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PART III

THE BIOTECH FUTURE

If history has taught us anything, it is that every new technological revolution brings with it both benefits and costs. The more powerful the technology is at controlling the forces of nature, the more exacting the price society will be forced to pay in terms of disruption and destruction wreaked on the ecosystems and social systems that sustain life.

By
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In the first two articles the vehicle of a hypothetical meeting was used to present several DNA subjects. (Frequently Used Sires, DNA ownership, health testing requirements and the new conditions for AKC registration.) This article takes a different approach and looks directly into the biotech future. If you plan to read further, I suggest that you visit Juan Valdez and get ready to settle down for the vastness of the biotech future.

OVERVIEW

A company called Celera which didn't exist three years ago announced in June of 2000 that they had just finished building the first complete copy of the entire human genome which is the biological map for laying out the exact sequence of the estimated 3.5 billion pairs of chemicals that make up the DNA in each human cell. What makes this so interesting is that the DNA chemicals can be arranged in specific ways to create the estimated 80,000 to 100,000 human genes, which in turn carry all of the instructions for the body's processes. You might be thinking, "what's next?" . Well, it's the proteins, and lots of them. Celera is now sequencing as many as they can find. As this work continues they will add memory and capacity to their computers in order to build a model for the entire metabolism of a cell. Building a virtual cell will give them the technology to plug in a copy of the human genome and sequence all of the proteins. Can they do it? They have already developed a program called "e-cell", which is a computer model of a living cell in which Celera already has about 100,000 human genes in its database. By 2001, they expect to have one million human proteins. With a massive parallel processor and a complete human genetic code for all of the human protein transcripts they can do what no one thought was possible in 1990. Today it takes about 6-7 years and close to \$370 million to bring one new drug to market. This is about to change as Celera develops the world's fastest algorithms and a computer

that can model a human cell. The implications of this achievement are mind-boggling. A virtual cell would allow biotech companies to test a drug without using either animal or human subjects, which is the most expensive activity of drug research. A workable e-cell will make the clinical trials obsolete.

This is all about to happen with computer power and bandwidth. Think of it, just three years ago the best research organizations were using computers that had 20 terabytes of memory (one terabyte is approximately the entire library of Congress). Today, they use 80 terabytes of memory, more than a 300% increase. The marriage of computers and genes has forever altered our reality of what might be possible.

HISTORICAL PERSPECTIVE

In retrospect, the distant past was a period of time measured in centuries. The concept of time began to change with the beginning of the industrial age. It caused rails to be laid across continents, followed in quick succession by telegraph and telephone lines and miles of paved roads. Those changes quickly altered our notions about time and distance. Vast sewer systems underground, coupled with aerated and purified water, improved our nutrition and increased our life expectancy. Vaccinations, anesthetics, antibiotics and other wonder drugs emerged. The industrial age, which had spread across five centuries and six continents, had fundamentally changed the way human beings lived. Now it is coming to an end. It is winding down in part because we are using up our dwindling energy reserves. More importantly it is a signal that the final stages of the Age of Fire have arrived. Fire, said Lewis Mumford, provided human beings with light, power, and heat - the three basic necessities for survival. When science makes a discovery in one area, others begin to look for new ways to apply it. And so it is with biotechnology. While the motivation behind genetic engineering is age-old, the technology itself represents something qualitatively new. This means appreciating the distinction between the traditional tinkering with biological organisms and real genetic engineering. In order to make that distinction more clear a few paragraphs about this remarkable technology should suffice.

Let's begin with 1983, when Ralph Brinster of the University of Pennsylvania Veterinary School inserted human growth hormone genes into mouse embryos. The mice grew twice as fast and became nearly twice as big as other mice. In 1984 a comparable feat was accomplished in England when scientists fused embryo cells from a goat and a sheep and placed the fused embryo into a surrogate animal who gave birth to a sheep-goat, the first such example of the "blending" of two completely unrelated animal species in history. By 1996 the first commercially grown gene-spliced food crops were planted, and by 1999 more than three-quarters of Alabama's' cotton crop had been genetically engineered to kill insects. Many of the changes that took place in agriculture were accompanied by revolutionary changes in the field of animal husbandry. Researchers began to develop genetically engineered "super animals" with enhanced characteristics for food production. They also began creating novel transgenic animals to serve as "chemical factories" to produce drugs and medicines as organ "donors" for human transplants. At the University

