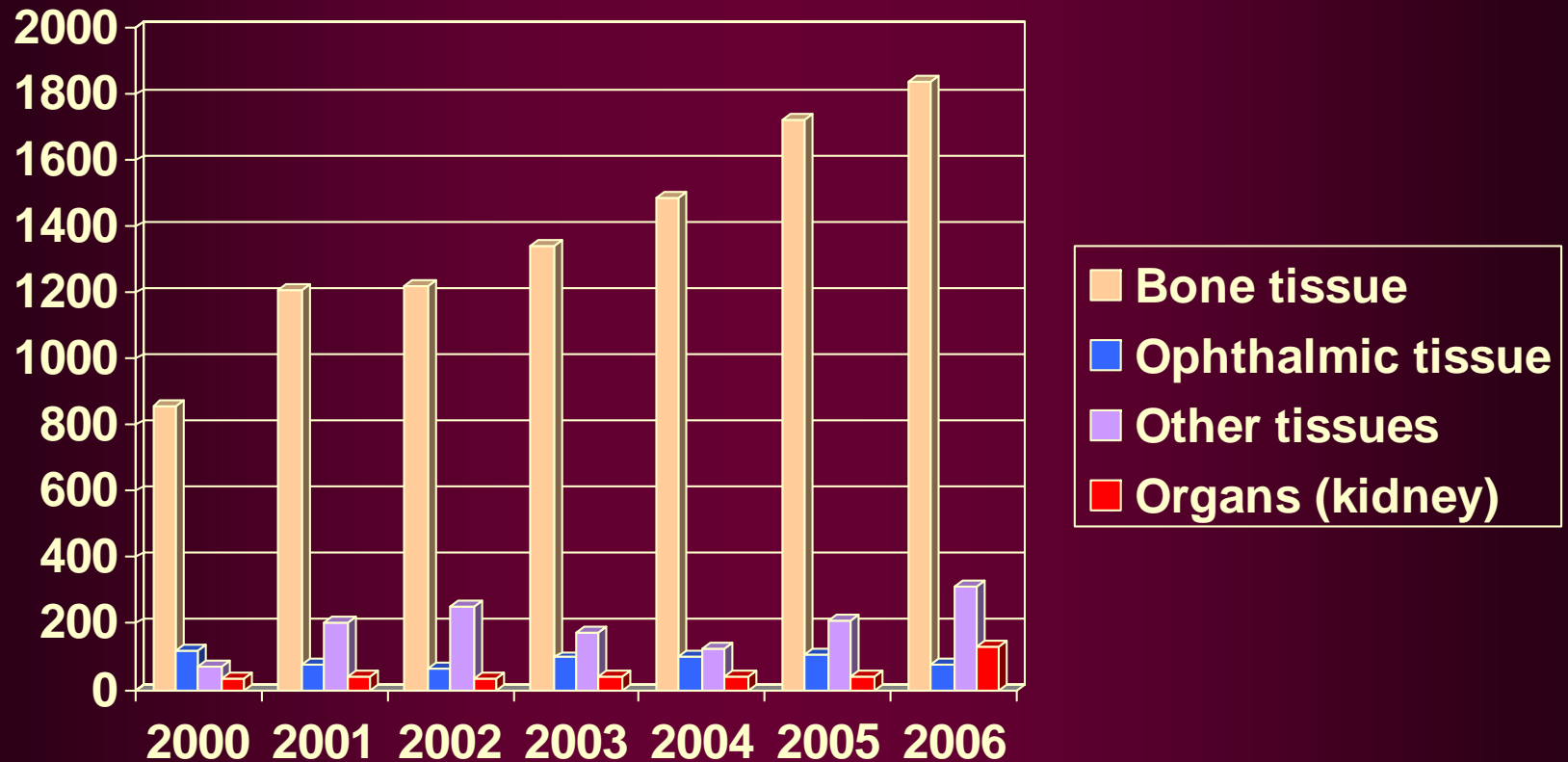


Malignancies, Autoimmune diseases, Neurologic disorders, & Genetic Entities



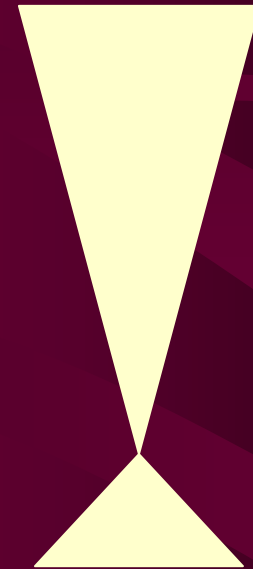
Lance D. Trainor, MD
William Beaumont Hospital
Royal Oak, MI

