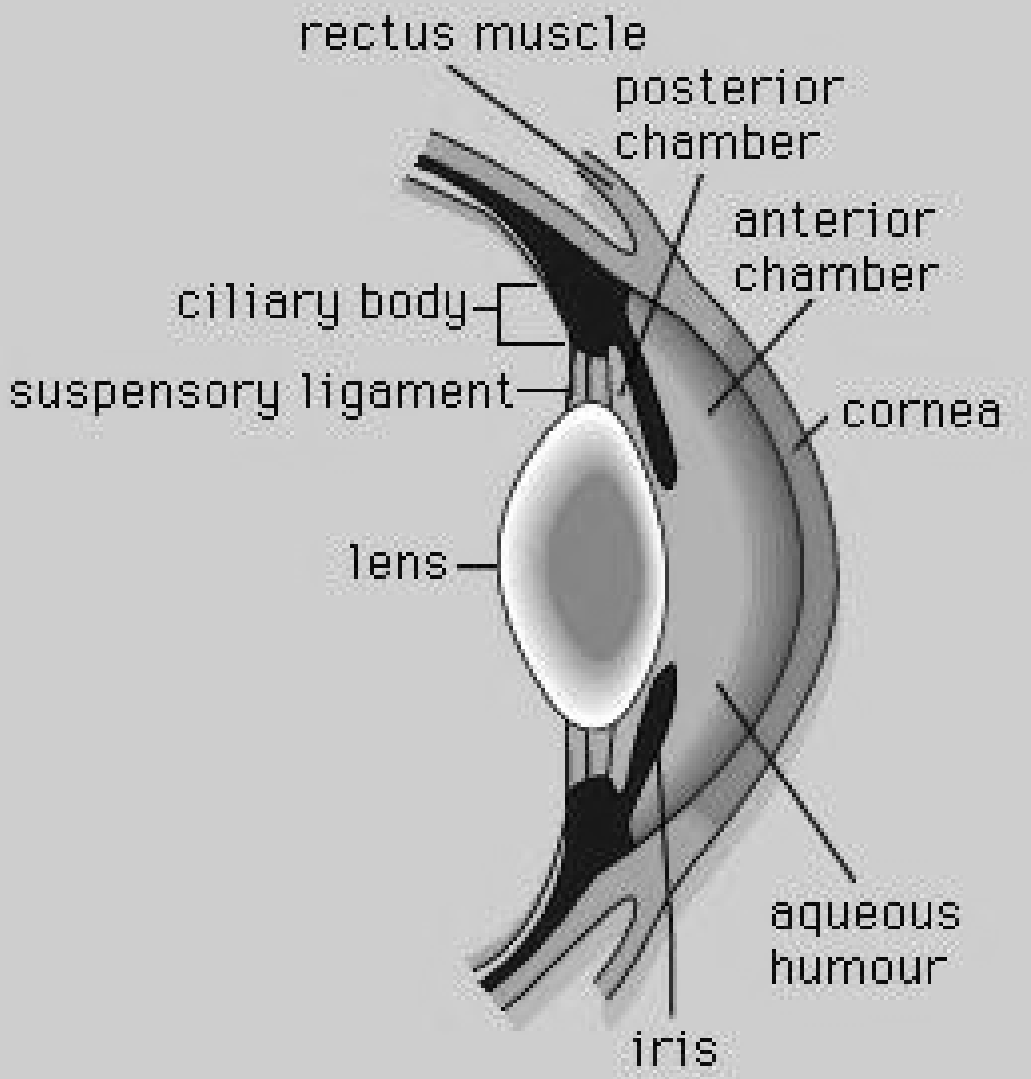
Purpose and Function of IRBs: Successes and Current Challenges

