Spectroscopic Light Scattering Diagnostic Techniques

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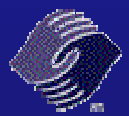


Biomedical Imaging and Spectroscopy Laboratory
Beth Israel Deaconess Medical Center

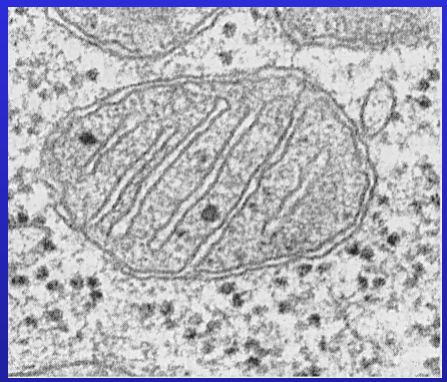
Diagnostic Medical Imaging on Various Scales

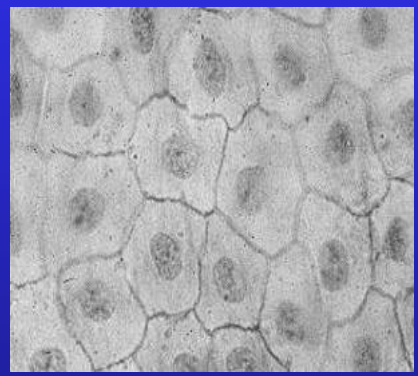
Sub-cellular organelles

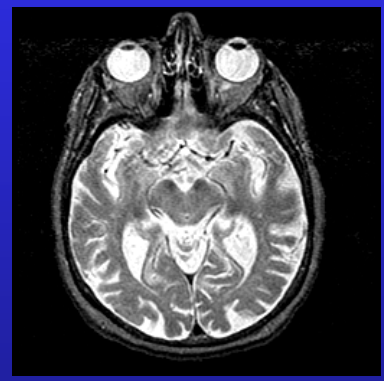
Cells

Epithelium

Bulk organs







(meters)

