はじめに

移植腎の管理をするためには，移植腎生検は必要な検査であるが，時として腎出血，腎血腫など重大な合併症を発症する恐れがある．今回我々は，移植腎生検後腎血腫を併発し，それによって急性腎不全におちいった2症例を経験したので報告する．

移植腎生検によって発症した血腫は，その容量が小さくても，腎被膜下や筋膜内において，移植腎を圧迫し腎血流が低下すると急性腎不全を併発してしまう．出血が増大してこない場合は，保存的に経過をみて血腫が吸収されるのをまったほうがよい場合と，あるいは今回の症例のように筋膜と腎被膜で囲まれたスペースでの出血においては，吸収される可能性が少ないため，早期に血腫除去術をするほうがよい場合とある．判断に難渋した場合，どのようにして治療方針を立てるべきか，文献的考察をまじえて報告する．

症例1

【症　例】19歳　男性

【主　訴】生体腎移植目的

【既往歴】【家族歴】特記すべきことなし

【透析歴】腹膜透析（CAPD）　9年

【現病歴】小学校のとき蛋白尿を指摘され，紫斑病性腎炎と診断され管理さたが，慢性腎不全となり10歳時よりCAPDに導入された．今回，母をドナーとし生体腎移植を目的に当院に入院となった．

入院時所見：身長150cm，（−3.0SD），体重43.5 kg，体温36.6℃，血圧115/68mmHg

脈拍：68/分 整，chest X-P；CTR49%と腎不全による成長障害を認めるのみであった．心エコー上は，EF67%，wall motion goodであった．

