BOOKS: ANIMAL CLONING

A Sheep and a Metaphor

Lee M. Silver

Is there any literate adult in any of the world's industrialized countries who has not heard of Dolly the cloned sheep? I doubt it. Since her debut just three years ago, Dolly has been mentioned in over 4000 news articles in major U.S. newspapers and magazines alone and in countless other news articles, radio broadcasts, and television programs around the globe. She has also been the subject of at least 14 books published for a lay audience. Now the two scientists most closely involved in Dolly's creation—Ian Wilmut and Keith Campbell—have added their own book, *The Second Creation*, to this long list. With coauthor Colin Tudge, a highly respected British science writer, translating their voices to prose, they provide an insider's account of cloning at Scotland's Roslin Institute.

The Second Creation
The Age of Biological Control by the Scientists Who Cloned Dolly
by Ian Wilmut, Keith Campbell, and Colin Tudge

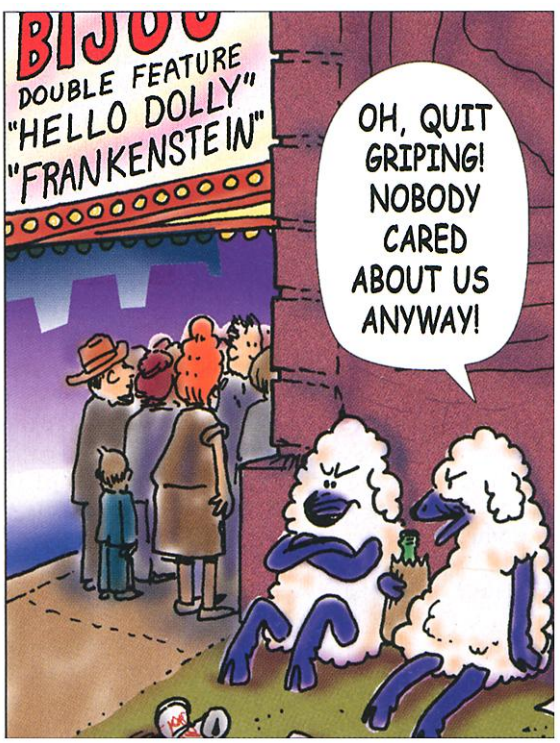
Headline, London, 2000. 366 pp. £18.99. ISBN 0-7472-2135-9.

At the outset, Wilmut and Campbell tell us that all of Dolly's other popularizers have misunderstood her importance. Dolly's true significance lies not in potential implications for future human reproduction, but rather in improved methods for the production of transgenic animals and other advances in biotechnology. These are the reasons, they tell us, that Dolly should matter to ordinary people.

The first 124 pages of *The Second Creation* present the reader with a whirlwind scientific and historical review of the biological disciplines that form the foundation for the cloning research done by Wilmut and Campbell. Surveys of cell biology, developmental biology, reproductive biology, and cytogenetics are presented along with more detailed descriptions of mitosis, meiosis, oogenesis, and fertilization. There are brief forays into recombinant DNA technology, molecular genetics, and the evolution of sex and sexual dimorphism. As Wilmut warns, the technical language has not been "ducked." But it is not clear who this section was written for. The coverage (lacking figures, footnotes, or bibliography) is too sketchy to satisfy biologists and science scholars, who would be better served by appropriate textbooks. For nonscientists, there is too much technical detail and jargon without relevance to cloning.

The text becomes more lively with each subsequent section. The authors offer an overview of earlier cloning research, including the contested experiments of Karl Illmense, the respected experiments of Davor Solter [who, in 1984, infamously declared that the cloning of mammals was impossible (*1*)], and the important contribution of Steen Willadsen (actually the first scientist to achieve success at mammalian cloning)—developments covered with detailed citations by science journalist Gina Kolata in her book *Clone* (*2*).

After these discussions, Wilmut and Campbell reach the heart of their story: autobiographical accounts of the events, ideas, and private thoughts that brought Wilmut (at least) from obscurity to international fame. They explain that the original impetus behind their research was the desire to develop an efficient method for producing transgenic farm animals. Step by step, they march the reader through the logic of each critical experiment along the path toward this goal.