William Beaumont Hospital Annual Transplants



Outline

- 1 Malignancies
- 2 Autoimmune diseases
- 3 Neurologic disorders
- 4 Genetic Entities
- 5 Case Example



Planned Time Allocation

Within Each Category

- Definitions
- Background, “fun facts”
- Risks to recipients
- Appropriate Standards/Guidelines
- Various Tissue Bank Practices

Grey Zone

- AATB Standards and FDA Guidelines predominantly address infectious disease risks
- Variation between banks is acceptable
 - More conservative \neq safer
- MS tissue unless otherwise specified
- Medical Director has essential role
- Evaluation
 - 1. Potential risks to recipients
 - 2. Expected quality of allograft

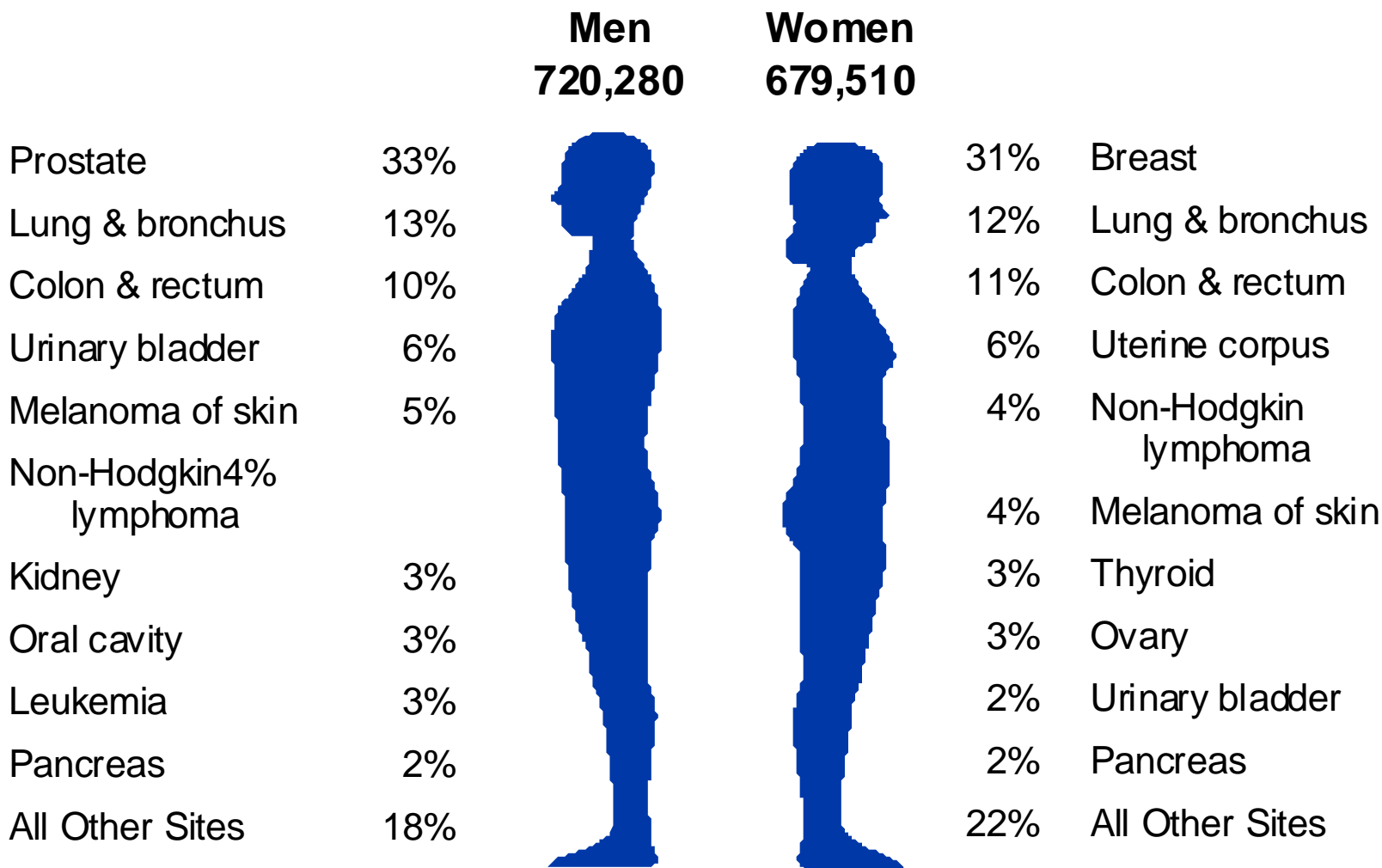
Malignancy

- a.k.a. “Cancer”, Neoplasm
- “A Neoplasm is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissue and persists in the same excessive manner after cessation of the stimulus that evoked the change”...Sir Rupert Willis

Mortality Causes in USA

Rank	Cause of Death	No. of deaths	% of all deaths
1.	Heart Diseases	685,089	28.0
2.	Cancer	556,902	22.7
3.	Cerebrovascular diseases	157,689	6.4
4.	Chronic lower respiratory diseases	126,382	5.2
5.	Accidents (Unintentional injuries)	109,277	4.5
6.	Diabetes mellitus	74,219	3.0
7.	Influenza and pneumonia	65,163	2.7
8.	Alzheimer disease	63,457	2.6
•	Nephritis	42,453	1.7
10.	Septicemia	34,069	1.4

2006 Estimated US Cancer Cases*



*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.

Source: American Cancer Society, 2006.

Lifetime Probability of Developing Cancer, by Site, Men, 2000-2002*

Site	Risk
All sites†	1 in 2
Prostate	1 in 6
Lung and bronchus	1 in 13
Colon and rectum	1 in 17
Urinary bladder‡	1 in 28
Non-Hodgkin lymphoma	1 in 46
Melanoma	1 in 52
Kidney	1 in 64
Leukemia	1 in 67
Oral Cavity	1 in 73
Stomach	1 in 82