of Adelaide in Australia, scientists have developed a novel breed of genetically altered pigs that are 30% more efficient and big enough to be sent to market seven weeks earlier than normal pigs. This seemed like a good beginning as the new technology moved even closer to commercial reality. Then on February 22, 1997, Ian Wilmut, a Scottish embryologist, announced the cloning of the first mammal in history- a sheep named Dolly. Wilmut had successfully replaced the DNA in a normal sheep and produced a clone from its parent.

The birth of Dolly was a milestone because it made a new idea possible. The ability to mass-produce identical copies of mammals, each indistinguishable from the original, had arrived. Shortly after Dolly's birth, Wilmut and a team led by Dr. Keith Campbell of PPL Therapeutics reported the birth of a second cloned sheep named Polly who contained a customized human gene in her biological code. The experiment caught even normally staid scientists by surprise. This kind of genetic manipulation and cloning allowed scientists to both customize and mass-produce animals. The significance of this development was that it allowed for a new use and the kind of quantifiable standards of measurement, such as predictability and efficiency that had not been used before. These achievements clearly demonstrated that science had developed the technology to use animal clones to harvest organs for human transplantation on a large scale. Even more astounding was the Japanese report of May 1997, which announced a successful transplant of an entire human chromosome into the genetic code of mice, a feat thought unattainable by most scientists. The Japanese had fused human skin cells containing human chromosomes into mouse embryo cells. Some of the mouse embryo cells took up human chromosomes numbers 14 and 22, which contain the genes that make human antibodies. The embryonic cells were then implanted into female mice, which resulted in their offspring carrying the human chromosomes to produce antibodies made of human components when a foreign protein was introduced into their bodies. While these animal experiments were making history the sequencing of the human genome was being accompanied by therapy trials on human patients for the treatment of cancer and Parkinson's disease. Up to this point, all of the genetic attempts at therapy had been on somatic cells - but with these new discoveries, scientists could now redirect their attention to the correction of genetic disorders at the germ line stage. In somatic therapy, the genetic changes affect only the individual patient, in germ line intervention gene changes are passed along to future generations, which affects the evolution of the entire species. With artificial chromosomes, the process is more akin to inserting an entire genetic cassette into the body. Each gene is already in place on its own chromosome, eliminating the random nature of treatments used in traditional gene therapy techniques. The use of artificial chromosomes had opened up unlimited possibilities for modifying the genetic structure of the individual and the species both in somatic and germ line cells.

In another area of science, research was advancing the process of in-vitro fertilization. It was also moving forward faster than anyone had noticed. The first child born of a frozen embryo was Zoe Leyland, which occurred on March 28, 1984, in Melbourne, Australia. The process was straightforward; eggs were harvested, fertilized, frozen and stored for their future implantation. In 1997, Lesley and John Brown of Oldham, England gave birth to the first child conceived in a test tube. It was the birth of Louise Brown. That announcement shocked the world and signaled the beginning of a new era in human

reproduction. In just three years, the use of in vitro fertilization (IVF) had become a wide spread practice with thousands of children being born using IVF technology. Clinics had opened for the purpose of collecting and storing frozen embryos and many families were using yet another way to ensure their reproduction.

Being able to shape the genetic destiny of a human being before birth was helped along by new developments in the creation of artificial wombs. By 2000, scientists had shortened the time unborn children needed to be nurtured in the womb from nine months to less than six. This has led to an increasing number of children who start their lives outside the human womb in petri dishes where, as embryonic cells, they divide and grow before implementation into their own or a surrogate mother's womb.

WHERE ARE THE SCIENTISTS GOING ?

Dr. Thomas Eisner, professor of biology and director of the institute for Research in Chemical Ecology at Cornell University in Ithaca, New York, perhaps gives us some insight when he writes, "As a consequence of recent advances in genetic engineering, (a biological species) must be viewed ... as a depository of genes that are potentially transferable. A species is not merely a hardbound volume of the library of nature. It is also a loose-leaf book, whose individual pages, the genes, might be available for selective transfer and modification of the species". If nothing else this should be a wake up call to those who make policy and ponder the future of where things are going and what rules should apply. Now that several biotech companies have located many of the desired traits in humans, animals and plants, they have given us things to think about. What will we do when they begin to implement them? They can now modify the genetics of an organism and then seek patent protection for their new "inventions". Is that not reason enough to become involved?

