DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Date: May 8, 2001

To: FDA Dockets Management Branch, HFA-305

From: Ruth Solomon, M.D., CBER, Human Tissue Staff, HFM-305 RS

Concerning: Submission to Docket No. 97N-484P, Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-based Products

Please accept to the docket, the attached:

1. FDA drafted minutes of 5/3/01 meeting with EBAA
2. EBAA agenda, 5/3/01
3. EBAA 2000 Eye Banking Statistical Report

97N-484P

MM1

Minutes
Meeting Between FDA and EBAA
Regarding Current Good Tissue Practice Issues

May 3, 2001
1:00-3:00pm
WOC-I, Conference Room 2

Present:

FDA: Jill Warner, Marty Wells, Ruth Solomon, Paula McKeever, Jerry Davis, Astrid Szeto, Areta Kupchyk

EBAA: Patricia Aiken O'Neill, Patricia Voljavec, Kurt Weber, Barbara Crow; Dr. Michael Hettinger (by telephone)

The Eye Bank Association of America (EBAA) requested this meeting with FDA to discuss the proposed regulation on "Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement," published for public comment on January 8, 2001, and how it will apply to eye banks. An agenda was distributed at the meeting (Attachment A), as well as the 2000 Eye Banking Statistical Report (Attachment B).

EBAA made the following introductory statements. There are approximately 95 eye banks in the U.S. Only one is not a member of EBAA. EBAA supports the framework of the GTPs, but has concerns about certain issues and wants clarification. Eye banks differ from blood banks in that most are small entities that do all their own procuring, processing, and distributing. Much time is spent outside of the bank, to procure eye tissue. The time and cost to adhere to all of the GTPs may be prohibitive for the smaller eye banks.

The following issues were discussed:

1. **Good Tissue Practices**

   Subcontractors--EBAA explained that eye banks generally have written agreements with subcontractors (e.g., testing laboratories) which require that the lab be CLIA-certified, use FDA-licensed test kits, follow manufacturer's test kit instructions, etc. Is this sufficient, or would each eye bank have to physically audit the subcontractor? An audit would be difficult because of the time, expense, and lack of technical expertise in testing.

   FDA responded that contracts and agreements are discussed in 1271.270(f). There is no proposed requirement that an eye bank audit the subcontractor. However, the eye bank would be ultimately responsible for ensuring that the final tissue product be in compliance with proposed regulations. It is up to the eye

bank to take whatever actions would ensure compliance by a subcontractor so that the final tissue product is in compliance with the regulations. CLIA certification is not sufficient to assure that a facility is in compliance with FDA requirements. In addition, a subcontractor that performs any step in a tissue manufacturing process is required under 21 CFR Part 1271 to register their establishment, list the products, and would be required under the proposed regulations to implement is own quality assurance program, including the performance of a self-audit.

Carriers--FDA clarified that carriers (e.g., Federal Express, airlines) are exempt under the proposed and final regulations.

2. **Primary Graft Failure**

Dr. Hettinger discussed the fact that the data given in the economic analysis of the regulation--Estimated Benefits of the Proposed Rule (pages 1539-1540), may not be accurate, in terms of frequency of occurrence of primary graft failure, cost, need for hospitalization. He pointed out that primary graft failure may not be due to the cornea itself, but rather to the surgical technique. EBAA mentioned that primary graft failure is reported to the eye bank, and then to EBAA.

FDA responded that EBAA should include in their comments to the docket a discussion of relevant data about primary graft failure.

3. **Computers**

EBAA explained that computers are used in eye banks to provide a backup for hard copy, and to summarize the donor medical history and serology results on a standardized form that accompanies the eye tissue. The software is off-the-shelf, such as FileMaker Pro. The computers are not involved in any decision-making process, such as determination of donor suitability. Would FDA expect computer software used for these purposes to be validated?

FDA responded that the proposed regulation states that records be accurate and legible. FDA did not propose to require validation of commercially distributed record keeping software, which is not intended or used to make decisions.

4. **Facilities**

EBAA asked if the statement in 1271.190(a) that adequate toilet facilities shall be provided means that toilet facilities need to be in the eye bank. All eye banks have access to sinks for hand washing in the lab itself.