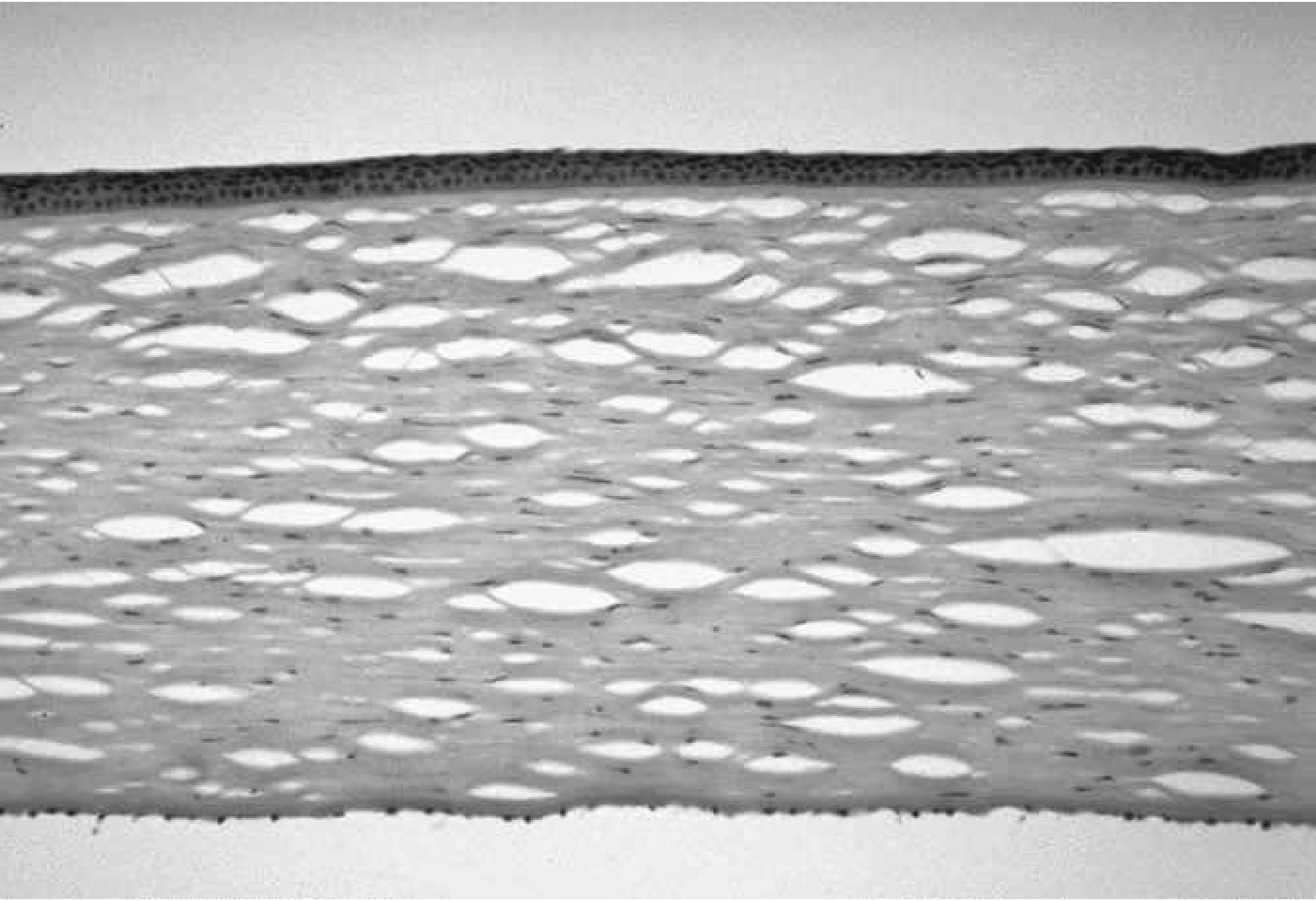
Jerry Menikoff

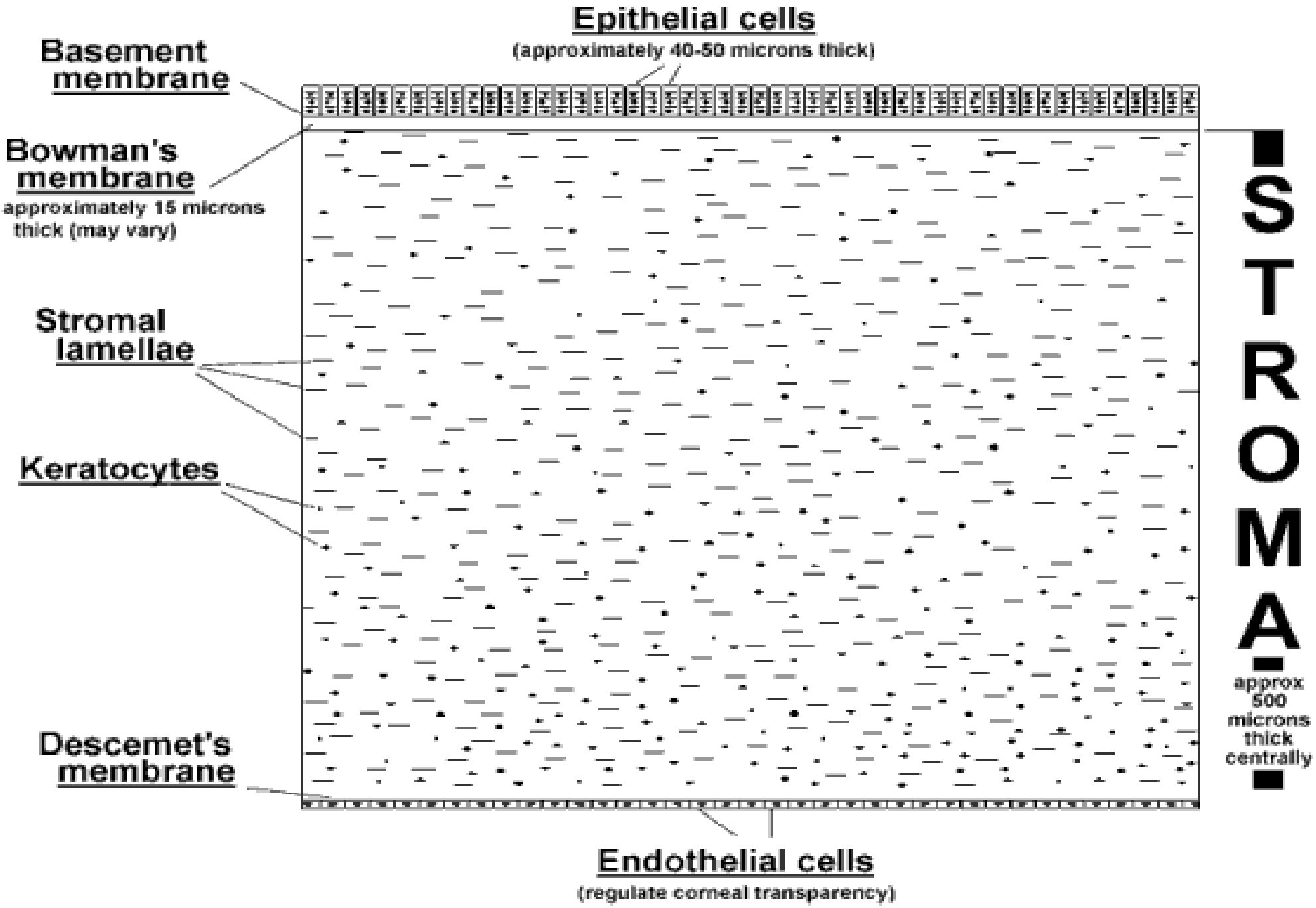
Disclaimer

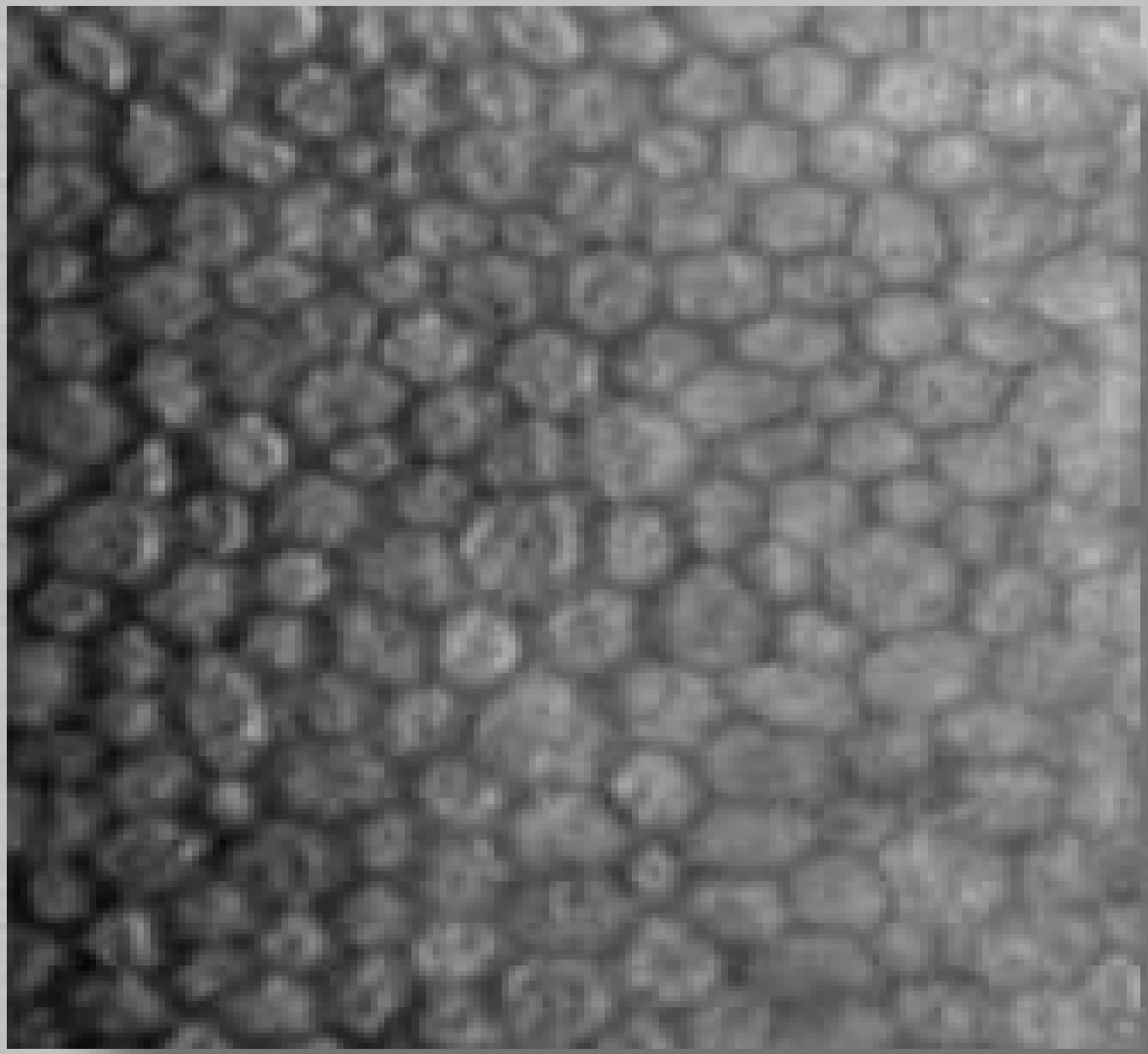
The views express in this presentation do not represent the views of the NIH or the Department of Health and Human Services.

