Diabetic Uropathy

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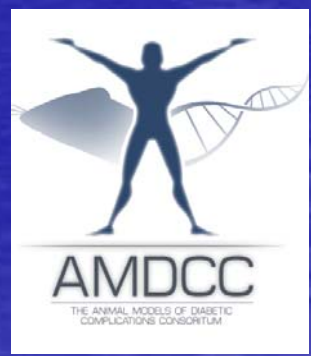
BACKGROUND

LUT complications are seen in up to 83% of patients with diabetes mellitus (DM

Diabetic Bladder Dysfunction

Traditional Findings

- Decreased Sensation
- Enlarged Bladder
- Poor Emptying/ Voiding Dysfunction
- Urinary incontinence
- High post void residual (PVR)



DBD in Human

- Bladder Overactivity in Diabetes?
  - 76% of diabetic patients had involuntary contraction as cause of their incontinence (Starer 1990)
  - 25% of diabetic subjects (Ueda 1997)
  - 55% of diabetic patients; 23% had impaired detrusor contractility (Kaplan 1995)

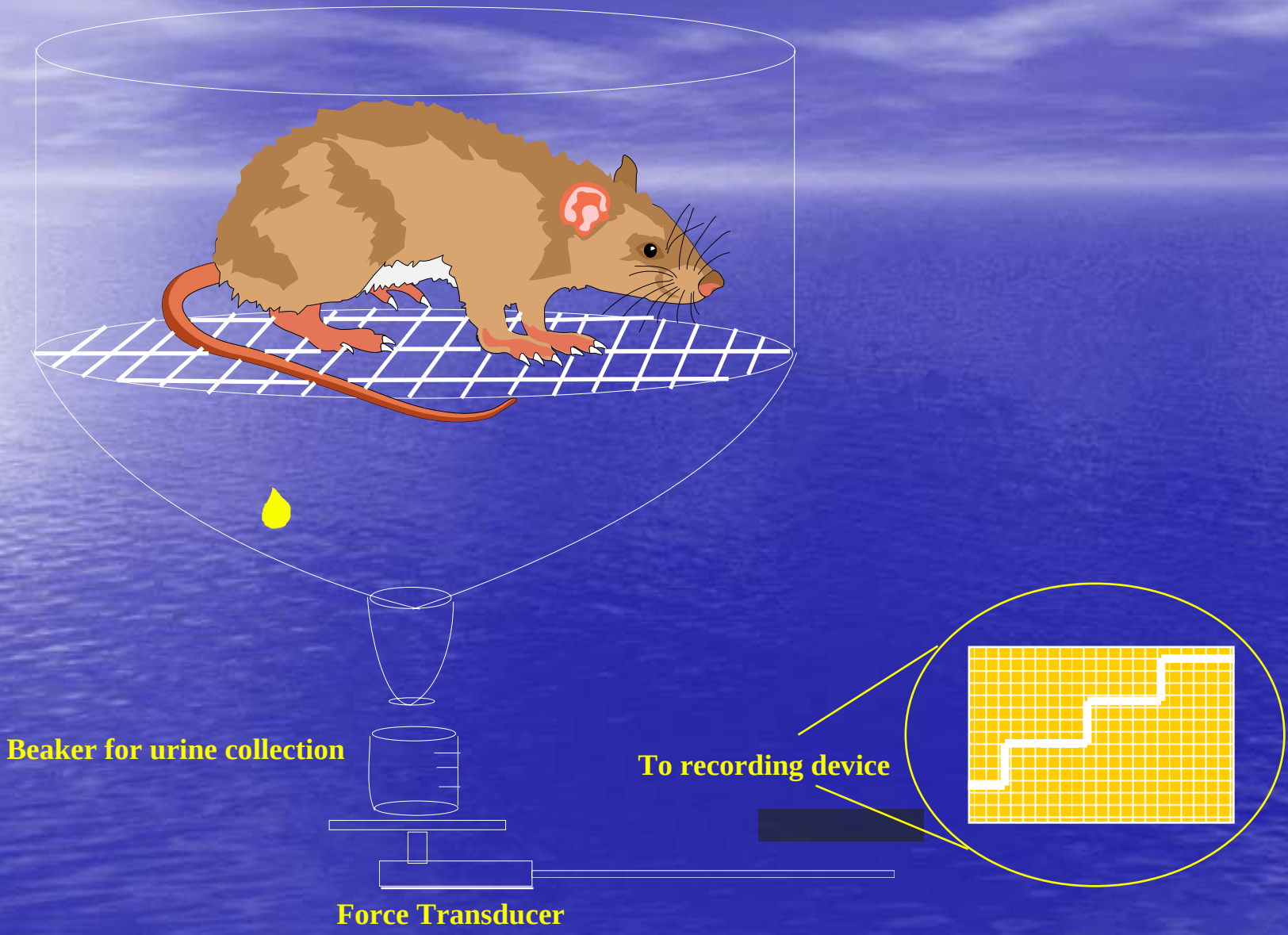
Proposed Natural History of Progression of Diabetic Bladder Dysfunction In Human and Animals

Early Phase → Late Phase

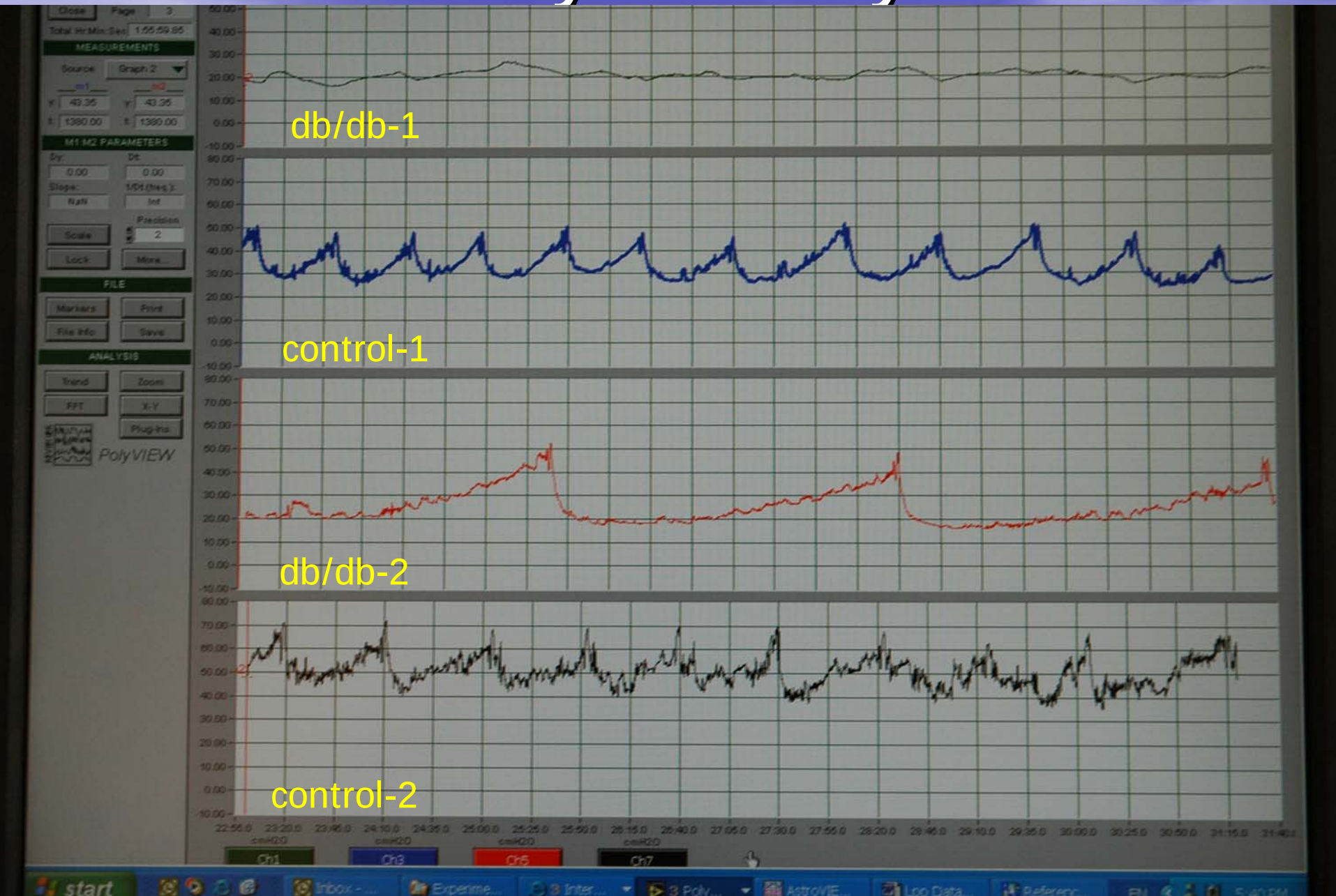
Time Course/Risk factors ??

