The Human Clone Market

We’ve had cloning in the South for years. It’s called cousins.
Robin Williams

4.1 Snapshot of the Future

Imagine the following scenario. A few years from now, those who can afford it will contract cloning labs to grow clones to supply duplicate organs or replace body parts. Clones will be genetically matched to clients so they can be used in transplants without being attacked by the client’s immune system. To side-step the ethical argument of what is considered human, the client’s clones will be grown as headless embryos, without a brain or a central nervous system. Destined never to leave the lab, these cloned embryos will develop all the necessary body parts, including a heart, a circulatory system, lungs, and a digestive system. For those without deep pockets, the cloning labs will offer economy clones featuring one or more specific organs. Using embryo cloning techniques developed in Britain in the late 1990s, the cloning labs will grow these headless clones to match each stage of a child’s or adult’s development, so that organs will be available throughout the client’s life.

For those at the lower end of the income scale, cloning labs will store human organs culled from the general population, inventoried by blood type and approximate genetic match. The supply of these organs will come primarily from the black market, fuelled by an underclass willing to be paid money to donate a kidney, a lung, or an eye. After all, in this imagined future, Organ Donor Centers are as common as Starbucks. The system works well, but sometimes the demand for organs exceeds supply, mirroring the problems of the 2010s. This poses no problem for the cloning labs: they employ procurement agents who scour the streets to gather new products. When the agents find a victim, they inject a sedative, rendering the unsuspecting prey unconscious. The victim is taken to the nearest cloning lab where an organ or two is harvested. Thanks to the latest anti-scarring procedures, the victim is returned to the street with little or no awareness they are missing a kidney or
a lung. They wake up in the gutter and may notice they are shorter of breath than usual or they may glance in a mirror and realize the colors of their irises no longer match. They shrug their shoulders and put it down to sleeping in the gutter. If the procurement agents can’t find what they’re looking for in the ghettos, they turn to another rich supply source: motor vehicle accidents. They monitor the emergency services’ communication channels and, when an accident sounds promising, they’re first on the scene to scout for “donors.”

In this potential, rather troubling, future, business is booming. Cloning labs have doubled their facilities in just 5 years and there is demand for more. In fact, the cloning labs have been so successful they have built a family alliance facility, where poor families are paid to breed children for the purpose of organ harvesting. Most of these “donors” are purchased when they are physically mature, but some are sold earlier to supply the growing need for baby organs.

4.2 Black Market Organs

If this all sounds too implausible then it’s worth highlighting two main issues affecting the organ market. First, most countries depend on altruistic motives for obtaining organs, which means depending on people becoming organ donors voluntarily. Unfortunately, despite increasing efforts, the gap between the number of people who need organs and the number of organs available is steadily increasing. In most countries only about a third of the population are donors, which means thousands of patients end up on transplant lists every year and thousands die while on the waiting lists because of the lack of donor organs. Many more die because, for whatever reason, their name never even made the list. Clearly the altruistic method isn’t working. Also, even if a person is lucky enough to be matched with an organ, there is always the risk of rejection: without anti-rejection drugs, such as cyclosporine, most who undergo transplantation (Fig. 4.1) will reject their new organs and die a short time after—some people die even with anti-rejection drugs.

The consequence of this gross imbalance between supply and demand is a black market dealing in organs (see newspaper article excerpt), including a robust transplant tourism industry, which connects those who need an organ with those who have them. Usually, the prized organ is a kidney, but partial livers and single corneas are also traded. Typically, the patient in need of the organ is from a wealthy nation, while the donor usually lives in an impoverished country. The transplant may take place in the recipient’s country, the donor’s country, or in a private hospital located to sidestep legal barriers.
Fig. 4.1  The queue for an organ can stretch for years, which is why the modern transplant and organ donation systems are gradually turning into a shady area of healthcare. According to the WHO’s 2012 report, over 10,000 cases of the illegal sale of transplant organs are registered throughout the world every year, and that figure is rising. (Courtesy: www.wikipedia.com)

An Organ Is Sold Every Hour, WHO Warns: Brutal Black Market on the Rise Again Thanks to Diseases of Affluence

An organ is sold once an hour, the World Health Organization has warned, amid fears that the illegal trade is again on the rise. The U.N. public health body estimates that 10,000 organs are now traded every year, with figures soaring off the back of a huge rise in black market kidney transplants. Wealthy patients are paying up to £128,500 for a kidney to gangs, often in China, India and Pakistan, who harvest the organs from desperate people for as little as £3,200. Eastern Europe also has a huge market for illegal organ donation and last month the Salvation Army revealed it had rescued a woman brought to the UK to have her organs harvested.