10^{-7} 10^{-6} 10^{-5} 10^{-4} 10^{-3} 10^{-2} 10^{-1} 10^{-0}

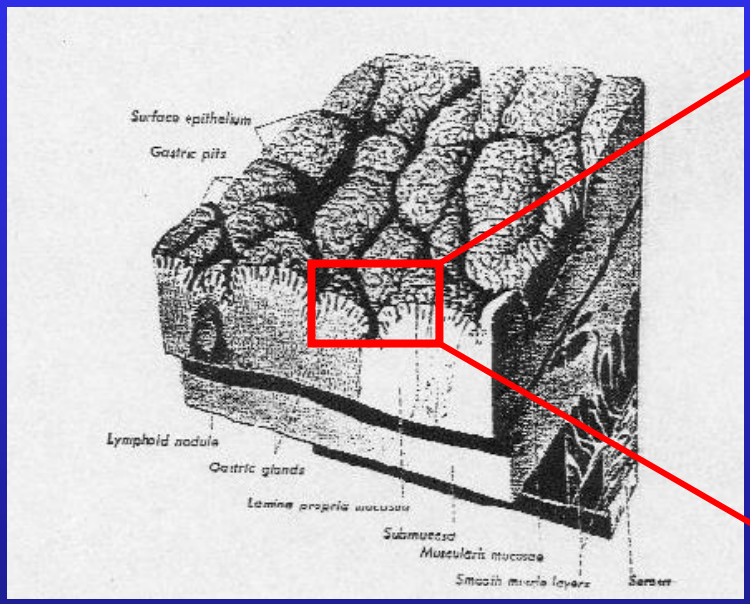
In vitro

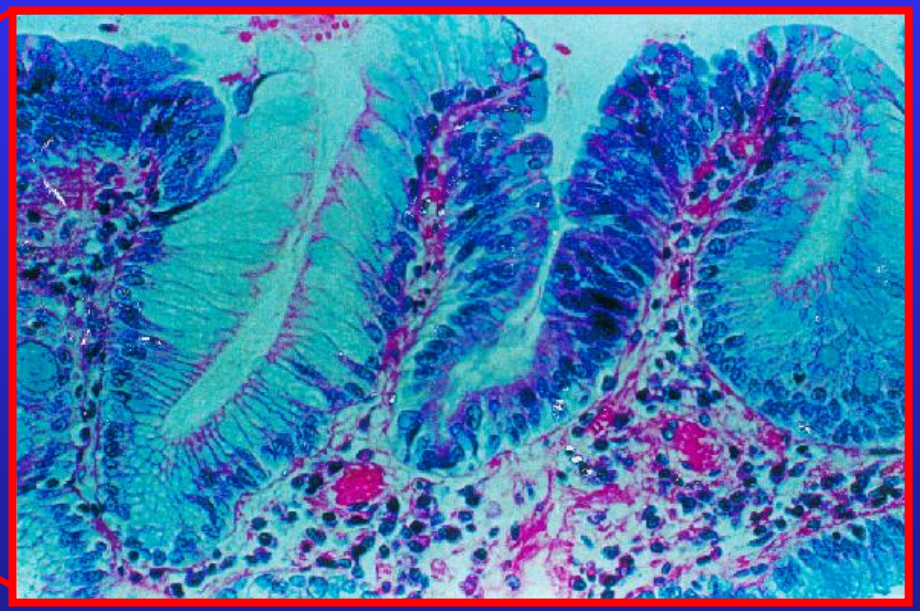
Invasive

In vivo

Non-invasive

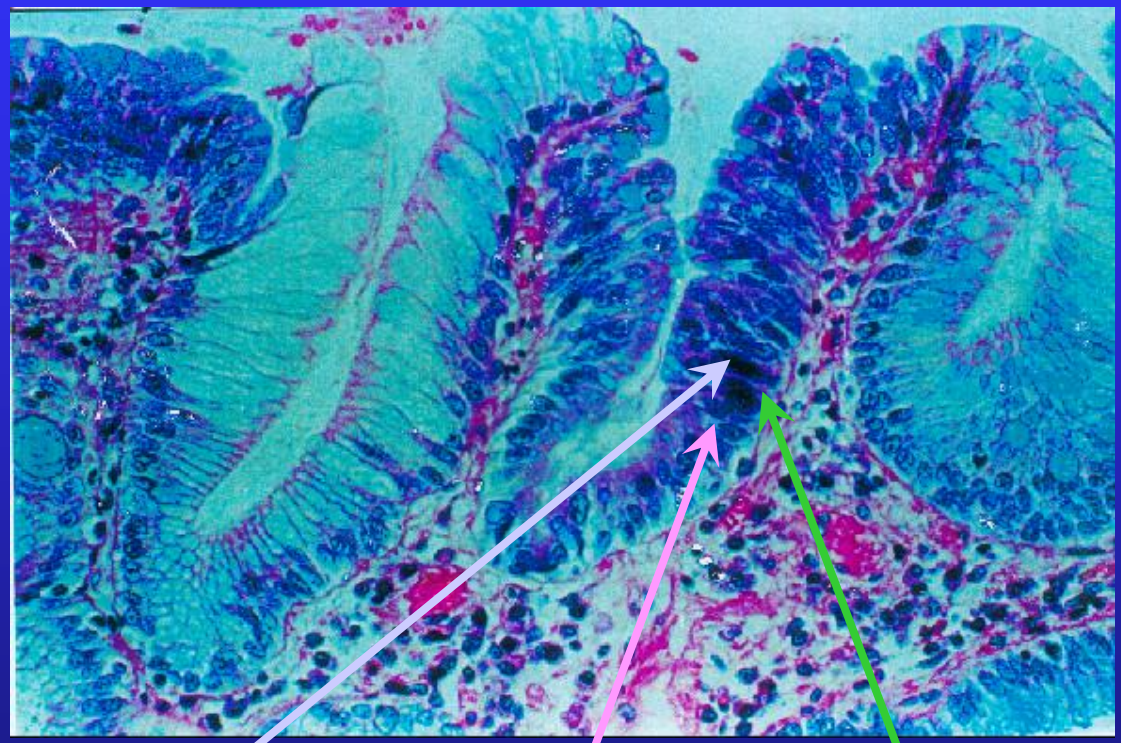
Morphology of Mucosal Tissue





Reproduced from Bloom and Fawcett “A Textbook of Histology”

Biopsy Slide of Dysplastic Barrett's Esophagus



Criteria used by pathologists

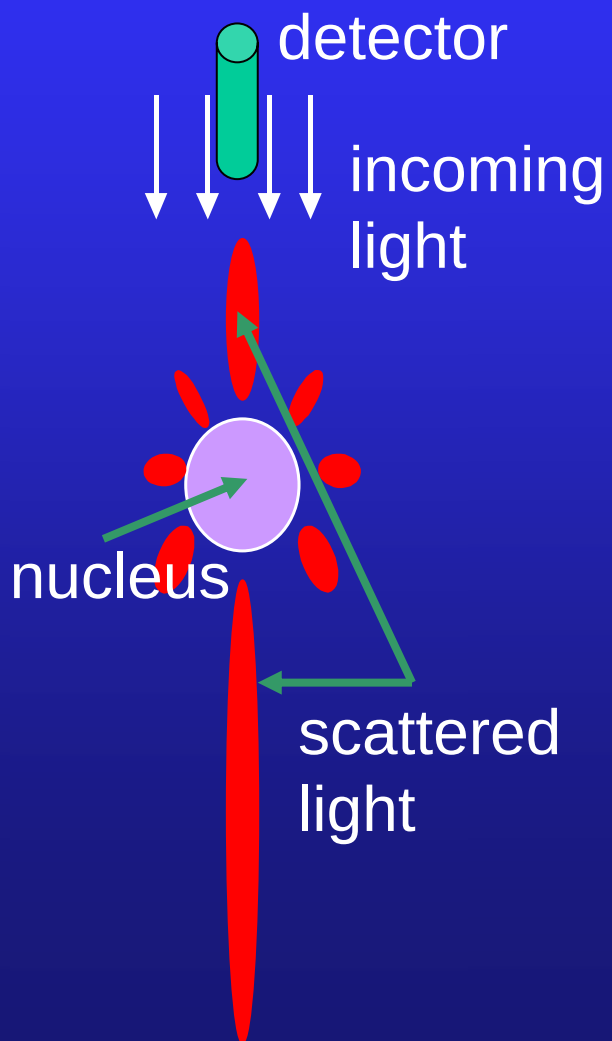
- Early precancerous changes occur only in epithelium

