Are Stem Cells Drugs?
The Regulation of Stem Cell Research and Development

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Abstract—Stem cell research and its clinical application have become political, social, and medical lightning rods, polarizing opinion among members of the lay community and among medical/scientific professionals. A potpourri of opinion, near-anecdotal observation, and scientifically sound data has sown confusion in ways rarely seen in the medical arts and sciences. A major issue is regulation, with different aspects of stem cell research falling within the purview of different government agencies and local offices. An overarching clearinghouse to review the field and recommend policy is lacking. In the following pages, I touch on the societal framework for regulation, the known and potential risks and benefits of cardiovascular stem cell therapies, whether stem cells should be regulated as drugs or in analogy to drugs, and if there is to be regulation, then by whom. In so doing, I refer to the stem cell literature only as it relates to the discussion of regulation because this is not a review of stem cell research; it is an opinion regarding regulation. (Circulation. 2006;114:1992-2000.)

Key Words: cardiovascular diseases ■ cells ■ heart failure ■ myocardial infarction ■ trials

To ask, “Are stem cells drugs?” is to broach a complexity of medical and scientific issues, as well as many that are social, religious, and political. Like “Do you love me?” it can be answered “yes” or “no.” Alternatively, as in the conversation between Tevye and Golde,1 it can initiate a series of convolutions terminating in an anticlimactic “I suppose... .” Yet, the quest for an answer can be important if it sharpens focus on the tools with which we are working—the stem cells—and on their potential to help or harm human beings.

The Case for Regulation

Regardless of whether stem cells are drugs, the burgeoning stem cell field reflects advances in science and technology, and both science and technology have a history of regulation in advanced societies. The consideration of regulation depends on philosophy: that of governing bodies, of subgroups of the population, and of individuals who perform or are subjects of research. Although we are a society that applauds biomedical advances, we are also a society whose pace of scientific and technological advancement far outstrips the pace of legislating regulatory policy.2 Legislation still depends on persuasion, on bargaining, on the political process; if science and especially technology move like lightning, the image for legislation approximates molasses.

Bohme3 makes a strong philosophical case for regulation of biomedical and other technology, stating “The more we succeed in reproducing nature technically... the less easy is it to understand how one would draw a boundary between the natural and the artificial.” He voices the concern that “modern technology has the potential not only to expand the modes of human existence to an unprecedented degree, but also to destroy humanity actually or to destroy qualitatively what we have regarded up to now as human values.”3

That certain forms of technology need at least regulation, if not prohibition, is noted by Warnock4 to derive in part from the desire to “allay public alarm.” Yet, she emphasizes that to “legislate in response to popular feeling is almost always a mistake... [Research] must not be controlled by those who are ignorant. [We] must trust those who know.” Warnock identifies “those who know” as the professionals in any field, charges them with providing the knowledge base for regulating technology, but insists that some form of review/inspection is required under the aegis of government.4 She suggests that a committee composed of scientists, practicing physicians, lawyers, and philosophers be entrusted with codification, evaluation, and education of the public and the legislature, yet she expresses concern that even thoughtfully designed legislation may “override and tend to inhibit valuable research.”4

As reviewed above, ethicists and lawyers have agonized over the means whereby guidelines can be responsibly set for those who pursue the advancement of knowledge and its application to the populace. Scientists also have weighed in thoughtfully. The Asilomar conference on the risks of recombinant DNA is a notable example.5 Yet, we must understand that guidelines set by the “thought leaders” in any field can still stultify evaluation of new knowledge; the fate of Galileo.
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immediately comes to mind. Those who labor in the new universe of human embryonic stem cells now negotiate a border manned not only by responsible commentators but also by guardians who view all stem cell research, therapeutic cloning, and reproductive cloning as a continuum and who codify that which is done in the interest of improving life to be a first step on the proverbial “slippery slope” leading to perdition. For Galileo, as for Yogi Berra, this would likely represent “deja vu all over again.”