入院時検査所見：WBC4200/mm^3, RBC282×10^4/mm^3，Hb8.9g/dl，Ht25.7%，Plt26×10^4/mm^3

TP6.6g/dLI，Alb3.9g/dL，BUN53mg/dL，Cr

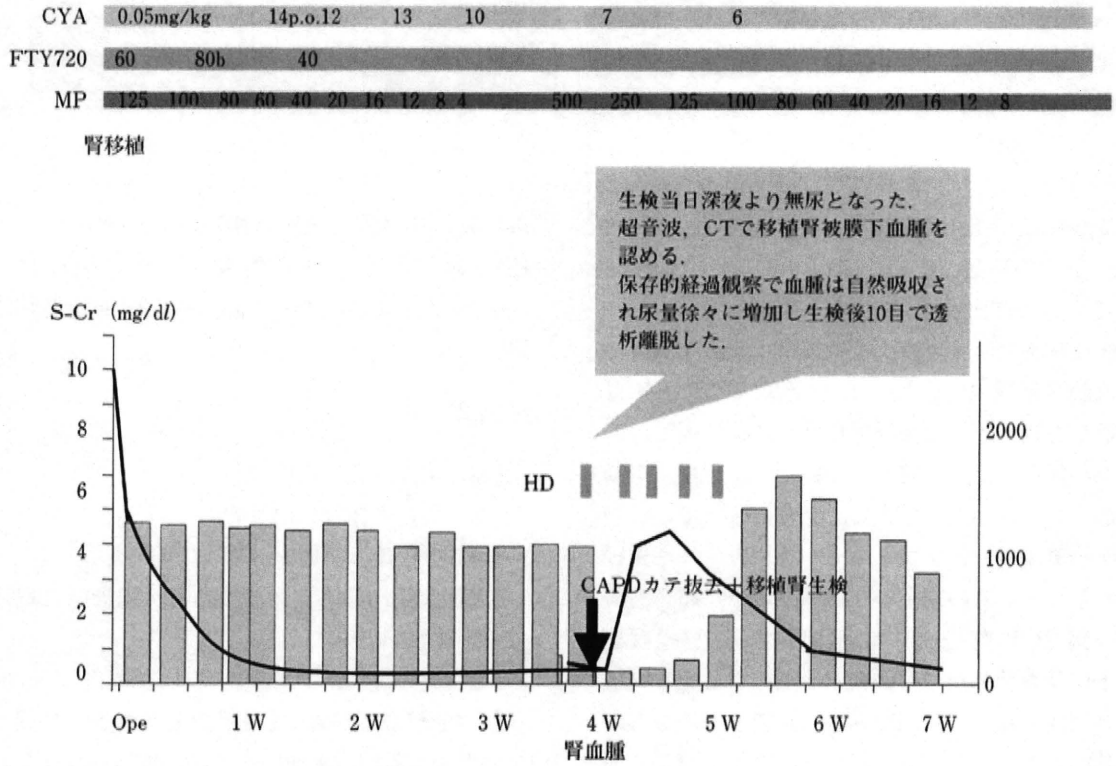

Fig. 1　移植後経過表
MP：metihylpredisolone,
CYA：cyclosporine，FK：tacrolimus

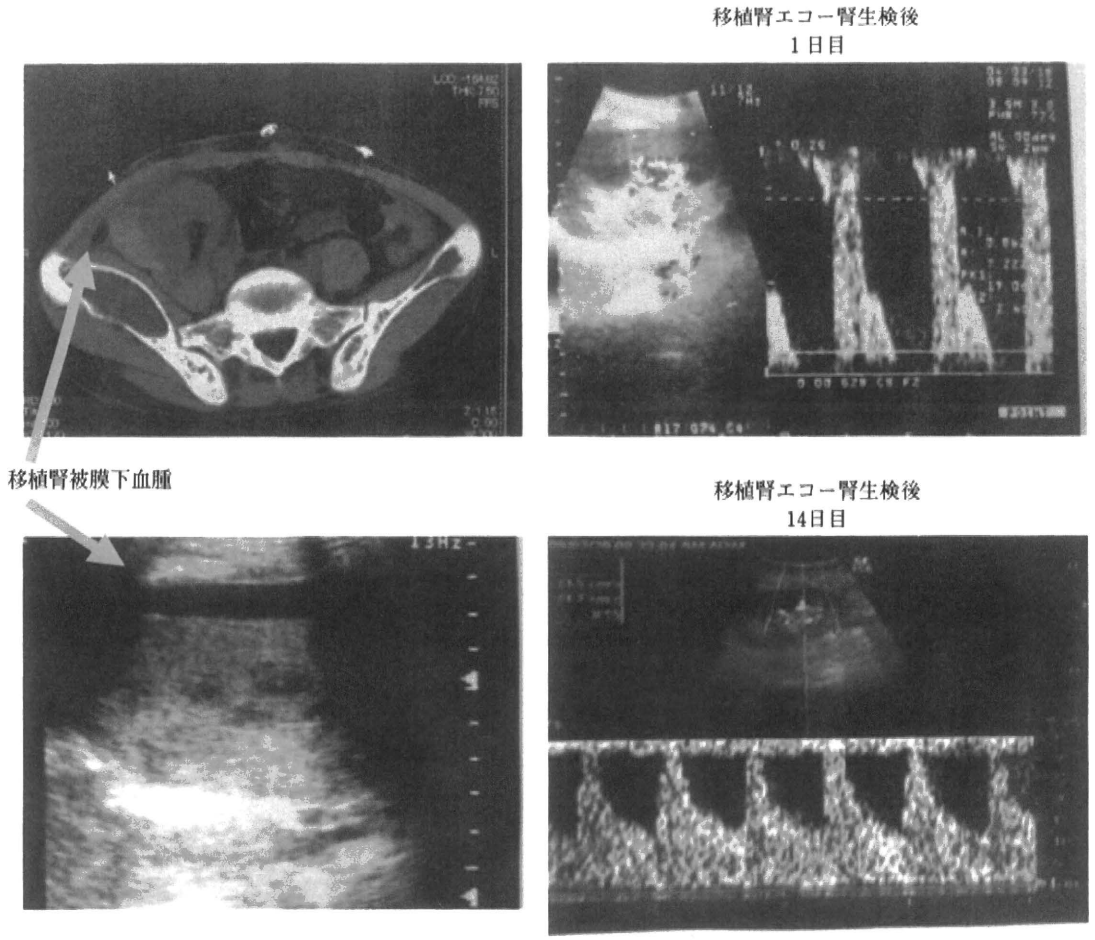

Fig. 2　症例1エコーCT所見

15.5mg/dL，Na139mEq/L，K4.1mEq/L，Cl 98 mEq/L，GOT16 IU/L，GPT 9 IU/L，LDH489 IU/L，γ-GTP24 IU/L，ALP308 IU/L

慢性腎不全所見以外，特に異常は認めなかった．

入院後経過（Fig. 1）；母をドナーとし生体腎移植を施行した．術後経過良好で，特に拒絶反応もなく経過した．退院前，移植後1ヶ月に，1週間前から抗凝固薬を中止し，全身麻酔下でCAPDカテーテル抜去とプロトコール移植腎生検を施行したところ，その夜半から無尿となり，超音波検査，緊急CT（Fig. 2）で移植腎後面に移植腎被膜下血腫を認めた．腎被膜下血腫による急性腎不全と判断したが，拒絶反応も否定できなかったのと移植腎の浮腫をとるためにステロイドパルス療法を開始し，血液透析（HD）を併用し保存的に経過を見ていたところ，その後血腫は拡大傾向なかった．10日程で血腫は吸収され，利尿を認めHDを離脱した．移植腎生検2週間後には，Cr1.2mg/dl，Ccr65.5mg/min，移植腎機能良好で退院となった．

症例2

【症　例】61歳　男性

【主　訴】生体腎移植目的

【家族歴】母：高血圧，姉；C型肝炎

【既往歴】2004年：2次性副甲状腺機能亢進症で副甲状腺摘出術

【透析歴】17年

【現病歴】22歳時，蛋白尿指摘されるも放置していた．34歳時，高血圧を認め，近医を受診した．慢性糸球体腎炎と診断され，保存的治療されるも慢性腎不全となり，44歳時よりHD導入された．

今回，妻をドナーとしAB（＋）→A（＋）のABO血液型不適合生体腎移植を目的に当院入院となった．

入院時所見：身長168.7cm，体重65.2kg，体温36.2℃，血圧120/67mmHg，脈拍68/分 整，chest X-P；CTR48%，心エコー：EF67%，wall motion goodと特に異常を認めなかった．

入院時検査所見：WBC7800/mm^3, RBC367×10^4/mm^3，Hb12.0g/dl，Ht35%，Plt725×10^4/mm^3，TP 6.2g/dLI，Alb3.5g/dL，BUN75mg/dL，Cr11.5 mg/dL，Na138mEq/L，K6.2mEq/L，Cl 98mEq/L，GOT 7 IU/L，GPT11 IU/L，LDH155 IU/L，γ-GTP34 IU/L，ALP108 IU/L