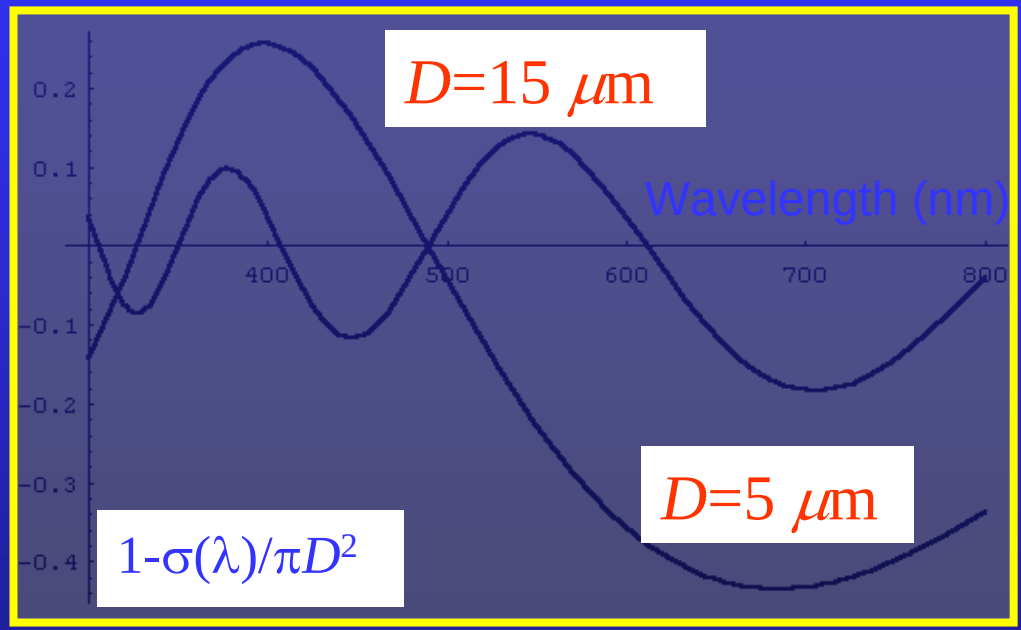
- Enlarged nuclei
- Crowding
- Hyperhromaticity
- Stratification
- Architectural changes

Dysplasia & Biopsy

- Precursor of cancer
- Most tumors are curable if diagnosed on the stage of dysplasia
- Detection of dysplasia requires removal of tissue via biopsy, followed by analysis via pathology
- Biopsy
  - ✓ Random - can easily miss dysplastic changes
  - ✓ Invasive - needs tissue removal
- Develop technique capable to detect invisible precancerous changes
  - ✓ Minimally Invasive
  - ✓ Real Time
  - ✓ Over Large Tissue Areas
- Light Scattering Spectroscopy has potential to do all of that

Light Scattering Spectroscopy



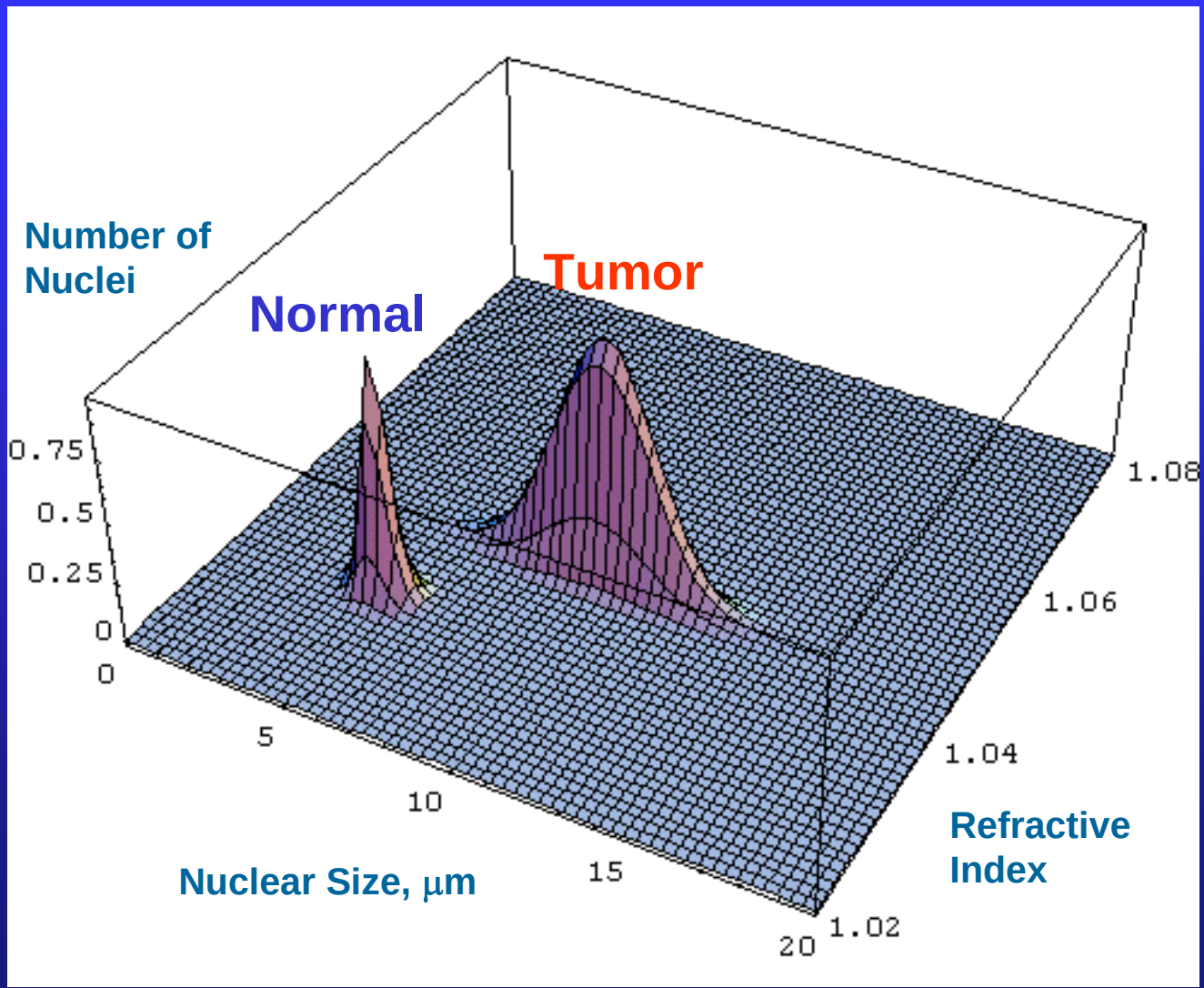


$$\sigma_s(\lambda, r) = \frac{\pi D^2}{2}\left(1 - \frac{\sin(2\delta/\lambda)}{\delta/\lambda} + \left(\frac{\sin(\delta/\lambda)}{\delta/\lambda}\right)^2\right)$$

