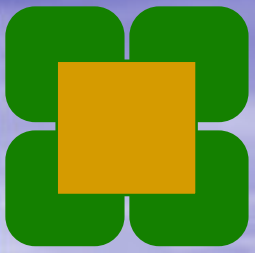
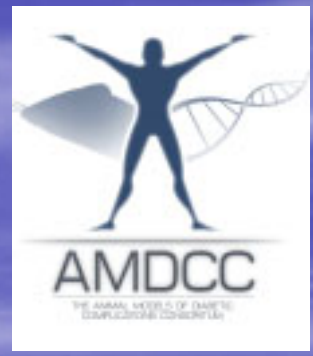




Diabetic Uropathy

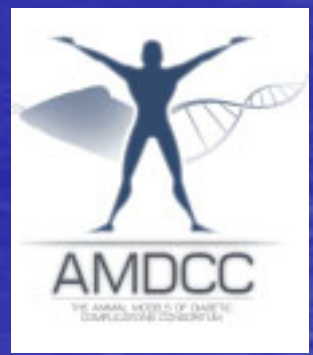
Firouz Daneshgari, M.D.

The Cleveland Clinic Foundation

November 2004

Diabetic Uropathy

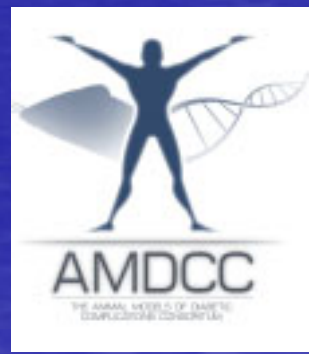
- Diabetic Bladder Dysfunction (DBD) or Diabetic Cystopathy
- Urinary Tract Infection
- Sexual Dysfunction



Diabetic Bladder Dysfunction

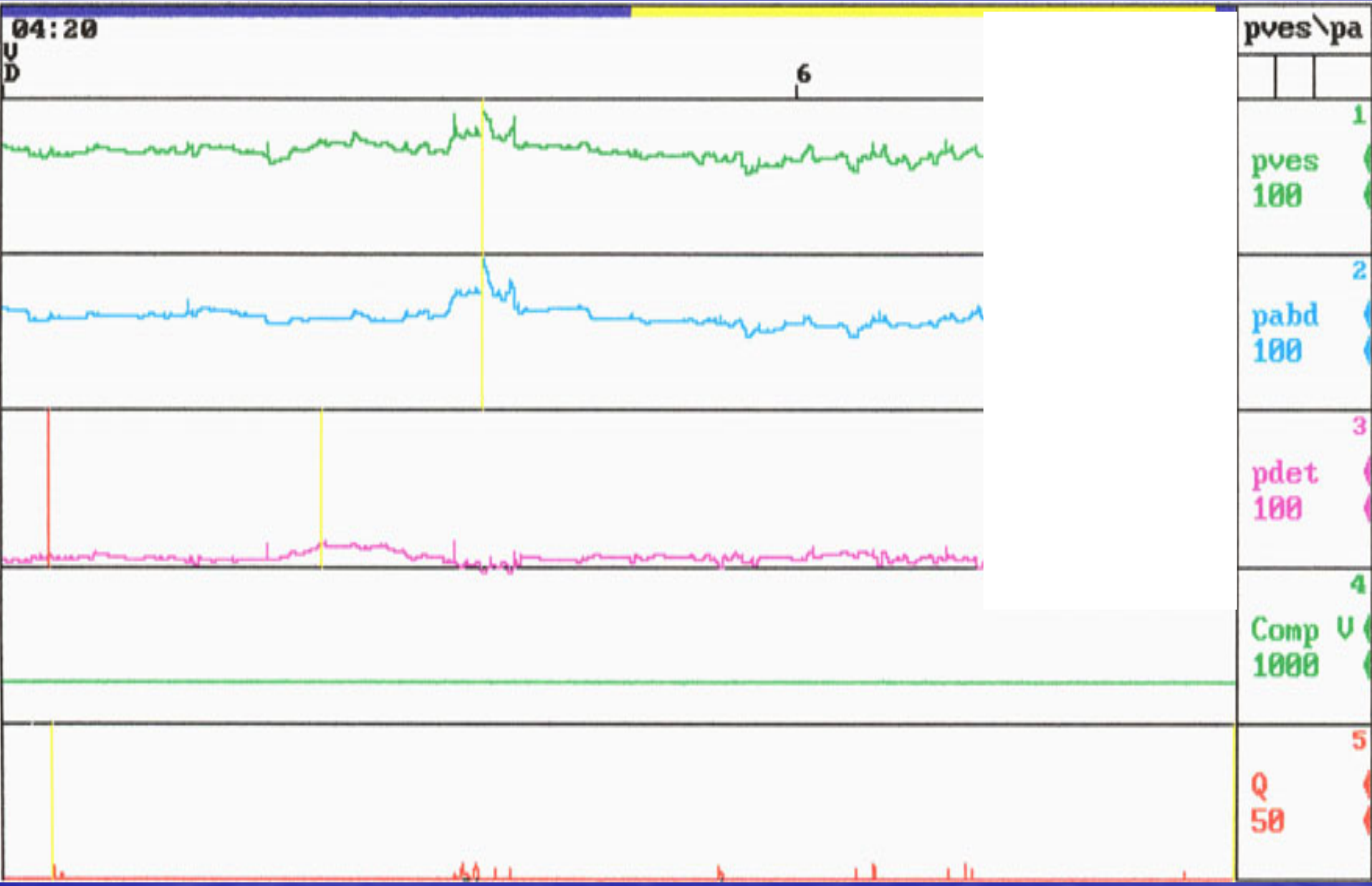
Traditional Findings

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



Voiding Phase of Urodynamic Studies:

