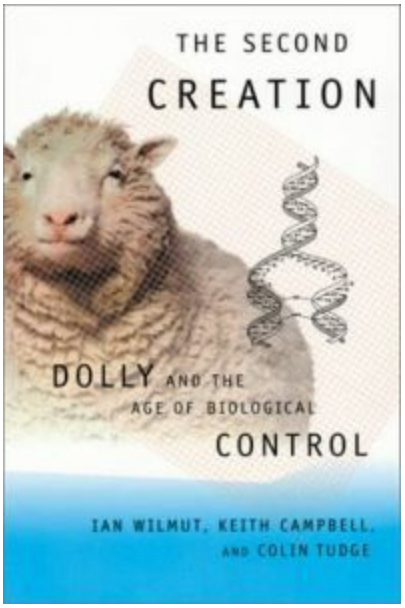

Book The Second Creation

Dolly and the Age of Biological Control

Ian Wilmut, Keith Campbell and Colin Tudge
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Recommendation

Science is breeding new technologies at an unprecedented rate, and with the birth of each advancement comes a new generation of ethical concerns. Few developments have rattled the world's moral cage more than cloning, and it behooves any professional to have a working knowledge of the foundations of the current debates surrounding the genetic sciences. Of course, understanding how Dolly the Lamb was cloned from an adult sheep is probably beyond the grasp of most readers. But authors Ian Wilmut, Keith Campbell (the two leaders of the cloning team) and Colin Tudge (an experienced science writer) examine every inch of scientific ground the project covered. While many details are presented densely, this clearly written, first-person account of a momentous, history-making event is fascinating, particularly for readers of a scientific bent. *BooksInShort* recommends this book to any and all readers as a basic education in a field that has the potential to impact all of our businesses and our lives. Hello, Dolly.

Take-Aways

- In 1996, the birth of a lamb made history, as Dolly became the first mammal cloned from a cultured adult cell.
- Ian Wilmut and Keith Campbell led the team of scientists who cloned Dolly.
- This breakthrough revolutionized genetic engineering, genomics and cloning.
- It brought science closer to the possibility of human cloning.
- Wilmut and Campbell oppose human cloning.
- Cloning is a powerful scientific tool for studying the interactions of genes and their surroundings, and for understanding the development of disease.
- Genetic engineering can improve medicine, agriculture and conservation.
- The Human Genome Project, a cooperative worldwide scientific program, is identifying all the genes in a human being.
- Genomics is the mapping of an organism's genes in the effort to understand the genes' structures and functions.
- Genomics will unleash the full power of genetic engineering.

Summary

What Hath Science Wrought?

A team of scientists led by Ian Wilmut and Keith Campbell made history at the Roslin Institute near Edinburgh, Scotland, in 1996 when they cloned Dolly, a lamb, from the cell of an adult sheep. This procedure marked the first time a whole mammal was cloned using a single cultured adult body cell. This breakthrough revolutionized three technologies - genetic engineering, genomics and cloning - and brought science even closer to the possibility of human cloning.

> "We should not see cloning as an isolated technology, single-mindedly directed at replication of livestock or of people." [Ian Wilmut]

But cloning's pioneer scientists aren't necessarily looking forward to human cloning. In fact, Wilmut and Campbell regret that human cloning, which they find distasteful, has taken hold of people's imaginations. To them, cloning has a different potential strength: as a powerful scientific model for studying the interactions of genes and their surroundings, and an extraordinary tool for understanding development and disease. Such scientific insights will ultimately move science into the age of biological control.

> "At Roslin the cloning of sheep by nuclear transfer has become routine - but it remains a routine of huge and irreducible complexity." [Ian Wilmut and Keith Campbell]

Already, researchers have incorporated into sheep the gene for human factor IX, a blood-clotting protein used to treat hemophilia. Scientists hope that, some day, mammary cell cultures may be valuable donor material. They theorize that genetically modified animal organs might be transplanted into humans, since modifications might prevent rejection by the human immune system. This could alleviate the shortage of transplantable organs.

> "In general, biologists now perceive that although the different genes of the genome cooperate with each other - of course they must - they also compete." [Ian Wilmut and Keith Campbell]

Scientists expect genetically engineered sheep to be valuable as models for genetic defects that mimic human disorders and diseases, such as cystic fibrosis. They could also lead to cell-based therapies for such diseases as diabetes, Parkinson's and muscular dystrophy.

Ethical issues abound as a result of the first mammal cloning, with its challenging future implications. Controversy ensues whenever people focus on taking this technology beyond research use in development and disease, and spotlight the idea of cloning humans.

