The Randomized Controlled Trial: An Ethical Victory or Dilemma for Biomedical Research?

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Since gaining acceptance from the late 1940s as exemplifying the gold standard of clinical reporting, the medical community has disputed the ethics of Randomized, Controlled Trials or RCTs (Friedman et al., 1996; Hellman and Hellman, 1991; Passamani, 1991). The rationale behind using RCTs is based on sound evidence that they reduce the potential for biased results within a study, and improve strategies for preventing and treating a wide variety of medical conditions and diseases (Elwood, 2000; Moher, 1993). Indeed, as modern pharmaceutical research continues to develop potential therapies, the RCT has flourished as the preferred method of evaluating the efficacy of new drugs and procedures. However, key components of RCTs present the opportunity for ethical inquiry (Beauchamp and Childress, 1994; Elwood, 2000). In this article, current arguments in favour and in criticism of randomization, informed consent and placebo use in RCTs will be presented.

Randomization refers to the process of assigning participants to either intervention or control groups of an RCT. It can be single-blinded (where only a physician or investigator is aware to which group a participant has been assigned), or double-blinded (where neither the physician nor the participant are aware to which group the participant has been assigned). Double-blinded studies are preferable, as they reduce the potential for bias on behalf of the investigators (Elwood, 2000). An investigator's preconceived ideas regarding possible outcomes will have little effect on the response of the participants, since he or she does not know the arm of the study in which the participant is taking part. Although it can never be totally eradicated, an effectively blinded, randomized trial substantially minimizes the possibility for bias in the results of an RCT (Beauchamp and Walters, 1999; Friedman et al., 1996).

Notwithstanding, randomization does present an ethical challenge. Inherent in the process of randomization is the concept of clinical equipoise, in which there is a "state of genuine uncertainty regarding the comparative merits of treatments A and B for a population P" (Freedman, 1996). In other words, no arm(s) of the RCT should be considered preferable in terms of efficacy of treatment. This requirement is considered ethically problematic by many physicians, especially in the case of RCTs dealing with terminal illness; illness for which there is no known cure, such as AIDS or advanced cancer (Beauchamp and Childress, 1994; Beauchamp and Walters, 1999). Here, a new treatment has the potential for effectiveness against a terminal disease, yet the control group must be assigned to either a placebo or a possibly less effective treatment (Friedman et al., 1996; Hellman and Hellman, 1991). Interest groups and physicians concerned with compassion for such patients put forth the argument that participating in a RCT may present the individual's only opportunity to receive the possibility of beneficial medication (Schuklenk, 1998). The fact that accepting this argument would require altering the present, historically supported means of legitimizing new drugs compounds the ethical difficulties of randomization, particularly in the case of terminal illness.

Another keystone feature of a RCT is the informed consent of the participant. Informed consent dictates that the individual has the right to choose whether or not to join a study based on a full disclosure of its methods, treatments, method of randomization, possible side effects and risks (Beauchamp and Walters, 1999; Beauchamp and Childress, 1994; Passamani, 1991). Presumably, if the potential participants possess this knowledge, they can make a reasonable judgement as to whether they should consent to participate in the study (Friedman et al., 1996). The Declaration of Helsinki, which outlines the principles of ethical

The Cloning Revolution

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Currently, human cloning has not been proven clinically viable; however, the importance of exploring the ethical and social concerns surrounding it transcends any specific cloning technique. (Robertson, 1998). This is because the genetic modification revolution is moving faster than ever before, and ethics are often being left to the backburner in pursuit of pushing human knowledge to its limits. It is during these times that steps must be taken to ensure that the public and government is well educated before hasty and uninformed decisions are made. Logical risk assessment, and not heated emotion, should be used in making any important decision. As a new and controversial science, human cloning may have potential benefits, but the detractors of cloning have wrongfully dismissed this area of study for erroneous reasons instead of the realistic dangers it may presents to society.