Advancing Technology in a Death-Denying Society

Western societies in centuries past accepted that in the absence of war and catastrophe, some combination of disease and age would inevitably bring an end to life. Death was seen as an expected part of a continuum rather than a lamentable interruption of an entitled existence. Over the last 2 centuries, Western attitudes toward death have changed. It has been suggested as unlikely that modern “Americans . . . would ever approve limitations on medical research whose focus is to discover [new therapies] that not only maintain qualitative existence but extend life,” and that in the “. . . technology-driven and death-denying American health care system . . . so long as individuals persist in their desire to live as long as possible, the frontiers of medical science will always be expanding.”

If the American healthcare system is “death denying,” it is likely because it reflects the demands of the society within which it operates. We must recognize that the sense of entitlement of the articulate and often affluent stratum that drives opinion has whipsawed the medical profession with a mix of expectations and lawsuits that define our universe of medical care. If society in the United States has a tendency to deny and even to demonize death and a desire to extend the limits of medical care beyond what the profession may reasonably deliver, how can this help but influence technology-driven research in general and that aimed at cardiovascular disease in particular?

With regard to stem cell research, cardiovascular clinical trials are being performed on patient populations varying from those having severe cardiac decompensation to others with relatively uncomplicated myocardial infarction. Both types of studies share the goals of advancing knowledge of the safety of stem cells while learning something of efficacy. The finding of efficacy fans hope on the part of patient and physician of improved health and quality of life, and if we accept society as “death denying,” then any attempts at regulation set limits on what can and cannot be done to or for patients. In such a milieu, the question of what cells can be given to which patients can provide (and has provided) a source of conflict within the community.

Levels of Conflict Over Stem Cell Research

There are at least 2 levels of conflict over stem cell research. One involves the medical/scientific and lay communities and focuses largely on the human embryonic stem cell. Although accepted as an appropriate tool for medical research in many countries, expansion of the human embryonic stem cell lines available for research remains anathema to the current administration in Washington, DC, and to a significant segment of the American public. The worldwide research performed using human embryonic stem cells is largely, but not entirely, basic; the administration of such cells to human subjects should await the answers to a host of questions.

The second level of conflict resides largely within the medical/scientific community and applies mainly to bone marrow–derived adult stem cells. This second level provides the primary focus for the following discussion, although the issues raised pertain also to embryonic stem cells, especially as the medical/scientific community comes nearer to responsible clinical use of these cells.

Most clinical cardiovascular research performed to date has administered autologous or allogeneic adult stem cells as infusions into the peripheral or coronary vasculature. Viewpoints concerning the administration of stem cells to patients with cardiac disease were summarized by Nicholas Wade: “Researchers acknowledge they cannot yet advise clinicians which kind of stem cell is the best candidate for heart repair and fear clinicians, in their desire to offer something immediately to patients who have run out of options, are being too hasty.” He quoted 4 individuals:

1. Irving Weissman: “. . . [until the science underlying clinical stem cell trials is better understood, clinical] studies are premature and may in fact place a group of sick patients at risk.”
2. Donald Orlic: “The literature is replete with contradictions that have generated widespread confusion.”
3. Kenneth Chien: “Let’s find the right cell first. The clinicians complain that will take years. They are right. It will take years.”
4. Emerson Perin: “Basic science guys don’t see patients that are going to die, but I have to look at them in the face every day. It’s ludicrous to say we must understand the molecular mechanisms before we can try anything.”

Clearly, clashing opinions have been expressed about the propriety of advancing in the clinic in light of our state of knowledge of stem cells. Although discourse and argument can only help, it is discomfiting that they are occurring in a medical/scientific environment in which regulation is halting and inconsistent, opinions are too frequently reduced to sound bites, and the line between professing one’s science and advertising one’s self is too often blurred. Given this dissonant setting, perspective can be sought by considering the history of cell therapy.