慢性腎不全所見以外，特に異常を認めなかった．

入院後経過（Fig. 3）：妻をドナーとし生体腎移植を施行した．移植後拒絶反応もなく経過良好であった．移植後1ヶ月半，1週間前から抗凝固薬を中止して，プロトコール生検を施行したが，その夜半から無尿となり，超音波検査，緊急CT（Fig. 4）で移植腎前面に移植腎被膜下血腫とおもわれる出血を認めた．腎被膜下血腫による急性腎不全と判断し，その後も血腫は拡大傾向になかったので，HDを併用し保存的に経過を見ていた．発症後，2週間しても血腫の吸収傾向はなく縮小してこない上に，移植腎血流が低下したままLDH＞1000 IU/Lと増加してきたため，緊急血腫除去術を試みた．前回移植術皮膚切開から入った．術中所見（Fig. 5）は，腹側筋膜と腎被膜に覆われたスペースに80gほどの血腫を認めた．血腫を除去して確認すると，腎被膜は保たれており，移植腎生検部と思われる部位から一部皮膜が損傷しそこから出血したと思われた．被膜外腎周囲血腫による移植腎圧迫による，急性腎不全であった．血腫除去直後より，移植腎血流が改善し，利尿を認めHDを離脱した．

血腫除去術後7日目には，Cr1.34mg/dl，Ccr 52.5mg/min，移植腎機能良好で退院となった．

考察

移植腎生検は，腎移植後の拒絶反応，薬剤性腎障害，原疾患の再発，感染症などの鑑別のため，移植腎の管理をする上で欠かせない検査である．

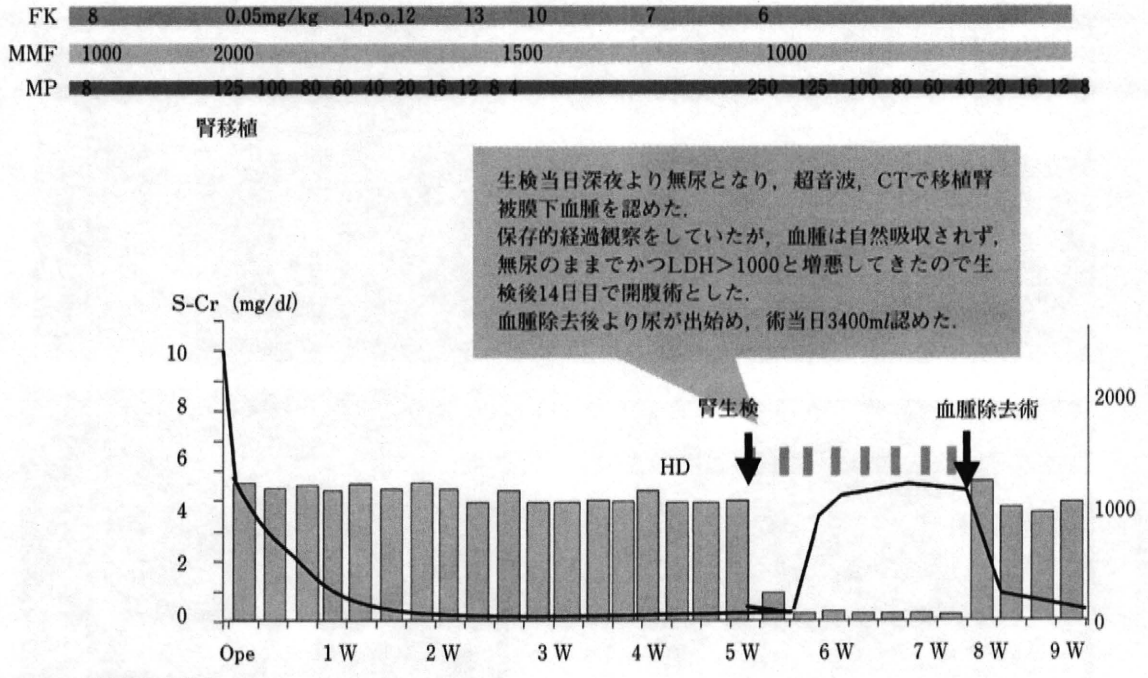

Fig. 3　移植後経過表
MP：metihylpredisolone，MMF：Mycophenolate mofetil
FK：tacrolimus

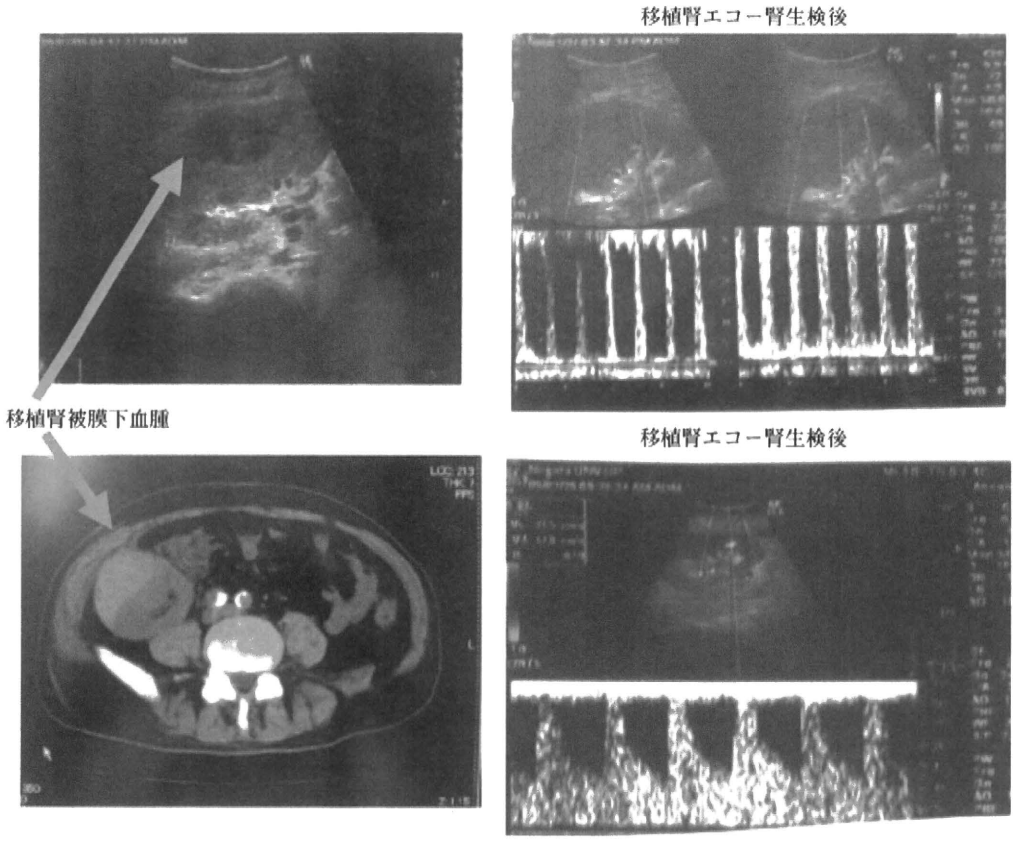

Fig. 4　症例2エコーCT所見

