される。また，20数名の移植コーディネーターしか所属していない日本臓器移植ネットワークで，全国の移植事例へのあっせん対応，医療機関の教育，ドナー家族の対応等がまかなえるはずも無く，これらの社会基盤整備を早急に実施する事は急務である。その中でも，統計的に評価のできるシステムを構築する事が現代の社会には重要であり，この概念からも世界的に通用するシステムとして評価されるのは，ドナーアクションデータベースを使用した，TPM教育である。

教育の水準や，教育者の質も評価されるので，当初は抵抗がある事は理解できるが，医療はすべて「患者様のため」である事を再認識し，国民に取って後悔の無い移植医療を提供する体制整備が急がれる。

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1) 本稿は，2008年11月23日に東京の六本木アカデミーヒルズで開催された第35回日本臓器保存生物医学会シンポジウム「ドネーションに関する欧米の相違――日本はどこを学ぶべきか――」において報告した原稿をもとに書き下ろしたものである。

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特集 わが国の小児臓器移植医療をいかに発展させるか 8

Key words
WHO Guiding Principle
イスタンブール宣言
小児救急医療体制
小児ドナー家族ケア

円滑な小児臓器移植医療の推進に向けて

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要旨

2009年7月に，参議院で臓器の移植に関する法律の一部改正案が可決成立し，2010年7月から施行される．世界的な標準である家族による承諾で，提供者本人の書面による意思表示が必要なくなり，また，15歳未満の小児の臓器提供が可能となる．この流れが世界的にみてどのようなものであったか．また，本特集の中から浮かび上がる施行に向けた問題点について言及する．

はじめに

1950年代に開始された臓器移植が，免疫抑制薬の発達に伴い技術的にも手術のみならず，術後管理の充実とともに，臨床成績も向上してきた．1980年代に入り，先進国での生活習慣病などによる腎不全を中心とする患者急増の影で臓器売買が横行し，1987年のWHO総会（WHA）にて，臓器移植のガイドラインを作成すべきとの決議が採択された．4年間の議論を経て，1991年にWHO移植ガイドライン“Guiding Principles on Transplantation”（WHA42.5）が作成された．

この議論の間にも多くの国々で「臓器移植法」が成立し（**表1**），わが国でも1997年に「臓器の移植に関する法律」（法律第104号）が国会で可決成立し，翌年施行されたことは，世界的な動向からみれば妥当であったと思われる．しかしながら，脳死下での臓器提供には，本人の書面による意思表示が義務化され，さらに15歳未満の書面による意思表示が，遺言書での有効年齢が15歳以上であるとの法的引用により認めないとする，国際的にも稀有な法律となった．そのために臓器提供者は非常に少数で，当然の結果として海外に移植を求める患者も後を絶たず，また，小児患者では現行法施行の1997年以降，100名を超える渡航移植が実施された．その間にも，臓器不全となったほとんどの小児は，国内でその短い命を絶つこととなった．

1991年のWHOガイドライン制定後も，国際的にも臓器売買が横行し，発展途上国では臓器ドナーとして小児の誘拐や，また，フィリピンのように金銭を求めた臓器提供が国際問題となり，WHAでは2003年5月に，移植ガイドラインの改正を決議した．

I WHOを中心とした国際的な流れ

2003年のWHAで，歯止めのかからない臓器売買を規制し，各国の自助努力を促すために，ガイドライン改正を行うことが決議され，同年10月6〜9日に，スペイン政府とWHOとの共

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表1　欧州各国の法整備状況

国名	法律名	制定年	死の定義
スペイン	Sobre extraccion y transplante de organos	1979	脳死（全脳死）
ベルギー	Wet betreffende het wegnemen en transplanteren van organen	1986	最新の科学による（法による規定はない）
ポルトガル	Portugal Transplant Law	1993	脳死（脳幹死）
フランス	Bioethics Acts	1994	脳死（全脳死）
フィンランド	Act on the removal of human organs and tissues for medical use	1985	脳死（脳幹死）
イギリス	Human Organ Transplant Act	1989	脳死（脳幹死）
ドイツ	German Transplant Law	1997	脳死（全脳死）
スイス	canton により異なる 法律のない canton もある	さまざま	脳死（脳幹死）および心臓死

（瓜生原葉子ほか：移植 2004；39：145-162 より改変）

同で「マドリッド予備会議」が開催された．厚生労働省健康局疾病対策課臓器移植対策室，日本移植学会，国立感染症研究所からの担当者とともに参加し，現状把握と問題点の抽出が行われた．この席で米国の人権擁護団体が実施した調査から，わが国をはじめ，米国，カナダの患者が，発展途上国で臓器移植を受けている事実が公表された．また，生体間移植の増加や挑戦的な異種移植による弊害なども同時に訴え，2004年1月のWHO執行理事会にitem 3.17として「マドリッドレポート」が提出され，同年5月のWHAで移植課の設置が決定された．

2009年のWHAでの決議を目標に，世界各地でさまざまな観点からの会議が開催された．WHOの各地域支部での政府担当者会議や（2007年のWPROマニラ会議等），細胞・組織の専門家による会議（2006年のオタワ会議等），さらには国際倫理を検討するBioethics，Medical Ethics会議（2006年のチューリッヒ会議等）などとともに，WHOでは適切な移植推進のための「World Day on Transplantation」（世界移植デー）を2005年にジュネーブでの第1回会議を皮切りに現在までに5回開催されている．

さらに，WHO移植課のAdvisory Panelとして，国際移植学会（TTS）が公式に参加したことが，今回の改正に関して大きな転換点となった．

Ⅱ 国際移植学会の動き

1991年のWHOガイドラインでも，臓器売買の禁止や生体間移植は死体からの移植の補助的な医療であるとの記載はあるものの，実質的にそれらの抑制にはならず，逆に増加傾向にあることが問題となった今回の改正の動きの中で，移植医療の現場に直結するTTSが，今回の改正に関して実効的な役割を示した．特筆すべきは，フィリピン政府の腎臓買取問題での政府との直接交渉により財団化を阻止した点，中国政府との交渉により死刑囚ドナーの臓器を外国人に移植することを禁止する法制化に成功した点，中東との交渉により臓器売買を阻止した点などが挙げられる．

さらに，これらの世界情勢を踏まえ，2008年4月30日～5月2日には，国際腎臓学会（ISN）とWHOの共同で，Istanbul Summit on Organ

Trafficking and Transplant Tourism を開催し，世界 78 カ国から 152 名の参加により「イスタンブール宣言」(**表 2**) が採択された．この会議でも，国際倫理問題として日本が取り上げられ，外国人の臓器が何例日本人に移植され，また，何例の日本人の臓器が外国人に移植されたのかという質問や，国内法で小児の臓器提供を規制していながら，小児の渡航移植を認めている根拠は何か，という質問もあり，国際的な「非難」ともとれる発言があった．これらが日本国内で大きく報道されないことも，また，会議参加者としては当惑したことを記憶している．この「イスタンブール宣言」が，WHO ガイドラインの改正案の中に，Report by Secretariat として引用されたことも歴史的な事柄である．

国内の報道では，WHO が渡航移植を禁止するというニュアンスが目立ち，一般国民には WHO が法的拘束力をもつかのような誤解を生んだことも事実であるが，国際的な倫理要綱として唱えられたものであり，加盟各国政府に対しての自助努力を促すものであるという本来の WHO 指針を忘れてはならない．しかしわが国は法的な整備を行う国際的なプレッシャーもあり，2009 年の法改正に結びついたことも事実である．基本的に，小児の臓器提供を法で規制し，さらに海外での移植の道が閉ざされた場合には，国民の生存権に抵触するという重大な責任を国会が負うこととなるため，政治的にも改正せざるを得ない状況であったことは事実である．