Modern Origins of Clinical Stem Cell Research

Colleagues have said that earlier successes with bone marrow transplantation justify the administration of adult stem cells to patients with heart disease. I have revisited these earlier successes to obtain a perspective. Bone marrow transplantation appeared on the scene as a heroic challenge to lethal disease. A transplantation performed in 1956 by E. Donnall Thomas resulted in long-term survival of a patient with leukemia; an initial series of such transplantations was reported the following year. The ensuing decades saw, in 1968, the first bone marrow transplantation for an illness
other than cancer (inherited combined immunodeficiency syndrome); in 1973, the first transplantation using an unrelated donor (also for combined immunodeficiency syndrome); and in 1992, the first xenotransplant (baboon bone marrow and kidney into a human subject). Preceding and accompanying these studies were a great number of articles on animal experimentation and additional human studies. My intent in mentioning this literature is to emphasize the nature of the illnesses suffered by the patients: All were life-endangering, and all patients at the time of transplantation were without other recourse. None of them was being treated for iron-deficiency anemia.

What we have learned from the history of bone marrow transplantation is priceless in terms of our understanding of the safety and the potential of stem cells, but the logic applied to cardiovascular studies is not a transparent derivative of that used to justify bone marrow transplantations. Most clinical cardiovascular studies administer bone marrow–derived stromal cells to patients after acute myocardial infarction; many have near-normal or normal ejection fractions. The argument favoring this approach has 2 parts: First, because such stem cells are safe in other settings, they will be safe here, too; this may not be a very farfetched statement. Second, appropriately selected postinfarction patients are healthy enough to be subjects in a phase 1 safety trial. Interestingly, short-term results (studies of up to 2 years) appear to have borne out the impression of stem cell safety (for those cells and time periods studied). What will happen long term and for other cell types remains to be seen.

But note how quickly this cardiovascular stem cell discourse has centered on evaluation of outcomes, of the “ends” of the experiments. With regard to the “means,” there are issues. We must ask whether it is medically and ethically right to include in a trial of an untested therapy a sick patient who has every expectation of uneventful recovery, or whether it is better to reserve trials of new and uncertain therapies for those who have no hope of recovery through traditional avenues of treatment. Stated another way, is a post–myocardial infarction patient to be considered a “healthy,” normal volunteer in a phase 1 drug safety trial, and is a stem cell innocuous, or should its testing be confined to the irrecoverably ill, as is the case with many new cancer treatments?

A number of investigators have already weighed in on these questions, and it is time that a consensus be reached not only by those actively in the practice of stem cell trials but by a panel of informed, yet disinterested, individuals who can best survey the needs of patients and of the field. A means for doing this was suggested by Warnock (see above) and refined by the National Academy of Sciences (see below).

The Need for Stem Cell Research in Heart Disease

The need for research into new technologies for treating cardiovascular disease is apparent from the following: “In 2004 more than a million Americans died from cardiac failure and stroke, and heart disease leads death by all causes, outpacing cancer by 40%. No longer does it afflict only the old. More than 64 million Americans suffer from it, but only 25 million are 65 years or older. The total cost of treating cardiovascular diseases and stroke in the United States in 2004 was estimated to reach $368 billion.” These statistics provide an important context for our interpretation of the outcomes of 20th century advances in drug and device therapy. They suggest that despite earlier advances new therapies are sorely needed.

Two longstanding approaches to cardiovascular disease therapy remain attractive: prevention, still by far the best strategy with regard to the well-being of individuals and economic costs to society, and repair or regeneration of damaged myocardium or vasculature. It is the demands of repair and regeneration that stem cells have the potential to meet: “Given an ever-widening chasm between treatment and morbidity, it is no wonder the stem cell has become a common denominator of hope. Behind the sobering facts, patients and their families ask, ‘Will there be a cure? And will it be in time for us?’”

The potential benefits of stem cells in the therapy of cardiovascular diseases can be appreciated through the following questions: Can we use autologous or allogeneic stem cells to replace dying or scarred myocardium with healthy myocardium? To replace aneurysms of heart and vasculature with healthy functioning tissue? To replace infarcted myocardial or neuronal tissues with normal tissue? To repopulate a failed myocardium with normal muscle? To mobilize the endogenous stem cells of the body to effect healing? To replace arrhythmic myocardium with that which initiates and propagates impulses and repolarizes normally? All these questions and more are currently being asked. If answered affirmatively, we will be enabled to avail a broad population of outcomes far exceeding anything now within our grasp.

