Human cells and tissues: the need for a global ethical framework

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There is a distinct difference between tissue and organ donation, although it is usually not well perceived by the public. Solid organs (e.g. kidney, liver and heart) can be taken only from donors who are brain-dead and on life support or immediately after irreversible cardio-respiratory arrest. Organs have to be transported quickly from donor to recipient and are not, or only slightly, processed. Their procurement is generally controlled by surgeons in transplant hospitals and allocation is usually coordinated by national or regional organizations. In contrast, human cells and tissues (e.g. bone, skin and heart valves) may come from live organ donors but more usually come from deceased donors in hospitals, morgues or even funeral homes. These cells and tissues are often transformed and stored, sometimes for years, in "tissue establishments" from which they can be distributed across the world. Tissue brokers, processors and distributors steer the allocation of the resulting human cells, tissues, cellular and tissue-based products.

In the past 10 years, there has been intensive interest and growth in the field of tissue transplantation. From this sudden growth arise some ethical issues, due to the attractive market value of harvesting replacement parts such as bone, skin and heart valves (not including solid organs) from one body, estimated at 230 000 United States dollars (US$).[1] In the year 2000, the media accused some tissue establishments in the United States of America (USA) of misleading an unsuspecting public into donating tissues while filling their pockets, and those of their investors, with money. Incidents involving non-consented procurement, inadequate testing, inaccurate or false donor files, irresponsible allocations and illegal trafficking of human cells, tissues and products were reported. Although these incidents were not representative of the entire tissue banking community, they drew public attention to some fraudulent and/or unethical practices, which resulted in a United States Senate hearing,[1] investigations, lawsuits, convictions and the resignation of transplant officials. The downside of these scandals was that they impacted on people's decision to donate.

In the USA and the European Union, it is illegal to buy and sell human organs, cells and tissues, but tissue establishments are allowed to charge "reasonable fees" for processing (from procurement to implantation). Unfortunately, the term "reasonable fee" has not been determined and it is clear that some opportunistic tissue establishments and brokers are using this loophole to make large profits.

This field is becoming much more complex with technical advances and extensive commercialization, which could lead to "cherry picking" practices and might influence decisions on processing. The interests of the general public are not necessarily the same as those of the tissue banks, which can choose either to maximize profit or to send tissue to processors that produce less lucrative, but medically important, grafts. Human donor skin and its derivatives, for example, were originally intended for use in severely burned patients, patients with chronic wounds or in reconstructive surgery, but plastic surgeons in beauty clinics have found an "off-label" use for these products in vanity procedures such as penis widening or lip enhancement. Dermal matrix derived from human donor skin is worth four times more when it is tailored into products for reconstructive or cosmetic procedures than if it is used in burn wound surgery (Table 1).

Corporate tissue establishments have not only raised the bar on tissue processing techniques, they have also introduced business techniques like marketing, patenting and advertising into the field. Sales representatives influence the prescribing habits of physicians with benefits such as gifts, free meals, "educational" trips or prestigious board appointments. Since the introduction of such business practices, tissue establishments have started to process human cells and tissues into products such as cubes, screws, paste, glue, sheets, powder or suspensions, which are advertised in glossy catalogues as if they were commodities. Scientific evidence to justify their use is rarely indicated.

An examination of consent-related issues in tissue banking by the Office of Inspector General of the United States Department of Health and Human Services revealed that donor families expect their donations to be treated with respect and recognized as coming from a human, as well as to represent the best option for recipients.[5] Tissue establishments have a responsibility towards the donor and donor families and should thus process donated tissues in a manner consistent with the intent of the donor, i.e. into products that fulfil medical needs, crucial research or medical education.[5]

Unfortunately, donor families are often not given adequate information concerning the ultimate use of the tissues and the profit made on them. Some argue that if families knew that their donation was going to be transformed into penis- and lip-fillers, they would oppose the donation. But, if the information meets the expectations of the donor family, why should full (public) disclosure lead to a decrease in donors?

Free organ, cell and tissue donation is meant to avoid conflicts of interest for

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Table 1. **Comparison of prices for human cell and tissue products: Belgium (2010) and United States of America (2000)**

Human cell and tissue product	Belgium – mainly hospital-based tissue establishments and reimbursement system (Euros)[a]	United States of America – free market with corporate tissue establishments (US$)[b]
Skin of one donor (5 000 cm^2), processed into dermal matrix for burn surgery	6 300	30 000[2]
Skin of one donor, processed into collagen suspensions for cosmetic procedures	No reimbursement	36 000[2]
Skin of one donor, processed into dermal matrix for plastic surgery	6 300	120 000[2]
Keratinocyte culture (150 cm^2)	869	2 475[3]
Heart valve	3 547	7 000[4]
Femoral vein (25 cm)	482	3 500[4]
Saphenous vein (25 cm)	482	3 500[4]
Cornea	1 245	3 000[4]
Sclera (4 fragments)	350	1 000[4]
Pelvis (half)	2 069	10 000[4]
Femur head	311	900[4]
Hip socket	1 293	1 200[4]
Femur (> 25 cm)	1 552	3 380[4]
Humerus (> 25 cm)	1 552	3 310[9]
Tibia (> 25 cm)	1 552	5 500[4]
Radius (10–25 cm)	1 293	1 950[4]
Ulna (10–25 cm)	1 293	1 880[4]
Knee cartilage	1 810	7 000[4]
Patella	311	525[4]
Powdered bone	233 (> 3 cm^3)	5 000 (100 cm^3)[4]
Chondrocyte culture (one application)	2 069	10 000[4]
Quadriceps tendon	1 035	2 000[4]
Patella tendon	1 035	2 500[4]

