2011 R. TOWNLEY PATON LECTURE: 
THE CORNEA DONOR STUDY AND 
IMPLICATIONS FOR EYE BANKING 

Presented by Alan Sugar, MD, during the 
EBAA/Cornea Society Fall Educational 
Symposium 

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2011 R. TOWNLEY PATON LECTURE:
THE CORNEA DONOR STUDY AND
IMPLICATIONS FOR EYE BANKING

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KELLOGG EYE CENTER
UNIVERSITY OF MICHIGAN
OCTOBER 21, 2011
NO FINANCIAL INTEREST

R. TOWNLEY PATON MD

• 1901-1984
• FOUNDER OF THE FIRST EYE BANK, 1944
• INNOVATOR IN CORNEAL TRANSPLANTATION

GOALS

• TO EVALUATE THE VALIDITY OF A FEW SELECTED EYE BANKING PRACTICES BY
• EXAMINING THE PORTIONS OF THE CDS RELATED TO EYE BANKING.
• TO COMPARE OTHER STUDIES TO THE CDS WHEN POSSIBLE.
• TO SUGGEST CHALLENGES TO SOME CONVENTIONAL POLICIES.
• TO ENCOURAGE CONTINUED AND EXPANDED SCIENTIFIC STUDY OF EYE BANKING.

CORNEA DONOR STUDY
Cornea Donor Study Coordinating Center
Jaeb Center for Health Research
Tampa, FL
Specular Microscopy Ancillary Study
Specular Microscopy Reading Center (SMRC)
Case Western Reserve University
Cleveland, OH
CDS DESIGN

- Determine effect of donor age on corneal transplant success
- Randomize donors <66 or >66
- Masked surgeon and recipient to age
- Surgery and treatment per surgeon’s routine
- Originally 5 year follow-up, now 10 years

PENETRATING KERATOPLASTY

INTERMEDIATE TERM STORAGE

Enrollment and Participation

- 1,101 subjects enrolled January, 2000 to August, 2002
  - 11 subjects with ineligible diagnoses
  - 1,090 eligible subjects
- 43 eye banks provided corneas to CDS subjects
- 105 surgeons at 80 sites enrolled subjects
Causes of Corneal Disease

- 62% Fuchs’ Dystrophy
- 34% Pseudophakic/Aphakic Corneal Edema
- 4% Other

Key Donor Eligibility Criteria

- Age 10 to 75 years
- Endothelial cell density 2300-3300
- EBAA criteria met

Donor Age

- Mean = 58 years
- Range 12 to 75 years

- Cornea from donor ≥ 66 yrs 383 (35%)
- Cornea from donor < 66 yrs 707 (65%)

Baseline Endothelial Cell Density (ECD)

<table>
<thead>
<tr>
<th>Donor Age</th>
<th>N</th>
<th>Baseline ECD* (Median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1,090</td>
<td>2666</td>
</tr>
<tr>
<td>66.0 to &lt;76.0 yrs</td>
<td>383</td>
<td>2624</td>
</tr>
<tr>
<td>12.0 to &lt;66.0 yrs</td>
<td>707</td>
<td>2680</td>
</tr>
</tbody>
</table>

*Baseline ECD from SMRC for 658 and from Eye Bank for 432
**Median Baseline Endothelial Cell Density by Donor Age**

*Note: Data from Eye Bank for 432 eyes and from Reading Center for 658 eyes*

**5-Year Graft Success Rates**

- Donor Age ≥ 66 years: 86%
- Donor Age < 66 years: 86%
- Difference = 0%
  - Limit of one-sided 95% CI = 4%
  - Less than pre-specified non-inferiority limit of 8%