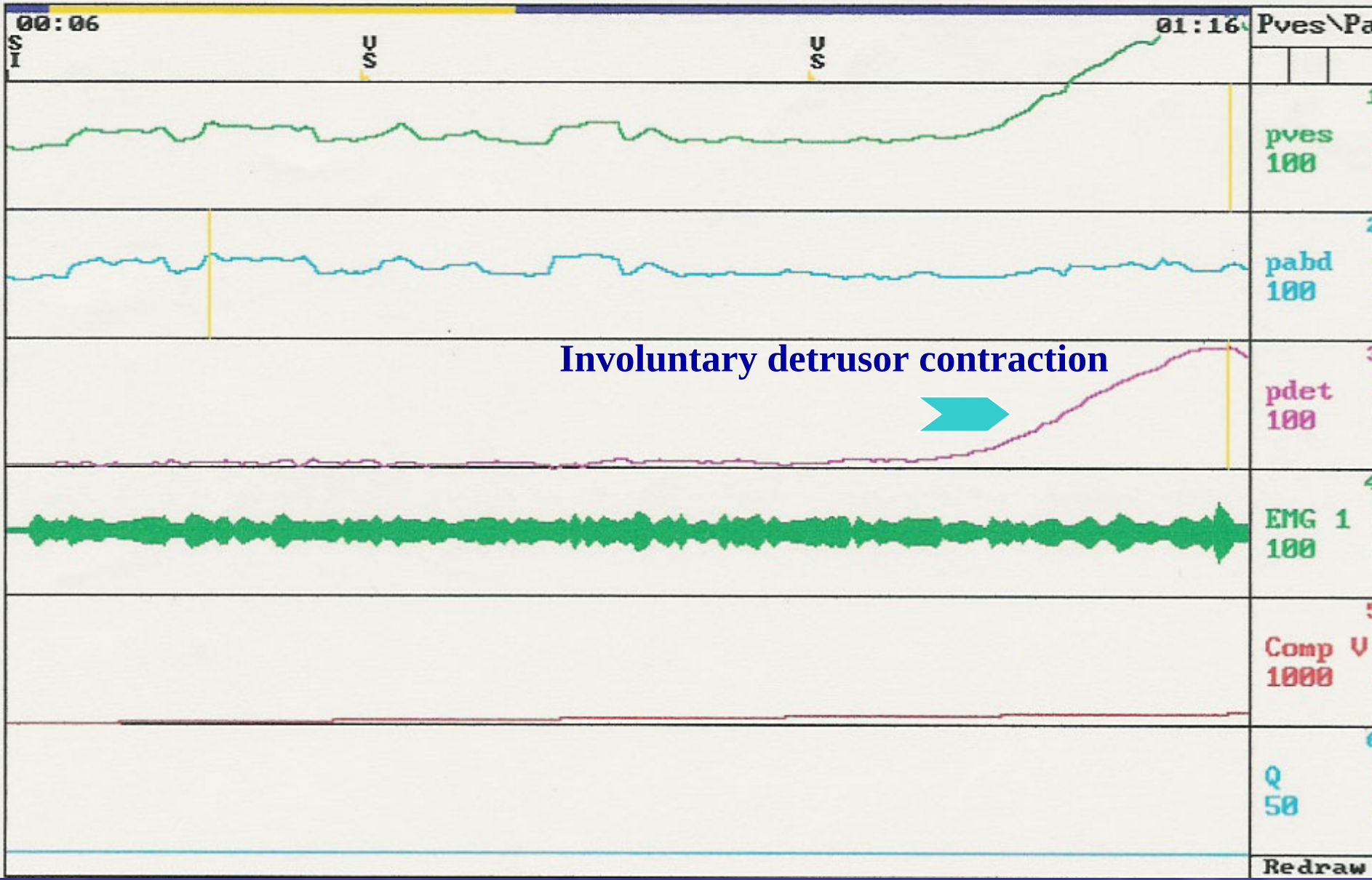
Acontractile Bladder



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)

Filling Phase of Urodynamic Studies: Detrusor Overactivity



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

Pathophysiology of DBD

- Autonomic Neuropathy leading to DBD:
  - Historical observational studies
    - High prevalence of DBD in patients with diabetic autonomic neuropathy
  - Scattered experimental data
- No role for effects of hyperglycemia on the muscle or other tissues of the lower urinary tract has been considered

Challenges to the Autonomic Neuropathy Theory

- Is AN a pre-requisite for DBD?
  - No/Don't know
  - DCCT did not record DBD
- Role of 'myopathy' in other organ complications of DM:
  - Vascular smooth muscle
  - Small bowel

Research Questions/Challenges

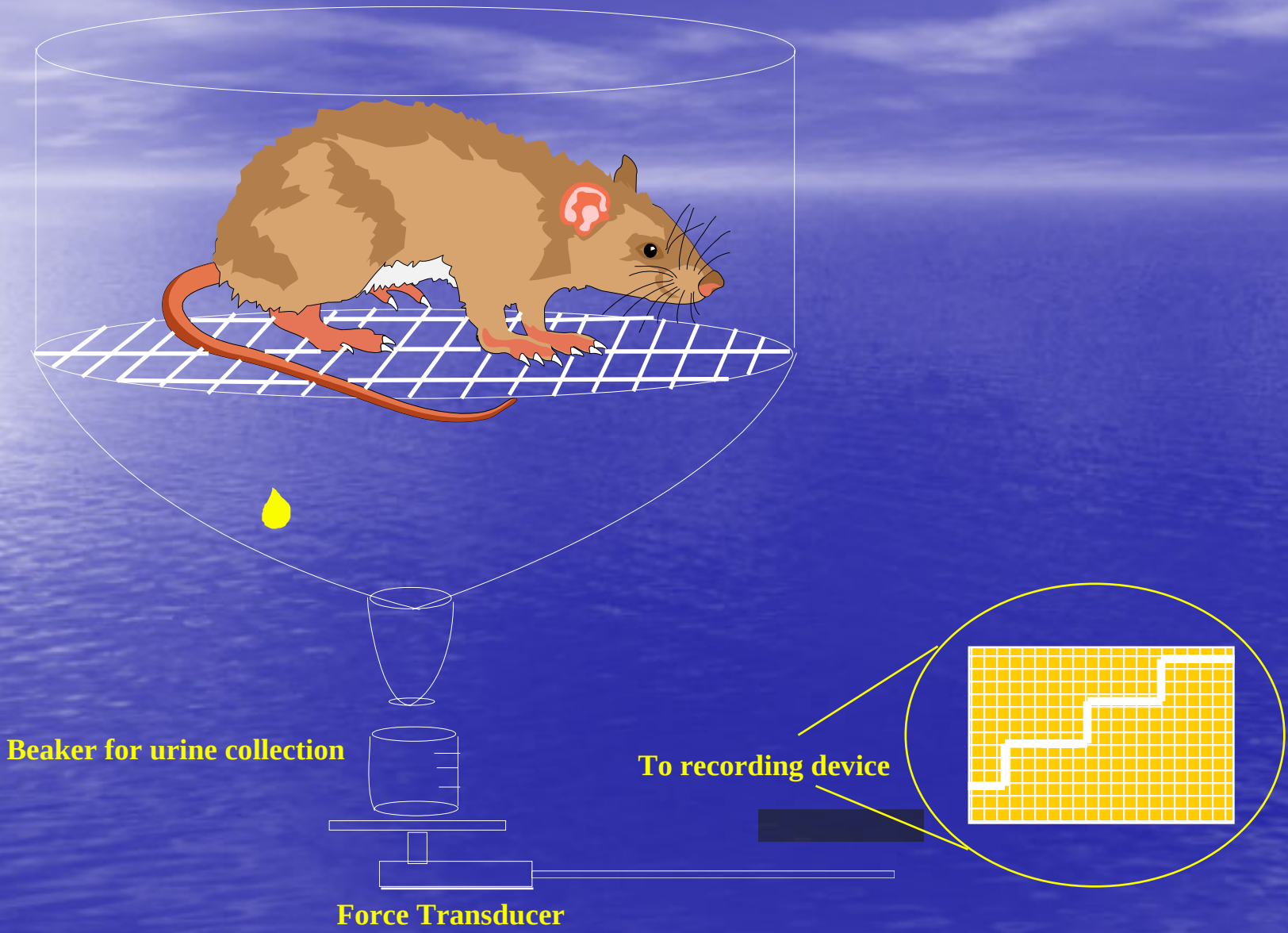
- Neuropathy or Myopathy?
- Effects of Diuresis on bladder dysfunction
- Lack of a phentoyping assay to detect loss of bladder sensation in diabetic cystopathy