Clinical: Filling problems	**Voiding Problems**
Urodynamics: Overactive Bladder	**Atonic Bladder**
In-vitro: Hypercontractile Detrusor	**Hypocontractile Detrusor**

Daneshgari 2003


Beaker for urine collection
To recording device
Force Transducer

Cystometry



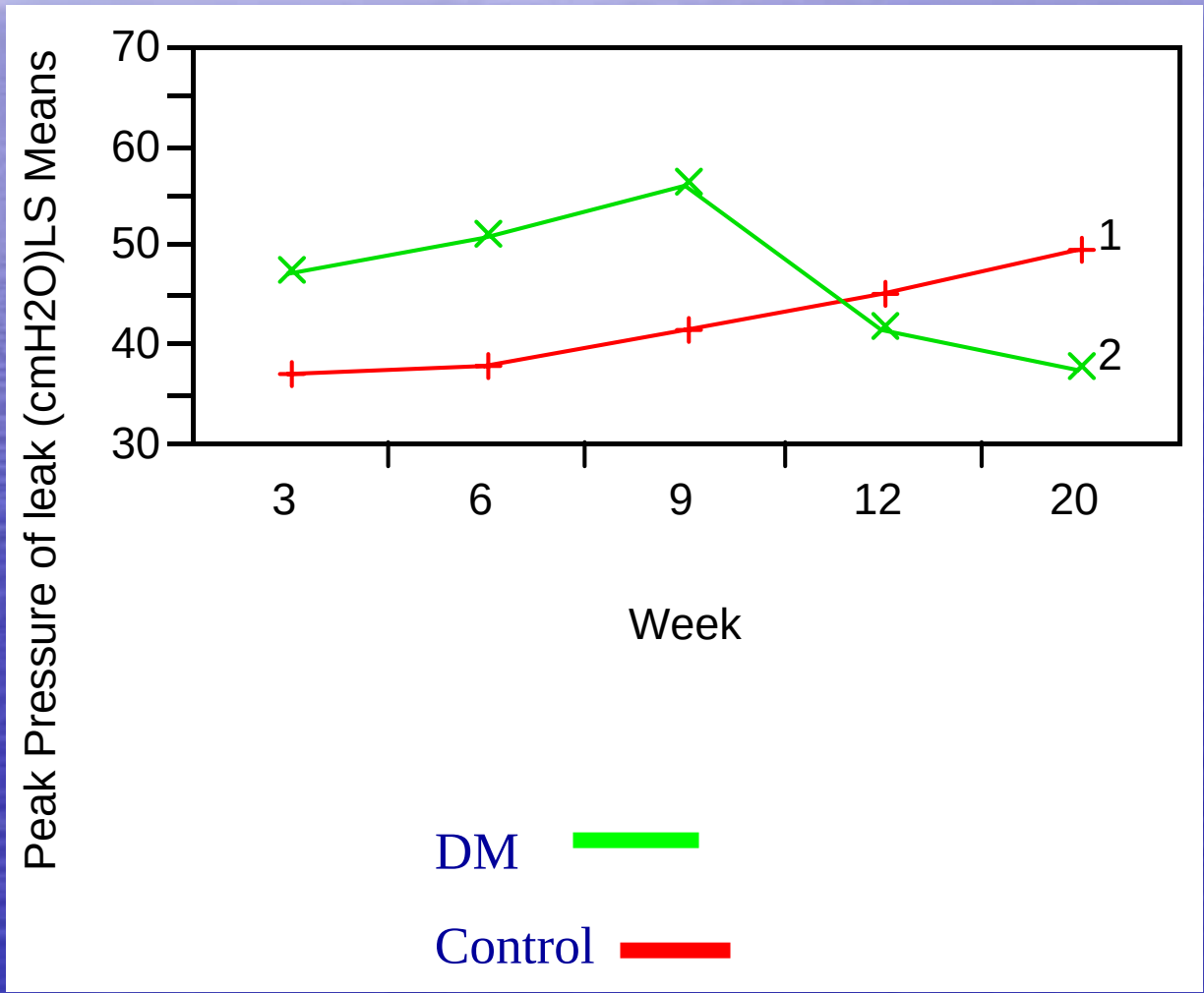
Diabetic Uropathy

Phenotyping Measures

- Frequency Volume Measurements
- Cystometrogram
- Remodeling Measures
- Contractility studies
- Assessment of alterations in autonomic function of the bladder
- Assessment of alterations in myogenic function of the bladder

Time course of DBD in SD STZ-Rats

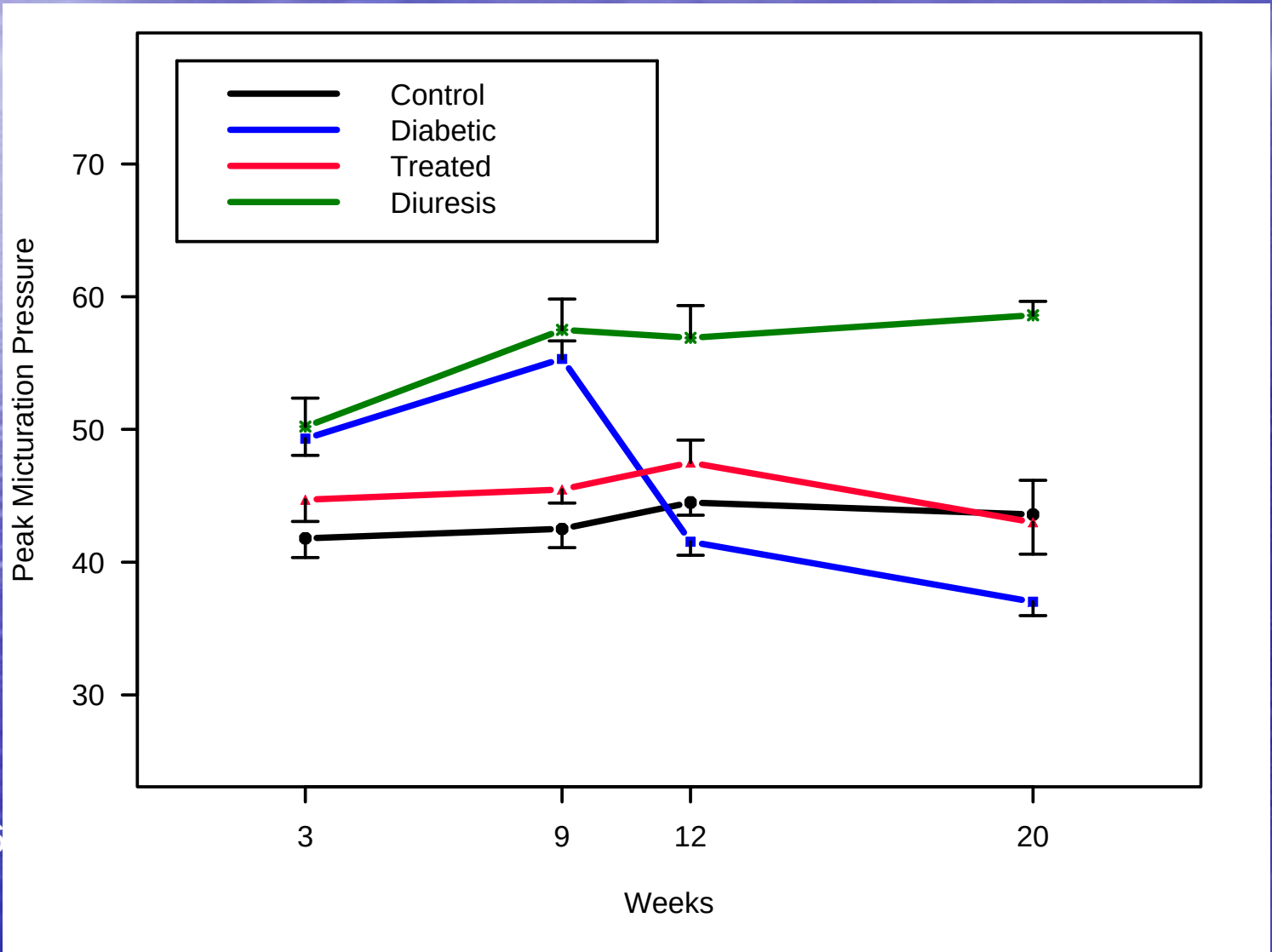
Peak Pressure of Leak: Adjusted Effects of Age and DM



