Part I

GENETICS: SETTING THE SCENE

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Stem Cells

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Introduction

The world of genetics has taken biology by storm over recent years. A four-letter code, strung together in different patterns within our genes, appears to determine everything from eye color, through various diseases to, perhaps, even intelligence. Through this blueprint, all the components of the living cell are encrypted. But it requires consistent repair and replacement – and, inevitably, flaws do occur leading to malformations of cell architecture and, in turn, disease. Thus, correcting genetic deficits through ''gene therapy'' is one of the goals of modern medicine and has attracted enormous investment both from international governments and industry. This research is spearheaded by a massive collaborative effort to sequence the entire human genome (the Human Genome Project). However, it is clear that in using these modern gene methods the doctor becomes the architect, correcting flaws in the human design, even enhancing the original plans with new ideas. Clearly this raises enormous philosophical and ethical issues, a core feature of this volume. But quietly, alongside this wild exuberance among all genetically inclined, a revolution of another sort is gaining momentum. A revolution that may soon compete alongside the four letters. Stem cell biology is developing at such a rapid pace it is almost impossible to keep up with the latest developments – and each new experiment raises tantalizing possibilities for novel types of therapy for a wide range of disorders. At the same time, stem cell research raises complex moral and philosophical questions with regard to who we are and the limits of medicine. This chapter is an attempt to explain the science behind the hype, and discuss the possible implications of stem cell biology for our modern and rapidly changing society.

The Mother of All Cells

If the genes are thought of as a blueprint for life, cells could be considered the building materials. Some are even shaped like bricks, such as the short-lived epithelial cells with their simple rectangular structures. Others are more complex, like rows of elegant ornaments placed in strategic locations within the building. The neuron of the

brain, for example, which can have a lifespan of over 100 years, has a small cell body, enormous dentritic tentacles, and a single thin cable of communication with other cells which can reach over a meter long. Together, these and many other cell types bind together to form multicellular life. But how do these different type of cells arise in the body? For many years scientists have known one simple fact – we all develop from a single cell. A sperm penetrates the thick wall of a receptive egg and generates a charged cell, or oocyte, with a full complement of 46 chromosomes – half from the mother and half from the father. This is the miracle of life, and the combining of the two sets of chromosomes, each carrying their own genetic history, underlies the wonderful and unique characteristics of each new being. The oocyte is truly totipotent, capable of producing total organism. It first splits into 2 cells, then 4, 8, 16 – the rate of growth is exponential and astounding, for it only takes 30 divisions to produce 1 billion individual cells from the single oocyte. At each division, both daughter cells are thought to inherit an identical copy of genes. However, different parts of various genes are switched on in different cell types by crucial molecules known as transcription factors (molecules capable of switching on specific sets of genes), leading to the cellular differences we see throughout the body. Some become brain cells, others heart, muscle, blood, or kidney. But how do cells from the mother egg know what to turn into and where? These are the fundamental issues of developmental biology and have been pondered over for many years. It is now becoming clear that cellular development involves the sequential expression of specific genes and transcription factors and is based around common founder cells, or *stem cells*.

Embryonic Stem (ES) Cells

The oocyte rapidly develops into a small, hollow ball of cells termed a blastocyst. The blastocyst is a remarkable structure which floats along the fallopian tubes until it reaches the uterus, dividing as it goes. It becomes polarized with primitive ''head'' and ''tail'' regions, crucial for subsequent development into a developing fetus once implantation to the womb has taken place. From it, a primitive form of stem cell, the embryonic stem cell, or ES cell, can be derived in the test tube (Svendsen and Smith 1999). This requires that the blastocyst is torn apart into single cells which are then no longer able to make a whole organism – a crucial procedure which is often misunderstood and deserves highlighting futher. Unlike the totipotent fertilized egg, ES cells are an artificial type of cell generated in the test tube and *cannot form a whole organism alone*, and as such could not be used to clone either animals or people. For this reason they are termed pluripotent, to emphasize the point that they cannot form a total organism. However, ES cells do retain the capacity to turn into any tissue type either within the culture dish or following transplantation. This has led to the term ''therapeutic cloning'' where single cells are replicated in the culture dish, as opposed to ''reproductive cloning'' where whole organisms are cloned. In mice, ES cells can be injected back into fresh blastocysts, which are then allowed to implant and develop. The resulting animals are chimeric, containing some tissues from the ES cells and some from the original blastocyst; they have been used widely to generate

genetically modified animals. ES cells are also capable of extensive self-renewal (where a cell makes an identical copy of itself) in the culture dish. So here is a cell that can essentially recapitulate most of the developmental steps leading to the generation of specific tissues in the body, without being capable of making a whole organism.

