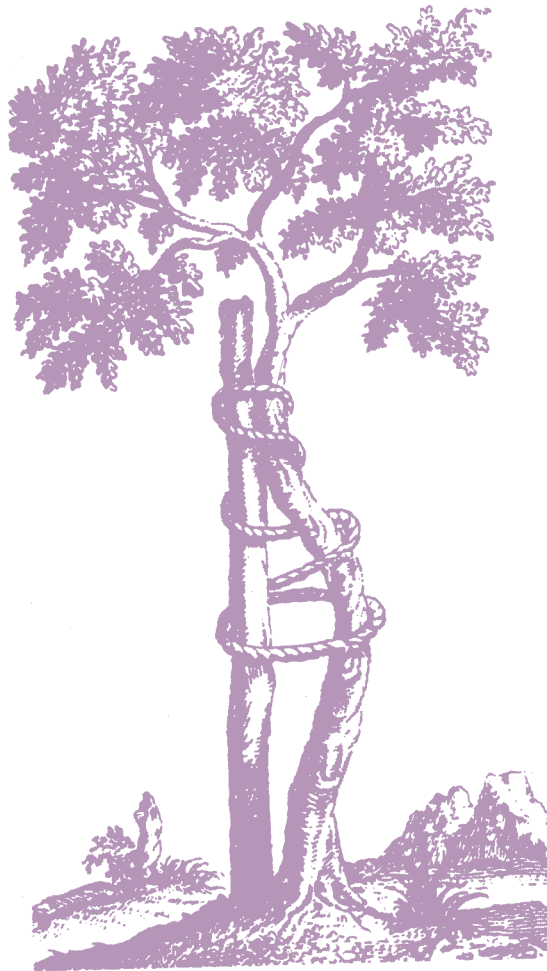

MUSCULOSKELETAL ALLOGRAFT TISSUE SAFETY



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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 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.

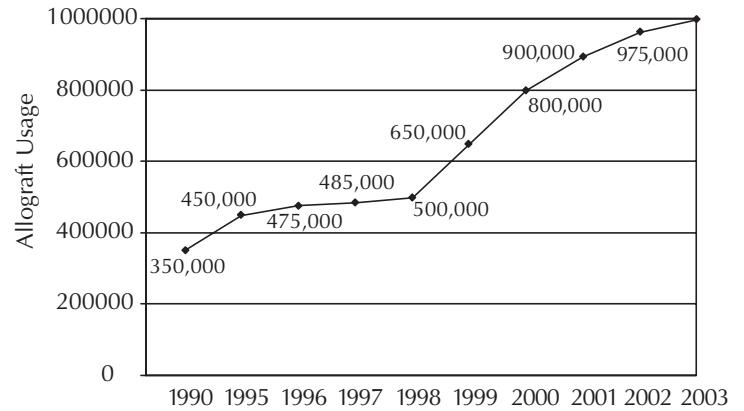


Figure 1: Musculoskeletal allograft distribution. Source: U.S. Census Bureau, Statistical Abstracts of US 2003; AATB Annual Survey.

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 2: Bone-patellar tendon-bone allograft.



Figure 3: Dowel and iliac crest allograft.



Figure 4: Femoral allograft.

What are the Milestones in Tissue Banking?

- 1881 First human bone transplant under aseptic conditions
- 1925 Lexer: First reported large series of bone transplants (50% success rate)
- 1950 U.S. Navy Tissue Bank established in Bethesda, Maryland (George Hyatt, M.D.)
- 1955 Low temperature preservation of bone (reduction of antigenicity)
- 1960s Early reports of successful use of tissue implants
- 1972 Ottolenghi: Long bone/osteoarticular allografts series
- 1973 Parrish: Long bone allograft replacement series
- 1983 Mankin: Two hundred large bone allograft series
- 1984 First Standards for Tissue Banking published by the American Association of Tissue Banks (AATB)
- 1986 AATB Inspection/Accreditation Program initiated
- 1989 AATB Training and Certification Program for Tissue Bank Specialists (CTBS)
- 1993 FDA: Interim Rule on Tissue Transplantation (FDA Auditing initiated)
- 1994 AATB Inspection/Accreditation Program using trained former FDA compliance officers
- 1997 FDA: Final Rule on Tissue Transplantation
- 2001 Establishment of Registration and Product Listing
Proposed Good Tissue Practices; Inspection and Enforcement
- 2002 Validation of Procedures for Processing of Human Tissues Intended for Transplantation:
Guidance for Industry (immediate implementation)
- 2003 More than 1,000,00 tissue transplants annually in the U.S.
- 2004 82 AATB Accredited Tissue Banks (Consult AATB Web Site at www.aatb.org)



Figure 5: First depicted allograft transplantation. 12th Century painting of Saints Cosmos and Damian.