$\delta = \pi D(n\text{-}1)$

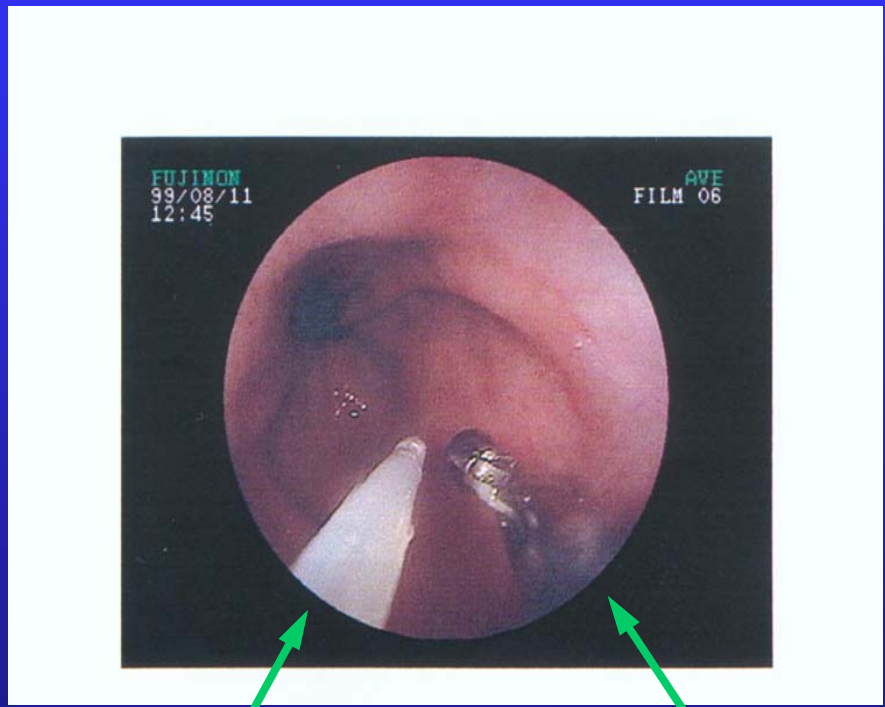
n - relative refractive index (n=1.06)

Size Distributions of Epithelial Nuclei



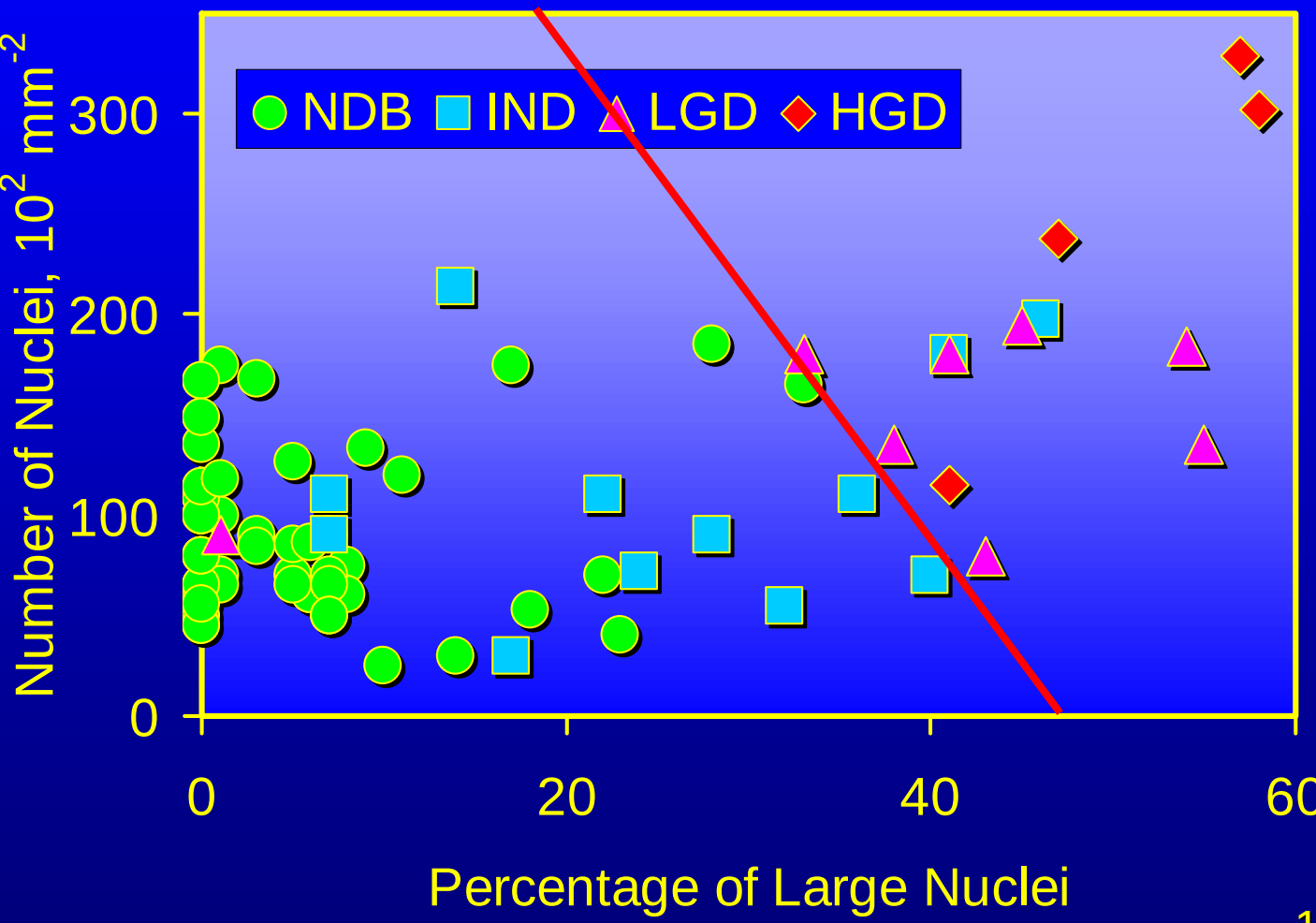
Collection of the Spectroscopic Data During Routine Esophagogastroduodenoscopy

