial business generally. Certainly not every case depends on the honesty of witness testimony. Some hinge on conclusions about reasonableness or negligence; others are determined by questions of law. Even factual questions might be the focus of subjectively honest, but nevertheless contradictory, testimony from different witnesses. Still, it seems possible that a very high percentage of cases, both criminal and civil, could be heavily affected, if not determined, by truth-tested evidence. If truth testing reduced the number of criminal trials tenfold, that would surely raise Justice Thomas's concern about the proper role of the jury, whether or not that concern has constitutional implications. It would also have major effects on the workload of the judiciary and, perhaps, on the structure of the courts.

The questions raised by a perfect method of truth testing are numerous and complicated. They are also probably unrealistic, given that no test will be perfect. Most of these questions would require reconsideration if truth testing turned out to be only 99.9 percent accurate, or 99 percent accurate, or 90 percent accurate. That reconsideration would have to examine not just overall "accuracy" but the rates of both false positives (the identification of a false statement as true) and false negatives (the identification of a true statement as false), as those may have different implications. Similarly, decisions on admissibility might differ if accuracy rates varied with a witness's age, sex, training in "beating" the machine, or other traits. And, of course, proving the accuracy of such methods as they are first introduced or as they are altered will be a major issue in court systems under the *Daubert* or *Frye* tests.

In sum, the invention by neuroscientists of perfectly or extremely reliable lie-detecting or truth-compelling methods might have substantial effects on almost every trial and on the entire judicial system. How those effects would play out in light of our current criminal justice system, including the constitutional protections of the Bill of Rights, is not obvious.

Determining Bias

Evidence produced by neuroscience may play other significant roles in the courtroom. Consider the possibility of testing, through neuroimaging, whether a witness or a juror reacts negatively to particular groups. Already, neuroimaging work is going on that looks for — and finds — differences in the reaction of a subject's brain to people of different races. If that research is able to associate certain patterns of activity with negative bias, its possible use in litigation could be widespread.

As with truth testing, courts would have to decide whether bias testing met *Daubert* or *Frye*, whether voluntary test results would be admissible, whether a party's or witness's refusal or agreement to take the test could be admitted into evidence, and whether the testing could ever be compelled. The analysis on these points seems similar to that for truth testing, with the possible exception of a lesser role for the privilege against self-incrimination.

If allowed, neuroscience testing for racial bias might be used where bias was a relevant fact in the case, as in claims of employment discrimination based on race. It might be used to test any witness for bias for or against a party of a particular race. It might be used to test jurors to ensure that they were not biased against parties because of race. One could even, barely, imagine it being used to test judges for bias, perhaps as part of a motion to disqualify for bias. And, of course, such bias testing need not be limited to bias based on race, nationality, sex, or other protected groups. One could seek to test, in appropriate cases, for bias against parties or witnesses based on their occupation (the police, for example), their looks (too fat, too thin), their voices (a Southern accent, a Boston accent), or many other characteristics.

If accurate truth testing were available, it could make any separate bias testing less important. Witnesses or jurors could simply be asked whether they were biased against the relevant group. On the other hand, it is possible that people might be able to answer honestly that they were not biased, when they were in fact biased. Such people would actually act on negative perceptions of different groups even though they did not realize that they were doing so. If the neuroimaging technique were able to detect people with that unconscious bias accurately, it might still be useful in addition to truth testing.

Bias testing might even force us to reevaluate some truisms. We say that the parties to litigation are entitled to unbiased judges and juries, but we mean that they are entitled to judges and juries that are not demonstrably biased in a context where demonstrating bias is difficult. What if demonstrating bias becomes easy — and bias is ubiquitous? Imagine a trial in which neuroimaging shows that all the prospective jurors are prejudiced against a defendant who looks like a stereotypical Hell's Angel because they think he looks like a criminal. Or what if the only potential jurors who didn't show bias were themselves members of quasi-criminal motorcycle gangs? What would the defendant's right to a fair trial mean in that context?

Evaluating or Eliciting Memory

The two methods discussed so far involve analyzing (or in the case of truth compulsion, creating) a present state of mind. It is conceivable that neuroscience might also provide courts with at least three relevant tools concerning memory. In each case, courts would again confront questions of the reliability of the tools, their admissibility with the witness's permission, the impeaching of witnesses for failing to use the tools, and the compelling of a witness to use such a memory enhancing tool.

The first tool might be an intervention, pharmacological or otherwise, that improved a witness's ability to remember events. It is certainly conceivable that researchers studying memory-linked diseases might create drugs that help people retrieve old memories or retrieve them in more detail. This kind of intervention would not be new in litigation. The courts have seen great controversy over the past few years over "repressed" or "recovered" memories, typically traumatic

early childhood experiences brought back to adult witnesses by therapy or hypnosis. Similarly, some of the child sex abuse trials over the past decade have featured testimony from young children about their experiences. In both cases, the validity of these memories has been questioned. We do know from research that people will often come to remember, in good faith, things that did not happen, particularly when those memories have been suggested to them.[40] Similar problems might arise with "enhanced" memories.[41]

A second tool might be the power to assess the validity of a witness's memory. What if neuroscience could give us tools to distinguish between "true" and "false" memory? One could imagine different parts of a witness's brain being used while recounting a "true" memory, a "false" memory, or a creative fiction. Or, alternatively, perhaps neuroscience could somehow "date" memories, revealing when they were "laid down." These methods seem more speculative than either truth testing or bias testing, but if either one (or some other method of testing memory) turned out to be feasible, courts would, after the *Daubert* or *Frye* hearings, again face questions of admitting testimony concerning their voluntary use, allowing comment on a witness's refusal to take a test, and possibly compelling their use.

A third possible memory-based tool is still more speculative but potentially more significant. There have long been reports that electrical stimulation can, sometimes, trigger a subject to have what appears to be an extremely detailed and vivid memory of a past scene, almost like reliving the experience. At this point, we do not know whether such an experience is truly a memory or is more akin to a hallucination; if it is a memory, how to reliably call it up; how many memories might potentially be recalled in this manner; or, perhaps most important, how to recall any specific memory. Whatever filing system the brain uses for memories seems to be, at this point, a mystery. Assume that it proves possible to cause a witness to recall a specific memory in its entirety, perhaps by localizing the site of the memory first through neuroimaging the witness while she calls up her existing memories of the event. A witness could then, perhaps, *relive* an event important to trial, either before trial or on the witness stand. One can even, just barely, imagine a technology that might be able to "read out" the witness's memories, intercepted as neuronal firings, and translate them directly into voice, text, or the equivalent of a movie for review by the finder of fact. Less speculatively, one can certainly imagine a drug that would improve a person's ability to retrieve specific long-term memories.

While a person's authentic memories, no matter how vividly they are recalled, may not be an accurate portrayal of what actually took place, they would be more compelling testimony than that provided by typically foggy recollections of past events. Once again, if the validity of these methods were established, the key questions would seem to be whether to allow the admission of evidence from such a recall experience, voluntarily undertaken; whether to admit the fact of a party's or witness's refusal or agreement to use such a method; and whether, under any circumstances, to compel the use of such a technique.[42]

Other Litigation-Related Uses

Neuroscience covers a wide range of brain-related activities. The three areas sketched above are issues where neuroscience could conceivably have an impact on almost any litigation, but neuroscience might also affect any specific kind of litigation where brain function was relevant. Consider four examples.