Cornea Donor Study Investigator Group, *Ophthalmology* 2008;115:620

**Causes of Graft Failure**

<table>
<thead>
<tr>
<th>Category</th>
<th>Total N=1,090</th>
<th>Donor Age &lt; 66.0 N=707</th>
<th>Donor Age ≥ 66.0 N=383</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Graft Failures</td>
<td>135 (12%)</td>
<td>90 (13%)</td>
<td>45 (12%)</td>
</tr>
<tr>
<td>Primary Donor</td>
<td>3 (&lt;1%)</td>
<td>3 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td>Refractive</td>
<td>8 (&lt;1%)</td>
<td>5 (&lt;1%)</td>
<td>3 (&lt;1%)</td>
</tr>
<tr>
<td>Graft Rejection</td>
<td>48 (4%)</td>
<td>32 (5%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td>Non-rejection</td>
<td>76 (7%)</td>
<td>50 (7%)</td>
<td>26 (7%)</td>
</tr>
</tbody>
</table>

Majority non-rejection failure
SECONDARY CDS OUTCOMES RELATED TO EYE BANKING AND DONOR CHARACTERISTICS

CADAVER STORAGE TIME

- D1.600 Interval Between Death, Enucleation, Excision, Preservation, and Processing
- Acceptable time intervals from death, enucleation or excision to preservation may vary according to the circumstances of death and interim means of storage of the body. It is generally recommended that corneal preservation occur as soon as possible after death. All time intervals for each donor, i.e., the time of death to the time of enucleation and preservation and/or the time to corneal excision, and/or the time to additional tissue processing, shall be recorded. The time that cooling of ocular tissues and/or refrigeration of the body was begun shall be recorded, if applicable.

EBAA Medical Standards

CDS: CADAVER REFRIGERATION

- BODY REFRIGERATED
  - YES
  - NO
- DURATION
  - 0-4 H
  - >4-8 H
  - >8-10 H
  - >10 H
- 5 YEAR FAILURE RATE
  - NO SIGNIFICANT DIFFERENCES

SUGAR J. CORNEA 2009;28:981
DONOR RISK FACTORS FOR GRAFT FAILURE

<table>
<thead>
<tr>
<th>Retrieval / Timing Factor</th>
<th>N</th>
<th>5-yr Graft Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Retrieval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enucleation</td>
<td>218</td>
<td>13%</td>
</tr>
<tr>
<td>In situ</td>
<td>872</td>
<td>14%</td>
</tr>
<tr>
<td>Death to Preservation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4 hours</td>
<td>206</td>
<td>17%</td>
</tr>
<tr>
<td>&gt;4-8 hours</td>
<td>577</td>
<td>13%</td>
</tr>
<tr>
<td>&gt;8-10 hours</td>
<td>165</td>
<td>12%</td>
</tr>
<tr>
<td>&gt;10 hours</td>
<td>142</td>
<td>18%</td>
</tr>
</tbody>
</table>


DONOR RISK FACTORS FOR GRAFT FAILURE

<table>
<thead>
<tr>
<th>Retrieval / Timing Factor</th>
<th>N</th>
<th>5-yr Graft Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Refrigerated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>255</td>
<td>15%</td>
</tr>
<tr>
<td>Yes</td>
<td>835</td>
<td>13%</td>
</tr>
<tr>
<td>Death to Surgery Time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 - &lt;3 days</td>
<td>146</td>
<td>16%</td>
</tr>
<tr>
<td>3 - &lt;4 days</td>
<td>597</td>
<td>14%</td>
</tr>
<tr>
<td>4 – 8 days</td>
<td>347</td>
<td>12%</td>
</tr>
</tbody>
</table>


REFRIGERATION

- C3.050 Equipment, Maintenance and Cleaning
  - Each eye bank laboratory shall have a refrigerator with a device, visible without opening the refrigerator, for recording temperature variations. The temperature recording device shall reflect the temperature of the stored tissue under normal storage conditions. Temperature variations must be recorded daily and remain within the range of 2 to 8 °C. The refrigerator’s continuous temperature recorder shall be calibrated against an NIST standard thermometer or a standard thermometer as defined by the eye bank’s regulatory agencies at least once a year and recalibrated if necessary. The eye bank shall have a system in place to ensure that temperature variations are recorded and that the refrigerator's continuous temperature recorder is calibrated against an NIST standard thermometer or a standard thermometer as defined by the eye bank’s regulatory agencies at least once a year. The eye bank shall have a system in place to ensure that temperature variations are recorded and that the refrigerator’s continuous temperature recorder is calibrated against an NIST standard thermometer or a standard thermometer as defined by the eye bank’s regulatory agencies at least once a year. In the event of a temperature deviation outside the acceptable range, there must be immediate notification and action to be taken. Testing of the alarm system must be performed and documented in the patient’s medical record.