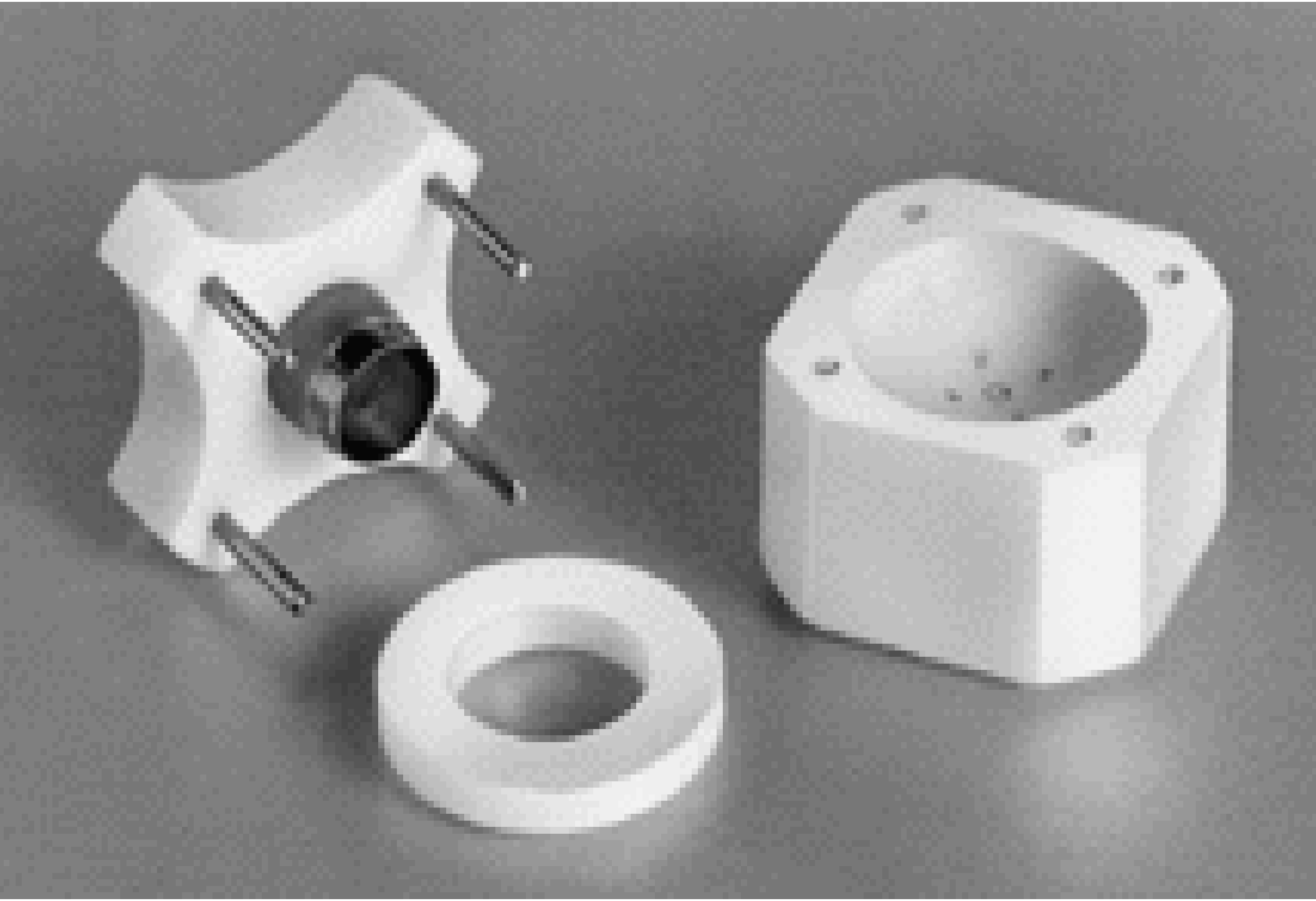
The Anterior Segment

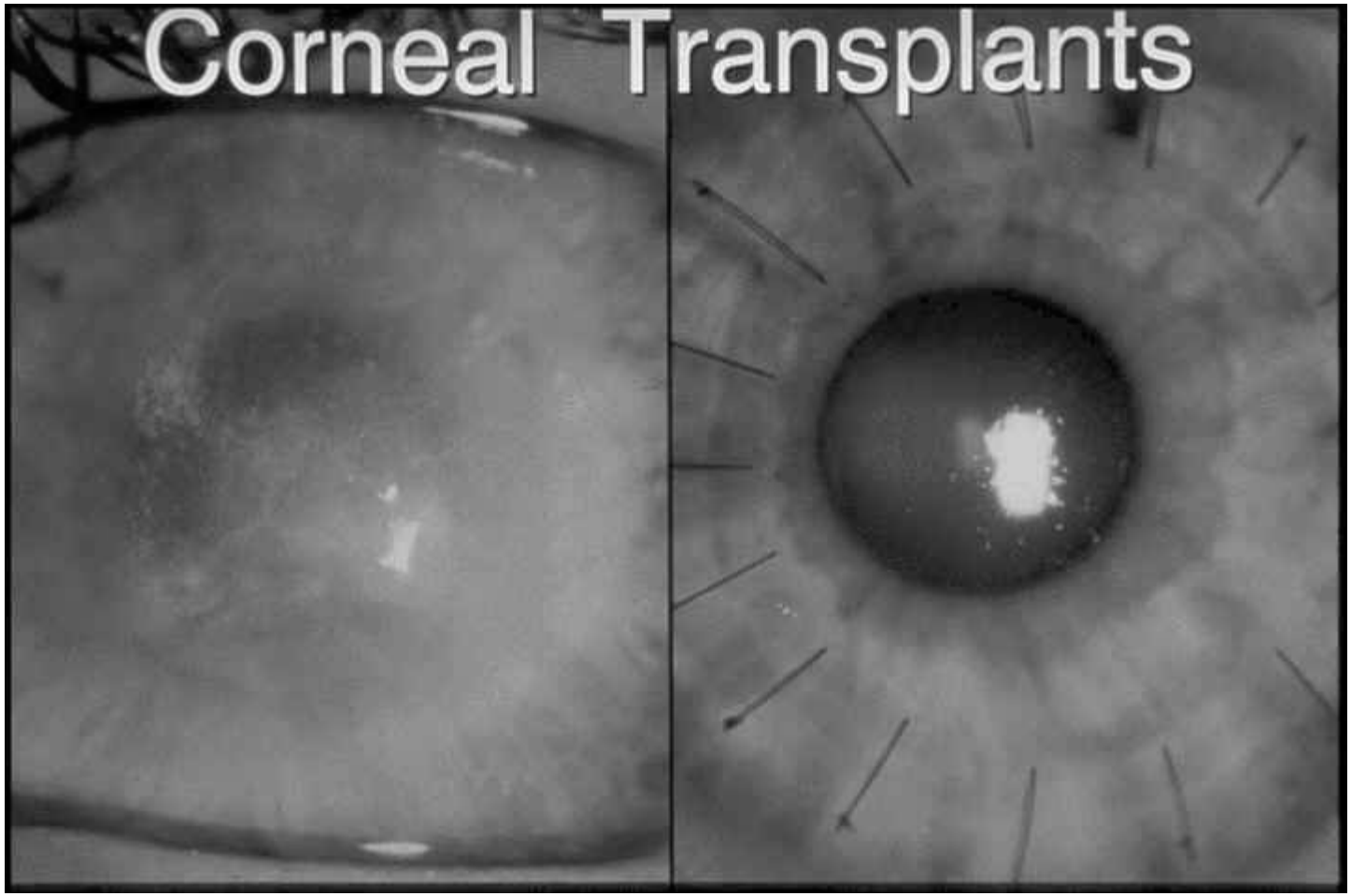





Epithelial cells
(approximately 40-50 microns thick)
Basement membrane
Bowman's membrane
approximately 15 microns thick (may vary)
Stromal lamellae
Keratocytes
Descemet's membrane
STROMA
approx 500 microns thick centrally
Endothelial cells
(regulate corneal transparency)