The most expensive medical malpractice cases are generally so-called bad baby cases. In these cases, children are born with profound brain damage. Damages can be enormous, sometimes amounting to the cost of round-the-clock nursing care for 70 years. Evidence of causation, however, is often very unclear. The plaintiff parents allege that the defendants managed the delivery negligently, which led to a lack of oxygen that in turn caused the brain damage. Defendants, in addition to denying negligence, usually claim that the damage had some other, often unknown, cause. Jurors are left with a family facing a catastrophic situation and no strong evidence about what caused it. Trial verdicts, and settlements, can be extremely high, accounting in part for the high price of malpractice insurance for obstetricians. If neuroscience could reliably distinguish between brain damage caused by oxygen deprivation near birth and that caused earlier, these cases would have more accurate results, in terms of compensating families only when the damage was caused around the time of delivery. Similarly, if fetal neuroimaging could reveal serious brain damage before labor, those images could be evidence about the cause of the damage. (One can even imagine obstetricians insisting on prenatal brain scans before delivery in order to establish a baseline.) A more certain determination of causation should also lead to more settlements and less wasteful litigation. (Of course, in cases where neuroscience showed that the damage was consistent with lack of oxygen around delivery, the defendants' negligence would still be in question.)

In many personal injury cases, the existence of intractable pain may be an issue. In some of those cases there may be a question whether the plaintiff is exaggerating the extent of the pain. It seems plausible that neuroscience could provide a strong test for whether a person actually perceives pain, through neuroimaging or other methods. It might be able to show whether signals were being sent by the sensory nerves to the brain from the painful location on the plaintiff's body. Alternatively, it might locate a region of the brain that is always activated when a person feels pain or a pattern of brain activation that is always found during physically painful experiences. Again, by reducing uncertainty about a very subjective (and hence falsifiable) aspect of a case, neuroscience could improve the litigation system.

A person's competency is relevant in several legal settings, including disputed guardianships and competency to stand trial. Neuroscience might be able to establish some more objective measures that could be considered relevant to competency. (It might also reveal that what the law seems pleased to regard as a general, undifferentiated competency does not, in fact, exist.) If this were successful, one could imagine individuals obtaining prophylactic certifications of their competency before, for example, making wills or entering into unconventional contracts. The degree of mental ability is also relevant in capital punishment,

where the Supreme Court has recently held that executing the mentally retarded violates the Eighth Amendment.[43] Neuroscience might supply better, or even determinative, evidence of mental retardation. Or, again, it may be that neuroscience would force the courts to recognize that "mental retardation" is not a discrete condition.

Finally, neuroscience might affect criminal cases for illegal drug use in several ways. Neuroscience might help determine whether a defendant was "truly" addicted to the drug in question, which could have some consequences for guilt and sentencing. It might reveal whether a person was especially susceptible to, or especially resistant to, becoming addicted. Or it could provide new ways to block addiction, or even pleasurable sensations, with possible consequences for sentencing and treatment. Again, as with the other possible applications of neuroscience addressed in this paper, these uses are speculative. It would be wrong to count on neuroscience to solve, *deus ex machina*, our drug problems. It does not seem irresponsible, however, to consider the possible implications of neuroscience breakthroughs in this area.[44]

ENDNOTES

1. I want to thank particularly my colleagues John Barton, George Fisher, and Tino Cuellar for their helpful advice on intellectual property, evidentiary issues, and neuroscience predictions in the criminal justice system, respectively. I also want to thank the participants at the AAAS/Dana Foundation workshop on law and neuroscience for their useful comments, as well as colleagues and students who made suggestions at talks on these topics I gave at Stanford during the fall of 2003. Last, but not least, I want to thank my research assistant, Melanie Blunschi, for her able help.
2. Shakespeare, *Macbeth*, act 1, scene 4, lines 11–14.
3. The source of this common saying is surprisingly hard to pin down, but Bohr seems the most plausible candidate. See Henry T. Greely, *Trusted Systems and Medical Records: Lowering Expectations, Stan. L. Rev.* 52: 1585, 1591 n. 9 (2000). [The saying has also been attributed to Yogi Berra – Ed.]
4. See, for example, Secretary's Advisory Committee on Genetic Testing, *Enhancing the Oversight of Genetic Tests: Recommendations of the SACGT*, National Institutes of Health (July 2000), report available at http://www4.od.nih.gov/oba/sacgt/reports/oversight_report.htm; N. A. Holtzman and M. S. Watson, eds., *Promoting Safe and Effective Genetic Testing in the United States: Final Report of the Task Force on Genetic Testing* (Baltimore: Johns Hopkins University Press, 1997); and Barbara A. Koenig, Henry T. Greely, Laura McConnell, Heather Silverberg, and Thomas A. Raffin, "PGES Recommendations on Genetic Testing for Breast Cancer Susceptibility." *Journal of Women's Health* (June 1998) 7: 531–545.
5. Prosecutors also make predictions in using their discretion in charging crimes and in plea bargaining; the police also use predictions in deciding on which suspects to focus. My colleague Tino Cuellar pointed out to me that neuroscience data, from a current prosecution or investigation of an individual or from earlier investigations of

that person, might play a role in deciding the criminal charge or whether to plea bargain.

6. The implications of neuroscientific assessments of a person's state of mind at the time of the crime for criminal liability are discussed in Professor [Stephen J.] Morse's paper [Chapter 9 in the book in which this article was originally published.]. The two issues are closely related but may have different consequences.
7. See H. G. Brunner, M. Nelen, X. O. Breakefield, H. H. Ropers, and B. A. van Oost, "Abnormal Behavior Associated with a Point Mutation in the Structural Gene for Monoamine Oxidase A." *Science* 262: 5133–5136 (October 22, 1993), discussed in V. Morrell "Evidence Found for a Possible 'Aggression' Gene." *Science* 260: 1722–1724 (June 18, 1993); and Avshalon Caspi, Joseph McClay, Terrie E. Moffitt, Jonathan Mill, Judy Martin, Ian W. Craig, Alan Taylor, and Richie Poulton, "Role of Genotype in the Cycle of Violence in Maltreated Children." *Science* 297: 851–854 (August 2, 2002), discussed in Erik Stokstad, "Violent Effects of Abuse Tied to Gene." *Science* 297: 752 (August 2, 2002).
8. See the discussion of the four unsuccessful efforts to use XYY status as a defense in criminal cases in Deborah W. Denno, "Human Biology and Criminal Responsibility: Free Will or Free Ride?" 137 U. PA. L. REV. 613, 620–622 (1988).
9. See two excellent recent discussions of these cases: Stephen J. Morse, *Uncontrollable Urges and Irrational People*, VA. L. REV. 88 (2002): 1025; and Peter C. Pfaffenroth, *The Need for Coherence: States' Civil Commitment of Sex Offenders in the Wake of Kansas v. Crane*, STAN. L. REV. 55 (2003): 2229.
10. Kan. Stat. Ann. §59–29a02(a) (2003).
11. 521 U.S. 346, 360 (1997).
12. Ibid.
13. 534 U.S. 407 (2002).
14. Ibid., p. 413.
15. For a representative sample of views, see Kathy L. Hudson, Karen H. Rothenberg, Lori B. Andrews, Mary Jo Ellis Kahn, and Francis S. Collins, "Genetic Discrimination and Health Insurance: An Urgent Need for Reform," *Science* 270 (1995): 391 (broadly favoring a ban on discrimination); Richard A. Epstein, *The Legal Regulation of Genetic Discrimination: Old Responses to New Technology*, B.U.L. REV. 74 (1994): 1 (opposing a ban on the use of genetic information in employment discrimination); Henry T. Greely, *Genotype Discrimination: The Complex Case for Some Legislative Protection*, U. PA. L. REV. 149 (2001): 1483 (favoring a carefully drawn ban, largely to combat exaggerated fears of discrimination); and Colin S. Diver and Jane M. Cohen, *Genophobia: What Is Wrong with Genetic Discrimination?* U. PA. L. REV. 149 (2001): 1439 (opposing a ban on its use in health insurance).
16. For the most up-to-date information on state law in this area, see Ellen W. Clayton, "Ethical, Legal, and Social Implications of Genomic Medicine." *New Eng. J. Med.* 349 (2003): 342.
17. After considering, but not adopting, similar legislation since 1997, the Senate in October 2003 passed the Genetic Information NonDiscrimination Act, S. 1053. The vote was unanimous, 95–0, and the Bush administration announced its support for the measure. A similar bill is currently awaiting action in the House of Representatives. See Aaron Zitner, "Senate Blocks Genetic Discrimination," *Los Angeles Times*, October 15, 2003, sec. 1, p. 16.