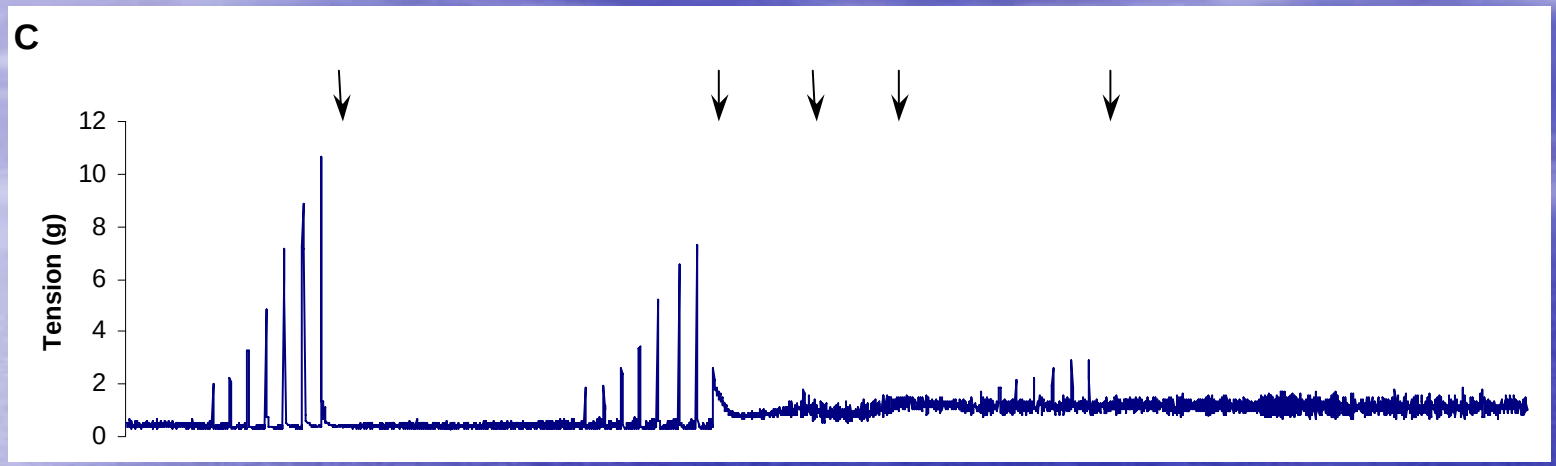
J of Urol. 2005

Time Course of DBD in C57BL/6

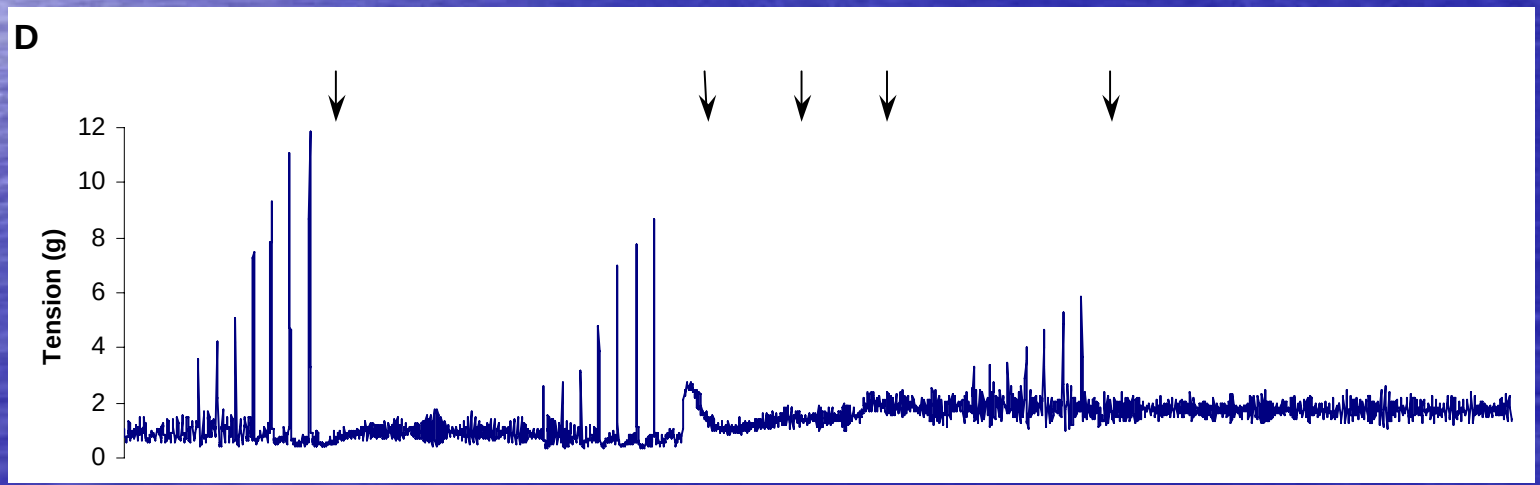
Peak Micturition Pressure of the Bladder



AJP 2006

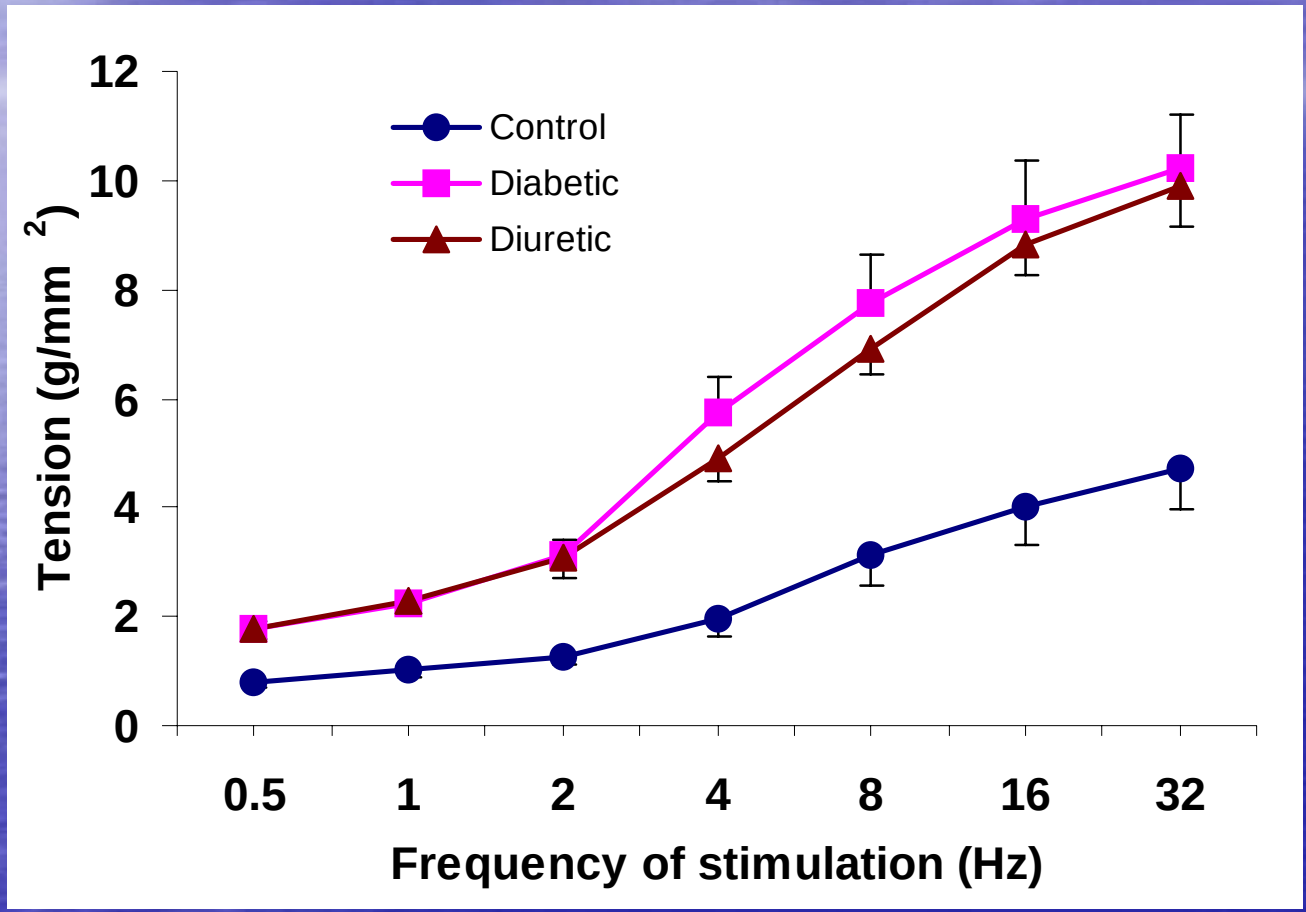


Diabetic

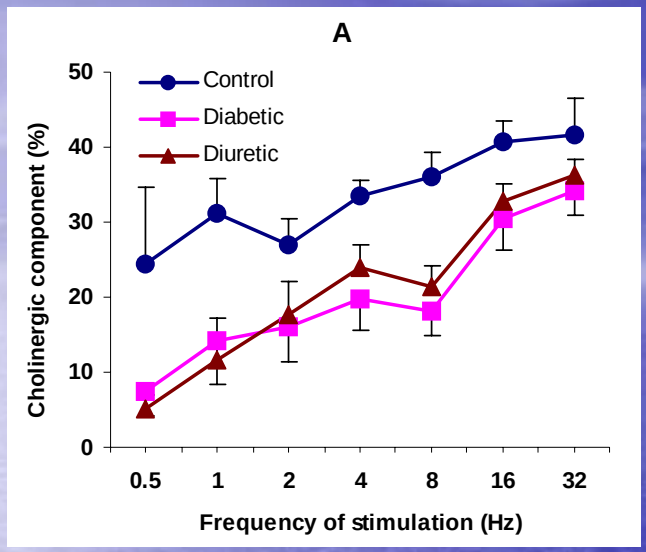


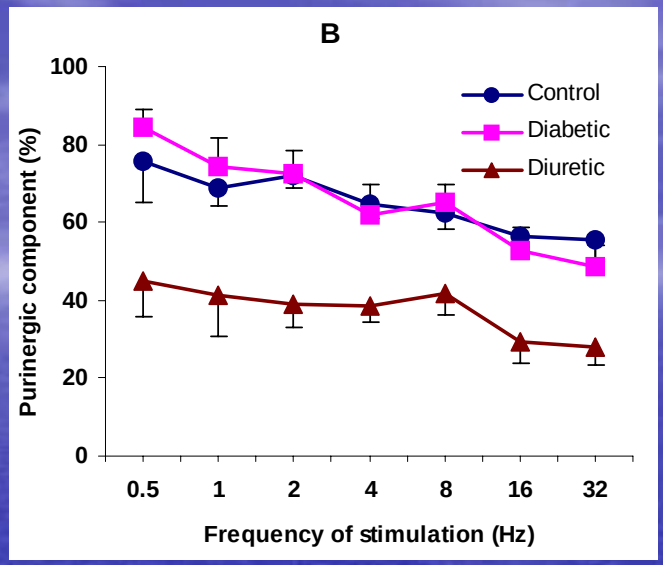
Diuretic

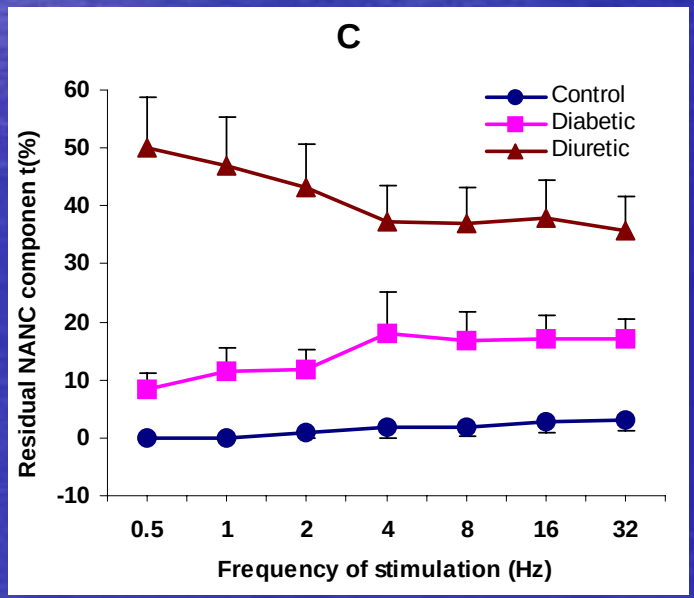
ALTERATIONS IN NEUROGENICALLY MEDIATED CONTRACTILE RESPONSES OF URINARY BLADDER IN RAT WITH DIABETES