Phenotyping of Animal Models for Diabetic Cystopathy

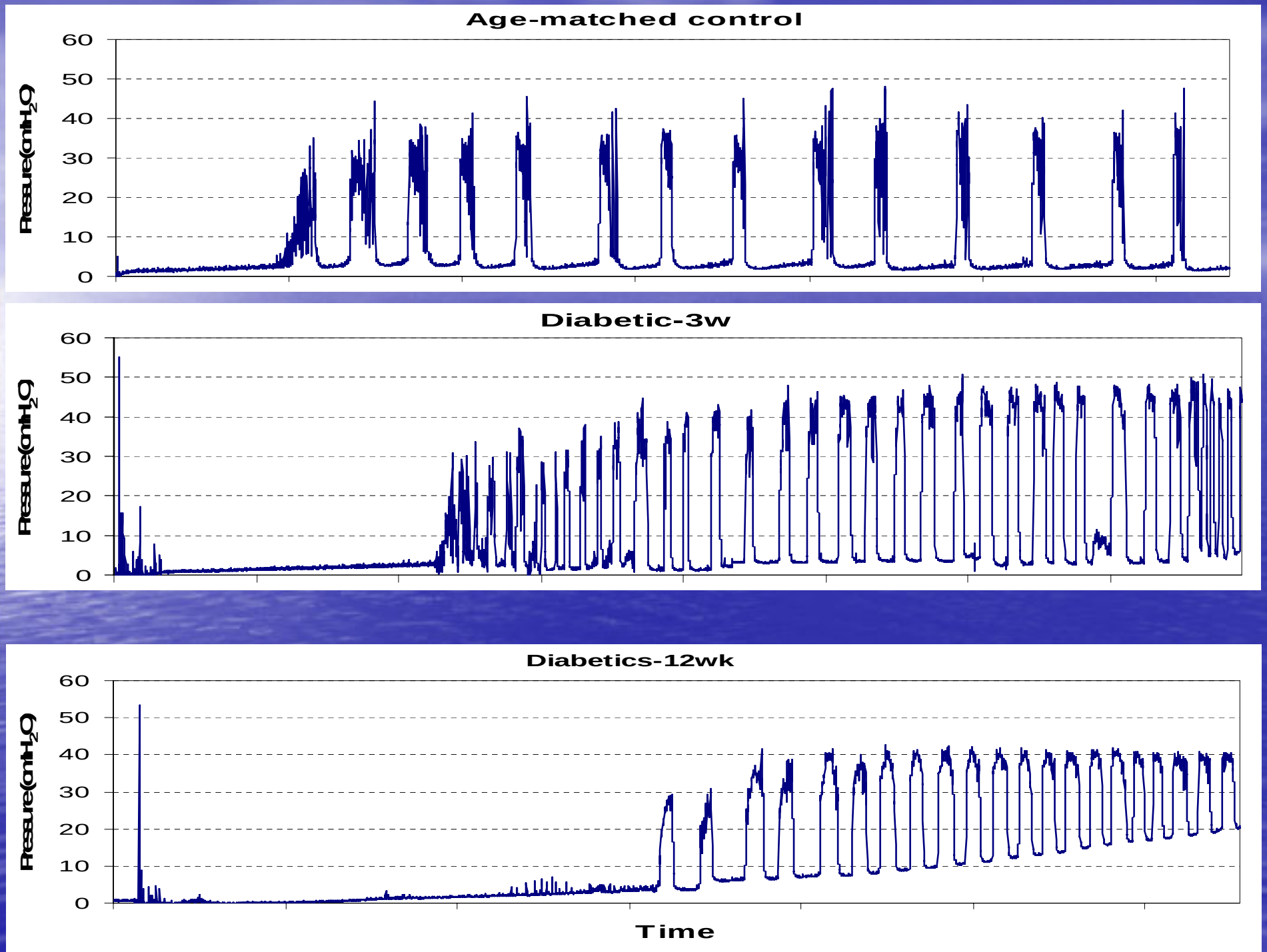
- In-vivo studies:
  - Metabolic cage for monitoring of:
    - Frequency of urination
    - Urine output
    - UTI
  - Cystometrogram (anesthetized or awake):
    - Bladder capacity, compliance, filling and voiding pressures
- In-vitro studies