18. "Brighthouse Institute for Thought Sciences Launches First 'Neuromarketing' Research Company," press release (June 22, 2002) found at http://www.prweb.com/releases/2002/6/prweb40936.php.
19. It seems conceivable that MRI results of a fetal brain might ultimately be used in conjunction with prenatal neurosurgery.
20. See, for example, *Pierce v. Society of Sisters*, 268 U.S. 510 (1925); *Meyer v. Nebraska*, 262 U.S. 390 (1923).
21. *Daubert v. Merrell Dow Pharmaceuticals*, 516 U.S. 869; 116 S. Ct. 189; 133 L. Ed. 2d 126 (1993).
22. *Frye v. United States*, 54 App. D.C. 46, 293 F. 1013 (1923, D.C. Cir.).
23. A National Academy of Sciences panel examining polygraph evidence dated the birth of the polygraph machine to William Marston, between 1915 and 1921. Committee to Review the Scientific Evidence on the Polygraph, National Research Council, *The Polygraph and Lie Detection* (2003) pp. 291–297. Marston was the polygraph examiner whose testimony was excluded in *Frye v. United States*.
24. See the discussion in *United States v. Scheffer*, 523 U.S. 303, 310–11 (1998). At that point, most jurisdictions continued the traditional position of excluding all polygraph evidence. Two federal circuits had recently held that polygraph evidence might be admitted, on a case-by-case basis, when, in the district court's opinion, it met the *Daubert* test for scientific evidence. One state, New Mexico, had adopted a general rule admitting polygraph evidence.
25. Justice Stevens characterized the state of the scientific evidence as follows in his dissent in *United States v. Scheffer*:

    There are a host of studies that place the reliability of polygraph tests at 85 percent to 90 percent. While critics of the polygraph argue that accuracy is much lower, even the studies cited by the critics place polygraph accuracy at 70 percent. Moreover, to the extent that the polygraph errs, studies have repeatedly shown that the polygraph is more likely to find innocent people guilty than vice versa. Thus, exculpatory polygraphs — like the one in this case — are likely to be more reliable than inculpatory ones.

    United States v. Scheffer, 523 U.S. 303, 333 (1998) (Stevens, J., dissenting) (footnotes omitted).

    A committee of the National Academy of Sciences has recently characterized the evidence as follows:

    Notwithstanding the limitations of the quality of the empirical research and the limited ability to generalize to real-world settings, we conclude that in populations of examinees such as those represented in the polygraph research literature, untrained in countermeasures, specific-incident polygraph tests can discriminate lying from truth telling at rates well above chance, though well below perfection.

    Committee to Review the Scientific Evidence on the Polygraph, p. 4.
26. 523 U.S. 303 (1998).
27. Ibid., p. 305.
28. Ibid., p. 306.
29. 44 M.J. 442 (1996).
30. 532 U.S. at 312–313.
31. Ibid., p. 318.

32. Ibid., p. 320.
33. I owe this useful insight to Professor Fisher.
34. 410 U.S. 284 (1973).
35. 483 U.S. 44 (1987).
36. A constitutional right to admit such evidence might also argue for a constitutional right for indigent defendants to have the government pay the cost of such truth testing, which might be small or great.
37. 396 U.S. 868 (1969).
38. 342 U.S. 165 (1952).
39. Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism Act ("USA PATRIOT Act") of 2001, PL 107–156 (2001).
40. As with bias detection, truth testing could limit the need for such memory assessment when the witness was conscious of the falsity of the memory. Memory assessment, however, could be useful in cases where the witness had actually come to believe in the accuracy of a questioned "false" memory.
41. It is quite plausible that researchers might create drugs that help people make, retain, and retrieve new memories, important in conditions such as Alzheimer's disease. One can imagine giving such a drug in advance to someone whom you expected to witness an important event — although providing such a person with a video recorder might be an easier option.
42. Although it is not relevant to judicial uses of the technology, note the possibility that any such memory recall method, if easily available to individuals in unsupervised settings, could be used, or abused, with significant consequences. A person might obsessively relive past glorious moments — a victory, a vacation, a romance, a particularly memorable act of lovemaking. A depressed person might dwell compulsively on bad memories. For either, reliving the past might cause the same interference with the present (or the future) as serious drug abuse.
43. *Atkins v. Virginia*, 536 U.S. 304 (2003).
44. At the same time, neuroscience could give rise to new drugs or drug equivalents. A neuroscience-devised trigger of pleasurable sensations — say, that would cause powerful orgasms — could function effectively as a powerful drug of abuse.

PART VI

Contemporary Technological Dilemmas: Information and Communications Technology

Whereas many of the social impacts of the new biology and other biomedical advances are speculative and in the future, the impacts of computers and information technology are being felt right now. One can hardly think or talk about technology without considering computers. In fact, in many contexts (for example, the "Technology Services" department of many organizations), "technology" is assumed to *mean* computers.

Computers, especially personal computers, are an integral part of most people's lives in the United States in the early twenty-first century. Increasingly, moreover, having a PC or a Mac means being connected to the Internet. Computers began decades ago to have substantial effects on human work, on power and control in society, and on social and economic equity. But the Internet, which during the 1990s exploded into an entirely new medium of communication, has intensified these effects, added new ones, and accelerated the pace at which they are being felt. Little of this was foreseen or planned. For starters, the engineers and scientists responsible for developing computers, and even the heads of the companies that produced the early versions, completely failed to see the extent to which computers would permeate society. In the first chapter in Part VI, historian Paul Ceruzzi of the Smithsonian Institution conducts a kind of retrospective technology assessment, looking at early expectations of the usefulness and impact of computers and finding these views remarkably myopic.

Following Ceruzzi, Wendell Berry, farmer, author, and poet, tells us why he rejects the computer and does his writing instead by daylight on a manual typewriter. Berry, who first published this essay in 1987, describes himself as a conservationist. If so, he is a rather extreme one. His essay expresses a profound distrust of government, large corporations, and other centralized institutions.

On the other hand, Deborah Johnson, a philosopher and ethicist, takes the existence of computers and their wide use in society as a given. She asks about the ethical issues they raise. Are they the same kinds of issues raised by other technologies and other areas of society? Or is there something unique about "computer ethics?" Nicholas Carr's chapter, which follows Johnson's, asks a rather different, but no less provocative question: "Is Google Making Us Stupid?" In a way, the question is an updated version of Marshall McLuhan's famous phrase, "The medium is the message." McLuhan was writing about television and other media of the mid- twentieth century and suggesting that our interactions with these media shape the way in which we see the world, indeed the nature of our consciousness. Carr makes a similar point about the Internet.