Specialized Stem Cells

There are also other types of stem cells that are more restricted in their potential. These are termed multipotent stem cells. These cells form founder colonies in specific regions of the developing embryo, which lay down the progenitor cell colonies required to build specific tissue types. Progenitor cells are rapidly dividing with a limited self-renewal potential – programmed to make one type of tissue fast and then stop. They are the workhorses of development, while the true stem cells remain quietly in the background, dividing just enough to maintain the progenitor cell pool. Once an organ is complete, a pool of stem cells will often reside in its deeper layers. These divide slowly under normal circumstances, but can be induced to divide faster by tissue damage, and have a remarkable capacity for self-renewal. The stem cells of the blood system are perhaps the most studied, and were discovered over 50 years ago. The blood is one body tissue that needs continual replacement. Blood stem cells lie deep within the bone marrow, producing enough progeny to replace cells lost through wear and tear. Other tissues such as skin, gut, and liver have their own multipotent stem cell pools. Thus, the body is in fact a mosaic of different tissue types, each with their own founder colonies of cells which in many cases can be recruited to repair damage or replace lost cells.

If this system is so efficient, why do tissues wear out at all? Why can't the cells simply replace each other continually? Herein lies one of the mysteries of the body – the process of aging. Clearly, if every tissue in the body could replace itself continually throughout life, aging would not take place. However, as discussed extensively in another chapter (see Kirkwood), there appears to be either a genetic preponderance or a preset program which leads to errors in both dividing and nondividing cells as they age. It is this accumulation of damage that leads to loss of skin tone, wrinkles, organ malfunction, and possibly brain diseases of old age. The adult stem cell pools appear to have a finite period in which they can continue to divide efficiently and replace their offspring in most organs. This process of regulating cell division is one of the major challenges our bodies face, and one can imagine a powerful struggle between cells which want to divide and cells which don't in the aging and tiring body. Get it wrong and the result is massive cellular division and the formation of a tumor. As cancer remains one of the most common killers in modern medicine, and the risk increases with age, it is clear that the body often loses this struggle, a rogue cell reverting to lost youth and immortality, with deadly consequences. Thus, once in place through the miracle of development, many of our cells live in a fine balance between division and death. Stem cells, buried deep within our organs, are perhaps the closest link with the past, and a potential target for increasing health in later life or following disease.

Therapeutic Implications of Stem Cell Biology

A major part of medicine has traditionally been linked with preventing diseases of advancing age, using either drugs or surgery. Novel chemical compounds, capable of changing or supplementing our existing biology, have been churned out in their millions in the never-ending quest for health. Surgeons have performed miracles by removing growths or repairing old or broken joints. But until recently the thought of replacing diseased parts of the body was pure science fiction.

Blood donation has been a feature of modern medicine and is one of the most basic types of cell transplantation from one patient to another. In some cases this is in the form of infusion following injury and massive loss of blood. In many forms of cancer, treatment using high-dose chemotherapy often destroys both the cancer and the patient's blood and the cells of the immune system. However, blood stem cells can be removed prior to chemotherapy, and then replaced to repopulate the bone marrow afterwards. In fact, there are now companies who specialize in storing blood stem cells from young, fit people just in case they need them later following chemotherapy (e.g. Stem Cell Science Inc.: www.stem-cell.com). Whole-organ transfer from ''brain dead'' patients on life support to patients with kidney, liver, or heart failure has also become part of everyday medicine. The final hurdles in organ transplants were not in fact surgical at all, but to do with the power of the body's immune system to repel all invaders. Any tissue not recognized as ''self'' was immediately destroyed by the immune system, and it took the development of powerful antirejection drugs to allow the first kidney transplants to take place. The success of these operations is tempered by the rather tragic waiting list which now faces all patients with serious heart or kidney disease, and the side-effects of the various types of antirejection drugs which have to be taken for extended periods of time. Less well known are brain transplant studies. Parkinson's disease involves the loss of specific neurons within the brain that produce the chemical dopamine. A number of reports have now shown that these neurons can be replaced by new dopamine neurons transplanted into the affected patient. Here, brain tissue harvested from terminal patients on life support cannot be used, as the neurons within the adult brain do not survive the trauma of being removed. However, postmortem fetal tissue survives with the brain of Parkinson's disease patients, and can develop into mature neurons, which in turn reverse some symptoms of the disease. The idea of using cells rather than whole organs to alleviate disease has led to the term ''cell therapy.'' Keyhole heart surgery is already being considered, where fresh heart muscle cells are injected into the ailing organ and may possibly integrate and revitalize without total replacement. In diabetes, pancreatic transplants are already available and new cell therapy approaches are already in clinical trials. These consist of using specialized cells, called ''Islets of Langerhans'' which produce insulin, as a source of tissue for grafting into the pancreas, thus obviating the need for a whole organ transplant.

