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Andrology Summary

Is There a Role for Cloning in Human Reproduction?

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Note: Postings to *Andrology* have been lightly edited before publication.

Certainly, the topic of cloning remains one of the most controversial issues in reproductive medicine and, for that matter, in modern science. In this Internet discussion, Robert Oates inquires regarding the current status of cloning in animals and points out the relevance to human reproduction.

Robert Oates asked

> I was wondering if anyone could enlighten me as to the outcomes of cloning in the animal world. We all hear about the "successes" of animal cloning in terms of live "normal" offspring. Can anyone provide updated information on how many in utero and/or delivered animals have had serious anomalies of one sort or other. How many defective clones are there—this is a much more interesting question at this moment than how many look normal. What are the data on premature aging or other consequences of telomeric shortening. The children of our patients are our patients also. We have a responsibility to them as well.

Jose Hernandez makes a number of interesting points on this topic, raising a number of important concerns:

> Nothing has created more controversy lately than the meeting in Italy on human cloning. A lot has been learned from animal cloning. Worldwide, there may be more groups working on cattle and laboratory animal cloning that in all other species combined. The lessons learned from those studies with no doubt should be applied in a judicious manner to benefit mankind. However, an alarming trend in human reproduction is to apply without hesitation what we perceive may have a benefit without consideration to the short- or long-term effect of that particular technique on the babies being produced. Intracytoplasmic sperm injection (ICSI), Round Spermatid Nucleus Injection (ROSNI), and cytoplasmic transfer may be a few prime examples of this trend.

We all know of the recent conference on cloning carried out in Italy. Most of the respected scientists and clinicians worldwide have voiced their concerns about cloning humans. Some of them even resigned to committees associated with the cloning group. While it may be safe to say that most of us agree with those concerns raised against cloning, it is unfortunate that most of us have remained silent while the group of people trying to clone humans has defiantly insisted on pursuing their work. While thousands of families have benefited from assisted reproductive technology, the public perception of this practice is not always positive. It is common to hear or read the news about the commercialization of human reproduction and that the practice of reproductive medicine is out of control. The human cloning project just came in time to make things even worse.

The ability of a few laboratories or groups to successfully clone cattle is the result not only of deep knowledge of nuclear transfer techniques and related laboratory procedures but also the enormous base of knowledge accumulated over the last decades involving the application of assisted reproductive technologies in cattle and our experience on the pharmacological manipulation of the estrous cycle. 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 culture of embryos 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 oocytes from abattoirs for use in research at a relative low cost has largely contributed to the progress of cloning. In terms of cloning a specific animal, the ability to obtain large numbers of oocytes at a relatively low cost also provides the opportunity to carry out numerous attempts of cloning, optimizing the procedure each time it is repeated. Therefore, even with a low efficiency but with the ability to repeat the experiment over and over and with the transfer of many embryos, a clone of most any cow or bull can be produced.

The efficiency of cloning animals is extremely variable. Because of the relatively low number of controlled studies, it is difficult to determine the sources of variation and analyze potential interactions between variables. Among the variables identified by researchers to affect cloning in cattle and laboratory animals are genotype, type of nuclei donor cell utilized, treatment of donor cells prior to nuclear transfer, source of recipient ova, techniques employed, and skill and knowledge of the laboratory group conducting the work.

In terms of efficiency, the percentage of nuclear transfer embryos developing to morula or blastocyst (BL) stage ranges from 5% to 65%. Live births range from 0% to 83%. Of the calves born alive, a significant percentage die within 1 week of birth because of health problems. Again, this varies from 0% to 100% of the calves failing to survive 1 week of age. Hill et al reported one case in which a steer was cloned from skin fibroblasts. Twenty-eight percent of the embryos developed to BL in culture (53 of 190). Six pregnancies resulted; 3 of these developed through 90 days of gestation, but only 1 survived to term. The resulting calf is older than 14 months now (if it is still alive). 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 1 week of age, the animal was diagnosed with type I insulin-dependent diabetes (*Biol Reprod.* 2000;62:1135). As a veterinarian and after working with cattle in the beginning of my professional career, I never saw that high a number of atypical health problems in entire

herds of cattle much less all of them concentrated in a single animal.