Part VI wraps up with two chapters on a somewhat more technical issue, but one that has major implications for the way in which computer networks are likely to develop in the future. This is the issue of "net neutrality," the matter of whether Internet service providers are allowed to discriminate among the different kinds of content and applications that they carry. Consumer advocates and others favoring an open Internet argue that network owners (ISPs) must not do so, that they must treat all content similarly. Others argue that discriminating among uses is the only way that rapidly increasing network traffic can be managed intelligently. Chapters 25 and 26 present these two opposing points of view.

21

An Unforeseen Revolution: Computers and Expectations, 1935–1985

PAUL CERUZZI

Paul Ceruzzi's fine essay, "An Unforeseen Revolution: Computers and Expectations, 1935–1985," is an excellent way to put the subject of information and communications technology in perspective. Ceruzzi looks back at the early forecasts of the societal impact of computers. He finds that the computer pioneers of the 1940s assumed that perhaps half a dozen of the giant new machines would serve the world's needs for the foreseeable future. As Joseph Corn notes in the introduction to his book, Imagining Tomorrow, *in which this reading was first published, this "dazzling failure of prophecy" is explained by the fact that most of the computer pioneers were physicists who viewed the new devices as equipment for their experiments and found it hard to imagine that their inventions might be applied to entirely different fields, such as payroll processing, trading recorded music, publishing books, and making animated films. More recently, since Corn's words were written some years ago, he fails to mention (because they did not exist) the convergence of computing with mobile communications and the remarkable growth of texting, mobile e-mail and web access, and all of the other ways in which iPhones, iPads, Blackberrys, Androids, etc. have changed our lives — not to mention Facebook, Twitter, and other social networking applications. The impact of computers on society has been staggering, and it is sobering*

Paul Ceruzzi, "An Unforeseen Revolution: Computers and Expectations, 1935–1985," From *Imagining Tomorrow: History, Technology and the American Future*, edited by Joseph J. Corn. Reprinted by permission of the author.

to realize how little of this impact was anticipated by those most responsible for developing and introducing this new technology.

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The "computer revolution" is here. Computers seem to be everywhere: at work, at play, and in all sorts of places in between. There are perhaps half a million large computers in use in America [in 1986], seven or eight million personal computers, five million programmable calculators, and millions of dedicated microprocessors built into other machines of every description. [*Editor's Note*: Since this article was written, the number of personal computers in use has increased vastly. The *Computer Industry Almanac* reported that the number of PCs in use worldwide exceeded 1.2 billion in 2008. The United States, which accounts for about 22 percent of these, is forecast to have more PCs than people by 2013.]

The changes these machines are bringing to society are profound, if not revolutionary. And, like many previous revolutions, the computer revolution is happening very quickly. The computer as defined today did not exist in 1950. Before World War II, the word *computer* meant a human being who worked at a desk with a calculating machine, or something built by a physics professor to solve a particular problem, used once or twice, and then retired to a basement storeroom. Modern computers — machines that do a wide variety of things, many having little to do with mathematics or physics — emerged after World War II from the work of a dozen or so individuals in England, Germany, and the United States. The "revolution," however one may define it, began only when their work became better known and appreciated.

The computer age dawned in the United States in the summer of 1944, when a Harvard physics instructor named Howard Aiken publicly unveiled a giant electromechanical machine called the Mark I. At the same time, in Philadelphia, J. Presper Eckert, Jr., a young electrical engineer, and John Mauchly, a physicist, were building the ENIAC, which, when completed in 1945, was the world's first machine to do numerical computing with electronic rather than mechanical switches.

Computing also got under way in Europe during the war. In 1943, the British built an electronic machine that allowed them to decode intercepted German radio messages. They built several copies of this so-called Colossus, and by the late 1940s general-purpose computers were being built at a number of British institutions. In Germany, Konrad Zuse, an engineer, was building computers out of used telephone equipment. One of them, the Z4, survived the war and had a long and productive life at the Federal Technical Institute in Zurich.

These machines were the ancestors of today's computers. They were among the first machines to have the ability to carry out any sequence of arithmetic operations, keep track of what they had just done, and adjust their actions

accordingly. But machines that only solve esoteric physics problems or replace a few human workers, as those computers did, do not a revolution make. The computer pioneers did not foresee their creations as doing much more than that. They had no glimmering of how thoroughly the computer would permeate modern life. The computer's inventors saw a market restricted to a few scientific, military, or large-scale business applications. For them, a computer was akin to a wind tunnel: a vital and necessary piece of apparatus, but one whose expense and size limited it to a few installations.

For example, when Howard Aiken heard of the plans of Eckert and Mauchly to produce and market a more elegant version of the ENIAC, he was skeptical. He felt they would never sell more than a few of them, and he stated that four or five electronic digital computers would satisfy all the country's computing needs.[1] In Britain in 1951, the physicist Douglas Hartree remarked, "We have a computer here in Cambridge; there is one in Manchester and one at the [National Physical Laboratory]. I suppose there ought to be one in Scotland, but that's about all."[2] Similar statements appear again and again in the folklore of computing.[3] This perception clearly dominated early discussions about the future of the new technology.[4] At least two other American computer pioneers, Edmund Berkeley and John V. Atanasoff, also recall hearing estimates that fewer than ten computers would satisfy all of America's computing needs.[5]

By 1951, about half a dozen electronic computers were running, and in May of that year companies in the United States and England began producing them for commercial customers. Eckert and Mauchly's dream became the UNIVAC — a commercial electronic machine that for a while was a synonym for *computer*, as *Scotch Tape* is for cellophane tape or *Thermos* is for vacuum bottles. It was the star of CBS's television coverage of the 1952 presidential election when it predicted, with only a few percent of the vote gathered, Eisenhower's landslide victory over Adlai Stevenson. With this election, Americans in large numbers suddenly became aware of this new and marvelous device. Projects got under way at universities and government agencies across the United States and Europe to build computers. Clearly, there was a demand for more than just a few of the large scale machines.

But not many more. The UNIVAC was large and expensive, and its market was limited to places like the U.S. Census Bureau, military installations, and a few large industries. (Only the fledgling aerospace industry seemed to have an insatiable appetite for those costly machines in the early years.) Nonetheless, UNIVAC and its peers set the stage for computing's next giant leap, from one of-a-kind special projects built at universities to mass-produced products designed for the world of commercial and business data processing, banking, sales, routine accounting, and inventory control.

Yet, despite the publicity accorded the UNIVAC, skepticism prevailed. The manufacturers were by no means sure of how many computers they could sell. Like the inventors before them, the manufacturers felt that only a few commercial computers would saturate the market. For example, an internal IBM study regarding the potential market for a computer called the Tape Processing Machine (a prototype of which had been completed by 1951) estimated that there was a market for no more than 25 machines of its size.[6] Two years later,

IBM developed a smaller computer for business use, the Model 650, which was designed to rent for $3,000 a month — far less than the going price for large computers like the UNIVAC, but nonetheless a lot more than IBM charged for its other office equipment. When it was announced in 1953, those who were backing the project optimistically foresaw a market for 250 machines. They had to convince others in the IBM organization that this figure was not inflated.[7]

As it turned out, businesses snapped up the 650 by the thousands. It became the Model T of computers, and its success helped establish IBM as the dominant computer manufacturer it is today [— or it was for many years, anyway — Ed.]. The idea finally caught on that a private company could manufacture and sell computers — of modest power, and at lower prices than the first monsters — in large quantities. The 650 established the notion of the computer as a machine for business as well as for science, and its success showed that the low estimates of how many computers the world needed were wrong.