⇒



Diagnosis of Dysplasia in Barrett's Esophagus

Specificity 97% **Sensitivity 92%**



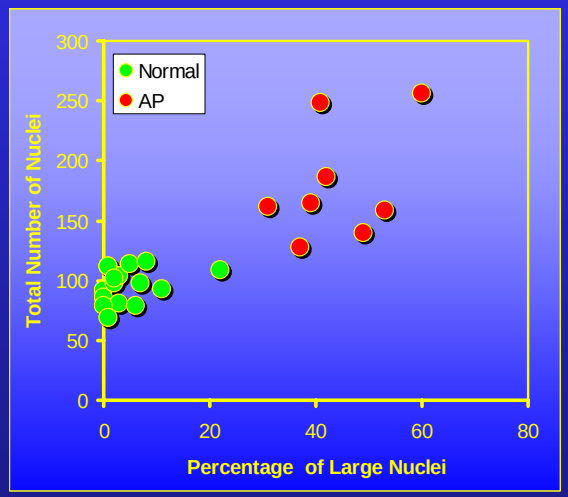
13 patients

76 sites

Diagnosis of Dysplasia in Various Tissues *In Vivo*

Colon

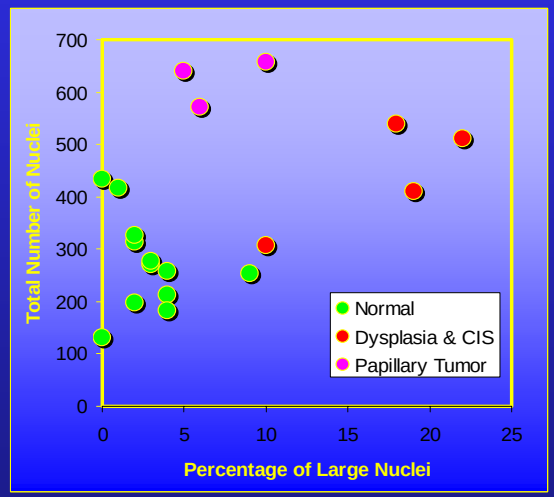
(Columnar Epithelium)



8 patients
23 sites

Bladder

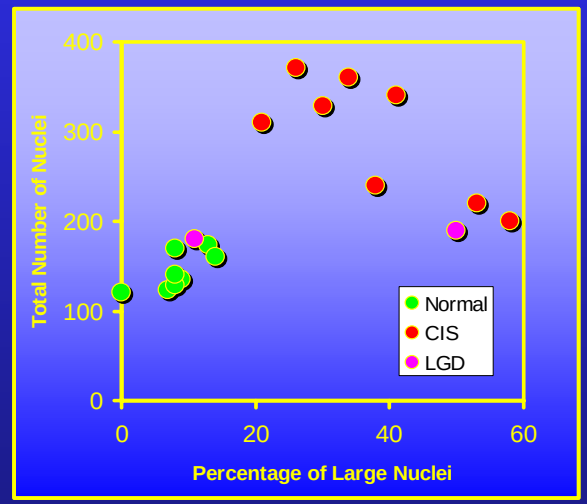
(Transitional Epithelium)



5 patients
17 sites

Oral Cavity

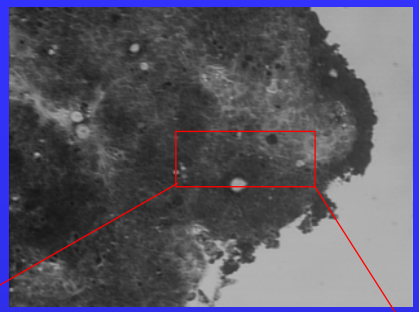
(Squamous Stratified Epithelium)