FDA responded that toilets would not have to be physically located in the eye bank, as long as they were available, particularly for hand washing. EBAA suggested that the preamble clarify this.

5. **Environmental Control**

EBAA explained that eye banks do not use clean room techniques. Rather, since the workspace for processing eye tissue is relatively contained, eye banks use

laminar flow cabinets. Would this satisfy 1271.195(a)(2)--control and monitoring of ventilation and air filtration?

FDA responded that the proposed regulation states that where environmental conditions could reasonably be expected to have an adverse effect on the function or integrity of the tissue, the environment would need to be controlled and monitored. If the laminar flow cabinet adequately controls and monitors the relevant environment, it could satisfy this requirement.

6. **Equipment**

EBAA asked about 1271.200(a)--any automated, mechanical, electronic, computer, or other equipment used for inspection, measuring, and testing shall be capable of producing valid results. Eye banks use a slit lamp microscope to assess the overall quality of the cornea--there are no measurements made, and the user makes the assessment of the cornea. Would a slit lamp microscope need to be validated, and if so, how?

FDA responded that the slit lamp microscope, based on the description provided by the EBAA representatives, does not appear to be capable of validation. A specular microscope, however, which actually counts cells, and produces a measurement, would have to be validated. FDA said that they would consult with CDRH about the slit lamp, and get back with EBAA.

7. **Process Validation**

EBAA asked for clarification on how process validation would apply to eye bank procedures.

FDA explained that the proposed regulation for process validation would apply when verification (evaluation) of each individual cornea was not possible. For instance, packaging procedures might need to be validated to ensure that temperature could be controlled during shipment. Other procedures, where each cornea was inspected, would not have to be validated.

8. **Tracking**

EBAA discussed their standards for tracking of tissue to the recipient, and expressed concern that while they had excellent compliance from U.S. ophthalmologists, other ophthalmologists outside the U.S. often did not return information about the recipient.

FDA responded that FDA regulations focus on having appropriate procedures in place. The proposed regulations would require establishments to put in place procedures to enable tracking. Establishments would be required to document that consignees agree to comply with tracking requirements. FDA's jurisdiction extends to tissue utilized within the U.S. International physician compliance with reporting recipient information or adverse reactions would remain voluntary.

9. **Other comments**

A. **Effective date**--EBAA indicated that there should be a long implementation period, (similar to that provided for hospitals under the recently published "Privacy" rule), before the GTP final rule would become effective, in order to allow small banks enough time to come into compliance. EBAA suggested a 2 year implementation period. FDA responded that EBAA should include this suggestion in their comments to the docket. When asked about the expected date of publication, FDA mentioned that a Unified Agenda, which publishes semi-annually, would contain this information.

B. **Future FDA and EBAA interaction**--EBAA and FDA discussed how they could best work together in the future. They discussed a possible role for FDA as liaison to the EBAA Medical Advisory Board. EBAA asked how FDA could be more involved in the development of EBAA standards. FDA responded that FDA representatives can act as liaisons to association committees, such as is done with the AATB Standards Committee and Medical Advisory Committee. EBAA said that they would look into formally inviting FDA to provide a liaison to their Medical Advisory Board, which updates their Medical Standards, and possibly also to their Accreditation Committee. EBAA also offered to invite FDA to participate in future EBAA inspections. EBAA further suggested that joint workshops with FDA inspectors and EBAA inspectors would be helpful. FDA agreed and suggested that co-sponsorship of a workshop should be pursued once the GTP regulation is final.

C. **Guidance documents**--Meeting attendees discussed the general nature of the proposed GTP regulations and the value of guidance specific to particular segments of the tissue industry. FDA suggested that EBAA might want to consider developing guidance on complying with the GTP regulations that would have specific applicability to the eye banking community. EBAA responded that they planned to do so. FDA outlined the process by which interested groups can submit proposed guidance documents to FDA, and if appropriate, FDA can issue such guidance or modified guidance as an FDA document after notice and comment procedures.

D. **Amniotic membrane**--FDA asked about the use of amniotic membrane for ocular repair. EBAA mentioned that eye banks might occasionally be asked by an ophthalmologist to get him amniotic membrane, and that the eye bank would facilitate this service. FDA mentioned that it considers the use of amniotic membrane for ocular repair a nonhomologous use, and EBAA agreed. EBAA stated that they only knew of a few tissue banks that procured amniotic membrane.

