International Stem Cell Tourism and the Need for Effective Regulation: Part I: Stem Cell Tourism in Russia and India: Clinical Research, Innovative Treatment, or Unproven Hype?

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Part I: Stem Cell Tourism in Russia and India: Clinical Research, Innovative Treatment, or Unproven Hype?

ABSTRACT. Persons with serious and disabling medical conditions have traveled abroad in search of stem cell treatments in recent years. However, weak or nonexistent oversight systems in some countries provide insufficient patient protections against unproven stem cell treatments, raising concerns about exposure to harm and exploitation. The present article, the first of two, describes and analyzes stem cell tourism in Russia and India and addresses several scientific/medical, ethical, and policy issues raised by the provision of unproven stem cell-based treatments within them. The distinction between treatment based on proven clinical research and "innovative treatment" is addressed and the authors conclude that the innovations at issue constitute neither. Regulatory measures need to be developed or strengthened in accord with internationally accepted standards in such countries to protect those seeking stem cell treatments.

Although most cells in the body, such as blood, kidney, and pancreatic cells, multiply to form only new cells of the same type, stem cells can differentiate into a variety of types of cells with different functions. Researchers have been attempting to use stem cells derived from somatic (body) cells, fetuses, embryos, and umbilical cords to repair damaged tissue in various parts of the body. They have had some success with blood-forming stem cells found in bone marrow. However, there have been relatively few clinical trials involving other sorts of stem cells or therapeutic uses of them (National Institutes of Health 2009).

To some who are ill and suffering, any kind of stem cells, regardless of their origin, may seem to offer the prospect of cure or amelioration of

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their condition due to the intense hype that has surrounded their discovery and the subsequent publicity regarding their possible uses. Those who are bound to wheel chairs hope to walk again and those with degenerative diseases or terminal illnesses seek renewed life using stem cells (Murdoch and Scott, forthcoming). Some among them have traveled abroad seeking stem cell treatments not available in their home country. They have been attracted by internet advertisements, blogs, articles in local newspapers, and word-of-mouth reports about putatively efficacious stem cell treatments available in countries stretching from Mexico through Russia and India to China and Africa (Lau et al. 2009; Regenberg et al. 2009; Ryan et al. 2010). This sort of medical travel, which has been dubbed "stem cell tourism," is part of a larger worldwide medical tourism industry. One category of medical tourism encompasses travel abroad to accredited and regulated institutions that offer proven treatments at lower cost than institutions in patients' home countries. Another category involves travel abroad to clinics and hospitals that may not be accredited and regulated and that offer unproven treatments not provided in patients' home countries. "Stem cell tourism" currently is taken to fall into the latter category—and with reason.

Concerns have been raised by well-regarded scientists and commentators that those seeking stem cell treatments abroad are being misled by overdrawn promises about dubious "magic bullet" treatments that could place them at serious risk (Braude, Minger, and Warwick 2005; Enserink 2006; Kiatpongsan and Sipp 2009; Creasy and Scott 2009). They point out that many stem cell treatment havens provide no cogent evidence of the safety and effectiveness of their treatments and that government agencies in these countries do little or nothing to stop the provision of unproven and possibly unsafe stem cell treatments within their borders. Yet some with serious maladies for whom proven stem cell treatments are unavailable in their home countries are determined to try whatever putative stem cell therapies they can find overseas, even if these might be risky, unproven, unregulated, and expensive.

In the present article, Part I of our exploration of several policy issues raised by stem cell tourism, we describe and analyze the provision of stem cell treatments in Russia and India, two countries that illustrate, in somewhat different ways, how countries to which those seeking stem cell treatments are attracted have responded—or failed to respond—to practitioners offering questionable stem cell therapies within their borders. We also examine measures adopted in these two countries to regulate such

stem cell treatments, how rigorously these are enforced, and ways in which those providing treatments at stem cell clinics and medical centers in each country have responded to them. We present criteria for demonstrating the safety and efficacy of stem cell therapies and conclude that the treatments at issue fail to meet them, finding that they constitute neither clinical research nor "innovative treatments." Countries in which such unproven treatments are offered owe it to those drawn within their borders for stem cell treatments and their own citizens to regulate the provision of these dubious therapies according to internationally accepted standards for proven treatments and to enforce such regulations.

Part II of our discussion, to appear in a subsequent issue of the *Kennedy Institute of Ethics Journal*, will draw upon the aforementioned criteria for proven treatments, as well as regulations developed in several countries, including the United States, the United Kingdom, Israel, and China, and guidelines of the International Society for Stem Cell Research, to develop a basic regulatory framework for the provision of stem cell treatments based on internationally accepted scientific and ethical standards. Countries seeking to regulate such treatments could draw from these to develop measures that would protect those receiving stem cell treatments from dubious and possibly harmful interventions. Further, we outline steps that home countries of those seeking stem cell treatments abroad could take to expose unproven stem cell treatments and we recommend measures that such persons could take themselves to avoid injury.