THE PAST

The worldwide race to patent the gene pool of the planet is the culmination of a 500-year odyssey of the commercial enclosures and privatization of our ecosystems that make up the earth's biosphere. Understanding the history of "enclosures" is critical to having an appreciation for the potential long-term consequences of the efforts now being made to enclose what's left of the world's gene pool as we know it.

The process of enclosure began with the codification of the global commons in Tudor England in the early 1500s when the enactment of the great "enclosure acts" occurred. These laws were designed to privatize real estate so that land could be bought and sold as individual units. This important change touched off a series of economic and social reforms that slowly began to remake society and reshape relationships. Until that time, much of what was considered the economic life of medieval Europe centered on the village commons. Feudal landlords owned the commons and peasants gave them a percent of their harvest. Medieval European agriculture was communally organized so that peasants were

forced to pool their individual holdings. Open fields were jointly cultivated, and common pastures were used to graze their animals. It served as their way of life. By the beginning of the 1500's all of that began to change. Enclosing was implemented by surrounding a piece of land with hedges, ditches or other barriers, which altered the free passage of men and animals. Enclosure placed the land under private control. Between 1600 and 1900 a series of political and legal acts were initiated in countries throughout Europe and the rest of the world that enclosed all of the publicly held lands. Past relationships and mutual obligations were severed. Enclosure had introduced a new concept about relationships. It had changed the basis of economic security and social life. Land was no longer something that belonged to the community but rather a commodity that could be owned and processed by people. Ownership brought about the privatization of the land commons. It became an idea that eventually spread throughout the civilized world. Today, every square foot of landmass on the planet with the exception of Antarctica is owned by international agreement or it is either under private commercial ownership, government control or organization or some governmental entity. But the concept of ownership did not stop with land. It has also been extended to the ocean and all of the coastal waters, which are now commercially leased. Next to be owned was space, the air we breathe and the air above us. It has also been converted into commercial air corridors and electromagnetic frequencies. Governments now lease air to private companies for radio, telephone, television and computer transmission. But that was not the end. The last and the most intimate of all the commons are the genetic blueprints of evolution, which represent the last remaining frontier of our natural world.

Enclosure and privatization of the planet's genetic commons is now in its infancy. If our understanding of the past can help to shape our future, consider the effects of the following chain of events which began in 1971, when Ananda Chakrabarty applied for a patent on a genetically engineered microorganism designed to consume oil spills. The courts by a slim margin of five to four set the stage for ownership when they ruled in favor of Chakrabarty granting him a patent on the first genetically engineered life form. Chakrabarty was an employee of the GE Corporation, which had applied for a patent on a genetically engineered microorganism to consume oil spills on the ocean. Chief Justice William Burger argued that "the reverent consideration was not between living and inanimate things", but whether Chakrabarty's microbe was a "human-made invention". On October 14, 1980, a few months after the Supreme Court cleared the way for the commercial use of life, Genentech offered one million shares of stock for sale and by the end of the trading day had raised \$36 million. These events led the way for the pharmaceutical, agribusiness and biotech companies to understand the profound implications afforded them by the law. By the year 2000, the US patent office had already begun to grant patents on several species with many still pending.

When historians look back at the twentieth century, they will probably view it as having been dominated by several macro events that affected large numbers of people such as World War I, the Great Depression of the 1930's, World War II and decades of the Cold War ending in 1991 with the collapse of the Soviet Union. By the time these events had come to an end, little attention was given too perhaps the greatest event of them all, the biotechnology revolution. It had already begun to affect the entire public, their pets, and

what they eat. Even today there has been little involvement and almost no debate about the uses of this technology or how the new research will pick its targets. What seems so remarkable about all of this is that just three years ago we were told that mouth saliva was only good enough to test parentage in canines and that it could not be used to test for diseases. But in early 2000, Dr. Houge of VetGen and Dr. Brewer at the University of Michigan were using the mouth swab and DNA technology for testing hip dysplasia in canines. With the thousands of DNA mouth swabs already in storage researchers may now have a head start on health problems from a resource which a few years ago was not considered usable.