7 patients
15 sites

Nature, 406, 35-36, 2000

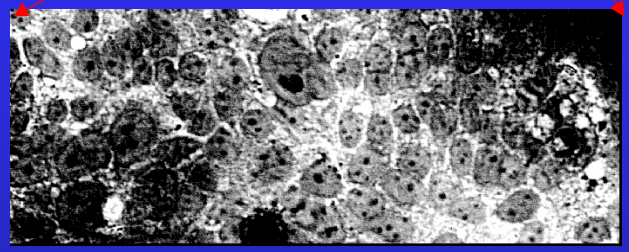
LSS-Based Diagnostic Imaging



300 μm

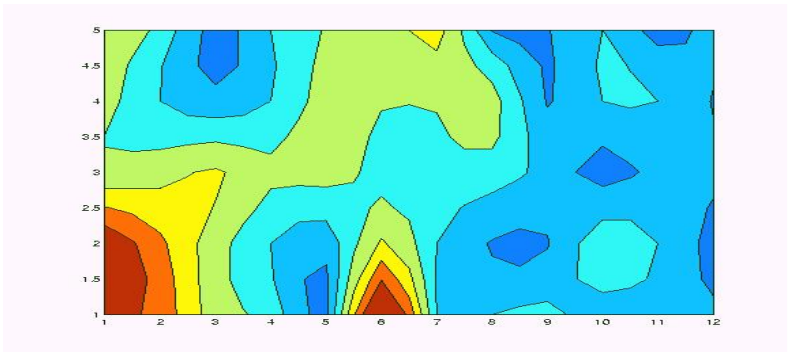
Stained ⇒

120 μm

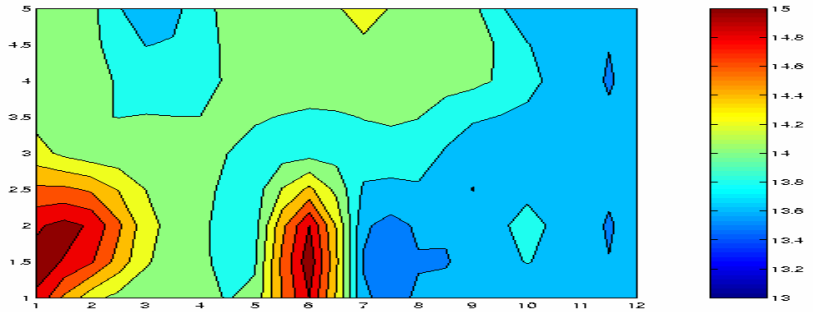


Microphotograph of Stained Cell Monolayer

15 μm



Microscopy Morphometry



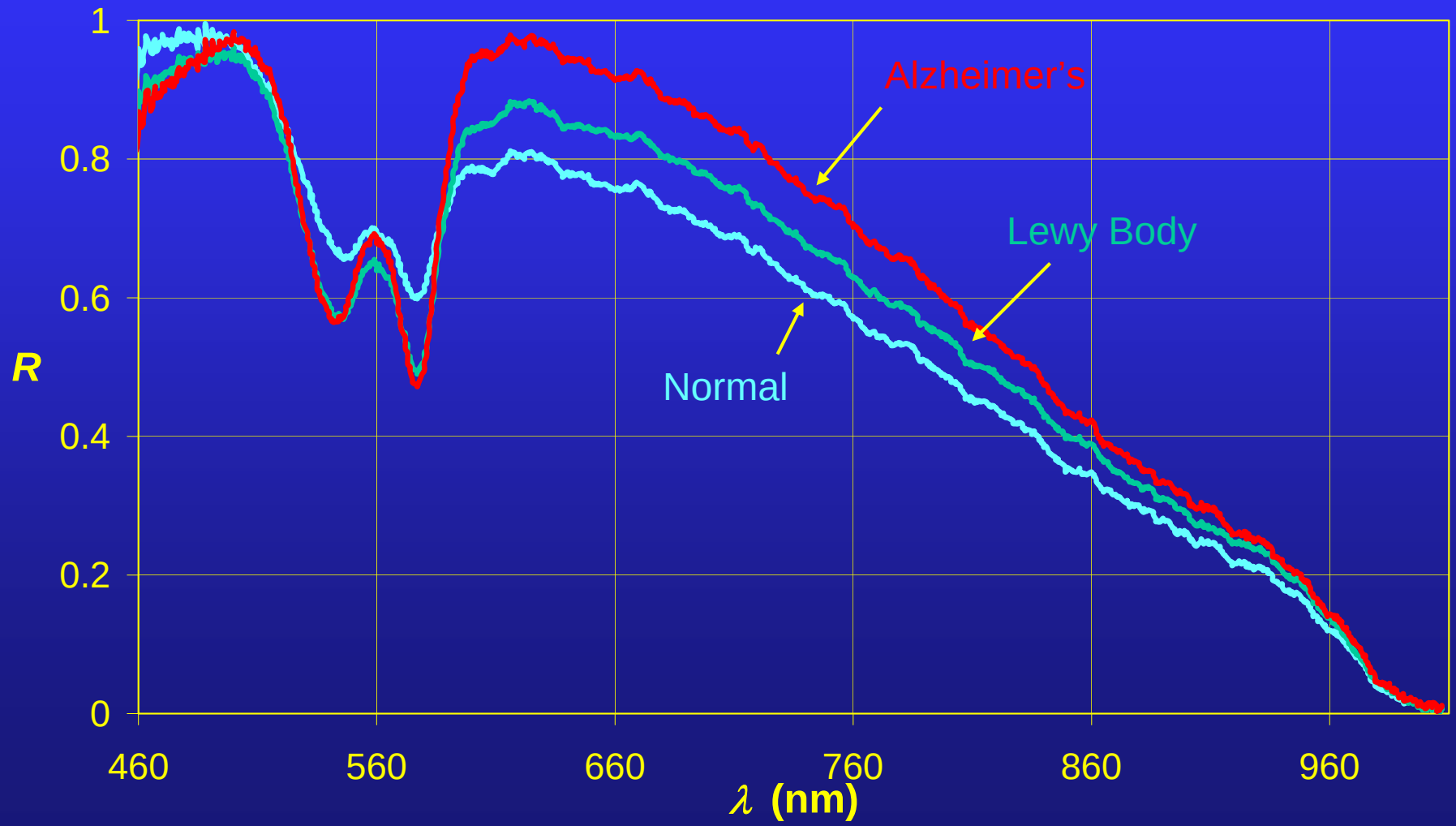
LSS Morphometry

13 μm

Nature Medicine, 7, 1245-8, 2001

Prototype Clinical Instrument for Diagnosing Alzheimer's Disease

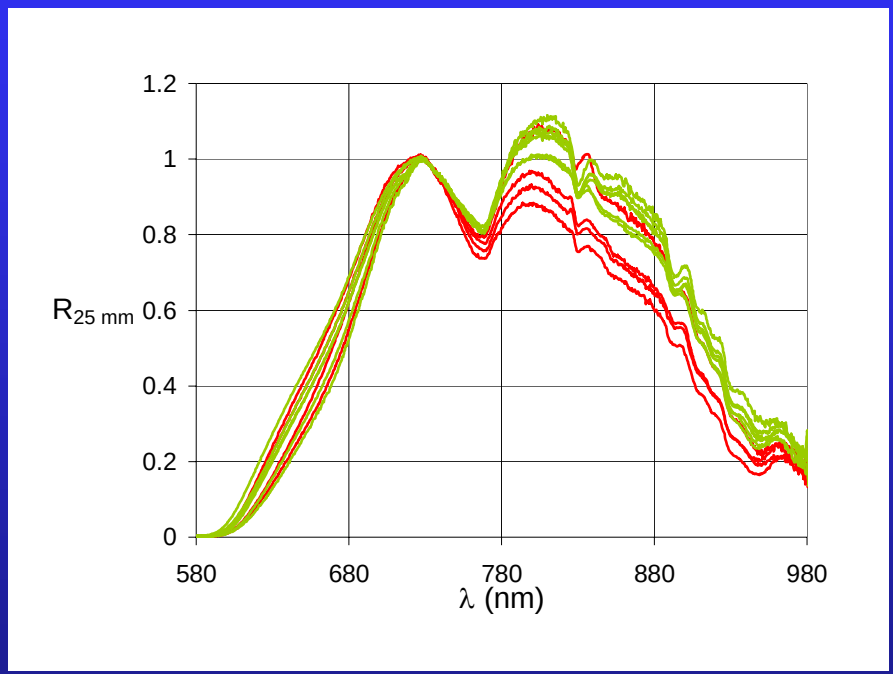
Average Reflectance Spectra for 15 Post-Mortem Brains

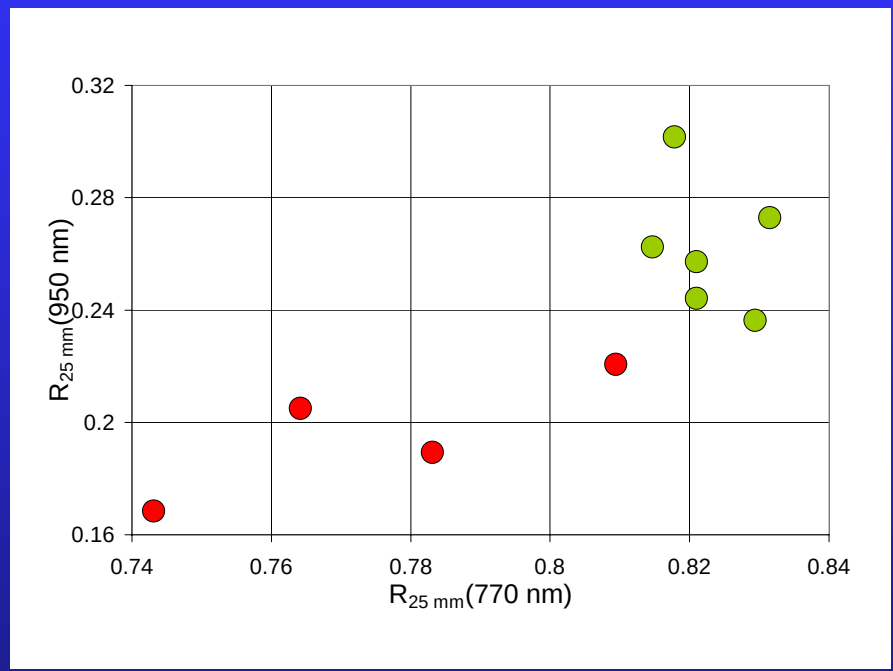


Morphological and Biochemical Properties Extracted from Post-Mortem Brains

Brain #	Diagnosis	n	R (μm)	Concentration	n	R (μm)	Concentration	Hb (%)	Lipids
1	Alzheimer's	1.04	0.329	3.08E+08	1.11	6.016	1.91E+04	7.56	1.24795