Phenotyping of Animal Models for Diabetic Uropathy

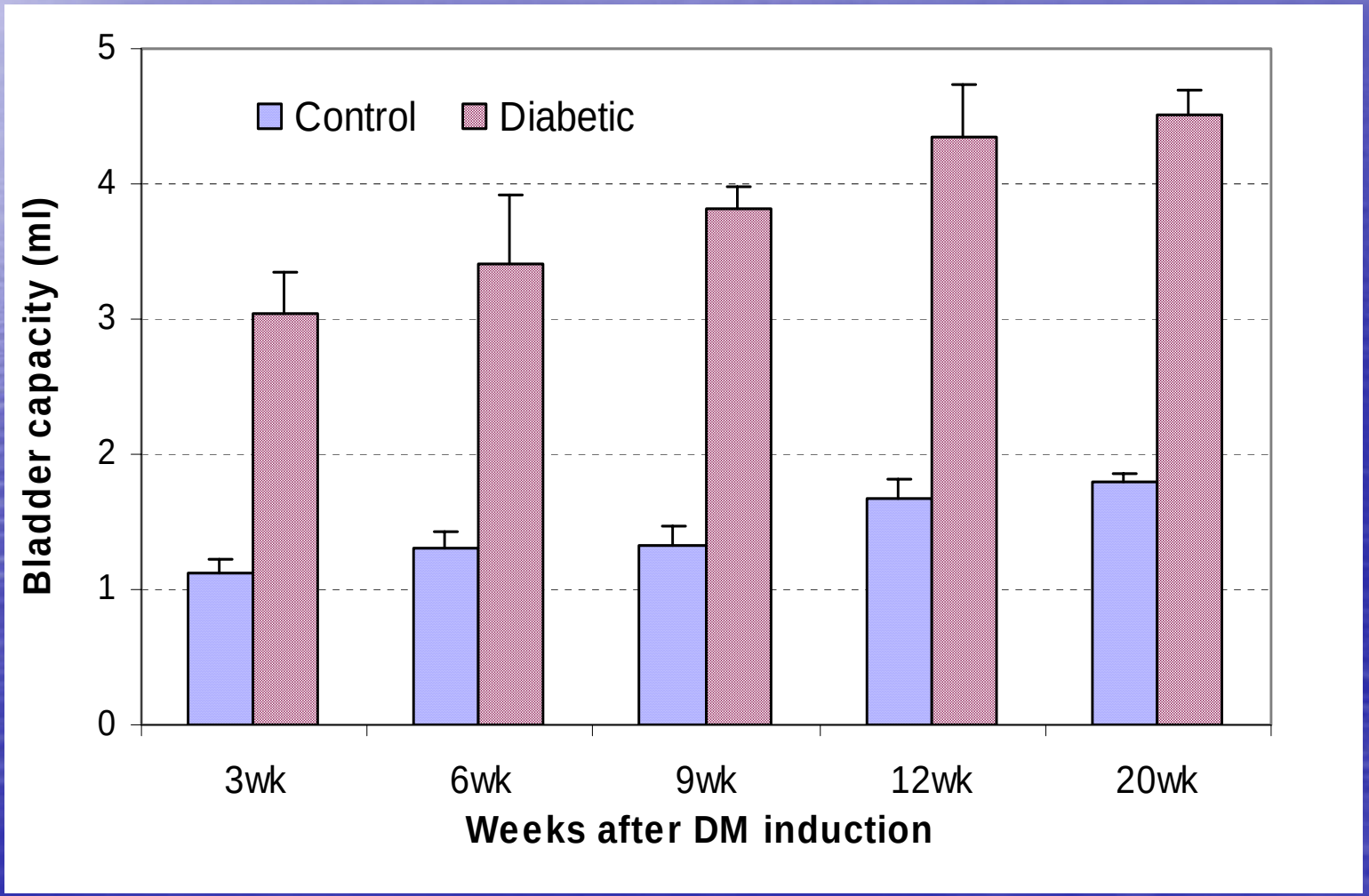
- In-vitro studies:
  - Morphometrical alterations
    - Gross or ultrastructures
  - Contractility studies
  - Biochemical and Molecular studies


Beaker for urine collection
To recording device
Force Transducer

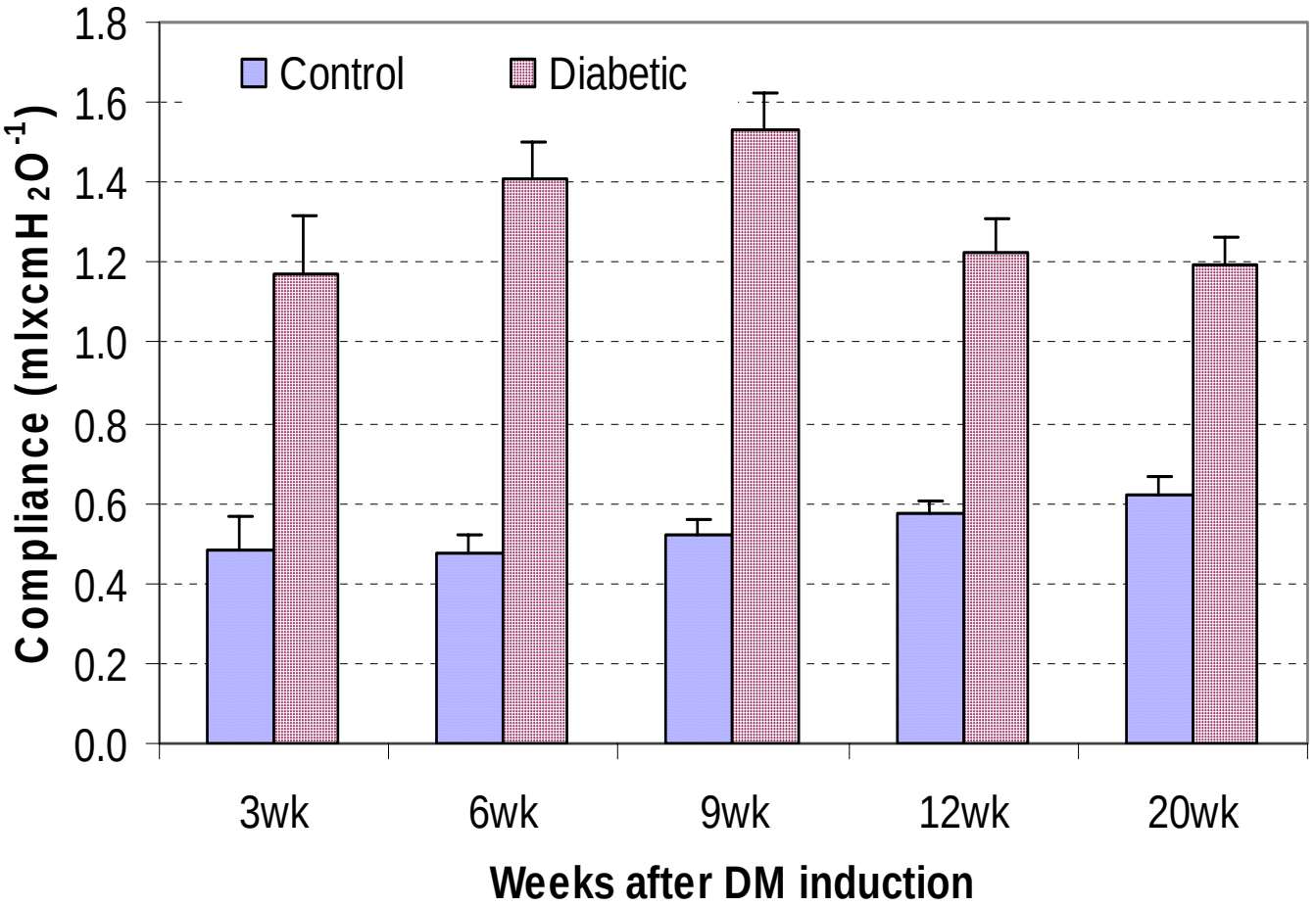
Time-course of STZ- induced Diabetic Bladder Dysfunction in SD Rat and C57Bl/6 Mouse