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Wilmut and Campbell began their experiments sharing the widely held assumption that viable embryos could only be formed with donor nuclei transferred from totipotent cells. But after an attempt to pinpoint the developmental stage at which cells lose their totipotency, their research progressed to the question of whether the loss of totipotency mattered at all. Campbell, in particular, felt that control over the cell cycle was more important to successful cloning.

Scientific vindication of this heretical idea arrived with the 1995 birth of Megan and Morag, two sheep created by nuclear transfer from clearly differentiated cultured cells. Their existence destroyed the dogmatic belief in the irreversibility of mammalian cell differentiation. At the same time, it demonstrated the feasibility of considering nuclear transfer from genetically transformed cells in culture as a vastly improved method for genetic engineering of large animals—the approach validated two years later with the birth of the genetically engineered sheep Polly.

Wilmut and Campbell confess that they don't understand why Megan and Morag are not as famous as Dolly. As Campbell says, "For me, Megan and Morag are the stars." To be sure, upon publication in March 1996 (*3*), the Megan and Morag cloning report was picked up by the British media and by many American papers as well. But, like nearly all stories of scientific advances, it was essentially a onetime news event. Wilmut thinks it might have been otherwise if the attention of the media had not been deflected by a horrible murder of British schoolchildren that occurred seven days later.

The experiment that produced Dolly had no relevance to the technological goals of the Roslin Institute. It was planned simply to complete the panel of developmental stages tested for competency in cloning. To Wilmut and Campbell, Dolly is merely the "gilt on the gingerbread." Kolata reports that Wilmut originally thought "the interest in Dolly might be somewhat less than the interest had been in Megan and Morag" (*2*, p. 222).

Why was Wilmut's prediction so far off the mark? Ironically, Dolly's true significance lies within an implication that her creators wish did not exist: Dolly is living proof that the genetic cloning of adult human beings is no longer in the realm of the impossible.

Even more ironically, Dolly is most sig-

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nificant by far to the billions of people who least understand her. Around the globe, her image was splashed across television screens interspersed with footage from films of *Boys from Brazil*, *Frankenstein*, *Brave New World*, and *Multiplicity*. Instantly, Dolly's public fame emerged not from what she really is, but from what she represents. She is a metaphor for the Promethean power that scientists now have to create and control life, and her innocent image drives fear into the hearts of those who think man has wrongly crossed into God's domain.

Although the title of *The Second Creation* is an echo of the metaphorical Dolly, in their text the authors try hard to bring readers back down to the real-life version. They end their story with an overview of the many benefits that humankind may derive from the biotechnology facilitated by genetic cloning. This section, at the very least, should be required reading for societal leaders who still mistake metaphor for reality in the promulgation of anti-cloning laws.

References

1. J. McGrath and D. Solter, *Science* **266**, 1317 (1984).
2. G. Kolata, *Clone: The Road to Dolly and the Path Ahead* (Morrow, New York, 1998).
3. K. H. S. Campbell, J. McWhir, W. A. Ritchie, I. Wilmut, *Nature* **380**, 64 (1996).