臓器提供，臓器移植には必ず担保されなければならない，下記の「4 つの権利」がある．

1）臓器提供を，する権利
2）臓器提供を，しない権利
3）臓器移植を，受ける権利
4）臓器移植を，受けない権利

これらは国際倫理上も何度も検討され，前述のチューリッヒ会議でも話題となった．その中でも臓器提供を希望しないが，自身が臓器不全で臓器移植が必要な場合には臓器移植を受けたい，という場合の利己的行動を社会が阻止できるのかという話題も持ち上がった．倫理的には許されるものではないが，同時に両方の決断を迫られる場面はないとしてその評価は，現実的にはできないとされた．しかし，このような議論を，日本国内の国会でも学会でもあまり耳にしたことがないように記憶している．これらの本質的な議論も，国民に考えさせる教育，啓発も必要であると感じている．

Ⅲ 小児救急医療体制の整備

特集②の筆者からも指摘のあるように，本邦における小児救急医療体制の不備は，最近の報道でも目にすることが多くなっている．これまでの医療体制の中で，NICU は大学病院などの ICU に付属的に考えられていた医療機関も少なくなかったのではないだろうか．それも全国に 20 カ所程度，100 床との報告に驚きを隠せない．この体制の中で，小児からの臓器提供がどのようにして円滑に行われるのかという本特集のテーマを考えても，あまりのギャップに多くの問題点を列挙することしか考えられない．2003 年の段階で，小児科学会員の 82.3%が脳死を人の死と認めていたことも，72.6%の学会員が小児からの臓器移植が必要と考えていたことも，その当時の世情から鑑みれば先進的であったと感じている．しかし小児科学会員として，前述のような医療体制の中で，小児の生存権を含めて小児救急医療体制が整備され，最大の医療を提供できる状況を国策として行っていない状態で，総意としての決断は行えないというのは当然のことであったと感じている．さらには虐待児の問題も単なる識別だけでなく，国の制度としての予防策，さらには救済策が欧米並みに明確に運用されてこそ，上記の複雑な感情を払拭できるものである．

今回の改正法で，小児からの臓器提供が可能

表2 イスタンブール宣言（概要）

The Declaration of Istanbul
on Organ Trafficking and Transplant Tourism

Participants in the International Summit on Transplant Tourism and Organ Trafficking
convened by The Transplantation Society and International Society of Nephrology
in Istanbul, Turkey, April 30-May 2, 2008

Preamble

Organ transplantation, one of the medical miracles of the twentieth century, has prolonged and improved the lives of hundreds of thousands of patients worldwide. The many great scientific and clinical advances of dedicated health professionals, as well as countless acts of generosity by organ donors and their families, have made transplantation not only a life-saving therapy but a shining symbol of human solidarity. Yet these accomplishments have been tarnished by numerous reports of trafficking in human beings who are used as sources of organs and of patient-tourists from rich countries who travel abroad to purchase organs from poor people. In 2004, the World Health Organization, called on member states "to take measures to protect the poorest and vulnerable groups from transplant tourism and the sale of tissues and organs, including attention to the wider problem of international trafficking in human tissues and organs" (1).

To address the urgent and growing problems of organ sales, transplant tourism and trafficking in organ donors in the context of the global shortage of organs, a Summit Meeting of more than 150 representatives of scientific and medical bodies from around the world, government officials, social scientists, and ethicists, was held in Istanbul from April 30 to May 2, 2008. Preparatory work for the meeting was undertaken by a Steering Committee convened by The Transplantation Society (TTS) and the International Society of Nephrology (ISN) in Dubai in December 2007. That committee's draft declaration was widely circulated and then revised in light of the comments received. At the Summit, the revised draft was reviewed by working groups and finalized in plenary deliberations.

This Declaration represents the consensus of the Summit participants. All countries need a legal and professional framework to govern organ donation and transplantation activities, as well as a transparent regulatory oversight system that ensures donor and recipient safety and the enforcement of standards and prohibitions on unethical practices.

Unethical practices are, in part, an undesirable consequence of the global shortage of organs for transplantation. Thus, each country should strive both to ensure that programs to prevent organ failure are implemented and to provide organs to meet the transplant needs of its residents from donors within its own population or through regional cooperation. The therapeutic potential of deceased organ donation should be maximized not only for kidneys but also for other organs, appropriate to the transplantation needs of each country. Efforts to initiate or enhance deceased donor transplantation are essential to minimize the burden on living donors. Educational programs are useful in addressing the barriers, misconceptions and mistrust that currently impede the development of sufficient deceased donor transplantation ; successful transplant programs also depend on the existence of the relevant health system infrastructure.

Access to healthcare is a human right but often not a reality. The provision of care for living donors before, during and after surgery—as described in the reports of the international forums organized by TTS in Amsterdam and Vancouver (2-4)—is no less essential than taking care of the transplant recipient. A positive outcome for a recipient can never justify harm to a live donor ; on the contrary, for a transplant with a live donor to be regarded as a success means that both the recipient and the donor have done well.

This Declaration builds on the principles of the Universal Declaration of Human Rights (5). The broad representation at the Istanbul Summit reflects the importance of international collaboration and global consensus to improve donation and transplantation practices. The Declaration will be submitted to relevant professional organizations and to the health authorities of all countries for consideration. The legacy of transplantation must not be the impoverished victims of organ trafficking and transplant tourism but rather a celebration of the gift of health by one individual to another.

Definitions

Organ trafficking is the recruitment, transport, transfer, harboring or receipt of living or deceased persons or their organs by means of the threat or use of force or other forms of coercion, of abduction, of fraud, of deception, of the abuse of power or of a position of vulnerability, or of the giving to, or the receiving by, a third party of payments or benefits to achieve the transfer of control over the potential donor, for the purpose of exploitation by the removal of organs for transplantation (6).

Transplant commercialism is a policy or practice in which an organ is treated as a commodity, including by being bought or sold or used for material gain.

表2 つづき

Travel for transplantation is the movement of organs, donors, recipients or transplant professionals across jurisdictional borders for transplantation purposes. Travel for transplantation becomes **transplant tourism** if it involves organ trafficking and/or transplant commercialism or if the resources (organs, professionals and transplant centers) devoted to providing transplants to patients from outside a country undermine the country's ability to provide transplant services for its own population.