Age-matched control
Diabetic-3w
Diabetics-12wk
Pressure(cmH2O)
60
50
40
30
20
10
0
Time

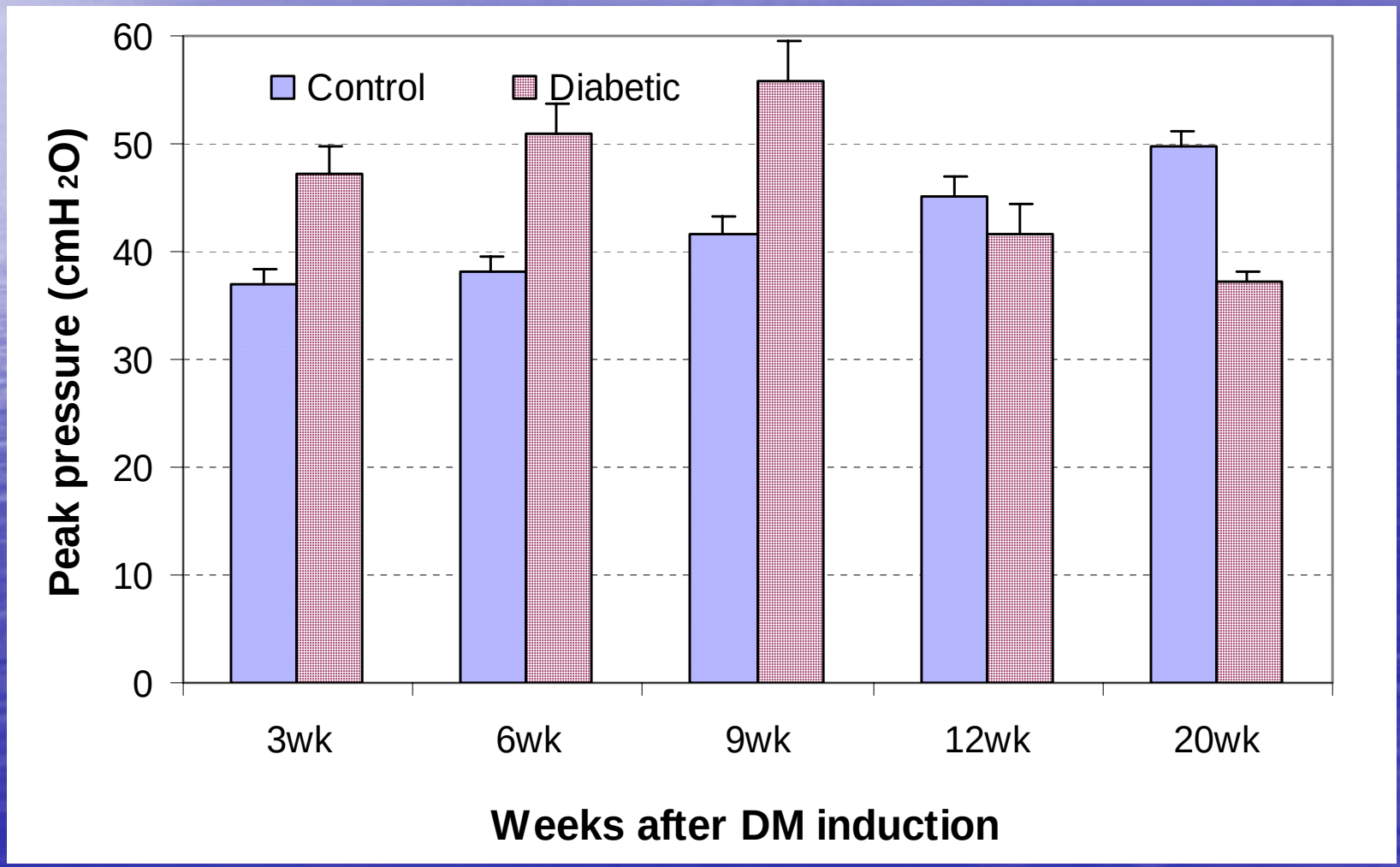
Change of bladder capacity



Change of compliance

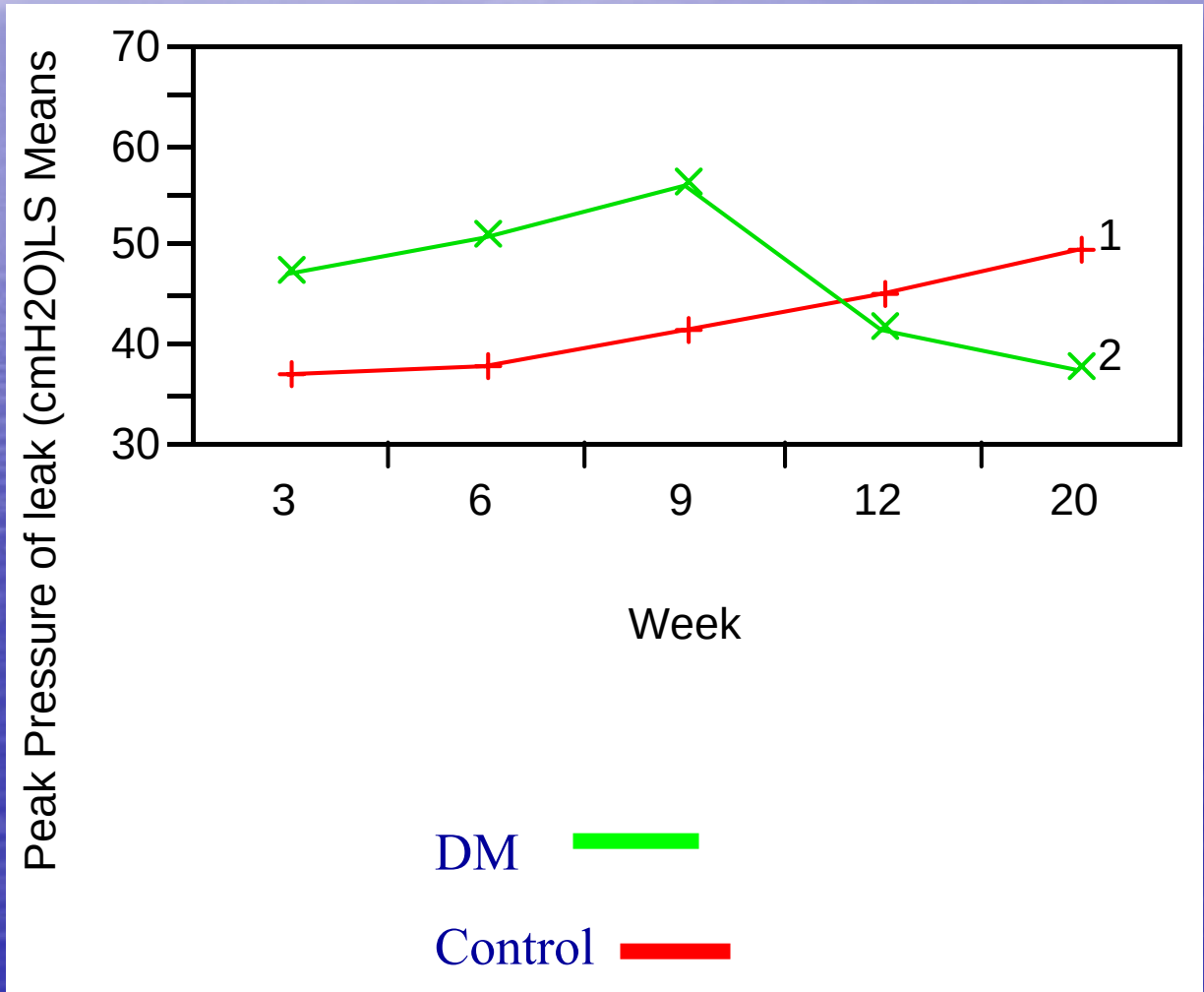


