Non-Invasive and Early Diagnosis of Ocular and Systemic Diseases Using "Eye as a Window to the Body"

Current Topics in Space Medicine

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Cleveland Clinic, March 16, 2012

Disclaimer

The views and opinions expressed in this talk are those of the speaker and *NOT* those of NASA or the Government of the United States of America

Disclosure/Financial Interest:

Patents: 6704588, 5973779, 5284149

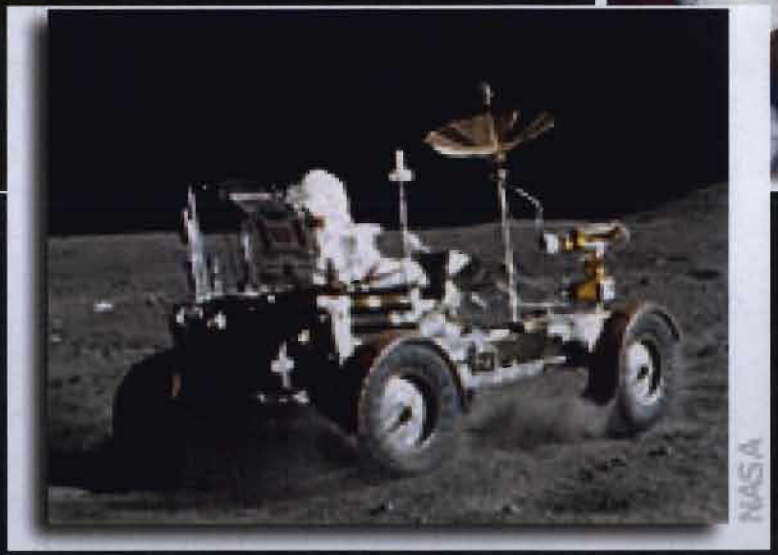
ABC NEWS, Houston, Nov. 8, 2004

Space Medicine Issues

Can Eye act as a Window to the Body?

"We leave as we came, and God willing as we shall return, with peace and hope for all mankind."

Eugene Cernan (Commander of last Apollo mission)
December 17, 1972



1973-date: Human Presence Remained in LEO

Robotic Probes have ventured throughout our Solar System and beyond

Current Vision for Space Exploration

First Stop - Our Moon as a Test Bed

Preparing for Mars Exploration

Space Travel: Serious Health Risks!

EYES BECOME MAIN WAY TO SENSE MOTION

OTOLITHS IN INNER EAR RESPOND DIFFERENTLY TO MOTION

FLUID REDISTRIBUTION CAUSES HEAD CONGESTION AND PUFFY FACE

CHANGED SENSORY INPUT CONFUSES BRAIN, CAUSING occasional DISORIENTATION

WEIGHT-BEARING BONES AND MUSCLES DETERIORATE

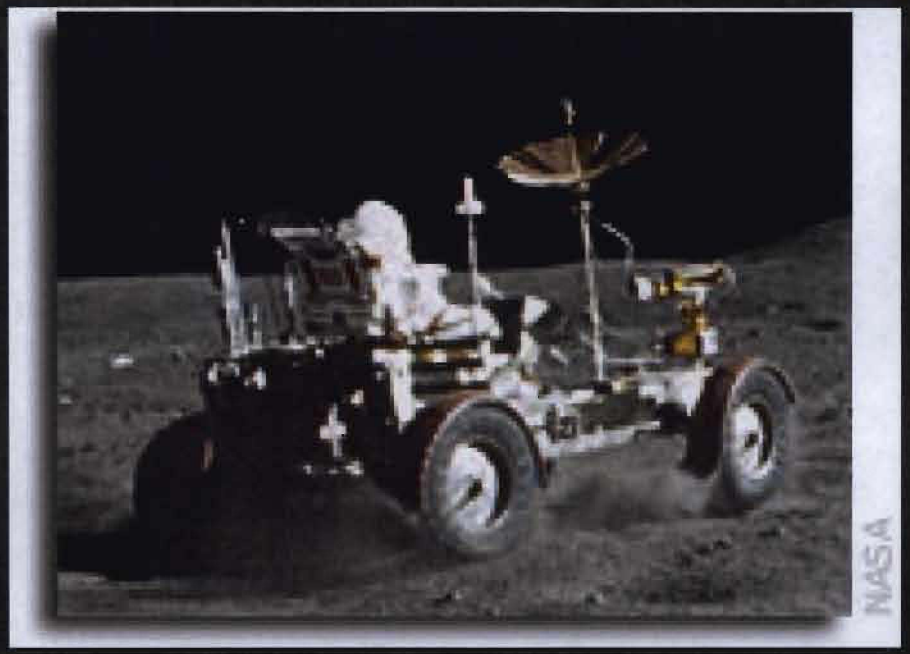
KIDNEY FILTRATION RATE INCREASES; BONE LOSS MAY CAUSE KIDNEY STONES

FLUID REDISTRIBUTION SHRINKS LEGS

TOUCH AND PRESSURE SENSORS REGISTER NO DOWNWARD FORCE

Scientific American
September 1998

Dust can be a Problem on Moon and Mars



Lunar Regolith

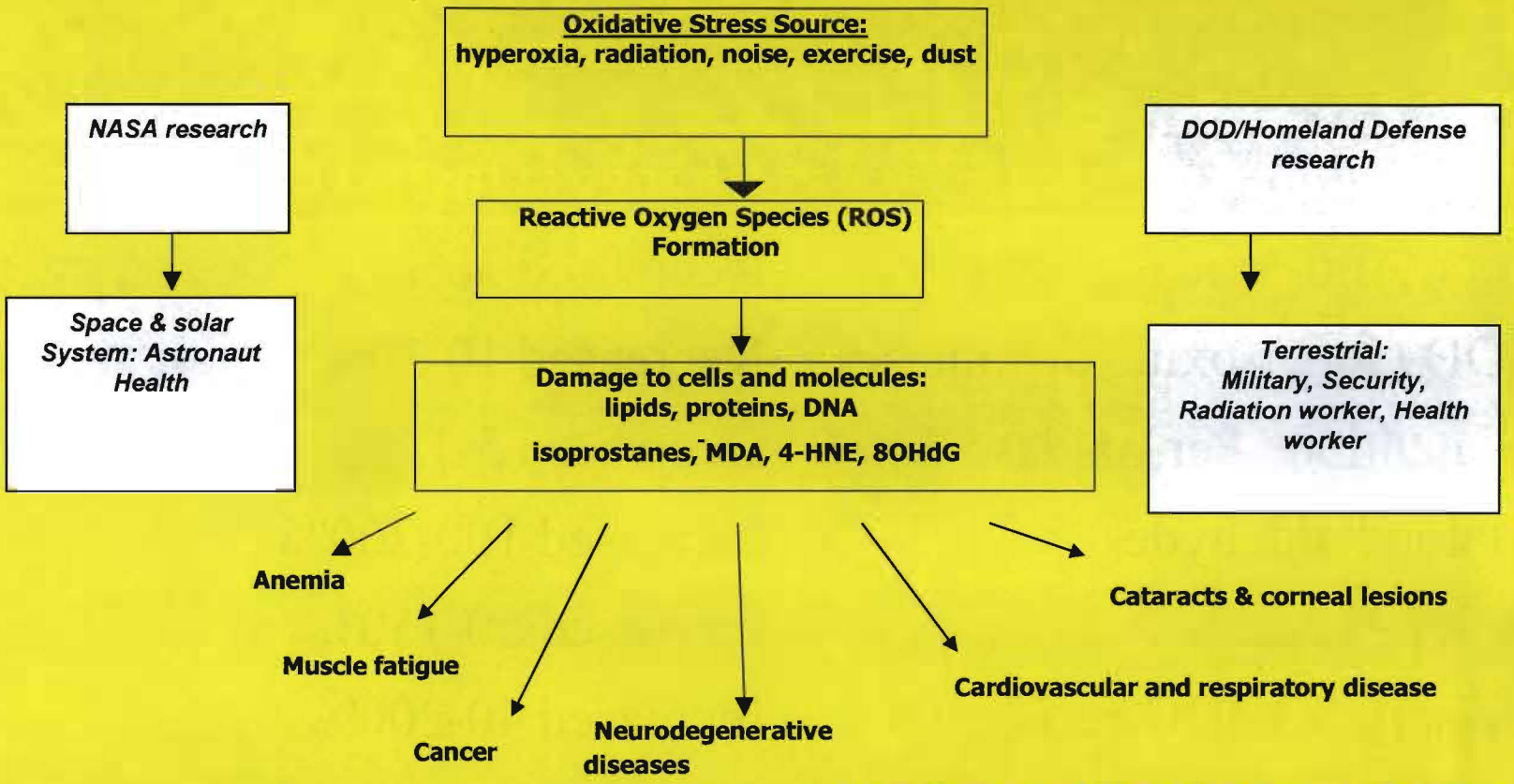
Eye Irritation, Lungs, Allergic Reactions and Equipment Failure

Potential Ocular Risk Factors in Space Flight

Condition	Cause	In-Flight	Moon	Mars
Cataract	Radiation	Yes	Yes	Yes
>IOP/ICP	<Gravity	Yes	Likely	Likely
<Acuity	<Gravity	Yes	Likely	Likely
MD	Radiation	Likely	Likely	Likely
Conjunctivitis	Air-Dust	Yes	Yes	Likely
Photopsia	Radiation	Yes	Likely	Likely
Macular	<Gravity	Possible	Possible	Possible
Nutrition	Radiation			
Irritation	Regolith	No	Yes	Yes
Injury	Objects	Yes	Possible	Possible

Ansari and Sebag in Teleophthalmology, 2006

Oxidative Stress Leads to Aging and Disease



Whole body cellular level injuries occur with oxidative stress due to reactive oxygen species (ROS)

Space Travel Accelerates Aging

Changes in Oxidative Bio-markers during a mission on International Space Station

Compound Analyzed	Changes Observed in Flight
Total Anti-oxidant Capacity	Decreased 30%
SOD (super-oxide dismutase)	Decreased 10-30%
Glutathione Per-oxidase	Decreased 5-15%
Malondialdehyde	Increased 100-200%
4-OH Alkenal	Increased 50-150%
Urinary 8OHDG (urinary 8 hydroxy-2 deoxyguanosine)	Increased 40-200%

Source: Jeff Jones, MD,
Flight Medicine-NASA JSC

295 Astronauts longitudinal study at NASA JSC

Relatively low doses of space radiation are causative of an increased incidence and early appearance of cataracts

Cucinotta et al., "Space radiation and cataracts in astronauts", Radiation Research, Vol 156, No. 5, 460-466, Nov. 2001

Rastegar et al., "Radiation Induced cataract in astronauts and Cosmonauts", Grae. Arch. Clin. Exp. Oph., 240 (7) 545, 2002.

Major Needs in Human Cataract Research (NEI/NIH)

- Ability to identify individuals at particular risk for developing cataracts
- Detection of early molecular (pre-cataractous) changes in the lens
- Objective means of measuring early cataract progression in vivo

Limitations in Measuring Cataract

•Problems with current optical methods for evaluating cataract

•Subjective Methods (Slit Lamp Clinical and Photographic Grading)

- **Requires continual evaluation/re-training of expert observers or graders**
- **Relatively insensitive to early lens changes**
- **Expensive contract (Photographic/Scanning)**
- **Time Consuming**

Objective Methods (Scheimpflug/Pentacam):

- **Expensive device**
- **Needs trained photographer- technician**
- **Relatively Insensitive to early lens changes**

PRESENTLY CATARACT DIAGNOSIS IS BASED ON PHOTOGRAPHIC IMAGING

Qualitative and not an Early Measure of Cataractogenesis

State-of-the-Art in Cataract Evaluation

Slit-lamp biomicroscopy

Scheimpflug imaging

Future ? Dynamic Light Scattering

Lens Opacity Classification System II

Leo T. Chylack, Jr., M.D.
Harvard Medical School

M. Cristina Leske, M.D., MPH
S.U.N.Y. at Stony Brook

Robert Sperduto, M.D.
National Eye Institute

DLS is 2-3 orders of magnitude more sensitive

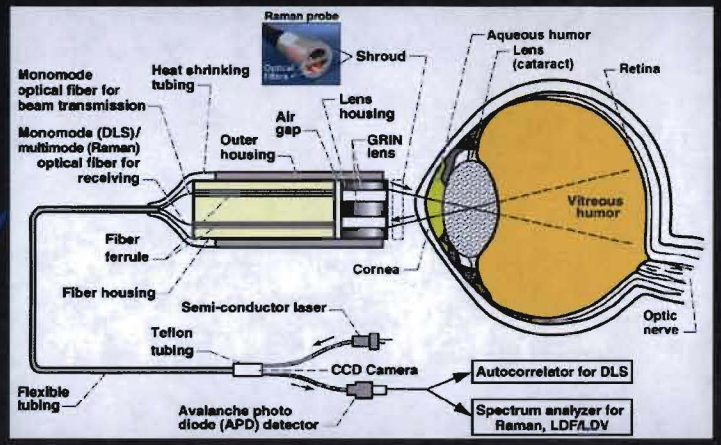
Datiles and Ansari, Chapter 73B, Duanne's Clinical Ophthalmology, 2004, 2009

Dynamic Light Scattering

Quasi-Elastic Light Scattering

Photon-Correlation Spectroscopy

New Developments and Use in Ophthalmology



Ansari, R.R., "Ocular Static and Dynamic Light Scattering: A Non-Invasive Diagnostic Tool for Eye Research and Clinical Practice", J. Biomed. Optics, 9(**1**) 22-37, 2004.

Ansari, R.R., "Quasi-Elastic Light Scattering in Ophthalmology", *Coherent-Domain Optical Methods for Biomedical Diagnostics, Environmental and Material Science*, Kluwer Academic Presss, Chapter 11, 2004.

Dynamic Light Scattering (DLS) Technology

- Detect and measure molecular changes in the lens in vivo, non invasively, objectively and more sensitively

- Based on random Brownian movement of particles: Large particles move slowly, small particles move fast

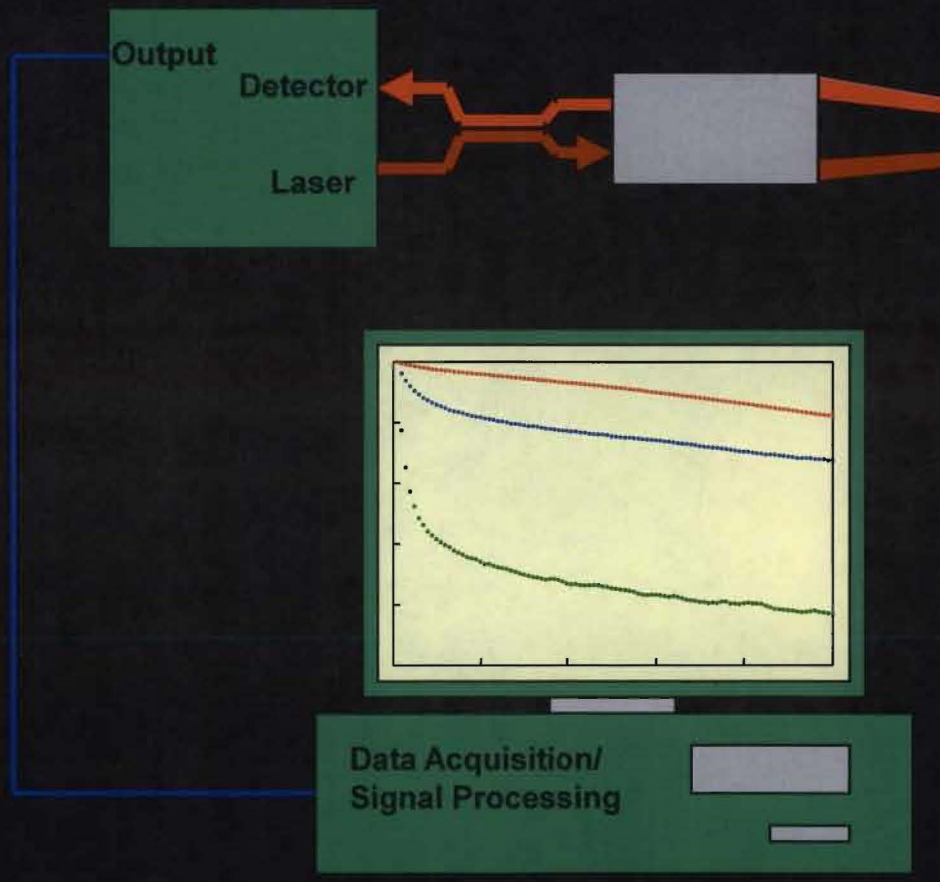
Extraction of DLS Information

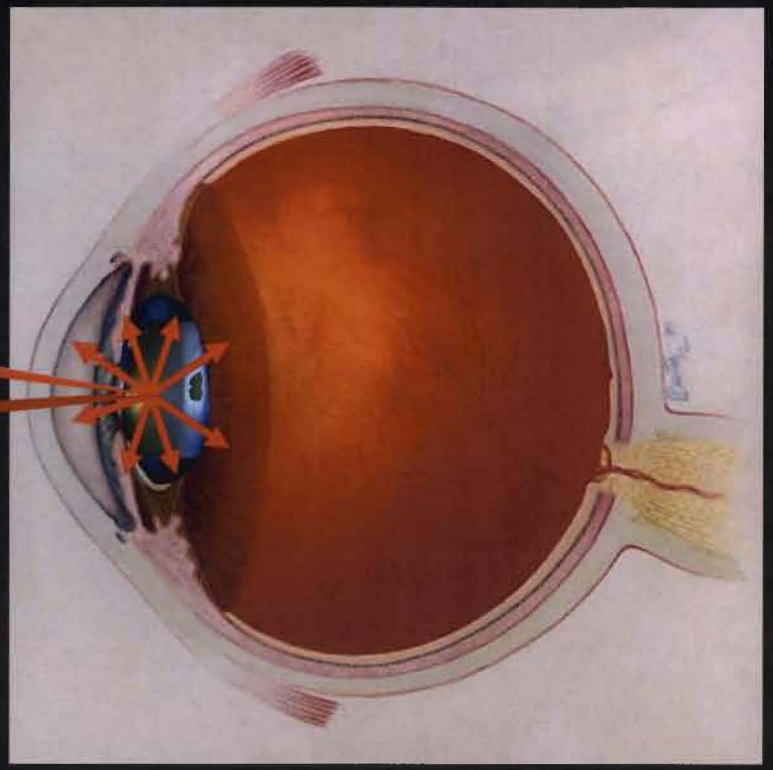
- The autocorrelation function is approximated by the sum of multiple exponential distributions
- The decay rate of each exponential distribution is inverted to estimate the corresponding particle diameter

- The relative intensity (scattered light) contributed by each particle diameter is computed, and the resulting data is expressed as a particle size distribution graph

- Brookhaven software, exponential sampling method, based on Stock and Ray, 1985

How the Early DLS Detection System Works?



