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Mary Cloned a Little Lamb

– Guest Editorial –

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In recent weeks the headline "Hello, Dolly" has been shouting from the front pages of newspapers and the covers of newsmagazines. Cloning has even overtaken comic strips and the internet is rich with parodies. The report in the journal *Nature* of the birth in Scotland of the lamb Dolly, the identical twin of an adult sheep, has attracted media attention unlike any recent development in the field of biology. What is it about this achievement that we find so intriguing?

Is it the scientific information that the birth of Dolly has confirmed? The question being asked is an old one: How does a fertilized egg, a single cell specialized mainly for rapid cell division, generate a complex adult organism, with such distinct types of functionally specialized cells as nerve, skin, liver or muscle? The information controlling any cell's behavior is encoded in DNA in the cell's nucleus, received from preexisting cells, and ultimately from the fertilized egg. How then to explain the differences among adult cells? Two alternatives have long been proposed: either information is lost from cells in particular lineages when no longer needed, or it is retained, but selectively suppressed, so that the only the information needed to specify the adult cell's fate is active.

Generation of a new individual from a single adult cell could demonstrate that the adult cell still has all the necessary information available. Clearly many plants show this ability. Cuttings and even single cells can generate entire new plants, such as common house plants. Some primitive animals also are able to regenerate new individuals from a relatively small portion of the adult, but more complex animals seem to have lost this capacity. Humans and other mammals can heal damage in some organs, such as skin. But only at the earliest stages of development, when the fertilized egg has divided just once, can separation of the two resulting cells lead to complete independent individuals. Such individuals, known

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as identical twins, have a physical resemblance accounted for by their identical genetic information.

Some other approach than regeneration must therefore be used to decide whether the information controlling development of complex animals has been irreversibly altered during development. The technique of nuclear transplantation is such an approach. John Gurdon showed in the 1970's that if the nucleus of a frog egg were removed, the egg would not develop normally, but if the nucleus were replaced with that of another cell from the frog, it could. The extent of development was limited, however, particularly when the donor nucleus was harvested from mature adult cells. Perhaps complex animals do in fact, lose important information needed for complete development.

This is the scientific question that the authors of the *Nature* paper asked. In fact they had already reported successful transplantation of embryonic cell nuclei. They grew dissociated embryo cells for a time in laboratory cultures; then after treatment to induce a non-growing quiescent state, single cells were fused with sheep eggs whose own nuclei had been removed. At this point the reproductive technology developed for in vitro fertilization nurtured the new developing embryos, first in cultures and then in the uteri of foster mothers. Several reached full- term pregnancy. The report of this work did not receive much notice in the popular press, though it was the first time that nuclear transplantation from a differentiated (albeit juvenile) cell of a mammal had succeeded. Then what is the news about the recent report? It is that in this instance, the cells in culture were obtained not from embryos, but from the udder of a pregnant sheep. These adult cells are quite fully differentiated and distinct from other cell types, whether primitive or differentiated for other purposes. The fact that their nuclei can provide all the information needed to generate a lamb that is (so far) physically indistinguishable from lambs produced by normal fertilization is thus ample confirmation that in that udder cell, at least, no information had been lost.

Other interest arises from actual or imagined applications of the cloning procedure. Could it succeed with mammals other than sheep? Animal research involves tests in which some groups receive a treatment while other groups serve as "controls." The more genetically similar, the smaller the groups can be without jeopardizing the validity of the research findings. If clones could be used, their genetic identity would mean that valid tests would require much smaller numbers of animals, and testing would be more economical.

Economic interests also drive another anticipated application of cloning: generation of many individuals with agriculturally desirable traits. Rather than putting a prize bull or stallion to stud and hoping that the offspring have at least some of the father's physical characteristics, one could be sure that any offspring of nuclear transplantation would be genetically identical to the nucleus donor. The benefits seem extraordinary, but there are costs, too. The technology is not very efficient: Dolly was one of 277 nuclei introduced into separate eggs; only 29 of these showed even enough development to warrant introduction into foster mothers, and only one pregnancy resulted. Thus until the efficiency can be improved, large-scale application seems unlikely. Even if it were successful, other costs arise from having a homogeneous population of organisms, should they encounter a disease or environmental catastrophe to which none is resistant. Midwestern farmers have become aware of this risk, having experienced the tremendous loss to the corn crop from one blight fungus.

The possibility that the nuclear transplantation technique might be applied to human cells raises still further issues. Certainly the procedure should work. And many of the necessary techniques, from in vitro culture of early embryos to implantation into the uteri of natural and even foster mothers have become tools that have assisted otherwise infertile couples to reproduce. But the notion of cloning humans seems abhorrent to most people. The repulsion predates the possibility: literature through the ages has cast the "Doppelgaenger" as a friend, a threat to the identity of the individual. Science fiction and Shakespeare alike find intriguing material in situations involving identical twins or multiple individuals with identical physical characteristics. Soon after the news of Dolly broke, the Clinton administration prohibited use of federal funds for similar procedures using human embryonic material. So there certainly is a perception that the cloning of humans is a possibility about which we should raise concern.

Is the perception the reality? Set aside for the moment the ethical issues arising from the decisions *whether* to clone and *whom* to clone. Assume that some justification could be raised to clone a particular human being currently inhabiting the earth. Assume also that the technical difficulties had been solved to the point that clones could be produced at reasonably high efficiency. What would those clones represent? Individuals identical to each other and to the nuclear donor in their inherited physical characteristics, perhaps. But unlikely to be mistaken for other than themselves as separate and distinct human beings. Why? Because heredity is not destiny. We are the products not only of our genes but of our experience, our environment, the influences of other human beings upon us. In fact, casual examination of naturally existing human clones (identical twins) reveals clearly distinct people and personalities, and often even physical differences that result from the interaction of heredity with environment.

I do not mean to suggest that important issues do not arise in discussions of the possibility of human cloning. Many of these reflect our profound ambivalence toward the role of technology in general in altering the "natural" course of human existence as much as a concern with cloning per se. Issues relate not only to the condition of individual humans but also to the organization of human societies and the responsibilities we owe each other in managing our collective destiny. I question whether much of scientific interest is to be learned from cloning human beings, but the discussion that the possibility stimulates is itself of great value. It reminds us of the power humans can exert over each other and over the rest of the natural world, a power to be exercised only with thought and care.