1. *The Decameron of Giovanni Boccaccio*, trans. J.M. Rigg (London, U.K.: A.H. Bullen, 1903), 1:9-10.
2. J.F. Stark, *Daily Hand-Book for Days of Rejoicing and of Sorrow* (Philadelphia, Penn.: Kohler Publishing, 1879), 5.

The Challenge of Regenerative Medicine

BY LEEN TROMMELMANS

Interventions to replace undeveloped, destroyed, or degenerated tissues are not new. However, regenerating tissue was thought to be impossible. "Regenerative medicine" aims to actually regenerate tissue. Therefore, it presents a significant shift in the goal of medicine. Regenerative medicine employs three strategies: (1) inducing the body's inherent regenerative capacities in vivo through the application of growth factors and/or stem cells; (2) "tissue engineering," or creating complex structures in vitro containing cells and custom-made scaffolds to implant in the patient; and (3) recolonizing donated, decellularized structures with patient-derived cells and implanting them in the patient.

Regenerative medicine has been enthusiastically received as it promises to make further interventions redundant. Also, it may provide solutions for as-yet-untreatable conditions, and it may benefit anyone from neonates (possibly even fetuses) to the elderly. All medical fields have embraced it, from dentistry and orthopedics to neurosurgery and cardiology. Its growth is based on our increased knowledge of cell—and especially stem cell—biology and biomaterials, and on the increasing prevalence of degenerative diseases. In the future, regenerative medicine may therefore touch most of our lives.

While there has been a steady increase in the volume of medical research, the field has been largely ignored in bioethics. A PubMed search on "regenerative medicine" resulted in 1,385 papers in 2008, 1,595 in 2009, and 1,282 in the first seven months of 2010, of which respectively 38, 33, and 17 included "bioethics." In the same years—2008, 2009, and 2010—the phrase "tissue engineering" resulted in 4,508, 5,024, and 3,387 papers, of which only 25, 17, and 12 included "bioethics." A literature review of 2008 brought up 203 papers when the search was guided by this string: "regenerative medicine AND/OR tissue engineering AND ethic*."[1] All but thirteen of these articles appeared in biomedical journals, and, out of the thirteen exceptions, very few were in bioethics journals. The ethical issue most commonly addressed in all of the articles was the use of human embryonic stem cells.

These data might suggest that there are no new ethical issues involved in regenerative medicine. In fact, a number of ethical challenges may arise.

While the principles of regenerative medicine are easy to explain and the possible benefits even easier to appraise, relatively few products have made it into clinical trials, and even fewer into therapy. So far, we know some of the "vocabulary" of tissue formation—the genes, cells, growth factors, and extracellular environment involved—but we know very little of the "syntax" of healthy and affected tissues: how these elements interact during the tissue formation process, how the native tissue (healthy and affected) interacts with the new, and whether these interactions are unique for each individual or common for all persons. For now, regenerative medicine is more akin to tissue *handicraft* than tissue engineering: products are developed on a case-by-case basis, and most research energy is spent on identifying and combining the pieces of the puzzle, then translating these findings into a therapeutically active product.

Another challenge the development of regenerative medicine presents is that it is not being pursued by the usual actors—the big pharmaceutical companies that have the money, infrastructure, and clinical trial experience to bring a therapy to market. Rather, the driving forces behind regenerative medicine are cell biologists and biomaterials experts, many of whom are not acquainted with bioethical issues. Ethics committees, on the other hand, are often unfamiliar with regenerative medicine. This disconnect may make it difficult to design ethically acceptable clinical trials on regenerative medicine. There is also the considerable time it takes to go from bench to bedside—if the bedside is ever reached. This lag, and the huge investment necessary for small and medium-sized enterprises to develop these products, requires the participation of private investors. This investment is happening in an international context, where Western ethical sensitivities are not always the prime concern. Which products make it after their initial development may thus depend not only on their therapeutic merits, but also on the expected return-on-investment and on the playing field that is created by international regulations—for instance, the European Union's regulation on advanced therapy medicinal products,

Leen Trommelmans, "The Challenge of Regenerative Medicine," *Hastings Center Report* 40, no. 6 (2010): 24-26.

which applies to all gene therapy, somatic cell therapy, and tissue-engineered products intended for the E.U. market.

Furthermore, decisions made early in the course of research concerning the condition targeted, the donor cells chosen, and the specific cell lines used in the therapy may have far-reaching consequences for the availability of the product for some or all patients. Consequently, the ethics of regenerative medicine must be evaluated in collaboration with involved scientists, and at the beginning of the research pipeline, not at the end.

So, given these features of regenerative medicine, which ethical issues need investigating?

Issues surrounding the use of human cells. Regenerative medicine depends on the availability of appropriate cells and cell lines. Since many people and organizations will be involved in handling and working with these lines and the products derived from them, new questions will arise regarding the "ownership" of human material and its derived products, and the rights that cell donors and the scientists developing new products can and cannot assert. This is a major challenge when cells and their derived products can be easily transferred between countries with different legal systems and ethical sensitivities, whose level of legislation concerning bodily material varies enormously.

Regenerative medicine combines questions that have been raised in other contexts, but the complexity of its products and processes will add new and complicated elements.