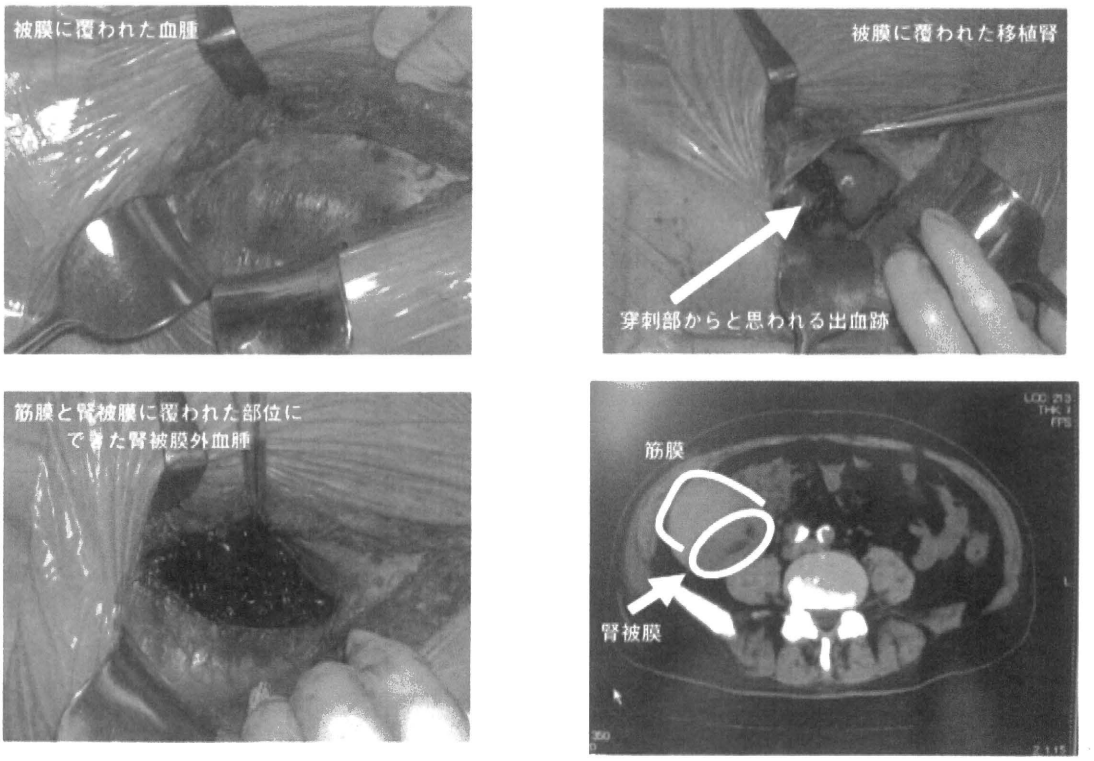

Fig. 5　症例2手術所見

移植腎生検は，固有腎生検と比較しても，腎が浅在性で触知でき，圧迫止血も可能な安全で簡便な検査であるが，時として腎出血，腎血腫，動静脈瘻，腎破裂など重大な合併症を発症する恐れがある．超音波観察下の経皮的移植腎針生検による合併症は，血尿4.4～13%，腎周囲血腫0.9～13%，膀胱タンポナーデ0.6～4.6%，腎動静脈瘻0.3～6.2%，出血・腎破裂0.2～2%など比較的多く報告されている[1～3]．

我々の施設において，移植腎生検は，超音波観察下での自動針生検装置（16G，Biopty，Bard，Covington，GA）で300症例以上行なっており，急性腎不全におちいるような移植腎血腫は，自験例の2症例のみである．移植腎生検によって発症した血腫は，容量としてはさほどでない出血であっても腎被膜下や筋膜内など移植腎を圧迫し腎血流が低下するような場合は，急性腎不全を併発してしまう．移植腎生検後の出血，被膜下血腫の0.5～1%が急性腎不全におちいるという報告もあり[4]，その治療方針は，基本的には積極的外科的治療で止血・血腫除去術を行なうべきである[5]．しかし，出血が増大してこない場合は，保存的にみたほうが，被膜による圧迫止血がなされ，血腫が自然吸収される可能性がある[4,6,7]．

本症例1のように，超音波検査にて，移植腎血流を確認し，血腫が吸収傾向にある場合は，保存的経過で改善する．

しかし，症例2のように筋膜と腎被膜で囲まれたスペースでの出血においては，血腫が吸収されず，移植腎を圧迫し，移植腎血流が低下するため，移植腎機能廃絶となる可能性がある．そのため早期に血腫除去術をするほうがよい．どこで保存的に経過をみるか積極的外科的治療を決断すべきか．以下にポイントをのべる．