STEM CELL TOURISM AND ITS REGULATION IN RUSSIA

Stem cell treatments are booming in Russia with almost no regulation. Patients from abroad have been attracted to Moscow by internet advertisements and claims of those returning that stem cell therapies offered at certain private clinics and boutique beauty salons in that city can cure a wide range of illnesses and conditions (Titova and Brown 2004; Osipova 2005; Parfitt 2005; Grammaticas 2006). Many of these facilities say they provide adult, fetal, placental, umbilical, and/or embryonic stem cell therapies for conditions ranging from Alzheimer's and Parkinson's diseases to baldness and facial skin wrinkling. However, almost none provides evidence that these are proven therapies or even that they involve the use of stem cells.

For instance, two women from Michigan who had been paralyzed in car accidents flew to Moscow for stem cell treatments at least six times each between 2001 and 2008 (Kozlowski 2007; Loechler 2008). There

they received injections of stem cells derived from their bone marrow into their spines, followed by hours of physical therapy—a trio of three-hour sessions every week. The first woman indicated that after five treatments she could contract a few leg muscles, sense hot and cold, and crawl; the second reported that after six treatments she could put one foot in front of the other with the aid of a walker. They regarded these as advances worth their time, effort, and expense. However, as a newspaper commentator points out, intensive physical therapy, rather than stem cell injections, may have been the cause of these improvements (Kozlowski 2007).

Russian citizens are also traveling within their country in hopes of utilizing stem cell treatments. Svetlana Galiyea, a Russian gynecologist who had lost control of her limbs due to multiple sclerosis, went from Perm to a private clinic in Moscow where she received a series of injections of what were said to be embryonic stem cells in 2005 (Danilova 2005; Parfitt 2005). These treatments left her immobile in a wheel chair with no proof that what she had been given were stem cells of any sort. Vladimir Bryntsalov, a Russian pharmaceutical magnate, sought injections of what were said to be human embryonic stem cells at a Moscow clinic in 2003 in order to get rid of gray hair and wrinkles (Titova and Brown 2004; Parfitt 2005; Kahn 2005). Three weeks afterward, his face exhibited multiple small tumors that it took three months to remove. He subsequently expressed doubt about the scientific legitimacy of this treatment, noting that the salon had no laboratory and provided no information about the source of the stem cells (Titova and Brown 2004).

In one confirmed instance, stem cell treatments offered in Russia proved dangerous. An Israeli boy with a rare brain and spinal disease that causes paralysis (ataxia telangiectasia) was flown to an unnamed Moscow clinic three times between 2001 and 2003. There he received injections of neural stem cells derived from multiple fetal sources directly into his cerebellum and spinal cord. Four years later, researchers in Israel found that these cells had triggered the growth of nonmalignant tumors in his brain stem and spinal cord. Although Israeli surgeons were able to remove the spinal cord mass, they were unable to eliminate the brain growth (Amariglio et al. 2009). The future status of this boy is uncertain.

Internationally recognized scientists maintain that this treatment was scientifically unjustified and risky. Mixing stem cells from multiple fetuses with growth-promoting compounds "may have created a high-risk situation where abnormal growth of more than one cell occurred," according to Ninette Amariglio and colleagues (2009, p. 29), who published the

results of their investigation of this treatment. Clive Svendsen (2009), a stem cell investigator at the University of Wisconsin, points out that those providing the treatment offered no rationale to explain how fetal stem cells could reverse the progress of this disease and states that there is no published evidence in nonhuman models that this treatment might be efficacious. Eugene Redmond, a psychiatrist and neurosurgeon at Yale University and a member of an American medical team that examined the Moscow clinic where the boy's treatment was provided, stated:

> We could not see any evidence of real clinical benefit, although the families and the doctors seemed desperate to find one. There were no control procedures . . . . They did not show us any evidence that the cells . . . were in fact stem cells of any type. . . . The whole effort was sufficiently poorly controlled that it is impossible to gain any useful scientific data from these tragic cases. (MacReady 2009)

Several of the providers of such treatments entertain the theory that injections of stem cells will generate new cells that will develop into whatever local tissue is needed to repair damage in almost any part of the body (Parfitt 2005; Kahn 2005). However, respected stem cell investigators point out that there is no way to predict where stem cells of unknown origin will go once injected into the body. Evan Snyder of the Burnham Institute in California, for instance, maintains that scientists need to gain a better understanding of the signaling mechanisms that send stem cells to the right place and cause them to stop dividing to avoid the risk that these cells could cause permanent injury to those receiving them (Kahn 2005).