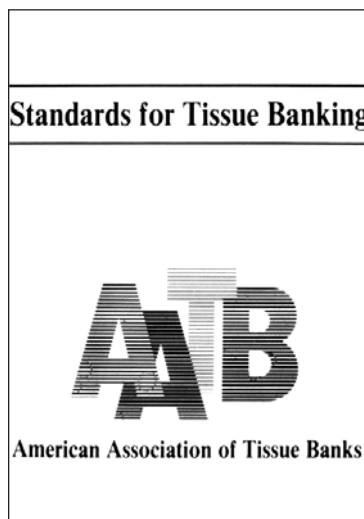


Figure 6: AATB Standards.



Figure 7: Femoral strut.

What has Occurred in Government Regulation?

- 1984 National Organ Transplant Act
- 1985 HIV antibody testing (FDA) for blood donors
- 1990 HCV antibody testing (FDA) for blood donors
- 1993 FDA Interim Rule on Tissue Transplantation
- 1995 JCAHO oversight in tissue banking
- 1997 FDA: Final Rule on Tissue Transplantation (with guidance documents)
- 1997 FDA: Proposed Approach to Regulation of Tissue Products
- 1998 HCFA: Requirements for hospital participation in organ/tissue donation
- 1999 FDA: Proposed Rule: Suitability Determination for Donation
- 2000 FDA: Blood Donor Testing of HIV RNA and HCV RNA by PCR
- 2001 FDA: Proposed Rule for Good Tissue Practice
FDA: Establishment of Registration of Tissue Banks and Manufacturers of Tissue Products
(1983 to 1998 multiple Public Health Service/Guidance documents)
- 2002 Validation of Procedures for Processing of Human Tissue Intended for Transplantation: Guidance for Industry (immediate implementation)
- 2002 Preventive Measures to Reduce CJD and vCJD by Human Tissue (HCT/Ps): Guidance draft document for comment only

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)

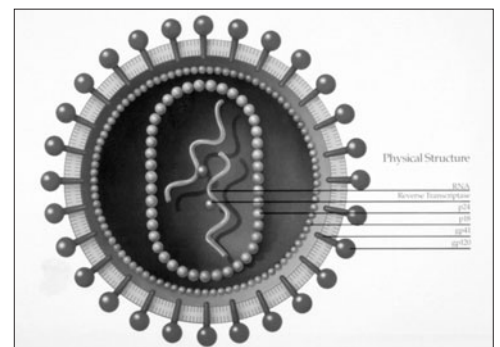


Figure 8: HIV virus - led to improved donor screening.

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, chancroid
- 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
- HB_sAg (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)

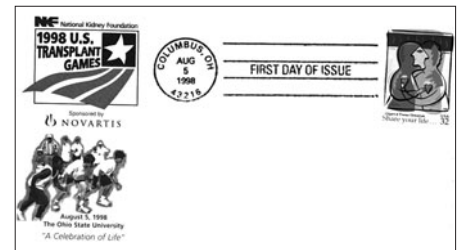
Residual Risk Source: GAO/HEHS-98-205 Blood Plasma Safety

Window Period Period between infection and time virus is detectable by screening tests.			
Virus			
	HIV	HCV	HBV
Window Period using FDA Licensed Tests	22 days (anti HIV _{1,2})	70 days (anti HCV)	56 days (HB _s Ag)
Window Period using NAT* Testing	7-12 days**	10-29 days	41-50 days

*Nucleic Acid Test
** p24 testing between 12 and 22 days
Source: Busch MP and Kleinman SH, Transfusion 40:143-146, 2000.

Additional Testing Usually Done:

- HIV Antigen
- HIV PCR Testing
- CMV
- Possible use of HIV RNA and HCV RNA by NAT testing as used in blood for living donor serum since 2000. U.S. residual risk for blood: HIV 1:1,400,000; HCV 1:1,200,000 and HBV 1:150,000: *Strong and Katz, TRENDS in Molecular Medicine 8:355-358, 2002.* Problem is validation/sensitivity for cadaveric serum.



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*
- Cases under investigation by CDC: *MMWR 50(48):1080-1083, December 7, 2001 and MMWR 51(10):207-210, March 15, 2002*

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 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 3, 2003*

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

Three cases: *Simonds et al, NEJM 326:726-732, 1992* (tissue retrieved 1985)

HTLV 1 - One case in Sweden: *Sanzen and Carlsson, Acta Orthop Scand 68:70-72, 1997* (1991 occurrence)



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.
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