Additional experiences from the same group involved cloning of 2 cows. In one, 16% of the embryos developed to BL stage. After transfer of 37 BL to 13 recipients, 6 of those 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. High pregnancy wastage is not usually observed with traditional embryo transfer or artificial insemination in cattle. Twin calves were produced from that pregnancy. Both died 7–10 days after birth. The second cloning candidate produced 43 BL; 3 of 14 cows got pregnant after transfer. None survived beyond 90 days of gestation (*Theriogenology.* 2001;55:38). Others in the past have reported that calves born of in vitro production of embryos are extremely large compared with those naturally produced. Any species with this high a number of embryonic losses and perinatal problems would have become extinct very many thousands of years ago!

In sheep and goats, problems with fetal loss during gestation and congenital abnormalities leading to high death loss are common. In pigs, less than 1% of the embryos transferred survive to term. This figure does not represent the numerous trials in which no offspring has been produced.

Many scientific hurdles must be overcome before this technology can be applied without risk to livestock and laboratory animals. One of them, as Dr Oates mentioned in his e-mail, is about the age of the nuclei donor and the issues of shortened telomeres. The simple thought of applying cloning techniques to humans indicates a complete disregard of our species and a complete ignorance of all that it takes to succeed in a project like this. Considering the background of those involved, most of those I have spoken with feel that the project is most likely to fail. However, it remains to be seen how the backlash of the press is going to affect the efforts of those real scientists working on cloning. A project like this is not a trivial task. It not only requires deep thinkers but also deep pockets. And I see only shallow and greedy dangerous minds. Greed and ignorance combined make a good recipe for failure. Obviously, the financial support will come from those suckers wanting to be cloned. I am afraid we are going to have a whole generation of cloned suckers!

If you are concerned about cloned humans, it may be reassuring to think that few can go from painting walls to creating masterpieces in 1 day!

I feel that the scientific and medical community worldwide MUST limit this kind of activities for our own and the public benefit. If we do not limit ourselves, someone else is going to do it for us! We cannot and should not remain silent; we should let our opposition be known to those involved in the cloning project. I feel that we must implement draconian but necessary measures to limit the damage that has already been done. I have severed all commercial ties with those involved in this particular cloning venture.

Dr Oates replies, amplifying the concerns voiced by Dr Hernandez:

I appreciate, as we all should, the comments made regarding cloning in response to the questions I posed earlier. I was hoping to generate this kind of discussion on Androlog about a subject so topical and controversial. I am obviously completely against efforts to clone human beings, as I have a great fear of the potential damage to the children that might be born alive—both physical and psychological, short and long term. I do not see

the people involved in this project as visionaries, which is how I believe they see themselves. What response should we who do not agree with their efforts have? I applaud Dr Hernandez and his actions. I feel strongly that these premature efforts may backfire terribly and harm those involved in legitimate and accepted research as well as harm the entire field of advanced reproduction that we have all contributed to and that has helped so many unfortunate couples.

Terry Turner then weighs in, expressing his own concerns:

I agree with the sensibilities of both of these men. I am especially concerned about the paucity of biological information we have about the results of cloning and cloning attempts in any species. While no one may care if some disturbance in the biology of a sheep or a mouse becomes evident only late in life or under a specifically tested type of stress, the consequences of similar disturbances to a human can be potentially enormous. I do not wish to align myself with the "Fear of Frankenstein" set, but I do align myself with those who urge caution when applying technological approaches to achieve what nature would never afford. While we take normal biological processes for granted, nature is an incredibly fine sieve, eliminating much that we never see for reasons we never know. If we learn to bypass the sieve, we should do so with extreme caution. I would see anyone who uses new techniques for improving human life as visionaries so long as they supported their advances with careful research prior to setting a human life on a course from which there is no return. Those who use new techniques in humans just to do it or just to do it first I see as charlatans. Knowing the latter from the former is an enduring challenge, but helping the lay public with the decision is perhaps that professionals should be more involved in. Thus, to Dr Oates' question about what can be done to prevent reproductive biology and medicine from being the theater of quacks. Perhaps professional societies touching on reproductive biology and medicine should gather the courage to make public statements about such things. The AUA, ASA, ASRM, SSR, SSF, European Society of Human Reproduction and Embryology (ESHRE), etc, are all in the position to make public statements of caution, even condemnation of particular practices. Certainly, it can be claimed that getting into the business of making such statements can open a Pandora's box of issues and consequences and can involve academic or professional societies in activities that detract energy and attention from already overstressed agendas. The question is, will we look back on the alternative of silence as having been a wise choice?