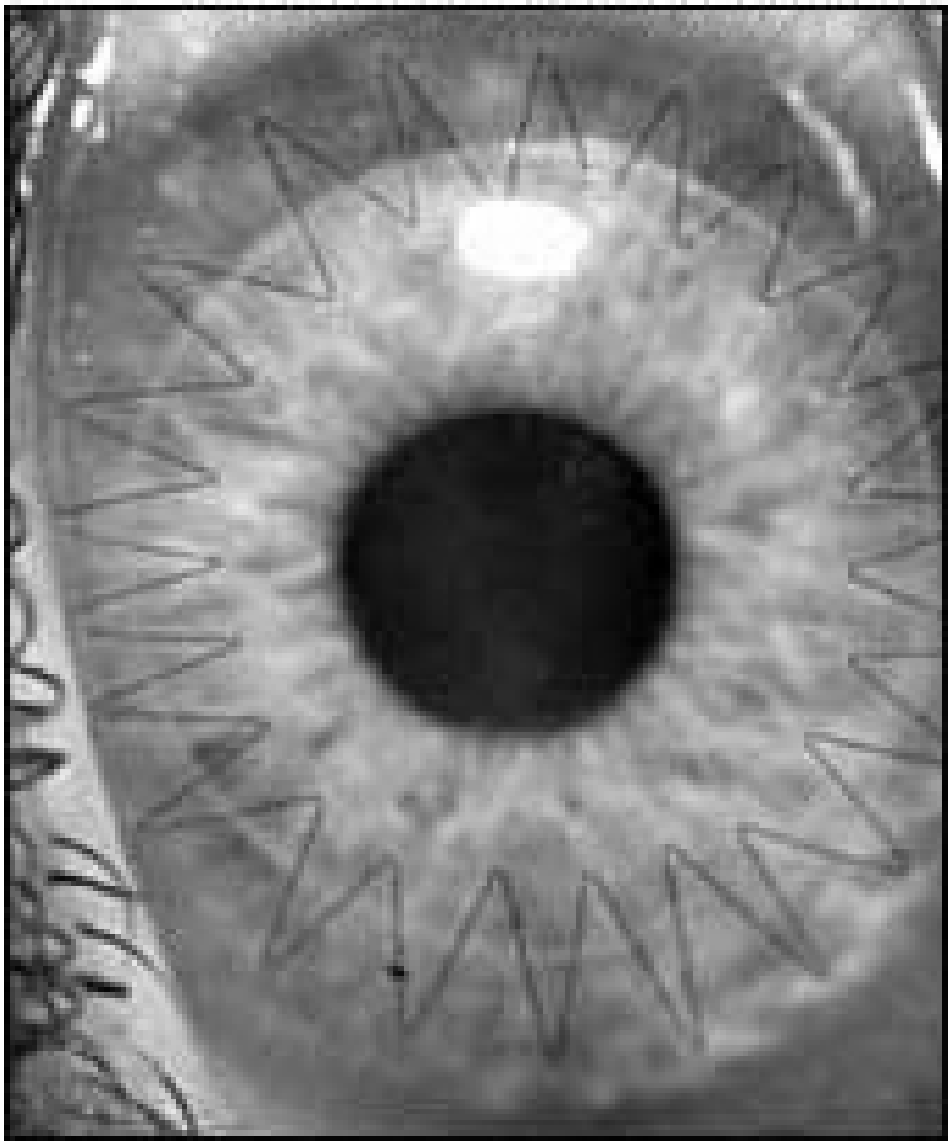



Corneal Transplants

A Cautionary Tale

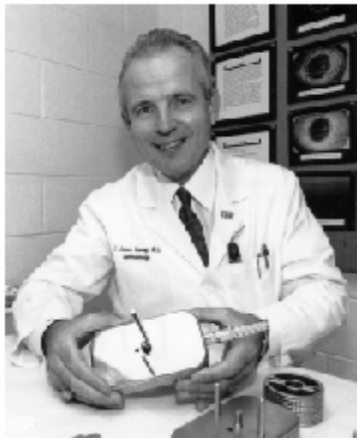
- **Standard Care**

(COURTESY DR EZRA MAGEUN)