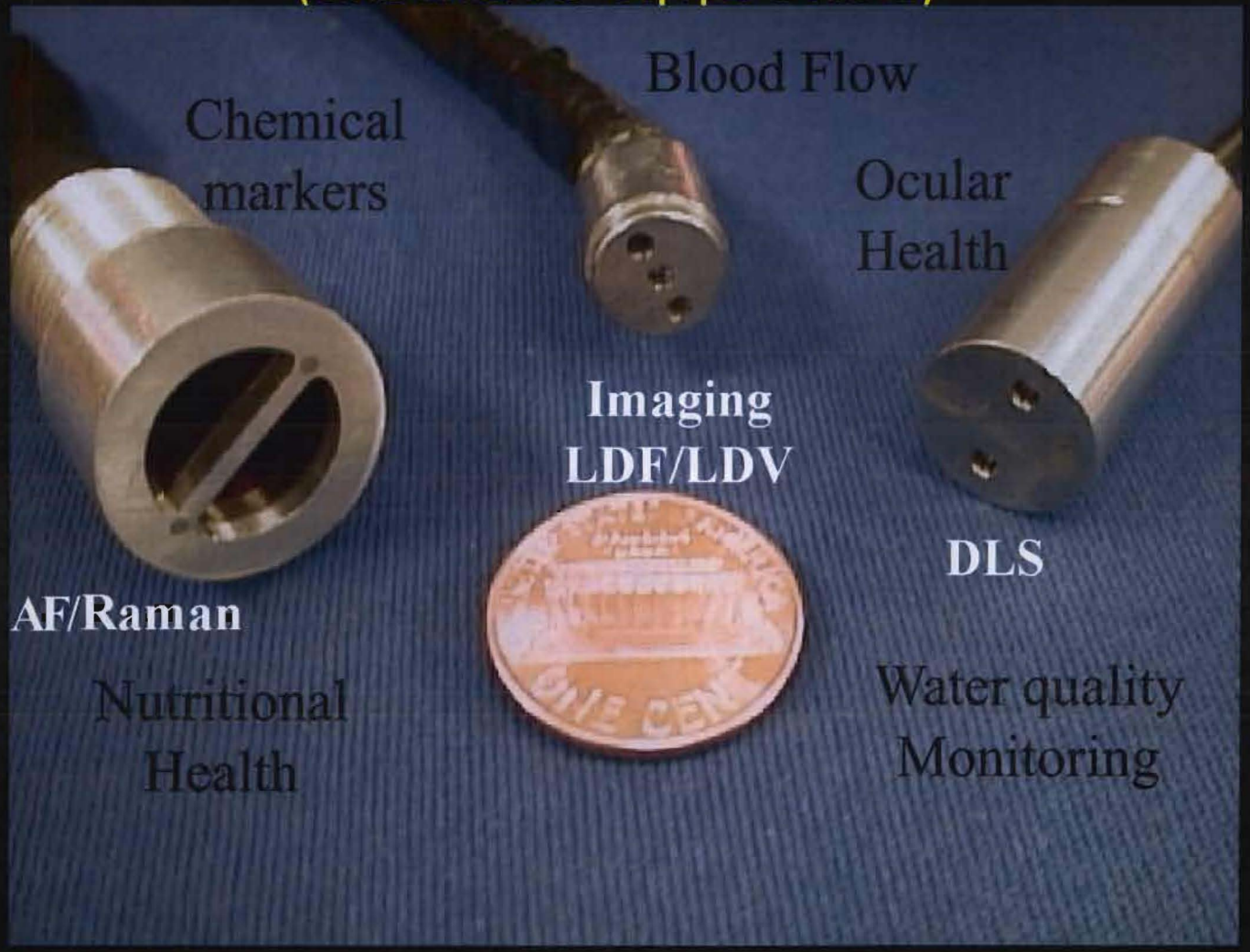


Laser Power: 100 Micro Watts
Exposure Time: 5 Seconds

Datiles and Ansari, "Evaluation of Cataracts", in Duannes Clinical Ophthalmology, Chapter 73-B, Lippincot Williams Wilkins, 2004

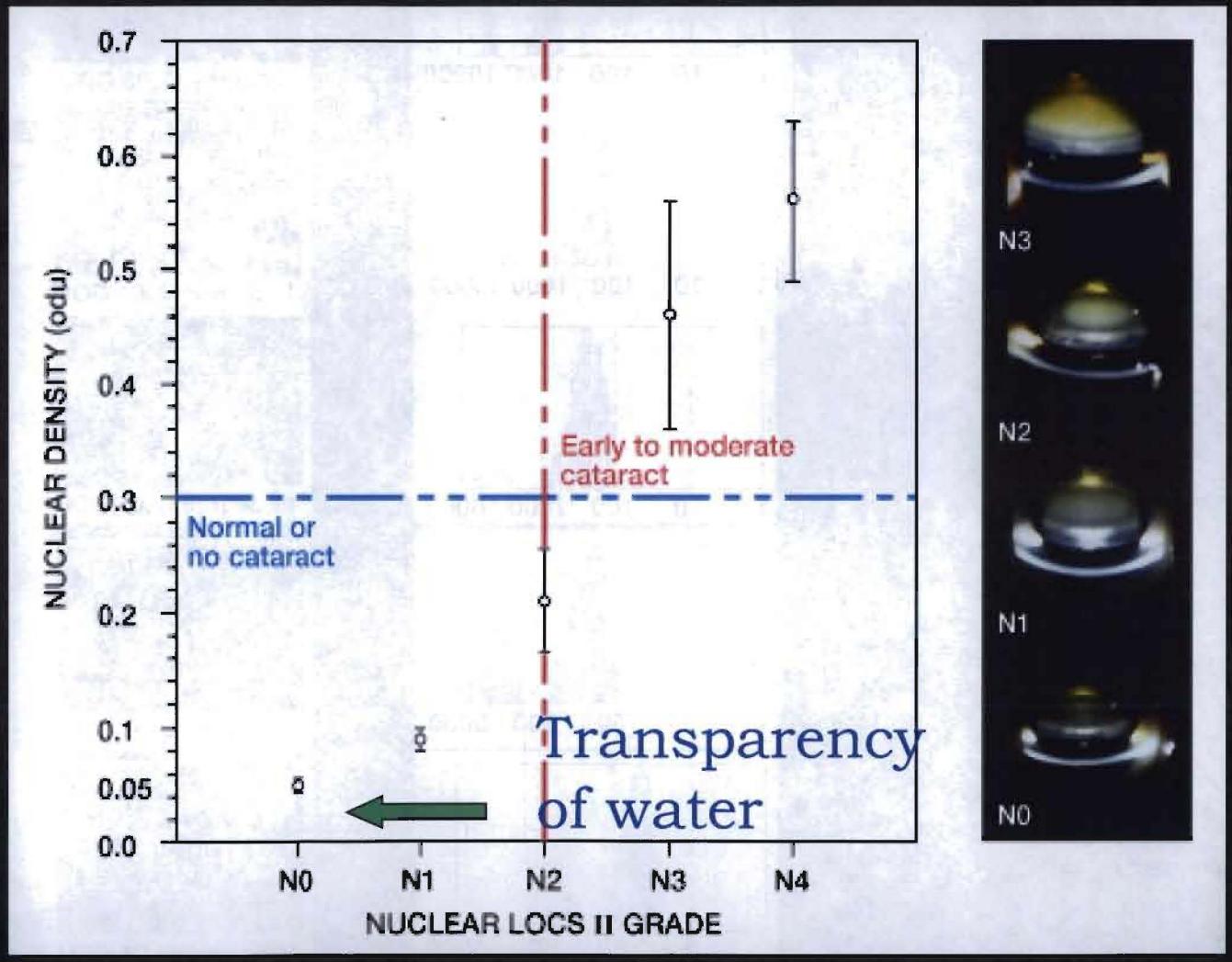
Non-Invasive Compact Fiber Optic Probes

(Modular approach)



Ansari and Suh, US Patent 5,973,779

Association Between Nuclear Opalescence LOCS II Grades Obtained Clinically and the Nuclear Densities (odu), Together With 95% Error Bars

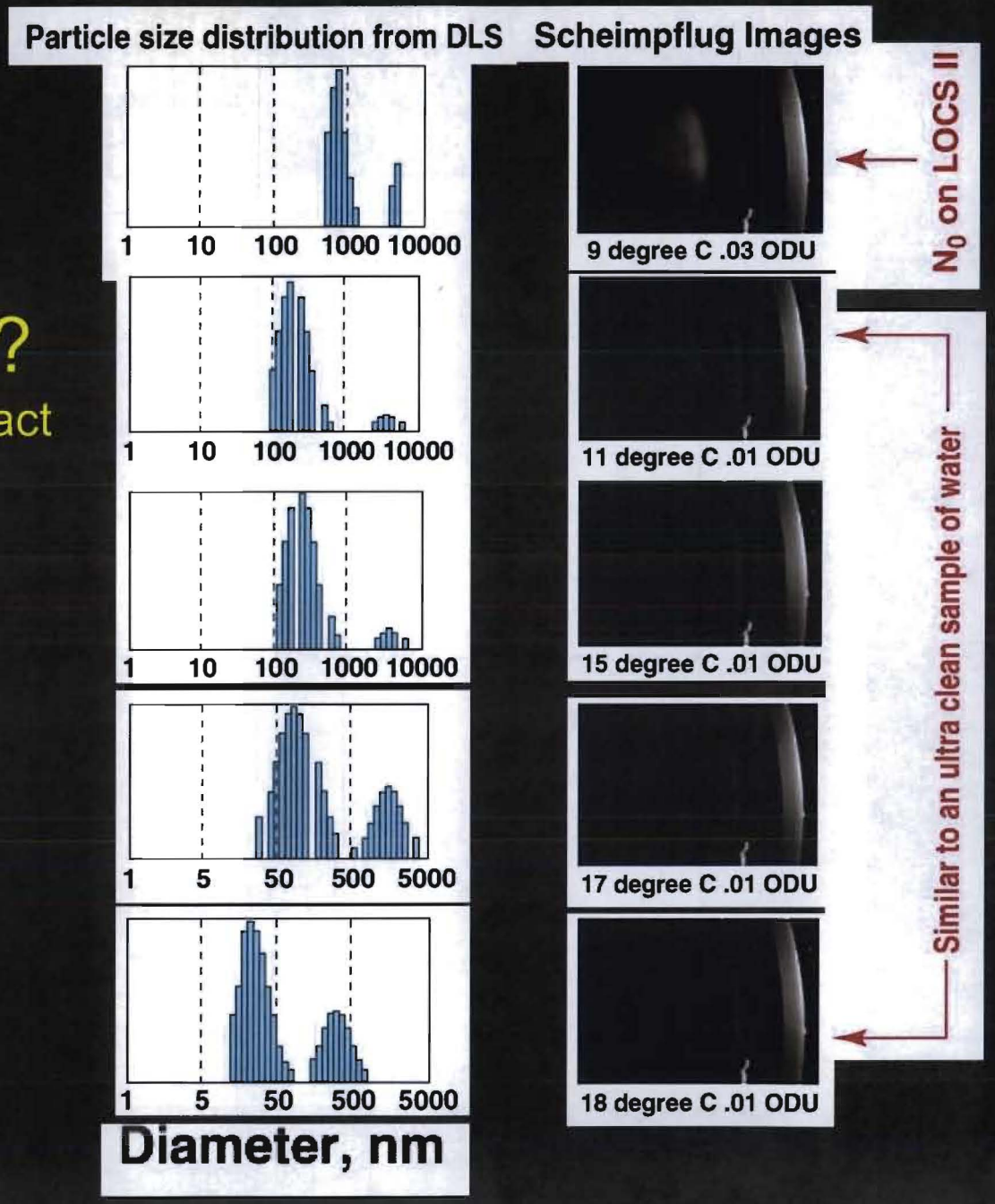


Datiles, M. et. al, Brit J. Ophthalmol. Vol. 79, 527-534, 1995

Sensitivity of DLS compared To Scheimpflug?

(in a Cold-Induced Cataract Model; Intact Calf Eyes)

Ansari and Datiles, Exp. Eye Res., Vol. 74, 93-102, 2002



Clinical Study: Evaluation of Pre-senile Cataract with DLS and Comparison with AREDS Optical Lens Grading System

NASA-NEI Collaboration

Manuel Datiles, MD

Rick Ferris, MD

George Reed, PhD

Susan Vitale, PhD

Kwang Suh, PhD

Rafat Ansari, PhD

Aims of this Clinical Study

To assess the association of Dynamic Light Scattering (DLS) measurements of the lens with aging and nuclear lens opacity.

To demonstrate that an "Alpha (α) -Crystallin Index" can be calculated, which is a measure of available α-crystallin in a living lens, and which is associated with the susceptibility of a lens to develop cataract.

Methods: Clinical Protocol

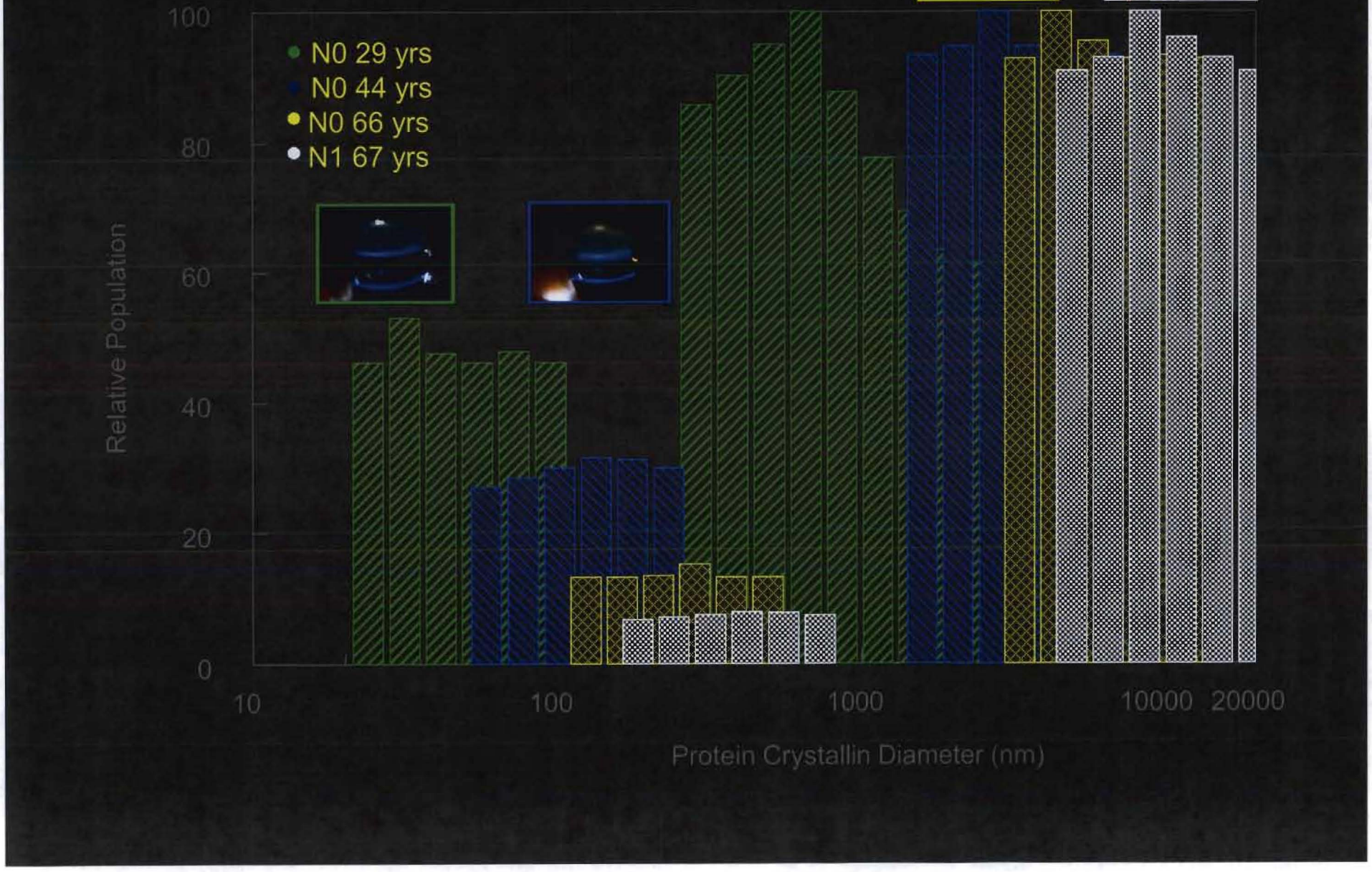
- NEI-IRB approved Cross Sectional study
- Normal and Nuclear Cataract Patients
- Age groups from 10 - 80 yrs represented
- Complete Dilated Eye Exams including Clinical and Photographic Grading
- Dynamic Light Scattering measurements on Nuclear region

NASA's Clinical DLS Device in use at NEI/NIH (M.B. Datiles III, M.D.)