It is important to understand the nuclear somatic transfer (NST) cloning technique that has caused a great deal of concern in order to get a basic and general understanding of the positives and negatives that can be attributed to this process. This procedure entails grafting an adult human somatic diploid nucleus into a human ovum where its original nucleus has been removed. (Pence, 1998). For this cloning technique to be completely successful a number of intricate transformations would have to occur, for example the fusion of the somatic nucleus to the modified ovum and differentiation of the adult cell nucleus in its new environment. (Kassirer and Rosenthal, 1998). Furthermore, the new cell must have the ability to divide into daughter pluripotent stem cells, which can differentiate into specific tissue (Kassirer and Rosenthal, 1998). A number of these steps have been successfully executed on animals in the laboratory, and it should be noted that this human cloning technique could facilitate the growth of a duplicate specialized cell or an entire organism depending on the alterations in culture. (Wade, 1998).

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Pandora's box has opened

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The rewards of human cloning are controversial at best, but they are benefits that simply cannot be ignored for the sake of convenience. Human cloning may serve as a mechanism to bring human life with a genetic connection to a couple that may not otherwise be able to create it, or potentially change the entire way medical therapeutics are viewed.

One possible circumstance for the use of human cloning may be for the infertile couple, which due to gametic deficiency must resort to egg, sperm or embryo donation from an anonymous donor (Robertson, 1998). If the couple wishes to have a biological link, they may decide to clone one of the partners, for example if the husband provided the nucleus and the wife provided the ovum, the child would have a biological relation to both parents (Robertson, 1998). The desire to have a biological relationship with one's offspring is not an innately harmful or evil desire, and human cloning allows the facilitation of this genetic bond (Robertson, 1998).

Another scenario of use for human cloning would be for couples with high risk of having children with genetic diseases (Robertson, 1998). This is not as uncommon as one may perceive considering the statistics, such as one in 25 are carriers of Cystic Fibrosis (Pence, 1998). Presently, the aforementioned couples must decide between: chancing the birth of an afflicted child, to undertake prenatal or preimplantation diagnosis and abortion or the discarding of embryos, to seek gamete donation, adoption or not to have children at all (Robertson, 1998). If human cloning were available it would present another option to the couple, granted likely not an option that would be used extensively, but an option regardless.

Finally, a third potential application of human cloning, relates to the technique working on the cellular level and the aforementioned pluripotent stem cells. If this research fulfills its potential, and these cells can differentiate, it has the promise to be a valuable therapeutic tool for tissue and possibly organ transplantation. This differentiation has occurred in the mouse model, as embryonic stem cells have been coaxed into a range of cell types including neurons (Kassirer and Rosenthal, 1998). NST opens the flood gates for valuable research in a wide variety of diseases and disorders. Parkinson's and Alzheimer's patients could be provided with neural tissue that is genetically identical to their own. Burn victims could receive skin cells that would graft perfectly around their injured regions. Individuals affected by myelogenous leukemia would have an instantaneous and unlimited supply of dependable and healthy bone marrow. (Nash, 1998). The possibility and consequences of rejection would be eliminated because of this human cloning technique, as they would be immunologically compatible with the patient and the immune system would not deem the new cells foreign (Kassirer and Rosenthal, 1998). However, these possibilites are just that – possibilities. They must be weighed accordingly; to think human cloning is the magic bullet to cure infertility, stop genetic disease and cure every illness imaginable is imprudent.

Many ill-informed scientists, ethicists, religious leaders and ordinary citizens of society have wrongfully dismissed human cloning for erroneous reasons instead of the real dangers. This stems from an endless supply of emotion that clouds the surrounding issue of cloning.

One such argument raised, contends that cloning would create severely disfigured babies and masses of wasted embryos and stillborns (Kassirer and Rosenthal, 1998). According to studies at Princeton University, cloning is in fact genetically safer than normal sexual reproduction due to its bypass of the most common form of birth defects – having the wrong number of chromosomes. (Kolata, 1998). This incorrect number of chromosomes, known as aneuploidy, occurs at surprisingly high percentages. Forty to fifty percent of the eggs of women under forty have the incorrect number of chromosomes (Kolata, 1998). The rates rise proportionally to the age of the women. As many as nine out of ten eggs may contain geneic flaws (Kolata, 1998). These zygotes with the incorrect number of chromosomes invariably lead to fatal conditions. With cloning, chromosomal mix ups don't occur frequently because one starts with a normal somatic cell, from a normal adult, with the proper number of chromosomes. Therefore, birth defects are greatly reduced when cloning is used (Kolata, 1998). Often accompanied with this flawed argument of higher incidence of birth defects, is the concern about the byproducts of cloning due to the 434 oocytes needs to clone "Dolly".[7] (Gilbert, 1998). However, only thirteen of those eggs even developed into embryos and twelve were miscarried very early in the pregnancy (Kolata, 1998). In examination cloning yields a success rate of one in thirteen, which even now has a far greater success rate than the early years of socially accepted, in vitro fertilization (Kolata, 1998).