At the end of the meeting, the attendees agreed that the discussion had been worthwhile.

FDA/EBAA Agenda

1401 Rockville Pike

May 3, 2001

1-3 pm

Discussion Items:

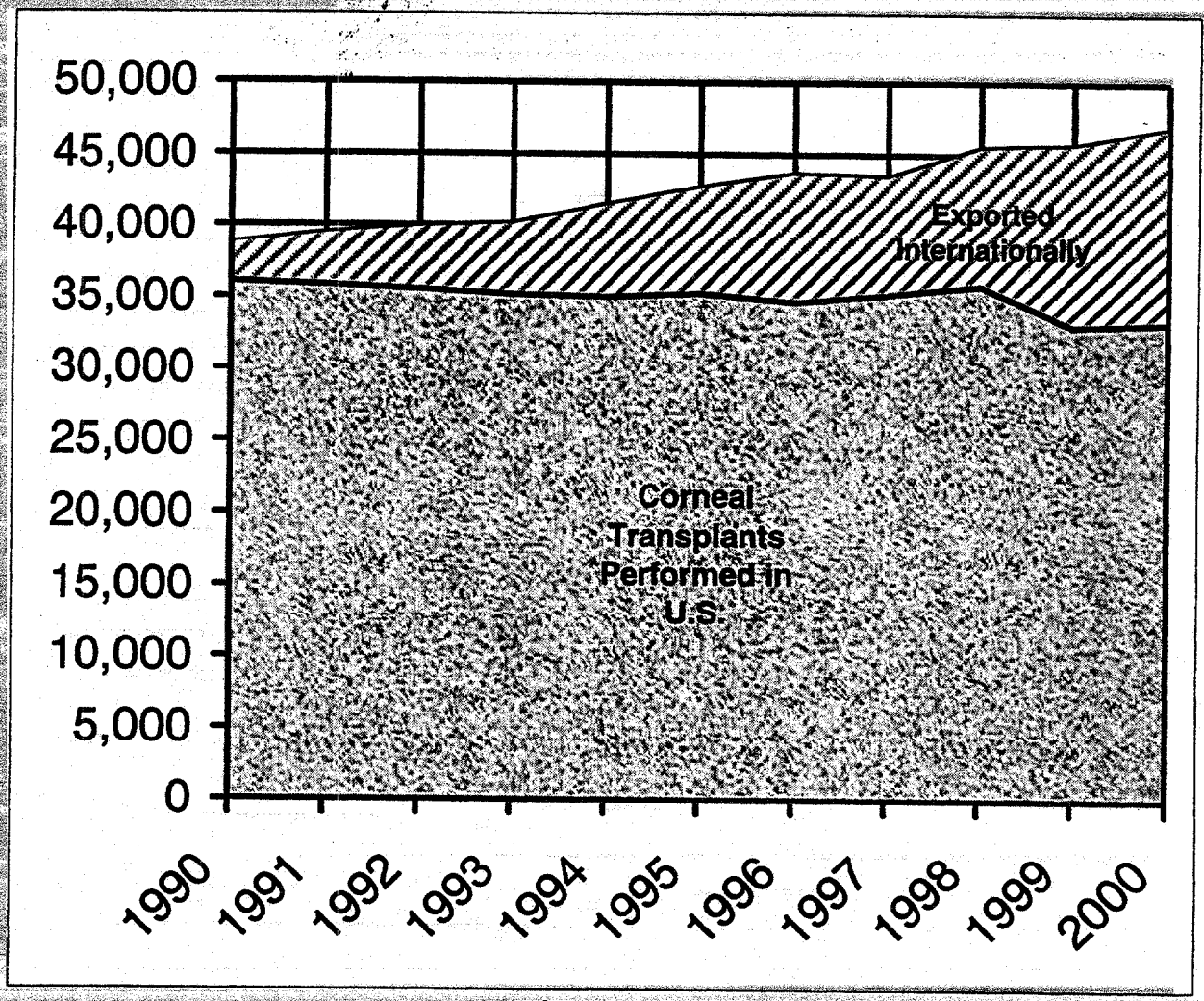
1. Section §1271.150 Good Tissue Practices
2. Section §1271.160 Quality Programs
3. Section §1271.190 Facilities
4. Section §1271.195 Environmental Controls
5. Section §1271.200 Equipment
6. Section §1271.230 Process Validation
7. Section §1271.265 Receipt and Distribution
8. Section §1271.290 Tracking