Why the inventors and the first commercial manufacturers underestimated the computer's potential market by a wide margin is an interesting question for followers of the computer industry and for historians of modern technology. There is no single cause that accounts for the misperception. Rather, three factors contributed to the erroneous picture of the computer's future: a mistaken feeling that computers were fragile and unreliable; the institutional biases of those who shaped policies toward computer use in the early days; and an almost universal failure, even among the computer pioneers themselves, to understand the very nature of computing (how one got a computer to do work, and just how much work it could do).

It was widely believed that computers were unreliable because their vacuum-tube circuits were so prone to failure. Large numbers of computers would not be built and sold, it was believed, because their unreliability made them totally unsuitable for routine use in a small business or factory. (Tubes failed so frequently they were plugged into sockets to make it easy to replace them. Other electronic components were more reliable and so were soldered in place.) Eckert and Mauchly's ENIAC had 18,000 vacuum tubes. Other electronic computers got by with fewer, but they all had many more than most other electronic equipment of the day. The ENIAC was a room-sized Leviathan whose tubes generated a lot of heat and used great quantities of Philadelphia's electric power. Tube failures were indeed a serious problem, for if even one tube blew out during a computation it might render the whole machine inoperative. Since tubes are most likely to blow out within a few minutes after being switched on, the ENIAC's power was left on all the time, whether it was performing a computation or not.

Howard Aiken was especially wary of computers that used thousands of vacuum tubes as their switching elements. His Mark I, an electromechanical machine using parts taken from standard IBM accounting equipment of the day, was much slower but more rugged than computers that used vacuum tubes. Aiken felt that the higher speeds vacuum tubes offered did not offset their tendency to burn out. He reluctantly designed computers that used vacuum tubes, but he always kept the numbers of tubes to a minimum and used

electromechanical relays wherever he could.[8] Not everyone shared Aiken's wariness, but his arguments against using vacuum-tube circuits were taken seriously by many other computer designers, especially those whose own computer projects were shaped by the policies of Aiken's Harvard laboratory.

That leads to the next reason for the low estimates: Scientists controlled the early development of the computer, and they steered postwar computing projects away from machines and applications that might have a mass market. Howard Aiken, John von Neumann, and Douglas Hartree were physicists or mathematicians, members of a scientific elite. For the most part, they were little concerned with the mundane payroll and accounting problems that business faced every day.

Such problems involved little in the way of higher mathematics, and their solutions contributed little to the advancement of scientific knowledge. Scientists perceived their own place in society as an important one but did not imagine that the world would need many more men like themselves. Because their own needs were satisfied by a few powerful computers, they could not imagine a need for many more such machines. Even at IBM, where commercial applications took precedence, scientists shaped the perceptions of the new invention. In the early 1950s, the mathematician John von Neumann was a part-time consultant to the company, where he played no little role in shaping expectations for the new technology.

The perception of a modest and limited future for electronic computing came, most of all, from misunderstandings of its very nature. The pioneers did not really understand how humans would interact with machines that worked at the speed of light, and they were far too modest in their assessments of what their inventions could really do. They felt they had made a breakthrough in numerical calculating, but they missed seeing that the breakthrough was in fact a much bigger one. Computing turned out to encompass far more than just doing complicated sequences of arithmetic. But just how much more was not apparent until much later, when other people gained familiarity with computers. A few examples of objections raised to computer projects in the early days will make this clear.

When Howard Aiken first proposed building an automatic computer, in 1937, his colleagues at Harvard objected. Such a machine, they said, would lie idle most of the time, because it would soon do all the work required of it. They were clearly thinking of his proposed machine in terms of a piece of experimental apparatus constructed by a physicist; after the experiment is performed and the results gathered, such an apparatus has no further use and is then either stored or dismantled so that the parts can be reused for new experiments. Aiken's proposed "automatic calculating machine," as he called it in 1937, was perceived that way. After he had used it to perform the calculations he wanted it to perform, would the machine be good for anything else? Probably not. No one had built computers before. One could not propose building one just to see what it would look like; a researcher had to demonstrate the need for a machine with which he could solve a specific problem that was otherwise insoluble. Even if he could show that only with the aid of a computer could he solve the problem, that did not necessarily justify its cost.[9]

Later on, when the much faster electronic computers appeared, this argument surfaced again. Mechanical computers had proved their worth, but some felt that electronic computers worked so fast that they would spew out results much faster than human beings could assimilate them. Once again, the expensive computer would lie idle, while its human operators pondered over the results of a few minutes of its activity. Even if enough work was found to keep an electronic computer busy, some felt that the work could not be fed into the machine rapidly enough to keep its internal circuits busy.[10]

Finally, it was noted that humans had to program a computer before it could do any work. Those programs took the form of long lists of arcane symbols punched into strips of paper tape. For the first electronic computers, it was mostly mathematicians who prepared those tapes. If someone wanted to use the computer to solve a problem, he was allotted some time during which he had complete control over the machine; he wrote the program, fed it into the computer, ran it, and took out the results. By the early 1950s, computing installations saw the need for a staff of mathematicians and programmers to assist the person who wanted a problem solved, since few users would be expected to know the details of programming each specific machine. That meant that every computer installation would require the services of skilled mathematicians, and there would never be enough of them to keep more than a few machines busy. R. F. Clippinger discussed this problem at a meeting of the American Mathematical Society in 1950, stating, "In order to operate the modern computing machine for maximum output, a staff of perhaps twenty mathematicians of varying degrees of training are required. There is currently such a shortage of persons trained for this work that machines are not working full time."[11] Clippinger forecast a need for 2,000 such persons by 1960, implying that there would be a mere 100 computers in operation by then.

These perceptions, which lay behind the widely held belief that computers would never find more than a limited (though important) market in the industrialized world, came mainly from looking at the new invention strictly in the context of what it was replacing: calculating machines and their human operators. That context was what limited the pioneers' vision.

Whenever a new technology is born, few see its ultimate place in society. The inventors of radio did not foresee its use for broadcasting entertainment, sports, and news; they saw it as a telegraph without wires. The early builders of automobiles did not see an age of "automobility"; they saw a "horseless carriage." Likewise, the computer's inventors perceived its role in future society in terms of the functions it was specifically replacing in contemporary society. The predictions that they made about potential applications for the new invention had to come from the context of "computing" that they knew. Though they recognized the electronic computer's novelty, they did not see how it would permit operations fundamentally different from those performed by human computers.

Before there were digital computers, a mathematician solved a complex computational problem by first recasting it into a set of simpler problems, usually involving only the four ordinary operations of arithmetic — addition, subtraction multiplication, and division. Then he would take this set of more elementary

problems to human computers who would do the arithmetic with the aid of mechanical desktop calculators. He would supply these persons with the initial input data, books of logarithmic and trigonometric tables, paper on which to record intermediate results, and instructions on how to proceed. Depending on the computer's mathematical skill, the instructions would be more or less detailed. An unskilled computer had to be told, for example, that the product of two negative numbers is a positive number; someone with more mathematical training might need only a general outline of the computation.[12]

The inventors of the first digital computers saw their machines as direct replacements for this system of humans, calculators, tables, pencils and paper, and instructions. We know this because many early experts on automatic computing used the human computing process as the standard against which the new electronic computers were compared. Writers of early textbooks on "automatic computing" started with the time a calculator took to multiply two ten-digit numbers. To that time they added the times for the other operations: writing and copying intermediate results, consulting tables, and keying in input values. Although a skilled operator could multiply two numbers in ten or twelve seconds, in an eight-hour day he or she could be expected to perform only 400 such operations, each of which required about seventy-two seconds.[13] The first electronic computers could multiply two ten-digit decimal numbers in about 0.003 second; they could copy and read internally stored numbers even faster. Not only that, they never had to take a coffee break, stop for a meal, or sleep; they could compute as long as their circuits were working.