2	Normal	1.065	0.301	1.96E+08	1.1	1.033	0.00E+00	9.21	0.35468
3	Normal	1.06	0.326	2.76E+08	1.1	4.968	0.00E+00	2.98	0.33826
4	Normal	1.065	1.315	5.12E+06	1.11	3.88	2.97E-11	2.51	0
5	Normal	1.045	1.5	1.55E+07	1.115	6.05	0.00E+00	1.42	0
6	Lewy Body	1.065	1.5	3.08E+06	1.115	3.42	4.34E-04	3.1	0.33169
7	Alzheimer's	1.05	0.683	1.78E+07	1.1	8.367	5.14E+03	5.2	1.3399
8	Alzheimer's	1.04	0.536	6.20E+07	1.11	7.495	1.05E+04	4.29	1.37274
9	Lewy Body	1.06	1.126	1.38E+07	1.11	4.605	0.00E+00	1.81	0
10	Alzheimer's	1.04	0.349	1.51E+08	1.105	5.494	2.15E+04	7.57	2.32184
11	Alzheimer's	1.065	0.32	1.65E+08	1.11	3.908	No Plaques	4.31	0
12	Alzheimer's	1.045	0.2	0.00E+00	1.1	1.254	3.66E+06	6.5	0
13	Alzheimer's	1.05	0.842	9.70E+06	1.1	7.532	7.53E+03	4.03	2.72578
14	Alzheimer's	1.05	0.363	7.62E+07	1.1	7.27	9.50E+03	4.71	0.33826
15	Alzheimer's	1.06	1.5	1.87E+06	1.1	7.625	8.77E+03	3.47	4.63054