EBAA Participants:
Barbara Crow, CEBT, EBAA Chair
Kurt Weber, CEBT, EBAA Legislative Committee
Patty Jarvis Vojavec, Legislative Strategies
Patricia Aiken O'Neill, Esq, EBAA President/CEO

VIA Conference:
Michael Hettinger, MD, EBAA Chair – Elect

Partial List of FDA Participants:
Ruth Solomon –Human Tissue Staff, Office of Blood
Marty Wells - Human Tissue Staff, Office of Blood
Jim Warner - Immediate Office of the Director, CBER
Areta Kupchyk - Office of General Counsel
Jerry Davis – Office of Compliance

EYE BANK ASSOCIATION of AMERICA



2000 Eye Banking Statistical Report

Eye Bank Association of America
1015 18th Street, N.W.
Suite 1010
Washington, DC 20036
Phone (202) 775-4999
Fax (202) 429-6036

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Abbreviated Version

2000 U.S. Eye Banking Statistics

80 U.S. Eye Banks Reporting (1)

Donations	2000	1999	% Change
Total Donations	85,548	86,877	-1.5%
Total Number of Donors	43,432	43,802	-0.8%

Distribution	2000	1999	% Change
Corneal Grafts (2)	46,949	45,765	2.6%
Epikeratophakia	73	61	19.7%
Sclera	3,898	4,003	-2.6%
Other Surgical Use (3)	79	97	-18.6%
Research	21,406	20,294	5.5%
Training	4,918	6,931	-29.0%

	Used Locally	Exported (4) Domestic and International	Total
Corneal Grafts (2)	23,941	23,008	46,949

Patients Awaiting Corneal Transplant

75 U.S. Eye Banks Reporting

Number of persons on waiting lists for corneal tissue in the U.S. as of 12/31/2000:	**1,125**
Number of persons scheduled for corneal transplant surgery in the U.S. as of 12/31/2000:	**2,307**

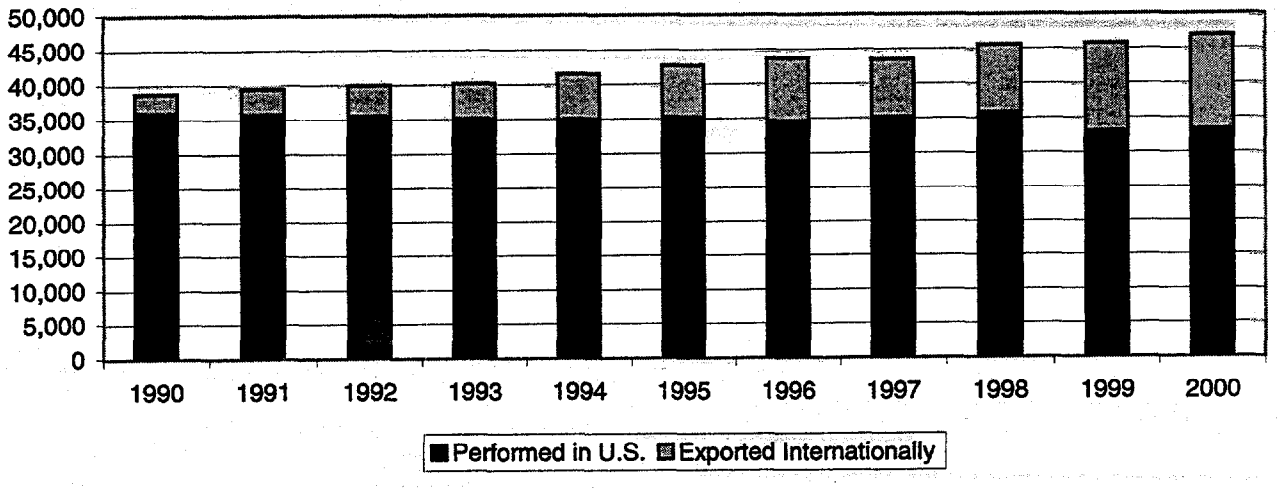
(1) In 1999, there were 83 U.S. eye banks reporting.