Indeed, there is no way to tell whether those who go to stem cell clinics in Russia receive stem cells and, if they do, what kind. Since the procedures and materials used are kept secret, others cannot check on their adequacy. Workers at the Kosmeton Clinic, which advertises that it uses stem cells, admit that they give some of their clients skin cells, rather than stem cells, and sometimes use cells from pigs and sheep, rather than humans, raising the possibility that patients might be contaminated by animal viruses residing in these cells (Titova and Brown 2004).

Thus, available evidence suggests that stem cell treatments offered at unknown numbers of clinics in Russia fall well below internationally accepted standards for the provision of proven treatments. It is not possible to ascertain whether whatever is injected into the patients might successfully treat serious conditions, much less wrinkles. Many of the treatments appear to bear the potential for injuring patients. Informed consent to such treatments cannot be obtained under these circumstances.

Russian regulations stipulate that stem cells of any kind can be extracted and stored at institutions but cannot be used in treatments without a license. These regulations are vague, and their enforcement is almost nonexistent (Osipova 2005; Parfitt 2005; Pravda 2005; Danilova 2005). Furthermore, they do not set standards to ensure that the materials injected into patients are stem cells and that they have been purified and tested, and derived ethically (Titova and Brown 2004; Grammaticas 2006). Alexander Teplyashin, director of a stem cell clinic in Moscow, acknowledges that stem cell treatments offered at his edifice are not permitted by state regulations, but that he ignores them. "We are taking advantage of the loopholes in the law," he maintains (Parfitt 2005; Danilova 2005).

In March 2005, a group of 13 prominent Russian scientists, concerned about damage to their country's scientific reputation that the widespread provision of unproven stem cell therapies at private clinics was creating, asked the State Duma to investigate clinics administering unregulated stem cell treatments (Parfitt 2005). In response, the Russian Ministry of Health set up an Expert Council comprised of some of the country's leading medical and biological specialists to review and license those clinics that warranted it (Parfitt 2005). Soon after, the head of Russia's Ministry of Health closed approximately 37 unlicensed clinics in Moscow offering fetal and embryonic stem cell treatments on grounds that they had violated the regulations, kept no patient records, and provided no proof that the doctors working in them were credentialed (Osipova 2005; Kahn 2005). Despite this crack-down, by mid-2007 there were approximately 500 unlicensed clinics still providing stem cell therapies in Moscow (Kuznetsov 2007).

In November 2007, IBMED, a Russian venture company, was given the first one-year license from the Ministry of Health for the use of stem cell treatments for a wide spectrum of conditions, including diabetes, multilocular sclerosis, heart disease, stroke, and hormonal irregularities (Kokurina 2007; Kuznetsov 2007). The head of the Bone Marrow Transplantation Department at the Hematological Scientific Center of the Russian Academy of Sciences maintained that "certain interests have been lobbied for" and were responsible for the success of IBMED's license application (Kokurina 2007). The Expert Council was scheduled to evaluate the results of the therapy used by IBMED at the end of 2008. No information could be found about any resulting report of action as of January 2010.

Stem cell treatments in Russia are offered in a weak—indeed, almost nonexistent—regulatory environment. There is, in effect, no national or

institutional oversight of the private centers at which they are offered. The Ministry of Health is the major health policymaking body in Russia (Danishevski and McKee 2005), but it has lost many of its traditional functions, including the management of research institutes (Tragakes and Lessof 2003). The Academy of Medical Sciences, which is responsible for the conduct of research at such institutes, is not authorized to regulate stem cell treatments offered at private clinics (Tragakes and Lessof 2003). Consequently, those providing stem cell treatments in the private sector simply shrug off weak regulations.

Well-regarded Russian scientists have expressed concern about this situation. For instance, Alexei Ivanov, of Moscow's Sechnov Medical Academy, declares that "there is still so much we don't know about [stem cells] and the effects that they have on the body. That's why we have to get all this unregulated practice under control" (Parfitt 2005). It is clear that the lack of effective oversight of stem cell treatments in Russia cannot be dismissed as mere propaganda. Concerns expressed by Russian scientists themselves support the premise that if Russia is to establish itself as a credible center for stem cell research and treatment, it will need to require that stem cell studies be carried out under scientific and ethical standards that address issues of patient safety, treatment efficacy, and informed consent.

STEM CELL TOURISM AND ITS REGULATION IN INDIA

Individuals from the United States and several other countries also have traveled to India in search of stem cell therapies. Although the government of India provides greater oversight of stem cell treatments than is apparent in Russia, it, too, has allowed dubious unproven stem cell treatments to proceed at clinics, as well as at some well-regarded medical centers.