With kidneys believed to make up 75% of the black market in organs, experts believe the rise of diseases of affluence—like diabetes, high blood pressure and heart problems—is spurring the trade. The disparity of wealth between rich countries and poor also means there is no shortage of willing customers who can pay a premium—and desperate sellers who need the cash.

Daily Mail article by Damien Gayle, 28 May 2012

This business is illegal, but in the organ black market, wealthy individuals with sick organs and poor people with healthy organs tend to gravitate together in the hopes of a profitable exchange. As so often happens in any black market, the exchange is a one-sided affair, because the transplant procedure is a bargain for the organ recipient. In India, the number one medical tourism destination of the world, this power distance between donor and potential recipient is significant, with kidneys sold for as little as $700 and the patient paying $180,000 for the transplant. Who pockets the difference? Usually the amount is divided among the kidney broker, the harvesting surgeon, and the transplant hospital. In India, despite being called “donors,” many part with their organ with the promise of a rich reward. Others are coerced or deceived;
in the hospital for one purpose, they wake up from surgery to discover their kidney has been removed without their consent, echoing the futuristic scenario described earlier.

Darker still is the effect of the physical abandonment of the donors. Once the recipient has the organ, the profiting parties tend to lose interest in the donor. Few donors have access to medical care, and many are maimed for life. In some areas of India, desperate neighborhoods, known as “kidney villages,” exist because so many residents have sold one of their kidneys. Having lost one kidney, these “donors” are more at risk for problems that could affect their remaining kidney. Also, the transplant operations themselves can be dangerous—particularly when carried out in clandestine and illegal facilities.

This exploitative and dangerous black market in organs has led to a dehumanizing trade in bodies and body parts. Unethical brokers and recipients exploit impoverished people, whose bodily organs become market commodities to prolong the lives of the wealthy. People have suggested that organ trafficking can be combated by global governance. Others have called for countries to play a more active role in putting pressure on foreign governments to acknowledge the problem and crack down on those involved in the trade. Some have held up their hands in resignation, saying organ trafficking will never be eliminated. But there is a solution that makes sense despite its potential for controversy, and that is cloning. We’re not talking about cloning humans for their organs but rather cloning specific organs: this is called therapeutic cloning as opposed to reproductive cloning. Therapeutic cloning would solve two problems. First, it would greatly reduce or perhaps even eliminate the organ shortage. Second, because the patient’s own cells would be used for the cloning, the patient’s body would not reject the organs and there would be no need for anti-rejection drugs, which would reduce the cost to patients, insurance companies, and the government.

Fanciful? Perhaps. But how would you like a (headless) clone of yourself stashed away somewhere in case you need a replacement organ? If you’ve just read Chapter 3, you’ll remember that was the plot of The Island. Chances are The Island isn’t a glimpse into the future, but the film did highlight the potential uses of human reproductive cloning. That’s because organ transplants are difficult undertakings for two reasons. First, you have to find a donor, a challenge in itself since organ demand outweighs current supply, with more than 100,000 people in the United States on an organ waiting list. Second, there is no guarantee your body will accept the new organ. What if you could eliminate the waiting time and risky odds of traditional organ transplants by creating cloned organs from your own cells that your body would recognize?
4.3 Organ Cloning