(2) Includes penetrating keratoplasty (PKP) and lamellar keratoplasty (LKP).

(3) Procedures performed, such as keratolimbal allograft (KLAL), use human eye tissue which does not apply to any previously listed category.

(4) Exported tissues are those sent by U.S. eye banks to other eye banks or to surgeons in different service areas within the U.S. or to other countries.

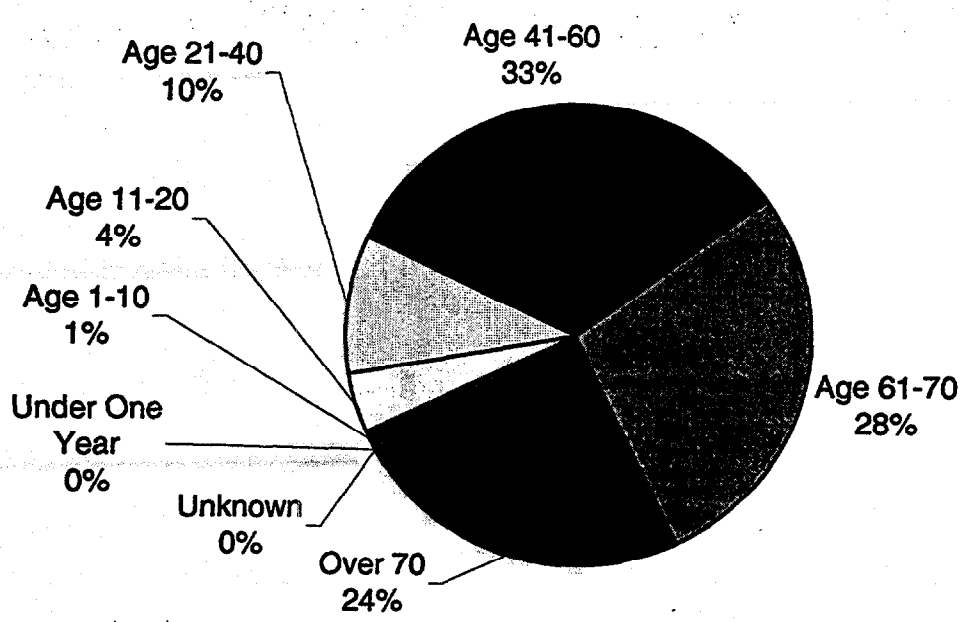
Annual Number of Corneal Transplants
1990-2000



Year	Provided by U.S.	Exported Internationally	Performed in U.S.
1990	38,762	2,725	36,037
1991	39,515	3,684	35,831
1992	39,973	4,448	35,525
1993	40,215	5,042	35,173
1994	41,539	6,517	35,022
1995	42,740	7,440	35,300
1996	43,711	9,043	34,668
1997	43,492	8,283	35,209
1998	45,579	9,718	35,861
1999	45,765	12,745	33,020
2000	46,949	13,689	33,260