1）基本的には，進行性の出血傾向（血腫が増大傾向）を認める場合は，外科的止血術・血栓除去術にふみきる．
2）超音波検査で，血流を確認し拡張期血流が少なくとも保たれている場合は，保存的に治療できる．
3）LDH上昇や血小板減少など，移植腎塞栓症の可能性を認めた場合は，外科的止血術・血栓除去術をするべきである．

本症例2においては，少なくとも進行性の出血ではなく，超音波検査で，拡張期血流も減弱はしていたが保たれていたので，2週間経過観察していた．しかし2週間しても血腫の縮小傾向を認めず，血小板減少は認めなかったが，LDHの上昇を認めたため移植腎塞栓を考慮して，血腫除去術にふみきった．結果的には移植腎機能は回復し，生着させることができた．

いずれにしても，超音波検査，血液学的検査，画像診断（CT）で経時的に注意深く見ていき，手術に移行する時期を見逃さない事が大切である．

おわりに

移植腎生検後に，移植腎出血・被膜下血腫によって急性腎不全となった症例を経験した．移植腎生検は移植腎を管理する上では必要不可欠な検査である．出血を含む合併症に対して厳重な監視・対応が必要と思われた．

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解説

ドナー移植コーディネーターの活動

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看護師

移植コーディネーターは、大切な人を亡くす場面の家族と接し、臓器提供に関する十分な情報提供と、自由な意思決定がなされるための支援を行います。

家族が提供を希望された場合は、提供や移植が円滑に進むように、家族のみならず提供病院や摘出チームの支援と調整の役割を担います。

本稿では、ドナー移植コーディネーター（臓器・組織提供のあっせんを担当。以下、ドナーコーディネーター）である院内コーディネーター（以下、IHCO）、都道府県コーディネーター（以下、都道府県CO）、日本臓器移植ネットワークコーディネーター（以下、NWCO）の活動の範囲を明らかにし、実際の業務について解説します。

ドナーコーディネーターの役割

日本臓器移植ネットワーク（以下、NW）では、ドナーコーディネーターの役割を、①ドナー情報への対応（あっせん活動）、②普及啓発活動、③移植希望者の登録とデータ整理（レシピエント登録）、としています。

その3つの業務について、それぞれの活動の範囲を表1に示します。

ドナーコーディネーターの活動紹介

筆者は都道府県COとして活動しています。都道府県COは、自分が担当する地域において臓器提供に関する理解向上のためのイベントや教育に携わる他、臓器提供の対象となる病院の把握や現場の課題へ対応するなど、その活動は多岐にわたります。

以下、主な活動を紹介します。

1 病院啓発事業

富山県では2009年現在、21カ所の病院に48名のIHCOを設置しています。IHCOには知事から委嘱状が交付されています。都道府県COは、IHCOとともに、病院啓発事業を展開しています。

今年度の活動は、IHCO連絡会開催（年6回）、移植講演会（年5回。県内各所の病院を会場とし、外部講師を招聘。県内IHCOへ参加の依頼）、病院定期事例検討会（3病院実施）、脳死下臓器提供に関わる団体との連絡会議（年1回）、透析施設対象

【表1】ドナーコーディネーターの活動範囲

	IHCO	都道府県CO	NWCO
①あっせん活動	院内で発生した提供に関与	都道府県内で発生した提供に関与	支部内および全国で発生した提供に関与
②普及啓発活動	院内における病院啓発	都道府県内を中心とした一般、病院啓発	支部内を中心とした一般、病院啓発
③レシピエント登録	原則、関与なし	一部関与	関与

講演会（年1回）、IHCOの企画事業への協力、病院体制整備のための支援などを行っています。

この活動により、各病院のIHCOとの信頼関係を構築することができます。また、病院ごとの啓発ポイントを理解し、関与しやすくなります。病院側としては、依頼や相談をしやすいという利点があります。こうした関係性は、実際の臓器提供場面において非常に役立っています。

2 一般啓発

富山県でのいちばん大きなイベントは、「いのちのおくりものポスターコンテスト」の実施です。臓器移植についての正しい理解と、いのちの大切さをアピールするためのイベントで、県内で広く参加を呼びかけています。

例年、300点前後の応募があり、知事賞、教育委員会長賞など、7つの賞と佳作20点を表彰します。その他、県内全域の開業医に臓器提供意思表示カードとポスターを送付して、設置の協力を得ています。今年は、カターレ富山（J2サッカーリーグ）の協力を得て、富山県オリジナルの意思表示カードを作成・配布しました。

3 教育活動

富山大学の医学部5年生が臨床研修で救急部を回る時に、臓器移植に関する授業を3時間行っています。2週間ごとのローテーションで、4、5名ずつの授業です。また、大学看護学科や看護専門学校など合計5カ所の場所でも定期的に授業を行っています。中学校や高校からの授業要請にも対応しています。

4 コーディネーション

都道府県COのコーディネーションを、事例で紹介します。

【事例1】

外傷性の脳血管障害で入院した患者の事例です。

搬送後、24時間以内に臨床的脳死状態に陥り、医師が「いわゆる脳死という状態です」と説明したところ、家族から臓器提供の申し出がありました。

IHCOから都道府県COに連絡があった時には、血圧は40以下。家族の申し出ケースであり、意思を最大限尊重するという考えに基づき摘出チームも都道府県COの出発と同時に召集しました。

都道府県COが病院に到着した後、主治医から情報を聴取し、適応判断を実施、すぐに家族への説明を行いました。都道府県COの説明の間、IHCOにはカルテからの情報収集と、摘出チームの到着受け入れをしてもらいました。バイタルサインから脳死提供が困難だと判断して意思表示カードを持参しなかった場合でも提供が可能であることを伝え、最後の時間、家族が患者に付き添えるように支援しました。一方で摘出チームには、主治医との情報交換、カニュレーションの準備を依頼しました。

