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COMMITTEE ON PATIENT SAFETY
COMMITTEE ON BIOLOGICAL IMPLANTS
TISSUE WORK GROUP

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BASIC AWARENESS

The use of musculoskeletal allograft tissue in reconstructive orthopaedic procedures has markedly increased over the last decade. (Figure 1)

Surgeon knowledge of tissue bank practices in donor consent and screening, serology testing and processing is important when making the decision to use these allograft tissues.

The orthopaedic surgeon also has the responsibility to inform the patient about the risks, benefits and alternatives of using allograft tissue.

This handout provides an overview of some of these issues.

What are the Commonly Used Allografts in Orthopaedic Procedures?

**Bone**
- Demineralized bone products (osteoinductive)
- Cortical/cancellous – powder, chips, wedges, dowels, crest, pegs and screws
- Structural – cortical segments, shafts, long bones, pelvis, acetabulum
- Osteochondral long bone (cryoprotected cartilage)
- Ribs, mandible, calvarium, ear ossicles

**Soft Tissue**
- Patellar ligament and Achilles tendon (bone block), other assorted tendons
- Fascia lata, rotator cuff

**Cartilage**
- Meniscus, osteoarticular segments (fresh and cryoprotected), costal cartilage

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*Figure 1: Musculoskeletal allograft distribution. Source: AATB Annual Survey.*

*Figure 2: Bone-patellar tendon-bone allograft.*

*Figure 3: Processed iliac crest wedge.*

*Figure 4: Femoral allograft.*
What are the Milestones in Tissue Banking?

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1881</td>
<td>First human bone transplant under aseptic conditions</td>
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<tr>
<td>1925</td>
<td>Lexer: First reported large series of bone transplants (50% success rate)</td>
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<tr>
<td>1950</td>
<td>U.S. Navy Tissue Bank established in Bethesda, Maryland (George Hyatt, M.D.)</td>
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<tr>
<td>1955</td>
<td>Low temperature preservation of bone (reduction of antigenicity)</td>
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<tr>
<td>1960s</td>
<td>Early reports of successful use of tissue implants</td>
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<tr>
<td>1972</td>
<td>Ottolenghi: Long bone/osteoarticular allografts series</td>
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<tr>
<td>1973</td>
<td>Parrish: Long bone allograft replacement series</td>
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<tr>
<td>1983</td>
<td>Mankin: Two hundred large bone allograft series</td>
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<tr>
<td>1984</td>
<td>First Standards for Tissue Banking published by the American Association of Tissue Banks (AATB)</td>
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<tr>
<td>1986</td>
<td>AATB Inspection/Accreditation Program initiated</td>
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<tr>
<td>1989</td>
<td>AATB Training and Certification Program for Tissue Bank Specialists (CTBS)</td>
</tr>
<tr>
<td>1993</td>
<td>FDA: Interim Rule, Human Tissue for Transplantation (FDA inspection of tissue banks initiated)</td>
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<tr>
<td>1994</td>
<td>AATB Inspection/Accreditation Program using contract, non-affiliated inspectors</td>
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<tr>
<td></td>
<td>CDC: Guidelines for Preventing HIV Transmission Through Transplantation of Human Tissue and Organs</td>
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<tr>
<td>1997</td>
<td>FDA: Final Rule, Human Tissue for Transplantation</td>
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<tr>
<td>2001</td>
<td>FDA: Final Rule, Establishment Registration and Product Listing</td>
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<tr>
<td></td>
<td>FDA: Proposed Rule, Good Tissue Practices; Inspection and Enforcement</td>
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<tr>
<td>2002</td>
<td>FDA: Guidance Document - Validation of Procedures for Processing of Human Tissues Intended for Transplantation</td>
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<tr>
<td>2003</td>
<td>More than 1,300,000 musculoskeletal allografts distributed in the U.S.</td>
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<tr>
<td>2005</td>
<td>91 AATB Accredited Tissue Banks (Consult AATB Web Site at <a href="http://www.aatb.org">www.aatb.org</a>)</td>
</tr>
</tbody>
</table>

Figure 5: First depicted allograft transplantation. 12th Century painting of Saints Cosmas and Damian. (circa 3rd century)

Figure 6: AATB Standards.