Achieving the Impossible

Mammals are normally brought into this world when a sperm joins with an egg to form a new embryo. But, in 1996, Ian Wilmut, Keith Campbell and their colleagues from both the Roslin Institute and PPL, a commercial biotech company, cloned Dolly the sheep from a cell that had been taken from the mammary gland of an old ewe and then grown in culture. That cultured cell was then fused with an egg from yet another ewe to reconstruct an embryo that the scientists transferred into the womb of a surrogate mother, where it developed to become Dolly the lamb. While Dolly wasn't the first mammal ever cloned, she was the first to be cloned from an adult body cell.

> "Human cloning is very far from Keith Campbell's and my own thoughts and ambitions, and we would rather that no one ever attempted it." [Ian Wilmut]

The Roslin researchers announced Dolly's existence in February 1997, in a letter published in the scientific journal, Nature. Most scientists were shocked - up until this announcement, they didn't believe that cloning in this manner, and from this kind of cell, was possible.

The long-term goals of the Roslin team and PPL focus on genetic engineering, which is the genetic transformation of animals - and of certain isolated animal and human tissues and cells - for a number of purposes in medicine, agriculture, conservation and pure science. They stress that the world shouldn't view cloning as an isolated technology directed merely at replicating livestock or people.

Genetic Achievements

Scientists began developing genetic engineering in the early 1970s. Genetic engineers transfer genes from one organism to another. In a development that is considered truly miraculous, these transferred genes can function perfectly in the new organism. This genetically engineered organism is said to be "transformed" or "transgenic." The transferred gene is called a transgene. Genetic engineers can cross the boundaries that define species. They can take genes from any organism and put them into any other, not just ones of matching species. For example, fungal genes can be placed into plants, mouse genes into bacteria, even human genes into other animals. This engineering isn't done for ghoulish reasons. Typically it's done to improve agriculture and livestock, or treat disease.

> "Until we started cloning sheep at Roslin, it simply was not possible to re-create whole animals from cultured cells." [Ian Wilmut]

Since its inception, genetic engineering has been severely limited by the fact that most genes in most organisms remain unidentified. Human beings, for example, have about 80,000 functional genes, but scientists know only a few thousand of them, in terms of what they look like and what they do. This has limited genetic engineers. While they have been developing the technology to transfer genes from one organism to another, they haven't known for the most part, which genes to transfer.

> "Of the creatures studied, frogs have the laziest genes. They do not become active until the embryo contains 3,000 to 4,000 cells." [Ian Wilmut and Keith Campbell]

Genomics is working on solving that dilemma. The science and technology of genomics has been developed only over the past few decades, and it boils down to this: the attempt to map all the genes in an organism and to understand their individual structures and functions. The genes of some simple organisms, including yeasts and the roundworm Caenorhabditis, have already been mapped completely. Biologists worldwide are now cooperating to identify all human genes in a program called the Human Genomic Project. Scientists at Roslin are working with other laboratories to identify and map all the genes in each common livestock species: poultry, sheep, cattle and pigs. Genomics will lead to knowledge that will allow the power of genetic engineering to be realized fully.

> "Sheep have proved excellent subjects for cloning, but there is no point in cloning them just for the sake of it." [Ian Wilmut and Keith Campbell]

Polly, another lamb, was born in 1997, the year after Dolly. Polly was the first animal to be both cloned and genetically transformed. Until Polly, this transformation was possible only in plants, but not animals. Scientists had found it relatively easy to transform bacteria genetically by growing it in a dish, adding DNA (the material in genes) and then selecting the individual bacteria that have taken up the added genes most satisfactorily. They use the same technique with plants. Scientists grow plant tissue in a dish using a process known as culturing. When they add new DNA, a whole new plant is regenerated from the previously selected cells, the ones that took up the added gene most effectively.

> "The cell cycle is the complete agenda of the cell: cell division, duplication of DNA and then (in most cases) more cell division. The science and technology of cloning needed input from a different branch of biology - the study of cell cycles. Not every cloning biologist realized that this was so, and even for those who did, the necessary information simply did not exist." [Colin Tudge]

Polly was the first animal created from cells grown in a dish, as if they were bacteria or cultured plant cells. This process is far superior to initial animal genetic engineering, which dates to the 1980s. For the first time, this process allows genetic engineers not only to add genes, but also to subtract them, alter them or add artificial genes. The Roslin sheep-cloning research led scientists to this superior form of genetic engineering, as well as to the breakthrough of cloning from cultured cells.

> "Actors are warned not to work with children and animals; reproductive biologists who want an easy life might be advised in similar vein to stay well clear of sheep." [Ian Wilmut and Keith Campbell]

The three technologies together - genetic engineering, genomics and cloning from cultured cells - are a powerful combination. Through genetic engineering, scientists can transfer genes from organism to organism, create new genes and, in principle, build new organisms. Genomics provides the necessary information: knowledge of which genes to transfer, where to find them and what each gene does. Cloning from cultured cells makes it possible, again in principle, to apply the power of genetic engineering and genomics

to animals.