EBAA Medical Standards

<table>
<thead>
<tr>
<th>Table 1: Risk of Donor Factors Predicted Ocular Failure (N = 1012)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor characteristic</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Overall</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>&lt;30 years</td>
</tr>
<tr>
<td>30 years or more</td>
</tr>
<tr>
<td>Cause of death</td>
</tr>
<tr>
<td>Accident</td>
</tr>
<tr>
<td>Suicide</td>
</tr>
<tr>
<td>Natural</td>
</tr>
<tr>
<td>Referral</td>
</tr>
<tr>
<td>Non-referral</td>
</tr>
<tr>
<td>Referral</td>
</tr>
</tbody>
</table>

EBAA Medical Standards
DONOR RISK FACTORS FOR GRAFT FAILURE

- Slit lamp characteristics
- No effect on graft outcomes

HLA MATCHING

- Collaborative Corneal Transplantation Studies
- Randomized by HLA match
- High Vs. Low Match
- No Significant Difference in Rejection or Failure

ABO MATCHING

- Collaborative Corneal Transplantation Studies
- ABO Matching a Secondary Outcome
- Small but Statistically Significant Benefit to ABO Match

CDS: ABO Compatibility (N=1002)

- Effect of ABO matching in CCTS trial
- 64% ABO compatible
- ABO compatibility did not vary by any recipient or donor demographics including self-reported race/ethnicity


CDS: ABO Compatibility and Graft Failure

<table>
<thead>
<tr>
<th>Graft Failure Type</th>
<th>ABO Compatible</th>
<th>ABO Incompatible</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rejection</td>
<td>6%</td>
<td>4%</td>
<td>0.20</td>
</tr>
<tr>
<td>Any Cause</td>
<td>13%</td>
<td>30%</td>
<td>0.30</td>
</tr>
</tbody>
</table>

CDS: ABO Compatibility and Graft Rejection

- Graft rejection not impacted by ABO compatibility
- 5-year cumulative incidence of definite rejection episode:
  - 12% ABO compatible vs. 8% ABO incompatible (p=0.09)

CDS: Donor Factors Associated with Graft Failure

- Graft failure rates were not significantly impacted by:
  - any donor characteristics
  - any factors related to the type of tissue retrieval, processing, timing of use of the cornea
  - any characteristics of the donor cornea
- Adjusting for donor age did not affect the results
CDS DATA QUESTION CURRENT STANDARDS FOR:

- Death to preservation time
- Death to surgery time
- Refrigeration time
- Cadaver storage time
- Slit lamp characteristics

CDS SPECULAR MICROSCOPY ANCILLARY STUDY (SMAS)

- 31 eye banks
- 41 sites
- 596 subjects
- 347 at 5 years

### Baseline Endothelial Cell Density
(only includes subjects with graft success through 5 years)

<table>
<thead>
<tr>
<th>Donor Age</th>
<th>N</th>
<th>Baseline ECD* (Median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>347</td>
<td>2698</td>
</tr>
<tr>
<td>66.0 to &lt;76.0 years</td>
<td>108</td>
<td>2585</td>
</tr>
<tr>
<td>12.0 to &lt;66.0 years</td>
<td>239</td>
<td>2731</td>
</tr>
</tbody>
</table>