Right away, these speeds radically altered the context of the arguments that electronic components were too unreliable to be used in more than a few computers. It was true that tubes were unreliable and that the failure of even one during a calculation might vitiate the results. But the measure of reliability was the number of operations between failures, not the absolute number of hours the machine was in service. In terms of the number of elementary operations it could do before a tube failed, a machine such as ENIAC turned out to be quite reliable after all. If it could be kept running for even one hour without a tube failure, during that hour it could do more arithmetic than the supposedly more reliable mechanical calculators could do in weeks. Eventually the ENIAC's operators were able to keep it running for more than twenty hours a day, seven days week. Computers were reliable enough long before the introduction of the transistor provided a smaller and more rugged alternative to the vacuum tube.

So an electronic computer like the ENIAC could do the equivalent of about thirty million elementary operations in a day — the equivalent of the work of 75,000 humans. By that standard, five or six computers of the ENIAC's speed and size could do the work of 400,000 humans. However, measuring electronic computing power by comparing it with that of humans makes no sense. It is like measuring the output of a steam engine in "horsepower." For a one- or two-horsepower engine, the comparison is appropriate, but it would be impossible to replace a locomotive with an equivalent number of horses. So it is with computing power. But the human measure was the only one the pioneers knew. Recall that between 1945 and 1950 the ENIAC was the only working electronic

computer in the United States. At its public dedication in February 1946, Arthur Burks demonstrated the machine's powers to the press by having it add a number to itself over and over again — an operation that reporters could easily visualize in terms of human abilities. Cables were plugged in, switches set, and a few numbers keyed in. Burks then said to the audience, "I am now going to add 5,000 numbers together," and pushed a button on the machine. The ENIAC took about a second to add the numbers.[14]

Almost from the day the first digital computers began working, they seldom lay idle. As long as they were in working order, they were busy, even long after they had done the computations for which they were built.

As electronic computers were fundamentally different from the human computers they replaced, they were also different from special-purpose pieces of experimental apparatus. The reason was that the computer, unlike other experimental apparatus, was programmable. That is, the computer itself was not just "a machine," but at any moment it was one of an almost infinite number of machines, depending on what its program told it to do. The ENIAC's users programmed it by plugging in cables from one part of the machine to another (an idea borrowed from telephone switchboards). This rewiring essentially changed it into a new machine for each new problem it solved. Other early computers got their instructions from punched strips of paper tape; the holes in the tape set switches in the machine, which amounted to the same kind of rewiring effected by the ENIAC's plugboards. Feeding the computer a new strip of paper tape transformed it into a completely different device that could do something entirely different from what its designers had intended it to do. Howard Aiken designed his Automatic Sequence Controlled Calculator to compute tables of mathematical functions, and that it did reliably for many years. But in between that work it also solved problems in hydrodynamics, nuclear physics, and even economics.[15]

The computer, by virtue of its programmability, is not a machine like a printing press or a player piano — devices that are configured to perform a specific function.[16] By the classical definition, a machine is a set of devices configured to perform a specific function: One employs motors, levers, gears, and wire to print newspapers; another uses motors, levers, gears, and wire to play a prerecorded song. A computer is also made by configuring a set of devices, but its function is not implied by that configuration. It acquires its function only when someone programs it. Before that time it is an abstract machine, one that can do "anything." (It can even be made to print a newspaper or play a tune.) To many people accustomed to the machines of the Industrial Revolution, a machine having such general capabilities seemed absurd, like a toaster that could sew buttons on a shirt. But the computer was just such a device; it could do many things its designers never anticipated.

The computer pioneers understood the concept of the computer as a general-purpose machine, but only in the narrow sense of its ability to solve a wide range of mathematical problems. Largely because of their institutional backgrounds, they did not anticipate that many of the applications computers would find would require the sorting and retrieval of nonnumeric data. Yet, outside the scientific and university milieu, especially after 1950, it was just such work in industry and business

that underlay the early expansion of the computer industry. Owing to the fact that the first computers did not do business work, the misunderstanding persisted that anything done by a computer was somehow more "mathematical" or precise than that same work, done by other means. Howard Aiken probably never fully understood that a computer could not only be programmed to do different mathematical problems but could also do problems having little to do with mathematics. In 1956, he made the following statement, "... if it should ever turn out that the basic logics of a machine designed for the numerical solution of differential equations coincide with the logics of a machine intended to make bills for a department store, I would regard this as the most amazing coincidence that I have ever encountered."[17] But the logical design of modern computers for scientific work in fact coincides with the logical design of computers for business purposes. It is a "coincidence," all right, but one fully intended by today's computer designers.

The question remained whether electronic computers worked too fast for humans to feed work into them. Engineers and computer designers met the problem of imbalance of speeds head-on, by technical advances at both the input and output stages of computing. To feed in programs and data, they developed magnetic tapes and disks instead of tedious plugboard wiring or slow paper tape. For displaying the results of a computation, high-speed line printers, plotters, and video terminals replaced the slow and cumbersome electric typewriters and card punches used by the first machines.

Still, the sheer bulk of the computer's output threatened to inundate the humans who ultimately wanted to use it. But that was not a fatal fault, owing (again) to the computer's programmability. Even if in the course of a computation a machine handles millions of numbers, it need not present them all as its output. The humans who use the computer need only a few numbers, which the computer's program itself can select and deliver. The program may not only direct the machine to solve a problem, it also may tell the machine to select only the "important" part of the answer and suppress the rest.

Ultimately, the spread of the computer beyond physics labs and large government agencies depended on whether people could write programs that would solve different types of problems and that would make efficient use of the high internal speed of electronic circuits. That challenge was not met by simply training and hiring armies of programmers (although sometimes it must have seemed that way). It was met by taking advantage of the computer's ability to store its programs internally. By transforming the programming into an activity that did not require mathematical training, computer designers exploited a property of the machine itself to sidestep the shortage of mathematically trained programmers.

Although the computer pioneers recognized the need for internal program storage, they did not at first see that such a feature would have such a significant effect on the nature of programming. The idea of storing both the program and data in the same internal memory grew from the realization that the high speed at which a computer could do arithmetic made sense only if it got its instructions at an equally high speed. The plugboard method used with the ENIAC got instructions to the machine quickly but made programming awkward and slow for humans. In 1944, Eckert proposed a successor to the ENIAC (eventually

called the EDVAC), whose program would be supplied not by plugboards but by instructions stored on a high-speed magnetic disk or drum.

In the summer of 1944, John von Neumann first learned (by chance) of the ENIAC project, and within a few months he had grasped that giant machine's fundamentals — and its deficiencies, which Eckert and Mauchly hoped to remedy with their next computer. Von Neumann then began to develop a general theory of computing that would influence computer design to the present day.[18] In a 1945 report on the progress of the EDVAC, he stated clearly the concept of the stored program and how a computer might be organized around it.[19] Von Neumann was not the only one to do that, but it was mainly from his report and others following it that many modern notions of how best to design a computer originated.

For von Neumann, programming a digital computer never seemed to be much of an intellectual challenge; once a problem was stated in mathematical terms, the "programming" was done. The actual writing of the binary codes that got a computer to carry out that program was an activity he called coding, and from his writings it is clear that he regarded the relationship of coding to programming as similar to that of typing to writing. That "coding" would be as difficult as it turned out to be, and that there could emerge a profession devoted to that task, seems not to have occurred to him. That was due in part to von Neumann's tremendous mental abilities and in part to the fact that the problems that interested him (such as long-range weather forecasting and complicated aspects of fluid dynamics)[20] required programs that were short relative to the time the computer took to digest the numbers. Von Neumann and Herman Goldstine developed a method (still used today) of representing programs by flow charts. However, such charts could not be fed directly into a machine. Humans still had to do that, and for those who lacked von Neumann's mental abilities, the job remained as difficult as ever.