How close are we to fulfilling these needs? The recently reported 18-month follow-up of the Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration (BOOST) trial (see below) suggests “not very.” Rather, it suggests that we may be moving too far and too fast, even if in a generally correct direction. On reviewing the trial and the field, Welt and Losordo argued that before convening further trials, we would be well advised to know far more about stem cells at a preclinical level and to recommit ourselves “to preclinical investigation as a means of better understanding basic mechanisms, and clinical trial design based on these preclinical data.”

Yet, performing more preclinical research using a variety of stem cells to understand their potential for improving various disease states is only part of the story. The other part is that we need review and advice, thoughtful and reasoned, that challenges unsupported claims and assumptions, encourages promising directions, and has the potential to reward the citizenry with results that have survived rigorous scrutiny.

Known and Potential Risks and Benefits of Cardiovascular Stem Cell Therapies

Some Issues

Many potential risks of stem cell therapy have been cataloged. Can we really expect that after we inject stem cells into a region of the heart directly intramyocardially or via a coronary artery, they will stay in place without a subset
migrating to other sites in the body?24-25 Or that when stem cells are injected into a peripheral vein and expected to follow a "homing signal" to regions of the heart in need, they will faithfully cluster at such a site?26-29 Although a body of research indicates that many stem cells will stay in place and that homing signals such as those produced by inflammation attract injected stem cells, it also appears that many cells either die or wander off.26-29 In other words, even in the face of apparent safety, we do not completely know the answers to these questions, nor do we know what percent of stem cells once injected will be lost to inflammation or apoptosis, resulting in fewer than a critical number residing at a specific site. Furthermore, it is not yet certain what percent will differentiate into myocytes as opposed to other cell types. In the latter event, we do not know if the new cell type will retain or lose the desired function or become malignant. We are not yet certain that if a subset of cells migrate elsewhere in the body, they will die at that site or, more problematically, differentiate into an inimical cell type.

Not only are there questions of inflammation and infection; there are also questions of rejection, in perhaps the short and long terms. With regard to rejection, there is some evidence that administration of embryonic stem cells may require immunosuppression. In contrast, investigators exploring allogeneic transplants report that mesenchymal stem cells may be immunoprivileged.29-31 Not only do they not express a number of surface antigens that elicit a T-cell response, but they may actually inhibit T-cell interactions.32-36 Clearly, more information is needed here; for example, even if an adult mesenchymal stem cell is immunoprivileged, does it remain so if it differentiates into another cell type?

Finally, are stem cells implanted in the heart arrhythmicogenic? This has been a major problem with skeletal myoblasts,37 which fail to form gap junctions with myocytes and appear to serve as loci favoring reentry. We still need to understand the extent to which arrhythmias complicate other forms of stem cell therapy.

**Administering Stem Cells as Therapeutic Agents**

At the simplest level, we want to administer stem cells that are therapeutic,29,38-40 manifest a paracrine function to recruit other cells,29,41,42 or are platforms carrying a therapeutic agent to a region.43,44 We need them to express their beneficial action or to recruit native cells to do so and either disappear when their intervention is no longer needed or persist to express their function for the life of the patient.

Most clinical work has used multipotent stem cells, especially adult human mesenchymal stem cells that are derived from bone marrow (see References 11 and 22). Research suggests that as for autologous bone marrow transplantation, we need have little concern about the safety of autologous administration of human mesenchymal stem cells or cardiac progenitor cells into the peripheral vasculature of a patient.29 The obvious question of "What if it turns out to be unsafe?" has been answered only in the short term and may not be completely answered until years after the procedure.

Also of concern is experimentation on a population of patients in whom there is every expectation of a decent recovery after infarction. Would we perform an initial trial of the latest incarnation of doxorubicin in a patient population with an uncomplicated, superficial skin cancer? Or would we seek patients in whom other therapies had failed, who had no hope and understood that their inclusion in the trial, while conceivably providing benefit, is being sought more for the acquisition of knowledge? A counterpart to such studies may be that reported by Perin et al,9 who administered autologous bone marrow cells transendocardially via a catheter to patients whose ejection fractions were <40% and who were not candidates for surgical or percutaneous revascularization. A variety of functional measures improved over the ensuing 4 months, with ejection fractions rising from 20% to 29%.