Some persons with serious conditions have gone to Nutech Mediworld, a private stem cell therapy clinic run by obstetrician Geeta Shroff in Delhi. She maintains that she has successfully used human embryonic stem cells to treat more than 600 patients suffering from such conditions as renal failure, cerebral palsy, Alzheimer's disease, and Parkinson's disease (Ramesh 2005; Basu 2005; Padma 2006; Srinivasan 2006; Khullar 2009). For example, in 2007, a young woman from Colorado who had been paralyzed from the waist down in a skiing accident received two months of human embryonic stem cell injections, along with extensive physical therapy, at her clinic (Havlen 2007). Afterward this woman was able to stand with the help of leg braces and to wiggle a big toe on one foot and some smaller toes on the other.

Stem cell treatments provided by Shroff came to international attention during a news conference in 2005 when she would offer no explanation of how the stem cells she uses are purified and tested or how they function in the body, indicating that this is a proprietary matter (Ramesh 2005; Basu 2005). She stated that she had submitted a protocol for her studies and details of cases to the Indian Council of Medical Research (ICMR), which funds biomedical research under the auspices of the Ministry of Health, before she had initiated her stem cell treatments. However, officials at the ICMR indicated that Shroff had already been providing treatments before she submitted a protocol, had not responded to their requests for further information, and had continued her treatments without ICMR approval (Ramesh 2005; Basu 2005).

Satish Totey, Secretary of the Stem Cell Research Forum of India (SCRFI), maintained that Shroff was putting her patients at a risk of developing teratomas that could become malignant (Ramesh 2005). Several well-regarded stem cell investigators in the U.K. also rejected Shroff's claims, maintaining that such treatments enter "into the realms of quackery" (Braude, Minger, and Warwick 2005). Although an enquiry into Shroff's stem cell treatments was initiated in 2006 by the Indian health minister (UNI 2006), no word could be found about its results as of the end of January 2010. Shroff has filed an application to patent her treatments but has declined to publish her findings (Khullar 2009). She was still providing human embryonic stem cell treatments to patients from around the world at her clinic in 2009 (Khullar 2009).

Patients from other countries also have sought stem cell treatments at leading medical centers in India. A man from the United States who had suffered from Parkinson's disease for 15 years flew to Manipal Hospital in Bangalore for stem cell treatments in 2007. There physicians harvested mesenchymal stem cells from his bone marrow and injected them into the affected part of his brain. At the time that this treatment was publicized in 2007, the hospital reported that he had received three such injections, was walking without support, and had experienced considerable reduction in his body tremors (Singh 2007; Biospectrum 2007). However, no follow-up information could be found at the hospital's website about this patient as of the end of January 2010 and no publications could be found in the peer-reviewed medical literature about this treatment.

Indian citizens also have received stem cell treatments at state medical institutions. Panangipalli Venugopal, director of New Delhi's prestigious All India Institute of Medical Sciences (AIIMS) announced in 2005 that he

had achieved a "global first" in that he had used stem cells derived from bone marrow to treat 35 patients with end-stage cardiac disease during coronary bypass surgery (Jayaraman 2005; Padma 2006; Srinivasan 2006). This study, however, had not received clearance from the ICMR (Jayaraman 2005). He also revealed that he had administered stem cells to patients with cerebral palsy, muscular dystrophy, and stroke. This research, too, had not been submitted to any government agency for approval (Jayarman 2005). After widespread negative publicity, the head of AIIMS announced that this research was being put on hold (Srinivasan 2006).

It was also reported in 2005 that fetal stem cells had been transplanted into the eyes of more than 240 patients with retinitis pigmentosa in a study at L. V. Prasad Eye Institute, a well-known private clinic in Hyderabad (Jayaraman 2005; Srinivasan 2006). This experimental treatment had been developed abroad and was funded by sources in the U.S.; it was being tested exclusively on Indian patients. The institute was refused additional funding for this research because, according to the ICMR, "undertaking clinical trials on Indian subjects for an experiment which was not being conducted on U.S. subjects was not ethical and hence not acceptable" (Srinivasan 2006). However, these stem cell transplants continued. Dorairajan Balasubramanian, research director at the institute is reported to have stated: "Guidelines are only guidelines. Any violations cannot be punished" (Mudur 2005).

Calls had been issued earlier for effective oversight of stem cell research and treatment in India (Srinivasan 2006). In response, the Department of Biotechnology (DBT), which comes under the auspices of the Ministry of Science and Technology and is responsible for coordinating and promoting biomedical research, issued one set of guidelines for stem cell research and treatment in 2001. The ICMR, which, as noted above, funds biomedical research under the auspices of the Ministry of Health, issued a second set of guidelines in 2002 (Srinivasan 2006). There were inconsistencies between these guidelines, since neither agency had consulted the other. Moreover, both sets of guidelines were viewed by commentators as unenforceable (Padma 2005b & c; Srinivasan 2006).