Change of peak voiding pressure

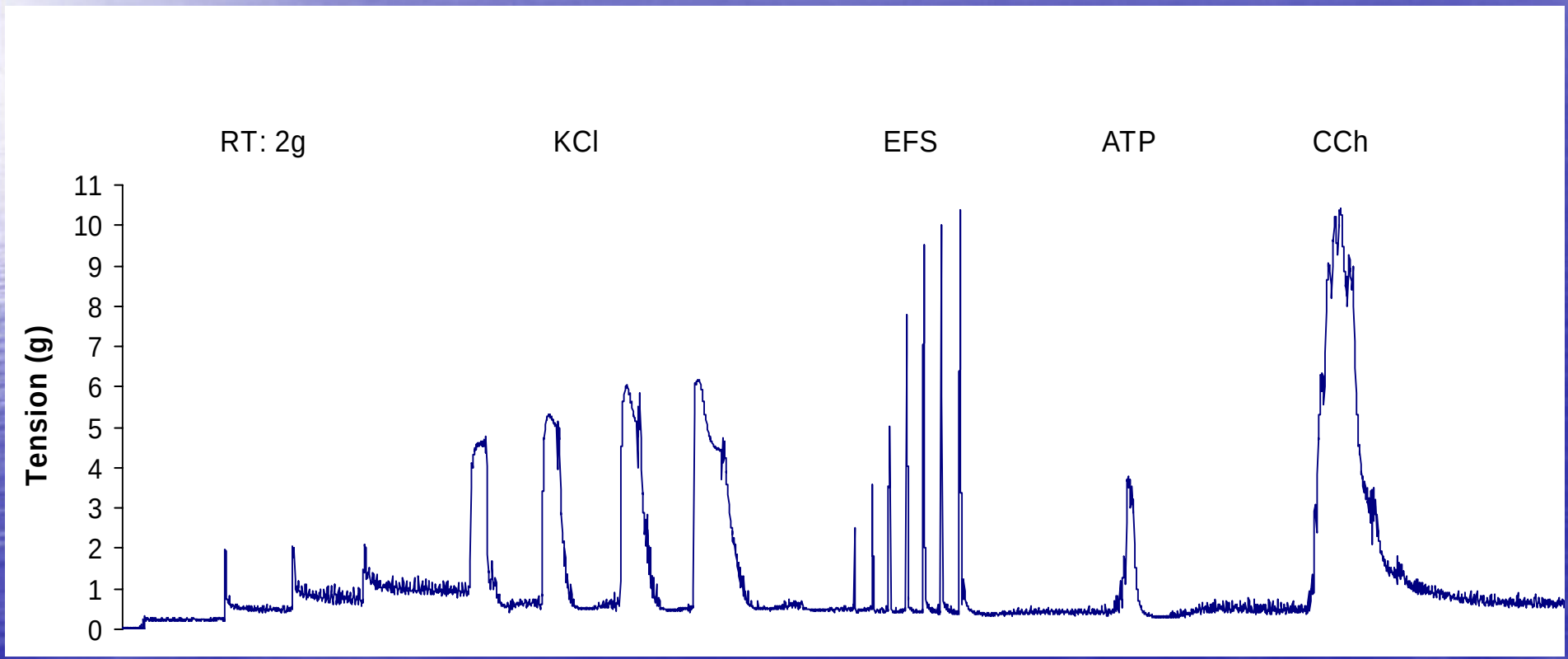


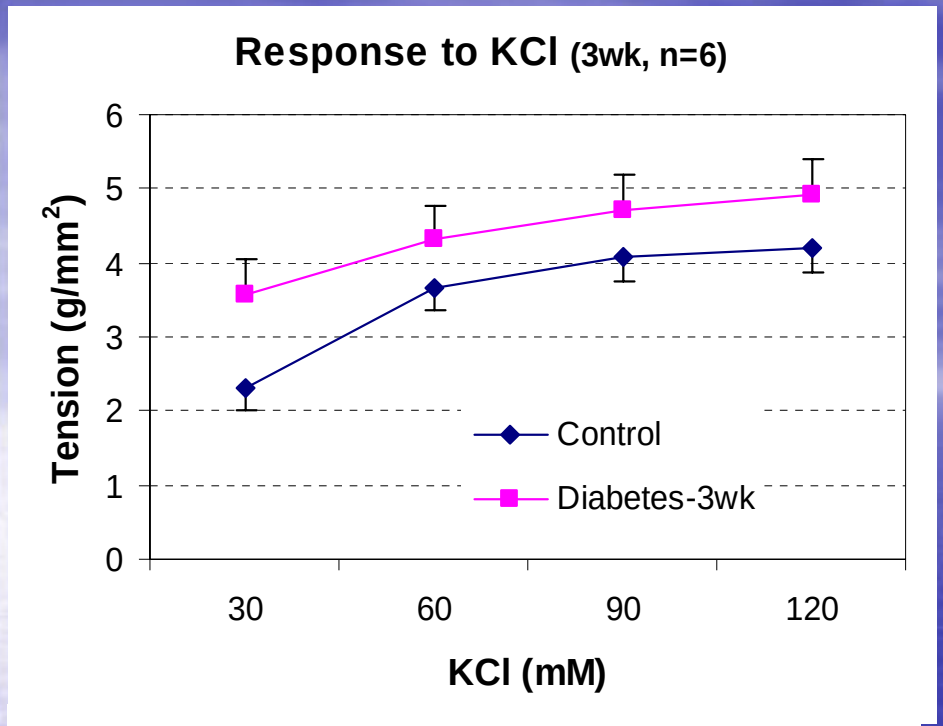
Time course of DBD in SD STZ-Rats

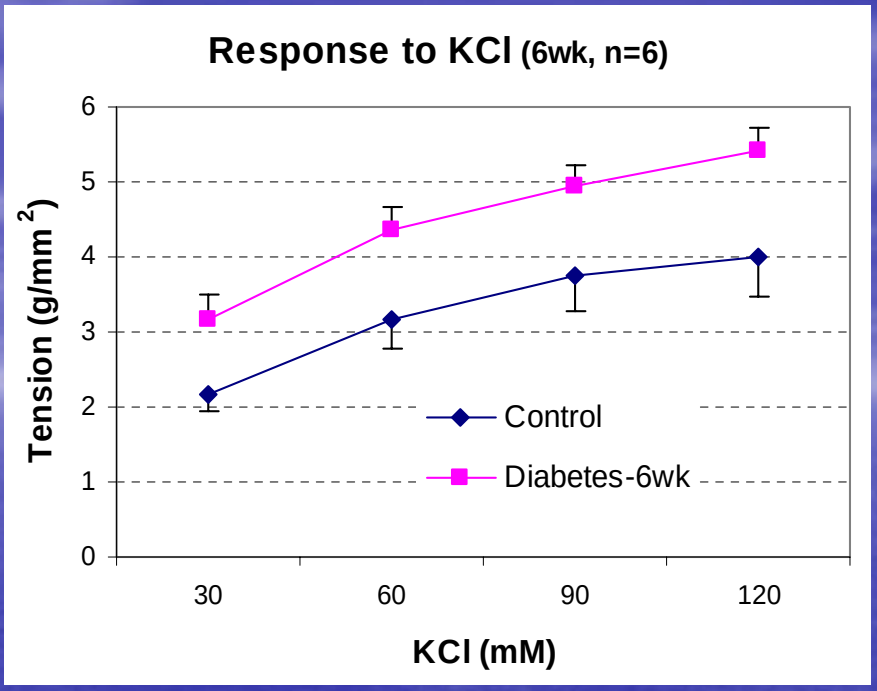
Peak Pressure of Leak: Adjusted Effects of Age and DM