The development of clinical trials and follow-up of participants and patients. From the patient's point of view, these treatments will resemble existing medical interventions, which might create the perception that they are a variant of existing technologies. However, the aim and mode of their action differs, presenting unique challenges regarding their production, the design and conduct of clinical trials, and their introduction in therapy.[2] Here are two problems: clinical trials require that researchers not know how the new treatments compare to existing interventions and that the participants consent to treatments. As so little is known about the "syntax" of tissue regeneration and consequently of short- and long-term effects, risks, and benefits, both aspects may be problematic, which challenges us to define criteria for the conduct of trials and for achieving genuine informed consent.

Justice and availability. Ideally, a new treatment will be more effective, safer, and cheaper than any comparable intervention, in which case it may become the standard of care. But more realistically, it will remain expensive, making its application in certain circumstances prohibitive. So, who will receive the new treatments, and who gets "second best"? The young? The elderly? As degenerative diseases will also increase in developing countries, which have larger health care needs and smaller budgets, access is a global concern. Do we invest in the creation of a tissue-engineered bladder for victims of schistosomiasis who will probably never be able to pay for this intervention?[3] Should the answer to this question be left to the market and to researchers? How and how much can other stakeholders push health care in a specific direction? These questions are not only about which regenerative therapies should be developed, but also about how much money should be devoted to regenerative medicine generally and how much to other innovations or approaches. Finally, the availability of regenerative products that contain cells not only depends on financial considerations but also on the availability of immunologically compatible material. People may be excluded from a potentially beneficial therapy as a result of earlier choices about which cell lines to use to develop the treatment.

Uses beyond therapy. So far, regenerative medicine is being developed for curative purposes. However, the principles of regenerative medicine could also be applied to prevent aging, for enhancement or cosmetic purposes.[4] These applications need further consideration, as the current regulations do not address them. Creating viable tissues outside of the body and regenerating the body may raise visions of posthumans enjoying eternal youth. Earlier discussions concerning the moral implications of enhancement technologies may reappear once regenerative medicine is better understood and more widely applied. Regenerative medicine may also alter our perception of the life cycle and of bodily integrity, if the person's body can be reconstituted and rejuvenated using living material derived from various people, making the person into a hybrid. If the products eventually make for perfect replacements of "natural" tissues and organs, the Cartesian view of the body as a machine may become even more predominant, which may lead to some interesting discussions about human nature.

Regenerative medicine combines questions that have been raised in other contexts, but the complexity of its products and processes will add new and complicated elements that call for more attention. First, bioethicists should explore the ethics both of research on regenerative medicine and of its applications, not only with regard to patients and subjects, but also to the more wide-ranging, global impact of the technology in competition with other approaches to good health

care. Second, they should examine the development of regenerative medicine and on its impact on our understanding of tissues, organs, and bodies. Third, bioethics should consider the various ways regenerative medicine might be used. In one of its forms, regenerative medicine will most probably affect many of us, and so it is important that it does not remain under bioethics' radar.

Leen Trommelmans *currently teaches ethics and philosophy to nursing, midwifery, and facility management students at KaHO Sint-Lieven in Belgium. She also does research at the Centre for Biomedical Ethics and Law at K.U. Leuven. She is involved in translating fundamental ethics research into nursing education, investigating how the gap between academia and bedside nursing can be bridged. She is equally involved in building bridges between the regenerative medicine community and the ethics community. Both activities derive from the discovery of a growing need to integrate high-tech scientific innovations, ethics, and the practice of nursing and medicine in order to provide better care for vulnerable patients with the increasing globalization of medicine in mind.*

1. R. de Vries et al., "Ethical Aspects of Tissue Engineering: A Review," *Tissue Engineering, Part B* 14 (2008): 367-75.

2. Committee for Advanced Therapies et al., "Challenges with Advanced Therapy Medicinal Products and How to Meet Them," *Nature Review Drug Discovery* 3 (2010): 195-201.

3. H. McAteer et al., "Cost-Effectiveness Analysis at the Development Phase of a Potential Health Technology: Examples Based on Tissue Engineering of Bladder and Urethra," *Journal of Tissue Engineering and Regenerative Medicine* 5 (2007): 343-49.

4. V. Glaser, "Interview with Prof. Dr. Augustinus Bader," *Rejuvenation Research* 13 (2010), 489-92.

Statement of Ownership, Management, and Circulation

The *Hastings Center Report* is a bimonthly journal published by The Hastings Center, 21 Malcolm Gordon Road, Garrison, NY 10524. The editor is Gregory Kaebnick, at the same address. The annual subscription price is $76; contact person is Anne Marie Schoonhoven; telephone number is 845-424-4040. The tax status of the organization has not changed during the preceding twelve months.

As of the filing date of October 15, 2010, the average number of copies of each issue during the preceding twelve months was 3,633; the actual number of copies of the single issue published nearest to the filing date was 3,550. The journal has a total paid and/or requested circulation of 3,047 (average) and 2,922 (actual, most recent issue). The average free distribution for the twelve months preceding the filing date was fifty (average) and fifty (actual, most recent issue). The total average distribution was 3,097; the actual distribution of the single issue published nearest to the filing date was 2,972.

This information is reported on U.S. Postal Service Form 3526 and here as required by 39 USC 3685.