* For those free of cancer at beginning of age interval. Based on cancer cases diagnosed during 2000 to 2002.

† All Sites exclude basal and squamous cell skin cancers and in situ cancers except urinary bladder.

‡ Includes invasive and *in situ* cancer cases

Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.0 Statistical Research and Applications Branch, NCI, 2005. <http://srab.cancer.gov/devcan>

Lifetime Probability of Developing Cancer, by Site, Women, US, 2000-2002*

Site	Risk
All sites†	1 in 3
Breast	1 in 8
Lung & bronchus	1 in 17
Colon & rectum	1 in 18
Uterine corpus	1 in 38
Non-Hodgkin lymphoma	1 in 55
Ovary	1 in 68
Melanoma	1 in 77
Pancreas	1 in 79
Urinary bladder‡	1 in 88
Uterine cervix	1 in 135

* For those free of cancer at beginning of age interval. Based on cancer cases diagnosed during 2000 to 2002.

† All Sites exclude basal and squamous cell skin cancers and *in situ* cancers except urinary bladder.

‡ Includes invasive and *in situ* cancer cases

Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.0 Statistical Research and Applications Branch, NCI, 2005. <http://srab.cancer.gov/devcan>

Considerations

- Potential risk to recipient
 - Failure of malignant cells to survive procurement, transport, & processing
 - Recipient's immune response to foreign cells
- Expected quality of allograft
 - Metastatic predisposition of specific malignancy
 - Structural integrity assessment during processing

Regulations

- AATB Standards, 11th Ed., D4.340 Malignancies
 - Donors with current or prior diagnosis of malignancy shall be evaluated by the Medical Director or licensed physician designee for suitability in accordance with the tissue bank's SOPM. The evaluation shall include: the type of malignancy, clinical course, and treatment prior to acceptance of a donor. The evaluation and reasons for acceptance shall be documented in the donor's record.

