Spontaneous Miscarriages as Source of Fetal Stem Cells

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Over a decade ago I, along with others, proposed that spontaneous miscarriages are a novel, untapped, and ethically acceptable source of hematopoietic stem cells (HSC), which are the most primitive, pluripotent, self-renewing cells. Shortly thereafter, a Task Force was convened at the National Catholic Bioethics Center under the auspices of Bernard Cardinal Law with the objective of defining the moral, legal, and biological aspects of human fetal tissue for transplantation. Cardinal Law has been deeply interested in issues of health care and its delivery. This effort resulted in a landmark publication that provided guidelines for the utilization of human fetal tissues for therapy. Also as a result of the Task Force, we received a promise of support and future collaboration for the collection of tissues from spontaneous second-trimester miscarriages from several hospitals, including the hospitals within the Daughters of Charity National Health System and Providence Hospital Foundation. As Ronald Lawler, O.F.M. Cap., has argued, “Christian charity should impel Catholic institutions to establish tissue banks from miscarriages.”


Catholic opposition to various unethical practices in medicine by Catholics requires some positive and moral alternatives. Unfortunately, since that time we have succeeded only in the establishment of a small cell bank (Protocell) which provided cells for our NIH grant-supported studies on HSC from miscarriages. This research focused on the biological properties of HSC derived from bone marrow of second trimester spontaneously aborted fetuses. We established the efficacy of these cells for transplantation, as revealed by long-term engraftment and high potential for reconstitution. Comparative studies carried out in our laboratory indicated strongly that fetal HSC had many superior properties when compared to HSC derived from other sources. These properties are presented in greater detail below.

Our interest in fetal HSC was based on many years of experience in fetal transplantation and surgery. We were always impressed by the striking regenerative and curative capacity of fetal tissue. Our research in this area was also prompted by the increasing demand for fetal tissues in cellular therapies and the potential for moral abuses in that area of medicine.

Advantages of Fetal Tissue

Fetal tissues have distinctive biologic and therapeutic properties that are almost ideal for transplantation, for successful stem cell engraftments, as well as for reconstitution of genetically-defective cells. Generally speaking, fetal tissues are not recognized and rejected as foreign to the same degree as postnatal tissues. Fetal tissue is characterized by a high proportion of primitive stem cells, rapid cellular proliferation, revascularization, and regeneration. These properties of the fetus make it an ideal transplant donor and the ideal transplant recipient. As a result, fetal tissue is the best source of cells for long-term engraftment, cell engineering, and various cellular therapies, including gene therapy.4

Recently, HSC derived from bone marrow have been increasingly utilized in novel treatments of various life-threatening diseases such as: hemoglobinopathies, immunodeficiencies, metabolic inborn errors (lysosomal storage diseases), malignancies, AIDS, and, more recently, autoimmune diseases (e.g., multiple sclerosis, lupus, scleroderma). Likewise, intrauterine treatment of inborn errors by fetal tissue transplantation is also expanding rapidly. These novel therapies include intrauterine transplantations of stem cells into defective fetuses for treatment of various genetic diseases and/or inborn errors before irreversible organ damage occurs. The treatment results are very encouraging and indicate that, in the future, utilization of fetal stem cells may be the treatment of choice for many life-threatening diseases and may represent a novel direction in preventive medicine.5


An Alternative Source

Unfortunately, up to now the only source of fetal tissue has been from elective abortions, which is morally objectionable, and from cord blood, which has its own set of problems. The solution to these difficulties is to turn to miscarriages (spontaneous abortions). However, one objection raised by some about our approach has been that there are not enough healthy and viable tissues from spontaneous abortions to satisfy the growing demand. The results of our earlier epidemiological study, together with our recent data on human fetal bone marrow characterization, indicated that this morally-acceptable source of tissue would be sufficient for the majority of currently envisioned needs if it is collected and preserved properly in various centers simultaneously. Parenthetically, in our experience the donation of fetal tissue from lost pregnancies is actually helpful to the parents in the grieving process, and especially to the mother who blames herself for the failure to carry the pregnancy to full term.