In all of these transplant scenarios, a major problem continues to re-emerge. Where will the tissue come from? Clearly, there are not enough donations to provide for the numbers of patients who could benefit from transplantation. This is related to

shortages in the blood supply, the small number of organ donor card holders, and the specific requirements of harvesting organs. One approach is the use of animal organs. Pigs share many characteristics with humans with regard to organ size and function. In addition, they have large litters and can be bred with relative ease. Recently, a genetically modified pig has been produced which has ''humanized'' cells which are less likely to produce an acute immune response. However, there remains the problem of long-term chronic rejection with pig organs, and following the BSE scare there is always the worry of transmitting an innocuous pig virus to man, where its effects would be unpredictable.

In November 1998 the world woke up to the discovery that human embryonic stem cells could be grown in culture. A research group, funded by a biotech company called Geron, reported in the journal *Science* that they had successfully grown human ES cells and that these cells could give rise to all the major tissue types of the body (Thomson et al. 1998). Although not all of the tests had been carried out to prove that these cells were bonafide ES cells, they had many characteristics that suggested they were at least very similar. Suddenly, it was possible to generate human tissues at will in the culture dish. The worlds of ES cell biology and medicine were now on a collision course, at least theoretically. In general, the idea of generating whole organs from single stem cells is simple to grasp. Yet, in practice this has been difficult to achieve. Although skin can now be artificially generated in the culture dish, complex three-dimensional organs again are proving more difficult. However, the field of complex polymers, combined with novel stem cell culture techniques, is pushing the field forward, with the first artificial bladder grown in a test tube currently awaiting clinical trials. Huge amounts of money are being invested in this field of research, and large companies such as Advanced Tissue Sciences (ATS) already provide bioengineered skin and cartilage substitutes and are working hard to develop the first artificial kidney or heart outside the body. The impact of these techniques on organ transplantation is obvious, and the idea of combining human ES cell technology with organ factories comes closer to reality with each passing day.

Although exciting, there are certain drawbacks to all of the above therapeutic possibilities of using human stem cells to treat various diseases. Of these the most serious might be the immune response to foreign cells. Although not as serious as xenografts (where cells from another species such as a pig are used), there is still rejection of transplanted cells derived from another human. Antirejection drugs are of course available, but they can have serious side-effects in certain patients. How might this be circumvented? There are two major possibilities.

The first approach is to take adult stem cells from the patient under treatment, expand these in the culture dish, genetically modify them, and then transplant them back. If organ construction in the culture dish becomes a reality, similar adult stem cells might be used to ''seed'' polymer matrixes with the patient's own cells to generate a new organ. A second approach has more ethical considerations. Nuclear transfer involves the removal of a nucleus from one cell into another. Early studies using amphibian embryos showed that it was possible to transfer the nucleus of one oocyte to another, and then generate a new organism. Years of speculation and controversy were ended with the production of Dolly, the world's first cloned mammal. Although this method was very inefficient, it proved that the DNA from

adult cells retains all the potential to generate a whole new organism, or clone (see Ian Wilmut's chapter 3) providing it was put into a quiescent state and transferred to a receptive egg. Using these methods, the nucleus from a patient's skin cell could be transferred to a donor egg, which could then be induced to grow to the blastula stage. ES cells isolated from this blastula and induced to turn into the appropriate tissue type could subsequently be transplanted back into the patient. The benefit here of course is that the cells would appear to belong to the patient (as they had copies of the patient's own DNA) and thus not be rejected. However, these methods involve generating and destroying a human blastocyst for medical reasons. This has prompted enormous debate in most countries and led to the formation of a new government advisory body, the Human Genetics Commission, to tackle this issue in the UK.