[a] Prices are from 2010. They are indexed and published in a ministerial decree that also fixes the prices of lyophilization (€ 25.86 per tissue) and WHO approved prion- and virus-inactivation techniques (€ 103.44 per tissue).
[b] Prices are from 2000 when € 1 was roughly equivalent to US$ 1.

the next-of-kin, the risk of exploitation of the most underprivileged who might donate for financial reasons, and should decrease the risk of false or inaccurate screening of potential donors. In comparison to the well known trafficking in solid organs (e.g. kidneys), the poorest countries are the ones most likely to sell human cells and tissues to profiteers, who distribute them in high-income countries or in private clinics in emerging countries. While tissue establishments in the USA do not export tissue types in short supply (e.g. skin for burns),[6] some low-income countries are known to export tissue without supplying their own country's needs first. Should low-income countries become the source of human raw materials for high-income countries?

Even within high-income countries, sophisticated human cell and tissue products are bound to generate inequities and abuses. Despite high hopes, tissue engineering and stem cell therapy are still in infancy with only a handful of successful clinical applications. Many so called "advanced therapies" that have never been validated through serious clinical trials are advertised, in particular on the internet, targeting wealthy patients in search of hope. Unscrupulous individuals are eager to exploit the vulnerability of desperate and misinformed patients, who are willing to pay for scientifically uncertain and potentially dangerous therapies.

Commercial autologous cord blood banks are emerging worldwide. They take advantage of the vulnerability of new parents to urge them to store the cord blood (autologous stem cells, i.e. genetically similar) for "possible" future clinical use in their child, its siblings or family members, a service for which they charge very handsome fees. There are, however, no indications that these autologous stem cells will be more effective than allogenic stem cells (i.e. genetically different), which are stored in public cord blood banks and are accessible to all patients in need. Despite this, two to three times more autologous than allogenic units of cord blood are stored in the USA and, in some (emerging) countries, cord blood banks are almost exclusively private.[7] If future scientific research supported autologous cord blood storage, shouldn't this service be made accessible for everybody through public banks?

Tissue scandals prompted increased governmental oversight[1] and in 2004 the USA Food and Drug Administration issued rules for human cells and tissue products with a simple and clear objective: to ensure that they do not contain communicable disease agents and that their function and integrity are not impaired as a result of improper processing. That same year, the European Commission issued the European Union Cells and Tissue Directive, designed to assure high standards of quality and safety, to facilitate cross-border movements and to ensure their availability in the European Union. Unfortunately, the Maastricht Treaty (that led to the creation of the

European Union) did not mandate the European Commission to address ethical issues. Both regulations introduced a list of special requirements for human cells and tissue banking such as quality management systems and standards similar to good manufacturing practices.

Small "altruistic" hospital-based tissue banks cannot meet these expensive requirements. In the future, they may have to merge or they will be reduced to facades for corporate for-profit tissue establishments. Excessive efforts to generate benefits (eventually for shareholders) may supersede the public interest. If not appropriately understood and debated, this situation may compromise ethical values and result in clinically unsafe products, an increase in prices (Table 1), inequities in access to health care, a deterioration of the altruistic act of donation and ultimately in a decrease in the number of donors. Some say the public understands that we live in a for-profit society and merely wants the assurance that the transplantation system is fair. But, wouldn't it be more acceptable if reasonable profits were used to improve quality, safety and availability or were invested in meaningful research and development?

The current patchwork of regulations and lack of global uniformity of technical standards create opportunities for exploitation and allow unethical, profit-maximizing practices.

In the field of solid organ transplantation, ethical issues have been addressed with some success over the past few decades. It is now time for the tissue banking community to develop ethical tools in line with the rapid evolutions in the field. We feel that in addition to the *WHO guiding principles on human cell, tissue and organ transplantation*,[8] there is an urgent need for a binding ethical framework for human cell and tissue product transplantation that prohibits financial gain on the human body and its parts. This framework should: (i) define and limit the concept "reasonable processing fee"; (ii) implement structured and explicit allocation rules; (iii) require disclosure of the product's origin (i.e. an altruistic donation of human tissue); (iv) require donor-informed consent acknowledging all the potential uses of the donated human cells and tissues (including, if applicable, non-therapeutic use and commercialization); (v) implement fair and transparent exportation rules with an emphasis on self-sufficiency; (vi) give priority to the solidarity principle of public tissue establishments; (vii) require scientific proof of efficacy for cell and tissue products; and (viii) be enforced through civil penalties.

This may eventually be an outcome of the recently released Joint Council of Europe/United Nations study on trafficking in organs, tissues and cells and trafficking in human beings for the purpose of the removal of organs.[9] ■

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