Of interest equal to autologous cell transplants—and of greater applicability to serving broad populations rapidly—are allogeneic mesenchymal stem cells, for which trials are now being performed. As stated recently by Zimmet and Hare,29 “What if the optimal cells for cardiomyoplasty could be...frozen in aliquots for allogeneic use at a moment’s notice, in large numbers of patients? Such cells could be used as a standard ‘drug,’ without the delay of collection and ex vivo culture of autologous cells, and without regard for the suitability and regenerative capacity of any individual patient’s own stem cells.”

Both human mesenchymal stem cells packaged in much the same way as drugs and autologous stem cells are being administered in clinical trials including some postinfarction patients whose ejection fractions are in the 30% to 60% range. Do these patients need these cells? Obviously, without understanding the efficacy of the cells, we cannot fully comment on need. But one might question whether a patient with an ejection fraction of 50% to 60% needs little else than current state-of-the-art care.

Although persistence of mesenchymal stem cells in host animals has been documented for intervals close to 1 year,24 we still are not certain about the extent to which stem cells implanted with the expectation of homing to a particular site or of residing long-term at the site of injection will uniformly do so. Markers to facilitate magnetic resonance imaging identification of stem cell localization and migration are available, but the resolution of available techniques renders a firm understanding about cell fate uncertain. Another factor is that some stromal cell data indicate the occurrence of microinfarction in a canine model.45,46 This issue also needs resolution.

Given the questions of safety and the limited to absent efficacy demonstrated to date, what is the propriety of administering such cells to patients in the equivalent of phase 1 trials? This brings me back to the Welt-Losordo comment on the BOOST trial mentioned earlier.23,24 The 18-month BOOST report of autologous, intracoronary bone marrow cell infusions to patients 4.8±1.3 days after percutaneous stent implantation was in some ways a letdown. Whereas at 6 months a nearly 7% increase in left ventricular ejection fraction was seen (which was significant compared with the 1% increase in control subjects), at 18 months, the ejection fractions of both groups were statistically indistinguishable. The authors suggested that improvement in the ejection fraction was accelerated significantly by cell therapy, but the overall result, together with that of the earlier Transplantation
of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI) study,\textsuperscript{10,11} suggested that at least for the cell types and patient populations included, cell therapy might be safe but confers either no important advantage or no advantage at all. Certainly, the patients who were the subjects of therapy in these trials received benefit that was far more noteworthy statistically than therapeutically.

The Roles of the Food and Drug Administration and Other Agencies

It is possible in some parts of the world for individuals with life-changing or life-threatening illness to register at a clinic for treatment with human embryonic stem cells.\textsuperscript{47} Although the United States and member nations of the European Community have made steps to regulate stem cell research, other nations are just awakening to the need. In the United States, the word “regulation” invokes the Food and Drug Administration (FDA) but also brings in other agencies like the National Institutes of Health (NIH).

Stem Cells Are Not Drugs in the Popular Sense of the Word, But They Fall Within the FDA’s Purview

According to the NIH, a stem cell is “a cell that has the ability to divide for indefinite periods—often throughout the life of the organism….” Included are cells that are pluripotent (embryonic stem cells that can give rise to mesodermal, endodermal, and ectodermal tissues) and those that are multipotent (undifferentiated cells found in most or all fully differentiated tissues that can give rise to all cell types of the tissue of origin).\textsuperscript{48}

The term drug means “(A) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C).”\textsuperscript{49}

On the basis of this definition, are stem cells drugs? At the very least they can be used as drugs or to deliver potentially therapeutic molecules\textsuperscript{43,44} to the heart. Moreover, we have consistently used cells from other species and products made from cells of other species as drugs; much of pharmacology owes its existence to botany and bacteriology. A template for likening stem cells to drugs is provided by allogeneic bone marrow transplantation, which falls within the FDA’s portfolio as the use of “articles . . . in the . . . cure, mitigation, treatment, or prevention of disease in man or other animals; and articles (other than food) intended to affect the structure or any function of the body of man or other animals.”\textsuperscript{49} But saying that stem cell is a drug because it falls within this definition misses the point. A stem cell, whether pluripotent or multipotent, has both an origin and a range of possibilities, potentially beneficial and catastrophic, that make many traditional drugs look like child’s play.