Principles

1. National governments, working in collaboration with international and non-governmental organizations, should develop and implement comprehensive programs for the screening, prevention and treatment of organ failure, which include:
   a. The advancement of clinical and basic science research;
   b. Effective programs, based on international guidelines, to treat and maintain patients with end-stage diseases, such as dialysis programs for renal patients, to minimize morbidity and mortality, alongside transplant programs for such diseases;
   c. Organ transplantation as the preferred treatment for organ failure for medically suitable recipients.
2. Legislation should be developed and implemented by each country or jurisdiction to govern the recovery of organs from deceased and living donors and the practice of transplantation, consistent with international standards.
   a. Policies and procedures should be developed and implemented to maximize the number of organs available for transplantation, consistent with these principles;
   b. The practice of donation and transplantation requires oversight and accountability by health authorities in each country to ensure transparency and safety;
   c. Oversight requires a national or regional registry to record deceased and living donor transplants;
   d. Key components of effective programs include public education and awareness, health professional education and training, and defined responsibilities and accountabilities for all stakeholders in the national organ donation and transplant system.
3. Organs for transplantation should be equitably allocated within countries or jurisdictions to suitable recipients without regard to gender, ethnicity, religion, or social or financial status.
   a. Financial considerations or material gain of any party must not influence the application of relevant allocation rules.
4. The primary objective of transplant policies and programs should be optimal short- and long-term medical care to promote the health of both donors and recipients.
   a. Financial considerations or material gain of any party must not override primary consideration for the health and well-being of donors and recipients.
5. Jurisdictions, countries and regions should strive to achieve self-sufficiency in organ donation by providing a sufficient number of organs for residents in need from within the country or through regional cooperation.
   a. Collaboration between countries is not inconsistent with national self- sufficiency as long as the collaboration protects the vulnerable, promotes equality between donor and recipient populations, and does not violate these principles;
   b. Treatment of patients from outside the country or jurisdiction is only acceptable if it does not undermine a country's ability to provide transplant services for its own population.
6. Organ trafficking and transplant tourism violate the principles of equity, justice and respect for human dignity and should be prohibited. Because transplant commercialism targets impoverished and otherwise vulnerable donors, it leads inexorably to inequity and injustice and should be prohibited. In Resolution 44. 25, the World Health Assembly called on countries to prevent the purchase and sale of human organs for transplantation.
   a. Prohibitions on these practices should include a ban on all types of advertising (including electronic and print media), soliciting, or brokering for the purpose of transplant commercialism, organ trafficking, or transplant tourism.
   b. Such prohibitions should also include penalties for acts—such as medically screening donors or organs, or transplanting organs—that aid, encourage, or use the products of, organ trafficking or transplant tourism.
   c. Practices that induce vulnerable individuals or groups (such as illiterate and impoverished persons, undocumented immigrants, prisoners, and political or economic refugees) to become living donors are incompatible with the aim of combating organ trafficking, transplant tourism and transplant commercialism.

となるのであれば，さらにこの点に関しても国策として，小児救急医療体制整備を実施する義務があるのは当然であり，これは臓器移植以前の国民の必要とする医療体制整備である．また，外科学的な側面のみならず，精神科学的な面からも，小児の救急時に対する家族のケアも，臓器移植とは関係なく十分に整備されてこそ，現実的な臓器提供が可能となるべきである．

家族の死（family loss）に関する心理学的研究も，とくに小児の死に関して家族が通過するその経路に関して，精神科学的な疾患に陥ることを防ぐための研究や，その対応体制が十分に整っているとは言い難い．とくに臓器提供がその上に発生する場合に，ドナー家族のケアとして，この点を考慮してグリーフケアが実践できる移植コーディネーターによる家族ケアは不可欠となる．特集⑥の項では，日本臓器移植ネットワークの移植コーディネーター教育として，このような体制整備に向けた習熟を期する教育体制が示されているが，過去の研究内容をみても，家族ごとの個別化や急性反応を示す母親の影で「忘れ去られた，遺族」として，将来的に重症化している父親の存在などにも，欧米の研究のみでなく，わが国独自の文化的要素を考慮した研究，それらの結果を踏まえた教育，研修体制の整備も必要である．

おわりに

これらの多くの問題を抱えている中，本改正法は2010年7月17日に施行される．十分な医療体制が整備された一部の医療機関に，初期の症例を期待する声も聞かれるが，小児の臓器不全患者への新たな希望の道が開かれる．その道は前途多難であることは明白である．さまざまな問題が生じる可能性は否定できないが，移植技術の医学的な発展とともに，忘れてならないのは，そのためには必ずドナーが存在し，また，その家族がいることである．小児救急医療体制がさらに充実し，最高の医療水準が確保されることこそが，万が一の際に家族も納得のゆく医療を受けられたことになるであろう．その上で，これらの家族の精神的なケアが行え，さらに臓器提供となった際も，その後も，対応できる体制と水準を整備することこそが，小児との死別という人生でもっとも過酷ともいえる状況下で，少なくとも臓器提供に関して，「後悔」のない状況が作れるものと考える．小児臓器不全の患者，およびその家族への希望の道を閉ざさないためにも，公平，かつ公正な医療として，小児臓器移植がわが国の医療として定着することを祈念する．

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お知らせ

第9回　NSTわからん会

日　　時：平成22年8月7日（土）13：00～17：00
場　　所：大阪樟蔭女子大学　小阪キャンパス（401教室）
最寄駅：近鉄奈良線「河内小阪」駅下車徒歩5分
テ ー マ：「Direct PEJか？　それともPTEG？」（仮題）
症例提示：東邦大学医療センター大森病院チーム（代表者：鷲澤　尚宏　東邦大学医療センター大森病院栄養サポートチームディレクター）

第5回　NSTわからん会（東京版）

日　　時：平成22年9月19日（日）13：00～17：00
場　　所：昭和大学（上條講堂）
最寄駅：東急大井町線・池上線「旗の台駅」下車徒歩5分
テ ー マ：「呼吸不全で人工呼吸器装着患者の栄養管理」
症例提示：市立岸和田市民病院チーム（代表者：加藤　裕子　市立岸和田市民病院看護局）

※以下の要項は第9回，第5回（東京版）ともに共通です．
対 象 者：医師・看護師・薬剤師・栄養士・その他の医療関係者（学生を含む）
参 加 費：1,000円（当日徴収）　学生無料（学生証の提示必要）
※必携品：当日，計算機を使用しますので，各自で御持参ください．
申し込み：別途申込用紙に氏名・所属・職種・連絡先を明記の上，①FAX：06-6723-8135または②http://nst-wakarankai.comの参加申込フォームよりお申込み下さい．
問合せ先：NSTわからん会事務局（大阪樟蔭女子大学大学院）
藤本　素子
TEL　06-6723-8135
E-Mail：jimu@nst-wakarankai.com
代表世話人：山東　勤弥
世 話 人：大石　雅子，加藤　裕子，佐々木　雅也，幣　憲一郎，東海林　徹，立花　貞信，土岐　彰，福原　真美，保木　昌徳，丸山　道生，宮澤　　靖，吉田　理香，鷲澤　尚宏

2.<オピニオン>

(1)「イスタンブール宣言以降の組織の取り扱い」

東京歯科大学　市川総合病院　角膜センター
WHO 移植課　Expert Advisory Panel センター長
篠崎　尚史

1960 年代に免疫抑制剤の普及とともに臓器移植の重要性が浸透し、80 年代には臓器不全の患者数の増大と供に発展途上国における臓器売買や渡航移植が問題となってきた。更には生体間移植にも歯止めがかからず、1985 年の WHO で、臓器移植におけるガイドラインの制定が可決され、1991 年に"Guiding Principles on Transplantation"が発行された。

この WHO の動きは、80 年代後半から 90 年代に多くの国々で世界的な臓器移植に関する法整備に貢献した。我が国においても 1996 年に国会で「臓器の移植に関する法律」が可決成立し翌 1997 年に施行された。

しかしながら、90 年代に入っても臓器不全患者数は、生活習慣病の増大や発展途上国での医療技術の発展に伴い爆発的増加を辿り、臓器提供者のリクルートは遅々として進まず生体間移植や臓器売買は WHO ガイドラインの存在にも関わらず、増加する結果となってしまった。2003 年 5 月の WHA で、臓器移植の現状調査を実施することが決議され、同年 10 月にスペイン政府の主催により、マドリッド予備会議が開催され、Madrid Report が翌 04 年の WHA に提出された。その席上、上記ガイドラインの改正が、2008 年 5 月の WHA までの 4 年間で行われることとなった。