Liu & Daneshgari: AJP 2005

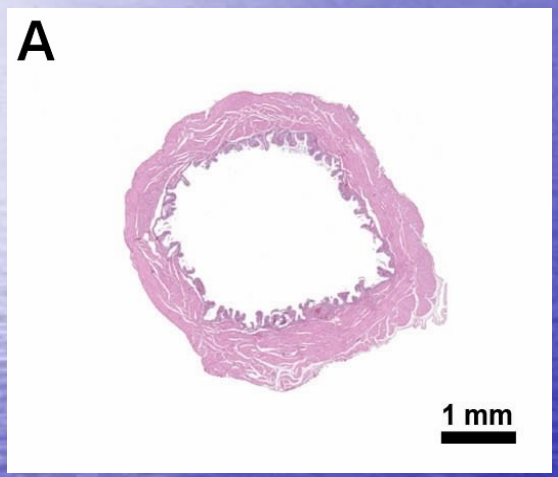


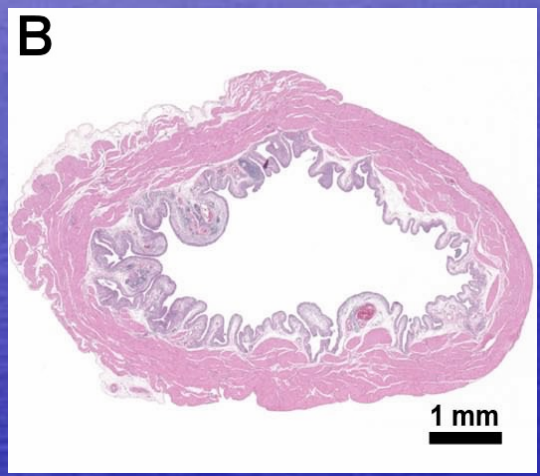


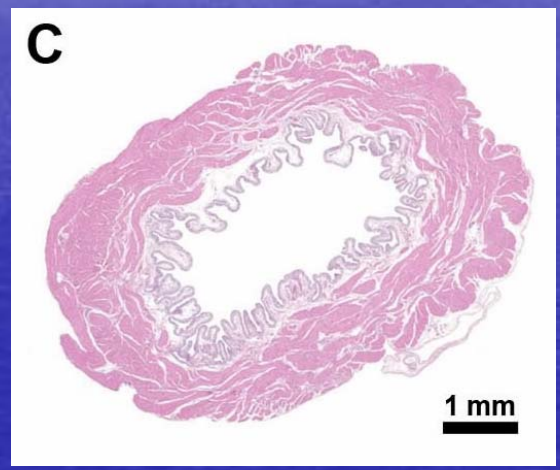


Liu & Daneshgari: AJP 2005

Remodeling of the Bladder in DBD







Control

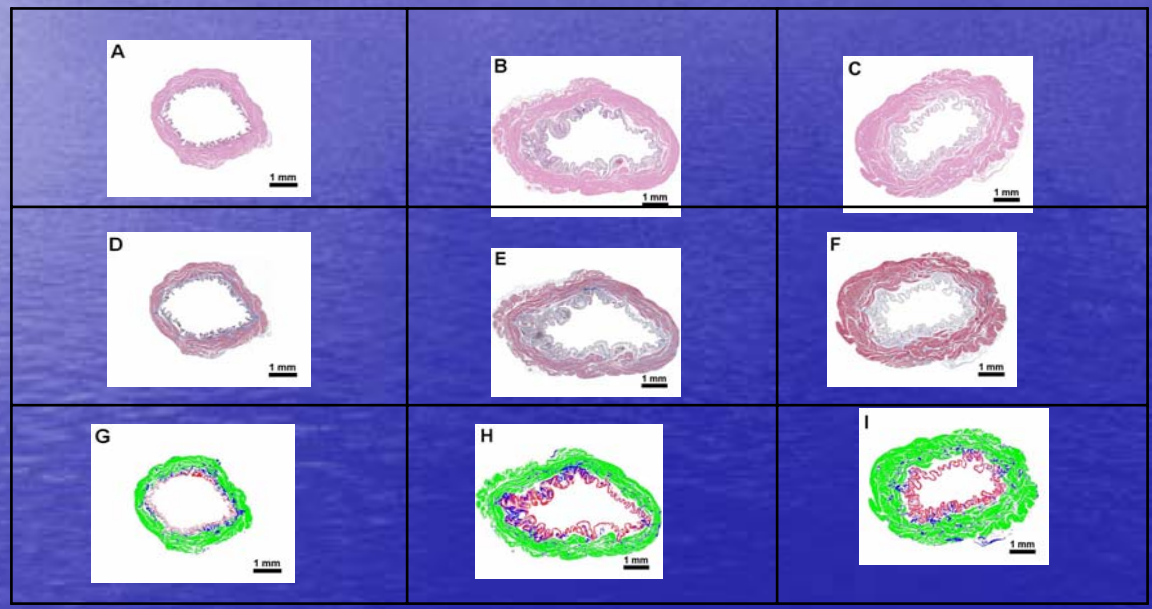
Diabetic

Diuretic

AJP 2005

Diabetic Uropathy

Remodeling Measures



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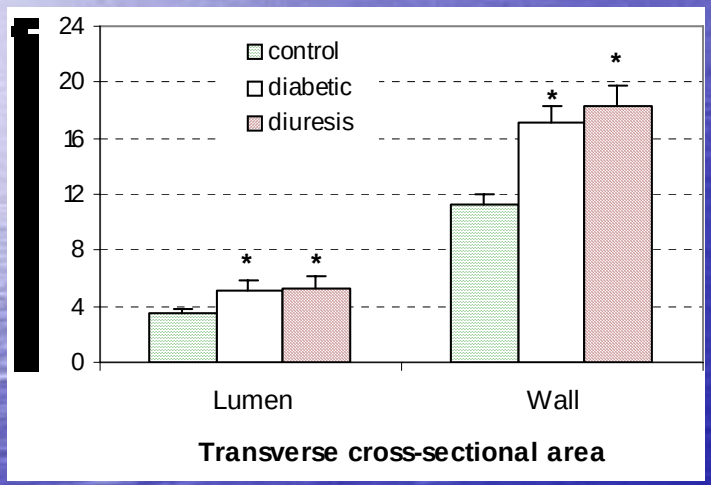
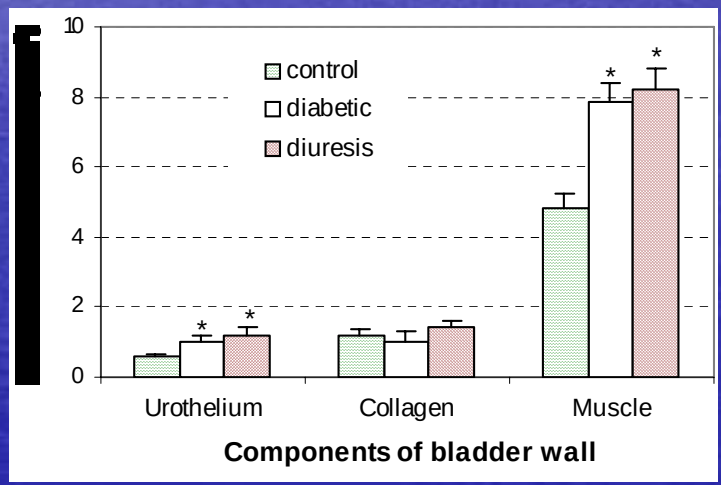
Diabetic Uropathy

Remodeling Measures





AJP 2006

Published

- Daneshgari F, Liu G, Imrey P: Time course changes in diabetic cystopathy in rats may include bladder over-and underactivity J. of Urology. December 2005
- Daneshgari F, Huang X, Liu G, Bena J, Saffore L, Powell CT: Temporal differences in bladder dysfuntion caused by diabetes, diuresis, and treated diabetes in mice. Am J Physiol Regul Integr Comp Physiology Jan 2006
- Liu G, Daneshgari F: Temporal diabetes and diuresis induced remodeling of the urinary bladder in the rat. Am J Physiol Regul Integr Comp Physiol March 2006
- Liu G, **Daneshgari F:** Alternations in Neurogenically Mediated Contractile Responses of Urinary Bladder in Rat with Diabetes. American Journal of Physiology Renal Physiol. June 2005 288(6):F1220-6. Epub 2005 Feb 1
- Liu G, **Daneshgari F:** Effects of Cold Storage on the Function and Morphology of Isolated Urinary Bladder in Rat. Neurourology and Urodynamics. 001-7, 2005
- Daneshgari, F, Moore C: Diabetic Uropathy. Semin Nephrol 2006 Mar: 26 (2): 182-5

Proposed Natural History of Progression of Diabetic Bladder Dysfunction In Human and Animals

Early Phase ⟶ Late Phase

Time Course/Risk factors ??