The intermediate step of casting a problem in the form of a flow chart, whatever its benefits, did not meet the challenge of making it easy for nonspecialists to program a computer. A more enduring method came from reconsidering, once again, the fact that the computer stored its program internally.

In his reports on the EDVAC, von Neumann had noted the fact that the computer could perform arithmetic on (and thus modify) its instructions as if they were data, since both were stored in the same physical device.[21] Therefore, the computer could give itself new orders. Von Neumann saw this as a way of getting a computer with a modest memory capacity to generate the longer sequences of instructions needed to solve complex problems. For von Neumann, that was a way of condensing the code and saving space.

However, von Neumann did not see that the output of a computer program could be, rather than numerical information, another program. That idea seemed preposterous at first, but once implemented it meant that users could write computer programs without having to be skilled mathematicians. Programs could take on forms resembling English and other natural languages. Computers then would translate these programs into long complex sequences of ones and zeroes, which would set their internal switches. One even could program a computer by simply selecting from a "menu" of commands (as at an automated bank teller) or

by paddles and buttons (as on a computerized video game). A person need not even be literate to program.

That innovation, the development of computer programs that translated commands simple for humans to learn into commands the computer needs to know, broke through the last barrier to the spread of the new invention.[22] Of course, the widespread use of computers today owes a lot to the technical revolution that has made the circuits so much smaller and cheaper. But today's computers-on-a-chip, like the "giant brains" before them, would never have found a large market had a way not been found to program them. When the low-cost, mass-produced integrated circuits are combined with programming languages and applications packages (such as those for word processing) that are fairly easy for the novice to grasp, all limits to the spread of computing seem to drop away. Predictions of the numbers of computers that will be in operation in the future become meaningless.

What of the computer pioneers' early predictions? They could not foresee the programming developments that would spread computer technology beyond anything imaginable in the 1940s. Today, students with pocket calculators solve the mathematical problems that prompted the pioneers of that era to build the first computers. Furthermore, general-purpose machines are now doing things, such as word processing and game playing, that no one then would have thought appropriate for a computer. The pioneers did recognize that they were creating a new type of machine, a device that could do more than one thing depending on its programming. It was this understanding that prompted their notion that a computer could do "anything." Paradoxically, the claim was more prophetic than they could ever have known. Its implications have given us the unforeseen computer revolution amid which we are living.

ENDNOTES

1. Harold Bergstein, "An Interview with Eckert and Mauchly," *Datamation* 8, no. 4 (1962), pp. 25–30.
2. Simon Lavington, *Early British Computers* (Bedford, MA: Digital Press, 1980), p. 104.
3. See, for example, John Wells, "The Origins of the Computer Industry: A Case Study in Radial Technological Change," Ph.D. Diss., Yale University, 1978, pp. 93, 96, 119; Robert N. Noyce, "Microelectronics," *Scientific American* 237 (September 1977), p. 674; Edmund C. Berkeley, "Sense and Nonsense about Computers and Their Applications," in *Proceedings of World Computer Pioneer Conference*, Llandudno, Wales, 1970, also in Phillip J. Davis and Reuben Hersh (eds.), *The Mathematical Experience* (New York: Houghton Mifflin, 1981).
4. See, for example, the proceedings of two early conferences: Symposium on Large-Scale Digital Calculation Machinery, Annals of Harvard University Computation Laboratory, vol. 16, 1949; The Moore School Lecturers: Theory and Techniques for Design of Electronic Digital Computers, lectures given at Moore School of Electrical Engineering, University of Pennsylvania, 1946 (Cambridge, MA: MIT Press, 1986).
5. Georgia G. Mollenhoff, "John V. Atanasoff, DP Pioneer," *Computerworld* 8, no. 11 (1974), pp. 1, 13.

6. Byron E. Phelps, *The Beginnings of Electronic Computation*, IBM Corporation Technical Report TR-00.2259, Poughkeepsie, NY, 1971, p. 19.
7. Cuthbert C. Hurd, "Early IBM Computers: Edited Testimony," *Annals of the History of Computing* 3 (1981), pp. 162–82.
8. Anthony Oettinger, "Howard Aiken," *Communications* ACM 5 (1962), pp. 298–9, 352.
9. Henry Tropp, "The Effervescent Years: A Retrospective," *IEEE Spectrum* 11 (February 1974), pp. 70–81.
10. For an example of this argument, and a refutation of it, see John von Neumann, *Collected Works*, vol. 5 (Oxford: Pergamon, 1961), pp. 182, 365.
11. R. F. Clippinger, "Mathematical Requirements of the Personnel of a Computing Laboratory," *American Mathematical Monthly* 57 (1950), p. 439; Edmund Berkeley, *Giant Brains, or Machines That Think* (New York: Wiley, 1949), pp. 108–9.
12. Ralph J. Slutz, "Memories of the Bureau of Standards SEAC," in N. Metropolis, J. Howlett, and G. Rota (eds.), *A History of Computing in the Twentieth Century* (New York: Academic, 1980), pp. 471–7.
13. In a typical computing installation of the 1930s, humans worked, with mechanical calculators that could perform the four elementary operations of arithmetic, on decimal numbers having up to ten digits, taking a few seconds per operation. Although the machines were powered by electric motors, the arithmetic itself was always done by mechanical parts — gears, wheels, racks, and levers. The machines were sophisticated and complex, and they were not cheap; good ones cost hundreds of dollars. For a survey of early mechanical calculators and early computers, see Francis J. Murray, *Mathematical Machines*, vol. 1: *Digital Computers* (New York: Columbia University Press, 1961); see also Engineering Research Associates, *High-Speed Computing Devices* (New York: McGraw-Hill, 1950; Cambridge, MA: MIT Press, 1984).
14. Quoted in Nancy Stern, *From ENIAC to UNIVAC* (Bedford, MA: Digital Press, 1981), p. 87.
15. Oettinger, "Howard Aiken."
16. Abbott Payson Usher, *A History of Mechanical Inventions*, second edition (Cambridge, MA: Harvard University Press, 1966), p. 117.
17. Howard Aiken, "The Future of Automatic Computing Machinery," in *Elektronische Rechenmaschinen und Informationsverarbeitung*, proceedings of a symposium, published in *Nachrichtentechnische Fachberichte*, no. 4 (Braunschweig: Vieweg, 1956), pp. 32–34.
18. Herman H. Goldstine, *The Computer from Pascal to von Neumann* (Princeton, NJ: Princeton University Press, 1972), p. 182.
19. Von Neumann's "First Draft of a Report on the EDVAC" was circulated in typescript for many years. It was not meant to be published, but it nonetheless had an influence on nearly every subsequent computer design. The complete text has been published for the first time as an appendix to Nancy Stern's *From ENIAC to UNIVAC*.
20. Von Neumann, *Collected Works*, vol. 5, pp. 182, 236.
21. Martin Campbell-Kelley, "Programming the EDVAC," *Annals of the History of Computing* 2 (1980), p. 15.
22. For a discussion of the concept of high-level programming languages and how they evolved, see H. Wexelblatt (ed.), *History of Programming Languages* (New York: Academic, 1981), especially the papers on FORTRAN, BASIC, and ALGOL.