How Tissue Banks Handle Malignancies

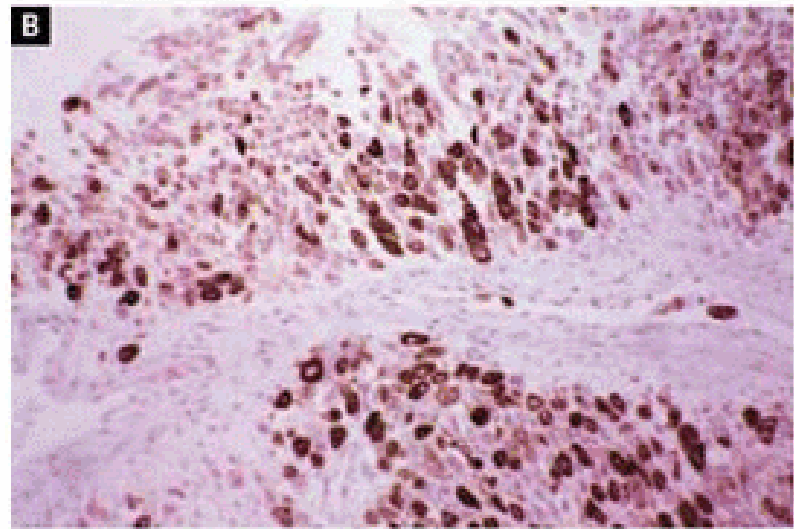
Tissue Bank ► Malignancy ▼	A	B	C	D	E
Cancer, Melanoma	5 yr disease free	Defer	Defer	Defer	5 yr disease free
Cancer, Skin	Accept	Accept	Accept, SCC after excision	Accept, MD review	Accept
Cancer, Infiltrating	5 yr disease free	Accept after MD review	Defer if present at death	Defer h/o, MD review at autopsy	5 yr disease free
Cancer, Metastatic	Defer	Defer	Defer	Defer	5 yr disease free
Cancer, Heme	Defer	5 yr disease free	Defer	Defer	Defer
Cancer, 1° Brain	Defer GBM, Accept Grade 1 & 2	Defer GBM, Accept after MD review	Accept GBM if no shunt/ surgery	Accept GBM if no shunt/ surgery	Accept

* All banks have Medical Director available for consultation

Melanoma

- Melanoma transmission has been clearly documented in renal transplantation
- In one case, organs were transplanted 16 years after donor's melanoma excision
- Disease progression attributed to immunosuppression of the recipient
- Melanoma incidence in transplant recipients is 4 - 8 X higher than general population

The excised kidney is necrotic and contains a large, central mass of melanoma tissue (Panel A). An S-100–stained specimen of the kidney shows striking cytologic atypia and strong S-100 positivity (Panel B).



Skin Cancer (not Melanoma)

- Common
 - Basal Cell Carcinoma, Squamous Cell Carcinoma
 - Low pathogenicity
 - Slow growing
- Local Spread
 - Infiltrate rather than metastasize
- Generally cured with excision

Cancer: Infiltrating, Metastatic

- Type of cancer
 - Different rates of growth
 - Variable metastatic predispositions
- Clinical Course
 - Extent of disease
 - Primary vs. recurrent
 - Response to therapy
- Treatment
 - Completely excised vs. inoperable
 - Responsive or resistant

Primary Brain Tumors

- Generally do not metastasize spontaneously
 - Blood brain barrier
 - Morbidity associated with physical location
- Case reports of cervical lymph node and peritoneal metastasis after surgical manipulation and ventriculoperitoneal shunt placement are published

Malignancy, etc.