How would organ cloning work? Say you had a failing liver and you needed a replacement. Doctors couldn’t remove your liver and clone a new one and you couldn’t take The Island route (see Chapter 3) and use your clone’s organs—scientifically this might be feasible, but ethically it’s a no go. Instead, doctors would use stem cells. Stem cells are perfect for organ cloning because they can differentiate into more than 200 types of cells. Scientists extract these stem cells (Fig. 4.2) when an embryo consists of around 150 cells. Unfortunately, removing the stem cells effectively destroys the embryo, which is why many oppose this practice.
Controversy aside, to understand how organ cloning might work, it’s useful to be familiar with the types of cloning procedure. The most common cloning method is somatic cell nuclear transfer (SCNT), a procedure in which the nucleus is removed from a donor egg and is replaced by DNA from a somatic cell of the organism to be cloned (in practice usually by fusing the two cells after the nucleus has been removed from the egg cell). Potentially, it might be possible to clone organs by using SCNT to clone embryos, extracting the stem cells, and stimulating the stem cells to differentiate into the desired organ, but this will require more research. One of the keys to organ cloning will be to understand what chemical or physical signals stem cells receive to properly differentiate, but this can be achieved by reverse engineering cell differentiation processes. The problem is that genetic information isn’t known for all of the more than 200 types of body cells. Another problem is that—in the United States at least—research into human therapeutic cloning has practically come to a halt. One reason is the lack of human eggs for research—perhaps aggravated by the regulations of the National Academy of Sciences and the International Society for Stem Cell Research, which prohibit monetary compensation for females who donate their eggs for embryonic stem cell research (in contrast to those used in fertility clinics)—another being the ethical questions raised by the destruction of embryos mentioned above.

Because of the potential risks involved with egg donation and the newness of the science, stem cell researchers have found it difficult to find donors. It’s a situation that doesn’t bode well for organ cloning because, given the low rate of success with embryonic cloning, researchers need an abundance of eggs for there to be any chance of progress. This is partly why Ian Wilmut, of Dolly fame, has suggested injecting human DNA into animal eggs instead. Despite all these restrictions, advancements in therapeutic cloning have been made. For example, in March 2008, researchers reported removing skin cells from mice with Parkinson’s disease to test a way to use stem cells as an effective treatment. They inserted the DNA from the mice skin cells into eggs with the nuclei removed, by SCNT, and created cloned mice embryos. Then they extracted stem cells from the cloned embryos and caused them to develop into dopamine neurons, the nerve cells affected by Parkinson’s disease. After implantation of the new nerve cells into the mice, the test animals showed signs of recovery.

The Parkinson’s mice research represents another step towards eventual organ cloning, but perhaps there’s a better—and faster away—to achieving this result: by transplanting animal organs into humans. This process is called xenotransplantation\(^1\), a concept pioneered a century ago, when transplanting

\(^1\) According to the US Food and Drug Administration (FDA), xenotransplantation refers to any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (1) live
human organs was considered ethically controversial. Interest in the procedure reemerged during the 1960s and, since then, chimpanzee kidneys have been transplanted into patients with renal failure and a baboon heart has been transplanted into a newborn infant, who lived for 20 days after the surgery. The rationale for using animal sources for organ transplantation is simple: supply and demand.

4.4 Xenotransplantation

First, it’s important to choose the right animal donor, and there are a number of factors scientists must consider when doing this. One of these is the interspecies transmission of genetically incompatible infectious agents and the potential for transmission of a genetically incompatible infectious agent from the recipient to the recipient’s close contacts, which could lead to propagation throughout the general human population. Another problem is the risk of mutation of an organism caused by the insertion of additional DNA bases into the organism’s preexisting DNA. There is also the risk of transmission of infectious agents from the recipient to a baby during gestation, which could result in the development of an infectious disease in the baby. These and a myriad other risks have to be assessed when determining which animal is safe to use for organ cloning. Since nonhuman primate donors are considered to pose the greatest threat of transmitting unidentified organisms and retroviruses, scientists won’t use these animals as a source of xenotransplantation products until more information is available. Monkeys were considered candidates, but they weren’t deemed suitable as organ donors because they are uncomfortably close to humans on the evolutionary ladder (ethics again) and they only produce a few offspring. After much risk analysis, scientists decided pigs (Fig. 4.3) were most suitable for organ donation. Pigs are plentiful, mature quickly, breed well in captivity, have large litters, and have vital organs roughly comparable in size to those of humans. Also, because humans have had close contact with pigs for a long time, their use for xenotransplantation is believed to be less likely to introduce new infectious agents. Having said that, recent experience has proved that pigs are not an ideal source of organs,