Donors by Age

80 U.S. Eye Banks Reporting (1)

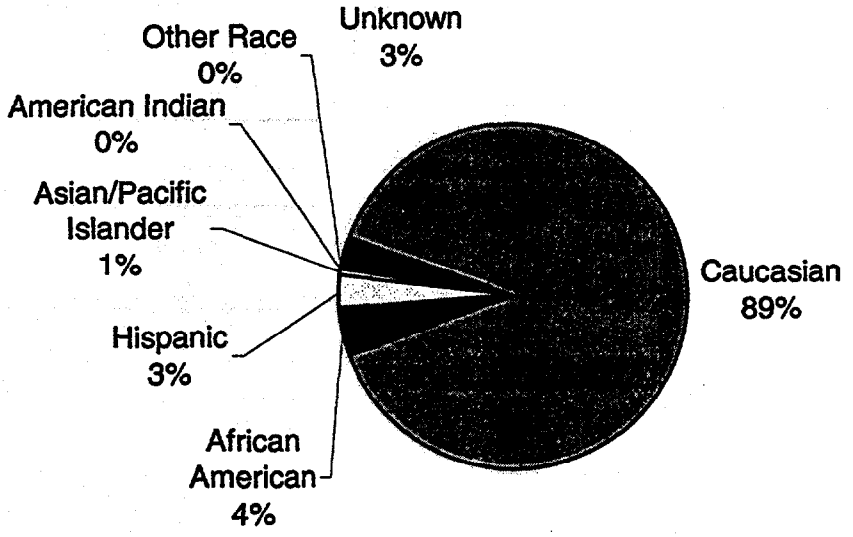


	2000		1999 #	
Under One Year	65	0.1%	49	0.1%
Age 1-10	532	1.2%	520	1.2%
Age 11-20	1,777	4.1%	1,763	4.0%
Age 21-40	4,215	9.7%	4,087	9.3%
Age 41-60	14,380	33.1%	13,653	31.2%
Age 61-70	12,105	27.9%	12,459	28.4%
Over 70	10,333	23.8%	11,134	25.4%
Unknown	25	0.1%	137	0.3%
Total Donors by Age	43,432		43,802	

(1) In 1999, there were 83 U.S. eye banks reporting.

Donors by Race

80 U.S. Eye Banks Reporting (1)

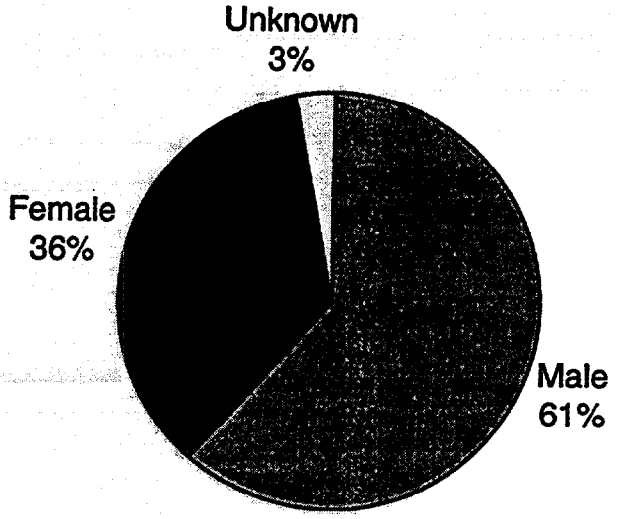


	2000		1999 #	
Caucasian	38,644	89.0%	39,135	89.3%
African American	1,951	4.5%	1,888	4.3%
Hispanic	1,277	2.9%	1,309	3.0%
Asian/Pacific Islander	261	0.6%	241	0.6%
American Indian	58	0.1%	41	0.1%
Other Race	96	0.2%	90	0.2%
Unknown	1,145	2.6%	1,098	2.5%
Total Donors by Race	43,432		43,802	

(1) In 1999, there were 83 U.S. eye banks reporting.

Donors by Gender

80 U.S. Eye Banks Reporting (1)

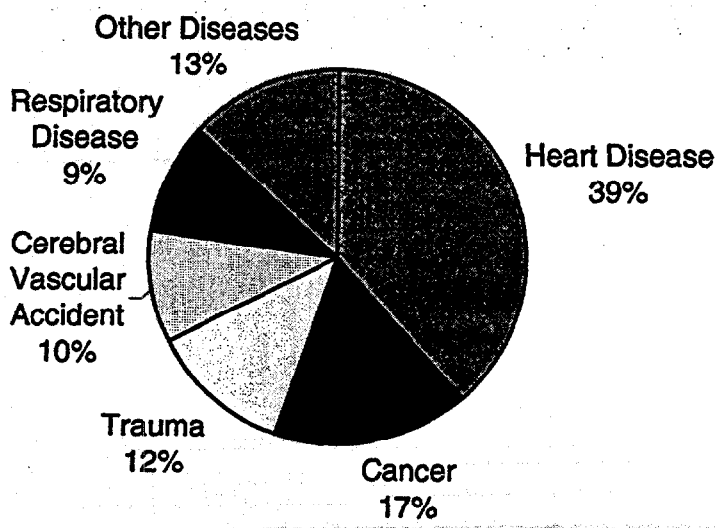


	2000		1999 #	
Male	26,687	61.4%	26,794	61.2%
Female	15,456	35.6%	15,978	36.5%
Unknown	1,289	3.0%	1,030	2.4%
Total Donors by Gender	43,432		43,802	

(1) In 1999, there were 83 U.S. eye banks reporting.

