Comments on Ethics of Experimental Therapies

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The rapid advances in biological sciences have allowed a better understanding and management of various diseases. Cellular therapies, cell engineering and gene therapies may improve and/or replace many conventional treatments. Unfortunately, the progress in the achievement of those goals is frequently marred by overly enthusiastic and poorly supported claims by some of the scientists involved in this rapidly developing cutting-edge research. There are a number of areas that should be of special concern. Above all, it is crucial to protect patients involved in experimental therapies and to preserve high standards of inquiry and scientific integrity.

The increasing demand for stem cells for transplantation has resulted in the exploitation of new sources of human stem cells, including embryonic stem cells. New methods of human cell cloning have opened an area of embryonic research that is associated with major ethical problems and controversies. As a result, opponents of research on human embryos have raised politically powerful arguments against embryonic stem cell research, suggesting that adult stem cells may offer the same therapeutic promise. Unfortunately, there is accumulating evidence that adult stem cells exhibit time-dependent changes,

which affect long-term engraftment and curative cell reconstitution. Moreover, recent studies show that adult stem cells have limited plasticity and extensive heterogeneity. These studies also suggest that enriched but impure cell populations may lead to a misinterpretation of in vitro results. Thus, it is impossible to draw a distinction between plasticity of adult stem cells and heterogeneity of stem cell types that may pre-exist within tissue. Consequently, the great excitement concerning trans-differentiation of adult stem cells has to be tempered by the new, conflicting findings. The scientific 'dogma' that adult stem cells can morph into many types of cells may be based on misinterpretation of somewhat uncritical interpretation of data. What was initially claimed to be cell re-programming in vitro has currently been recognized by many as simple cell fusion with enlarged nuclei and double chromosomes, typical of hybrid cells. It is also recognized that the number of adult stem cells is limited and that the engraftment as well as reconstitution is impaired due to telomere shortening and DNA replicative exhaustion. It is clear that new discoveries continue to refine the understanding of what adult stem cells are capable of doing and more relevant animal studies are needed to establish the suitability of these cells for therapy.

Embryonic stem cells have been suggested as a virtually inexhaustible source of stem cells for therapeutic uses because they can be propagated easily in culture. Unfortun-

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nately, they also exhibit multiple biological problems, which are magnified by serious ethical concerns. It is known that embryonic stem cells are characterized by uncontrolled replication and differentiation, which results in tumor formation, chromosomal aberrations and mosaicism. In fact, recently reported results of intrauterine transplantation of embryonic stem cells into primates have shown extensive formation of fetal teratomas. Moreover, an oncogene associated with teratomas was reported. It was demonstrated that embryonic stem cells express a novel Ras-like gene called E-Ras, which is responsible for the tumorigenic properties of these cells.

Vigorous attempts to increase the pool of embryonic cells for future therapies by therapeutic cloning have serious ethical and biological problems. Here the biological problems include gene imprinting and epigenetic instability. Many of the biological problems appear to originate from the fact that cloned embryonic stem cells arise from a single parent somatic cell. This abnormal condition contributes to the appearance of many conditions including congenital skeletal defects and immunological impairments, which may become manifested late in life. Thus, the promise of successful treatment of many diseases by transplantation of these cells is very premature and could have disastrous consequences for patients. Data indicate that the choice of animal models is crucial and what may work in a rodent model will not be possible in humans. Consequently, the utilization of relevant primate models is necessary. It is important to realize that the first 30 days of embryogenesis is virtually identical in non-human primates and in man. Thus, much of the information concerning early embryogenesis and pathogenesis of various diseases can be obtained from those models. We had previously shown that the primate model (baboons and rhe-

sus monkeys) was clearly superior to ungulates such as sheep for intrauterine transplantation, particularly for studies of hematopoiesis and immunologic responses. While primates closely mimic the human condition, ungulates exhibit a different intrauterine milieu because of major anatomic differences in the placental chorionic and vascular base structures. There are also significant differences in transplacental transport, including the lack of transport of IgG in sheep. The primate model also appears to be superior for investigations of various viral vectors for gene therapy and in the elucidation of the mechanisms of toxicity of various gene products.

In view of the increasing demand and limited supply of oocytes, 'the embryonic industry' depends on the female reproductive system. There are serious ethical and medical problems associated with the harvesting of oocytes from healthy young women. Significant payments are offered to women to donate eggs. This procedure involves hormonal overstimulation and is associated with high risk of infections, hemorrhage, malignancies and infertility. Consequently, the procedure can be viewed as exploitive of women in lower economic circumstances.

The primary moral obligation of the biomedical research community is to protect human life as well as patients from the harmful effects of unproven experimental therapies and commercialization of human tissue. Another obligation of the research community is to refrain from overoptimistic and frequently erroneous claims for imminent treatment of devastating conditions. It is unethical to raise unsubstantiated hope for 'miracle' cures during a period of great confusion and controversy that invariably accompanies the development of a new field of biology and scientific endeavor.