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cells, tissues, or organs from a nonhuman animal source or (2) human body fluids, cells, tissues, or organs that have had contact with live nonhuman animal cells, tissues, or organs. By this definition, nonliving biological products from nonhuman animals, such as porcine heart valves, are not xenotransplantation products. Depending on the relationship between donor and recipient species, the xenotransplant can be concordant or discordant. Concordant species are closely related species, for example mouse and rat. In contrast, discordant species are not closely related, as in the case of pig and human. A concordant recipient takes many days to reject an organ, whereas a discordant recipient may reject the organ within a few minutes or hours.
because the use of pig grafts has been associated with major immunologic barriers, resulting in rejection when transplanted into a human recipient.

Rejection is caused because humans have preformed antibodies, which are directed against nonprimate species. These antibodies act against pig cells, causing a strong immune response to be triggered during the rejection, the end result being the destruction of the transplanted organ. Even if the transplanted organ isn’t rejected immediately, a delayed type of immune response may occur that results in organ rejection. These rejection problems have caused scientists to scratch their heads and try to devise a strategy to defeat organ rejection. Some research groups have developed genetically engineered pigs designed to minimize the expression of various immunogenic substances. These efforts have been partially successful, with the result that grafts survived 6 months. Other groups have developed genetically engineered pigs to interfere with the mechanisms of graft rejection. To test the scientists’ theories, genetically transformed pig organs have been infused with human blood to see if rejection occurs. The results have been mixed. Genetically modified pig organs have also been transplanted into baboons undergoing immunosuppressive therapy, also with varied results; some transgenic pigs increased the survival of their grafts in baboons that had undergone xenotransplantation, but survival times were measured in days. Another strategy has been to devel-
op immune-adjusting therapies to prolong xenograft survival. For example, combinations of immunosuppressive agents have resulted in the prolonged survival of some pig xenografts (hearts) in primates. Graft survival has also been attempted by giving the graft a break from attack when circulating antibodies are removed from the system, a procedure that allows the graft to express protective genes.

Assuming scientists can solve the rejection problem, they still have to wrestle with the issue of infection. Infection is a serious risk because the transmission of infectious agents from animals to humans has already resulted in thousands of deaths worldwide from Creutzfeldt–Jakob disease\(^2\), Ebola virus outbreaks, and, more recently, severe acute respiratory syndrome (SARS). Just like the problem of rejection, the difficulties of eliminating or reducing the infectious risks associated with xenotransplantation are significant. For example, organisms carried by the graft may not be known human pathogens or they may not be pathogens in the native host species but cause disease in other species—the human recipient. There may also exist novel animal-derived organisms that may cause unrecognized clinical syndromes. Also, the genetic modification of the donor animals may alter the host’s susceptibility to organisms, leaving the door open for infection.

The term used to describe the transmission of infections by the transplantation of organs is xenosis. The problem with xenosis is scientists don’t know what will happen when an infectious agent enters a new host species. For example, in its natural host, the macaque monkey, herpes simian B virus infection presents symptoms very similar to those of herpes simplex virus type 1 infection (cold sores) in humans. But, B virus infection of humans or other non-macaque primates results in myeloencephalitis (inflammation of the spinal cord and brain) with a mortality rate of approximately 70%.

Another means of infection is the action of retroviruses, which can become inserted into host chromosomal DNA. In fact it has been suggested that the HIV pandemic resulted from the adaptation of simian retroviruses introduced across the species border into humans. There are a number of retroviruses that scientists have to worry about, including porcine endogenous retrovirus (PERV), capable of infecting human cells. This is of particular concern because pigs are expected to be the most common animal source of xenografts once rejection has been overcome. There has been cause for optimism,

\(^2\) Transmissible spongiform encephalopathies are a family of fatal diseases of humans and animals that cause irreversible brain damage. The diseases are believed to be caused by prions (specific proteins), which can jump the species barrier from, for example, cattle to humans. Transmissible spongiform encephalopathies have exhibited transmission to new hosts through transplanted grafts and across species lines. That patients manifesting signs of a possible xenosis after transplantation would have to be quarantined is not inconceivable.
however, following experimental xenotransplantation of organs from swine to nonhuman primates, a procedure that has demonstrated the absence of PERV transmission. Also, more sensitive diagnostic assays are being developed to detect most potential viruses associated with xenotransplantation of organs into humans.