- Risk of transmitting cancer is remote
- Recent study shows recipients of blood from donors deemed to have subclinical cancer at the time of donation have no increased cancer rates
- Many cancers are undiagnosed prior to death
 - Approximately 1 - 2% of male autopsies reveal latent prostate CA

Autoimmune Diseases

- Occur when self tissues are attacked by the immune system
- Often due to antibodies circulating in the blood
- More frequent in women than in men.

Overview of the Immune System

1. Protects us against foreign invaders

- proteins, viruses, bacteria

2. Two major divisions:

Non-Specific Response

- block entry of foreign agents into the body
- block spread of foreign agents in the body

Specific Responses

- antibody-mediated or “humoral” response
- cell mediated response

1. Nonspecific Response

Physical barriers

- skin, mucous membranes, secretions

Innate defense mechanisms

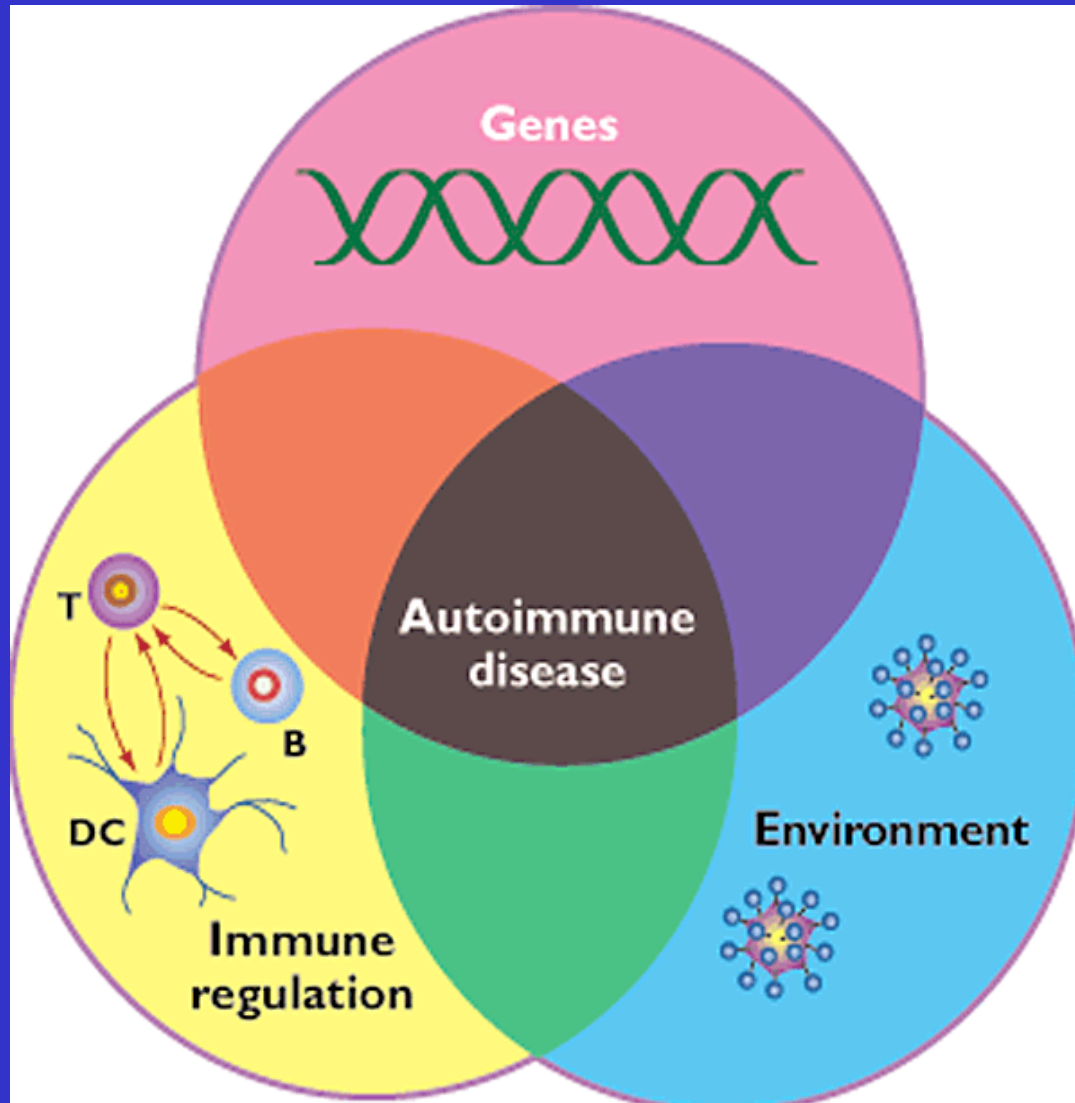
- phagocytosis (engulfing cells)
- inflammatory response, fever
- anti-microbial proteins (complement, cytokines)