A Cautionary Tale

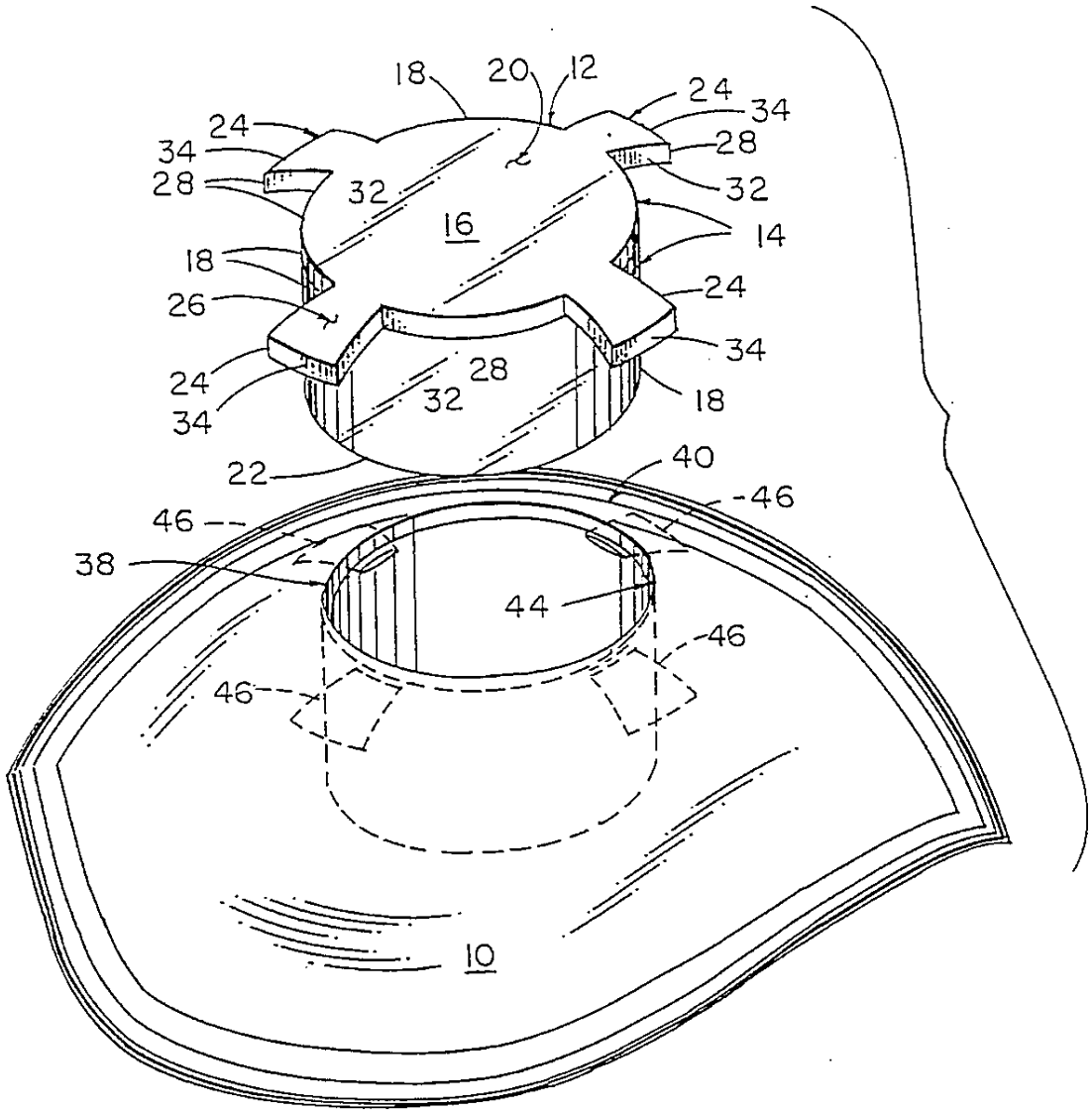
- Dr. Rowsey



A Cautionary Tale

Sutureless Corneal Transplant Technique:

- This invention involves a technique for transplanting corneal tissue in a much safer way with far less complications than previous methods.
- U.S. Patent 5,584,881 issued Dec. 17, 1996


18
20
12
24
34
28
32
16
14
26
22
40
46
38
44
10

A Cautionary Tale

- Studied in cats
- Began use in humans
- Never filed with IRB

A Cautionary Tale

How it became public:

- **Rowsey wanted "best Christian ophthalmology dept”**
- **Prayer at faculty meetings**
- **Non-participating staff were ridiculed, denied coveted positions and appointments**

A Cautionary Tale

USA Today, Feb. 26, 2001:

- **In 1994, eye surgeon James Rowsey invented a medical device that he thought would revolutionize corneal transplantation surgery and make millions of dollars. It did neither. Instead, it cost him a high-paying university job and led to federal findings that he performed unapproved research on more than 60 people, including children.**

A Cautionary Tale

OHRP, Sept 2000:

- **Rowsey proposed randomized trial (but didn't conduct it); used an untested new technique in 60 people; presented abstracts of results at meetings**
- **This is systematic collection of data, an open-label trial, and meets def. of doing research**

A Cautionary Tale

OHRP, Nov 2000:

- **USF must tell patients that they were research subjects, and underwent experimental surgery.**

A Cautionary Tale

- Standard Care
- Non-Standard Care
- Research

A Cautionary Tale

- Dr. Rowsey's defense was that he wasn't doing research.
- He says the technique "was never used on my patients as part of any systematic investigation."

A Cautionary Tale

- Why was everyone so interested in proving he was doing research?
- What if he kept no research records, merely told patients this was a new experimental technique, and he thought it was the best thing for them?

A Cautionary Tale

- **Would this have been OK if he was just *giving non-standard care*?**
- **Perhaps Dr. Rowsey was just careless, and did too many "research-like" things**

A Cautionary Tale (Truog, *NEJM*, 1999)

- **Consider this paradox: if a physician reads a case report about a novel method of ventilation for critically ill patients and wants to try it in the next several patients with respiratory failure he or she treats, the physician may do so provided the patients have given general consent for treatment. On the other hand, if a physician is interested in performing a randomized, controlled trial to determine rigorously which of two widely used antibiotics is more effective at treating bronchitis, he or she must prepare a formal protocol, obtain approval from the institutional review board, and seek written informed consent from potential participants.**