*Baseline ECD from SMRC for 229 and from Eye Bank for 118

### 5-Year Endothelial Cell Density
(only includes subjects with graft success through 5 years)

<table>
<thead>
<tr>
<th>Donor Age</th>
<th>N</th>
<th>5-Year ECD (Median)</th>
<th>% Loss (Median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>347</td>
<td>778</td>
<td>70%</td>
</tr>
<tr>
<td>66.0 to &lt;76.0 years</td>
<td>108</td>
<td>654</td>
<td>75%</td>
</tr>
<tr>
<td>12.0 to &lt;66.0 years</td>
<td>239</td>
<td>824</td>
<td>69%</td>
</tr>
</tbody>
</table>
Endothelial Cell Density over 5 Years by Donor Age Group

Cornea Donor Study Investigator Group, Ophthalmology 2008;115:627

Endothelial Cell Density: Baseline vs. 5 Years
(only includes subjects with graft success through 5 years N=347)

Spearman Correlation Coefficient (95% CI) = 0.27 (0.17, 0.36, $r^2=0.07$)

Median 5-Year Endothelial Cell Density

Spearman Correlation Coefficient (95% CI) = −0.23 (−0.33, −0.13)

Percent Endothelial Cell Loss from Baseline to 5 Years

Spearman Correlation Coefficient (95% CI) = −0.20 (−0.30, −0.09)
11/14/2011

Endothelial Cell Density Loss by Donor Age (N=347)

Spearman Correlation Coefficient (95% CI) = -0.20 (-0.30, -0.09)

Effect of Donor and Recipient Factors on Endothelial Cell Loss

• Younger Donor Age (P<0.001)
  – 12-<40 62%
  – 70-76 75%

• Larger Graft Size (P<0.001)
  – >8.0 mm 68%
  – ≤8.0 mm 75%

• Female Donor (P=0.004) 67% vs. Male 72%

5-yr Cumulative Incidence of Graft Failure

Baseline ECD cells/mm²

<2500 (N=141) 2501-2999 (N=280) ≥3000 (N=79)

3% 5% 3%

Analysis of ECD Predictive of Graft Failure


Female donors had less cell loss than male donors.
CDS: Endothelial Cell Density Predictive of Endothelial Graft Failure

- Pre-op ECD unrelated to graft failure due to endothelial decompensation
- Strong correlation of ECD at 6 months with failure due to endothelial decompensation
- 62 grafts clear at 5 years with ECD < 500 cells/mm² (178-497)

BIEXPONENTIAL MODEL OF ENDOTHELIAL CELL LOSS

- Age related cell loss in normal eyes

Armitage, Dick, Bourne. IOVS 2003;44:3326
BIEXPONENTIAL MODEL OF POST KERATOPLASTY CELL LOSS

• Endothelial cell loss fitted to data of Bourne

Armitage, Dick, Bourne. IOVS 2003;44:3326

BIEXPONENTIAL MODEL OF POST KERATOPLASTY CELL LOSS

• Predicted cell loss by initial density
• Theoretical support for 2000 ECD limit

Armitage, Dick, Bourne. IOVS 2003;44:3326

BIEXPONENTIAL MODEL OF POST KERATOPLASTY CELL LOSS

• If ECD at 5 years is only minimally related to pre-op ECD,
• Then donor cell count may not be as important as we now assume
• If initial severe cell loss correlates with graft failure,
• Then we need to develop better understanding of the causes for initial/early cell loss
• Also, these models assume all recipients act alike

CELL LOSS POST KERATOCONUS PKP

• Representative case
• Less than PKP for endothelial disease
• Predicted 27 years to ECD < 500

PREDICTED GRAFT SURVIVAL BY HOST ENDOTHELIAL STATUS

Böhringer ET AL HYPOTHESIS

- Half-lives of donor and recipient endothelium differ
- Recipient half-life longer than donor in keratoconus
- Donor half-life longer than recipient in bullous keratopathy
- Healthier endothelium moves toward the unhealthy endothelial gradient, or
- Autologous endothelium moves along gradient