ロワンポイント解説ロ

日本の移植医療への対応の遅れは、国際社会との隔たりを益々広げているようです。臓器の他にも組織・細胞のトレーサビリティーなどの国際化が求められます。

今回の改定のポイントは、これまで臓器移植を対象としていたが、今後、臓器・組織・細胞を対象とする点、また、単にガイドラインを提唱するだけでなく、国際移植学会(TTS)を中心に移植学会が国際的に参画し、実質的な施策を実行できる体制を取った点があげられる。その最大のアクションが、TTS と国際腎臓学会が共同で開催した、Istanbul Summit で提唱された、「イスタンブール宣言」である。

臓器売買は、従来より「悪」とされていたが、イスタンブール宣言では、渡航移植も「悪」とした点が大きな変更点である。倫理的に自国内で、最大のドナー獲得に向けた努力をすることなく、他国に依存することは国際的に許されない、とのメッセージを宣言したものである。国際通念として、WHO 加盟各国が、臓器移植に必要な臓器を自国内で提供できるよう、政府が認識すべ

きであるという認識である。

この解釈で注意しなければならない点が 2 つある。第一に、臓器移植でしか救えない個々の患者に対して、他国での加療を妨げるものではなく、患者が発生した国の政府に対して、自国内での治療が可能となる方策、努力を行うべきであるという警鐘を鳴らす事が目的である。第二に、対象は臓器移植における、臓器売買の禁止とドナー増加に向けた国レベルでの取組みを促すものであり、細胞、組織に関しては現状での国際的な sharing からみて対象としていない点である。

米国のアイバンク協会の統計でも、年間 9 万眼を超える献眼に対し国内での移植が 4 万 5 千件程度であり、1 万数千例の角膜は国際的に sharing されている。組織バンク協会でも数千例に及ぶ組織の国際 sharing が実施されており、細胞における国際的な数量に関しては総合的なデータ収集が実施されていない。

WHO では TTS のイスタンブール宣言を引用し、新型インフルエンザの影響で 1 年遅れとなった 2009 年 WHA にて、Guiding Principle on Transplantation を決議した。その中で、細胞・組織・臓器におけるトレーサビリティーの確保が義務付けられている。基礎研究に使用される細胞、組織は別として、臨床研究や移植医療、再生医療等に使用されるものに関しては、ドナーからレシピエントまでの登録制度とその検索機能、有害事象に対する surveillance & vigilance の確保が急務である。

日本移植学会では、厚生科研で登録事業の Web 化に関する事業を実施しており、平成 23 年度より組織移植も統合した事業化プロジェクトが開始される。また、2011 年 2 月には、イタリアの Bologna において、EU と WHO 合同の移植医療に関する surveillance & vigilance 会議が開始され、欧州においては有害事象発生時に即時警告が発報できるシステムに向けたシステム開発が開始される。

細胞・組織においても国際化の中でグローバルなデータ共有化が必要となり、現在、EU と米国でのコーディングが組織バンクやアイバンク協会で協議されている。このような環境下で、我が国のヒト由来医療材料や組織の取り扱いに関しても、世界基準で収集、解析できるシステムが必要である。更に、2006 年 6 月に、Zurich で開催された WHO Human Cell and Transplantation, An International Symposium on Ethics and Policy Issue でも議論となったヒト細胞、組織における倫理と規制に関する国際的な視野も、年々変化しており、多角的な視野に立った次世代の議論も必要であると感じている。現実にヒト細胞、組織を医療材料とした企業が世界で活動を開始しており、実際に治療効果も著しい発展を遂げている中で、従来の「移植」という概念では把握しきれない実情に、根本的な倫理性や国際レベルでの規制を議論、研究し導入することが我が国の医学の発展からも求められている。

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ORIGINAL PAPER

Coding and traceability for cells, tissues and organs for transplantation

D. Michael Strong · Naoshi Shinozaki

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Abstract Modern transplantation of cells, tissues and organs has been practiced within the last century achieving both life saving and enhancing results. Associated risks have been recognized including infectious disease transmission, malignancy, immune mediated disease and graft failure. This has resulted in establishment of government regulation, professional standard setting and establishment of vigilance and surveillance systems for early detection and prevention and to improve patient safety. The increased transportation of grafts across national boundaries has made traceability difficult and sometimes impossible. Experience during the first Gulf War with miss-identification of blood units coming from multiple countries without standardized coding and labeling has led international organizations to develop standardized nomenclature and coding for blood. Following this example, cell therapy and tissue transplant practitioners have also moved to standardization of coding systems. Establishment of an international coding system has progressed rapidly and implementation for blood has demonstrated multiple advantages. WHO has held two global consultations on human cells and tissues for transplantation, which recognized the global circulation of cells and tissues and growing commercialization and the need for means of coding to identify tissues and cells used in transplantation, are essential for full traceability. There is currently a wide diversity in the identification and coding of tissue and cell products. For tissues, with a few exceptions, product terminology has not been standardized even at the national level. Progress has been made in blood and cell therapies with a slow and steady trend towards implementation of the international code ISBT 128. Across all fields, there are now 3,700 licensed facilities in 66 countries. Efforts are necessary to encourage the introduction of a standardized international coding system for donation identification numbers, such as ISBT 128, for all donated biologic products.

Keywords Coding · Traceability · Tissues · Organs · Cells · Transplantation · ISBT 128

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Background

Development of cell, tissue and organ transplantation

The history of skin grafts has its beginnings in ancient India, where Sanskrit texts document skin transplants performed by Hindus in 3000–2500 BC (Herman 2002). The concept of transplantation of body parts from one individual to another can be found in paintings from the Middle Ages depicting the transplanting of a leg from an African donor to an Italian noble. Even grafting of animal bone to a human was described as early as 1668. The first clinical autograft was performed in Germany in 1820 and the first human bone allograft in 1880 in Scotland (DeBoer 1986). Eduard Zirm performed the first corneal transplant in Vienna, Austria in 1905, initiating this practice in ophthalmology (Moffat et al. 2005). Alexis Carrel is credited with the earliest studies on the storage of tissues and was prophetic in his predictions of the use of cadavers for organ and tissue donation. He was the first to transplant vascular tissues (Carel 1912) and was the recipient of a Nobel Prize.

The use of banked tissues in surgical procedures is credited to Albee who used both autologous and allogeneic-banked bone as early as 1910 (Albee 1912). The first eye bank opened in New York in 1944, marking the first organized attempt at banking donor tissue, facilitating the transfer of eye tissue from donor to recipient. It wasn't until the 1940s that bone banking became common practice, primarily with autologous grafts (Wilson 1947; Bush and Garber 1948). Established in 1961 by the American Academy of Ophthalmology's Committee on Eye Banks, the Eye Bank Association of America is the oldest national transplantation association, leading the transplant field with the establishment of medical standards for the procurement and distribution of eyes, comprehensive education programs for technicians, and accreditation of eye banks. Modern day tissue banking was initiated in the US Navy in 1949 and many of today's standards are due to their experience over several decades along with the establishment of the American Association of Tissue Banks (AATB) in 1976 (Strong 2000). By the early 1950s, tissue banks were also established in Europe. By 1971, the recognition that ionizing radiation was being used to sterilize tissue (non-ocular) engaged the International Atomic Energy Agency (IAEA), which sponsored an expert meeting in Hungary (Phillips and Strong 1997). Over the ensuing years, assistance was provided to developing countries in both Asia and South America and workshops, training programmes and educational materials were provided. Support for Tissue Banks was provided for: Argentina, Bangladesh, Brazil, Chile, China, Cuba, India, Indonesia, Republic of Korea, Malaysia, Pakistan, Philippines, Singapore, Sri Lanka, Thailand and Vietnam. In addition training scholarships were provided for individuals from these countries as well as participants from countries such as Algeria, Turkey, Hungary, Costa Rica, Peru, Mexico and Zambia to train in established tissue banks in Europe and the United States. As an example of the success of these programmes, the Sri Lanka Eye Donation Society had distributed over 33,000 corneas by the mid 1980s.