Steven Ward suggests that there are ethical issues to be considered, apart from the technical feasibility of the cloning process.

There is another side to cloning that we as scientists and human beings need to be discussing—the ethics of the process regardless of the safety. We must have opinions, pro or con, and discuss them publicly. My own feeling is that human beings have such a sense of unique identity with their persona that it is cruel to produce one that is the exact DNA replica of another. We know that such a person would not be identical because his or her emotional context would be formed by a different environment than the donor. But the stigma of being an exact replica of another human being and being produced for that reason would undoubtedly harm that person. In my view, human cloning cannot be considered a form of assisted reproduction for any reason. We should draw the line ourselves.

Once again, we find ourselves in a unique position— assisted reproduction is the ONLY medical field that is so self-regulated. Moreover, there is an inherent conflict of

interest that the best of us have a hard time avoiding—we are to decide which techniques are not ethical to use, techniques that bring clinics a lot of money. It is our duty to police this as carefully as possible, but we will always have the conflict of interest criticism.

We need to be discussing the ethics of cloning not only from a scientific standpoint but also from a human one.

Kimball Pomeroy strikes a somewhat different chord on the topic in his contribution:

I find it ironic that there is such an uproar by infertility scientists to even conduct a conference to "discuss" human cloning. Where was this same uproar when ICSI was initiated throughout the world or nuclear transfer was practiced on many desperate infertility patients? Didn't a similar possibility exist to produce an abnormal form due to possible injection of DNA, viruses, mutagens, or somatic cells? Wasn't there also a risk of creating abnormal offspring either through physical damage or improper interactions between nuclear and mitochondrial DNA? Many of these technologies were not fully investigated in animal species prior to attempting them in humans, nor were experimental embryos first tested for at least obvious chromosomal normality prior to transfer.

I still feel we were pretty lucky that the initial trials did not result in any abnormal humans. Even if the procedures did not cause an abnormality, can you imagine the backlash that would have occurred if the first nuclear transfer baby had some major malformations? The paucity of data (animal models or human genetic studies prior to actual transfer) would have left the in vitro fertilization industry naked without any recourse except conceding to further governmental restrictions and regulation, not to mention the loss of confidence by the public. Instead of letting an uninformed institutional review board determine the safety or ethics of a particular experiment, let's first use our own judgment and the judgment of peers as guides.

Lynn Fraser offers the last comment on this topic by noting the position of The European Society of Human Reproduction and Embryology (ESHRE) on the topic of cloning.

I have been following with great interest the comments regarding cloning. Having just read Terry Turner's comments and his suggestion that various professional societies should make public statements regarding cloning, I thought it would be appropriate to point out that both ESHRE and the ASRM have issued press releases expressing grave concern over the recent declaration of intent to clone human babies. The ESHRE press release was as follows:

ESHRE reiterates its opposition to human reproductive cloning.

The European Society of Human Reproduction and Embryology (ESHRE) has reiterated its opposition to the cloning of human babies.

In a statement today (15 March) ESHRE said: `While ESHRE supports cloning for therapeutic purposes and believes that it is vital if we are to develop potential new treatments for serious human diseases, we do not support human cloning for reproductive purposes—that is, for producing babies.

`ESHRE took a consensus decision in 1999 to impose a voluntary moratorium on reproductive

cloning and we see no reason to change that decision.

`We strongly oppose the recent proposal to attempt human reproductive cloning. While we fully acknowledge the distress that infertility can cause, the available assisted reproduction techniques can provide very successful treatment for the vast majority of infertile couples.'