In view of the growing demand for stem cells, and the ethical problems associated with the current sources of these cells, and the controversies involving their harvesting the human cells, we initiated epidemiological studies of an alternative source of viable human tissue from second-trimester lost pregnancies. The optimal time for harvesting of the highest number and the best quality of stem cells from bone marrow is eighteen to twenty weeks of gestation. This period, which is in the second trimester, coincides with the seeding of the stem cells from liver to bone marrow in the fetus.

Numerous reports, together with our own epidemiological studies, indicated that over fifteen percent of the about three hundred thousand second-trimester miscarriages were suitable for transplantation. We developed a network of hospitals that have agreed to collect these tissues and to deposit them in a tissue bank. A crucial aspect of the Protocell bank is the insistence on high quality control of the acquired fetal tissue. All tissues are screened for various types of contaminations and, in cooperation with the donor hospitals, also are examined for genetic aberrations. Thus, the bank is able to provide high-quality fetal cells for research and clinical use.

In the early eighties, we reported the first successful intrauterine allogeneic (nonmatching) bone transplantation in primates. These initial results provided a basis for a better understanding of fetal tissue characteristics as well as visibility for the utilization of fetal tissue in allogeneic transplantation for the treatment of genetic diseases. The results represent the first successful demonstration of intrauterine transplantation carried out in phylogenetically different species when engraftment of donor stem cells into fetal recipients was achieved without any immunologic sequelae and resulted in stable chimerism across the phylogenetic barrier. These studies provided a new animal model for the study of human fetal stem cells in a xenogeneic system.

6Thorne, Michejda, “Fetal tissue from spontaneous abortions.”
7Michejda, Peters, Bellanti, “Xenotransplantation, bone marrow transplantation and stem cell reconstitution.”
Our results, together with the earlier reports of the successful fetal liver stem cell transplantation in patients, encouraged us to further examine human fetal stem cells derived from miscarriages, in vitro and in vivo. The in vivo studies utilizing human fetal stem cells (donor) infused into fetal baboons (recipients) achieved high cellular chimerism and engraftment across the phylogenetic barrier without immunosuppressive treatment, and no signs of graft versus host reactions. Studies in vitro determined the phenotypic and functional characteristics of human fetal stem cells from fetal bone marrow and compared them with stem cells from other sources, such as adult bone marrow, peripheral and cord blood. These results showed that fetal bone marrow cells have distinct advantages over other hemopoietic stem cells for transplantation. These included the highest percentage of the most primitive (CD34+) stem cells, as measured by flow cytometry, the greatest clonogenic potential, as assessed by assays which measure the ability of the cells to grow and form colonies in tissue cultures (CFU-c), and the lowest immunoreactivity, as determined by mixed lymphocyte reaction assays. Further, comparative cytokinetic studies also confirmed the unique properties of fetal stem cells for engraftment, stem cell targeting, and gene therapy. Our most recent comparative studies of the fetal stromal (mesenchymal) cells strongly indicate that the fetal stage of development provides a large volume of pluripotent cells of proven curative potential for cell reconstitution and long-term engraftment in various cellular therapies and cell engineering. Our interest in the utilization of stem cells from miscarriages has encouraged others to study this alternative source of fetal tissue. The data obtained in these studies are in agreement with our findings.

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Promise for the Future

Our data clearly show that stem cells derived from lost pregnancies can be utilized for transplantation. When compared to other sources of stem cells, fetal bone marrow has the optimal and proven potential for engraftment. In fact, the rapid progress in the treatment of various life-threatening diseases utilizing stem cells will lead to an increased demand for these cells. It is now suggested that tissues from elective abortions, and from embryos and embryonic clones, could also meet this demand. This is unacceptable from an ethical point of view and would most certainly lead to abuses. It is our opinion that the only ethically-acceptable source of fetal tissue is from spontaneous miscarriages, which we proposed several years ago. We are strongly committed to this issue and would like to generate an understanding and appreciation of the importance of this task, as well as to generate support from the Catholic community. In fact, we have received strong interest from many Church leaders in the United States and from the Vatican. As previously mentioned, we started to develop a network of collaborating hospitals that would collect fetal tissues and deposit them for processing at the Protocell bank. We hope to be able to utilize these resources efficiently with the help of those who share our views on human life. With this support, tissues derived from spontaneous miscarriages could be collected, processed, and preserved at Protocell, and made available at cost for therapeutic transplantations in many life-threatening diseases.