Continued negative publicity about unauthorized stem cell treatments offered at private clinics and well-known medical institutions led the Indian government to decide in 2005 that the country needed a single set of stem cell research and treatment guidelines and a national regulatory body to clear all research and therapeutic projects involving stem cells (Padma 2005a). The ICMR and the DBT joined forces to negotiate a new

set of stem cell guidelines and in November 2007, they announced that they had jointly developed *National Guidelines for Stem Cell Research and Therapy* (Indian Council of Medical Research 2007).

In brief, these guidelines call for a National Apex Committee for Stem Cell Research and Therapy charged with supervising stem cell research and treatment provided within India. They also establish Institutional Committees for Stem Cell Research and Therapy to oversee such research at both public and private institutions throughout the country. Research pertaining to adult and umbilical cord blood stem cells requires approval from an Institutional Committee for Stem Cell Research and Therapy and the Drug Controller General. Embryonic stem cell research requires, in addition, the approval of the National Apex Committee.

Although these guidelines establish a more unified system of oversight for stem cell research and treatment, they have certain significant drawbacks. One is that the National Apex Committee does not appear to have authority over all stem cell research in the country. Moreover, it is unclear whether its decisions could be nullified by a higher authority, such as the Drug Controller General, and how it would address violations of the guidelines, since no sanctions are built into them. Saionton Basu, an Indian legal commentator, argues that India needs to institute stronger regulations. He maintains that centers should be licensed by a statutory body to carry out stem cell research and that this body also should maintain a code of practice and a register of licensed treatments; provide advice and information to the public, prospective patients, and clinics; and keep the field under active review (Basu 2006).

In early 2010, the assistant director general of ICMR announced that the guidelines would be open to public debate in four public meetings (Chennai Online 2010). At the first of these in February 2010, the ICMR announced that it would set up a National Apex Committee for Stem Cell Research and Therapy by April 2010 (DNA India 2010). This development suggests that the guidelines are moving toward legal status in India, although it is uncertain when this might occur and whether their legal adoption would deter the provision of unproven stem cell treatments in India.

Clearly, stem cell therapies have been offered at some clinics and medical centers in India in ways that do not adhere to internationally accepted standards for proven treatments. Those offering them provide few or no details about whether nonhuman or human studies have been carried out prior to the introduction of stem cells into patients, whether patients have been rigorously assessed before and after treatment, whether controls are

used to allow a reliable basis for comparison of human subjects, whether patients have provided informed consent to these treatments, and whether these treatments have been approved by an authorized regulatory body.

Even as such unregulated stem cell treatments have been allowed to proceed in India, however, the country has fostered the development of research-oriented hospitals and institutes, as well as stem cell scientists who have published in the peer-reviewed literature (Sharma 2006; Lander et al. 2008; Rao 2009). Indeed, five human embryonic stem cell lines have been isolated by scientists within India, and two of these have been deposited in the United Kingdom Stem Cell Bank (Inamdar 2009). The country is building the $50 million Institute for Stem Cell Biology and Regenerative Medicine (InStem) in hopes of launching an international collaboration in certain forms of basic stem cell research and linking with the Christian Medical College in Vellore in translational and clinical research (Sachitanand 2009). Moreover, major corporate interests in India are beginning to offer to support stem cell research, tissue engineering, and related treatment (Salter et al. 2007). There appears to be a growing consensus among policy analysts and scientists in India and abroad that the country could play a key role in the scientific, clinical, and commercial development of stem cell research and therapy in the future (Mukherjee 2008; Frew, Kettler, and Singer 2008).

Yet the apparent lack of effective regulation of stem cell therapy in India could prove an overwhelming disadvantage to the country, as scientists and corporate investors from other countries who consider cooperating with Indian stem cell researchers will insist that they adhere to strict standards for stem cell research and treatment before they join them in such research. If India is to realize its promise and become respected and competitive in the field, the Indian government will have to institute an effective legally-grounded national stem cell research and treatment regulatory program. It will also need to ban the provision of questionable stem cell treatments by practitioners within its borders.

STEM CELL TOURISM, CLINICAL RESEARCH, AND INNOVATIVE TREATMENTS

Those who travel to other countries for stem cell treatments enter into a sort of medical Russian roulette. They may be helped by such treatments—although there is little evidence for this provided in the instances we have described above—or they may be harmed. Indeed, documented evidence of the latter possibility is being developed, as exemplified by the case previously described of the Israeli boy who suffered serious ill effects from stem cell

treatments he was given at a center in Russia. Such findings, however, appear to be ignored by those providing stem cell treatments in the Russian and Indian clinics and medical centers we have considered. A number of them offer such treatments without adequate scientific justification and despite existing regulations—even when weak—governing stem cell research and treatments, possibly putting those who receive them in peril.