It is perhaps becoming clear that stem cells may come close to providing a panacea for certain areas of medicine. New cells, new organs: when its worn out, replace it. Are there philosophical issues here? Certainly, the borders between a person and their individual parts become blurred when thinking in terms of cells and man. Continual replacement of tissues and organs also raises the idea of immortality – for those who can afford it. Because these new technologies will not come cheap, state-run hospitals will be hard pressed to keep up with demand. But another major issue remains: it may be possible to have forever-young bodies, but what of the mind?

Cellular Philosophy and the Mind Problem

Although the presence of stem cells in tissues requiring many new cells during life, such as the skin and blood, may seem obvious, it was more of a surprise to find similar stem cells also existed within the adult brain. Why? Because the brain is classically thought of as a static structure. The old dogma reads, ''we are born with so many brain cells and then they die gradually as we get older – our memory often dying with them.'' Recent developments in neuroscience have put this idea to rest. Certain regions of the adult brain have cells which divide all through life, generating new neurons which may even contribute to new memories. Early remarkable studies in songbirds showed that new nerve cells replace old ones each year and contributed to novel songs. Although this was long thought to be an isolated avian example, more recent studies in rats have shown conclusively that stem cells lining the ventricular caverns of the brain continue to proliferate in two regions. The first is in the front of the brain. Here, dividing cells migrate along established pathways down to the olfactory bulbs, the region of the rodent brain devoted to smell. Once they arrive in the olfactory bulb, these cells turn into neurons that integrate and begin to function as a new component of this brain region. A remarkable number of newly generated cells migrate along this pathway throughout the rodent's life, although the exact function of this process remains a mystery. Another region of the brain where new neurons are produced is the hippocampus (the region of the brain responsible for short-term memory). When rats are exposed to an enriched environment (i.e. their cages have toys and bigger areas of space), more new neurons are produced in the hippocampus, suggesting that the process of cell division in this brain region is linked to the environment. Some of these new cells may also play a role in new memory

formation, although this is a hotly debated topic at present. Remarkably, similar cells have also been found in the human brain, and thus represent a fascinating feature of the adult nervous system (Kempermann and Gage 1999). These dividing cells can be removed from the adult brain and grown in the culture dish. There they continue to divide if given the right nutrient broth, and have been intensely studied. In most cases, a percentage of the dividing cells are multipotent neural stem cells, capable of making new neurons and glia, the major cell types of the brain. New ways of growing these neural stem cells have shown that large numbers can be generated in the culture dish over relatively short periods of time.

Human neural stem cells can more readily be isolated from postmortem fetal tissue and subsequently grown for long periods of time in the culture dish. These cells retain the ability to survive and integrate into the damaged rodent brain (Svendsen et al. 1999). Other groups have shown that using a cocktail of genetic manipulation and certain chemicals in the culture, similar cells from the rodent can be turned into dopamine neurons. These types of cells may bring partial relief in diseases such as Parkinson's, through simply releasing chemicals within a defined brain region. However, restoring full neural circuitry may be far more of a challenge, requiring that the cells not only survive and release specific chemicals, but also that they link up in the correct fashion. Only then will full brain repair be possible.

For most body parts it may appear that we are simply taking the next logical step in medicine. Instead of treating the diseased tissues of the body, we are replacing them with new ones. But how long can this go on? How many cells do we have to replace before the ''self'' is lost? If one thinks of the body as a machine, controlled by the brain, then perhaps it is allowable to exchange all of our body parts on a regular basis in order to stay at maximum health, rather like a conscientious owner changes the parts of a car as they wear out. The car continues to age, but its parts are kept in premium condition. At the end of its life it is still an MGB or E-type Jaguar, even though its original parts have been replaced many times. But change the shape of the car and suddenly it's not the same anymore. It has been modified, adapted to a form that is no longer recognizable. With the human body it is obviously possible to change looks through plastic surgery or reconstruction of the face. But a friend or family member would soon realize it was the person they knew once a conversation had begun, memories were rerun, likes and dislikes discussed. But changing the mind is a different concept.

For diseases such as Parkinson's, where the idea of transplants at present is to simply replace a missing chemical responsible for the flow of movement, there appears to be no philosophical problem. But if diseases such as Alzheimer's are considered for cell therapy, an interesting conundrum arises. In its early stages, Alzheimer's consist of episodic short-term memory loss and changes in personality. As it progresses the memory impairments become worse and there is a dramatic transition in character, back to an almost childlike state. In its final stages, the sufferer is practically unconscious to the surrounding world, living in a body with no free mind, no past or present, no sense of being, and no recognition of family or friends. As brain studies have shown an enormous loss of cells in many regions of the brains of patients with Alzheimer's, it is clear that one possible therapeutic approach would be to replace these with new ones. But even if this were possible in the future (at present restoring

these types of connections is very difficult), what would be the outcome of such a transplant? ''Who'' would the resulting person be? Would the new cells link the patient's past world with the current one? Or would they simply feel as if they had been born into an old body? This same argument could be applied when considering using neural cell therapy to restore memory loss and cognitive decline seen in normal aging.