Early Remodeling

Early Neurogenic Changes

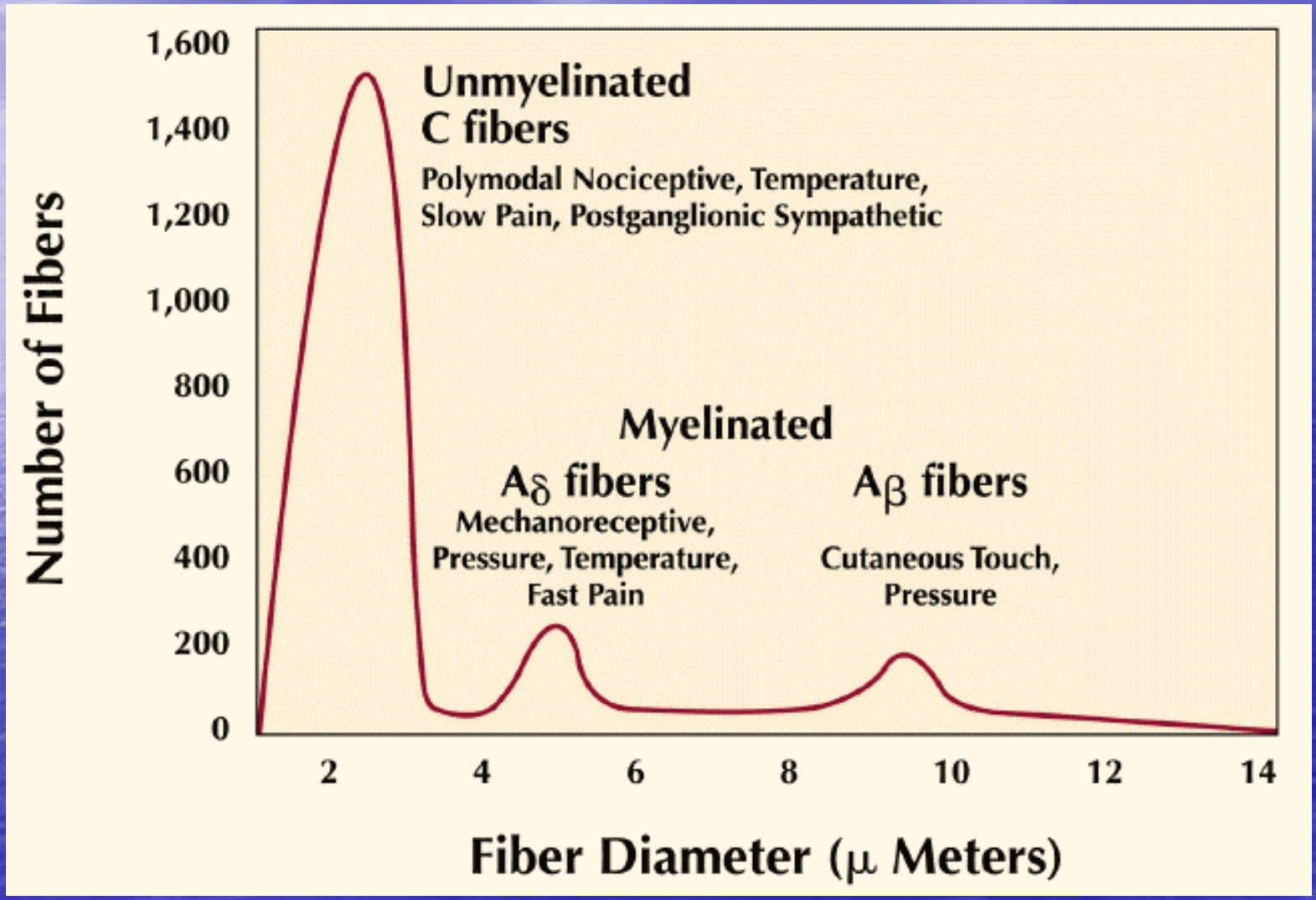
Early Myogenic Changes

Early Remodeling

Early Neurogenic Changes

Early Myogenic Changes

Sensory nerve fiber composition chart



Testing of Bladder Sensation

Neuroselective Current Perception Threshold Evaluation of Bladder Mucosal Sensory Function

Osamu Ukimura*, So Ushijima, Hisashi Honjo, Tsuyoshi Iwata, Kei Suzuki, Naoki Hirahara, Koji Okihara, Yoichi Mizutani, Akihiro Kawauchi, Tsuneharu Miki

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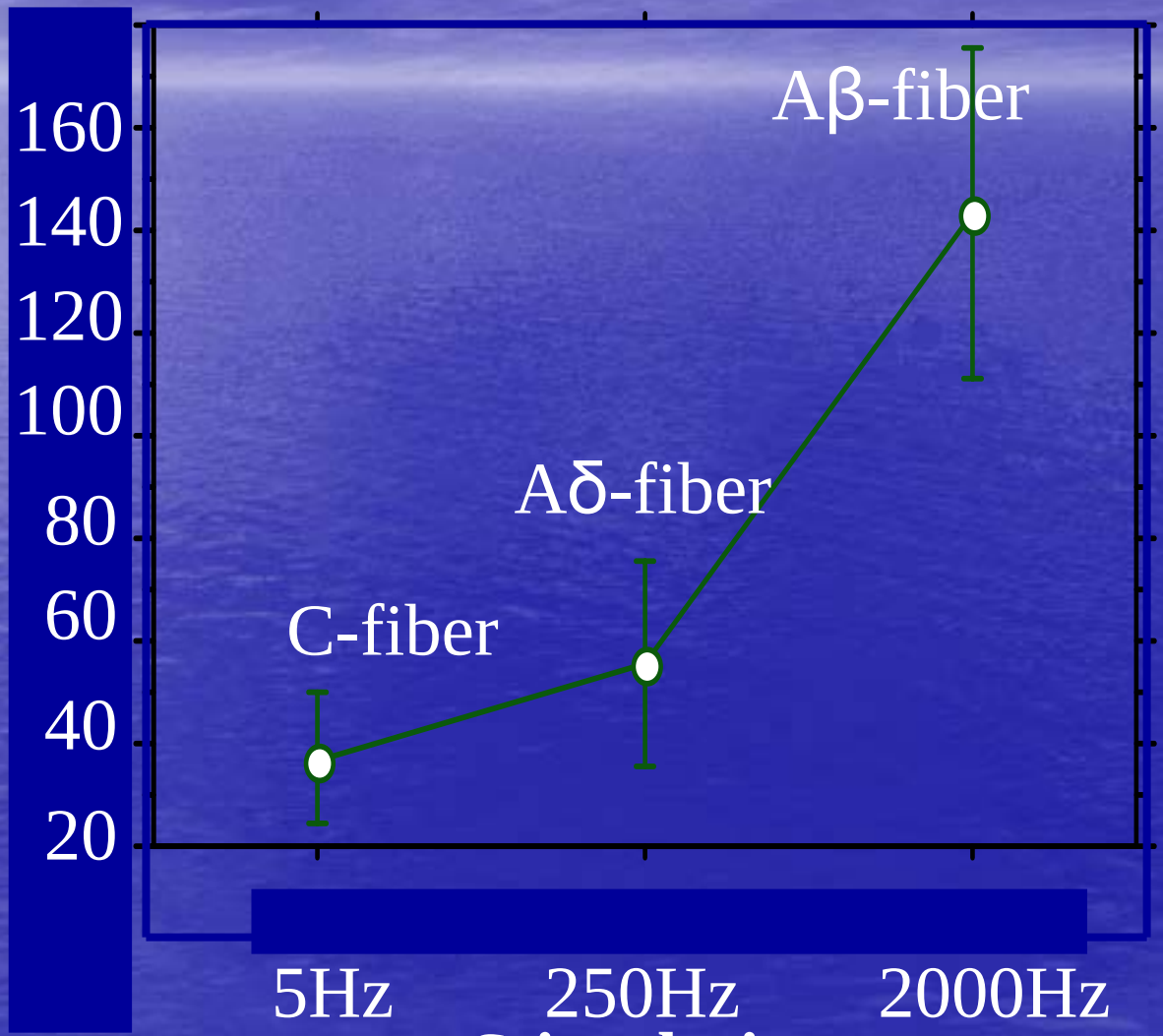
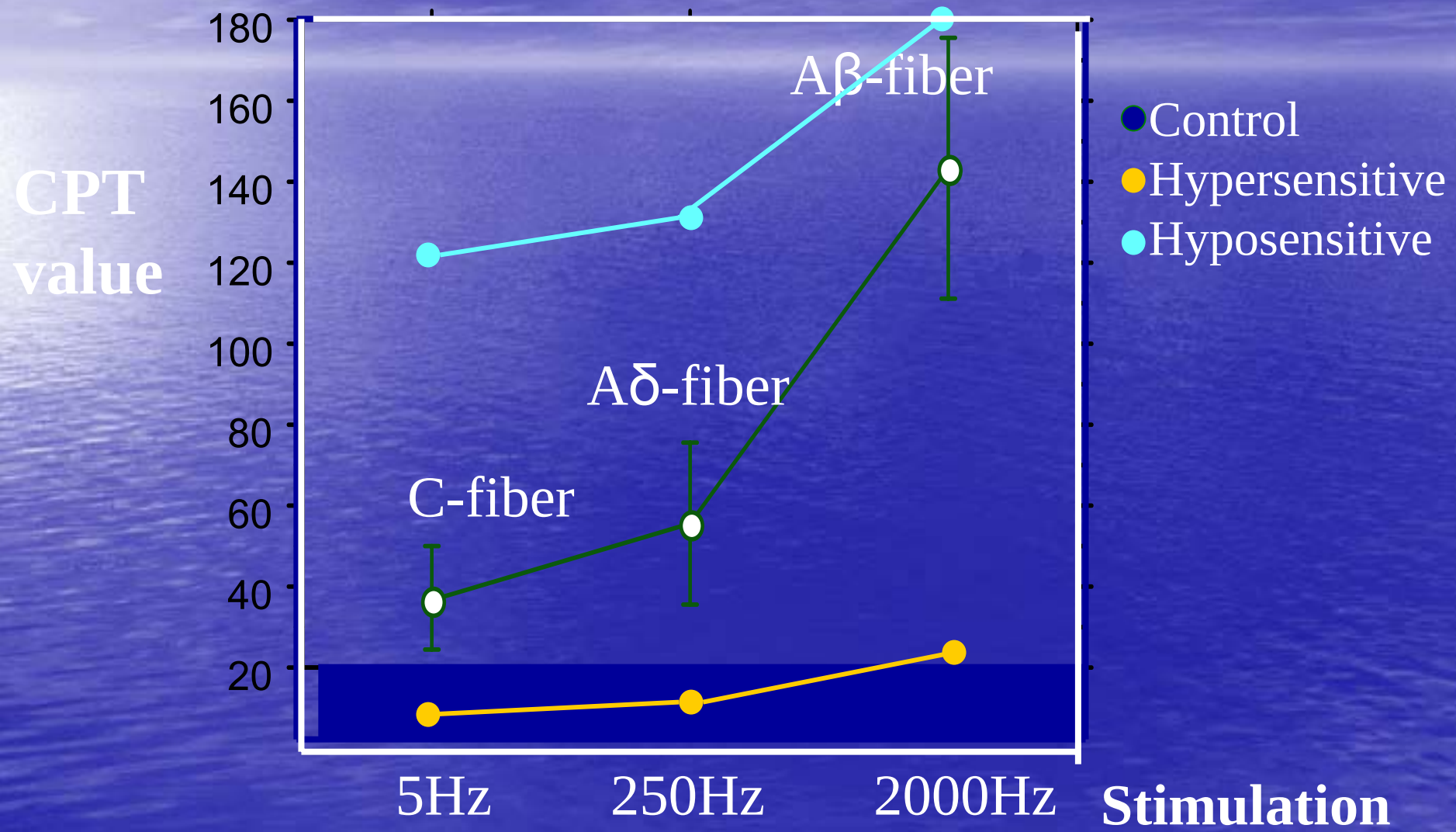
Accepted 13 August 2003