It should be axiomatic that clinical research must be carried out in order to establish definitively the safety and efficacy of a proposed treatment modality for the care of patients. Well-controlled clinical research is necessary for the development of generalizable knowledge that could benefit many future patients (National Commission 1978). Clinical stem cell research should be subject to explicit evidentiary and methodological requirements set out in advance to ensure that it is conducted according to recognized scientific and ethical standards. Clinical research standards should address the following major questions:

- Do the investigators take into account the natural history of the disease for which stem cells are to be administered and all treatments currently available (since the beneficial effects of standard therapy and even spontaneous improvement may be significant factors affecting the research outcome)? (Spooren et al. 2008; Wirth et al. 2008).
- Will the investigators compare the results of administering stem cells with those following use of a placebo and/or standard therapy?
- Have disinterested observers verified the safety and efficacy of the proposed stem cell treatment in preclinical and clinical studies conducted in a few volunteers?
- Has a neutral party made a definitive diagnosis prior to the institution of stem cell therapy? Will this neutral party be involved in objective follow-up evaluations?
- Is there evidence that the patient has been given information necessary to provide an informed consent to undergo this stem cell research and treatment, including information about the source of the stem cells, whether they are pluripotent or differentiated, how they will be directed to the area of the body being treated, the risks, the possible benefits, and the side effects?
- Is there evidence that the patients participating in this research and treatment are doing so voluntarily?
- Have the investigators pledged to subject findings to peer review and to make a good faith effort to publish the data, whether positive or negative?

The minimum basic requirements of *bona fide* clinical research are outlined in Figure 1.

Figure 1. A Continuum of Clinical Research from Concept to Standard Therapy

Many of the treatments provided to stem cell patients in Russia and India that we have considered do not follow this clinical research paradigm. They lack transparency, follow no publicly available protocol, and have not undergone peer review and publication, thereby failing to provide data sufficient to allow other investigators to attempt to replicate their claimed benefits and safety. Moreover, few of those conducting them seek informed consent from persons who will undergo these putative treatments. Consequently, they do not constitute legitimate clinical research aimed at providing safe and efficacious stem cell interventions to a broad range of patients. They are unproven.

Furthermore, these interventions do not amount to "innovative treatments." George Agich (2001) points out that that in some clinical situations, although there are no proven treatments for patients or else available treatments are ineffective or burdensome, it appears that an unproven "clinical innovation" might benefit some. When this is the case, he maintains, it can be appropriate to provide such treatment outside the formal mechanisms of a clinical research protocol if patient consent is obtained. Olle Lindvall and Insoo Hyun (2009) agree that certain interventions fall into the category of unproven medically innovative therapies and maintain that it is ethically sound to offer such treatments to seriously ill patients who have few or no alternatives, rather than enroll them in a clinical trial. Innovative stem cell treatments, they assert, should be distinguished from "objectionable stem cell tourism" in order to allow for the possibility that

some of the stem cell treatments provided to patients abroad, although unproven, might be innovative interventions that are appropriate to offer to patients outside a research protocol (Lindvall and Hyun 2009, p. 1664). They provide no examples of countries in which such innovative stem cell interventions are provided.

Innovative stem cell interventions are unlike drug interventions that can be conducted according to a multistage clinical trials approach, Lindvall and Hyun (2009, p. 1664) explain, but instead are more appropriately viewed along the lines of a surgical or transplantation procedure for which the clinical trials approach is initially impractical. When this is the case, they maintain, a few seriously ill patients for whom there are few good treatment options could be provided with such stem cell interventions. Before such innovative treatments are initiated in patients, they state:

> There should be a written plan that includes a scientific rationale, available evidence of efficacy and safety from preclinical studies in animal models as well as from applications of this intervention for other indications in humans, full characteristics of the cells to be delivered and description of mode of cell delivery and clinical follow-up. This plan should be approved through a review process performed by experts, and there should then be a rigorous voluntary informed consent. Transparency of this review process and institutional accountability are also desirable and crucial . . . . (Lindvall and Hyun 2009, p. 1665)

If the use of such therapies appears to be safe and efficacious in these few patients, they indicate, clinical trials of these innovative treatments should be pursued "when possible" (Lindvall and Hyun 2009, p. 1665, middle track).