Patient Demographics

- 235 patients (380 eyes) Males and Females
- Mean Age: 57.7 Years (Range: 7-86 years)
- AREDS Clinical Nuclear Grades ranged from 0.0-3.8 (Mean 0.75, SD 0.74)

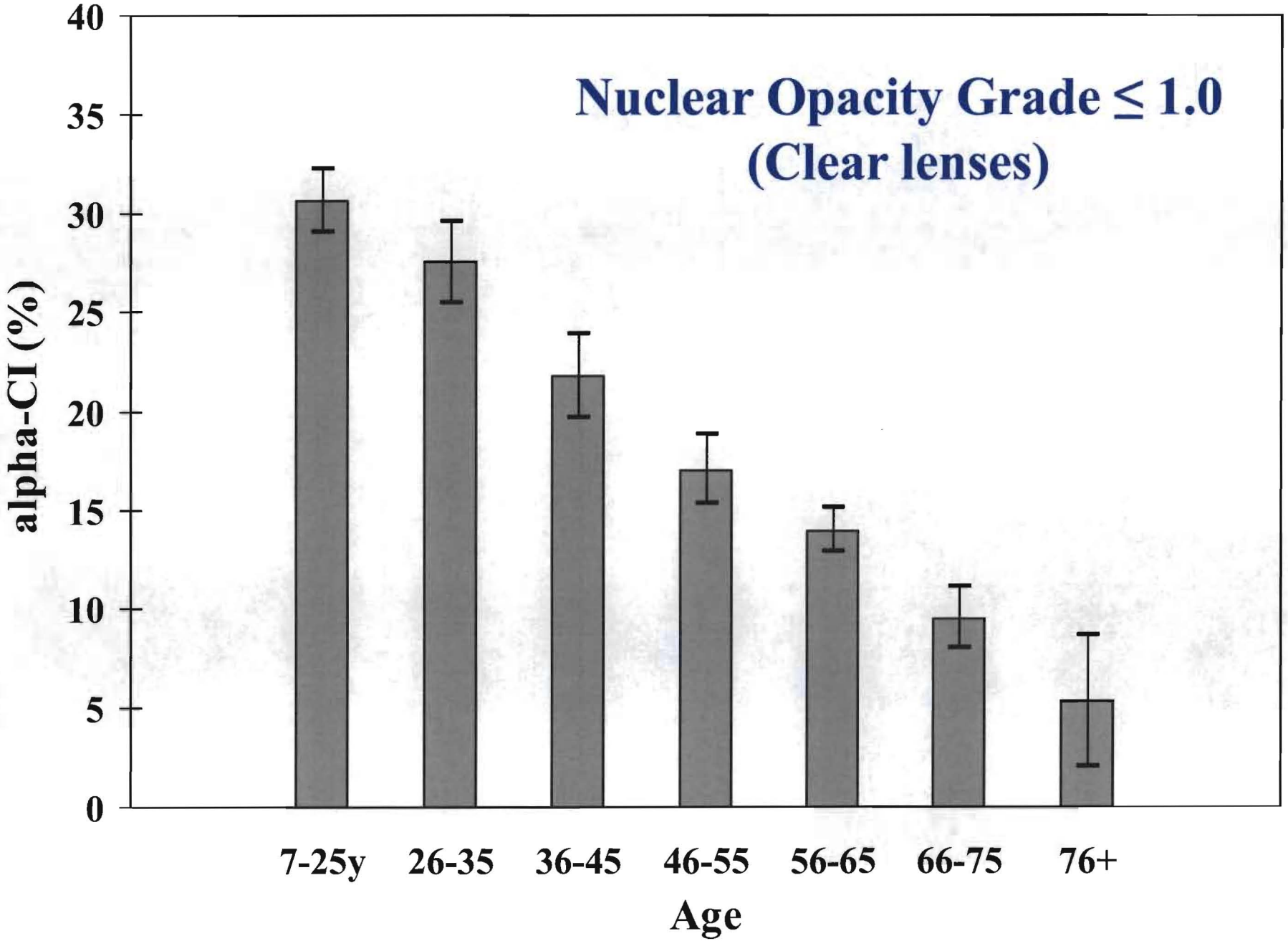
DLS Size Distribution (Age/AREDS)

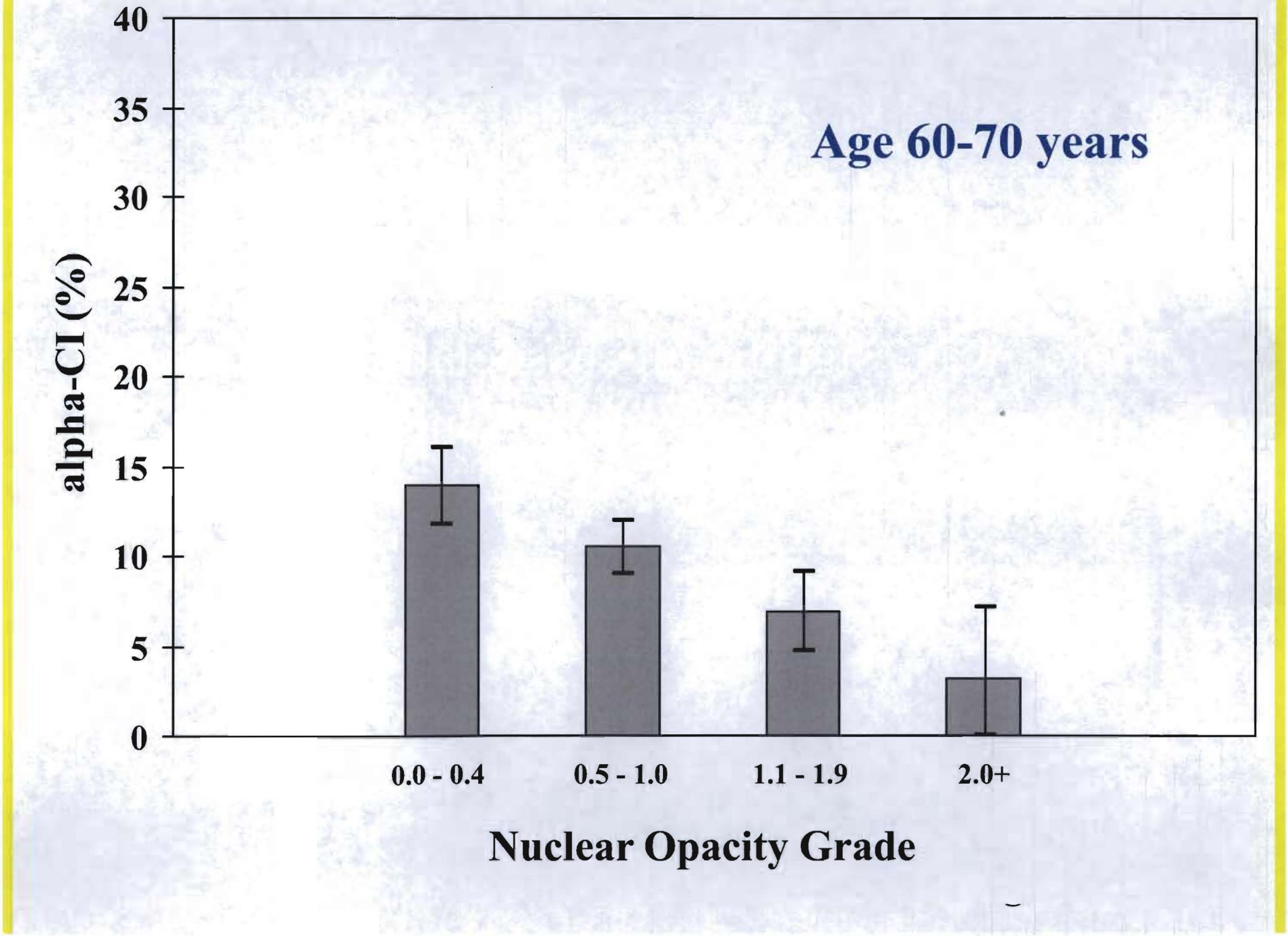


The α -Crystallin Index: a new parameter obtained from DLS to assess susceptibility to cataract

- α Index is a new objective clinical measure of the amount of unbound alpha-crystallin in the lens.
- Unbound alpha-crystallins act as molecular chaperones which prevent lens protein aggregation and cataract formation.
- Associations of this index with age and the AREDS clinical and photographic lens grading were evaluated.
- Decreasing levels of alpha-crystallin are associated with increased risk of nuclear sclerosis

Datiles et al., Arch. Opthalmol, 2008; 126:12:1687-93


Nuclear Opacity Grade ≤ 1.0
(Clear lenses)
alpha-CI (%)
40
35
30
25
20
15
10
5
0
7-25y
26-35
36-45
46-55
56-65
66-75
76+
Age


Age 60-70 years
alpha-CI (%)
40
35
30
25
20
15
10
5
0
0.0 - 0.4
0.5 - 1.0
1.1 - 1.9
2.0+
Nuclear Opacity Grade

Results: DLS vs Age

There was significant association between decrease in ACI and increasing age ($p<0.001$)

--For every decade of life, the aCI declines by 4.4%.

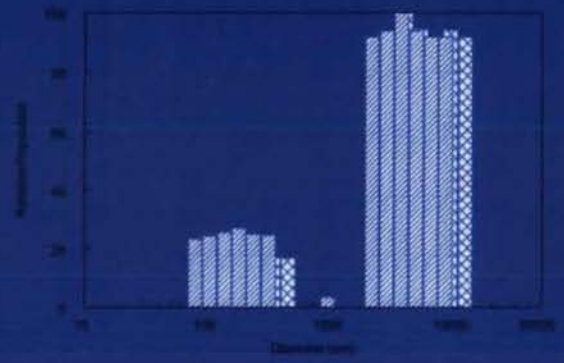
α-Crystallin:

- Chaperone-like activity
  - prevents uncontrolled protein aggregation
  - prevents light scattering in the lens (cataract)

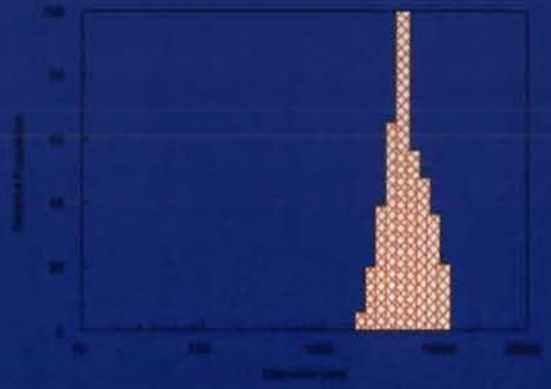
- Disappears from lens nucleus with age
  - » (Roy and Spector, 1976)

One Year Follow up Study: Pre Senile Nuclear Cataract

No Alpha Reserve-no protection



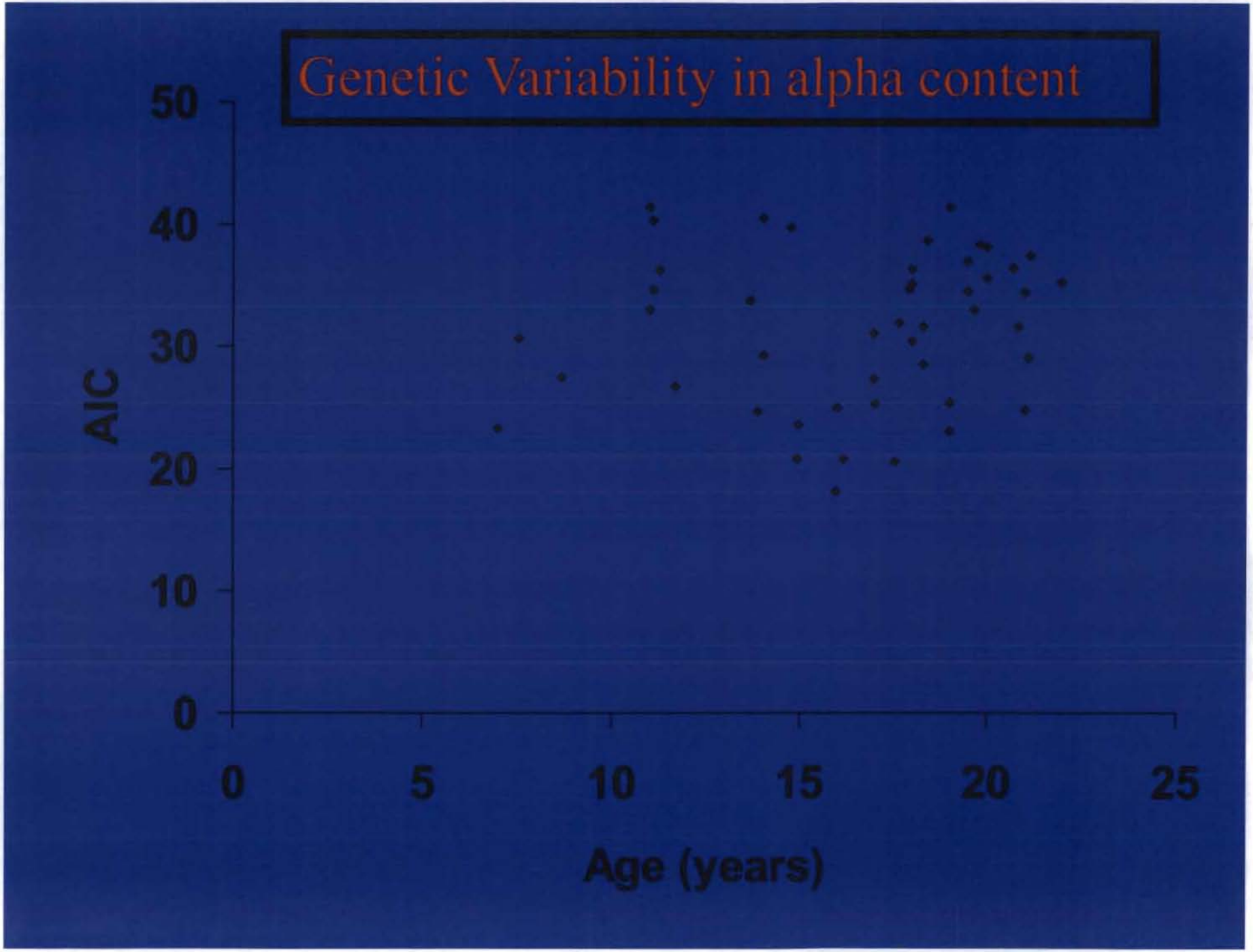
6/14/2004



5/24/2005

Dynamic Light Scattering Estimation of α-Crystallin Content of the *Young Human* Lens Nucleus in Vivo:

Clinical Implication


Genetic Variability in alpha content
AIC
50
40
30
20
10
0
0
5
10
15
20
25
Age (years)

Summary

- α-Crystallin is an important anti-cataract factor.
- DLS can approximate the amount of "free" α-crystallin present in the lens in vivo.
- There may be significant genetic variability in the α-crystallin content of young human lenses – could this help in astronaut selection? Or finding medical treatment?

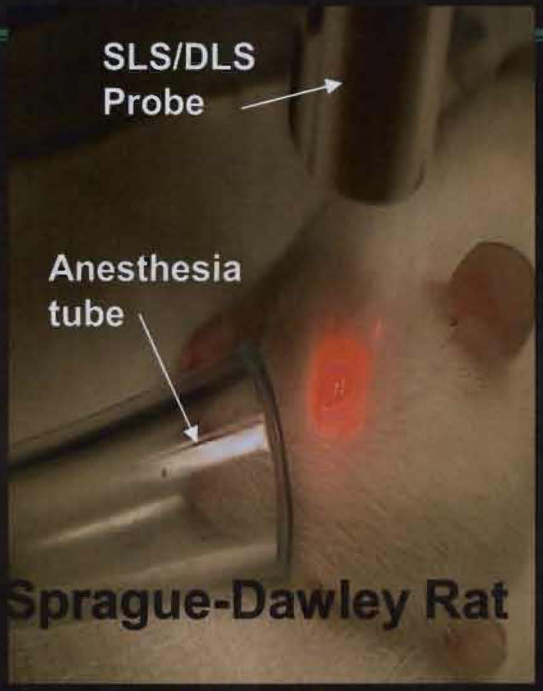
Cataract Prevention or Reversal ?

Is Treatment Possible ?