The underlying motivation for the effective utilization of fetal tissue from that source is that it will prevent further abuse of the unborn baby and the mother. If this effort is successful, it should have an important impact on future developments in medicine, while maintaining acceptable standards of ethics; however time is escaping rapidly, since contrary developments in commercialization of human body parts, including embryonic and fetal cells from elective abortions, human clones, and organs and human ova, are occurring at an increased rate.

Biological Characteristics of Stem Cells

The moral, ethical, and logistical aspects of acquiring human embryonic cells and cells obtained from elective abortions have been extensively discussed by Catholic theologians, bioethicists, and genetics experts. These sources of cells for transplantation are rejected on moral grounds in accord with Catholic tradition. So-called reproductive and therapeutic (sometimes referred to as nuclear transfer) cloning are equally illicit and morally unacceptable from the perspective of Catholic ethics. From a purely scientific perspective, however, information on the biologic limitations of these cells, including the oversold curative properties of embryonic stem cells, have not been made sufficiently available to the public. Some of these limitations may have disastrous consequences in the proposed therapeutic applications. They are described below.

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13 Michejda, “Fetal tissue transplantation: Miscarriages and tissue banks.”
15 The National Catholic Bioethics Quarterly 1.2 (Summer 2001).
**Recent Stem Cell Advances**

Dramatic recent advances in cell biology and transplantation immunology have provided a new basis for a novel concept of cellular transplantation. Progress in this area led to the formation of the National Institutes of Health Bioengineering Consortium, which is charged with the monitoring of novel cellular therapies and cell engineering. It is widely believed that further progress in these areas may revolutionize medicine and replace many conventional treatment modalities. As the fields of stem cell and tissue engineering progress, the use of various fetus- or embryo-derived cell lines for cellular reconstitution and organ reconstruction may become a reality. However, there are numerous barriers to overcome before significant progress in this area can be made.

As mentioned above, stem cells are very primitive, self-renewing cells that can give rise to many different types of cell differentiations. This property makes them exceedingly useful for transplantation and cellular reconstitution, and places them in the forefront of many exciting therapeutic procedures. There are numerous sources of stem cells in the human body but the most important are the adult bone marrow, adult peripheral blood, cord blood, fetal liver, pancreas, thymus, brain, fetal bone marrow stem cells, and those derived from embryos or embryonic clones.

The implantation of stem cells to promote rapid wound healing in chronic conditions, skin or cartilage reconstruction, and angiogenesis (development of new vascular tissue) for myocardial ischemic diseases is under investigation. It has been shown that myogenic (muscle forming) cell lines derived from embryonic or fetal bone marrow stem cells may be propagated in a culture to produce greatly expanded, homogeneous cell populations. Additionally, these cells can be differentiated to specific connective tissue cell lines, including fibroblasts, myoblasts, and osteoblasts (bone forming cells). Clinical trials involving the infusion of these cells into infarcted (damaged) parts of the myocardium are very promising. Therapeutic injections of osteoblasts in children with bone diseases, such as osteogenesis imperfecta (congenital weak bones), have been shown to be curative. The stem cells utilized in these experimental therapies were derived from neonatal or adult tissue engineering.

It is well established that fetal neuronal tissue or cells exhibit additional unique characteristics such as high plasticity (ability to adapt) and self repair. These properties of neuronal stem cells have been used for experimental treatment of various neurodegenerative diseases such as Parkinson’s disease, Alzheimer’s disease, and

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17Ibid.


Huntington’s disease. Transplantation of stem cells that are too immature results in only short-term engraftment. This was especially true in the treatment of Parkinson’s disease and juvenile diabetes. Clearly, in those cases, the immature transplanted stem cells (from first-trimester elective abortions) failed to establish the proper secretory characteristics. Cells derived from second-trimester miscarriages should be more functionally efficient, in addition they will be immuno-incompetent and non-reactive, which will eliminate the problem of matching donors and extensive immuno-suppressive pretreatment.

It is reasonable to assume that stem cells are integral components of all types of adult tissues, and are probably involved in different degrees of regeneration. However, it is also clear that stem cells are a very small fraction of adult tissues, which has made their isolation, purification, and characterization very difficult. Research over the last ten years has provided abundant evidence that stem cells possess unique curative properties and are particularly important for novel therapies. However stem cells from various sources differ according to cell maturation, quantity, and function, as well as curative potentials, which appear to be a function of age.