Cause of Death

80 U.S. Eye Banks Reporting (1)



	2000		1999 #	
Heart Disease	16,591	38.2%	17,459	39.9%
Cancer	7,390	17.0%	7,406	16.9%
Trauma	5,381	12.4%	5,154	11.8%
Cerebral Vascular Accident	4,174	9.6%	4,073	9.3%
Respiratory Disease	4,083	9.4%	4,009	9.2%
Other Diseases	5,813	13.4%	5,701	13.0%
Total Donors by Cause of Death	43,432		43,802	

(1) In 1999, there were 83 U.S. eye banks reporting.

Corneal Transplant Recipient Diagnoses Report – 2000

Seventy-seven eye banks reported recipient diagnoses for the year 2000, the same as 1999. The total number of cases with reported recipient diagnoses also remained about the same -- 31,532 in 2000 compared to 32,394 in 1999. This represents 67% of the corneas distributed by the 80 U.S. eye banks reporting for the year 2000.

The percentage of corneal transplants done for pseudophakic corneal edema (PCE), still the most common recipient diagnosis, hovers just under 20%. Combining PCE and aphakic corneal edema (ACE) gives the corneal transplants done following previous eye surgery, except previous corneal transplant, and this combination rose slightly due to the PCE component.

A slowly increasing trend continues in regrafts with and without allograft rejection. The combination of these regraft categories has risen 5 percentage points, or 70% in the past decade.

Corneal transplants for PCE		Corneal transplants for PCE + ACE		Repeat corneal transplants		
1991	25.1%	1991	33.6%	1991	1,418	7.1%
1992	23.0%	1992	30.9%	1992	1,879	6.9%
1993	21.4%	1993	28.1%	1993	2,333	7.8%
1994	22.1%	1994	28.3%	1994	2,822	9.1%
1995	20.4%	1995	26.1%	1995	2,854	10.4%
1996	24.9%	1996	30.2%	1996	2,850	10.5%
1997	21.2%	1997	25.2%	1997	3,278	11.0%
1998	20.8%	1998	24.7%	1998	3,390	11.5%
1999	18.6%	1999	21.5%	1999	3,675	11.3%
2000	19.6%	2000	22.3%	2000	3,830	12.1%

Fuchs' dystrophy and keratoconus show a slight increasing trend in recent years that is probably real in both percentage and actual numbers.

Infectious causes taken separately and together (viral + syphilitic + bacterial) continue to show little change, with small numbers that show no trend. The same is true for traumatic causes (mechanical + chemical).

James I. McNeill, M.D.
Kennewick, WA
Clinical Professor of Ophthalmology
Loma Linda University School of Medicine
April 2, 2001

Corneal Transplant Recipient Diagnoses

77 U.S. Eye Banks Reporting (1)

	2000		1999 #	
Indications for Penetrating Keratoplasty				
Pseudophakic Corneal Edema	6,174	19.6%	6,014	18.6%
Endothelial Corneal Dystrophies	4,708	14.9%	4,342	13.4%
Ectasias/Thinnings	4,575	14.5%	4,379	13.5%
Regraft unrelated to Allograft Rejection	2,304	7.3%	2,186	6.7%
Regraft related to Allograft Rejection	1,526	4.8%	1,489	4.6%
Noninfectious Ulcerative Keratitis	1,084	3.4%	1,177	3.6%
Corneal Degenerations	993	3.1%	989	3.1%
Aphakic Corneal Edema	867	2.7%	933	2.9%
Stromal Corneal Dystrophies	658	2.1%	589	1.8%
Mechanical Trauma	543	1.7%	572	1.8%
Viral/Post-Viral Keratitis	446	1.4%	420	1.3%
Congenital Opacities	317	1.0%	412	1.3%
Microbial/Post-Microbial Keratitis	244	0.8%	300	0.9%
Syphilitic/Post-Syphilitic Keratitis	104	0.3%	173	0.5%
Chemical Injuries	97	0.3%	85	0.3%
Other	6,892	21.9%	8,334	25.7%
Total Indications for PKP	31,532		32,394	
Indications for Lamellar Keratoplasty				
Unspecified Anterior Stromal Scarring	116	30.1%	89	23.0%
Ulcerative Keratitis or Perforation	106	27.5%	59	15.2%
Keratoconus	51	13.2%	74	19.1%
Corneal Degenerations	48	12.4%	76	19.6%
Trauma	48	12.4%	76	19.6%
Pterygium	10	2.6%	6	1.6%
Post-Keratectomy	5	1.3%	4	1.0%
Reis-Buckler's Dystrophy	2	0.5%	3	0.8%
Total Indications for LKP	386		387	