A Cautionary Tale (Truog, *NEJM*, 1999)

- **In each case, the physician is performing an experiment. In each case, there is uncertainty about the best way to treat the patient. Yet in the context of clinical care, the experiment can be done with virtually no external scrutiny, whereas in the context of a clinical trial, the experiment is prohibited unless substantial hurdles are overcome. This is true even when the experimental therapy . . . involves risks that are unknown or substantially different from those of the alternatives.**
- **To put it another way, physicians can do almost anything they want in the name of therapeutic innovation, but only if there is no attempt to gain systematic knowledge from the intervention. Or, . . . "I need permission to give a new drug to half my patients but not to give it to all of them."**

A Cautionary Tale (Truog, *NEJM*, 1999)

- **Is it true that: "Physicians can do almost anything they want in the name of therapeutic innovation, but only if there is no attempt to gain systematic knowledge from the intervention."**
- ***NO!*** **To know why we have IRBs, need to understand rules for *non-standard care.***

A Cautionary Tale

- **Standard Care: *Patient is #1!***
- **Non-Standard Care: *Patient is #1!***
- **Research**

A Cautionary Tale (Truog, *NEJM*, 1999)

- **What happens if a doctor fails to follow the "Patient is #1" rule?** ***Malpractice!***
- **Does the fact that patient gave consent fully absolve the doctor? In general,** ***No!***

An Example

- Barbara Rojas, age 52, successfully lost huge amounts of weight
- She wanted drooping skin removed
- Guillermo Falconi, Ecuador MD, no U.S. license, did bedroom surgery
- She died, he went to jail

Another Example

- Daniel Burton, 1953, exposed to high O_2 as infant
- Put in study without consent of parents
- Malpractice found, though no informed consent rules at the time
- Many other infants got identical treatment based on doctors' clinical judgment
- Daniel was denied his doctor's best judgment

A Cautionary Tale

- **Dr. Rowsey was sued by at least 2 patients claiming malpractice**
- **Rule for non-standard care: in terms of best interests of the patients, was it *reasonable* to depart from standard care?**
- **Compare risks v. benefits of change**

Why Special Research Rules?