Embryonic cells and fetal stem cells are the most primitive, immature pluripotent cells, which are capable of initiation of multiple cell lines and have the property of self-renewal. They are also immunologically immature, which means that they do not react to foreign tissue; and they have the highest proliferative ability. All these characteristics are essential for transplantation and engraftment. The suggested utility of the embryonic cells in transplantation however may be more problematic than the initial enthusiastic claims, which were made on the basis of in vitro studies. For example, it was reported recently that murine embryonic stem cells give rise to tumors in vivo.


Recently Verfaillie discussed the age-related functional characteristics of adult HSCs, including their ability to undergo ex vivo expansion. Accumulating evidence reveals that HSCs in general show time-dependent changes that affect long-term engraftment and curative cell reconstitution. Moreover, a recent study suggests that adult stem cells exhibit limited plasticity and/or extensive heterogeneity. This study also suggests that enriched and impure cell populations may lead to misinterpretation of in vitro results. Consequently, it is impossible to draw “the distinction between plasticity of adult stem cells and the heterogeneity of stem cell types that pre-exist within tissue.” The great excitement concerning the transdifferentiation of adult HSCs is being tempered by the conflicting findings. There is increasing evidence that defined scientific dogma that stem cells can morph into many types of cells may be misinterpreted. What was initially recognized as cell reprogramming in vitro, is, according to many investigators, simple cell fusion with enlarged nuclei and doubled chromosomes, typical of hybrid cells. New discoveries continue to refine the understanding of what adult stem cells are capable of doing and more in vivo studies are needed to establish the efficacy of these cells for therapy.

Proliferation of Stem Cells

The quantities of stem cells that can be obtained from adult tissues are much smaller than from fetal sources. Moreover it has been observed that the functional capacities for engraftment of stem cells derived from adults are much lower than fetal cells. There is a strong indication that the adult cells have lower self-renewal ability, and graft failures can occur after transplantation of these cells. In fact, only sixty percent of adult bone marrow transplantations are successful. It has been suggested that these poor results are due to age-related replicative exhaustion of the adult stem cells and shortening of telomeres. In contrast, transplantation of fetal stem cells induces rapid cellular reconstitution in affected organs. Fetal stem cells have a high capacity for integration and replacement of defective cells in diseased


28Vaziri, Dragowska, Thomas, “Evidence for a mitotic clock in human hematopoietic stem cells: Loss of telomeric DNA with age.”

29Touraine, Royo, Roncarolo, “Unmatched stem cell transplantation as a possible alternative to bone marrow transplantation”; Touraine, Raudrant, Royo, “In utero transplantation of hematopoietic stem cells; Touraine, “In utero transplantation of fetal liver stem cells in humans.”
tissue.\textsuperscript{30} It is now believed that, with proper manipulation of growth factors, new technologies can be developed to guide stem cells to form organ-specific tissue. This could ultimately be used to form whole complex organs such as a kidney or liver, thereby alleviating the terrible shortage of donor organs, or to provide specific cell types cultured for curative transplantations. Obviously, it is not known yet whether organs engineered in this fashion will be fully functional, given the many poorly-understood complexities of interactions on the molecular and cellular levels in the human body.

Pluripotent stem cells derived from fetal bone marrow exhibit an especially high capacity for initiating the formation of a large repertoire of cell lineages. Moreover, human bone marrow contains stromal or mesenchymal cells. Mesenchymal cells are the progenitor cells which give rise to bone, muscle, and cartilage.\textsuperscript{31} It is believed that these cells can be utilized in many treatment modalities; and they have an important role in sustaining hemopoiesis (blood cell development). Hemopoietic stem cells derived from fetal bone marrow, which give rise to the various cells of the blood, can be used for treatment of a large number of life-threatening genetic and acquired diseases.\textsuperscript{32}