THE FUTURE FOR CANINES

But what if you could go one step beyond storing frozen semen, and actually store DNA for the "reconstitution" of your favorite dog at some later date? Just what if? If the price were right, would you do it? Most of the breeders who were asked this question said they would store some to clone their favorite pet if they could, meaning if the price was right. Think about how big agriculture and medicine have already moved things forward and turned this technology towards the cloning of all kinds of organisms. The public will likely begin to use this technology once the price becomes affordable.

Over the past 25 years scientists and medicine have learned about what is acceptable and what is not. Some of their problems have centered on the kind of labels they used to describe what they were doing. At one major California University, there used to be a sign on a building that read "Genetic Engineering." When the public began to protest, the sign was changed to "Molecular Engineering" . Now they were seen as good and the people no longer saw it as a danger to the public. Hospital signs that used to say "nuclear medicine" on laboratory doors were changed to read " MRI" and "CAT Scan". Now they were seen as good. The use of radioactive isotopes injected into patients also had to be renamed. Now they are called "dyes." The learning process was short and they were quick learners. What became apparent was that new labels resulted in new perceptions that made people feel good about many of the technological advances that were being used as therapy. While technology moves quickly forward, advances occurred with little public notice. Science had learned how to phrase things with carefully crafted words and gave it a spin that made it politically correct. It did not take long for them to learn that without acceptance, nothing moves forward. Ten years ago traditional organizations such as the American Kennel Club did not allow the use of artificial insemination or chilled and frozen semen. But as the availability of this technology became affordable and popular, the restriction was relaxed. In 2000, the AKC added multiple sired litters and embryo transplants to their list of DNA programs for canines.

A friend once said, if you want to cause real confusion, ask the question: "now that I have just cloned my big-time champion of record, how do I register him?" At this time, the AKC is moving towards a two-year moratorium for its DNA programs. It has not addressed the use of cloning or any of the other important technology questions, one of which is the

future of its 100-year-old policy, which says (paraphrased). A registered dog, bred to a registered dog, produces a registered dog even if it has faults or disqualification's". Will DNA be made mandatory for all sires, dams and breeding stock? What about the first clone and the progeny of the clone? How many clones will each dog be allowed? The technology will likely make the most of these events possible. When they become affordable people will begin to use them like any other discovery. But with the use of any new technology you also get the crackpots who seek to shock the world with some new revelation or claim. Some want the choice of having their whole body, head, or just their DNA preserved. Most of us have not learned enough about this so we probably would settle for preserving our DNA. But for those seeking immortality, this technology gives new meaning to the phrase "I'll be back." As soon as one research lab announces a new success, regulators and legislators shift into high gear in an attempt to control it. Perhaps the FDA can serve as a good example. It has already said it will control human cloning. But the reader should note that FDA's Center for Veterinary Medicine (CVM) has an exceptionally poor track record of having successfully controlled any new technology. In the United States, elected officials have tried to ban cloning at the state and federal levels but the regulation of this new technology has been resistant to their efforts. This is because their approach has been based on an emotional and irrational process firmly centered in superstition, cult and mainstream religions. Regardless of the good (or bad) intentions of the regulators and legislators, the rate of technological advances will always continue to outstrip the power of any government or organizations to keep pace and regulate it. Even if the legislators could keep pace, the scientific information upon which they base their laws and regulations are preliminary at best and lag far behind those who are using their minds and computers to expose new areas of science. A problem that the dog world needs to address is whether it is worth saving the best in order to avoid genetic problems in the future. With frozen semen, direct descendents can be bred but they may not have the right genes. With frozen DNA, the future seems to promise that you can get a near identical twin and fix any of its heritable problems using somatic and germ line therapy. It seems a certainty that this technology has already side stepped the countries with quarantines. Breeders can now simply import the genes, embryos or semen they need.

