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Are We Ready for Cloning?

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Nothing has created more controversy in human reproductive medicine lately than the plans announced early this year in Italy for cloning humans. The announcement was the onset of unsurpassed attention from the news media around the world where most of the coverage was, and still is, focused on the cloning team. Several experts in the field of cloning as well as medical and professional societies quickly voiced their concerns and the general opinion was to condemn such plans. The European Society of Human Reproduction and Embryology (ESHRE) released a statement reiterating its opposition to human cloning for reproductive reasons. ESHRE took a consensus decision in 1999 to impose a voluntary moratorium on cloning, and they see no reason to change their decision. Earlier in June 1997, the American Society for Reproductive Medicine released a statement indicating that the practice of cloning an existing human is unacceptable. While it may be safe to say that most of the informed and responsible members of the medical and scientific community are against cloning humans, it is unfortunate that most of us have remained silent while those trying to clone a human being have defiantly insisted on pursuing their work.

Cloning experiments with farm animals have given us sufficient information to determine that the practice is not ready to be applied commercially on animals, much less on a human being. However, an alarming trend in human reproduction is to apply without hesitation what we perceive may have a benefit, without giving sufficient consideration of the short-term or long-term effects of particular techniques on the welfare of the family, mother, and babies being produced. Cytoplasmic transfer, intracytoplasmic sperm injection, round spermatid nuclear injection (ROSNI), and the like may be a few prime examples of this trend, not to mention the vibrant industry surrounding bogus claims of success in the diagnosis and treatment of immunological infertility. We and our professional societies face a tremendous task to limit the negative effect of the scientists who are working hard to make reproductive medicine a showcase of quackery medicine. While thousands of families have benefited from assisted reproductive technologies, the public perception of this practice is not always positive. It is common to hear or read news about the commercialization of human reproduction and that the practice of reproductive medicine is out of control. For starters, take a quick view of the different Web pages that address immunological infertility and some of the ''self tests'' that patients can use at home. Current efforts to clone humans are sure to exacerbate this problem.

The ability of a few laboratories to successfully clone cattle is the result of their having knowledge of nuclear transfer techniques and related laboratory procedures, pharmacological manipulation of the estrous cycle, and an enormous base of knowledge that has been accumulated over the last few decades. Animal cloning is in the end a composite of many different technologies and scientific breakthroughs. Successful and repeatable procedures for in vitro maturation, in vitro fertilization, and embryo culture are now well established in cattle and other laboratory animals. However, this has involved the enormous task of working with thousands and thousands of oocytes. The availability of large numbers of female gametes from abattoirs for use in research at a relative low cost has largely contributed to the progress of cloning, and has presented the opportunity to carry out numerous cloning attempts, and to optimize the procedure each time it is repeated. Even with low efficiency, but the ability to repeat the experiments multiple times, a clone of most any cow or bull eventually can be produced.

The efficiency of cloning animals is extremely variable. Due to the relative low number of controlled studies, it is difficult to determine the sources of variation and analyze potential interactions between variables. Among the variables that affect cloning in cattle and laboratory animals are genotype, type of donor cell nuclei used, treatment of donor cells before nuclear transfer, source of recipient ova, techniques employed, and skill and knowledge of the laboratory staff performing the work.

In terms of efficiency, the percentage of nuclear transfer embryos developing to morula or blastocyst stage ranges from 5% to 65%, and live births from 0% to 83%. Of the calves born alive, a significant percentage die within 1 week of birth due to health problems. This varies from 0% to 100% of calves failing to survive to 1 week of age. Hill et al (2000) reported one case in which a steer was cloned from skin fibroblasts. Twenty-eight percent of the embryos developed to the blastocyst stage in culture (53 out of 190). Six pregnancies resulted, 3 of

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these developed through 90 days of gestation, but only 1 survived to term. During the first week of life this animal required intensive critical care and therapy for treatment of pulmonary hypertension and lung immaturity. In addition, within a week of age the animal was diagnosed with Type I insulin-dependent diabetes (Hill et al, 2000). Veterinarians never see that high number of atypical health problems in entire herds of cattle, much less all of them concentrated in few individuals.

Additional experiences from the same group involved cloning 2 cows. In 1 cow, 16% of the embryos developed to the blastocyst stage. After 37 blastocysts were transferred to 13 recipients, 6 were pregnant at 30 days of gestation. Only 4 remained pregnant 30 days later. One additional pregnancy was lost, 2 were terminated for research purposes, and 1 continued to term. Twin calves were produced from that pregnancy; both died at 7 to 10 days after birth. Such a high pregnancy wastage is not usually observed with traditional embryo transfer or artificial insemination in cattle. The second cloning candidate produced 43 blastocysts, and 3 out of 14 cows became pregnant after transfer. None of the 3 pregnancies survived beyond 90 days of gestation (Westhusin et al, 2001). Others in the past have reported that calves born out of in vitro production of embryos are extremely large compared with those produced naturally. It appears that in cattle, some of the first trimester fetal losses are related to abnormal allantoic development within the conceptus (Thompson and Petersen, 2000). The cause of disrupted allantois development remains to be identified, but it may share a common cause-effect mechanism with the large calf syndrome observed by others. In sheep and goats, the situation is not different, and problems with fetal loss during gestation and congenital abnormalities leading to high death loss are common. In pigs, although success has been reported, less than 1% of embryos transferred have survived to term. This figure does not represent the numerous trials in which no offspring have been produced.

In short, many scientific hurdles must be overcome before this technology can be applied without risk to livestock and laboratory animals. The thought of applying cloning techniques to humans is both irresponsible and unlikely to be successful.

After the initial announcement of this venture in Italy, several people raised serious doubts about the knowledge, credibility, honesty, and ethical standards of those involved with the project. Similar concerns were voiced during an hour-long discussion on cloning on the National Public Radio talk show ''Talk of the Nation/Science Friday'' and later discussed in more detail in newspapers. We feel that the scientific and medical community worldwide must work together to create policies and guidelines to limit cloning and to protect the public. However, care must be taken to ensure that the research on cloning is not hampered within those guidelines. If the profession does not impose limits on itself, others will do it for us. Our view is that draconian measures are necessary to limit further damage to the profession and risk to the public. We cannot and should not remain silent.

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