Nevertheless, given the risk of xenosis, researchers working on xenotransplantation have recommended comprehensive monitoring and surveillance of xenograft recipients. And, given the time it may take for some of these diseases to develop, monitoring could be lengthy. Suffice to say, the organ cloning problem is a formidable one, so it stands to reason that cloning humans may represent an even greater challenge. Can it be done? Probably, but we’ll approach that question from another angle. Consider the mammoth.

### 4.5 Resurrection

“Woolly mammoth to be brought back to life from cloned bone marrow within 5 years.” You’ve probably read similar articles about mammoth carcasses frozen in Siberia. Each time one of these animals is unearthed there is a flurry of speculation about resurrecting this Ice Age giant. Can it be done? Well, it seems researchers have refined at least some of the tools needed to turn those headlines into reality. A team of reproductive biologists in Kobe, Japan, cloned mice that had been frozen for 16 years, and the scientists suggested the same techniques might lead the way to cloning mammoths (Fig. 4.4) and other extinct species. I’ll explain what resurrecting a mammoth has to do with cloning humans shortly.
The Kobe resurrection breakthrough, reported in 2008, was followed in the same year by an announcement by a group at Pennsylvania State University that they had mapped 70% of the mammoth genome, laying out much of the data that might be required to make a mammoth. For some scientists who had scoffed at the plot of *Jurassic Park*, bringing back the mammoth didn’t seem so far-fetched anymore, although there are still hurdles. One of the first steps is to recover the mammoth’s complete DNA sequence. In the case of mammoths, this sequence is estimated to be more than 4.5 billion base pairs long. That’s a lot of information to express in flesh and blood, but the publication of the partial mammoth genome is a good start. Once scientists have mapped the remaining 30% of the genome, the entire genome will need to be re-sequenced several times to screen out errors that may have crept into the ancient DNA as it degraded. Scientists will also have to package the DNA into chromosomes, which may take a while because they don’t know how many chromosomes the mammoth had. But, given technical advances such as high speed gene sequencing and improvements in recovering DNA from mammoth hair, none of these tasks appears insurmountable; it’s really a question of time and money.

Where the process becomes tricky is transforming this data into an actual woolly mammoth, although the fact the woolly mammoth has some close living relatives (Asian elephants) helps; scientists have already used the elephant genome as a guide to reassemble mammoth DNA, although the DNA they used was too fragmented to create the actual animal. In fact, fragmented DNA may prove to be a stumbling block in the resurrection of these creatures, which is why scientists may have to employ a different strategy. One approach may be to modify elephant chromosomes at each of the estimated 400,000 sites where they differ from the mammoth’s, a procedure that would effectively rewrite an elephant’s cells into a mammoth’s. Another tactic could be employed if researchers can decipher how mammoth DNA was organized into chromosomes, a feat that would allow them to synthesize the entire genome from scratch. The latter possibility may take a while because the largest genome synthesized to date was only a thousandth the size of the mammoth’s.

But, once scientists have functional mammoth chromosomes in hand, what will they do with them? One approach would be to follow the route pioneered by the Roslin Institute and wrap the chromosomes in a membrane to create an artificial cell nucleus. If the nucleus of an elephant’s egg could be removed and replaced with the rebuilt mammoth nucleus, electrical stimulation of the egg would trigger initial cell division into a mammoth embryo, and eventually the embryo could be transferred into an elephant’s womb for gestation. In theory, this sounds doable, but there are several unknowns. For example, no one knows how to build a mammoth nucleus and, even if it can
be done, there is the challenge of harvesting an elephant egg and bringing a mammoth fetus to term in an elephant uterus. So, in the interim, scientists are tackling less daunting challenges, such as cloning endangered or recently extinct animals. For example, the San Diego Zoo maintains a “frozen zoo,” where the DNA of endangered species is stored in tanks of liquid nitrogen. Cloning attempts have been encouraging. In 2003 scientists used cells stored at the zoo’s facility to successfully clone across the species barrier by inserting banteng DNA into domestic cow eggs and placing the resulting embryos in cow foster-mothers. The result was two bantengs (Fig. 4.5).