The early clinical success with bone and corneal transplants was due to the non-vascularized nature of such grafts. The use of organs was impeded until the recognition of the histocompatibility system, first described in 1951 (Billingham and Medawar 1951), which led to a Nobel Prize. Their work also led to the discovery of glycerol as a cryopreservative for skin thus opening the possibilities for skin banking for the treatment of burns. Dr Joseph Murray performed the first successful kidney transplant, between identical twins, in 1954, which also led to a Nobel Prize and the advent of solid organ transplantation (Guild et al. 1955). Dr Murray shared the Prize with Dr E. Donnell Thomas who was instrumental in advancing the field of bone marrow transplantation (Thomas et al. 1957). Both the solid organ and stem cell transplantation fields have been able to progress due to advances in immunosuppressive drugs and histocompatibilty matching. Establishment of organ sharing networks in developed countries such as the United Network for Organ Sharing in the U.S. and Eurotransplant for some countries in Europe, along with registries for unrelated stem cell transplants such as the Anthony Nolan Trust in the United Kingdom, OneMatch in Canada and the National Marrow Donor Program in the U.S. have expanded the scope and ability to share these valuable resources worldwide.

Advances in healthcare technologies have led to an increasing number and wider array of tissues of human origin being collected to sustain and improve the quality of life. Solid organs, corneas and eye tissues, including sclera, bone, skin, and stem cells, are all examples of human tissues derived from living or deceased donors, otherwise known as allografts. In the United States in 2007, 28,000 organs, 50,000 corneas, 18,000 stem cell grafts and over two million tissue allografts were distributed. Despite the increase in numbers over time, demand often exceeds supply, particularly for solid organs. In the U.S., over 100,000 patients are on waiting lists for organ transplants. Efforts to increase the availability of these vital products generate challenges to monitor and ensure appropriate access and safety both in the domestic and global arenas since these products often cross national boundaries. Moreover, the lucrative nature of the selling of so-called "body parts" has generated unethical behavior. Recent scandals such as the trafficking of solid organs sold from Israel to New York (Feyerick 2009) and the alleged theft of tissues from Ukraine (Keller and Grill 2009) have generated much interest in the press and exemplify the global nature of the problem (Chaney 2006). In addition to importation of organs and tissues, patients are traveling abroad to receive organ transplants and thus the risk of importing new diseases in immunosuppressed recipients is amplified.

Noting the global increase in allogeneic transplantation of cells, tissues and organs, the World Health Organization (WHO) urged member states:

To implement effective national oversight of procurement, processing and transplantation of human cells, tissues and organs, including ensuring accountability for human material for transplantation and traceability.

To cooperate in the formulation of recommendations and guidelines to harmonize global practices in the procurement, processing and transplantation of human cells, tissues and organs, including development of minimum criteria for suitability of donors of tissues and cells.

To consider setting up ethics commissions to ensure the ethics of cell, tissue and organ transplantation.

To extend the use of living kidney donations when possible, in addition to donations from deceased donors.

To take measures to protect the poorest and vulnerable groups from "transplant tourism" and the sale of tissues and organs, including attention to the wider problem of international trafficking in human tissues and organs (WHO 2006).

Risks associated with cells, tissues and organs

The transmission of infections or malignancies to recipients of solid organs, tissues, and eye grafts is well documented (Fishman 2007; Eastlund and Strong 2004; Trotter 2008; Tugwell et al. 2005; Gandhi and Strong 2007). Infectious pathogens can include viruses, bacteria, parasites and prions. The risks of amplification of transmission increase when there are multiple recipients from a common donor since as many as 100 tissues and organs can be recovered from a single donor. Due to the organ shortage in particular, donors with known high-risk behavior are sometimes accepted for organ transplantation which can result in multiple infectious risks (Ahn and Cohen 2008). Other adverse events can occur including malignancies, reactions to toxins, unexpected malfunction, adverse immunological responses and immune mediated disease transmissions and administrative errors.

In addition, the organ, tissue and eye banking communities function independently and communication between them is inconsistent and often lacking. This lack of a formal communication can result in an inability to track organs and tissues from a common donor. For example, a report in 2005 described a number of hepatitis C virus (HCV) transmissions to several organ and tissue recipients from a single donor. This case generated much publicity because there were 91 grafts produced from the donor (7 organs, 2 corneas and 82 other tissues), 44 transplants and 40 recipients in 16 states and 2 other countries over a period of 22 months. Three organ recipients were infected and 32 of the tissue recipients could be identified and tested of which 5 were HCV positive and infected. To date, no recipient of the transplanted eye tissue has seroconverted (thus, the recipients remain HCV negative). One tissue recipient could not be identified. All of the tissue recipient infections would have been prevented if recognition of infection in the organ recipients had resulted in notification of the tissue bank before tissue was processed or released. More than 6 months elapsed between recognition of the organ recipient

infections, donor linkage, and the time that tissue was processed (Tugwell et al. 2005). Events of this nature can only be avoided by the introduction of a comprehensive and unified traceability system covering all biologics derived from a single donor.

The recall of allograft tissues in the U.S. underscores the problem related to allograft safety. The FDA, between 1994 and June 2007, recalled 61,607 tissue allografts. The vast majority of these (59,476 or 96.5%) were musculoskeletal allografts (Mroz et al. 2008).

Biologic-based products or technologies are always likely to carry an inherent risk. While solid organs and some tissues such as the cornea cannot be altered to reduce infectivity, some tissue types can be processed with chemicals or radiation For instance, blood can be modified through leukocyte filtration or irradiation. However, no process can eliminate the risk of transmission. The role of patient safety efforts is to drive that risk to the lowest level reasonably achievable without unduly decreasing the availability of these life saving resources, so that the overall benefit outweighs risk. Risk must also be assessed using vigilance and surveillance programmes which to date have not been universally developed for tissues and cells and are insufficiently developed for organs through regional organ sharing programmes such as UNOS in the U.S. The U.S. does require mandatory reporting of infectious adverse reactions to the FDA by regulated establishments, and eye banks accredited by the EBAA comply with requirements to electronically report adverse reaction, including those due to biologic dysfunction. The successes of this reporting is made possible since eye banks typically distribute ocular tissue directly to the surgeon and identify the recipient prior to transplantation. A critical component of a biovigilance system is constructive feedback to ongoing analysis efforts. The World Health Organization (WHO) guideline on adverse event reporting emphasizes that the effectiveness of surveillance systems should be measured not only by transplant outcome data reporting and analysis but also by the use of such systems to improve patient safety through active response to data that are generated (WHO 2005).