- **Standard Care: *Patient is #1!***
- **Non-Standard Care: *Patient is #1!***
- **Research: *Patient is not #1!***

Why Special Research Rules?

- **Research involves a *conflict of interest***
- **Researcher is pursuing two goals:**
  1. **Answering research question**
  2. **(Sometimes) treating the patient**

Why Special Research Rules?

- **Researcher (unlike clinician) is *allowed* to do things that can be *bad* for patient:**
  1. **Randomization**
  2. **Standardization**
  3. **Non-disclosure of interim results**
  4. **Extra tests and procedures**

Why Special Research Rules?

- **Research regulations help *manage* that conflict of interest.**
- **They make sure that the goal of answering the research question does not *inappropriately* override the patient's interests.**

Why Special Research Rules?

- IRBs are the entities that have the major responsibility for enforcing these rules

Scope of Research Rules

- **Rules apply to *Research* involving *Human Subjects***

What is Research?

- **Research means a systematic investigation . . . designed to develop or contribute to *generalizable knowledge*.**

What is *Not* Research?

- ***Quality Assurance***: you are doing something for internal purposes.
- No one would care about the results—it is not generalizable.

When are you using a human subject?

- ***Human Subject*** **means a** ***living*** **individual about whom a researcher gets:**

  (1) data through ***intervention*** **or** ***interaction*** **with the individual,** ***or***

  (2) identifiable private information

What Criteria does IRB Apply?

1. *Informed consent*
2. *Substantive rules* about how the study is designed

Informed Consent

- *Informed consent* will be sought from each prospective subject or the subject's legally authorized representative.
- Consent is documented by a signed consent form.
- These requirements can be waived, under specific criteria

Substantive Rules About the Study

- **Risks to subjects are *minimized*:**

  (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and

  (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

Substantive Rules About the Study

- ***Risks*** **to subjects are reasonable in relation to anticipated *benefits*, if any, to subjects, and the *importance of the knowledge* that may reasonably be expected to result.**

Substantive Rules About the Study

Risks to subjects ≈

(Benefits to subjects) + (Benefits to society)

Substantive Rules About the Study

Benefits to society are especially hard to quantify. That leads to two common IRB behaviors:

1. **Emphasizing informed consent.**
2. **Assume benefits to society are close to zero; equation becomes: Risks to subjects ≈ Benefits to subjects**

Substantive Rules About the Study

- **Selection of subjects is equitable.**

Substantive Rules About the Study

- If subjects *vulnerable* to coercion or undue influence (children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged) persons, need additional safeguards

What if IRB reviewed Rowsey Study?

- **Study would likely pass *substantive tests*—possible benefit to future thousands of patients**
- **Informed Consent—disclose that benefits from participation outweighed by risks**

Problems with the IRB System

- The system is too *lax*
- The system is too *stringent*

Problems with IRB System: Too Lax

- System is underfunded
- Too little training about rules and regulations
- Holes in the regulations—non-US funded, non-FDA, etc.
- IRB determinations are inconsistent

Problems with IRB System: Too Lax

- IRBs have too little power
- IRBs are conflicted, since they are usually “institutional”, and most members are employees
- IRBs dominated by scientists, who are pro-research
- IRBs interpret regs in lax ways

Problems with System: Too Stringent

- System is hugely inefficient
- Deters or delays research at great costs in time and effort
- Little evidence that IRB produce benefits to subjects
- Too much emphasis on compliance with petty regulations
- Absurd adverse events reporting requirements
- Violates First Amendment

Possible Solutions

Lack of resources and training:

- **Give IRBs more money, staff, training**
- **Reduce inefficiencies (e.g., make adverse event reporting more rational)**

Possible Solutions

Accreditation:

- **Association for the Accreditation of Human Research Protection Programs, at www.aahrpp.org**
- **Voluntary, like JCAHO**

Possible Solutions

Get rid of "I" (institutional):

- **Have more (25%+) outside members**
- **Acknowledge no reason for local**
- **National or regional IRBs**
- **NCI Central IRB, www.ncicirb.org**

Possible Solutions

Get rid of IRB scientific review:

- **Delegate fully to separate group**
- **IRB should just concentrate on ethics, be Ethics Review Board**

Possible Solutions

Loosen up the regs:

- **Reduce types of studies requiring IRB review**
- **Reduce the frequency of required IRB review**

Possible Solutions

Study the problem!

- **Do empirical research to figure out which things that IRBs do are most effective, which are least effective**
- **Change the rules based on the results of such research**

THE END