都道府県COや摘出チーム到着から数時間後、心停止となり提供に至りました。（財）日本アイバンク協会にも速やかに連絡を行い、腎臓提供に引き続き、眼球の摘出が行われ、退院となりました。

この事例では、IHCOが提供の過程と移植の緊急度を理解しており、多くの説明を必要とせず手順のとおりに短時間で円滑に提供することができました。

【事例2】

内因性の脳血管障害で入院した患者が、治療の過程で、状態が悪化し脳死状態になった事例です。

脳死状態が配偶者に伝えられると、配偶者から意思表示カードの提示があり、脳死下臓器提供となりました。提供日は、申し出から3日後に決まりました。

連絡後、都道府県COはすぐに病院に入り、状況を把握しました。さらに到着したNWCOが統括者となり、提供病院との綿密な打ち合わせやNW本部との連絡に当たり、都道府県COとIHCOは家族対応や院内調整を担いました。その他の役割としては、NWCOはデータの収集や県外の搬送手配、都道府県COは県内搬送の手配など、チームで役割の分担を行いつつ、相互に補完しました。

提供に関する会議には、関与する部署責任者にオブザーバーとして出席を求め、情報の共有を図りました。時間配分予測は、IHCOの配置や手術室の準備、病理医の待機など多くの部署の準備に必要な情報です。臓器提供の承諾後に予測が立つ大まかな時間配分を伝えると、準備する部署の負担がより少なくなり、安心が得られます。

また、同院のIHCO7名のうち、4名はICU勤務でした。そこで臓器提供の説明、法的脳死判定および臓器提供の承諾、法的脳死判定、提供のそれぞれの場面には、IHCOが勤務するようにシフトを組み換えてもらいました。

家族、NWCO、都道府県COにそれぞれ、病院からPHSを貸与してもらいました。また、人間ドックの個室2部屋を家族待機室として準備してもらったことで、家族だけの静かな時間と空間を確保することができたと思われます。

各コーディネーターの待機室は、現地本部を兼ねる広めの会議室が準備され、摘出チームが来院した際もこの会議室を待機室としました。同じ場にいることで情報の交換がスムーズにでき、3日間不眠不休で働くコーディネーターにとっても負担が軽減されました。

この事例においても、院内での体制がしっかり整えられ十分な協力が得られること、手順について理解がされていること、院外のコーディネーターとの連携がうまく取れる関係性が平素より確立していることが重要であると実感させられました。

表2にIHCOの業務を簡単に記載しておきます。

【表2】臓器提供の際のIHCO業務

段階	業務項目
情報受信～連絡まで	●患者の医学的状態の把握・ドナー適応判断 ●家族状況の把握 ●病院連絡網に沿った報告
承諾～摘出まで	●都道府県CO・NWCOとの連携・業務補助 ●患者・家族支援（精神的支援、環境支援） ●担当医師・看護師支援 ●手術部への連絡
摘出～帰宅まで	●手術室内支援 ●家族支援 ●帰宅準備（エンゼルケアなど）

今後の課題

1997年に臓器の移植に関する法律が施行され、2009年に改正が行われました。今後、病院マニュアルの見直しや体制再編の支援、わかりやすい解説が求められていくでしょう。これを機に臓器移植への関心を高めていただき、“提供の意思が尊重され、家族にとって後悔のない看取りができるよう”私たちコーディネーターは、啓発に努めていかなければならないでしょう。K

●参考資料
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2）内閣府大臣官房政府広報室：世論調査報告書　平成16年8月調査　臓器移植に関する世論調査.
http://www8.cao.go.jp/survey/h16/h16-zouki/index.html［2009.12.16確認］
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4）篠崎尚史：厚生労働科学研究費補助金免疫アレルギー疾患等予防・治療研究事業　臓器移植の社会的基盤に関する研究，平成20年度総括・分担研究報告書，p.381，2009.

脳性小児まひ・胃瘻造設下の小児における心停止後の腎臓摘出と成人レシピエントへの献腎移植

力石辰也・佐藤雄一・宮野佐哲・堤　久・佐々木秀郎・
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第19回新潟移植再生研究会シンポジウム

"総排泄腔遺残を伴う慢性腎不全患児の二次献腎移植"

Non heart beating donor nephrectomy in a scoliotic boy with a gastrostomy tube : a case report

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key words：小児，献腎ドナー，腎移植

腎臓摘出手術の経過

小野元先生から発表がありましたので，詳細は省きますが，ドナーは11歳の男児，低酸素脳症で寝たきりの状態であり10年間が経過していました．気管切開があって，チューブの先端に肉芽があるため，呼吸困難をときどき起こしています．そして，胃瘻が造設されています．

2009年2月，自宅にて呼吸困難を起こし，心肺停止状態となり，当院救命センターに来院．蘇生措置によって心拍は再開しましたが，脳死と判定され，両親から臓器提供の希望がありました．

ドナーは身長113 cm，体重17 kg，インフルエンザB型に罹患したことが確認され，リン酸オセルタミビル(タミフル)を投与して解熱しています．検査データでは入院時，臓器提供前ともに大きな問題はありませんでしたが，scoliosisの強い，寝たきり状態が長かったことがわかります(**図1**)．