- Aldose Reductase Inhibitors
- Pantethine
- Tempol-H (NIH)
- Antioxidants (red wine, tea caretonoids, isoflavones)
- Vitamin Supplements (AREDS Study)

NASA is also developing an antioxidant compound

Countermeasures
Cataract Treatment in Rats (33 Animals Studied)

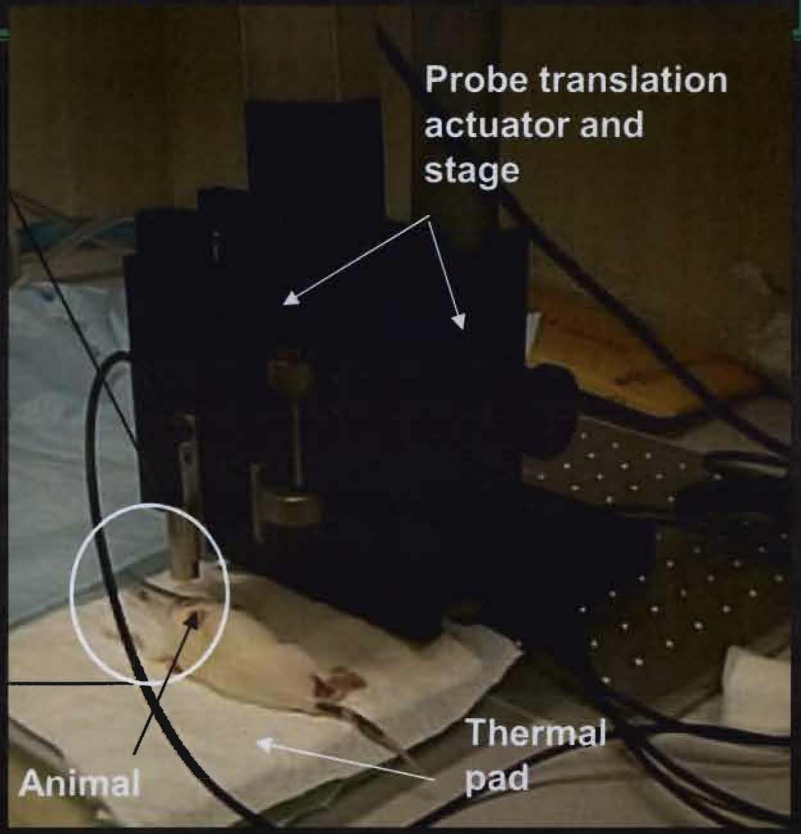


Animal Close-up

Measurement Time: 5 Sec

Wave-length: 670 nm

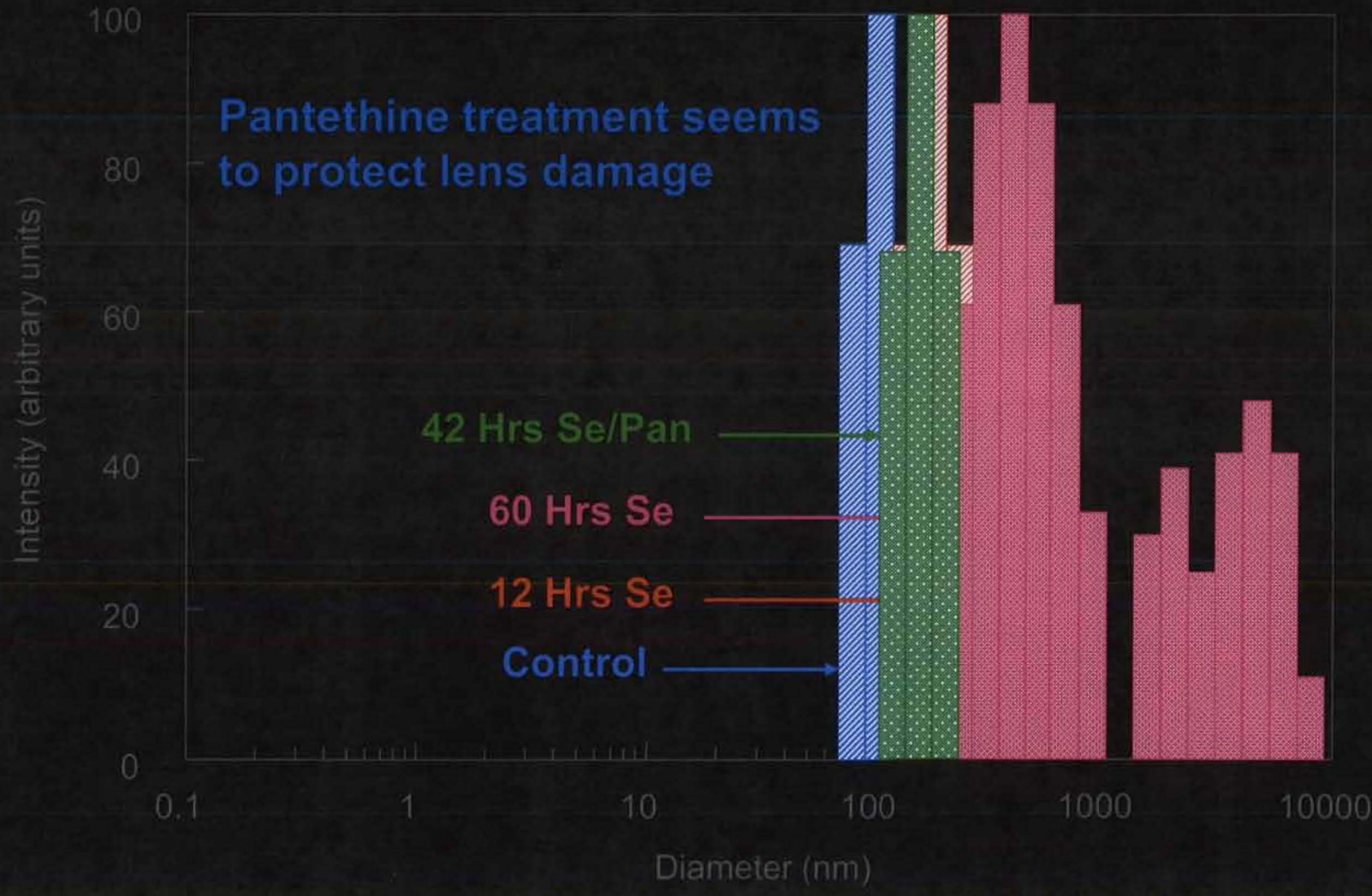
Power: 80 microwatts



Ansari et al, Ophthalmic Tech. XIII,
SPIE Vol. 4951, 2003

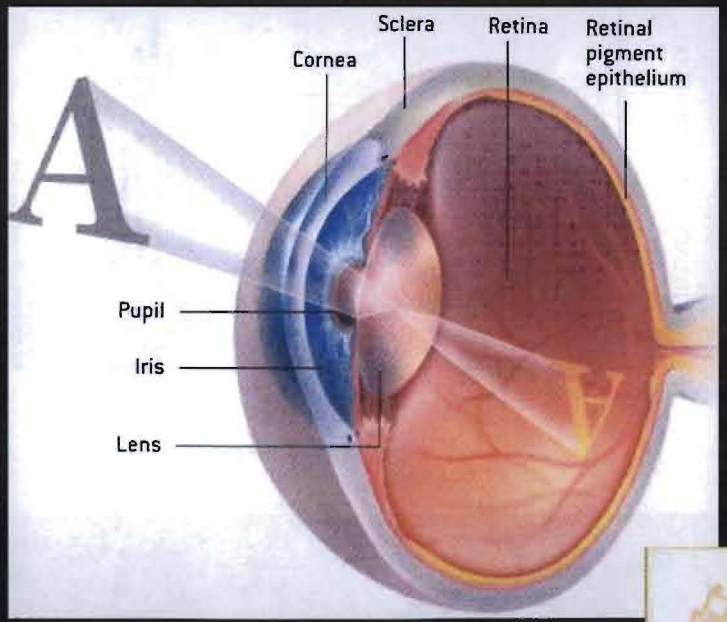
Pantethine Treatment in Rats

Particle-Size Distributions after DLS Exponential Sampling Analysis



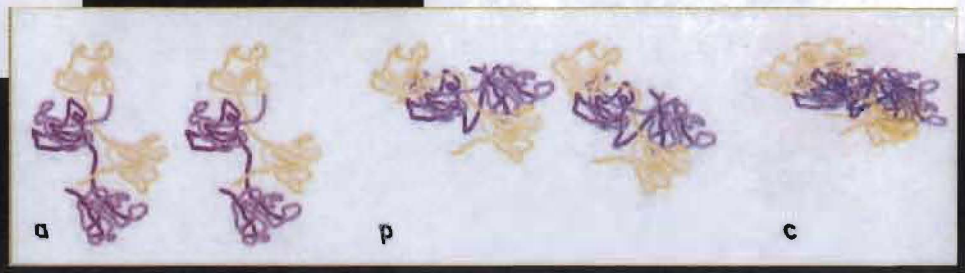
SCIENTIFIC AMERICAN

OCTOBER 2004

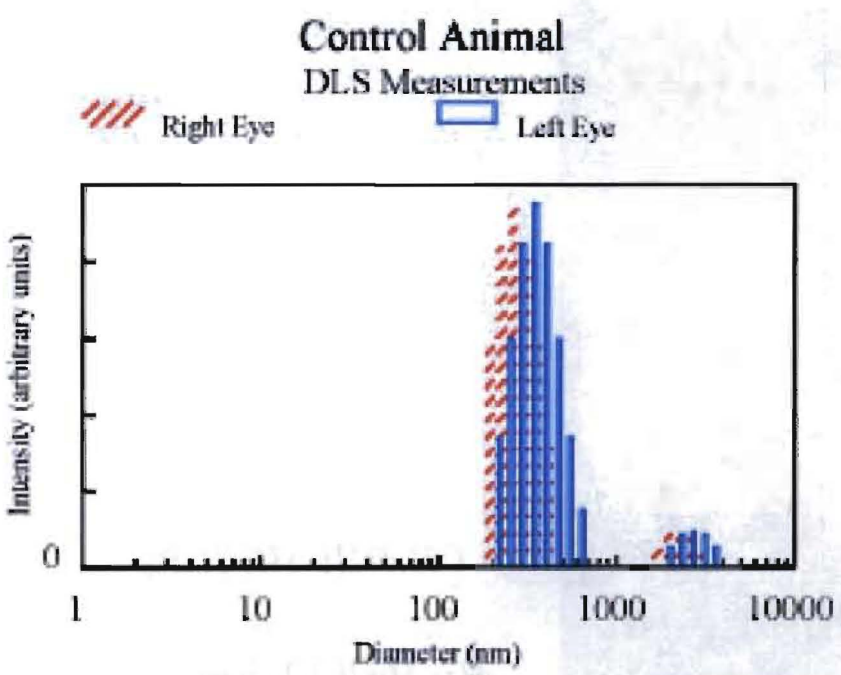


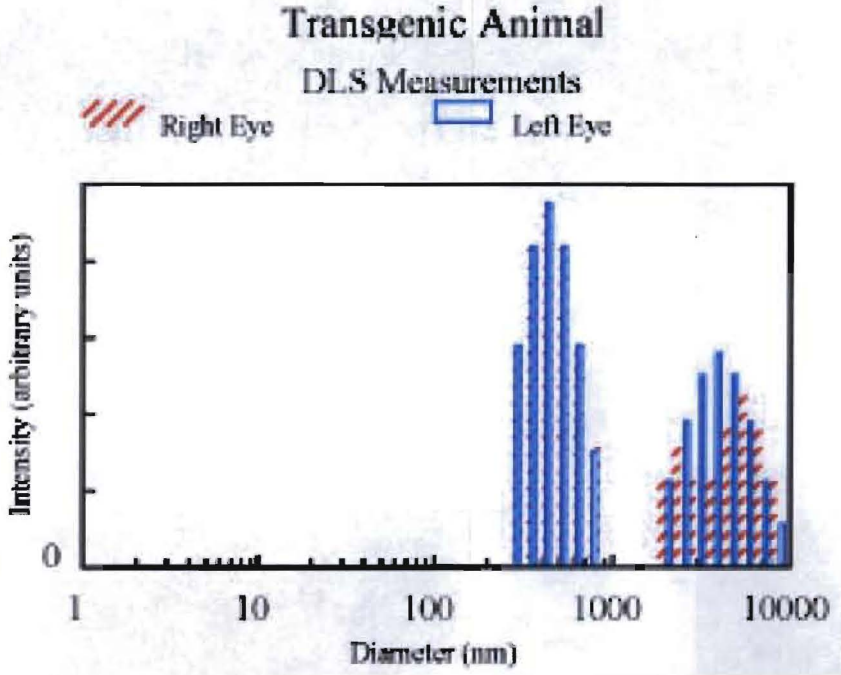
Studies of the lens of the eye not only could reveal ways to prevent cataracts but also might illuminate the biology of Alzheimer's, Parkinson's and other diseases in which cells commit suicide

By Ralf Dahm



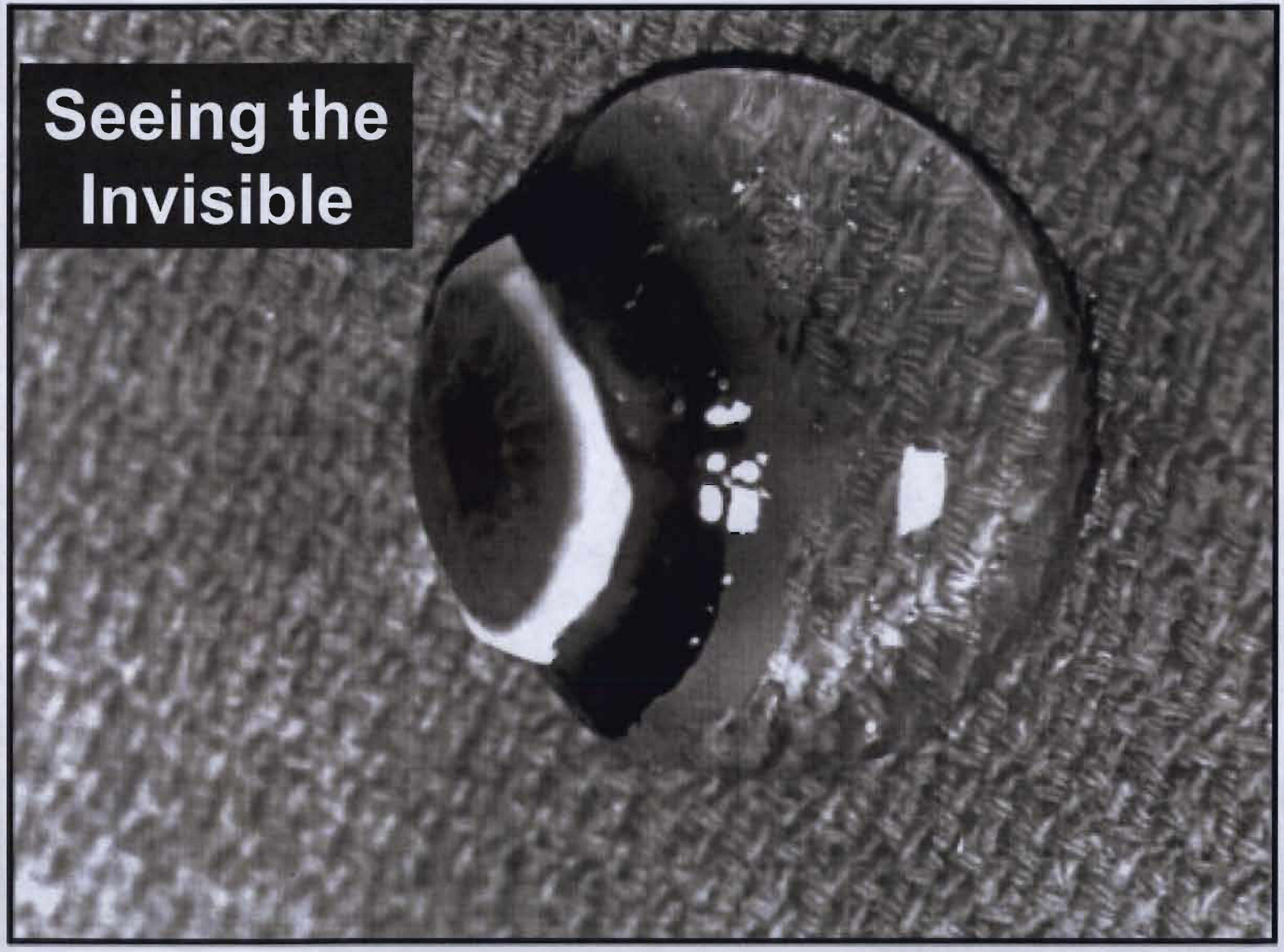
Early Detection of Amyloidogenesis (Alzheimer's)