22

Why I Am Not Going to Buy a Computer

WENDELL BERRY

Wendell Berry is not impressed by the hundreds of millions of computers being used by other people around the world. His short essay — concise and spare — explains why he prefers a thirty-year-old manual typewriter to a PC or even an electric typewriter. The essay, originally published in the New England Review and Bread Loaf Quarterly *in 1987, was reprinted in* Harper's *and is followed by several letters to the editor that* Harper's *received, together with Berry's response. It is a simple, elegant indictment of centralization, bigness, and consumption-driven technological society that some will resonate with and others will find utterly absurd.*

A writer and farmer, Wendell Berry lives in Lane's Landing, a 125-acre homestead near Port Royal, Kentucky, and is a former member of the English faculty at the University of Kentucky. "Why I Am Not Going to Buy a Computer" is included in a book of his essays entitled, What Are People For? *Berry's other writings include several novels and collections of short stories, poems, and essays. In March 2011 he received the 2010 National Medal of Humanities from President Obama.*

Like almost everybody else, I am hooked to the energy corporations, which I do not admire. I hope to become less hooked to them. In my work, I try to be as little hooked to them as possible. As a farmer, I do almost all of my work with horses. As a writer, I work with a pencil or a pen and a piece of paper.

My wife types my work on a Royal standard typewriter bought new in 1956 and as good now as it was then. As she types, she sees things that are

wrong and marks them with small checks in the margins. She is my best critic because she is the one most familiar with my habitual errors and weaknesses. She also understands, sometimes better than I do, what ought to be said. We have, I think, a literary cottage industry that works well and pleasantly. I do not see anything wrong with it.

A number of people, by now, have told me that I could greatly improve things by buying a computer. My answer is that I am not going to do it. I have several reasons, and they are good ones.

The first is the one I mentioned at the beginning. I would hate to think that my work as a writer could not be done without a direct dependence on strip-mined coal. How could I write conscientiously against the rape of nature if I were, in the act of writing, implicated in the rape? For the same reason, it matters to me that my writing is done in the daytime, without electric light.

I do not admire the computer manufacturers a great deal more than I admire the energy industries. I have seen their advertisements, attempting to seduce struggling or failing farmers into the belief that they can solve their problems by buying yet another piece of expensive equipment. I am familiar with their propaganda campaigns that have put computers into public schools in need of books. That computers are expected to become as common as TV sets in "the future" does not impress me or matter to me. I do not own a TV set. I do not see that computers are bringing us one step nearer to anything that does matter to me: peace, economic justice, ecological health, political honesty, family and community stability, good work.

What would a computer cost me? More money, for one thing, than I can afford, and more than I wish to pay to people whom I do not admire. But the cost would not be just monetary. It is well understood that technological innovation always requires the discarding of the "old model" — the "old model" in this case being not just our old Royal standard, but my wife, my critic, my closest reader, my fellow worker. Thus (and I think this is typical of present-day technological innovation), what would be superseded would be not only something, but somebody. In order to be technologically up to date as a writer, I would have to sacrifice an association that I am dependent upon and that I treasure.

My final and perhaps my best reason for not owning a computer is that I do not wish to fool myself. I disbelieve, and therefore strongly resent, the assertion that I or anybody else could write better or more easily with a computer than with a pencil. I do not see why I should not be as scientific about this as the next fellow: When somebody has used a computer to write work that is demonstrably better than Dante's, and when this better is demonstrably attributable to the use of a computer, then I will speak of computers with a more respectful tone of voice, though I still will not buy one.

To make myself as plain as I can, I should give my standards for technological innovation in my own work. They are as follows:

1. The new tool should be cheaper than the one it replaces.
2. It should be at least as small in scale as the one it replaces.
3. It should do work that is clearly and demonstrably better than the one it replaces

4. It should use less energy than the one it replaces.
5. If possible, it should use some form of solar energy, such as that of the body.
6. It should be repairable by a person of ordinary intelligence, provided that he or she has the necessary tools.
7. It should be purchasable and repairable as near to home as possible.
8. It should come from a small, privately owned shop or store that will take it back for maintenance and repair.
9. It should not replace or disrupt anything good that already exists, and this includes family and community relationships.

1987

After the foregoing essay, first published in the *New England Review and Bread Loaf Quarterly*, was reprinted in *Harper's*, the *Harper's* editors published the following letters in response and permitted me a reply.

W. B.

LETTERS

Wendell Berry provides writers enslaved by the computer with a handy alternative: Wife — a low-tech, energy-saving device. Drop a pile of handwritten notes on Wife and you get back a finished manuscript, edited while it was typed. What computer can do that? Wife meets all of Berry's uncompromising standards for technological innovation: She's cheap, repairable near home, and good for the family structure. Best of all, Wife is politically correct because she breaks a writer's "direct dependence on strip-mined coal."

History teaches us that Wife can also be used to beat rugs and wash clothes by hand, thus eliminating the need for the vacuum cleaner and washing machine, two more nasty machines that threaten the act of writing.

Gordon Inkeles
Miranda, Calif.

I have no quarrel with Berry because he prefers to write with pencil and paper; that is his choice. But he implies that I and others are somehow impure because we choose to write on a computer. I do not admire the energy corporations, either. Their shortcoming is not that they produce electricity but how they go about it. They are poorly managed because they are blind to long-term consequences. To solve this problem, wouldn't it make more sense to correct the precise error they are making rather than simply ignore their product? I would be happy to join Berry in a protest against strip mining, but I intend to keep plugging this computer into the wall with a clear conscience.

James Rhoads
Battle Creek, Mich.

I enjoyed reading Berry's declaration of intent never to buy a personal computer in the same way that I enjoy reading about the belief systems of unfamiliar tribal cultures. I tried to imagine a tool that would meet Berry's criteria for superiority to his old manual typewriter. The clear winner is the quill pen. It is cheaper, smaller, more energy efficient, human powered, easily repaired, and nondisruptive of existing relationships.

Berry also requires that this tool must be "clearly and demonstrably better" than the one it replaces. But surely we all recognize by now that "better" is in the mind of the beholder. To the quill-pen aficionado, the benefits obtained from elegant calligraphy might well outweigh all others.

I have no particular desire to see Berry use a word processor; if he doesn't like computers, that's fine with me. However, I do object to his portrayal of this reluctance as a moral virtue. Many of us have found that computers can be an invaluable tool in the fight to protect our environment. In addition to helping me write, my personal computer gives me access to up-to-the-minute reports on the workings of the EPA and the nuclear industry. I participate in electronic bulletin boards on which environmental activists discuss strategy and warn each other about urgent legislative issues. Perhaps Berry feels that the Sierra Club should eschew modern printing technology, which is highly wasteful of energy, in favor of having its members hand-copy the club's magazines and other mailings each month?

Nathaniel S. Borenstein
Pittsburgh, Pa.

The value of a computer to a writer is that it is a tool not for generating ideas but for typing and editing words. It is cheaper than a secretary (or a wife!) and arguably more fuel efficient. And it enables spouses who are not inclined to provide free labor more time to concentrate on their own work.

We should support alternatives both to coal-generated electricity and to IBM-style technocracy. But I am reluctant to entertain alternatives that presuppose the traditional subservience of one class to another. Let the PCs come and the wives and servants go seek more meaningful work.

Toby Koosman
Knoxville, Tenn.

Berry asks how he could write conscientiously against the rape of nature if in the act of writing on a computer he was implicated in the rape. I find it ironic that a writer who sees the underlying connectedness of things would allow his diatribe against computers to be published in a magazine that carries ads for the National Rural Electric Cooperative Association, Marlboro, Phillips Petroleum, McDonnell Douglas, and yes, even Smith Corona. If Berry rests comfortably at night, he must be using sleeping pills.

Bradley C. Johnson
Grand Forks, N.D.