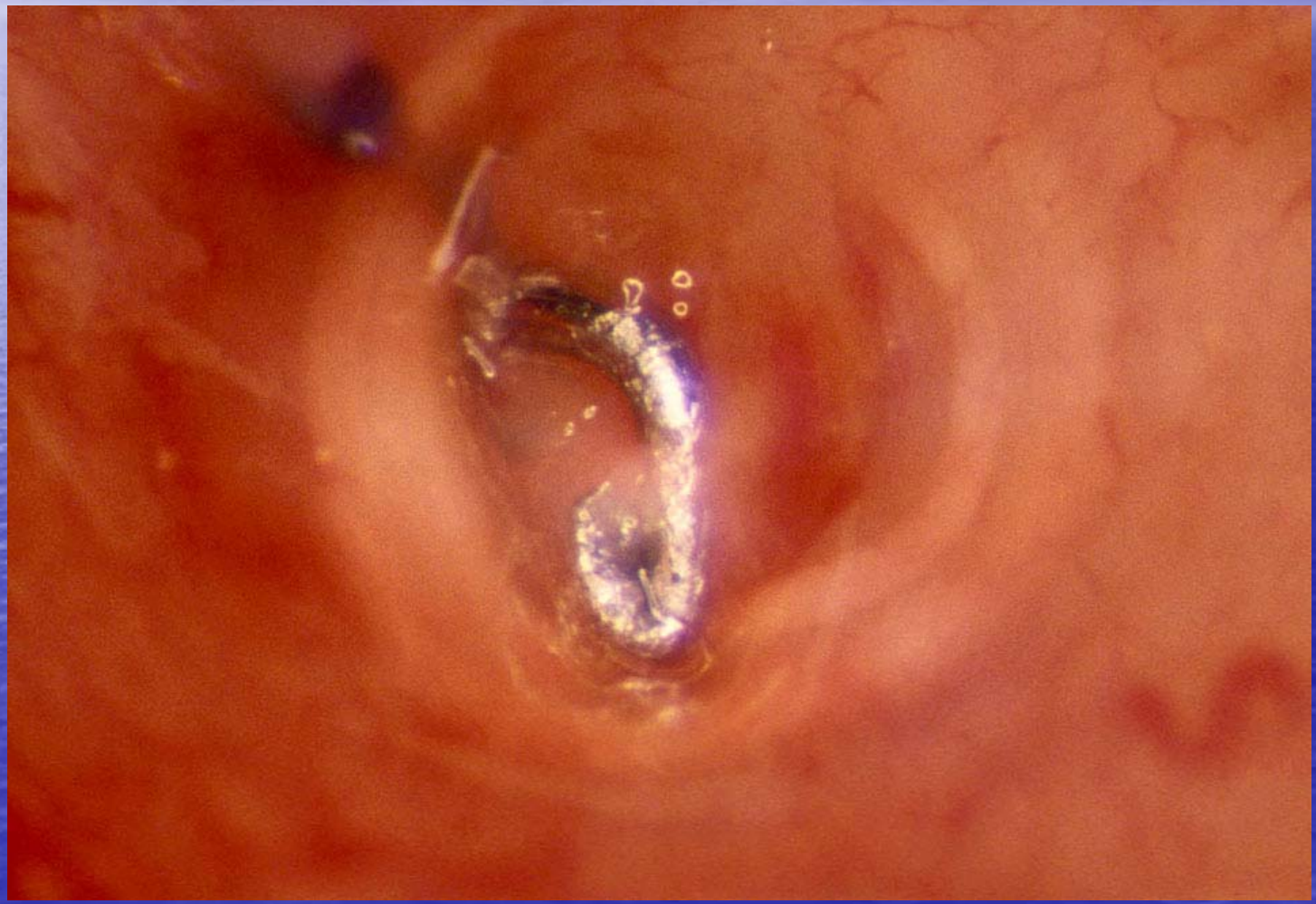
Preliminary Results of Quantitative Measurement of Urinary Sensory Function in Normal Bladder



Results of CPT values in individual cases comparing to the values in control



Bladder Electrode for assessment of afferent autonomic sensation



CPT values (mean ± SD)

Frequency	Day 1	Day 2	Day 3
5 Hz	29.4 ± 10	24.3 ± 6.9	20.4 ± 9.6
250 Hz	35.5 ± 12	34.6 ± 14	28.2 ± 12
2000 Hz	75.4 ± 18	67.8 ± 18	67.1 ± 21

Sensory Perception after instillation of Capsacin

	CPT 5Hz (Pre)	CPT 5Hz (Post)	CPT 250Hz (Pre)	CPT 250Hz (Post)	CPT 2000Hz (Pre)	CPT 2000Hz (Post)
Group 1 (Cap) n=4	15.5 ± 4.7	19.5 ± 5.9	32 ± 14	25 ± 10	56.8 ± 24	70.3 ± 19
Group 2 (EtOH) n=2	20	26	27	40	45	85.5
Group 3 (NS) n=2	19.5	44.5	35	56.5	80.5	90.5

Assessment of afferent autonomic sensation of the bladder

- EFFICACY OF A NOVEL DEVICE FOR ASSESSMENT OF AFFERENT AUTONOMIC SENSORY FUNCTION IN THE RAT BLADDER
- NEUROSELECTIVITY OF THE SENSORY PERCEPTION THRESHOLD (SPT) OF THE BLADDER
- ALTERATIONS IN THE AFFERENT AUTONOMIC SENSATION OF THE BLADDER IN DIABETIC CYSTOPATHY

Robert Abouassaly, M.D.
Guiming Liu, M.D. Ph.D.
Osamu Ukimura, M.D., Ph.D.
Jefferson Katims, M.D.
Firouz Daneshgari, M.D.

Diabetic Uropathy

Phenotyping Measures

- Frequency Volume Measurements
- Cystometrogram
- Remodeling Measures
- Contractility studies
- Assessment of alterations in autonomic function of the bladder
- Assessment of alterations in myogenic function of the bladder

Diabetic Uropathy

Phenotyping Measures

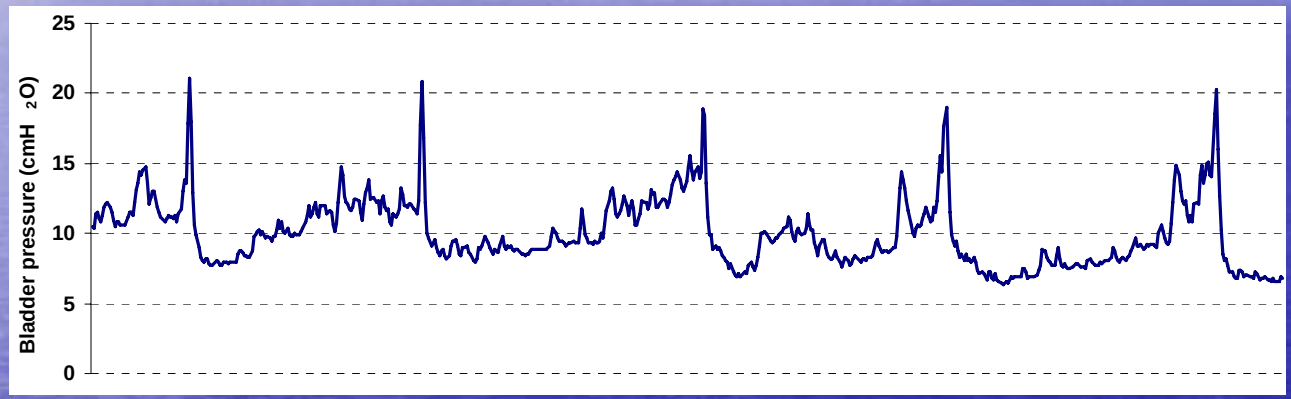
- Screening Measures:
  - Frequency Volume Measurements
  - Remodeling Measures
- Advanced Measures
  - Cystometrogram
  - Contractility studies
- Exploratory:
  - Assessment of alterations in autonomic function of the bladder
  - Assessment of alterations in myogenic function of the bladder