Ansari, R.R., JBO, Jan. 2004

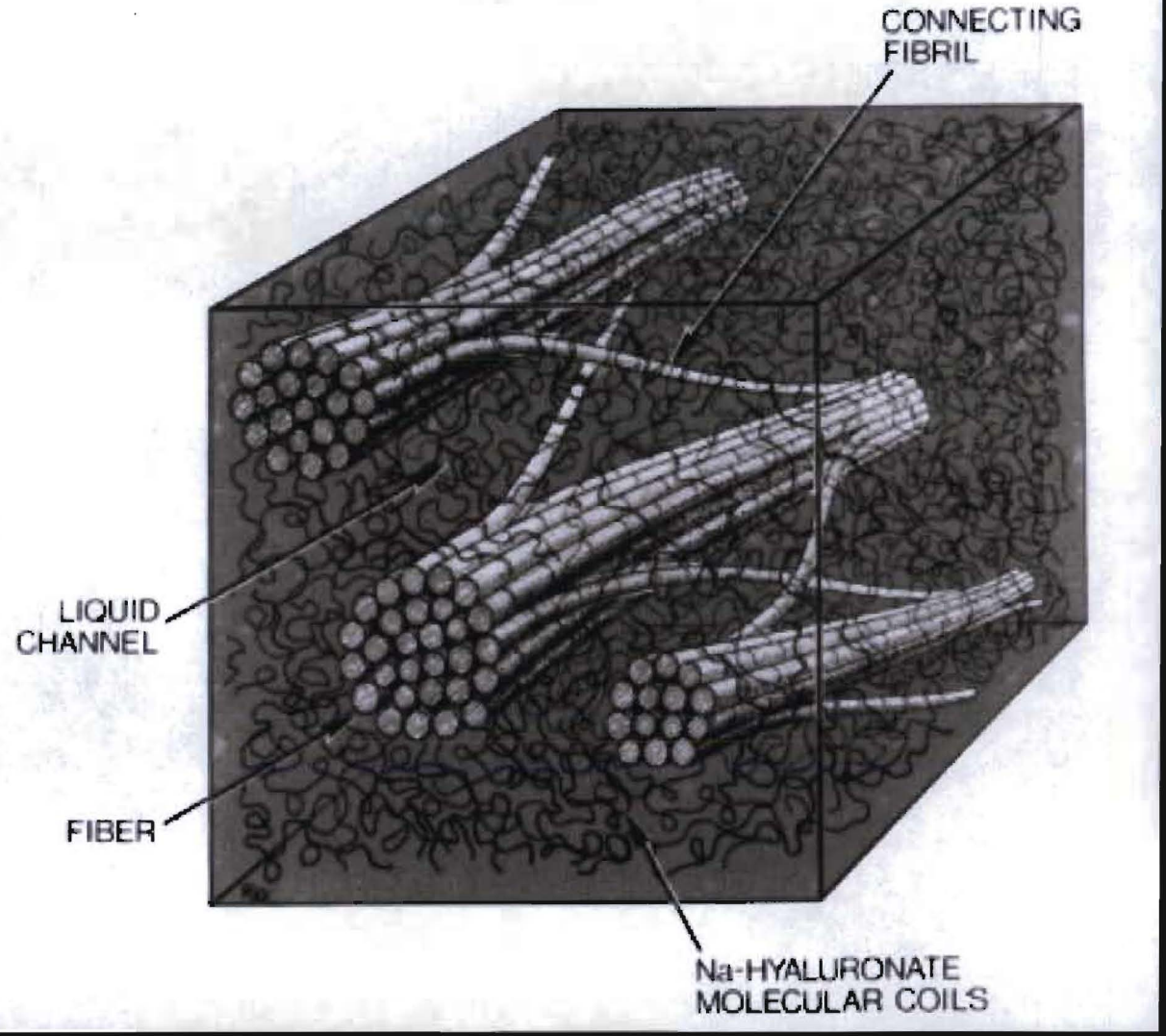
Vitreous of a 9 Month Old Baby Boy



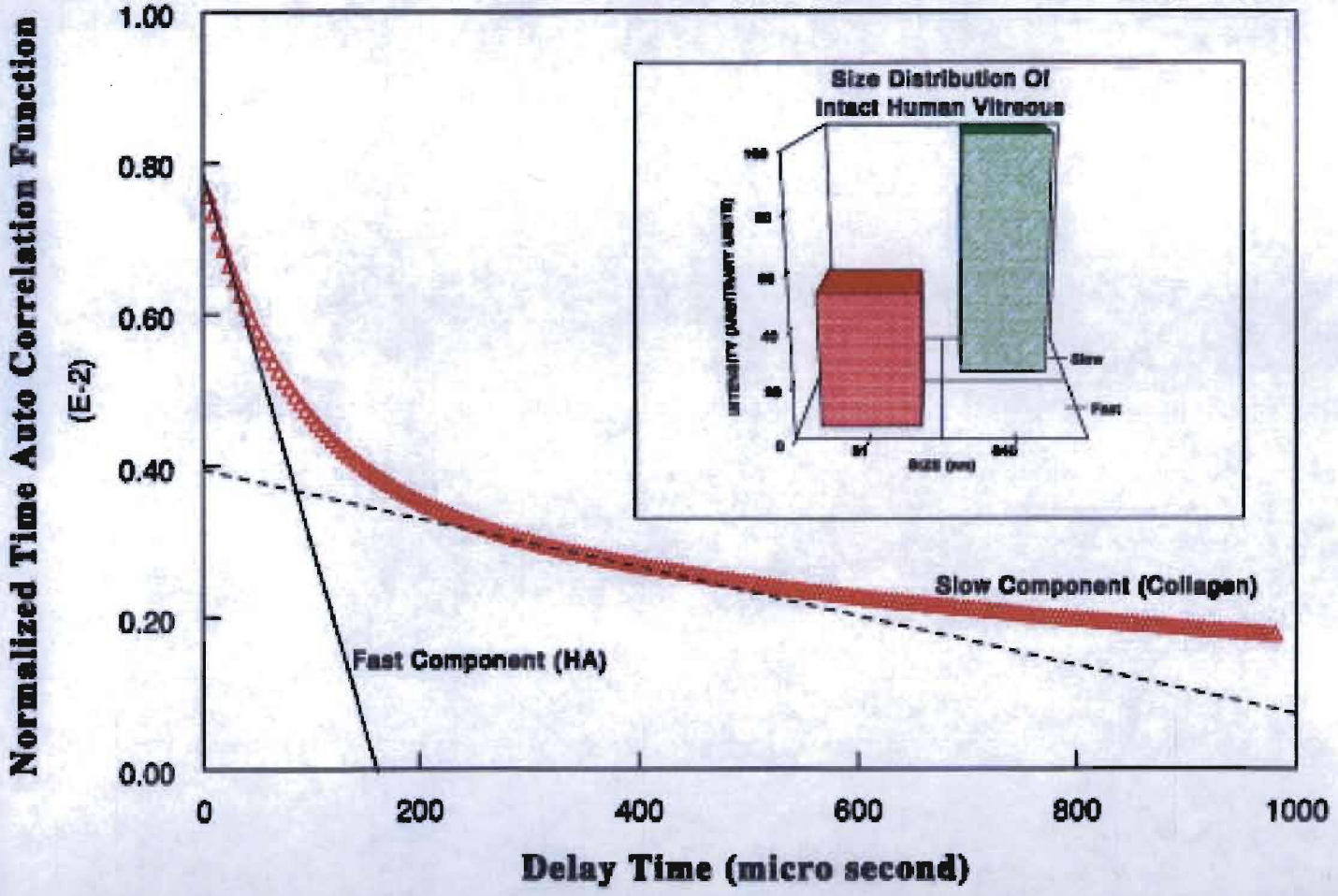
J. Sebag, Doheny Eye Clinic

The Vitreous

J. Sebag, Springer-Verlag 1989

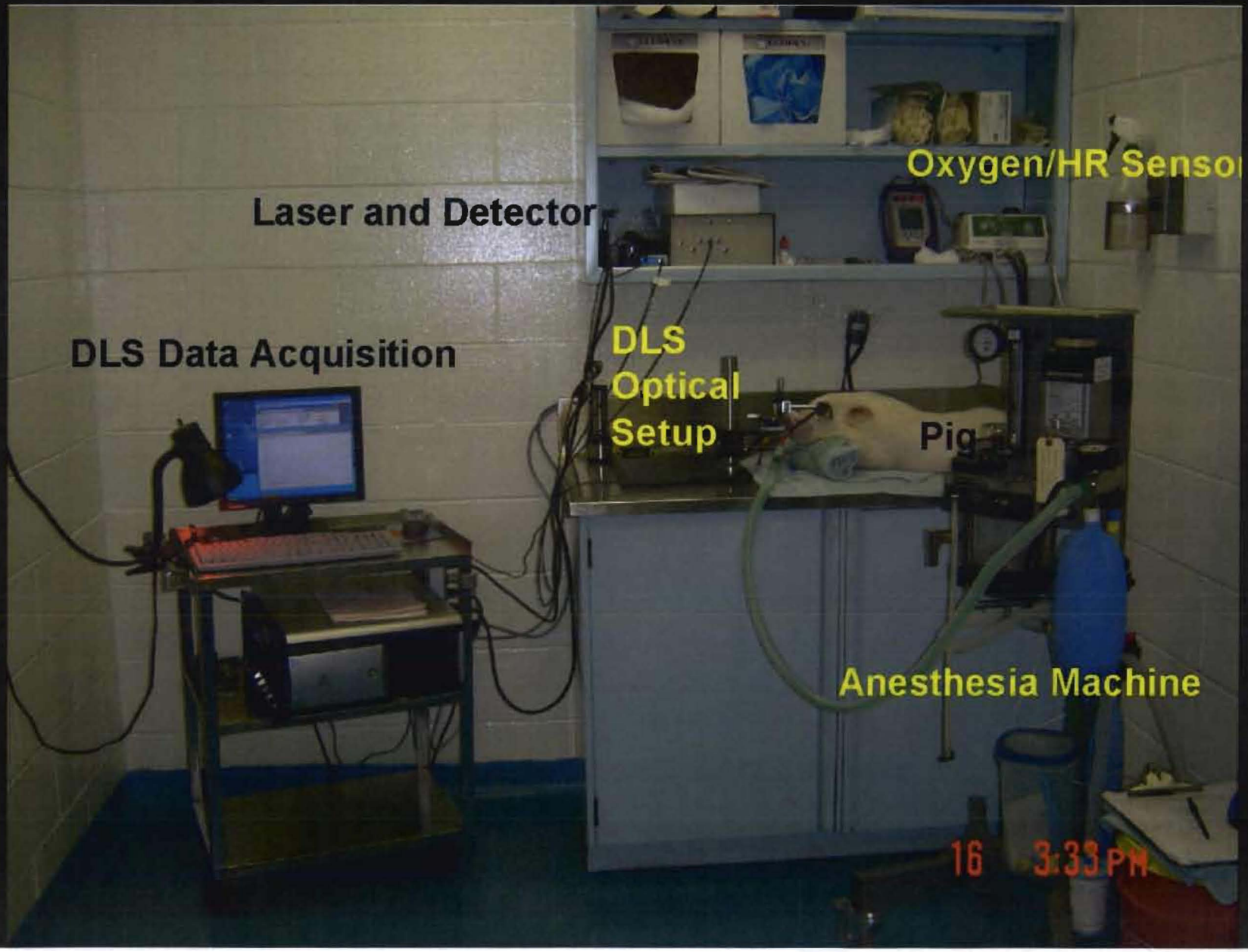


Time Relaxation of Intact Human Vitreous Diffusive Motions of Hyalurunan/Collagen



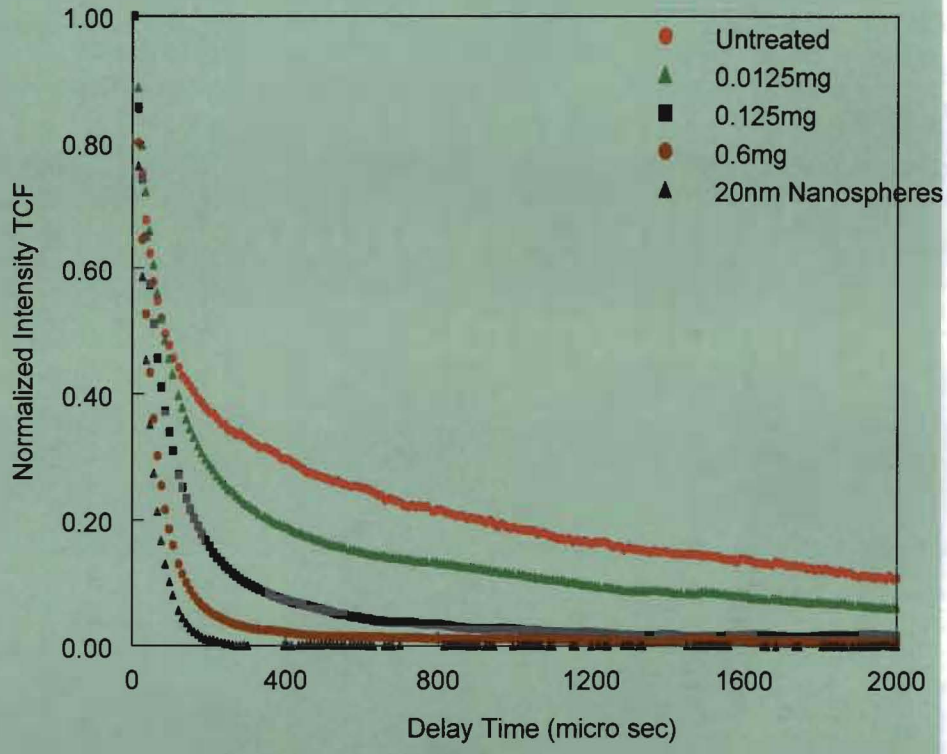
Ansari et al, Exp. Eye Res. Vol. 73, 859-866 December 2001

Microplasmin-Induced Vitreolysis (Retinopathy of Pre-maturity)



Dynamic Light Scattering Quantifies the Effect of Microplasmin Pharmacologic Vitreolysis

- Results
  - Diffussion coefficient increases with increasing upl dose
  - Particle size decreases with increasing upl dose
  - Polydispersity decreases with increasing upl dose
  - Dose-effect corrln' highly statistically significant
- Conclusion
  - Microplasmin induces pharmacologic vitreolysis.



Sebag and Ansari, and Suh, Graef's Arch. Oph. August 2006

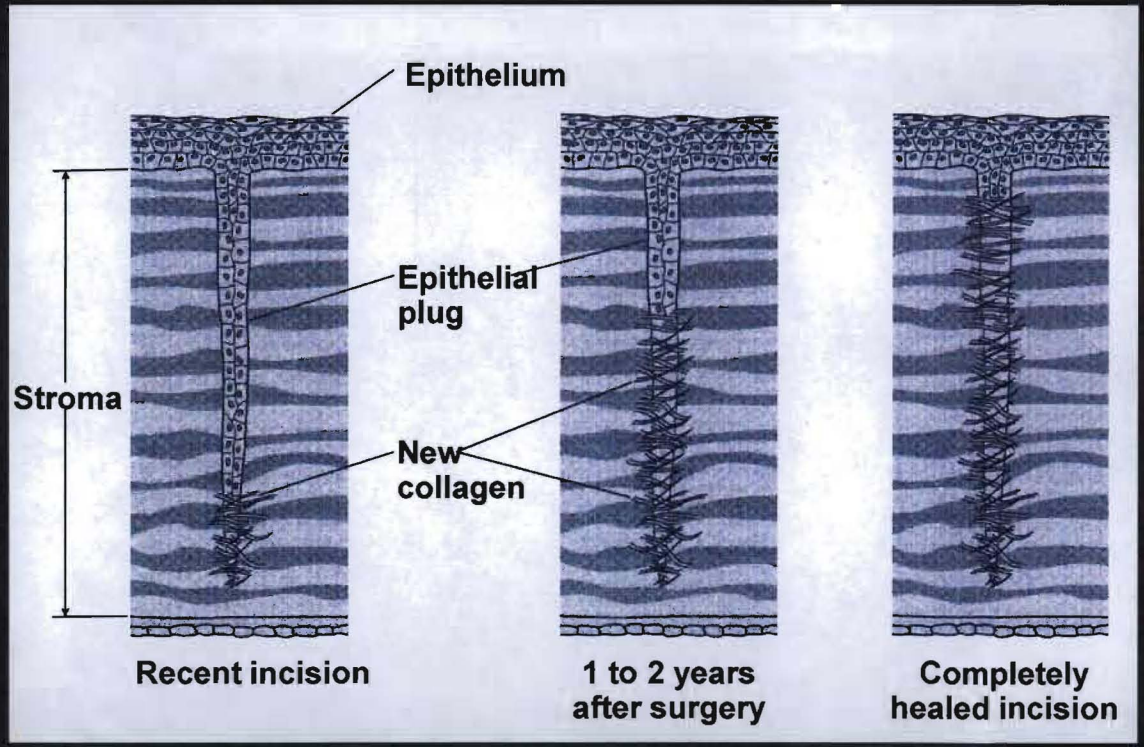
CORNEAL EVALUATION

Need for new diagnostic capabilities to better evaluate current refractive surgery outcomes.

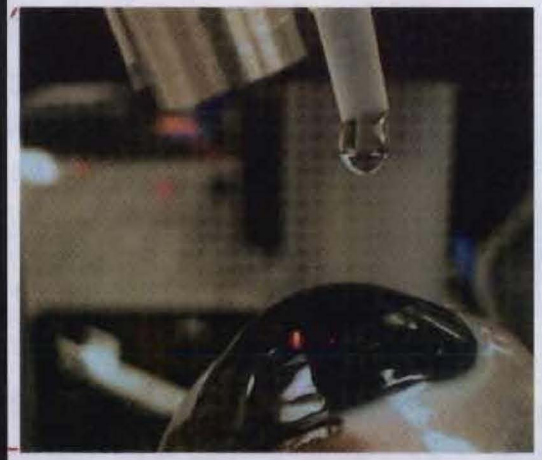
McLeod, S.D., Editorial "Beyond Snellen Acuity: The Assessment of Visual Function After Refractive Surgery." Arch Ophthalmol, September 2001.

Dr. Ron Krueger performed LASIK & PRK

Corneal Repair



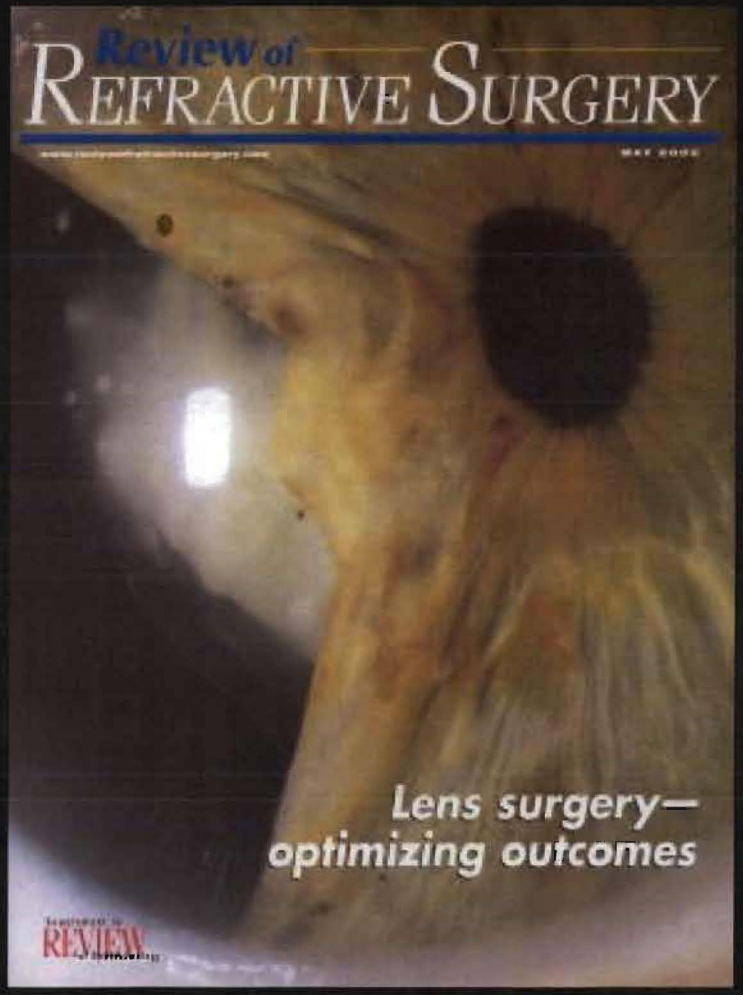
Eye irrigator and DLS probe



From "The Human Eye" by C.L. Oyster

DYNAMIC Light Scattering FOCUSES ON THE Cornea

Molecular measures of clarity



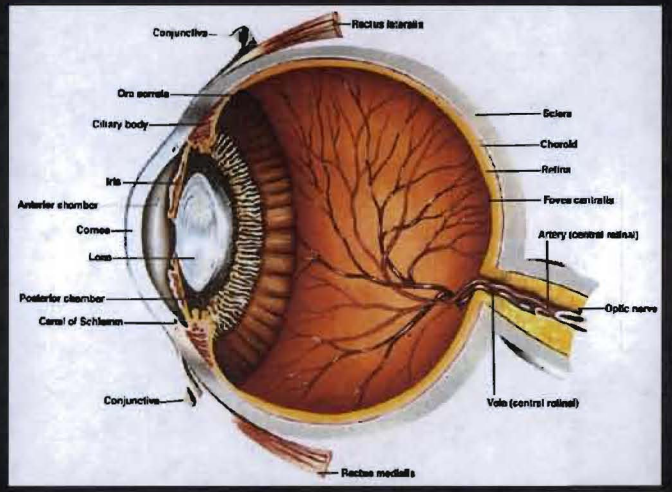
Successful early evaluation of Haze and Healing