Vigilance and surveillance of tissues and cells used in transplantation is a recent development all over the world. Biovigilance was established in France by a decree in 2003. The European Union Standards and Training for the Inspection of Tissue Establishments (EUSTITE) co-funded by the European Commission, is assisting member states by providing guidance documents and training in the areas of inspection and adverse event and reaction reporting. The project has developed vigilance and surveillance tools consistent with and complementary to those existing, such as hemovigilance systems, and under development globally. The Department of Essential Health Technologies at the WHO has led these efforts. A survey of member states conducted early in the project indicated that most countries did not have a system of vigilance in place for tissues and cells. In line with the requirements of the European Tissue and Cell Directives, almost all member states have now set up such systems. The EUSTITE vigilance tools have been piloted in 20 Member States during 2008/2009 and over 300 adverse events and reactions have been reported and assessed using the tools. These tools are able to objectively evaluate severity and imputability as well as impact assessment of adverse reactions and events. The key elements of the tools have been incorporated into guidance produced by the European Commission to member states for the compilation of their annual vigilance reports.

Challenges for traceability of cells, tissues and organs

During 2005, a report from the state of New York in the U.S. identified a serious problem with tissue recovery being done outside of all standards and regulations. It was discovered that a non-AATB accredited organization was recovering donors from funeral homes without the permission of families, without adequate medical screening, and were, in many cases, falsifying records. Tissue was sold to a number of tissue processing centres and distributed. Over 1,000 donors were recovered during a three-year period of time. Nearly 50,000 tissues were produced of which 15,000 could be recalled prior to transplantation. Over 25,000 tissues were distributed to unsuspecting patients without appropriate testing or medical review (Warren 2006). Because records from these donors had been forged, over 2,000 of these tissues were untraceable including 800 that had been distributed outside of the United States. The real concern however, is that even apart from these

unusual scandals, there is not a uniform system for tracking many tissues, with the exception of corneal tissue, or to detect adverse events from their use. In fact, most of the reported infectious transmissions from tissue transplants have included the inability to identify common recipients of tissues from the same donor (applicable to tissues, not eyes).

Voluntary standard setting organizations, such as the AATB and the European Association of Tissue Banks (EATB) in Europe, have published standards which require facilities that store and issue tissue, including tissue distribution intermediaries, to maintain an adverse reaction file, develop recall procedures and report adverse events and reactions to Tissue Banks. Tissue Banks are required to maintain adverse event policies and procedures including reports that must be reviewed by the Medical Director. Tissue Banks also include transplant records/implant cards with each allograft that is distributed. These records contain graft information. Hospitals are requested to return these records following transplants, although this is not required of healthcare facilities, unless accredited by the Joint Commission (TJC). Unfortunately, unless accredited by the TJC, compliance with returns cannot be enforced, which can hinder investigations and traceability. AATB also perform periodic surveys of its members to determine statistics concerning donation and distribution. These surveys have demonstrated that compliance with the return of transplant records ranges from 10 to 95% thus further emphasizing the difficulties with traceability.

In 1991, the Medical Advisory Board of the The Eye Bank Association of America (EBAA) instituted a requirement for its member eye banks to seek three to twelve month follow-up reporting of all cornea recipient outcomes. Their Adverse Reaction Registry System (OARRS) was redesigned in 2005 for online submissions of adverse reactions deemed "reasonably likely due to donor tissue." Through its Medical Advisory Board, OARRS submissions are reviewed and reported to EBAA members on a biannual basis. Eye banks employ a number of methods to seek the follow-up outcomes, including regular mailings to transplant surgeons, as well as providing institutions with adverse reaction reporting forms. Information submitted through OARRS includes a description of the adverse reaction, date of surgery, microbiology results, tissue mate status, data about the donor. EBAA requires its members to seek recipient information and outcomes as part of its accreditation process. With a limited number of non-stocked ocular tissues being distributed per donor, compliance is easier to attain for eye banks.

In response to increased recognition of fatal events due to diseases transmitted through organ transplantation, there are relatively new policies in place to require reporting of suspected disease transmission, that are in the process of implementation. In the US these efforts include the creation of a UNOS Disease Transmission Advisory Committee (DTAC) to facilitate and monitor reports of organ donor-derived practices for organ donors. These reports are required under new UNOS policy. A total of 97 reports of possible solid organ transplantation transmission were reported to federal authorities in 2007 alone, affecting a significant percentage of the recipients of over 28,000 organ transplantations annually. Recently an estimate of the scope of disease transmission has been roughly placed as involving approximately 1% of recipients (Ison et al. 2009).

The Center for International Blood and Marrow Transplant Research (CIBMTR) manages data on hematopoietic cellular therapies (HCT) through an affiliation with the International Bone Marrow Transplant Registry (IBMTR) of the Medical College of Wisconsin and the research arm of the National Marrow Donor Program (NMDP). IBMTR is a voluntary organization involving more than 400 transplant centers in 50 countries that have collaborated to share patient data and conduct scientific studies since 1972. They collect data from all U.S. stem cell transplants and from about 25% of the rest of the world. The NMDP was formally established in 1987 to provide unrelated donors for patients in need of HCT. Their network includes 164 transplant centers, 80 donor centers, 101 collection centers, 89 apheresis centers and 17 cord blood banks (CIBMTR Progress Report 2008). Data are collected annually on transplant recipients including follow-up information on previously reported patients and adverse reactions. Adverse events and reactions are also monitored at the local center level using a variety of center/hospital specific definitions.

In 2005 the Joint Commission (TJC) in the U.S. published standards relating to tissue storage and issuance. TJC accredits and certifies more than 15,000 health care organizations and programs in

the United States. One of the problems associated with the lack of traceability was the recognition that tissue is often dispersed among a variety of surgical services with no central management, unlike traceable blood and pharmaceuticals which are distributed within the hospital via licensed/accredited laboratories and pharmacies, and organs where the recipient is identified and recorded prior to the donation event, tissue are distributed and stored within surgical environments and can be mistaken and utilized as mere 'consumables'. Therefore the new standards require the assignment of responsibility for handling tissue within a hospital to a single coordinating entity. The oversight responsibility includes: supplier certification, incoming inspection and logging in of tissue, traceability and record keeping, storage temperature monitoring, investigation of adverse outcomes, reporting tissue-related infections to the tissue supplier, sequestering tissue reported by the supplier as contaminated, the notification of surgeons and recipients if tissue donors are subsequently found to harbor infection, and compliance with federal and state regulations if supplying tissues to any other facility. Although compliance with TJC standards is voluntary, most hospitals in the U.S. comply with TJC requirements in order to qualify for Medicare reimbursement, and the College of American Pathologists (CAP), the accrediting body of most hospital laboratories, has adopted similar requirements. In many cases, hospitals have turned to their blood bank where many of these capabilities are already in existence.

Professional Associations also responded to the problems of traceability by strengthening their standards and working to harmonize their standards with that of the TJC. The AABB (formerly the American Association of Blood Banks, both modified their standards as well as published a series of handbooks to assist hospital transfusion services to manage tissue (Eisenbrey and Eastlund 2008).

