AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS
71st Annual Meeting
March 10 - 14, 2004
San Francisco, California

COMMITTEE ON PATIENT SAFETY
COMMITTEE ON BIOLOGICAL IMPLANTS
TISSUE WORK GROUP

Prepared by:
Michael J. Joyce, M.D.
A. Seth Greenwald, D.Phil.(Oxon)
Robert Rigney, Jr., J.D. (AATB)
Jeanie Kennedy
Donna Toohey
Christine S. Heim, B.Sc.
Randy N. Rosier, M.D., Ph.D.
David Wong, M.D.
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 gifting 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 and Achilles tendon (bone block), rotator cuff, other tendons
- Fascia lata

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

Figure 1: Musculoskeletal allograft distribution. Source: U.S. Census Bureau, Statistical Abstracts of US 2003; AATB Annual Survey.
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1881</td>
<td>First human bone transplant under aseptic conditions</td>
</tr>
<tr>
<td>1925</td>
<td>Lexer: First reported large series of bone transplants (50% success rate)</td>
</tr>
<tr>
<td>1950</td>
<td>U.S. Navy Tissue Bank established in Bethesda, Maryland (George Hyatt, M.D.)</td>
</tr>
<tr>
<td>1955</td>
<td>Low temperature preservation of bone (reduction of antigenicity)</td>
</tr>
<tr>
<td>1960s</td>
<td>Early reports of successful use of tissue implants</td>
</tr>
<tr>
<td>1972</td>
<td>Ottolenghi: Long bone/osteoarticular allografts series</td>
</tr>
<tr>
<td>1973</td>
<td>Parrish: Long bone allograft replacement series</td>
</tr>
<tr>
<td>1983</td>
<td>Mankin: Two hundred large bone allograft series</td>
</tr>
<tr>
<td>1984</td>
<td>First Standards for Tissue Banking published by the American Association of Tissue Banks (AATB)</td>
</tr>
<tr>
<td>1986</td>
<td>AATB Inspection/Accreditation Program initiated</td>
</tr>
<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 on Tissue Transplantation (FDA Auditing initiated)</td>
</tr>
<tr>
<td>1994</td>
<td>AATB Inspection/Accreditation Program using trained former FDA compliance officers</td>
</tr>
<tr>
<td>1997</td>
<td>FDA: Final Rule on Tissue Transplantation</td>
</tr>
<tr>
<td>2001</td>
<td>Establishment of Registration and Product Listing Proposed Good Tissue Practices; Inspection and Enforcement</td>
</tr>
<tr>
<td>2002</td>
<td>Validation of Procedures for Processing of Human Tissues Intended for Transplantation: Guidance for Industry (immediate implementation)</td>
</tr>
<tr>
<td>2003</td>
<td>More than 1,000,00 tissue transplants annually in the U.S.</td>
</tr>
<tr>
<td>2004</td>
<td>82 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 Cosmos and Damian.

Figure 6: AATB Standards.

Figure 7: Femoral strut.
What has Occurred in Government Regulation?

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<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 on Tissue Transplantation</td>
</tr>
<tr>
<td>1995</td>
<td>JCAHO oversight in tissue banking</td>
</tr>
<tr>
<td>1997</td>
<td>FDA: Final Rule on Tissue Transplantation (with guidance documents)</td>
</tr>
<tr>
<td>1997</td>
<td>FDA: Proposed Approach to Regulation of Tissue Products</td>
</tr>
<tr>
<td>1998</td>
<td>HCFA: 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</td>
</tr>
<tr>
<td>2001</td>
<td>FDA: Proposed Rule for Good Tissue Practice</td>
</tr>
<tr>
<td></td>
<td>FDA: Establishment of Registration of Tissue Banks and Manufacturers of Tissue Products (1983 to 1998 multiple Public Health Service/Guidance documents)</td>
</tr>
<tr>
<td>2002</td>
<td>Validation of Procedures for Processing of Human Tissue Intended for Transplantation: Guidance for Industry (immediate implementation)</td>
</tr>
<tr>
<td>2002</td>
<td>Preventive Measures to Reduce CJD and vCJD by Human Tissue (HCT/Ps): Guidance draft document for comment only</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 accomplished)