May 2002

Astronauts Report Changes in Visual Acuity and IOP in Orbital Flight

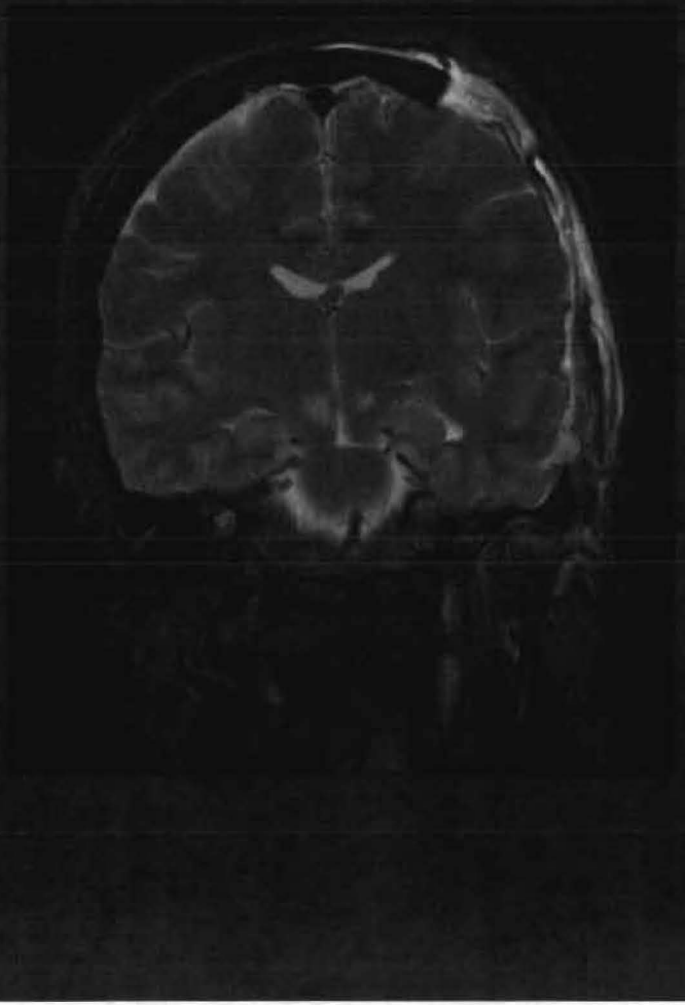
To this date this remains of unknown etiology

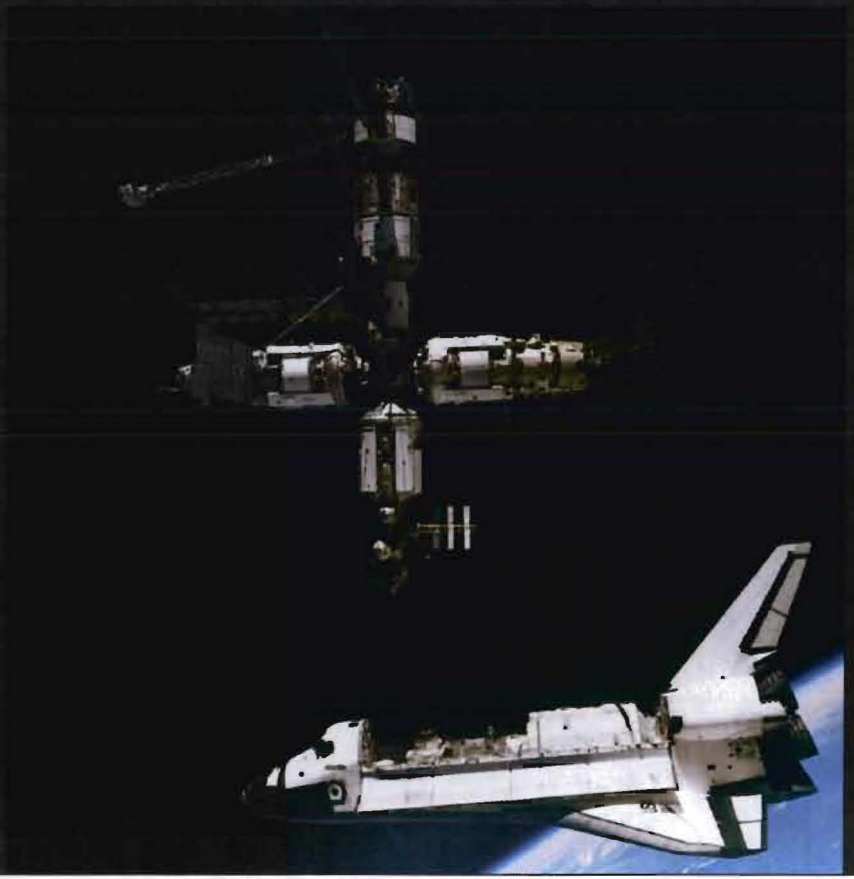
Dryden Flight Research Center EC94-42845-1 Photographed 1994
Untethered astronaut using new Extravehicular Maneuvering System (EVA)
STS-64 Discovery Mission



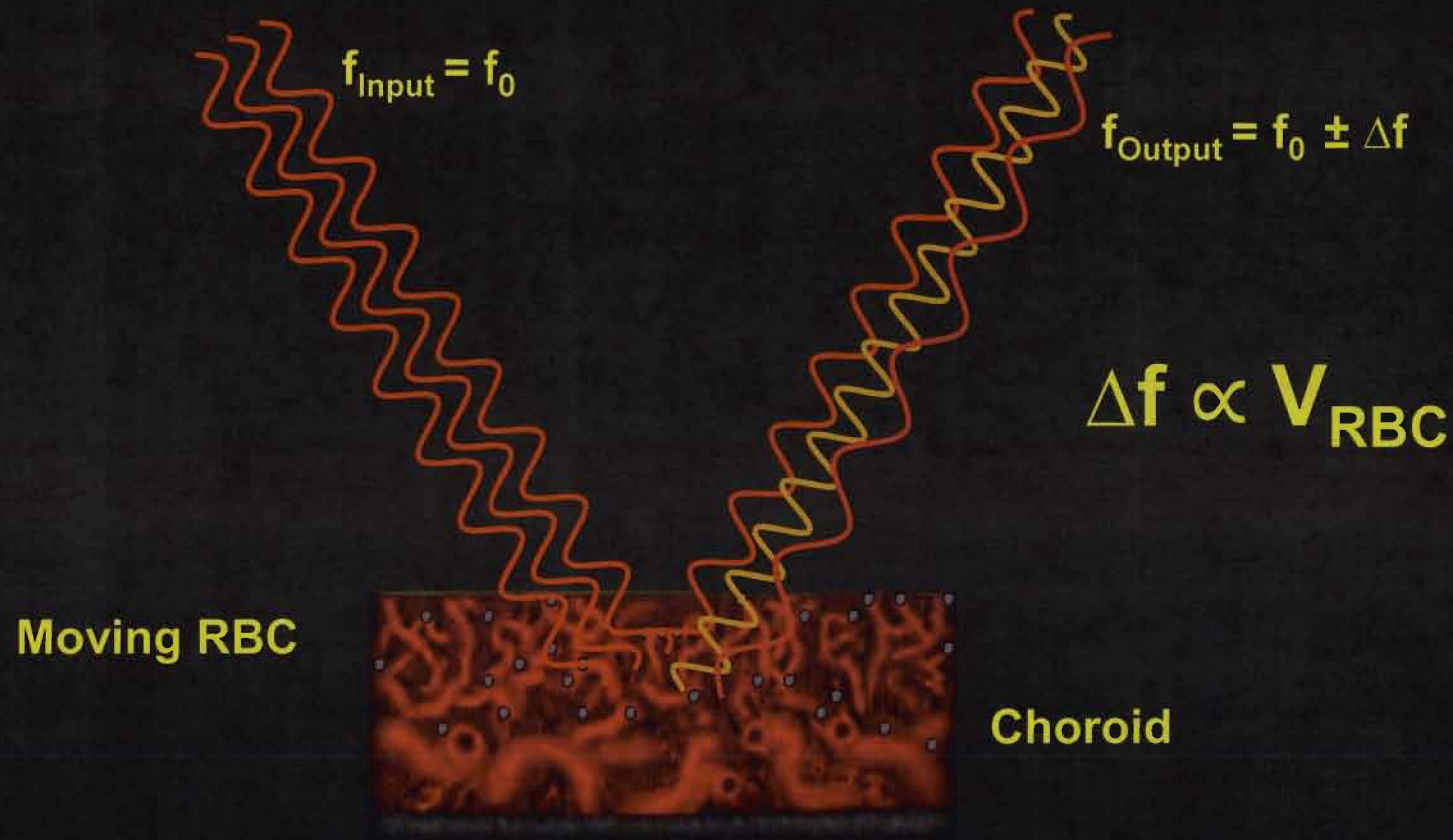
ChBF in response to changing fluid levels in weightless conditions

Increased ICP and Vision Problems in Astronauts





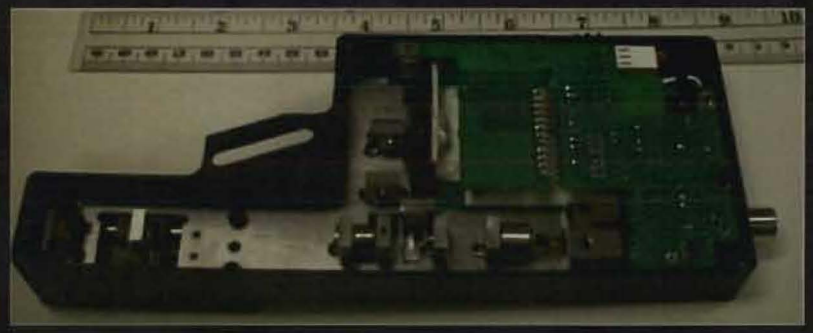
LDF Principle of Operation in Choroid



ChBF plays a major role in the supply of nutrients to the photoreceptors and pigment epithelium in humans

KC-135 Head-mounted LDF Apparatus

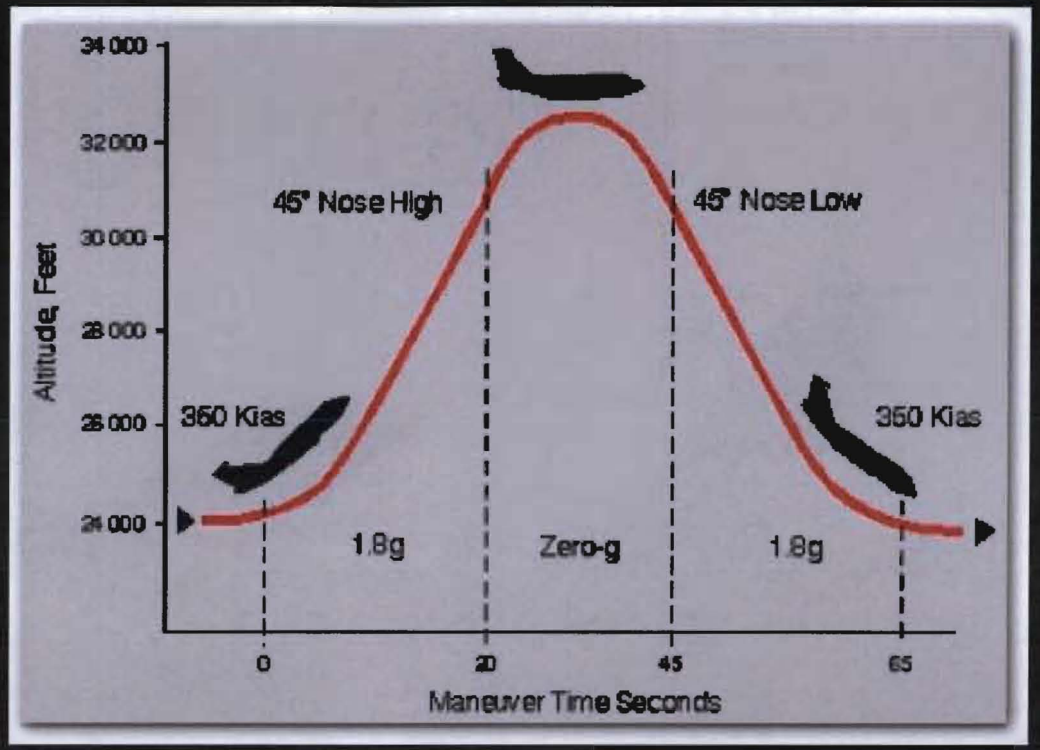
Weight: ~2 Lbs
Laser: 875 nm
Power: 100 μW
Duration: 10 s
Non-mydriatic



- 25 subjects studied (18 males, 7 females)
- Age: 23-51 Years old
- Subjects were allowed to blink

KC-135 Flight Tests

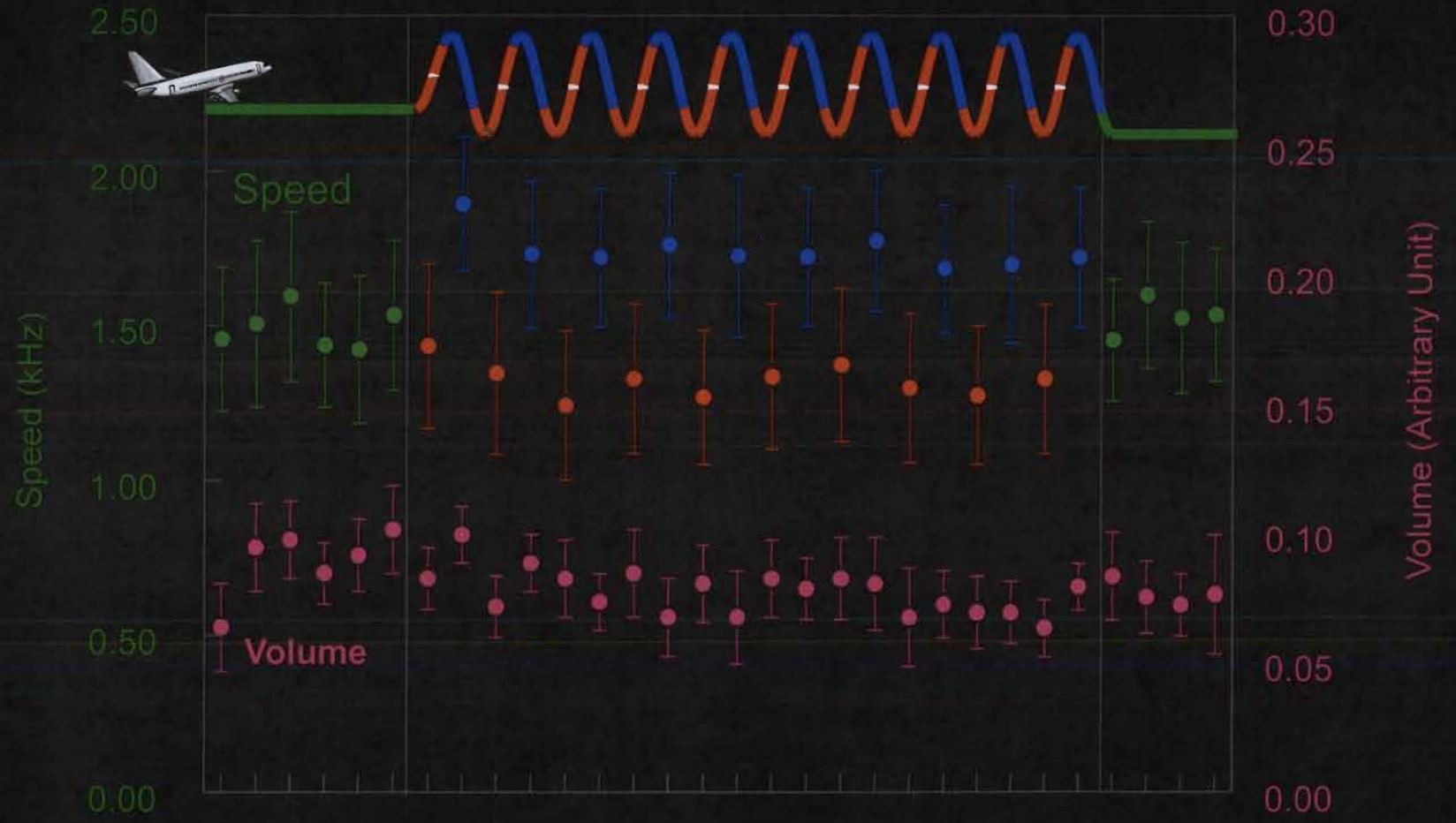
"Vomit Comet"



Sudanyl and/or Scopolamine

Choroidal Blood Flow Measurements in 0-G-2G

Sample Flight LDF Data: MD (49 years old)



Since there are no Baro Receptors Does the Choroid Self Regulate in Long-Duration Missions?

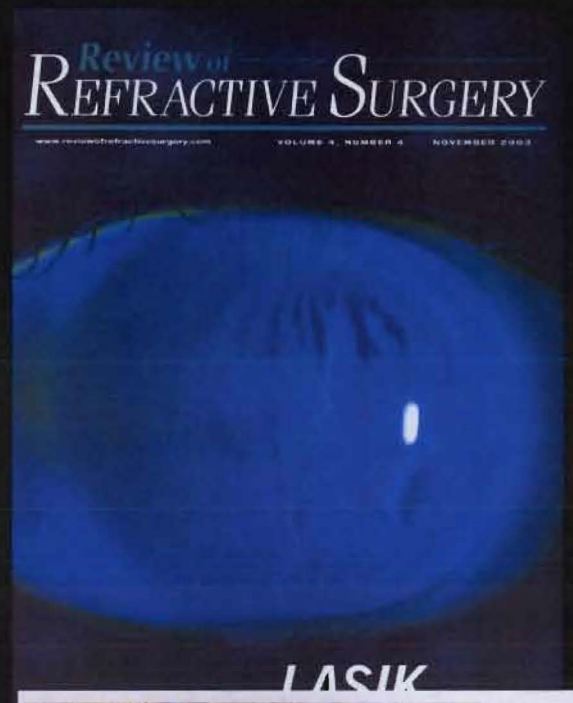


Figure 2. Blood pressure and LDF measurements in zero-g. left to right, (Upside down) Keith Manuel, (Back) Bobby Clark, King, (Front) Raul Blanco (blood pressure test subject), Ansari, and Geoffrey Iszard (LDF test subject).