The FDA and NIH

At present, different cell therapies are in widely different states of clinical and preclinical development and are being administered to a diversity of patients. Let us consider this landscape in light of the mission of the FDA, which is to protect “the public health by assuring the safety, efficiency, and security of human and veterinary drugs, biological products, medical devices, our nation’s food supply, cosmetics, and products that emit radiation . . . [and to advance] . . . the public health by helping to speed innovations that make medicines and food more effective, safe and more affordable; and helping the public get accurate, science-based information.”\textsuperscript{50}

The FDA is an agency on a hot seat.\textsuperscript{51} In the last 50 years, it has regulated not only drugs but devices and tissues and has had to recognize the differences among them as well as the need for different, partially overlapping, guidelines.\textsuperscript{52} Moreover, the FDA of late has been driven by politics.\textsuperscript{51} This is dramatically evidenced by decisions relating not so much to stem cells but to other therapies such as the “morning-after pill.”\textsuperscript{53,54} Despite favorable evidence and expert testimony, the FDA has been subjected to and yielded to pressures that go well beyond what is acceptable for an agency that is the last bastion of quality control of therapeutic interventions administered to our citizenry.

In the FDA, stem cells largely fall under the aegis of the Center for Biologics Evaluation and Research and the Office of Cellular, Tissue and Gene Therapies. The FDA regulates tissues on the basis of section 361 of the Public Health Safety Act, which has the intent of preventing the introduction, transmission, and spread of communicable diseases. Two supporting documents were put forth in 1997: “A Proposed Approach to the Regulation of Cellular and Tissue-Based Products” and “Reinventing the Regulation of Human Tissue.”

In ensuing years, the FDA has reviewed not only cell therapies and the preclinical research related to them\textsuperscript{55} but also the use of cells and tissues in coordination with drugs or devices.\textsuperscript{56} Diversity in serving national needs is key here; for example, one interest of the FDA has been to facilitate approaches to counterterrorism; the intent is to treat both the immediate and long-term consequences of terrorism-related injuries with tissue, cell, and gene therapy.\textsuperscript{56}

In May 2005, Good Tissue Practices and Inspection and Enforcement criteria (proposed in 2001) were enacted for enforcement by the FDA.\textsuperscript{57} These cover a variety of issues, as do the European guidelines (see below), but the focus is on stem cells that are to be used as therapies. And this is the problem: the FDA and its review processes are therapy driven. On the one hand, this is appropriate because the FDA has a gatekeeper function with regard to public welfare. But it also means that stem cell research that has no immediate (or stated) intent for administration to human subjects is not the FDA’s concern. Who regulates the remainder of stem cell research? This is a potpourri. To some extent, it is the NIH, but most of its regulation is intended to ensure that federal support goes only to research using approved human embryonic stem cell lines. If non–federally approved cell lines are used, regulation occurs at institutional levels, subject to local
committees such as institutional review boards, animal care and use committees, and biological safety committees.

Given that there is often overlap between grant-supported research and that which results in new therapeutics, having 1 agency manage issues of therapeutics and related preclinical studies (FDA) and another concentrating on science per se that is federally funded (NIH) with local committees filling in with regard to all other research creates a gap in review and management. One might argue cogently that in a complex society, gaps are not only inevitable but also not inherently harmful. And what we certainly do not need is a “Homeland Security” approach to stem cell research and development, with a stem cell tsar and his apparatchiks controlling the landscape. A central review panel having the mandate to review and to advise local regulatory offices would likely serve a useful purpose, however.