STORE YOUR DOG'S DNA

Unlike DNA testing protocols, the storing of cells for the cloning of parts or the whole individual is a little more complex than just storing semen for breeding. Cloning protocols involve the services of a veterinarian who will take tissue samples about the diameter of a pencil eraser. This process typically takes only a few minutes. Once the lab receives the sample it is prepared for culturing by washing it in a special nutrient solution. This procedure removes all the dead cells. The prepared tissue is then washed with a sterile solution and cultured in a specialized incubator. It normally takes about four weeks to grow enough cells for freezing. The cells are then removed from the culture dish, placed in specialized vials, and treated with a solution that protects them from the freezing process. This procedure requires that the temperature be lowered very slowly. As ice crystals form, the concentration of liquid outside the cells becomes less because water is removed and

turned into solid ice. The process continues until the cells are almost completely dehydrated. The vials are then placed in storage tanks and filled with liquid nitrogen at minus 320 ° Fahrenheit. At this temperature all metabolic processes cease and the cells are in a state of suspended animation. This process is reversed when the cells are thawed and given their “wake-up” call. Cells that have been frozen in liquid nitrogen for over 50 years have retained their viability and science believes that they could last for hundreds of years.

Most reproductive specialists when asked about the major strides they have noticed in canines during the last century would point to artificial insemination, frozen and fresh chilled semen, embryo transplants and retaining the reproductive capability of bitches with antibiotics. Most of the new technology already in use to treat humans can be applied to canines. When that begins to happen on a large scale many things are likely to change. Regardless of the moral or ethical issues involved, the advances in genetic manipulation have outstripped the ability of the regulators and organizations like the AKC to control these new technologies. Cloning, gene therapy and reproduction will have an economic importance to each species and this technology will be no different, than the others. It will be market driven. The research being conducted in the world of canines has temporally lagged behind the other more economically viable species. But that is likely to change sooner than we think. Many researchers have already suggested to breeders that they store their dog's DNA now, so that they can reap the new and unforeseen benefits of the technology.

TECHNICAL DIFFICULTIES IN CLONING CANINES

Now that money is available for this research, it is only a matter of time before the first clone will occur. In the past, one of the problems to cloning a canine was money, the other was the singular nature of the canine reproductive system. Not only do dogs cycle irregularly but they are also unique in that bitches ovulate immature eggs – which normally takes several days to mature. Researchers must replicate the internal environment of the bitch's oviduct so that the eggs will continue to mature before they can be harvested and used in cloning research.

At College Station Texas, on the campus of Texas A&M, there are at least 60 bitches who serve as doggy hens. They are egg machines to supply the raw material for one of the world's only canine-cloning projects. The Texas project is a joint venture between A&M and California-based Bio-Arts and Research Corporation (BARC). The \$2.5 million effort called Missyplicity is privately funded by an anonymous Bay Area billionaire who wants to make an exact copy of his "mutt" called Missy. After the eggs are collected from the donor bitches, they will be retrofitted with Missy's DNA, then cultured in vitro and if the embryo is viable, surgically implanted into another dog's oviduct for gestation. Five dogs are now pregnant using this procedure.

If the technology could speak and if we listened as they talked about the problems of the Missyplicity scientists, we would learn that they are slowly solving and overcoming the

problems one by one. But they're still playing a numbers game that is hard to win. Egg harvesting, tissue culture, renucleation, embryo culture and gestation all lead to birth. The history of other efforts show that even with all of this knowledge, most of the clone teams tend to make a lot of mistakes. The whole sequence for each species takes time to perfect. The tally was at 277 in sheep before Dolly was born. So far the Missyplicity project has had 83 attempts. If the scientists continue to let time remain their friend instead of their enemy, and if we are patient, the results will be forthcoming. We know that time and money are on the side of the researchers and both seem to be readily available.

But what about the application of this technology and the questions of a clone and it's offspring?. What about DNA storage and DNA usage?. How should the AKC registration policies be changed? What will be required and mandated? If the clone is a copy of its parent, which is already AKC registered, how will its DNA foot print differentiate between the two of them? Remember that a cloned sire could be bred to a cloned bitch and produce a pedigree of clones. Some have suggested that perhaps an occasional out cross should be used to a regular purebred to bring in some needed trait and to maintain gene diversity in the gene pool.

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