Another common argument that cloning's detractors assert is that clones would be predisposed to age-linked diseases, because a newborn clone would have DNA that was as old as the DNA of the adult whose cells were used to create the clone. These critics depend on the telomere hypothesis. At the ends of chromosomes are repeated sequences of DNA, called telomeres. Some scientists contend that telomeres shorten each time that a cell is divided. Since telomeres are longest in the embryo and grow progressively shorter as a person ages, some believe that when telomeres degenerate an individual dies (Kolata, 1998). There are several key discrepancies in this hypothesis, the first being that more than 90% of all cell division that occurs to an organism transpires in the pre – birth stages (Kolata, 1998). Hence, if a clone only had a sparse number of divisions left, she never would have been born as a result of exhausted telomeres. Another problem with the telomere hypothesis is that enzymes that lengthen telomeres surround eggs. Therefore, even if one assumes the improbable, that clones start out with short telomeres, it is safe to stipulate that the telomerases would lengthen them (Kolata, 1998). In the end, cloning's critic have a number of reasons to ban cloning but most of them are faulty and based on scientific half - truths.

Having painted a pretty picture and dispelled some commonly held notions regarding human cloning, it is time to examine the true concerns of human cloning. The most realistic and gravest fears relate to the psychological pressures that the first human clones would encounter. The fact is there are enough problems throughout life; to further generate enhanced stresses is detrimental to the health of the clone and to society in general.

The first such specific apprehension outlined by the National Bioethics Advisory Commission about the welfare of the clone, is the pressures related to the lack of individuality of the clone and the lack of freedom to set out on his or her own path because of expectations or confusion caused directly by being a clone (Robertson, 1998). This fear is conveyed clearly through a hypothetical situation, illustrating one of the many potential abuses of human cloning.

A family has had a tragic car accident, claiming the life of their daughter. In order to fill their emotional void and "replace" their daughter, they decide to clone her. As the child is born, the parents will most likely attempt to mold and shape the life of the clone as similar to that of their deceased daughter. This violates the most basic rights of a human being. When the clone finds out about the situation a range of harmful emotions and a general backlash will likely be exhibited by the clone. This unqiue psychological pressure to "be" the deceased child is one that would be confusing and stressful. The fact that many adolescents and individuals in general, deal with identity issues rather unsuccessfuly, does not fair well when the stakes are raised to a psychological confusion that a clone will likely face in this scenario. Rebellion, extremely low self-esteem and potential suicide tendencies are effects that may take place. Supporters of human cloning are quick to point out that same situation could take place for a child conceived coitally or even through assited reporductive technology, but it is important to weigh the degree of the psychological pressures and in that respect the clone would certainly feel more confused psychologically (Robertson, 1998).

Another type of fear expressed by the National Bioethics Advisory Commission is that parents who use NST to determine their child's genome will view their offspring as a product to benefit themselves, instead of lookout for the best interest of the child. (National Bioethics Advisory Commission, 1997). Again, the clearest way to illustrate this fear and its respective abuses is to propose another hypothetical scenario, which takes into account both fears expressed by the National Bioethics Advisory Commission.

A family has bought some skin cells of Michael Jordan and want to have a "copy". From the first day the child is born, he will likely be forced into basketball regardless of what the clone wants to accomplish or fulfill in his life. Firstly, the clone though genetically identical to Michael Jordan, may not be an adequate basketball player based on the nature vs. nurture theory. (Bornstein, 1997). The nature vs. nurture theory states that both heredity and environment play significant parts in determining the characteristics of an individual. Essentially, it is unknown to what degree Michael Jordan's environment (ie. coaches, practice, effort.etc.) determined his basketball talents and hence, it is not guaranteed that the clone would excel in basketball. Regardless, a child would be forced to play basketball because he might be taken advantage of, from an economic perspective. This economic situation might stem from the fact that the parents cloned the child based solely on financial incentives, which would add even more pressure on the child to perform. The emotional pressure on the child from both himself, his parents, and most likely society at large, clearly violates the clone's rights and is without a doubt unhealthy.