MIGRATION OF DONOR ENDOTHELium TO HOST

DONOR ENDOTHELIAL DENSITY: TENTATIVE CONCLUSIONS

- The 2300 cells/mm² ECD used in the CDS should not be the standard lower limit for PKP donors
- The Böehringer hypothesis suggests using older donors for conditions with good endothelium (KC) and younger donors for endothelial disease
- There is little evidence for current limits on ECD
IMPACT OF DONOR CRITERIA ON TISSUE AVAILABILITY AND COST

<table>
<thead>
<tr>
<th>Maximum Age</th>
<th>Minimum Cell Density</th>
<th>Percent of Suitable Tissue</th>
<th>Relative Fee</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>2000</td>
<td>100.0%</td>
<td>2,000</td>
</tr>
<tr>
<td>75</td>
<td>2300</td>
<td>87.5%</td>
<td>2,285</td>
</tr>
<tr>
<td>75</td>
<td>2500</td>
<td>71.1%</td>
<td>2,813</td>
</tr>
<tr>
<td>75</td>
<td>2800</td>
<td>36.9%</td>
<td>5,427</td>
</tr>
</tbody>
</table>

Effect of Limiting Donor Age

<table>
<thead>
<tr>
<th>Maximum Age</th>
<th>Minimum Cell Density</th>
<th>Percent of Suitable Tissue</th>
<th>Relative Fee</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>2000</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>2000</td>
<td>90.0%</td>
<td></td>
</tr>
<tr>
<td>65</td>
<td>2000</td>
<td>74.4%</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>2000</td>
<td>56.4%</td>
<td></td>
</tr>
<tr>
<td>55</td>
<td>2000</td>
<td>41.7%</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>2000</td>
<td>29.1%</td>
<td></td>
</tr>
</tbody>
</table>

Effect of Combined Restrictions

REVOLUTION IN CORNEAL TRANSPLANTATION

• “SOMETIMES DECADES PASS AND NOTHING HAPPENS; AND THEN SOMETIMES WEEKS PASS AND DECADES HAPPEN”
  V. LENIN, R. COHEN NYT 4/12/11
• CORNEAL TRANSPLANTATION IS IN THE MIDST OF REVOLUTIONARY CHANGE
• CDS EXAMINED ONLY PENETRATING KERATOPLASTY FOR ENDOTHELIAL DYSFUNCTION
• CDS BEGAN 10+ YEARS AGO

ENDOTHELIAL KERATOPLASTY

• 2005 1,398
• 2006 6,027
• 2007 14,159
• 2008 17,468
• 2009 18,221
• 2010 19,159
40% of PKP in 2010 potentially EK

ENDOTHELIAL KERATOPLASTY
PKP VS. DSEK

Van Dooren BTH, et al.
JVO S Sept 12, 2011

Price MO et al.
Ophthalmology
2011;118:725

EYE BANKING FOR ENDOTHELIAL KERATOPLASTY

- Few studies of:
  - Donor characteristics
  - Donor preparation
  - Storage parameters

Future Studies on Eye Banking and Keratoplasty
- Better define the endothelial cell requirements for both penetrating and endothelial keratoplasty
- Better define criteria for utilization
- Explore the criteria for “pre-cut” tissue (DSEA, DMEA)
- Improve understanding of endothelial cell loss
- Improve prevention and treatment of rejection
- Refine Eye Banking Criteria for PKP/EK

CORNEAL PRESERVATION TIME STUDY (CPTS)
- NEI funded multicenter study of donor storage duration
- Jonathan Lass MD, Principal Investigator
- Up to 7 day storage vs >7 day storage
- Endothelial keratoplasty only

COMPREHENSIVE NATIONAL CORNEAL GRAFT REGISTRY
- Cornea Society
- David Glasser MD
THANKS TO:

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  — Christopher Hood

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  — Kevin Ross
  — Bradley Tennant
  — Chuck Pivoney
  — Kyle Mavin

• Jaeb Center for Health Research/CDS Steering Committee
  — Roy Bach
  — Robin Gel
  — Jonathan Lass
  — Monty Montoya
  — Maryann Redford
  — Mark Mannis
  — Ed Holland

• EBAA