Figure 7: 16-year-old with aneurysmal bone cyst; repair using bone graft cancellous chips.
What has Occurred in Government Regulation?

<table>
<thead>
<tr>
<th>Year</th>
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</thead>
<tbody>
<tr>
<td>1968</td>
<td>Uniform Anatomical Gift Act (UAGA) provided to states for adoption and enactment</td>
</tr>
<tr>
<td>1984</td>
<td>National Organ Transplant Act</td>
</tr>
<tr>
<td>1985</td>
<td>HIV antibody testing (FDA) for blood donors</td>
</tr>
<tr>
<td>1990</td>
<td>HCV antibody testing (FDA) for blood donors</td>
</tr>
<tr>
<td>1993</td>
<td>FDA: Interim Rule, Human Tissue Intended for Transplantation</td>
</tr>
<tr>
<td>1995</td>
<td>JCAHO oversight in tissue banking (limited to Laboratory inspection manual)</td>
</tr>
<tr>
<td>1997</td>
<td>FDA: Proposed Approach to Regulation of Tissue Products (Tissue Action Plan)</td>
</tr>
<tr>
<td>1998</td>
<td>Medicare Requirements for hospital participation in organ/tissue donation</td>
</tr>
<tr>
<td>1999</td>
<td>FDA: Proposed Rule: Suitability Determination for Donation</td>
</tr>
<tr>
<td>2000</td>
<td>FDA: Blood Donor Testing of HIV RNA and HCV RNA by PCR (NAT)</td>
</tr>
<tr>
<td></td>
<td>FDA: Guidance Document, Availability of Licensed Donor Screening Tests Labeled for Use with Cadaveric Blood Specimens</td>
</tr>
<tr>
<td>2001</td>
<td>FDA: Proposed Rule for Good Tissue Practices</td>
</tr>
<tr>
<td></td>
<td>FDA: Final Rule: Establishment Registration and Listing, Manufacturers of Human Tissue Products</td>
</tr>
<tr>
<td></td>
<td>OIG (Office of the Inspector General): reports on Informed Consent and, Oversight of Tissue Banking</td>
</tr>
<tr>
<td>2002</td>
<td>FDA: Guidance Document, Validation of Procedures for Processing of Human Tissue Intended for Transplantation</td>
</tr>
<tr>
<td></td>
<td>FDA: Draft Guidance Document, Preventive Measures to Reduce the Possible Risk of Transmission of CJD and vCJD by Human Tissue (HCT/Ps)</td>
</tr>
<tr>
<td>2004</td>
<td>FDA: Final Rule and draft Guidance Document - Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-based Products (HCT/P) (the Rule was effective May 25, 2005)</td>
</tr>
<tr>
<td></td>
<td>FDA: Final Rule, Current Good Tissue Practice (CGTPs) for HCT/P Establishments; Inspection and Enforcement (Effective May 25, 2005)</td>
</tr>
<tr>
<td>2005</td>
<td>JCAHO: Tissue Storage and Issuance Standards for hospitals and surgical centers</td>
</tr>
<tr>
<td></td>
<td>FDA: Guidance Document, MedWatch Form FDA 3500A: Mandatory Reporting of Adverse Reactions Related to Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)</td>
</tr>
</tbody>
</table>

What Practical Steps are Taken in Tissue Banking in Assessment and Processing?