AMDCC Models

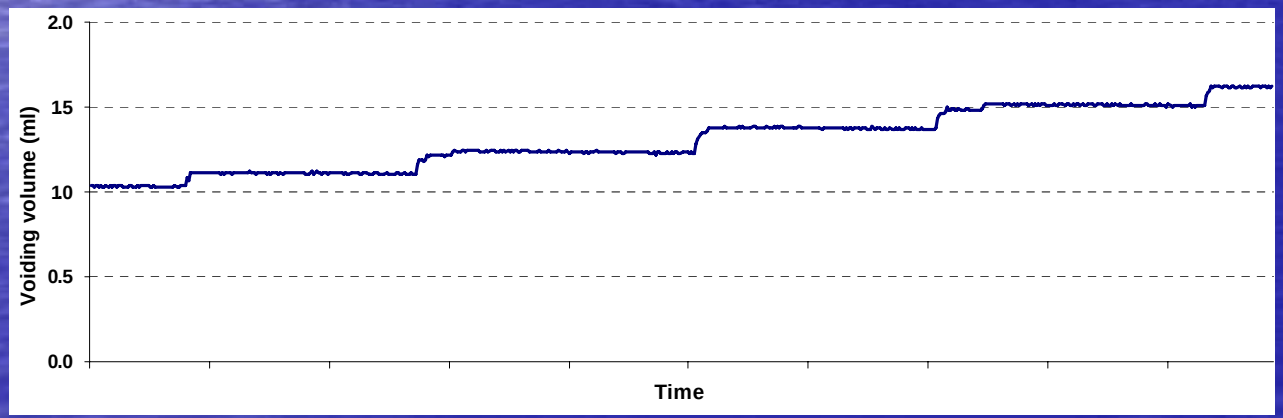
- C57BL\KLS (Michigan)
- Akita (Ins2+) (Vendor)
- C57BL\Glute 4 (Michigan)
- C57BL\db/db (Vendor)
- C57BL\ob/ob (Vendor)
- LDLR-/-(UCLA)
- LDLR-/-, Akt2+\- (Rockefeller)