Although Lindvall and Hyun's argument depends on designating some therapies as "innovative," they do not provide criteria for determining when an experimental treatment should come under this rubric other than to say that it could be offered to "patients with few or no acceptable alternatives." This description would apply to many new and experimental means of therapy and to a large number of patients. Lindvall and Hyun indicate that innovative stem cell treatments resemble surgical or transplantation procedures that could not readily be developed through a clinical trials approach. However, they do not explain in what respects these interventions resemble such procedures and do not furnish reasons why clinical trials are not possible for them. (Indeed, we describe two surgical innovations below for which clinical trials should have been conducted before they were adopted as standard treatments.) Further

clarification is needed of what specific types of treatment constitute innovative stem cell treatments, when it is appropriate to introduce them in patients, how long to use them, and when to consider them ready to move into clinical trials. It is also unclear how clinicians, investigators, and reviewers should go about evaluating the success or failure of innovative treatments and determine when follow-up clinical investigations of them should be pursued. Moreover, criteria are needed for determining when a formal follow-up clinical study of such treatments should *not* be undertaken. In short, the notion of innovative treatments requires more complete elaboration so that clinicians, investigators, and reviewers can determine just what they are, when they should be provided, according to what standards they should be conducted, whether or not they should move into clinical trials, and, if so, when.

Lindvall and Hyun (2009, p. 1665) also indicate in the text and an accompanying diagram (middle track) that medical innovation should be preceded by scientific and ethical peer review and an assurance of appropriate patient protections. However, it is unclear what body would conduct such reviews and who would serve on it. Such questions have haunted stem cell research since its inception (Cohen 2007 pp. 196–225). These authors suggest that it should be an institutional body composed of "experts." However, this raises the possibility of bias on the part of colleagues working in the field of stem cell research at the same institution who are appointed to such a body. There is a need to include individuals who are not involved in this area of research in the committee membership, along with those who have expertise in the field from outside the institution, in order to minimize even the perception of such bias.

Finally, and most important, Lindvall and Hyun (2009, p. 1664) are willing to proceed with innovative treatments without first conducting clinical trials because "patients with precious little time might not care much about expanding knowledge; what they care about is getting better and surviving." This declaration overlooks the troubling reality that patients, clinicians, and investigators may be taking a considerable gamble if they proceed with an innovative intervention in the hope that the hypothesis supporting its introduction is correct and it will be successful. They do not discuss the troubling reality that should that hypothesis turn out be wrong, the innovative stem cell treatment might be ineffective or, worse, harmful to patients receiving it. The scientific literature provides numerous examples of innovative surgical and medical treatments that appeared to be effective in some patients and therefore became accepted standard

patient care—until randomized clinical trials conducted according to protocols that met recognized clinical research standards demonstrated that the apparent efficacy of such innovative treatments represented a placebo effect, rather than the results of the therapy itself (Cohen 1998). In some of these instances, subsequent clinical research demonstrated that these innovative treatments had resulted in serious harm to patients.

For instance, superficial temporal to middle cerebral artery anastomosis (grafting the two blood vessels together), which was introduced to treat cerebral vascular insufficiency, and the Vineberg Procedure (implanting the left internal mammary artery into the heart muscle) to ameliorate coronary vascular disease, considered innovative surgical treatments, became widely used. Their safety and efficacy were considered so obvious as to not require further clinical investigations. However, when such investigations were conducted, these treatments were found to be without benefit while subjecting the patients to the risks attendant on any surgery (C-IC Bypass Study Group 1985; Dimond, Kittle, and Crockett 1960).

In another case, more than 41,000 patients underwent high-dose chemotherapy plus autologous bone marrow transplant for breast cancer in the 1990s, despite a paucity of clinical evidence of its efficacy. Those advocating this innovative approach were so persuasive that a number of states mandated that insurance had to pay for this therapy. Yet a randomized clinical trial eventually demonstrated that this treatment did not alter the course of disease (Mello and Brennan 2001).

In a third case, the administration of oxygen to premature infants was considered an obligatory innovative therapy during the first half of the twentieth century (Lanman 1976). However, when a controlled prospective study was conducted in 1951 to determine the relationship between oxygen administration and retrolental fibroplasia (RLF), with its attendant permanent blindness, it was determined that the innovative oxygen therapy was associated with a 60 percent incidence of RLF, while infants "deprived" of oxygen had only a 20 percent incidence of incurring the disease and becoming blind (Lanman 1976, pp. 608–9). Thus, the "innovative treatment" was extraordinarily harmful and "no treatment" was the best approach. These examples are not inclusive but serve to point out the hazards of accepting unproven modes of therapy on the basis of innovation or claimed obviousness.