> "Despite the folklore, sheep are not relaxing animals. They are notoriously prone to obstetric problems, which is why shepherds traditionally spend their nights out in the fields." [Keith Campbell]

As powerful as they are, these technologies are just the beginning. Beyond technology is pure science. Technology is about changing things, providing machines and medicines, and altering your surroundings to make life more comfortable and to create wealth. But, science is about understanding how the universe works and understanding all the life forms in it. The pursuit of technology and the pursuit of science are two different endeavors. Cloning is a powerful technology, but it also creates an opportunity for scientific insight and increased knowledge. Science and technology work together. Yet, ideas don't flow just one way, from science into technology. Ideas run in both directions. Without technology, science would grind to a halt. Science and the craft of cloning depends on technological input - for evidence of that, just look at the complexity of the step-by-step process.

The Science of Cloning

Dolly is not a 100% replica of the old ewe that provided her first cell - Dolly's "clone mother." Dolly isn't as similar to her clone mother as two identical twins would be to each other. Dolly, is merely a genomic, or DNA, clone. A huge difference separates the kinds of clones produced by nuclear transfer (such as Dolly) and the kinds of clones produced by embryo splitting, which is the natural occurrence that creates identical twins. Twins have identical DNA and identical cytoplasm, since the cytoplasm of the original embryo cell simply splits after the DNA duplicates. But clones such as Dolly are made by transferring a nucleus from one cell into the cytoplasm of another, an egg cell from a different animal: Dolly and the ewe who provided the original nucleus have identical DNA, but they don't have identical cytoplasm. That is why Dolly isn't a "true" clone, merely a "DNA clone."

The ewe that supplied the nucleus for Dolly was a Finn-Dorset sheep, and the ewe who supplied the cytoplasm was a Scottish Blackface, a very different breed. But, Dolly is a Finn-Dorset. Even though this clearly shows that the nuclear DNA prevails, but the DNA doesn't operate in isolation. It is in constant dialogue with its cytoplasmic environment - the cytoplasm makes a difference. Although Dolly's body cells are descended from a cell with mainly Scottish Blackface cytoplasm, that cell also contained some Finn-Dorset cytoplasm, which surrounded the donor nucleus. To make true clones by nuclear transfer, scientists would transfer a body cell from the ewe into egg cytoplasm from the very same ewe. That way, the offspring would contain a clone both of the clone mother's DNA and of her cytoplasm.

Creating Dolly was not a one-shot deal. First, 277 embryos were constructed from the Finn-Dorset ewe's mammary cells. All of these embryos were transferred into the oviducts of temporary recipients, and 247 were then recovered. Only 29 successfully developed into blastocysts. These were transferred into 13 ewes. Only one became pregnant, the Scottish Blackface that gave birth to Dolly, a Finn-Dorset lamb. Only one out of 277 embryos stayed the whole course and became a live lamb. If none of the 277 had succeeded, scientists may not have tried again. Getting the funding to continue would certainly have been quite difficult. The figures can be looked at many ways. One in 277 this time, but maybe next time more... or none. Only 13 ewes became pregnant during the process, and Dolly came from this 13. One out of 13 is actually a very good rate.

As with all powerful technologies, contradictions abound. Cloning has incredible potential for good, especially when combined with genetic engineering and genomics. But, such power can also be abused, and the most obvious abuse would be human cloning. Even though the pressures for human cloning are quite powerful, and it's likely that somebody will attempt it, it won't necessarily become common. Society doesn't have to adopt technologies that feel uncomfortable. People in many countries have already proven that they can resist such uncomfortable technologies. Various European countries reject nuclear power, the British said no to the high-rise answer to mass housing and many people won't accept genetically modified crops.

Would people undertake the risks and implications of cloning? No doubt some people would. A philosophy of supporting personal liberty leads those who object to the idea of human cloning to defend the rights of those who would welcome it. But, will it become common, broadly accepted and pervasive? That is not inevitable. The answer will come soon, as human cloning is likely during this decade.

About the Authors

Ian Wilmut studied embryology at Nottingham University and received his doctorate at Cambridge University. He joined the independent Animal Breeding Research Station, which became the Roslin Institute, where he led the team that cloned Dolly.
Keith Campbell studied microbiology at Queen Elizabeth College, London, obtained a D.Phil. from the University of Sussex and is now a cell biologist and embryologist at the University of Nottingham. He joined the Roslin Institute in 1991 to work on the project that resulted in Dolly. Writer and broadcaster **Colin Tudge** majored in zoology at Cambridge University. He is a Research Fellow at the Centre for Philosophy at the London School of Economics. He has written more than a dozen books, including *The Variety of Life: A Survey and a Celebration of All the Creatures That Have Ever Lived,* published by Oxford University Press.