Diabetic Uropathy

CMG

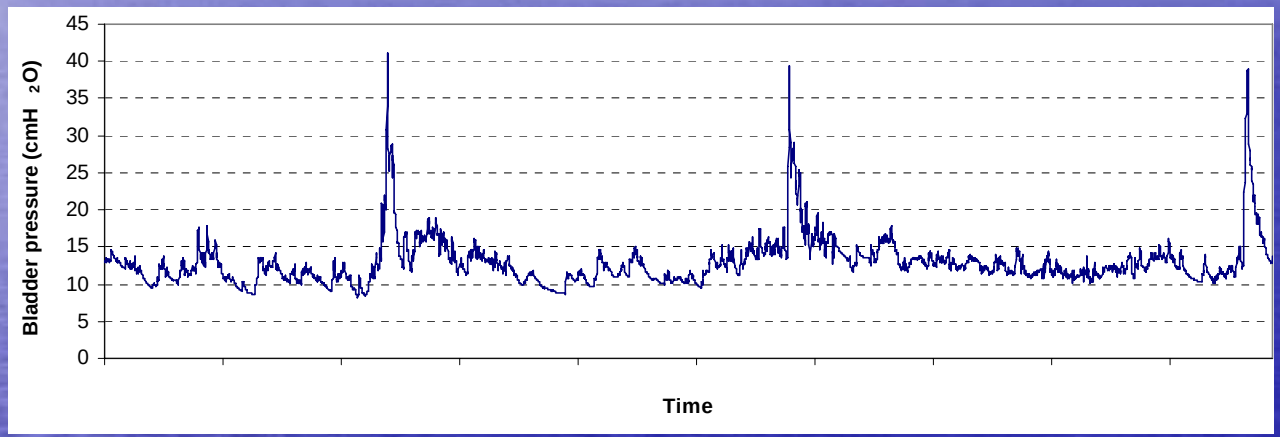


FVC

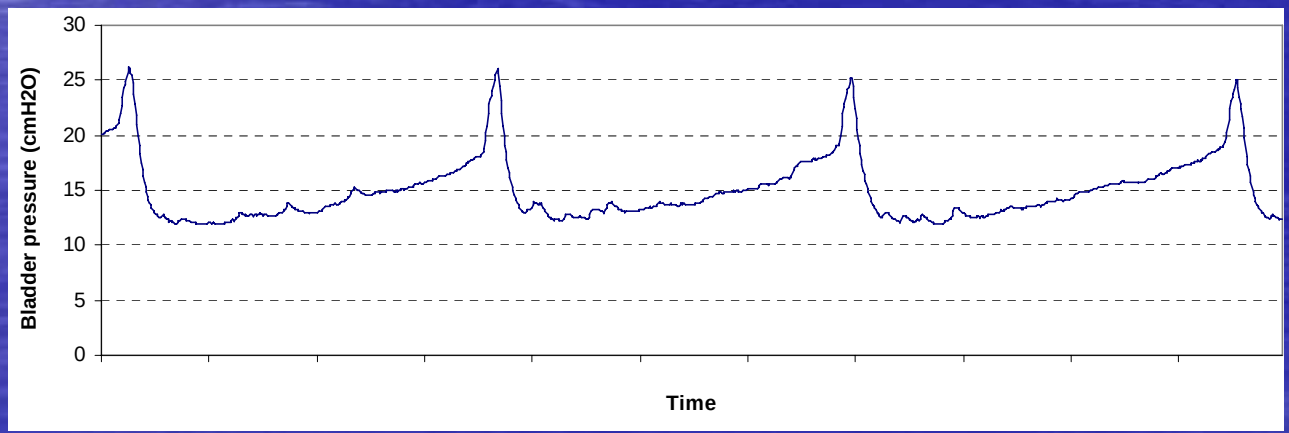


Cystometry

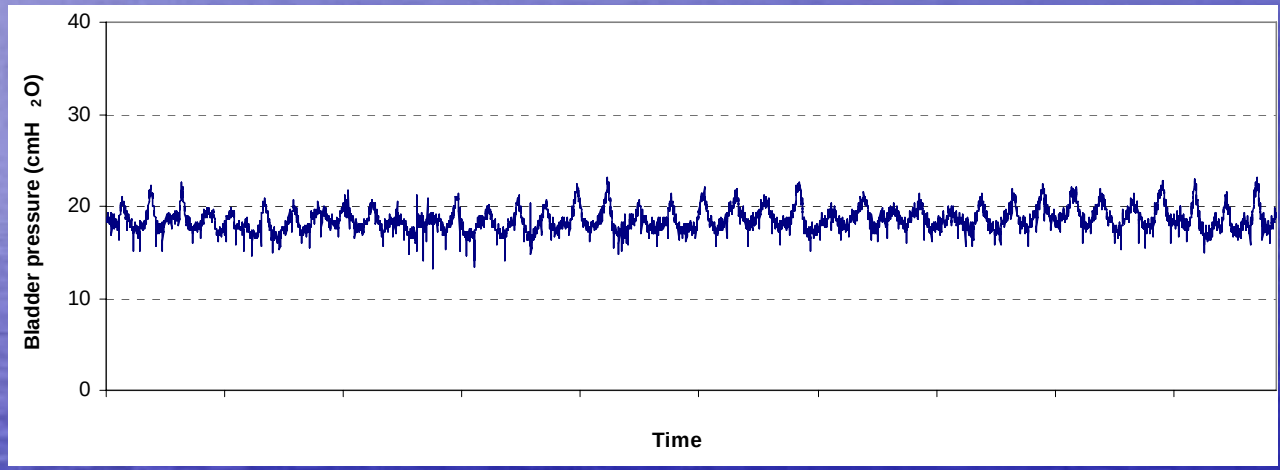
Db/db



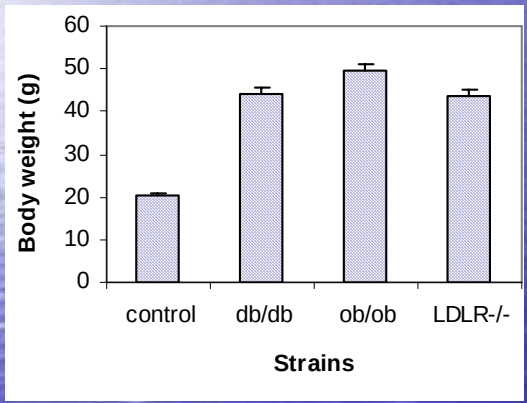
Ob/ob

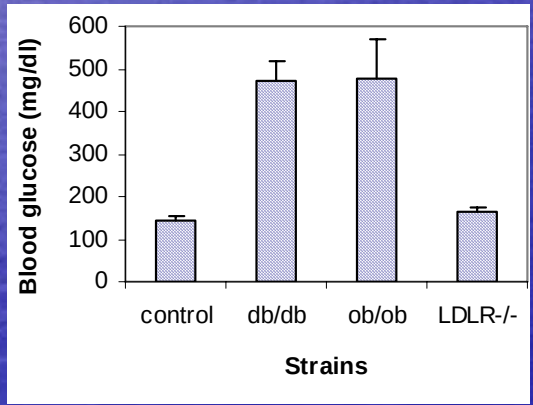


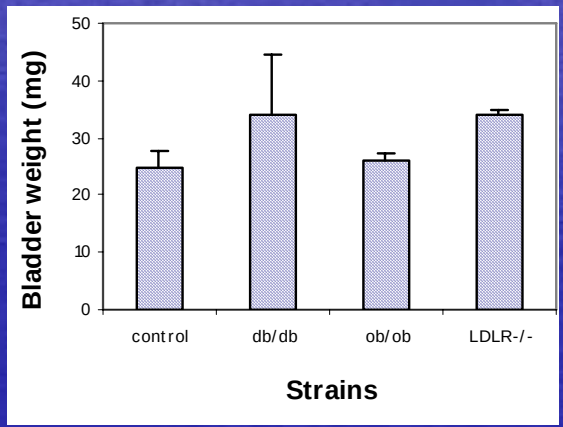
LDLR-/-



AMDCC Models





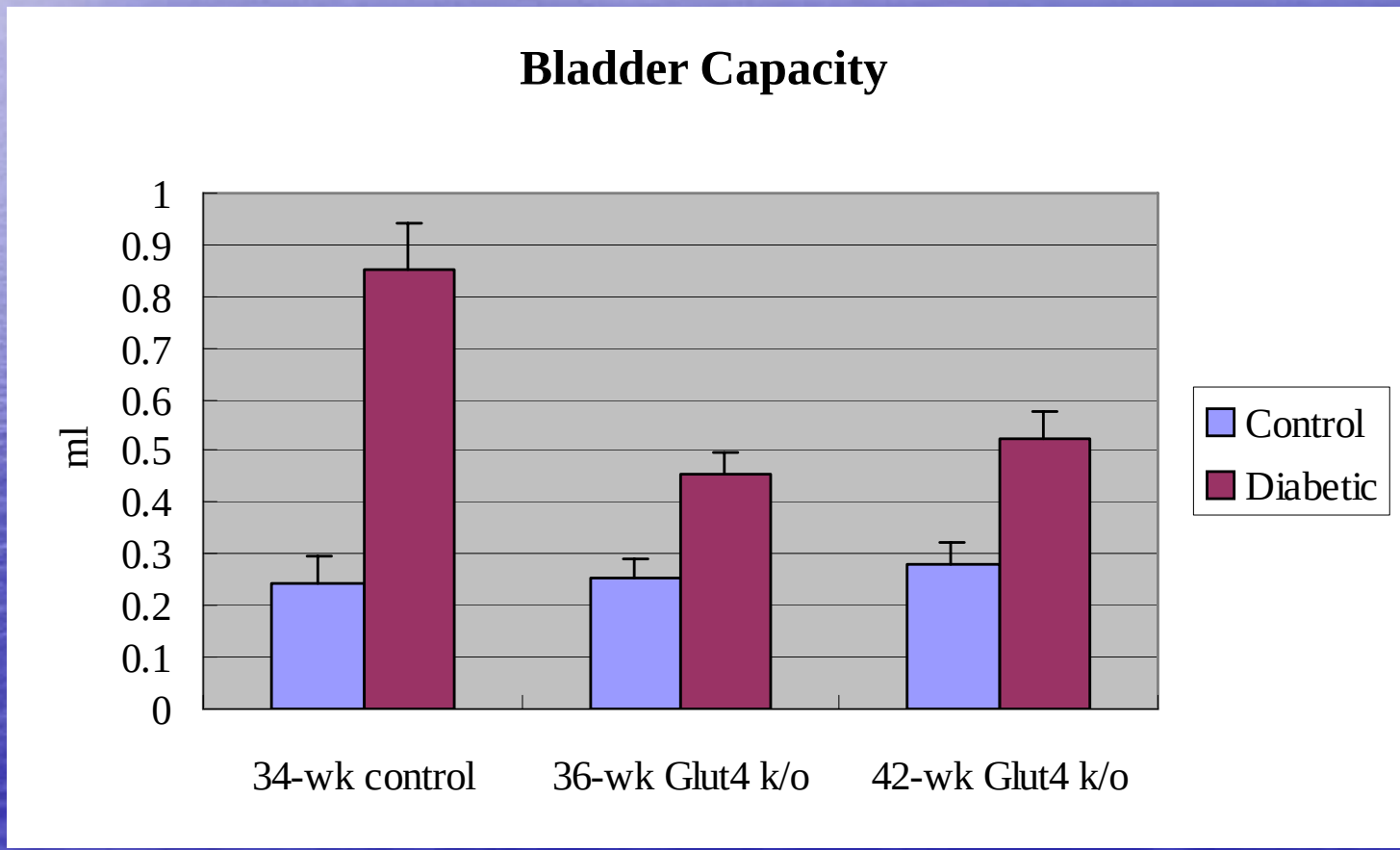


General characteristics of mice used for AMDCC phenotyping of diabetic uropathy: db\db; ob\ob and LDLR-\- on C57BL\6 mice (n=8)

AMDCC models

Total Body Glut4/ko-C57Bl/6

Bladder Capacity



Future

- Screening of the most models
- Time course of DBD in:
  - Db/db
  - Ob/ob
  - the AMDCC selected animals (Rage tg; Nestin Cre//SOD 2; NOS)
- Exploration of alterations in the myogenic vs neurogenic mechanisms of DBD

Xiao Huang, MD, Ph.D.

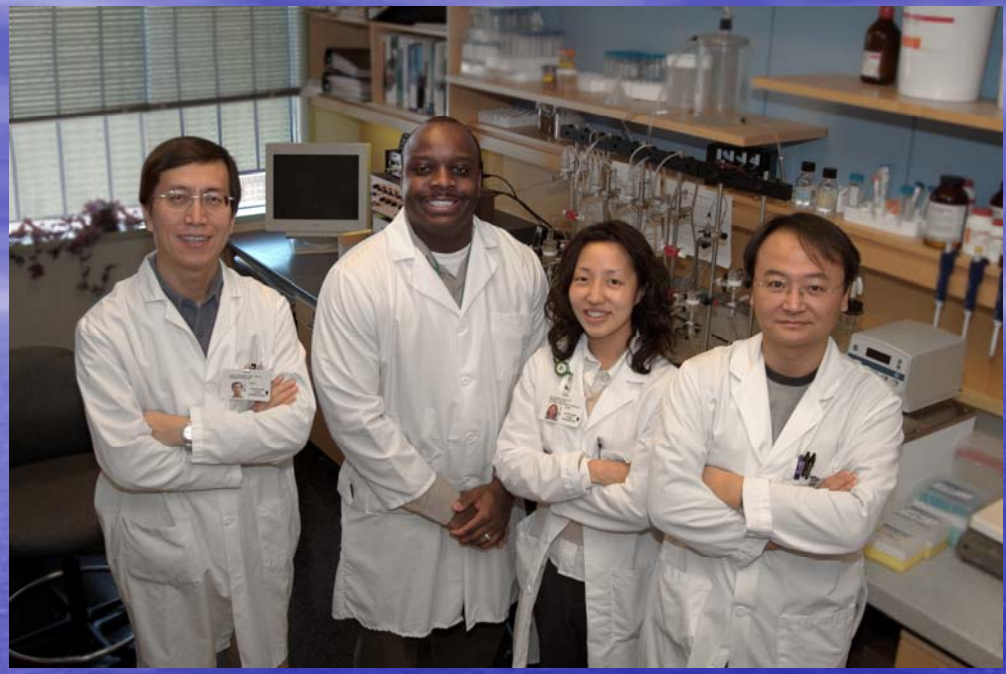
Lateef Saffore, M.S.

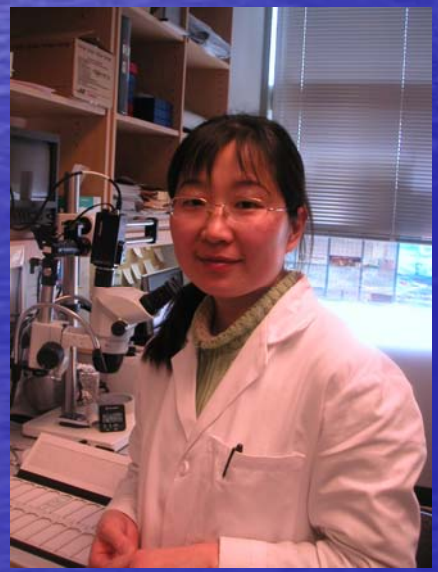
Ja-Hong Kim, M.D.

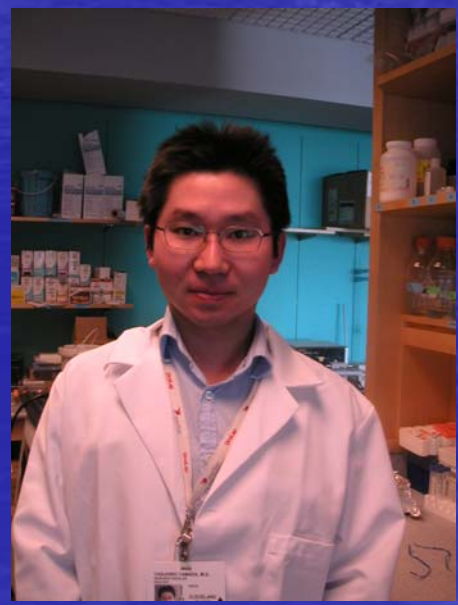
Guiming Liu, MD, Ph.D.

Mei Li, M.D.

Yoshihiro Yamada, M.D.







Thank you

- **NIH-NIDDK K08-DK02631**
- **NIH-NIDDK U01-DK61018-02S1**-AMDCC
- **JDRF**

- **NIH-NIDDK R41 -HD-04-018-** Transurethral Assessment of Altered Autonomic Function in Diabetic Bladder
- JDRF Fellowship Award to Guiming Liu: Pathogenesis of diabetic cystopathy

- Frank Brusius, M.D. Ph.D.
- Eva Feldman, M.D. Ph.D.
- Tim Kern, Ph.D.
- Matt Bryer, M.D.
- AMDCC Steering Committee and External Advisory Committee
- Wade Bushman, M.D., Ph.D.
- Chris Ketchum, Ph.D.