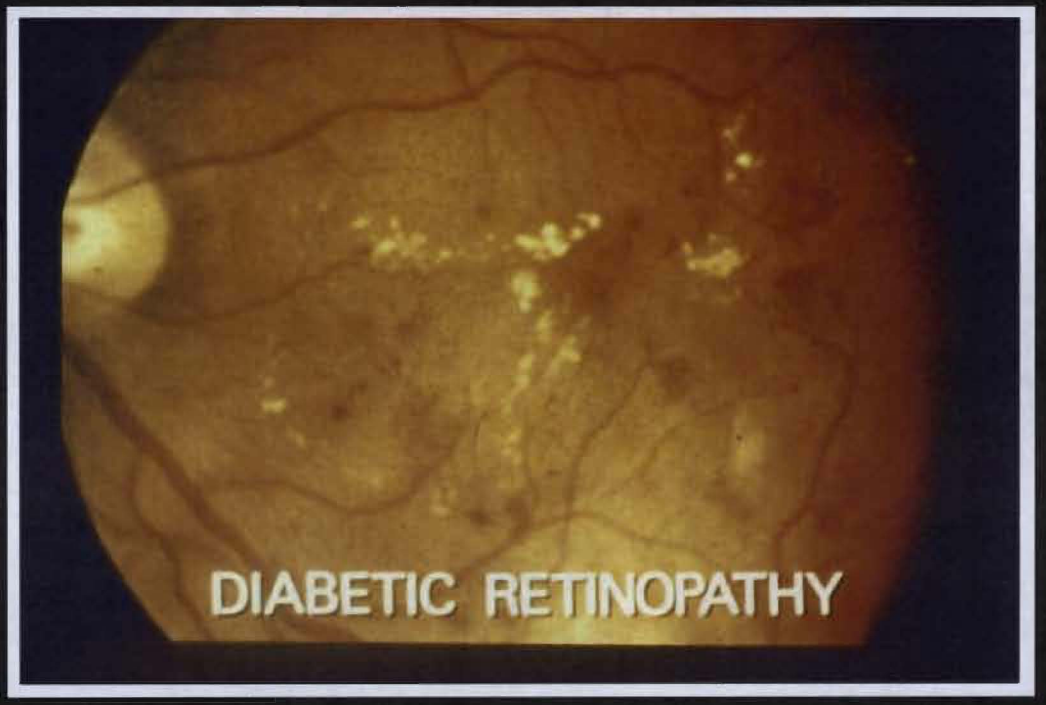
SPECIAL REPORT

Microgravity Measures OF Acuity

Leslie Sabbagh, Editor in Chief

Figure 1. The KC-135 microgravity airplane at NASA's Glenn Research Center in Cleveland. (left to right): Kwang Suh, (senior research associate), James King (design engineer), Rafat Ansari, (principal investigator), Ace Beall (pilot), Frank Marlow (co-pilot), John Yaniec (lead flight test director), John Lamb (flight engineer), James Withrow (flight test director).

Present: Fluorescene Angiography is the Most Widely Used Technique

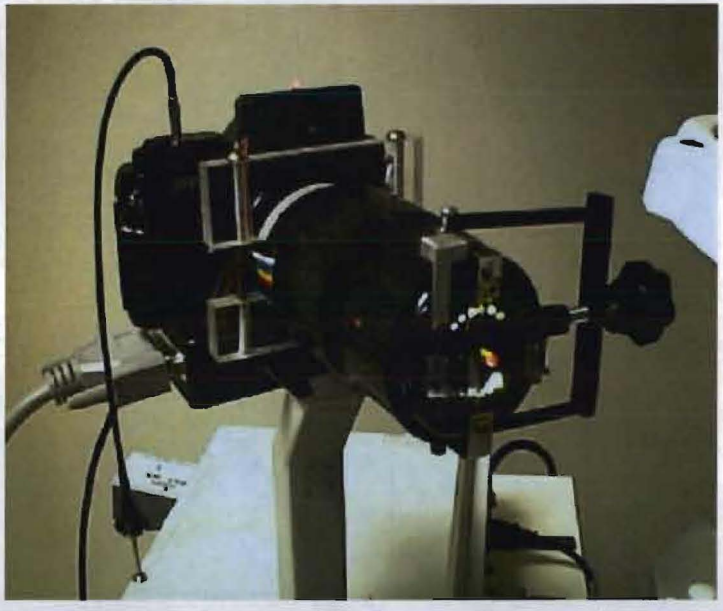


NON-INVASIVE AUTO FLUORESENCE MEASUREMENTS

Fundus Photo Courtesy of J. Sebag, MD, USC

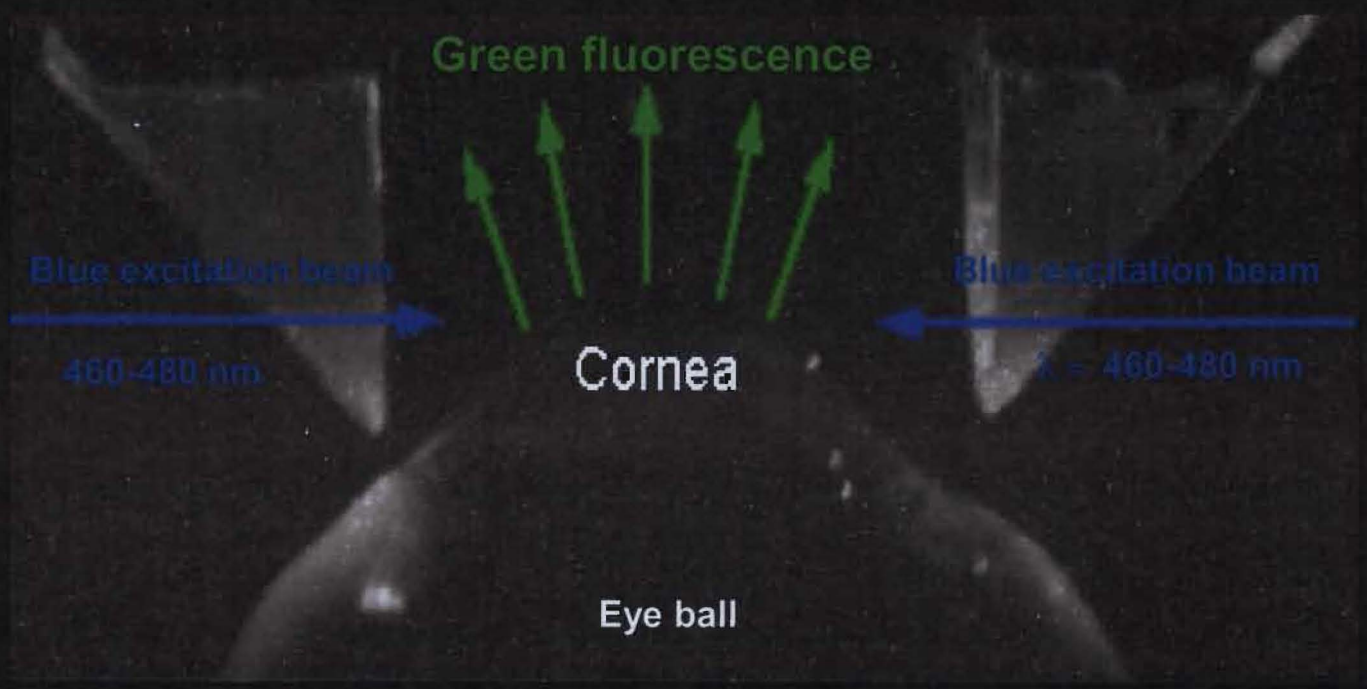
Non-Invasive Measurements of Diabetic Retinopathy through the Cornea

Autofluorescence Camera



Metabolically active Epithelial and Endothelial cells contain fluorophores: pyridine nucleotides (NADPH) and flavins (FMN and protein-linked flavins)

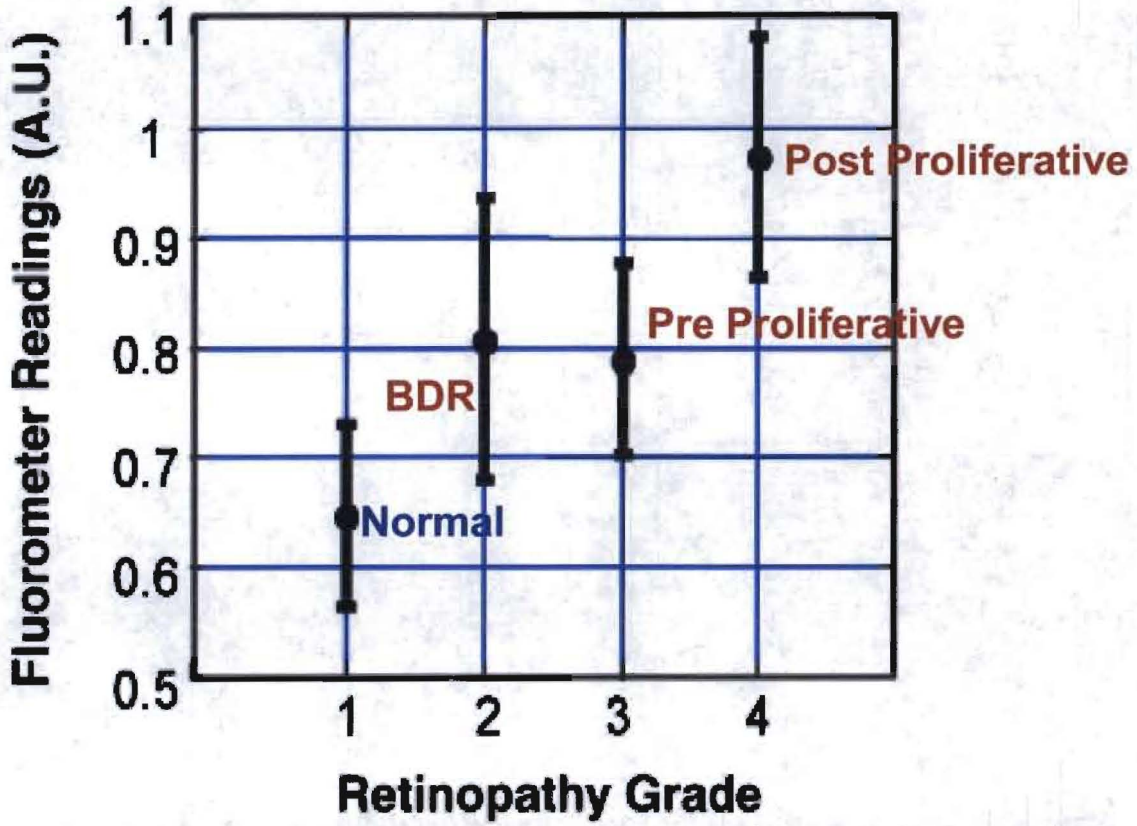
Corneal Auto-Fluorescence and Diabetic Retinopathy



NADPH fluoresce in the reduced redox state and flavins in the oxidized redox state

Results of a Preliminary Clinical Test Performed on about 90 Diabetic Subjects

(the bars represent the standard error in the measurements)



Rovati et al., J. Biomedical Opt. Vol 3, 357-363, 1999

DIABETES

"Between the time you wake up this morning and the time you wake up tomorrow morning, there are going to be 2,000 people diagnosed with diabetes. There will be 150 amputations, about 70 people who go blind from diabetes, and approximately 75 people who enter end-stage kidney disease programs because of diabetes." *(Frank Vinicor, MD, MPH, Director of the Division of Diabetes Translation, CDC)*

Cost to Society: 132 Billion Dollars in USA alone (Diabetes Care 26:917-932, 2003)

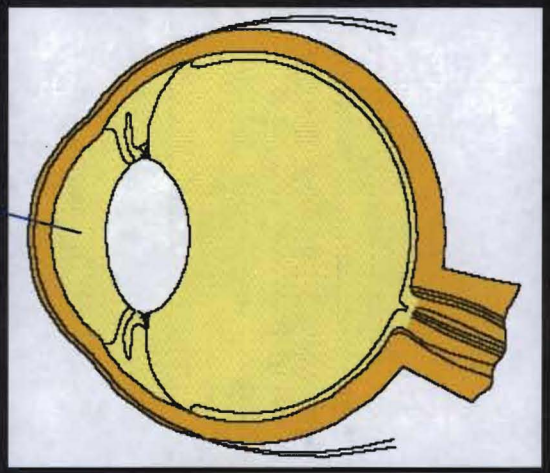
Motivation

- 140 million people are afflected by diabetes
- Diabetes is the fourth leading cause of death by disease in the United States, killing more than 169,000 people each year
- Diabetes can lead to severe complications over time
- Accurate determination of glucose levels can reduce the long-term risk for developing several diseases

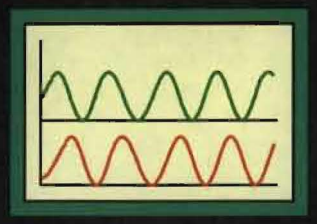
DIABETES MANAGEMENT

Non-invasive glucose detection:

aqueous humor



Glucose levels in the aqueous humor reflect the blood glucose levels with a delay of only a few minutes



Data Acquisition/
Analysis System

$C_6H_{12}O_6$

$\Delta\phi \propto$ Glucose Concentration

Detector
(APD or PIN PD)

Filter

Green (532nm)

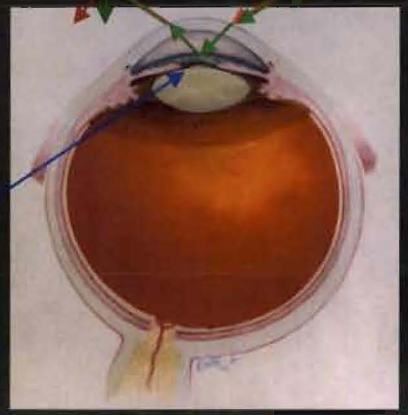
Light Source
(Laser or LED)

Red (632nm)

Beam Splitter

Beam Splitter

Rotating
Polarizer



Brewster Reflection

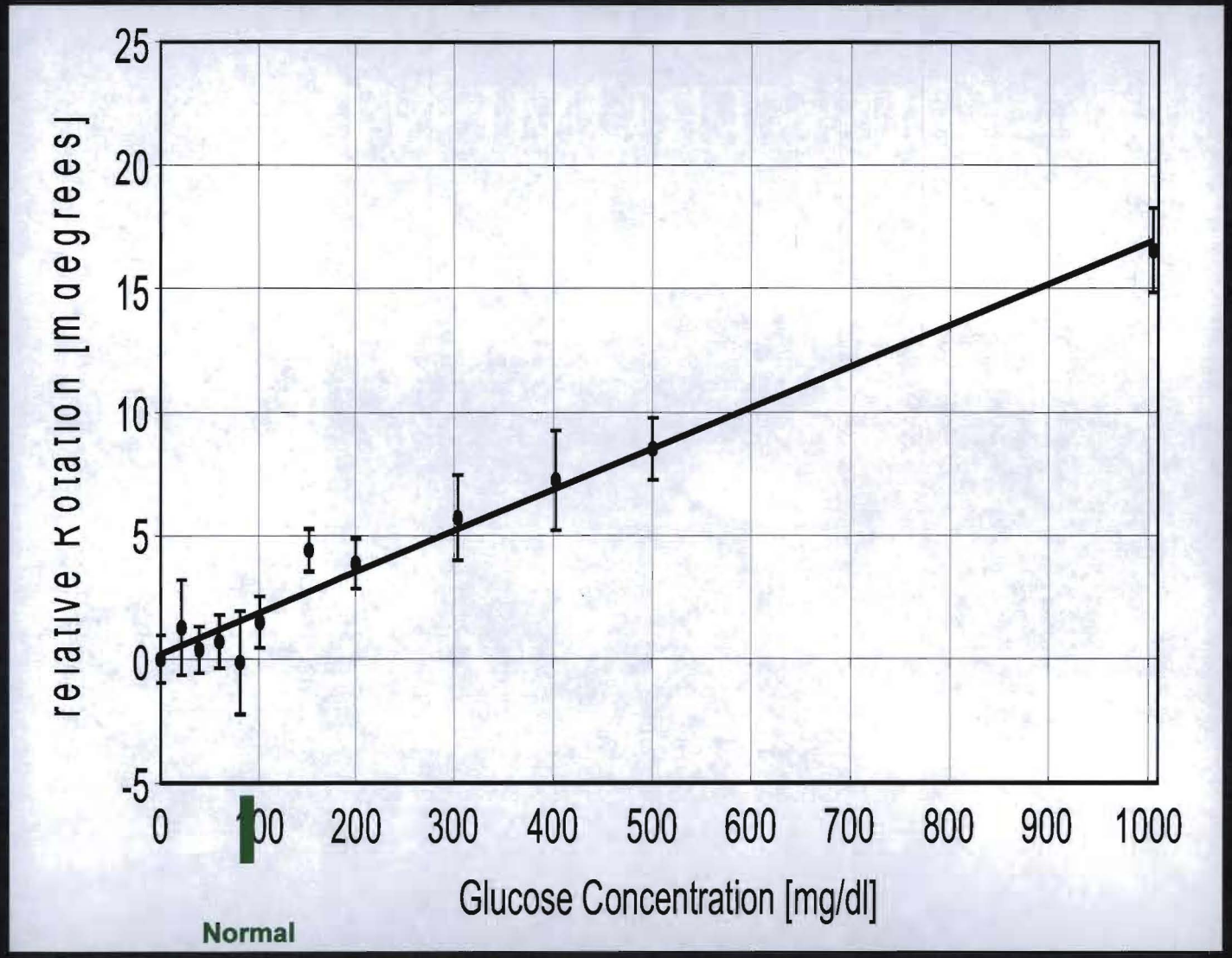
March 2003 www.nasatech.com Vol. 27 No. 3