(1) In 1999, there were 77 eye banks reporting.

Introduction
2000 Eye Banking Statistics

Enclosed is the Eye Bank Association of America's statistical report for 2000. 80 U.S. member eye banks reported statistics for the year 2000 (83 in 1999). This is close to 100%. When EBAA reports the total number of member eye banks as it routinely does in its materials, it bases its count on an accreditation list that separates out each facility that is inspected, even if it belongs to an umbrella entity. For statistical reporting purposes, many eye banks count all of their facilities that distribute from a centralized area, under one legal entity. Banks are identified according to designated information submitted to the EBAA.

There were three non-reporting eye banks in 2000. Those eye banks are:

- Lions Eye Bank of Central Pennsylvania, Hershey (124 transplants reported in 1999)
- Lions Eye Bank of Puerto Rico, San Juan (277 transplants reported in 1999)
- Life Bank of East Texas, Tyler (25 transplants reported in 1999)

In addition, Montana Eye Bank, Inc., Missoula merged with Northwest Lions Eye Bank, Seattle. The data provided by Montana Eye Bank represents their activity for the period 1/1/00-6/30/00, prior to the merger.

Four eye banks reported under new names in 2000. The four eye banks are:

- Indiana Lions Eye & Tissue Transplant Bank reported as Indiana Lions Eye Bank in 1999
- Lions Eye Bank of Wisconsin reported as The EyeBank of Wisconsin in 1999
- Old Dominion Eye Foundation, Inc. reported as Old Dominion Eye Bank in 1999
- Texas Lions Eye Bank Alliance reported as District 2-A1 Lions Eye Bank in 1999

The 2000 report also includes data from eight international eye banks, down from ten reporting in 1999. One eye bank, Regional Tissue Bank, Halifax, Nova Scotia, reported in 2000 but did not report in 1999. Three international eye banks that reported in 1999 did not report in 2000. The three non-reporting international eye banks are:

- East Grinstead Eye Bank, East Grinstead, England (9 transplants reported in 1999)
- Cornea Center Eye Bank, Ichikawa-shi, Japan (36 transplants reported in 1999)
- King Khaled Eye Specialist Hospital Eye Bank, Riyadh, Saudi Arabia (11 transplants reported in 1999)

Two eye banks became associate members in the year 2000, but no activity was reported. Those eye banks are:

- Tennessee Donor Services, Nashville
- Lions Eye Bank of Lexington, Lexington

While there was a slight decrease in donors, 0.8%, corneal grafts increased by 2.6%, thereby meeting demand in the U.S.

This report represents information provided by individual eye banks and summarized by the EBAA.

2000 Eye Banking Statistics

88 U.S. and International Eye Banks Reporting (1)

Donations	2000	1999	1998	1997	1996
Number of Eye Banks Reporting	88	93	99	102	108
Total Donations	94,186	95,366	95,103	90,465	92,162
Total Number of Donors	47,796	48,122	47,889	45,696	46,045

Distribution	2000	1999	1998	1997	1996
Corneal Grafts (2)	50,197	48,623	47,425	45,493	46,300
Epikeratophakia	73	61	112	129	142
Sclera	4,299	4,352	5,107	4,679	5,791
Other Surgical Use (3)	79	107	183	488	162
Research	21,881	20,861	21,904	21,766	24,163
Training	5,729	7,697	7,803	8,318	9,458

(1) In 1999, there were 93 U.S. and international eye banks reporting

(2) Includes penetrating keratoplasty (PKP) and lamellar keratoplasty (LKP).

(3) Procedures performed, such as keratolimbal allograft (KLAL), use human eye tissue which does not apply to any previously listed category.