These findings do not indicate that innovative treatment should never be conducted. Short-term medical innovation in a few carefully selected instances could constitute one step in the continuum of developing and

validating some new treatments. Innovative stem cell treatment could be introduced on a small scale with patient consent in instances in which it is arguable that delay for formal clinical evaluation would be detrimental to specific patients. As outlined in Figure 2 below, the protocol for innovative therapy requires a supervised, well-designed, and transparent feasibility study in a few patients. The treatments used in such instances should be preceded by studies in nonhumans that indicate not only that they might be efficacious, but also that it seems highly unlikely that they would result in harm to patients. Such treatments should be identified as having a strong scientific rationale and as falling within a class of stem cell treatments directed toward patients who have no other good options and who have been made aware of any known risks that they run. The rationale for such unproven treatments—that they are appropriate to provide to patients for whom there are few or no alternatives—centers on compassion and hope, motives on which it is difficult for caring professionals to forbear from acting. Yet such treatments should be provided sparingly and under strict review because of their possible dangers.

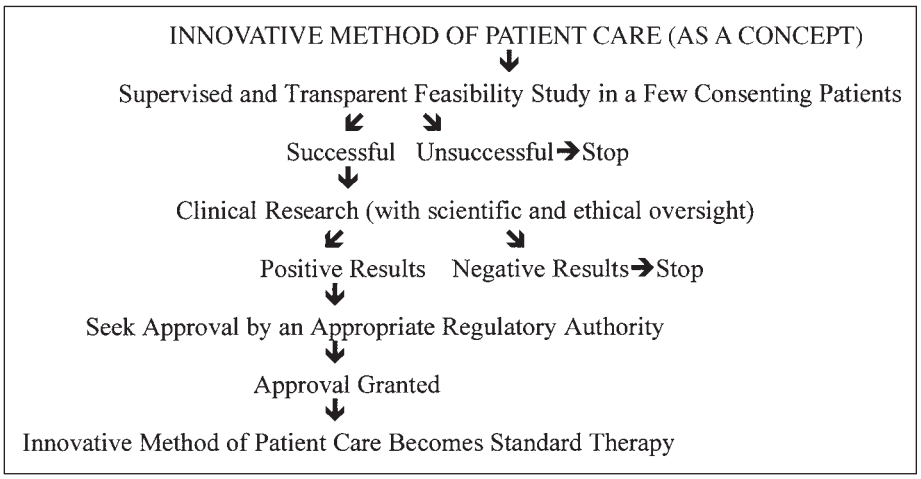

Figure 2. An Additional Step for "Innovative Therapy"

If small-scale innovative treatments appear to have achieved success in a few patients—the criteria should be established prior to treating the first patient—and proof of principle is established, formal confirmatory clinical research that includes among its objectives validation of the safety and efficacy of the therapy should be instituted. Conversely, if there is

objective evidence of failure in the first few patients, such therapy should be halted at once.

We agree with Lindvall and Hyun (2009, pp. 1664–65) that:

> developing a stem cell-based therapy via medical innovation alone is, however, not optimal. The clinical trials process enables one to compare the results of a procedure with the long-term outcome of alternative interventions, which is particularly relevant for stem cell-based therapies. These are in most cases meant to be replacement or regenerative therapies, for which long-term survival, lasting efficacy, and lack of serious side-effects are essential. The stem cell-based therapies must also be clinically competitive. Compared to available treatments, stem cell-based therapies have to offer more pronounced clinical improvement, fewer side effects, and/or lower costs.

Unless there are specific reasons for engaging in innovative stem cell treatments that are clearly and defensibly related to patient care, failure to move to the clinical research paradigm is unjustifiable when considering the institution of a new treatment.

The centers in India and Russia that we have criticized here do not satisfy the minimum standards of clinical research or those of innovative treatment. They have failed to establish a scientific rationale for their treatments, to conduct a preclinical safety and efficacy studies of them in nonhumans and humans, to establish protocols for careful screening of patients, to obtain informed consent from patients, and to carry out follow-up studies. They make no pretense that they are engaging in small-sale investigations of novel stem cell treatments in a few patients. Consequently, their conduct cannot be excused by the claim that they provide unproven but innovative treatments. The therapies they provide are unproven by any standards and, in some instances, may be unsafe. More complete regulatory measures that are in accord with internationally accepted standards for the provision of *bona fide* medical treatments should be introduced and enforced in such countries so that such questionable and possibly dangerous treatments can be ended.

In Part II of our discussion of stem cell tourism, which is forthcoming, we examine regulations for clinical stem cell research and therapy developed in several countries, as well as international research guidelines and the stem cell treatment guidelines of the International Society for Stem Cell Research. On the basis of this assessment, we recommend a general framework for the regulation of stem cell treatments from which countries setting out to oversee such treatments with an eye to efficacy and patient safety could draw, adapting them to local needs and conditions. In ad-

dition, we discuss how the "off-label" use of stem cell treatments that have successfully run the clinical research course fit into this regulatory picture. To insist on appropriate regulation of stem cell treatments is not to ignore patients' hopes and demonize their acts, but instead is to respect their autonomy, recognizing who they are as persons, and to protect their well-being as they seek effective ways to address their debilitating and disheartening conditions.

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