2. Specific Response

Acquired Immunity

- Humoral immune response
 - B cells, antibodies, memory cells
- Cellular immune response
 - T cells, cytokines, memory cells

Factors Involved in Autoimmunity



From
Joerg Ermann &
C. Garrison Fathman
Nature Immunology
2, 759 - 761 (2001)

Considerations

- Potential risk to recipient
 - Failure of immune cells (lymphocytes) to survive procurement, transport, & processing
 - Recipient's immune response to foreign cells
- Expected quality of allograft
 - Tissue specificity of autoimmune condition
 - Severity of tissue damage

Regulations

- AATB Standards, D4.320 Miscellaneous Adverse Conditions
 - Cells and/or tissue from donors with any of the following conditions shall be evaluated by the Medical Director for suitability for transplantation in accordance with the tissue bank's SOPM:
 - 1. History of autoimmune disease
 - 2. Ingestion of, or exposure to, toxic substances
 - In addition to the general exclusion criteria, the following medical conditions shall also preclude musculoskeletal tissue donation:
 - 1. Rheumatoid Arthritis
 - 2. Systemic lupus erythematosus
 - 3. Polyarteritis nodosa
 - 4. Sarcoidosis
 - 5. Clinically significant bone disease

Rheumatoid Arthritis

- Symmetric chronic inflammatory arthritis
- Destructive and progressive
- Prevalence: 1-2% of population
- Women > Men, usual onset age 25-55 yr.
- Treatment: Lifelong, includes medication, physical therapy, exercise

How Tissue Banks Handle Autoimmune Disorders

Tissue Bank ▶ Autoimmune ▼	A	B	C	D	E
ITP	Accept	Accept	Accept Prior h/o	MD Discretion	Accept
Hashimoto Thyroiditis	Accept	Accept	Accept	Accept	Accept
Myasthenia Gravis	Accept	Accept	Accept	Defer	Accept

End organ affected...

ITP (Idiopathic Thrombocytopenic Purpura)...Platelets

Hashimoto's Thyroiditis...thyroid peroxidases

Myasthenia Gravis...muscle acetylcholine receptors

Neurologic Disorders

- Central Nervous System : The portion of the nervous system consisting of the brain and spinal cord

Considerations

- Potential risk to recipient
 - Transmission of Creutzfeldt Jakob Disease (CJD)
- Expected quality of allograft
 - Not an issue

Human Prion Protein



PrP: manufactured in cytoplasm, localized to neuromuscular junctions, unascertained function



- Stanley Prusiner, May 28, 1942
- July 1972, patient with CJD
- July 1974, Scrapie Lab
- 1982, “Prion” used in paper
- 1997, Nobel Prize in Medicine

Regulations

- AATB Standards, Appendix II (Exclusion Criteria)
 - Persons with a diagnosis of dementia or any degenerative or demyelinating disease of the central nervous system (CNS) or other neurologic disease of unknown etiology. (Note: Cells and/or tissues from donors with dementia, confirmed by gross and microscopic examination of the brain to be caused by cerebrovascular accident, brain tumor, head trauma, or toxic/metabolic dementia and who are confirmed not to have evidence of TSE on microscopic examination of the brain, may be acceptable based on an evaluation of this information by the Medical Director)
- FDA, Guidance for Industry, Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)
 - Similar to above