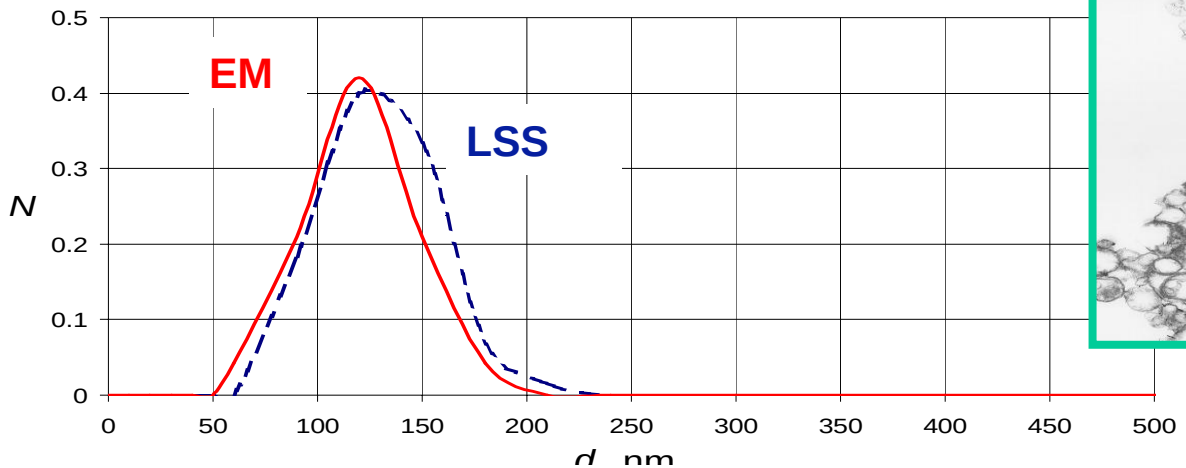
In Vivo Differentiation of Human AD and Control Subjects

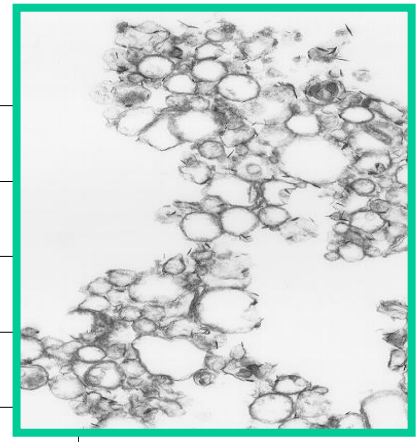




Sizing of Subcellular Organelles

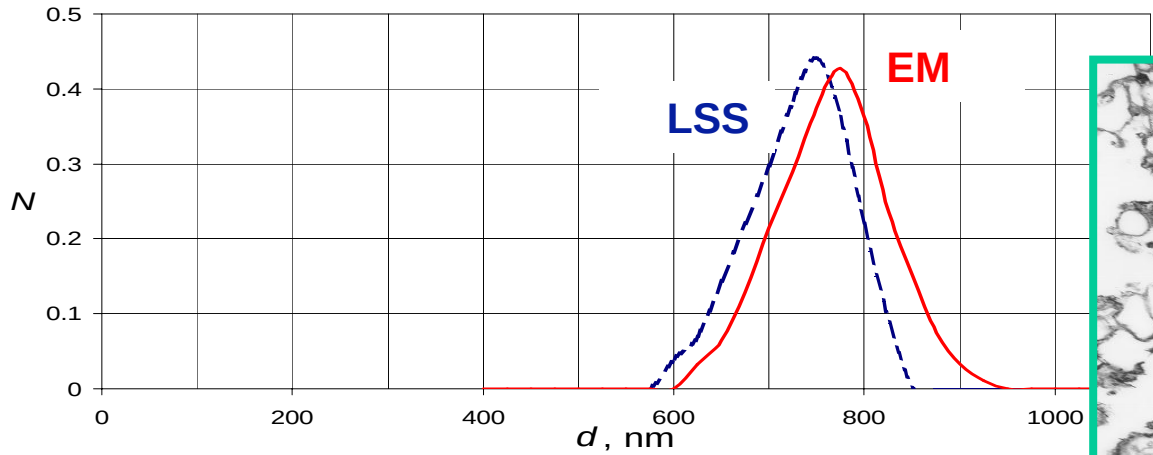
Microsomes

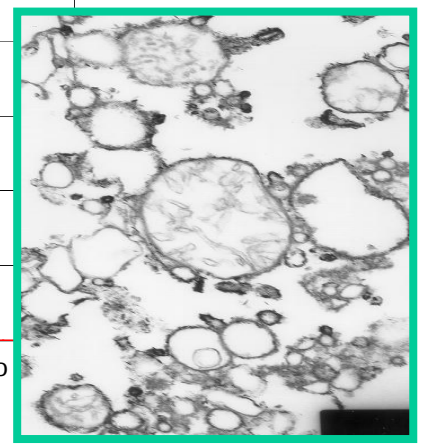




Electron microscope photographs

Mitochondria





LSS Predictions Agree with Electron Microscopy Results

Conclusions

Light scattering spectroscopic techniques

- require no exogenous labels
- are noninvasive and nondestructive
- are capable of quantitative measurement of microscopic morphological and biochemical changes in various tissues on submicron scale
- can be an important tool for early detection of disease in various organs of human body and for image guided interventions

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