献腎提供にあたって，日本臓器移植ネットワークから「腎臓が二つあることを確認してほしい」

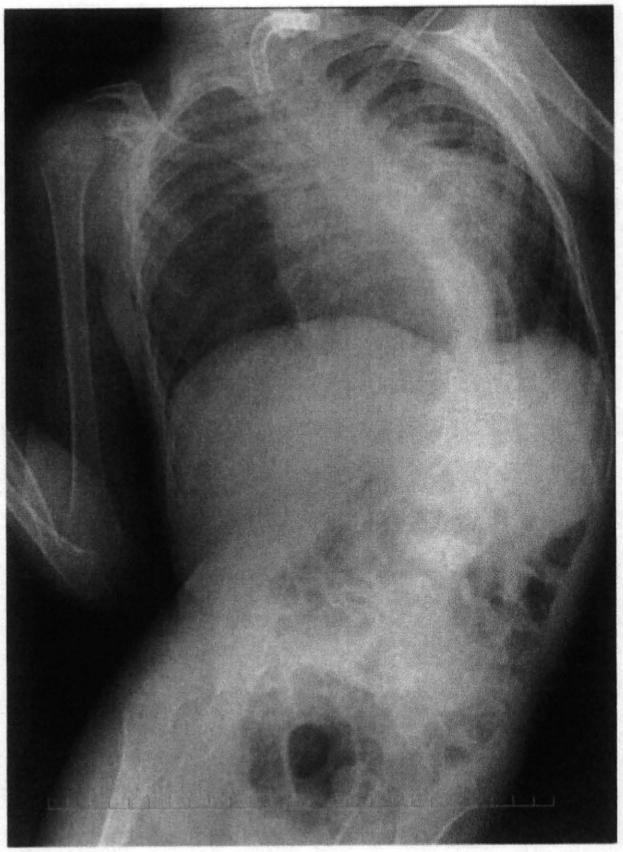

図1　胸腹部X-P

と依頼を受け調べたところ，右の腎臓は超音波検査では描出しにくく，推定の体積は何回測っても100 mLいきませんでした．非常に小さかったのですが，超音波のビームが入りにくいことも影響していたと思います．左の腎臓に関しては特に問題はなく，充分な大きさがありました．

家族からカニュレーションの承諾をいただいて，まず右の大腿静脈からカテーテルを入れよう

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と考えましたが，これが少し甘かったようです．右の大腿動脈は細いながらも同定して把持ができましたが，大腿静脈は閉塞していてカテーテルがまったく入りません．その間に血圧が不安定となってきたため，カテーテルの挿入を断念しました．

右の大腿静脈はブラッドアクセスとして使いやすいので，こういうケースでは先に左を見る，あるいは超音波検査で使える動静脈があることを確認してからカニュレーションを行うべきでした．

心停止ののち，ドナーを手術室へ運んで腎臓の摘出手術を行いました．大動脈，大静脈からカニュレーションを行いました．温阻血時間(WIT)は16分です．

胃瘻造設のため，腹腔内が強く癒着していたことと，右の腎臓が頭側の深い位置にあったことで，摘出手術は非常にやりにくく時間がかかりました．それでも新潟大学移植チームの齋藤和英先生に手伝っていただいて，なんとかアンブロック(en bloc)で腎臓を摘出しました．実際に測ってみると，先ほどの田崎正行先生の発表と重さが少し違いますが，右の腎臓が99 g，左の腎臓が105 gでした．右の腎臓を当院の成人レシピエントに，左の腎臓を新潟大学の小児レシピエントに移植することになりました．

腎移植手術の経過

当院のレシピエントは第2候補で，身長170 cm，体重60 kgの35歳の男性です．アルポート症候群で透析導入となり，以後状態はずっと安定していました．入院時の胸部写真，心電図，採血には特に問題はありません．CT所見をみると，後天性嚢胞性腎疾患(ACDK)がありましたが，それ以外は問題なく，動脈硬化もなく，よく保たれていました．

移植手術は，通常のreverse J incisionで後腹膜を展開して，動脈は外腸骨動脈と端側吻合，静脈は外腸骨静脈と端側吻合，尿管は自己尿管と端側吻合を行いました．手術時間は短く，全阻血時間(TIT)が5時間20分，術中から尿が出て，安心して移植手術を終わりました．

表1　小児ドナーからの献腎移植

①	年齢が高く，体格が大きいほど移植腎の予後はよい． (Pelltier SJ et al.：Am J Transplant　86：1646-1652, 2006[1]))
②	en bloc移植のほうが移植腎の予後はよい． (Pelltier SJ et al.：Am J Transplant　86：1646-1652, 2006[1])；van Heurn E et al.：Ped Surg Int　25：385-393, 2009[2]))
③	en blocに移植を行うか，2腎にわけるか． ドナー体重15 kg以下はen blocをすすめる． (Kälble T et al.：Eur Urol　47：156-166, 2005[3])；Mohanka R et al.：Transplantation　86：264-268, 2008[4]))

免疫抑制剤は当科の標準であるタクロリムス，ミコフェノール酸モフェチル(MMF)，ステロイド，バシリキシマブの四剤併用です．術後経過に問題はなく，移植手術の翌月から仕事に復帰され，現在はクレアチニン1.4 mg/dL前後で順調に経過しています．

考　察

今回このドナー情報をいただいたときに一番心配したのは，当院のレシピエントに右の腎臓を移植することになった場合に，非常に小さい小児の腎臓を成人に移植していいのかどうかということでした．

いろいろ文献を見てみると，小児ドナーでは年齢が高く，体格が大きいほど移植腎の予後がいい[1]，また，アンブロックのほうが予後がよく[1,2]，EAU(欧州泌尿器科学会)のガイドラインでは，体重15 kg以下のドナーにはアンブロックをすすめるとしています[3,4](**表1**)．ただ，これは腎臓の大きさが左右同じ場合を想定していると思われます．今回のケースにおいては，超音波検査で見る限りでは右の腎臓のほうが小さかったので，実際に摘出して小さな腎臓だった場合，当院のレシピエントに移植をしていいかどうか心配でした．