In a way this problem touches on the complex issue of what ''self'' is, or perhaps, depending on definitions, consciousness (see Carol Rovane's chapter 18). Are we simply a collection of neurons organized in a specific way, or is there a grander plan to things, which only arises during the mystery of development, among the millions of dividing cells in the brain. Of course we are not born with a feeling of self. At birth we are only able to communicate in a very basic way, perhaps less than a dog or cat, and we have no concept of good and evil, no social skills, no ability to predict the future or even rationalize about the past. Yet the entire brain is there. What is missing is experience. Experience is known to shape the brain from the moment we are born. If cats are prevented from seeing the outside world throughout development it might be predicted that once able to see again these animals would regain normal sight. However, experiments designed to test this revealed a different outcome. The adult cats showed visual deficits not only just after regaining vision, but also for an indefinite period of time afterwards. It is now clear that during development, it is not enough to have the cells in place, they must have input in order to organize. The example for vision is almost certainly true for other senses, and is probably true for our overall character, which is forged during our formative developmental years and difficult to change in later life. Thus, the destruction of the basic character of a person through disease will not readily be reversed by simply transplanting cells. One could take this argument further. Assuming stem cells can be transplanted into the brain of Alzheimer's patients and encouraged to restore circuits, would the recipient ''come back'' to the world as a young child? Would the transplanted cells then require new experiences to mature and develop? There is some evidence from animal studies that transplanted cells will respond to new environmental stimuli – in particular with regard to memory tasks. In other words, the animal needs to learn how to use the new transplant, which without this new training does nothing. Therefore, to restore the lost personality of a patient (or elderly person with many replacement organs) may be difficult, but it may well be possible to give the patient an opportunity to develop a new personality. Perhaps we really will be able to teach an old dog new tricks in the future!

There is a genuine concern that stem cell transplants, or other types of transplant, will drastically change the personality of a patient. This led to the suggestion that brain transplants be limited to a certain percentage of the whole brain to avoid drastic changes in personality. But with the current trend of continual improvement in health, intelligence, and life expectancy it may not be long before healthy people begin to ask for transplants to improve their basic learning abilities. Surely more cells will mean more intelligence? Mind improving drugs may be supplemented with mind improving cells, carefully topping up regions of the brain which undergo the greatest reduction in cell number during normal aging. It is perhaps this idea of continually replacing damaged or worn out cells during *normal aging*, or improving our natural

brain capacity, which highlights one of the potential discussion points of this type of research.

Of course in some cases the actual memories may remain in undamaged parts of the brain, but the conduit to these is destroyed. One may think here of more focal brain damage, such as that which occurs in stroke patients. Specific key parts of the brain can be destroyed with apparently global effects, as those parts serve as the platform upon which thoughts are translated into actions. In these cases, stem cell or other cell transplants may have better effects and ''bring back'' lost personalities through providing a new interface between intact brain regions and the outside world.

The New Alchemists

The pace of research in stem cell biology is such that every month one has to reassess the field in light of new papers. And the really exciting experiments are just beginning. If a single adult cell, from the skin for example, has the capacity to generate a whole organism, surely it could be made to produce different tissue types in a test tube. In fact, this type of research is now becoming the focus of a number of companies and academic labs. As discussed previously, the reason a skin cell is a skin cell is not that it has lost all the other genes required to make different tissues, but that only a subset of genes (''skin cell genes'') are expressed within that cell, while the others are silenced. By waking up dormant genes using specific transcription factors, it may be possible to generate a wide variety of cells from such a humble skin cell. A recent report has shown that stem cells derived from mouse brain tissue can convert into blood cells under certain circumstances (Bjornson et al. 1999). This lends support to the idea that cells from the skin or brain may be switched into other cell types providing the correct genes are turned on or off, or the cells are exposed to an appropriate environment.