Ultimately, human cloning is the most influential and controversial bioethical issue since Darwin's Evolution. Risk assesment and the weighing of clonings potential benefits and harm, must be done cautiously, because the repercussions of any decision will revolutionize the new millennium. It is up to society to decide *how* much it will do so.

Professor in Focus (contd)

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into many facets of interest such as behaviour and cognition, feeding, immunology, physiology, genetics, reproduction, growth, and longevity. Because of this varied range of areas brought about through research, Dr. Kajiura's labs have contributed to several fields of study.

Dr. Kajiura stated, "It has been a pleasure exchanging insights about research with members of the McMaster faculty, students, and graduate students".

One piece of advice that Dr. Kajiura directed to students is, "always strive "to learn" and "to gain knowledge." She insists that in order to do this, students must maintain a high level of motivation and enthusiasm. In addition, she said that a person should not procrastinate, and he/she should take the initiative to plan their future careers.

Dr. Kajiura is a very confident professor who is readily available to assist her students. In her classes, she encourages students to take an active role in their learning, and in choosing their post-graduate careers. Dr. Kajiura also informs students that the department of Biology has a very resourceful Graduate Studies package that clearly outlines and notifies students about available programs. The package is extremely well prepared and organized by experts.

When Dr. Kajiura was asked if there was one aspect of which she would like to explore in her educational pursuits, she responded by explaining that when she looks through the undergraduate student calendar, as well as the graduate student calendar, she sees many interesting courses offered at McMaster University (in Science and in non-Science disciplines). Due to the fact that Dr. Kajiura is interested in gaining knowledge, she eagerly said "I would find any aspect interesting!"

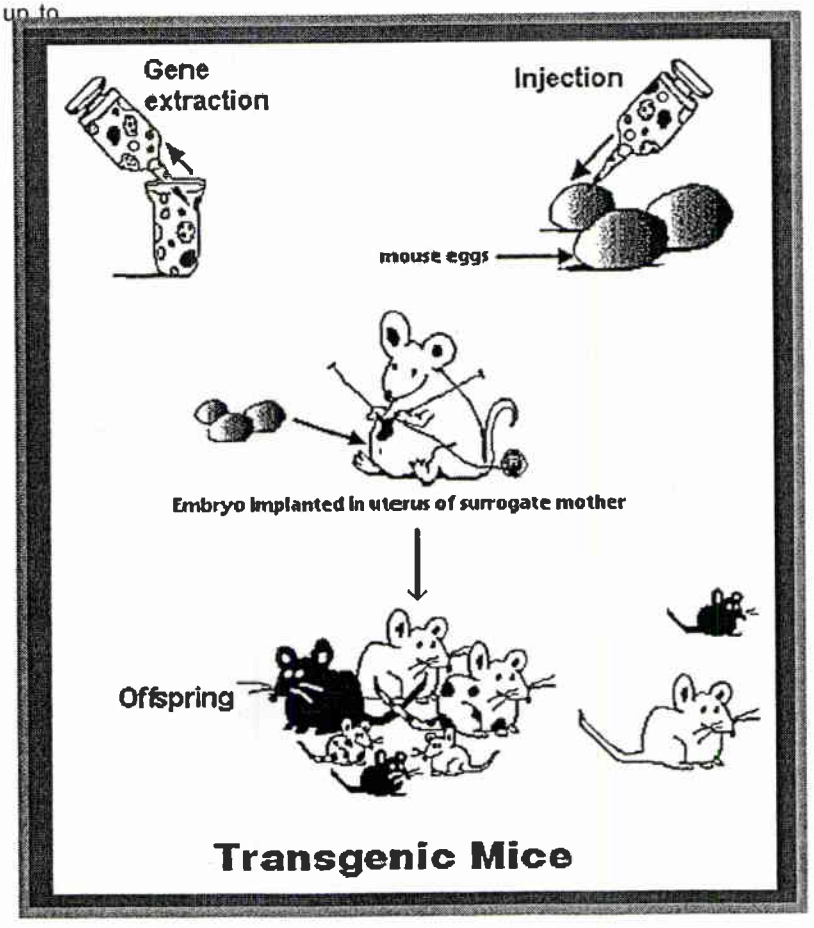

Figure 1

Insertion of growth hormone genes into transgenic (organisms that contain genes from another spcies) mice.