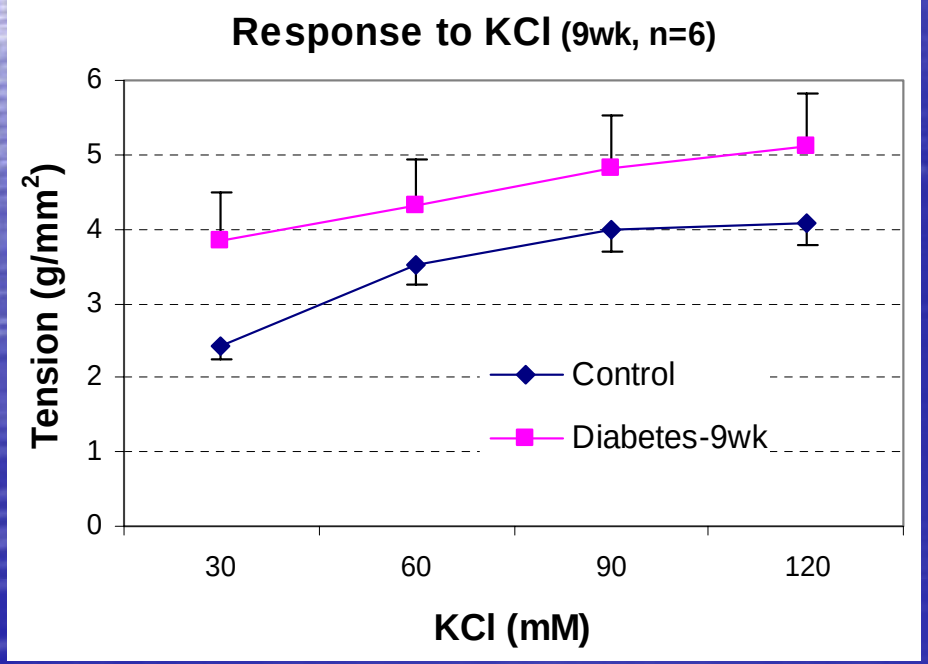


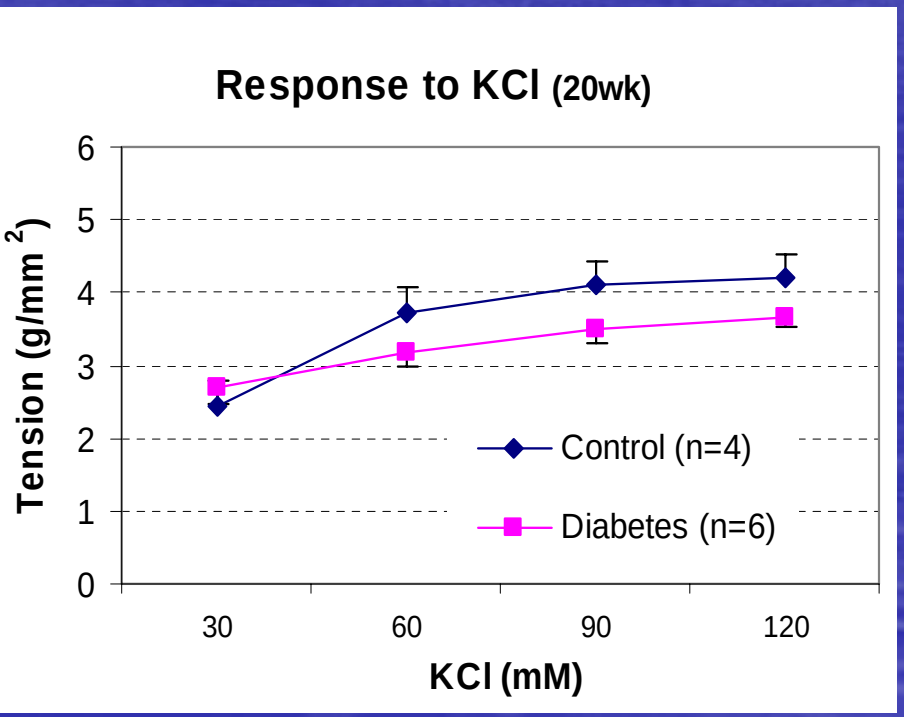
Protocol of contractility study

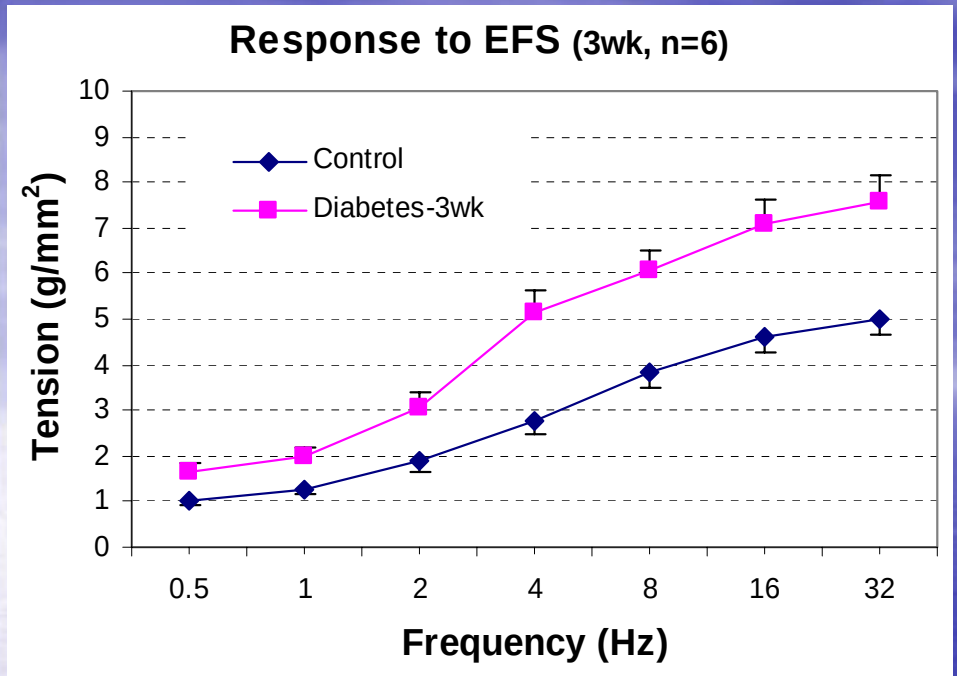


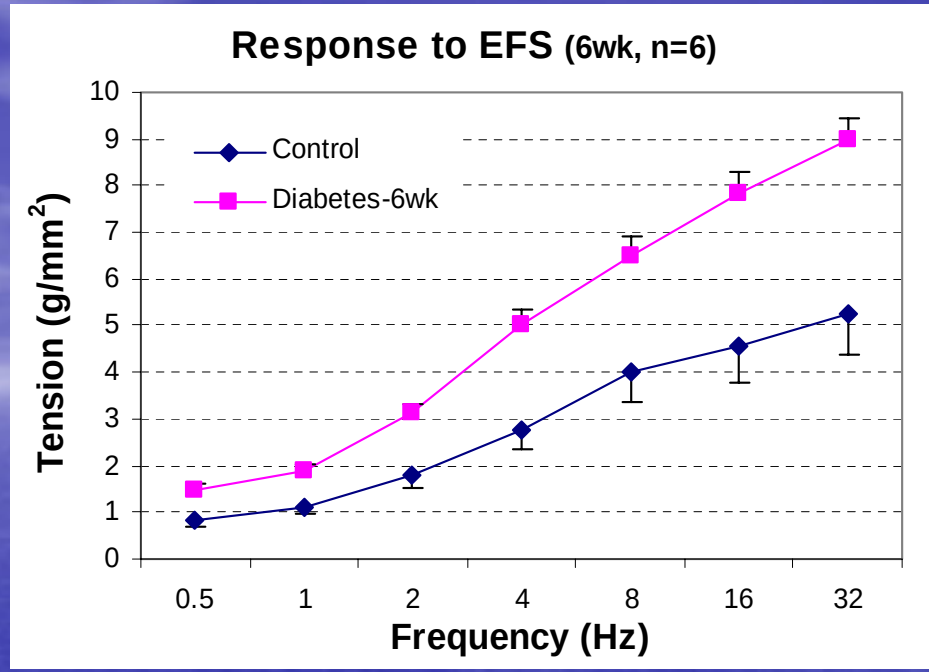

Response to KCl (3wk, n=6)