Detailed inquiry into donor’s medical, social and sexual history (including autopsy if performed)

**Donor Screening: Medical History and Behavioral Risk Assessment**

At Time of Donation, Exclusionary Criteria:

- Active infection, sepsis, or TB
- History of systemic viral illness (Hepatitis, HIV, recent West Nile Virus, etc.)
- Untreated syphilis, Hansen’s Disease
- Certain autoimmune diseases
- Ingestion of toxic substances that may affect tissues
- Rheumatoid arthritis, systemic lupus, polyarteritis nodosa, and sarcoidosis
- Clinically significant metabolic bone disease
- Clinically significant malignancy
- Implantation of dura mater or use of human derived pituitary growth hormone (Spongiform Disease, CJD)
- Risk factors associated with HIV, Hepatitis, sepsis, HTLV infection, WNV, SARS
- Dementia of infectious or unknown etiology
Donor Screening: Physical Assessment
Examination of Potential Donors Includes Looking for Evidence of:
- Active infection: viral, bacterial or fungal
- Sexually transmitted diseases such as genital ulcerative disease: herpes simplex, syphilis and chancroid
- Needle tracks (nonmedical); recent tattoos and piercings (within past 12 months)
- Lymph node enlargement
- Jaundice, icterus, hepatomegaly
- Blue/purple (gray/black) spots consistent with Kaposi’s sarcoma
- Evidence of anal intercourse (perianal condyloma, insertion trauma)
- Oral thrush
- Trauma to recovery sites
- Clinically significant skin lesions (rash, scabs)

Infectious Disease Testing
Tests Required by FDA; performed by CLIA-registered or CMS-approved laboratories:
- HIV 1/HIV 2 Antibody
- HB Core Antibody (total, IgM + IgG)
- HBsAg
- HCV Antibody
- Syphilis (T. pallidum)

Reference: FDA CGTP Rule and Donor Eligibility Guidance Document
AATB Required Additional Testing:
- HTLV-I/II Antibody
- HIV-1 NAT
- HCV NAT

Window Period
Period between infection and time virus is detectable by screening tests.

<table>
<thead>
<tr>
<th>Virus</th>
<th>HIV</th>
<th>HCV</th>
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<tbody>
<tr>
<td>HIV antibody</td>
<td>22 days</td>
<td>70 days</td>
</tr>
<tr>
<td>NAT* - 7 days</td>
<td>7 days</td>
<td></td>
</tr>
<tr>
<td>Blood Donor Estimated Risk (repeat donor)(a)</td>
<td>with NAT*</td>
<td>with NAT*</td>
</tr>
<tr>
<td>1:2 million</td>
<td>1:2 million</td>
<td></td>
</tr>
<tr>
<td>Tissue Donor Estimated Risk (b)**</td>
<td>without NAT*</td>
<td>without NAT*</td>
</tr>
<tr>
<td>1:55,000</td>
<td>1:42,000</td>
<td></td>
</tr>
<tr>
<td>with NAT*</td>
<td>with NAT*</td>
<td></td>
</tr>
<tr>
<td>1:173,000</td>
<td>1:421,000</td>
<td></td>
</tr>
</tbody>
</table>

*Nucleic Acid-Amplification Test
Source: (a) Stramer et al, NEJM 351:760-768, 2004
(b) Zou et al, NEJM 351:751-759, 2004
** This is difficult to estimate for tissue donors because of increased prevalence and smaller donor pool.

Tissue Processing
- Audited or accredited facility following current Good Tissue Practices
- Possesses a Quality Control/Quality Assurance Program
- Elimination or reduction of blood, debris and cells from allografts to reduce disease transmission potential
- Validation of bacteriologic and virucidal washes
- Evaluation of bacteriologic bioburden (pre-processing cultures to evaluate contamination)
- Possible use of gamma radiation 1.5 Mrads (15 kilogray) or more (pre-processing or terminal sterilization)
- Final product testing for bacteriologic contamination (swabs, immersion, or destructive testing)
- Potential discard of tissue or donor lot based on certain types of early bacteriologic contamination (Streptococcus Group A, Clostridium)
- Final review by tissue bank medical director of screening/testing prior to release of tissue for transplantation

Sterilization (Selected Tissues)
- Gamma or E beam radiation 1.5 - 2.0 Mrads [15 - 20 kilogray] (these amounts or higher may raise concern for integrity of tissues especially soft tissues)
What are the Episodes of Documented Disease Transmission?