The increased recognition of issues related to traceability has also resulted in various governmental actions in addition to existing regulations. In June 2005, the U. S. Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), and Health Resources and Services Administration (HRSA) convened a workshop entitled "Preventing Organ and Tissue Allograft-Transmitted Infection: Priorities for Public Health Intervention." Attendees included members from blood, organ and tissue communities along with government representatives. This workshop identified gaps in organ and tissue safety in the United States (Fishman et al. 2009). Four areas for possible intervention were identified:

1. Communication among organ procurement organizations (OPOs), tissue banks, clinicians and public health agencies related to donors, samples and test results;
2. Tissue bank systems for tracking and notification of testing;
3. Hospital systems for tracking organs and tissues;
4. Recipient adverse event recognition. The workshop concluded that the most critical need was for development of a communication network for the tracking and reporting of disease transmissions for tissues and organs. Such a network would require a unique donor identifier linking organs and tissues, a tracking mechanism for all allografts, and processes for reporting of adverse events for the notification of clinicians, patients, and public health authorities.

As a result of the 2005 workshop, CDC published a Request for Proposal for the development of a "Sentinel Network for Detecting Emerging Infections Among Allograft Recipients" (Federal Register 2005). The United Network for Organ Sharing (UNOS) on behalf of an alliance including: The Association of Organ Procurement Organizations (AOPO); the AATB; the Eye Bank Association of America (EBAA); the American Society of Transplantation (AST); and the American Society of Transplant Surgeons (ASTS) submitted a proposal and entered into a cooperative agreement with CDC in 2006 to develop what was called the Transplantation Transmission Sentinel Network (TTSN). The purpose of the network was to provide a system for detecting emerging infections among allograft donors and recipients and aid healthcare personnel in detecting, communicating, tracking and preventing the transmission of infections.

A Transplantation Transmission Sentinel Network (TTSN) data base prototype was created by UNOS over a three-year cooperative agreement (and one-year extension) with CDC. A pilot study was carried out after development of a prototype, which led to a number of conclusions. Unfortunately, no additional

funding was available to take the system to production. TTSN was an important step forward in determining the needs for a national system integrating organ and tissue safety. Lessons learned included the need to create a partnership with two separate industry groups, the solid organ transplant community and tissue banking and user community. Building an adverse event system without a foundation of existing nomenclature or tracking for tissue allografts resulted in a daunting task to organize what is essentially a chaotic environment. The prototype proved that a system can be built, however, only with an impetus from legislation or regulation to track allograft use nationally and internationally. The lack of a uniform labeling standard in the U.S. and other countries, as exists for blood and blood products, may also contribute to the problems of tracking and traceability. The key to satisfying these requirements lies in standardization: globally unique identifiers for products, standardized terminology and a means to convey information electronically that is recognized by computer systems throughout the world.

Importation and exportation of cells, tissues and organs across national boundaries

In the previously reported Biomedical Tissue Services (BTS) scandal, there were more than 800 tissues that couldn't be traced outside the U.S. More than 25 hospitals in the United Kingdom alone reported receiving tissues from this case. The AATB reports that US tissue banks export tissue to more than 30 countries. A survey of the 5 largest US tissue banks demonstrated that from 2 to 8% of their distributions are international with major markets in: Korea, Turkey, Greece, Canada, the Middle East, Central American, South America, Australia and the EU. In Canada, over 90% of tissue transplanted is imported from the U.S. In the BTS recall, Health Canada was only able to provide approximate estimates of the number of recalled tissue products imported into Canada and was dependent on multiple tissue banks and tissue importers for tracing allografts to end users and notifying patients (Health Canada News Release 2005). The US FDA investigations in 1993 documented the legitimate importation of tissue by some US banks from Eastern Europe (Henkel 1994). The trafficking of solid organs sold from Israel to New York (Feyerick 2009) and the alleged theft of tissues from Ukraine (Keller and Grill 2009) are other examples of international trade. It is also worth noting that donated tissue may be from a non US source, processed in the US and issued in and out of the US, making traceability even more complex.

For cellular therapies, the Cellular Therapy Coding and Labeling Advisory Group began its work in 2004. Over 40% of unrelated bone marrow donations are transplanted in a country other than the one where they were donated. Unrelated cord blood donations are increasingly being exported around the world for stem cell replacement. This is a steady upward trend from just 30% in 1997. Recognizing the high proportion of grafts crossing national borders, the US FDA published in the Code of Federal Regulations (21CFR 1271.55), rules governing imports. These included that cells and tissues must have distinct identification codes that relate to the donor and to all records pertaining to the graft. Import and export regulations of cell therapy products are based on the FDA's risk based approach, recognizing the need for traceability.

Corneas are also exported on a large scale. The Eye Bank in Sri Lanka exports corneas to 65 countries and claims to have exported over 40,000 corneas since it's founding in 1964. It is common practice in the US to export corneas to Africa and South America where the need is great and the supply scarce. Over 10,000 corneas are exported from the US each year. The total numbers of cell, tissue and organ exports is not known since there is no central control or agency that captures this data.

Recognition of the need for global standardization

The need for globally unique identification

Blood Services have long recognized the need to ensure that each unit of blood can be individually identified in order to relate sample test results and cross matching outcomes to the correct unit, and to allow tracking from donor to recipient. Initially each blood center assigned its own numbers to the units it collected, and ensured uniqueness of identification within its organization and the transfusion services it served.

With the introduction of policies in some countries to share blood resources between blood centers in order to more effectively satisfy supply and demand,

a need was recognized for blood unit identification to be unique at a national level to prevent duplication of numbers in hospital transfusion laboratories. Without this capability, patient safety is at risk as exemplified by the common problem of misidentification of patients and wrong blood units being transfused, sometimes resulting in death.

The experience during the Persian Gulf War in 1990 and 1991 was the primary stimulus to solve the labeling and coding issues. Because the military contracted with many agencies to provide blood, the military experienced thousands of labeling mistakes resulting in misidentification of units (Blood Products Advisory Committee 1997). Additionally, during the 1990s it became increasingly common to establish centralized testing laboratories. When multiple blood centers submitted their samples to a single laboratory for testing, identifiers were often unique only within the context of the facility in which products were drawn. The International Society of Blood Transfusion (ISBT) established a Working Party, with international membership from multiple countries, which created a standardized means of labeling blood products so that identifiers were globally unique and bar codes (as well as other means of electronic information transfer) would have the same meaning internationally. The new coding system was named ISBT 128, the '128' in ISBT 128 comes from the barcode symbology which was selected at the time the standard was developed—this symbology is called Code 128, so the ISBT coding system using Code 128 bar codes became known as ISBT 128. This standard was formally approved in 1994.

Although the transfer of blood across national boundaries is not a common occurrence, the situation for cells and tissues is very different as has been indicated above. For this reason the case for globally unique identification is at least as strong as that for blood transfusion. A globally unique identification system is required, and this should extend across all biologic materials—blood, cells, tissues and organs.

Previous experience gained from managing adverse events and reactions has led to a widespread understanding of the need for traceability—the ability to track from donor to recipient and vice versa in order to ensure that all individuals associated with an event or reaction can be identified. Full traceability goes well beyond the single strand of information following the path of one product from donor to recipient, and becomes a complex web where multiple products are produced, pooled products are prepared, donors can make multiple donations of different biologic materials and multiple agencies can be involved in the procurement of organs and tissues. This web of information has multiple data owners, frequently extends across continents, and has to be retained for long periods of time (European Tissues and Cells Directive requires information to be stored for 30 years from the time of clinical use).

Retaining such large amounts of information for long periods in a format that allows rapid retrieval demands the use of computer data storage. In order to ensure a complete and secure information trail across the multiple computerized systems that may be involved, a means of uniquely identifying each donation, and each product prepared from that donation, is essential. It is clear that uniqueness of identification at national or regional level is not sufficient when cells, tissues and organs can and do travel worldwide.