**The European Community**

Since the 1990s, the European Community has played a role in regulating stem cell research and therapy that is summarized in publications of the European Parliament and expressed in the Council of 31 March 2004. This document identifies the tissues and cells of interest, provides a set of definitions, and indicates means for implementation by member states. These include, but are not limited to, supervision of tissue and cell procurement, accreditation of institutions, mechanisms for oversight and reporting of adverse events, donor selection and evaluation, consent procedures, and responsibilities of personnel involved. This has been a “living document” with continued updating (eg, Directive 2004/23/EC of the European Parliament). However, not all European Union states have shown equal commitment to the rules; indeed, within member nations, interpretations and practices vary. In other words, many of the issues that confound the US scene also confront our European colleagues.

**The National Academy of Sciences**

Perceived national shortcomings in the regulation of stem cell research led the National Academy of Sciences to issue its own recommendations. Although the academy guidelines focus on human embryonic stem cells, they are in part applicable to other human stem cells. If a variation on the academy plan moves ahead, it would be desirable for all human stem cell lines to be included in the mandate for any federal oversight committee.

The academy’s concern was triggered by the observation that the stem cell field is not so much unregulated as “subject to a patchwork of regulations.” The academy committee noted that federal regulations are usually triggered when research is funded by the federal government, when privately funded research is aimed at developing data for a product to be approved by FDA, and in some instances when research is privately funded. The academy perception was that unless stem cell research is of a type that falls under stated federal regulatory policy (as in the human embryonic stem cell lines either permitted or proscribed for use in federally funded institutions) or aimed directly at the development of a therapy, guidelines are wanting.

Central to academy recommendations is oversight at both the national and institutional levels. At the national level, the academy recommends a body to review the policies and guidelines covering practices in the field and to provide a forum for continuing discussion of issues in human embryonic stem cell research and updating of guidelines. This board would not supplant the FDA. At the local level, the academy recommends the establishment of Embryonic Stem Cell Research Oversight (ESCRo) committees, having professional and lay membership that would not supplant institutional review boards. Although targeted at human embryonic stem cells, this type of committee also seems appropriate for other cell lines. Among the duties recommended for the ESCRo are documenting the provenance of human embryonic stem cells and dividing research into that requiring 1 of 3 levels of review: permissible after informing ESCRo and completion of reviews required by current guidelines (eg, in vitro research with preexisting coded or anonymous cell lines), permissible only after additional review, or not permissible at present (eg, in vitro culture of any intact human embryo or introduction of human embryonic stem cells into human or nonhuman blastocysts).

It is not my intent to review completely the academy guidelines; they are readily available. They are a welcome attempt at providing organization and structure to an area in which government regulation has been inconsistent. There are concerns, however, about the promulgation of academy recommendations: While they are thoughtfully and carefully constructed, in the absence of a strong, central regulatory office that can formulate and recommend guidelines, they are too heavily vested in local control. Local control exerted within a state or nation translates to uneven control across the sum of local agencies. Try as institutions may to successfully exert such controls, some will do better than others, with the likely result that patients will suffer, as will the evolution of proper knowledge of stem cells and their place in medicine. Unless a national (or international) body like that recommended by the academy is not only empowered but interdigitates effectively with the FDA and NIH, it is conceivable that any proliferation of local infrastructure will only add to the regulatory patchwork that the academy decrees.

**Conclusions and Some Final Questions to Consider**

I believe that a panel established at the national level would be good for the oversight of stem cell research and development in this country. This opinion mirrors that of the National Academy of Sciences. I endorse this approach despite 1 major fear: the propensity of government (some administrations more than others) to appoint individuals and committees who pass a policy-based litmus test rather than take an open and frank view of a field. Among the questions we need to consider in moving ahead are the following.

**Is It Government “of the People, by the People, for the People,” or Is It the Other Way Around?**

Among the government’s jobs are protecting the populace from unnecessary risk by assigning experts to that role, standing out of their way as they make a judgment, and then
acting intelligently and positively on that judgment. Regardless of the fine points of safety and efficacy of a medication—the morning-after pill is an example—a government that interposes itself between the conclusions of its experts and their logical promulgation shames itself while reflecting sadly on those who elected it. With respect to stem cell research, appointing a panel incorporating the expertise that can perform the tasks proposed by Warnock and by the National Academy of Sciences appears to be in the best interests of the people. A complementary approach saw support at the 2006 meeting of the International Society for Stem Cell Research. Guidelines applicable to researchers worldwide have been drafted, and a final document is anticipated by year’s end.