In relation to this chapter, the idea of manipulating any cell to change its ''personality'' suddenly frees this area of research from the ethical and moral dilemmas it currently finds itself in when dealing with human embryos. Surely there can be no opposition to removing a skin cell from a Parkinson's patient, growing it in culture and changing it into a nerve cell, and then transplanting it back into the patient's brain to alleviate some aspects of the disease? The added beauty of this approach is that the patient's own cells are the source for transplantation, so there are no rejection issues. If the skin cell can be modified to produce kidney or liver cells, and the combined technologies applied to produce whole organs, this type of method may prove enormously powerful in all aspects of cell therapy. The bottom line with these studies, once again, is understanding the genes which direct our cells to be what they are.

Stem Cell Biology: God in a Test Tube?

We stand on the threshold of a new era of cell biology. We evolved over millions of years from a single cell in the primordial soup of the cooling earth, a process which is

replayed millions of times as the human fetus develops. As we struggle to understand this remarkable event where a few billion cells come together to form human beings, the reductionists are beginning to win. We are starting to control the very process of life – cellular division and differentiation. In controlling this we get closer to playing God. Cloning animals from single oocytes may become routine. Replacing worn out organs, even worn out brain cells, could become normal practice – in effect providing a form of immortality. Therefore, the combination of genetics and cell biology will throw up some of the most important philosophical, moral, ethical, and theological questions faced by modern man. Inevitably this will lead to enormous amounts of scare-mongering, exaggeration of the facts, and in some cases vindictive and ill-informed attacks on the scientists doing this work. It is the cutting edge of science that leads this process. It is equivalent to the space race of the 1960s and every bit as competitive. Everyone wants to be first, to take the next step – and the top journals encourage these steps. Publish or perish. Under these pressures are the scientists able to make moral decisions about their research? Caught up in the race, is it possible to look rationally at where the work is going and the possible implications?

In some cases the issues are taken out of the hands of the scientists and into the hands of politicians. The transplantation of fetal tissue to treat Parkinson's disease was not funded by the National Institutes of Health in America (the largest government biological science funding body) for a number of years because the Reagan administration banned any funding of studies using human aborted fetuses. Clinton recently overturned this law, and new clinical trials involving transplantation for Parkinson's are currently underway in the USA. A similar ruling banning the use of fertilized eggs for research and the generation of ES cells has been in place in the USA for some time. Ironically, it was an American lab which published the first data showing that human ES cells could be grown in culture which highlights one of the major problems when government attempts to restrict science. Industry simply stepped in and provided the funding required to do the research. There is a danger here that companies will end up in the role of God, rather than society, which is surely less acceptable. There is certainly money in both reproduction and immortality, not to mention restoring function following disease, which will drive companies to pursue this type of research.

What is needed is debate and decisions such that effective laws can be passed and extended, where possible, to a worldwide set of guidelines. It also needs timely and extensive investment from government research councils throughout the world. This type of biology is going to keep going in some form, and by avoiding solid funding, governments run the risk of losing regulatory control. Research using human embryonic tissues is highly emotive and ethically complicated. Who is to determine when life really begins and how the early fertilized egg should be treated? Should there be commercial gain from using cells derived from human embryos? If there is commercial gain, the woman donating the eggs or terminating her pregnancy must be made aware of this as part of the informed consent process. This has the danger of encouraging egg and fetal donations simply for financial gain, and should clearly not be encouraged. One possible way to avoid this scenario is for government to take a more active role in embryo-based stem cell technologies, to regulate this field of research and invest in developing cell therapy methods, from the basic science to

the establishment of ''cell factories'' for the production of tissues for transplantation. In this way, although it would be expensive at the start, governments would be able to utilize these technologies within nonprofit systems, thus overcoming commercial complications connected with selling human tissues. Because of these issues, many cell-based companies are focusing on modifying normal adult human cells grown in culture – either using gene transfer techniques or environmental switches. Here the ethical issues are less involved, although the impact on medicine and society will be no less dramatic if they are successful.

Clearly, as outlined in this chapter, stem cell biology could deliver real therapy for diseases affecting millions of people, and may lead to many exciting discoveries with regard to how humans develop. As such it must be worth pursuing. But in the process of generating human embryos or continually renewing body tissues with ''spare parts'' we will open a Pandora's box of ethical and moral issues. Just what we should take out will be the focus of the next millennium, and the center of many interesting discussions. Let's hope that these are based on reasoned thought, rather than radical and extremist science phobias. This will only come about if the scientists, public, government, industry, and religious bodies work together in a transparent fashion. We all derive from a single cell, but its clear that the miracle of life has produced a plethora of different views on these issues – in itself a testament to the majesty and power of biology.

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