Donor Screening: History

At Time of Donation, No History of:
- Recent active infection or sepsis
- Systemic viral illness (Hepatitis, HIV, West Nile, etc.)
- Untreated syphilis, active tuberculosis, leprosy
- Autoimmune disease
- Ingestion toxic substances
- Rheumatoid arthritis, systemic lupus, polyarteritis nodosa, sarcoidosis, myasthenia gravis
- Clinically significant metabolic bone disease
- Clinically significant malignancy
- Dementia, dura mater transplant or use of human derived pituitary growth factor (Spongiform Disease, CJD)
- Risk factors for HIV and Hepatitis (as listed by US Public Health Service)

Figure 8: HIV virus - led to improved donor screening.
Donor Screening: Physical Examination

Physical Examination of Potential Donors Includes No Evidence of:

- Active infection: viral, bacterial or fungal
- Physical evidence of risk for sexually transmitted diseases such as genital ulcers, herpes simplex, syphilis, chancreoid
- Needle tracts (nonmedical); recent tattoos (12 months)
- Lymph node enlargement (disseminated)
- Jaundice, icterus, hepatomegaly
- Blue/purple spots consistent with Kaposi’s sarcoma
- Evidence anal intercourse (perianal condyloma)
- Oral thrush
- Open local wounds
- Clinically significant skin lesions

Serologic Testing

Tests Required by FDA; performed by CLIA - approved laboratories:

- HIV 1/HIV 2 Antibody (residual risk 1:689,655)
- HTLV I/HTLV II Antibody
- HBsAg (residual risk 1:77,220)
- HCV Antibody (residual risk 1:19,850)
- Syphilis
- HB Core Antibody (FDA: For living donors) (general New York State requirement)

Residual Risk Source: GAO/HEHS-98-205 Blood Plasma Safety

Additional Testing Usually Done:

- HIV Antigen
- HIV PCR Testing
- CMV

Window Period

<table>
<thead>
<tr>
<th>Virus</th>
<th>HIV</th>
<th>HCV</th>
<th>HBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Window Period using FDA Licensed Tests</td>
<td>22 days (anti HIV&lt;sub&gt;1&lt;/sub&gt;,2)</td>
<td>70 days (anti HCV)</td>
<td>56 days (HBsAg)</td>
</tr>
<tr>
<td>Window Period using NAT* Testing</td>
<td>7-12 days**</td>
<td>10-29 days</td>
<td>41-50 days</td>
</tr>
</tbody>
</table>

* Nucleic Acid Test
** p24 testing between 12 and 22 days

Tissue Processing

- Audited or accredited facility following Good Tissue Practice guidelines
- Validated Quality Control/Quality Assurance Program
- Elimination or reduction of blood, debris and cells to reduce disease transmission
- Bacteriologic and virucidal washes
- Evaluation bacteriologic bioburden (preprocessing cultures to evaluate contamination)
- Possible use of gamma radiation 1.5 Mrads (15 kilogray) or more (pre- or post-processing)
- Final product testing for bacteriologic contamination (swabs vs. culture of entire tissue piece)
- Potential discard of tissue or donor lot based on certain types of early bacteriologic contamination
- Final review by tissue bank medical director of screening/serology/processing prior to release of tissue for transplantation

Sterilization (Selected Tissues)

- Gamma radiation 1.5 - 2.0 Mrads [15 - 20 kilogray] (these amounts or higher may raise concern for integrity of tissues especially soft tissues)
- Ethylene Oxide (concern for residual toxicity and penetration depth)
**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
  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

Total of 26 cases under review as of March 2002: 13 of 26 were infected with clostridium with 85% of these positive clostridial associated infections coming from a single non-AATB accredited tissue bank. These reports and other allograft “associated” infection reports are under review by CDC. Some of these reports were not allograft “caused” infections. Approximately 70 total cases have been submitted for review. No further published report has been generated.
- One case: bone-tendon-bone; Group A streptococcus: MMWR 52(48):1173, December 5, 2003

**Viral:**
- 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 3, 2003
- HIV - One case: MMWR 37:397-399, 1983 (Pre-HIV antibody testing)

**What is the Message?**
- More than 1,000,000 musculoskeletal allografts distributed in US in 2003.
- Disease transmission is very rare.
- 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 kilogray) or more to reduce contamination. This may affect properties of the allograft.
- Inherent safety of the graft is based upon Good Tissue Practices:
  - Donor screening and physical examination
  - Serological and infectious disease testing
  - Careful processing techniques
  - Attention to quality control/quality assurance
- Need for centralized reporting of adverse episodes by surgeons with subsequent investigation and documentation.
- 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.