Stem Cells May Be Safe for People, But Are People Safe From Stem Cells?

Cells may be safe for people, but if not properly given (if based on incomplete or wrong information), people will suffer. The history of blood transfusion and bone marrow transplantation has taught us much about limits. We know that autologous cells will not hurt a patient when administered via a peripheral vein. More recent information suggests that intracoronary administration of bone marrow cells may not hurt a patient, although the microinfarction literature leaves some doubt here. The possible introduction into human subjects of viruses derived from animal feeder cells is an additional concern. Reports that adult human mesenchymal stem cells may be immunoprivileged are encouraging, but a good deal more research is needed before we accept this information as immutable.

Until we contend with these issues and other questions raised earlier, adult human mesenchymal stem cells should likely be administered only to patients whose condition demands it. A stem cell that loses its immunoprotection over time is a time bomb in the making (for as long as there is the demand, the stem cells are safe). The history of blood transfusion and bone marrow transplantation has taught us much about limits. We know that autologous cells will not hurt a patient when administered via a peripheral vein. More recent information suggests that intracoronary administration of bone marrow cells may not hurt a patient, although the microinfarction literature leaves some doubt here. The possible introduction into human subjects of viruses derived from animal feeder cells is an additional concern. Reports that adult human mesenchymal stem cells may be immunoprivileged are encouraging, but a good deal more research is needed before we accept this information as immutable.

Until we contend with these issues and other questions raised earlier, adult human mesenchymal stem cells should likely be administered only to patients whose condition demands it. A stem cell that loses its immunoprotection over time is a time bomb in the making (for as long as there is the possibility of a delayed immune response). A central review panel to monitor progress regarding these and other issues that arise would benefit society.

Stem Cell Therapies and Considerations of Their Benefits and Risks Should Be Regulated in Analogy to Drugs in Development

Human embryonic stem cells have occasioned a politically-religious debate that has tied the hands of investigators in the United States and put us well behind investigators elsewhere. Yet, investigators elsewhere in the world are having difficulty establishing lineages that are consistently and uniformly cardiac and are taking a great deal of time to work these issues out in the basic research laboratory. Much effort is needed to contend with these issues, and it is unfortunate that in forward-looking states like California—the first to revolt against federal restrictions in human embryonic stem cell research—efforts to advance research are tied up in the courts.

With regard to mesenchymal stem cells, use is far freer; in some instances, the word “promiscuous” comes to mind. Desperately needed is a thoughtful, measured correction of what the National Academy of Sciences has decreed as a patchwork of regulations.

“First, Do No Harm” and “First in Man”: Are the Two Antithetical?

Primum non nocere (first do no harm) has been a guiding principle for medicine since the times of the ancients. “First in man” has been a goal in the commercialization and delivery of medical discovery. While the two are not irreconcilable, the overhasty pursuit of the second clearly can negatively affect the first.

Has this been the case in the stem cell field? Clearly there have been abuses. Consider recent events in Korea and less publicized events in India as examples. However, both of these examples also may incorporate arrogance and/or self-aggrandizement as motives (I say “may” because I have no direct understanding of motive here).

Have published, peer-reviewed stem cell trials or others in progress crossed the line? Although the answer may be yes, it is important now to avail ourselves of all information gathered thus far to design further preclinical research, as suggested by Welt and Losordo. This research effort should be reported not only to the journals and the community but also to a central regulatory body that has the scope of expertise and responsibility to interpret results disinterestedly and to make recommendations regarding next steps. I would expect that any committee of intelligent individuals would begin with the understanding that it is far more important to be right than to be first. While primum non nocere must remain at the forefront in all considerations, we must accept that for stem cells, as for any new therapy, intelligent risk assessment and management likely hold the keys to success or failure.

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