Dementia

- Progressive loss of cognitive function independent of the state of attention
- Not part of normal aging and always represents a pathologic process
- Common causes include cerebrovascular disease and neurodegenerative disorders
- The major degenerative disease associated with dementia is Alzheimer's disease

Alzheimer's Disease

- Clinical: insidious impairment of higher intellectual function, with alterations in mood and behavior
- Incidence:
 - Uncommon before 50
 - 3% age 65 - 74
 - 19% age 75-84
 - 47% age 85+
- Cortical atrophy
- Neurofibrillary tangles

Genetic Entities

- Genetic disorders include diseases caused by 1) variant genes called mutations or 2) unusual number of genes (chromosomes)
- Genetic disorders can be gene passed down through a family
- Most diseases have a genetic aspect

Considerations

- Potential risk to recipient
 - Reproductive Tissue risk
 - Oocytes, Spermatazoa, Embryos, etc.
 - Transmission of genetic disorder to offspring
 - Musculoskeletal Tissue Risk
 - No transmission of genetic disorder
- Expected quality of allograft
 - Musculoskeletal Tissue
 - Primarily related to physical activity limitations

Regulations

- AATB Standards, D4.221 Family History and Genetic Background
 - Evaluation of a three generation family history
 - Donor disqualified if risk of producing an offspring with a genetic disease greater than the general population, unless
 - carrier status testing is performed and negative
 - director donor selected by recipient

How Tissue Banks Handle Genetic Entities

Tissue Bank ► Genetic Dx. ▼	A	B	C	D	E
Huntington Chorea	Accept	Accept	Accept	Accept	Accept
Muscular Dystrophy	Accept	Accept	Accept	Defer	Accept
Trrisomy 13	Accept	Accept	Accept	Accept	Accept

Note: All banks utilize physical assessment of donor to determine if entity listed above acceptable

Case Example

- 43 y/o male roofer suffers cardiac arrest after sustaining multiple traumatic injuries in 17 ft. fall.
- Pt. Expires after unsuccessful resuscitation efforts.
- Family requests donation of “everything possible”
- PMH: Renal Cell Carcinoma, excised 4.5 yr.
PTD, no recurrence
- PSH: multiple traumatic fractures from prior falls
- Social History: unremarkable
- Autopsy: Absence of left kidney, overlying surgical scar, no residual carcinoma

Do you take the donor?

Tissue Bank ► Malignancy ▼	A	B	C	D	E
Cancer, Infiltrating	5 yr disease free	Accept after MD review	Defer if present at death	Defer h/o, MD review at autopsy	5 yr disease free

Tissue Bank A - NO

Tissue Bank B - YES

Tissue Bank C - YES

Tissue Bank D - NO

Tissue Bank E - NO

Renal Cell Carcinoma

- 85 - 90% of all renal cancers in adults
- usually present in sixth and seventh decades
- male predominance
- symptoms: pain, palpable mass, hematuria
- symptoms only present in 10% of cases
- approximately 7 of 1,000 autopsies reveals latent, unknown renal cell carcinoma
- metastasize to lungs, bone, lymph nodes, liver, adrenal glands, brain

Do you accept the donor?

Tissue Bank ► Malignancy ▼	A	B	C	D	E
Cancer, Infiltrating	5 yr disease free	Accept after MD review	Defer if present at death	Defer h/o, MD review at autopsy	5 yr disease free
Cancer, Metastatic	Defer	Defer	Defer	Defer	5 yr disease free

Tissue Bank A - NO

Tissue Bank B - NO

Tissue Bank C - NO

Tissue Bank D - NO

Tissue Bank E - NO

Case Example Summary

- Donor with h/o Renal Cell Carcinoma, 4.5 yr. PTD
- Accepted per Tissue Bank SOPM
- Lesion found in tibia at processing
- Presumed metastatic renal cell carcinoma
- Diagnosed as fibrous dysplasia
- No cause for deferral

Final Thoughts

- There are gray zones in donor eligibility determination
- Malignancies, Autoimmune diseases, Neurologic disorders, & Genetic Entities are some of the most interesting challenges in donor suitability
- A thoughtful approach to the process is required