Utilization of human embryonic cells for therapy is not only unproven but also carries an unacceptable moral burden. The commercial exploitation of embryonic cells is already alarming and frequently jeopardizes scientific and professional integrity. Some IVF clinics recruit young university women to sell oocytes for twenty thousand dollars. The general demand for embryonic cells is rapidly increasing, while the supply generated by IVF clinics is decreasing. One of the reasons for the latter is an improvement of the stimulation and implantation techniques, which require fewer cells for achievement of pregnancy. Moreover, the existing cell lines are mostly contaminated with murine pathogens as a result of having been cultured on murine feeder layers and therefore are not suitable for future therapies. Recent attempts to increase

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the pool of embryonic cells for future therapeutic use by so-called therapeutic cloning have multiple ethical and biological problems.\textsuperscript{33} It is now well established that embryonic stem cells are characterized by uncontrolled replication, which leads tumor formation such as teratomas, malignancies, and chromosomal mosaicism.\textsuperscript{34}

\textit{Cloning for Stem Cells}

Therapeutic cloning is achieved by asexual reproduction methods, which involve so-called somatic cell nuclear transfer. This is accomplished by microinjection of the nucleus from a human donor cell that carries a complete set of chromosomes into a human ovum from which the nucleus has been removed. If the transfer is successful the oocyte containing the implanted genomic material will undergo several divisions to produce a preimplantation embryo known as the blastocyst. After five days, this entity is composed of one hundred to one hundred fifty embryonic cells. It is then destroyed in order to create new embryonic cell lines in culture. In reproductive cloning, the blastocyst is placed in the uterus and may develop into a baby. This has not been accomplished in humans but many animal examples are known.

Both therapeutic and reproductive cloning face the very serious problem of gene imprinting. All the genetic material comes from one somatic cell. The consequences of gene imprinting are profound and affect the very process of cloning as well as the product of the cloning.\textsuperscript{35} Simply put, the product can be defective. It is now well appreciated that the nuclear transfer process is highly inefficient and would be prohibitively costly and impractical for therapeutic purposes. Moreover, most clones die before birth during animal reproductive cloning and many survivors display various abnormalities. These include placental and fetal overgrowth, immunologic impairments expressed by autoimmune diseases (such as the early arthritis diagnosed in the famous Dolly), and accelerated aging. The consequences of gene imprinting in humans are potentially devastating. Animals may be more tolerant to epigenetic aberrations, which may initially result in only subtle abnormalities.\textsuperscript{36} Such abnormalities cannot be ignored in human materials, particularly in embryonic cells derived from therapeutic cloning and used for transplantation, which could result in the transfer of the abnormalities to the recipient. Such aberrations may not be evident at early stages but would become expressed at a later age. Consequently, cloning techniques to acquire stem cells for transplantation are impractical, costly, may lead to serious medical problems, and are beset with very serious ethical problems.


Besides the major ethical and medical problems associated with cloning, one should also take into account the possible legal consequences of professional responsibility and malpractice when something goes wrong. In addition, there is a limited supply of oocytes suitable for nuclear transfer. This will result in moral and medical pressures on women of reproductive age. Harvesting of human eggs is not free from dangers of infection, hemorrhage, malignancy, and infertility. This will particularly affect women in financial need.

The initial euphoria associated with the promise of therapeutic cloning has now been tempered by the realization of the multiple problems. This has become evident in the research community and is beginning to be expressed in the popular press. The problems associated with human cloning are profound and cannot be ignored. In fact, this could retard progress in the development of cellular therapies, which are in large measure one of the most exciting developments in medicine. It should be reemphasized, however, that pluripotent fetal stem cells derived from second trimester spontaneous miscarriages exhibit proven highly effective proliferative engraftments and curative potentials that were made evident in transplantations many years ago. Fetal stem cells have most of the properties of embryonic stem cells but do not exhibit the uncontrolled replication that is characteristic of the embryonic cells, which leads to teratomas, malignancies, and chromosomal mosaicism upon transplantation.

Technologies for safe and efficient cloning do not exist. The use of embryonic cells in human therapies may have disastrous medical consequences. The argument that human cloning and embryonic cell research are necessary for a better understanding of early human embryogenesis or pathogenesis of various diseases is unsubstantiated since the first thirty days of embryogenesis in nonhuman primates and in humans are virtually identical. Our obligation is to protect human life and the safety of patients, but we must also prevent the dissemination of erroneous information about curative potentials of unproven sources of stem cells.