これについて調べてみると，当時東京女子医大の石川暢夫先生から，42歳の体重53 kgのレシピエントに70 gの腎臓を移植して10年以上クレアチニンが良好に保たれているという報告がありま

した[5]．では，これなら当院のレシピエントにも移植できるのではないかと思いました．

日本臓器移植ネットワークに問い合わせたところ，腎臓をアンブロックで提供するか，それとも2腎にわけて提供するかは，ドナーの担当医，レシピエント第1候補の移植施設の移植医の診断，腎臓摘出時の所見，腎臓の重さなどを総合して決定していて，決まったルールはないということでした．ネットワークのデータでは，過去14年間に15歳未満の献腎ドナーは37例ありましたが，アンブロックに提供したのは2例でした．1例は体重17 kgの4歳の男児から，もう1例は体重10.5 kgの9カ月の男児からでした．

まとめ

今回の経験から学んだことは，ドナーはインフルエンザに罹患していましたが，サイトメガロウイルスなどとは異なり潜伏感染になりませんから，臓器提供の妨げにはならないこと，右の大腿静脈が過去に血管ルートとして使われている可能性が高いときには，動静脈の状態をUSで確認してからカニュレーションすればよかったこと，体重17 kgの小児ドナーの約100 gの腎臓を，体重60 kgの成人レシピエントに移植して，短期的には満足できる腎機能が得られたことです．

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討　論

齋藤　成人ドナーの腎臓でも代償性肥大があり，小児ドナーの腎臓も移植後には大きくなるという話を聞きますが，このレシピエントに関してはその後の腎臓のサイズはいかがでしょうか．

力石　毎日測っていましたが，私たちでは移植腎のサイズが大きくなってほしいというバイアスがどうしてもかかるものですから，測るたびに大きくなる．一方で，そのバイアスをもってない者が測ると急に小さくなったりしているのですね．

ですから，今回はデータとして示すことができませんでした．移植後3カ月，半年，1年経ったところで超音波検査を経時的に行いますので，もう少し長期の結果が出たら発表しようと思っています．

齋藤　小さな腎臓が大きな体に入って，ハイパーフィルトレーションなどが危惧されますが，蛋白尿や血圧等はいかがでしょうか．

力石　血圧はまったく問題ありませんし，蛋白尿も出ていません．ノンエピソード生検を行っていますが，特に変化はみられませんでした．

齋藤　私たちのレシピエントの移植腎のほうに血管を長くいただいたので，力石先生たちの移植腎がどうなのか，心配でした．

力石　ありがとうございます．大丈夫でした．

齋藤　力石先生たちは，ドナーから腎臓を摘出してすぐにレシピエントに移植していましたので，私たちが新潟に戻って移植手術をはじめるまえにもう手術を終わられていて，尿が出たと聞いていました．ですから，私たちも希望をもって移植手術に入ることができました．

小野元先生からドナーについて発表がありまし

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たが，麻酔科医による酸素化や，人工呼吸，心臓マッサージを行い，心肺停止前にカニュレーションができなかったので，結局開腹してカテーテルを挿入．WITは16分ありましたが，腎臓の状態としては良好に保たれたのではないかと思います．

私が遅れて手術室に入ったときも，まだ腹腔内が癒着していましたよね．*in situ*でのカニュレーションはいかがでしたか．

力石　カニュレーションは問題なくできました．下のほうはまったく癒着していませんでした．

齋藤　最後に，高橋先生からお願いします．

おわりに

高橋　本日発表していただきましたシンポジストをはじめ，本会を盛りたてていただきました会場のみなさまに，主催者を代表して感謝申し上げます．

今回は，なにより腎臓を提供していただきましたドナーのお子さんと，移植医療に理解を示していただいたご家族に，心から哀悼の意を示すとともに敬意を表します．そして，聖マリアンナ医科大学の救急部，脳外科，および泌尿器科，さらに臓器移植コーディネーターに深謝申し上げます．

今回の献腎提供および献腎移植は，みなさまもおわかりだと思いますが，“愛と献身”の賜物でした．

当院のレシピエントであるお子さんは生まれながらに慢性腎不全を患い，献腎移植希望登録をしましたが，当時は正直言って，レシピエント候補になっても移植できないのではないかと懸念していました．その理由は，総排泄腔遺残のために便と尿が混ざり合い，感染症や敗血症をたびたび併発していたからです．

いままで20回以上，日本臓器移植ネットワークからレシピエント候補に選ばれた連絡をいただきましたが，そのつどこのような理由で適応から外れてしまいました．腎移植適応となるまで育てていただいたご家族はもちろんのこと，小児科と小児外科の先生方もさぞかし大変であったと思います．当院各科の医療スタッフにもご協力をいただきました．

今回は献腎移植でしたので，緊急手術として2009年2月のある夜の9時ころから開始され，翌日の早朝に終わりました．移植手術が終わって，レシピエントのご家族が待っている小児科病棟に行き，手術がうまくいって，すぐに利尿がえられたことを説明したところ，お母さんは号泣しました．

私たちはその時，「ああ良かった，良いことをしたなあ」と満足感と達成感でいっぱいでした．このような，またとない機会を与えられたことは，腎臓を提供していただいたドナーをはじめ，ご家族の厚意であり，本当に感謝にたえません．

本日はシンポジウムを盛会のうちに終わらせることができました．最後に，今回の献腎移植のために尽力していただいたみなさまに心から感謝し，終わりたいと思います．ご静聴ありがとうございました．

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ORIGINAL PAPER

Coding and traceability for cells, tissues and organs for transplantation

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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".