WHO guiding principles

WHO has held 2 global consultations on human cells and tissues for transplantation, the first in Ottawa in December 2004 and the second in Geneva in June 2006, both of which resulted in reports. Participants recognized the significant global circulation of certain human tissues and cells and the substantial role-played by a commercial market in many of these tissue and cell products. Transparency in these activities is essential to ensure public support and understanding. A key element of oversight includes effective systems of vigilance and surveillance worldwide, which requires, as an essential prerequisite, a robust system for traceability of donated material from donor to recipient. WHO is participating in a EU funded project that is working to develop common systems for the reporting and management of adverse events and reactions (EUSTITE). The WHO has clearly stated its position concerning coding and traceability of cells, tissues and organs. At the Second Global Consultation on Regulatory Requirements for Human Cells and Tissues for Transplantation in 2006, the WHO published a statement that "As this globalization of cells and tissue transplantation develops, the need for common product names and definitions for unique product identification becomes essential".

The updated WHO Guiding Principles on Human Cell Tissue and Organ Transplantation as approved by the 124th Executive Board in resolution 124.R13 includes Guiding Principle 10 dedicated to the necessity of detailed assessment of transplantation procedures as well as of the outcome of transplanted human cells, tissues and organs. In the commentary of Guiding Principle 10 is the following sentence: "Internationally agreed means of coding to identify tissues and cells used in transplantation are essential for full traceability".

Work carried out during and after the two Global consultations has resulted in the development of two WHO Aide-Memoires specifying basic requirements in this field. The Aide-Mémoire on "Access to Safe and Effective Cells and Tissues for Transplantation" provides an overview for National Health Authorities, but also for all stakeholders, of all key aspects to be considered and requirements to be met for the setting up and/or the oversight of human cell and tissue transplantation services (WHO 2009).

European directive and CEN workshop

In 2004, a European Union Directive mandated a single coding system for cells and tissues [European Tissues and Cells DIRECTIVE 2004/23/EC (ECD)]. To this end, the European Committee for Standardization (or Comité Européen de Normalisation or CEN) evaluated various standardized coding systems for use within the European Union (CEN Workshop Agreement 2008). It was recognized that "...there are real problems with meaning-shift when using common terms between languages. For that reason many nomenclature schemes use a very rigid set of syntactical rules to ensure that the term being coded is capable of being interpreted faithfully in any language, whatever its real-world syntax and grammar". The report promoted ISBT 128 as the preferred option but they also proposed allowing member states to use two other variations (one with national ID numbers but ISBT 128 product descriptions and one without any internationally agreed component). They determined that one of the major benefits of ISBT 128 was that it could be used for four groups of biologics: blood, cells, tissues and organs. The CWA work analyzed existing relevant public activities at European, national, regional and international levels, and also considered relevant international activities. There were 3 candidates proposed by Member State (MS) and a panel recommended use of ISBT 128 as the basis for the EU coding scheme. Although it was considered a good match to requirements, it was not perfect in its current design. Further work was identified to meet the need for an additional component to be created to support both use of ISBT 128 and those organizations electing to retain existing coding schemes. This new component was temporarily named in the CEN report as the "key code". Because a donation event may result in tissues sent to different Tissue Establishments ICCBBA offered a new component, incorporating Country code, Responsible organization (e.g. Competent Authority) and Tissue Establishment, to be developed with the EU to meet international requirements. The Key Code would not invalidate existing ISBT 128 code structures but augment them. The "key code" could also be used with existing coding systems to provide unique identification and allow EU (potentially global) traceability of all materials from one donation event. Among the other CEN CWA conclusions were:

1. The ability to share coded data between different donor sectors in the future may help with risk prevention measures and provide clearer indications of donor suitability.
2. It may also reduce duplication and ensure better recall management.
3. It is feasible that with technological advances in regenerative medicine that the interfaces between blood, tissues, cells, and organs may become less defined.

The CEN solution supports the long-term migration to ISBT 128 whilst providing a short-term solution to unique identification through the use of the key code.

In transposing the EC Directive into national legislation, some countries (notably Poland and Austria) made the use of ISBT 128 for coding and labeling cells and tissues a legal obligation.

Mechanisms for providing globally unique identification

A number of mechanisms exist for providing globally unique identifiers, and in general when a large number of items have to be identified, they work on a layered principle. An overarching international

body assigns a portion of the identifier to reference an organization responsible for lower level assignment, and the sub-body assigns unique identifiers within its jurisdiction. Together the two parts provide a unique identification. An example is the telephone numbering system where a United Nations Agency, the International Telecommunications Union, assigns the 'country code' and the actual number of each telephone in the country is assigned by a 'national' body. (Although 'country code' is used in this context, it is not an exact match to country identification—for example the country code '1' covers both the USA and Canada.)

A similar mechanism is used by GS1, the supply chain standards body that maintains the GS1 standard used by many commercial organizations for bar coding their products. Using GS1, each type of product from a manufacturer can be uniquely identified using a Global Trade Item Number (GTIN). GS1 assigns one portion of the GTIN identifier to uniquely identify each manufacturer, and the manufacturer assigns the second portion to uniquely identify the type of product within their organization.

In the transfusion and transplantation field, ICCBBA uses a similar model by assigning a facility code to each organization that will assign ISBT 128 donation identification numbers (e.g. blood center, tissue establishment, competent authority) and the relevant organization assigning a sequence number.

In all the above cases the combination of the two elements provides a globally unique identification for the item or, in the case of tissues, the donation event.

The case for bar coding and electronic data transfer

Traceability depends not only on the use of unique identifiers, but also on the accurate transcription of those identifiers at all parts of the traceability chain. The risks of error during manual transcription of information are well documented, and in the blood transfusion field, which has some well-developed hemovigilance systems, cases of incorrect blood component transfused are a major source of adverse events, with administrative errors in identification forming a major cause of these. Use of electronic information capture provides a means of improving safety by eliminating the risk of manual transcription error, and speeding up the information transfer process.

Clearly not all countries have the necessary infrastructure to support the use of computerized systems throughout the transplant process, however where systems are available they should be used, and the ability to introduce such safety measures should not be impeded by the lack of bar coded information on the tissue product label. For this reason, any move towards adopting globally unique identification should be compatible with a well established standard coding system so that the progression towards automated data capture and computerized records can be achieved.

Coding systems

What is a coding system?

A coding system is a means by which distinct items within a system can be uniquely identified and consistently characterized to all participants within that system. It requires as a minimum a means to allocate identifiers in a manner that avoids duplication, and a standard reference for describing items.

The degree to which unique identification is required depends upon a number of factors. For a manufactured drug identification of the manufacturer and the unique lot number assigned by that manufacturer is sufficient to trace back to the manufacturing records for the batch. In this situation it is common to use a single identifier for all items in the batch. For donated biologics such as blood or tissue each donation has unique characteristics and is thus a 'batch' in its own right. In such cases there is a need for unique identification to be at the individual donation level, and for each product prepared from the donation to also be individually identified.

Uniqueness within a system requires that a boundary be defined to the system and controls need to be in place to ensure that the item does not travel outside the boundary. If, for example, the system is contained within a national boundary, then uniqueness at the national level is adequate, but as soon as an item travels beyond the boundary, the risk of duplication exists. For biologic products, which increasingly travel worldwide, global uniqueness is essential.

With the increasing use of computers, coding systems are commonly associated with information standards to allow the coding information to be electronically transmitted between computer systems.