Over the past decade more than 6 million musculoskeletal allografts have been safely transplanted in the United States. Relatively few incidents of disease transmission have been reported:

**Bacterial:** Tuberculosis

- One case (four recipients): *James et al, JBJS 35B:578, 1953*

  Infections
  - One case: *Tomford et al, JBJS 63A:244-248, 1981*
  - Three cases: *Lord et al, JBJS 70A:369-376, 1988*

**Situation One**
- Death November 2001 Clostridium sordellii
  - Fresh osteochondral femoral allograft segment in 23 y/o male

**Situation Two:** Tissue from same donor - tissues were irradiated
- Patient A bone-tendon-bone; *Pseudomonas aeruginosa, Staph. aureus, Enterococcus*
- Patient B bone-tendon-bone; *Pseudomonas aeruginosa*

**Situation Three:** Tissue from same donor - radiation planned but not accomplished
- Patient A bone-tendon-bone; *Citrobacter werkmanii youngae; Group B Streptococci*
- Patient B bone-tendon-bone; *Klebsiella oxytoca/Halfnia alvei*

- One case: bone-tendon-bone; *Group A streptococcus: MMWR 52(48):1173, December 5, 2003*
- 14 probable Clostridium cases: *Kainer et al, NEJM 350:2564-2571, 2004*
  - Major findings include:
    - Clostridium infections traced to allograft implantation (occurring between Jan 1988 to Mar 2002);
    - All “sports medicine” allografts; all processed by one tissue bank not accredited by AATB
    - Gaps identified include lack of pre-processing cultures and probability of false negative cultures due to culturing method used post-processing
    - Interim recommendations proposed: validate processes and culture methods; and sterilization methods are needed that do not compromise function of the tissue

**Viral:**
- Hepatitis B - One case: *Shutkin, JBJS 36A:160-162, 1954*
- Hepatitis C - One case: *Eggen and Nordbo, NEJM 326:411, 1992*
  - Two cases: *Conrad et al, JBJS 77A:214-224, 1995*
  - Four cases: three bone-tendon-bone (non-irradiated) and one tendon: *MMWR 52(13):273-276, April 4, 2003; Tugwell et al, Transmission of Hepatitis C Virus to Several Organ and Tissue Recipients from an Antibody-Negative Donor, Annals of Internal Medicine 143(9):648-654, 2005*
- HIV - One case: *MMWR 37(39):597-599, 1988 (pre-HIV antibody testing)*

What is the Message?

- Estimated more than 1.3 million musculoskeletal allografts distributed in US in 2005.
- Disease transmission is rare when comparing reports of infection versus the number of allografts distributed annually.
- Tissue availability is predicated on the gracious altruistic act of numerous donors and donor families.
- Conventional sterilization techniques used for metallic implants may adversely affect functional, biological and mechanical properties of most allografts.
- No reports of disease transmission using demineralized bone products.
- Some grafts can be treated with 1.5 Mrads (15 kilogramay) or more to reduce contamination. This may affect properties of the allograft.
- Inherent safety of the graft is based upon Current Good Tissue Practices and AATB Standards:
  - Donor screening and physical assessment
  - Infectious disease testing
  - Validated processing techniques
  - Attention to quality control/quality assurance
- Reporting of suspected allograft-associated infections by surgeons to tissue banks and the FDA using MedWatch (www.fda.gov/medwatch/).
- Need outcome studies to improve safety and efficacy.
- Orthopaedic surgeon needs to know “the tissue banker”.
- Surgeon/patient interaction regarding the risks and benefit of using allograft tissue in their procedure is requisite.