NASA TECH BRIEFS

ENGINEERING SOLUTIONS FOR DESIGN & MANUFACTURING

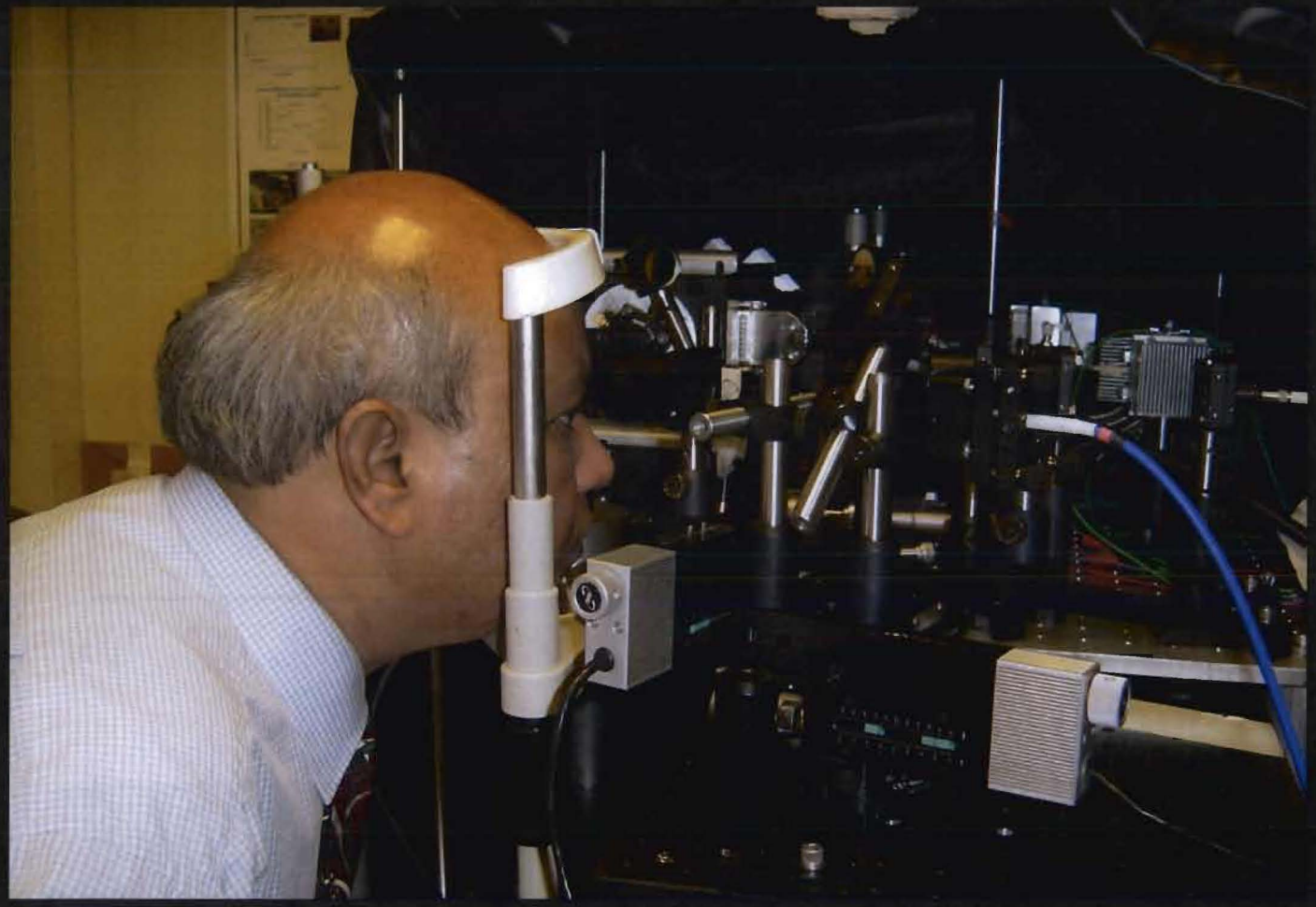
Ansari & Rovati, US PATENT
6,704,588, 2004

Glucose Sensing Results



Ansari et al., JBO, Vol 9, NO. 1, (2004)

PROTOTYPE GLUCOSE SENSING INSTRUMENT

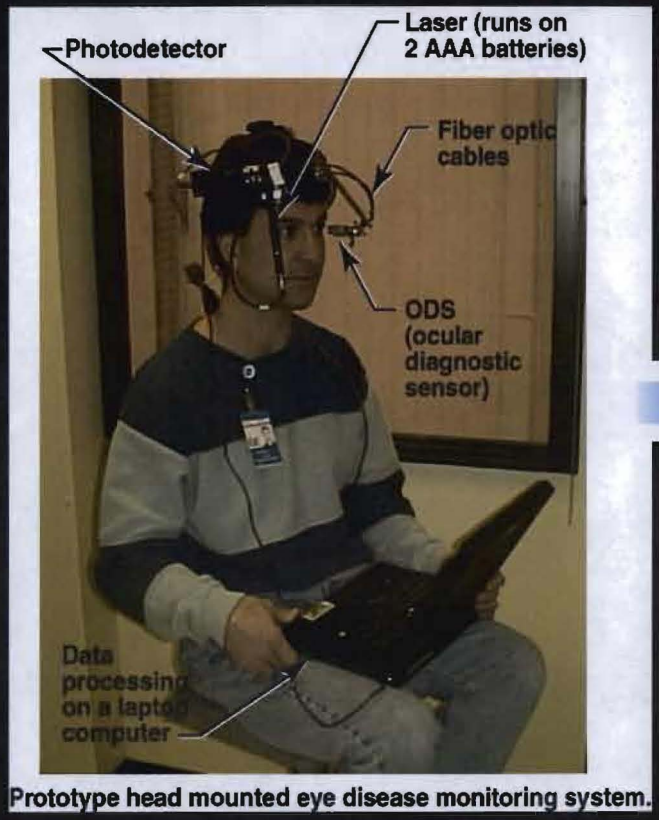


In the Future ---

Eye-Brain-Coordination

In Flight

Non-Invasive Detection of Ocular & Systemic Diseases



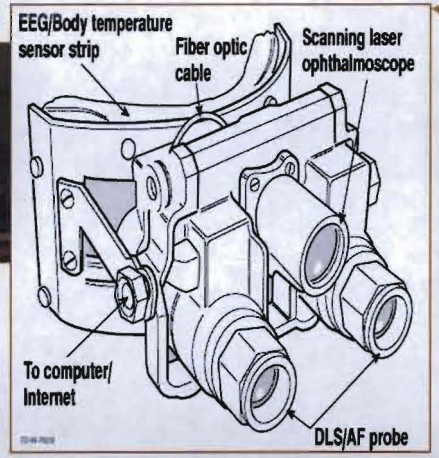
Prototype head mounted eye disease monitoring system.

Ophthalmic Tele-Health: For the Benefit of All Human Kind


Space Exploration


World Wide Usage


Space Vision Goggles



Doctor Monitoring Data

- Cataracts
- Diabetic Retinopathy
- Alzheimer's
- Age-related Macular Degeneration (AMD)
- Blood-Glucose
- Retinal Detachment
- EEG/Heart Monitor
- Body Temperature
- Tele-Health (Astronauts, Mars Explorers, Terrestrial Patients)

NEW Clinical Capabilities (Effective Countermeasures)

A Hypothesis on Biological Protection from Space Radiation Through the Use of New Therapeutic Gases

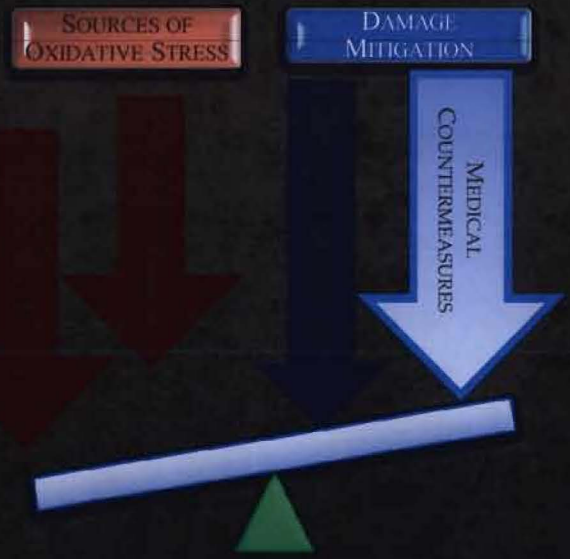
Michael Schoenfeld
NASA Marshall Space Flight Center

Dr. Rafat Ansari
NASA Glenn Research Center

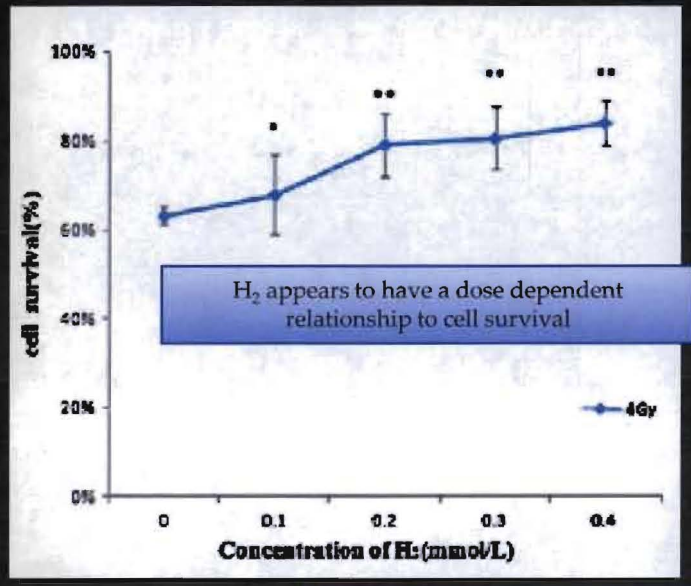
Dr. Atsunori Nakao
University of Pittsburgh

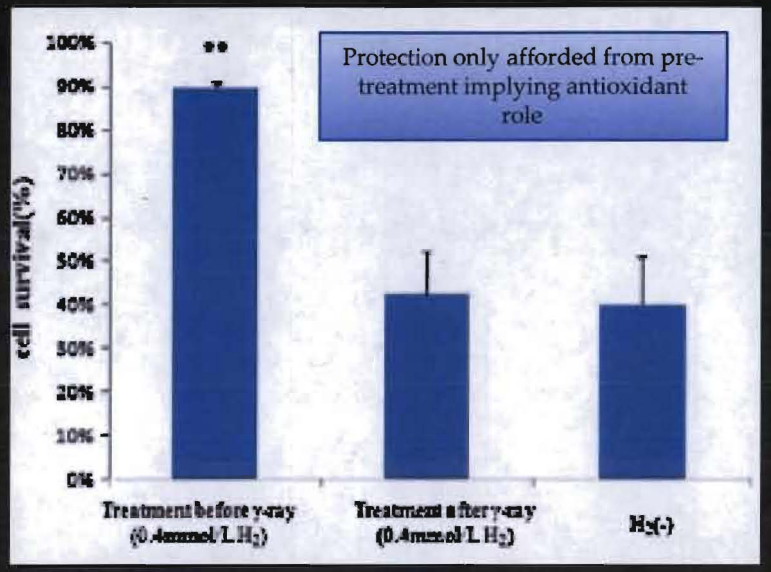
Dr. David Wink
National Institute of Health
National Cancer Institute

H_2, CO, & H_2S Medical Gas Countermeasure to Support & Supplement Our Natural Repair System to Increase Tolerance Before Damage Causes Disease

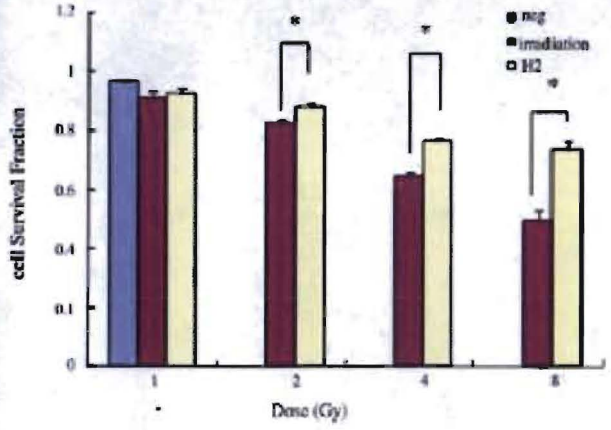


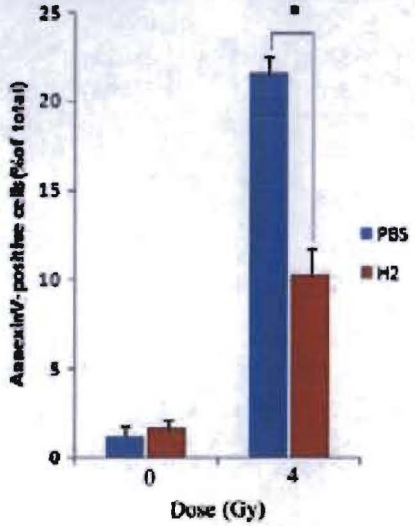
H_2 Protects Human Lymphocyte Cells from γ Irradiation

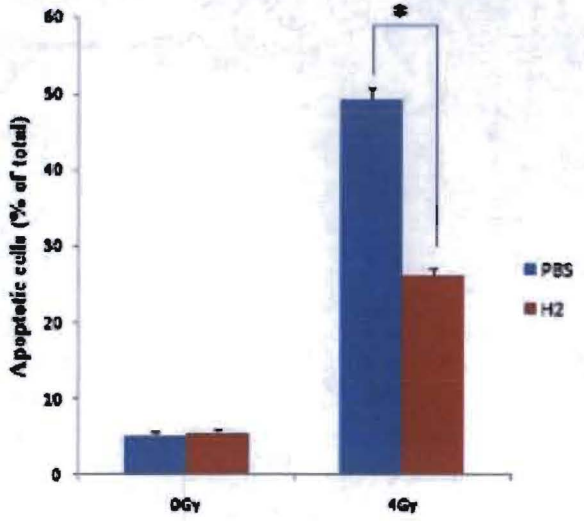




Cell survival stems from a decrease of apoptosis either from enhanced repair or damage prevention

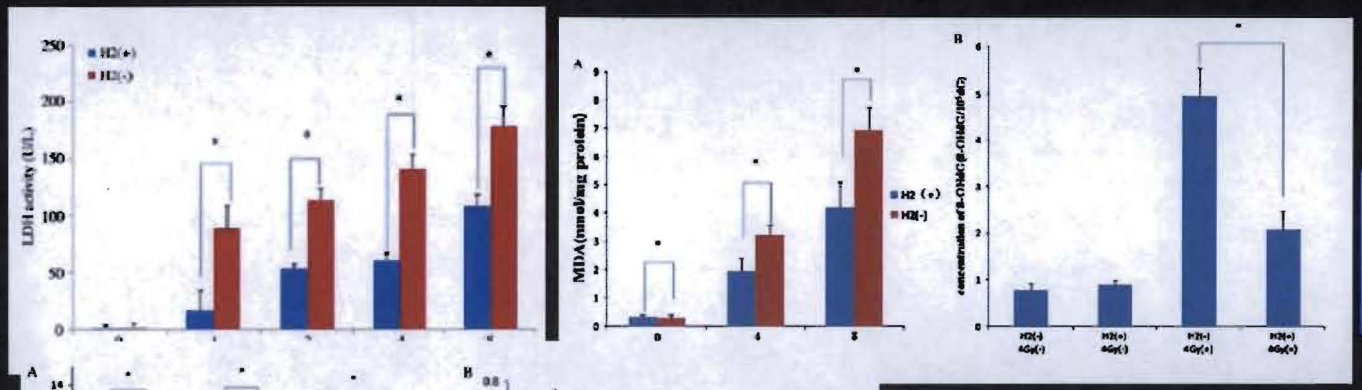




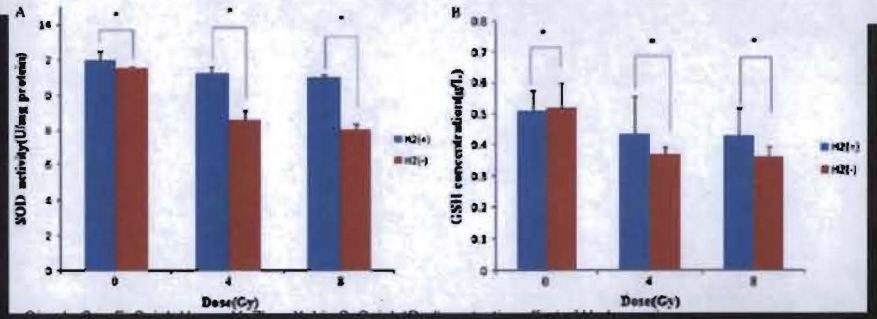


Qian L, Cao F, Cui J, Huang Y, Zhou X, Liu S, Cai J, "Radioprotective effect of Hydrogen in Cultured Cells and Mice", *Free Radical Research* 2010. **44(3)**:275-282.

H_2 Protection and Damage Prevention

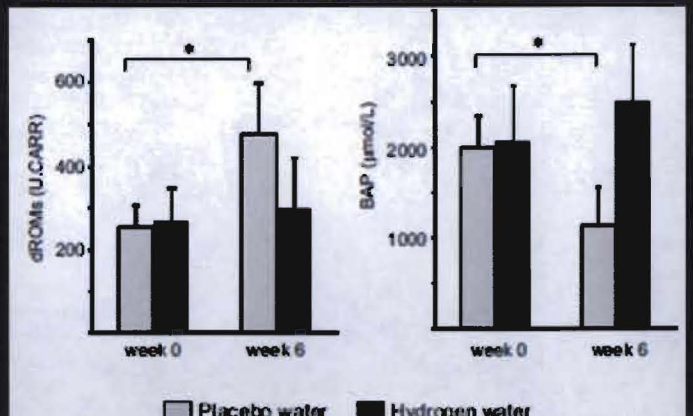


H_2 reduced lipid (MDA) & DNA (8-oHdG) oxidation in mice and cellular membrane oxidation (LDH) in Human lymphocyte AHHH-1 cells exposed to γ irradiation



H_2 supports antioxidants as natural antioxidant levels (SOD & GSH) in mice are sustained through exposure to γ irradiation

Cultured Cells and Mice" *Free Radical Research* 2010 **44(3)**:275-282



H_2 decreases dROMs & increases BAP in patients undergoing radiotherapy

Nakao A, Toyoda Y, Sharma P, Evans M, Guthrie N. "Effectiveness of Hydrogen Rich Water on Antioxidant Status on Subjects with Potential Metabolic Syndrome—An Open Label Pilot Study" *J Clin Biochem Nutr* 2010 **46**:140-149

Acknowledgments

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- *J. Clark, Ph.D. (UW)*
- *Martial Geiser (IRO)*
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- *K. Suh, Ph.D. (OAI)*

Students: Drexel Univ. (PA), IRO (Swiss), and U. Modena (Italy)