BOOKS: NEUROSCIENCE

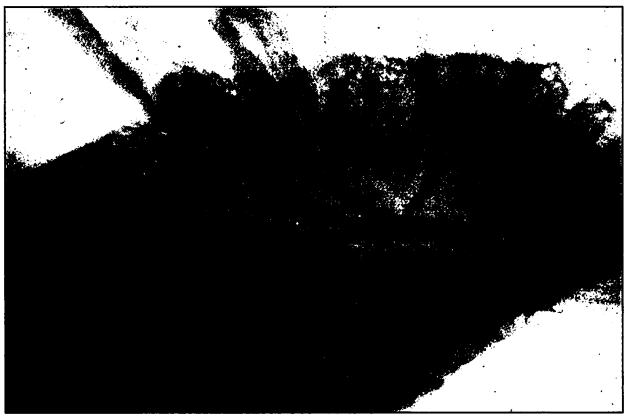
Big Synapse Stories

George J. Augustine

Given that the brain consists of some 100 billion nerve cells, understanding how synapses allow these cells to communicate with each other has been a core question in neuroscience. The past 50 years have seen remarkable advances in this area, largely due to a small number of experimental systems—such as neuromuscular synapses and the squid giant synapse—whose great advantages for physiological analyses have illuminated the beauty of synaptic function. Thus a book, such as *The Squid Giant Synapse*, that concisely highlights the contributions of one such model system is a very good idea. An even better idea is to have the book written by Rodolfo Llinás, a distinguished synaptic physiologist who now has been working on this preparation for five decades.

The Squid Giant Synapse
A Model for Chemical Transmission
by Rodolfo R. Llinás
Oxford University Press, New York, 1999. 332 pp. + CD-ROM. $85, £49.95. ISBN 0-19-511652-6.

The Squid Giant Synapse is billed as an introductory text for graduate and advanced undergraduate courses and has much to offer students in such classes. Llinás covers the main breakthroughs in unraveling the long-standing mystery of how neurotransmitters are released. He starts with the 1957 demonstration by Ted Bullock and Susumu Hagiwara of a presynaptic action potential, discusses the 1967 "calcium hypothesis" of Bernard Katz and Ricardo Miledi, and continues through contemporary studies of the molecular biology of exocytosis. As I had hoped, the author gives prominent attention to his own seminal contributions, such as the first voltage-clamp analysis of presynaptic calcium channels, his elegant biophysical analyses of calcium-secretion coupling mechanisms, and his pioneering efforts in using microinjection experiments to implicate synapsin and other proteins in the molecular apparatus of neurotransmitter release. There is no substitute for hearing such first-person accounts, and Llinás's perspectives are certainly the main attraction of the book.



Giant synapse study site. Within the pallial nerve, the presynaptic giant axon (green dye) branches into fingerlike extensions, each of which contacts a postsynaptic giant axon. The largest postsynaptic axon (red dye) passes rearward through the squid's muscular mantle.

Giant synapse junction. This confocal microscopy image shows postsynaptic "claws" (red) terminating as rounded fingerprint-like contacts (1 μm in diameter) on the smooth presynaptic terminal (green).

The author's colorful prose is also a big plus. For example, who else would see the giant postsynaptic neuron as "a bouquet of smaller axons"? And who else would dare admit that "in the end, our complete understanding of this process (synaptic transmission) will manifest itself not as a simple insight, but rather as an ungainly reconstruction of parallel events more numerous than elegant"? Another strength of the book is the accompanying simulation software, which allows both students and advanced researchers to model the electrical signaling events that occur during synaptic transmission. This user-friendly software should provide a painless tool for students to understand the complex interplay between membrane potential, calcium influx, and transmitter release.

On the other hand, Llinás's personal perspective necessarily limits the utility of the volume as a textbook. His personal approach lacks sufficient scientific balance to give students a clear sense of perspective. To give but one example, over five pages are devoted to the somewhat exotic question of how temperature affects synaptic transmission, but the more clear-cut and important presynaptic current-clamp results of Katz and Miledi (1967), as well as those of Kiyoshi Kusano and colleagues, receive much less coverage. Also, though the squid giant synapse has been unparalleled for understanding presynaptic mechanisms, it has played a relatively minor role in elucidating postsynaptic mechanisms. As a result, Llinás has too little to say about the postsynaptic half of brain function. Finally, although the author devotes many pages to the molecular biology of transmitter release, this field is moving so rapidly that the material already is dated. Given these characteristics, *The Squid Giant Synapse* really is best viewed as a monograph rather than as a full-service textbook.

In summary, the value of this book lies in its personal narration of one scientist's journey through the synapse. Llinás has done a good job of capturing the excitement that has kept the field of synaptic physiology energized. By its example, *The Squid Giant Synapse* offers a strong argument for the continued value of physiological analyses of brain function, even in these genomic times.

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