With the success of the bantengs it’s not surprising there is talk of using similar methods to clone endangered giant pandas, Sumatran tigers, and even re-create extinct species such as the Pyrenean ibex. Of course, if you can re-create these animals—or a mammoth—you can re-create anything else that’s dead … including humans. There are some who question the ethics of this, but scientists contend that much could be learned about the relationship between modern humans and our ancient forebears by cloning, say, … a Neanderthal. As always, Hollywood has taken the concept and made a film about it. Sort of.

*Encino Man* begins during the Ice Age, as a caveman attempts to make fire with his girlfriend but an earthquake causes a cave-in that buries them. Fast forward thousands of years to present-day Los Angeles, where Dave is digging a pool in his backyard when he comes across a chunk of ice with the body of a man in it. He melts the ice block, releasing the caveman from the opening of the film. Mayhem ensues. To disguise his discovery, Dave washes and trims the caveman, who he calls Link, to look like a teenager and fools people into
thinking Link is an Estonian exchange student. Eventually, evidence that Link is a caveman is uncovered, but this just makes him even more popular.

In the real world, cloning a Neanderthal makes perfect sense because genetically they are our most closely related hominid species. For a long time scientists thought that reconstructing ancient Neanderthal DNA was close to impossible because of the age of the samples. That all changed thanks to the work of Svante Pääbo, a Swedish paleontologist, who managed to extract and analyze short stretches of DNA from a 2400-year-old mummy of an infant boy. He reported his findings, published in 1985 while he was still a graduate student, in *Nature* under the title “Molecular Cloning of Ancient Egyptian Mummy DNA.” He later turned his attention to Neanderthal DNA and managed to extract recognizable mitochondrial DNA fragments from a 42,000-year-old Neanderthal fossil. In 2010, Pääbo published the paper “A Draft Sequence of the Neanderthal Genome” in *Science*. One of the findings was the presence of a gene which is involved in speech and language, which means when scientists do clone a Neanderthal into existence, we might be able to talk with him or her! Perhaps Hollywood wasn’t so far off the mark after all.

So does Pääbo’s work mean that one day scientists will be able to bring back the dead? Probably. But even if you clone your dead loved ones, it’s impossible to recreate the memories and experiences that will have shaped the person you once knew. Uncle Bill will look like Uncle Bill, but the chances are he won’t know who Uncle Bill is. That’s because when the person is “born,” he or she will be just like any other baby, and will have to mature just like any other human being.

### 4.6 Ethics

Despite all this talk about advancements in cloning research, organ replacement, and resurrection, the biggest hurdle facing cloning scientists is ethical, despite cloning pioneers making the case that the technology itself is not immoral, however immorally it could be used. Another way cloning scientists try to promote the technology is to highlight the broader benefits such as stem-cell research. But biotech companies using cloning technology to develop human medicines worry about the potential fallout if someone creates a cloned human, which is why they are loathe to reveal too much about their animal-cloning research, much less their work on human embryos. While these companies are taking the first steps toward cloning a human, they’re not actually cloning humans. Instead, the real miracle scientists foresee is not making a genetically identical copy of a human, but using the technology to
solve problems such as rejection and infection in transplantation. It’s exciting technology, which is why scientists are begging to work on these stem cells, but the main source of embryonic stem cells is leftover embryos from IVF clinics; cloning embryos could provide an almost unlimited source and progress would be faster. So work continues and, despite the restrictions, progress is being made. For example, in 2010, researchers at the Wake Forest Institute for Regenerative Medicine in North Carolina became the first to use human liver cells to successfully engineer miniature livers that function—at least in a laboratory setting—like human livers. The next step will be to see if the livers will continue to function after transplantation in an animal model. After that goal is achieved, scientists will be on their way to providing a solution to the shortage of donor livers available for patients who need transplants. Cloned humans may follow.