Tension (g/mm2)
0
1
2
3
4
5
6
30
60
90
120
KCl (mM)
Control
Diabetes-3wk

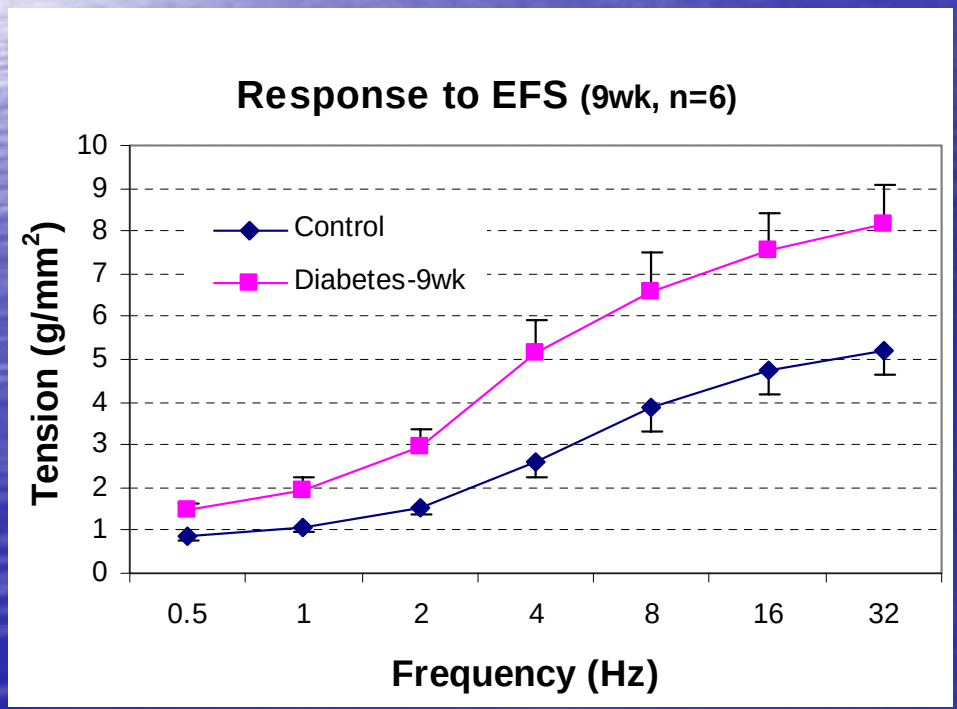

Response to KCl (6wk, n=6)
Tension (g/mm 2)
0
1
2
3
4
5
6
30
60
90
120
KCl (mM)
Control
Diabetes-6wk

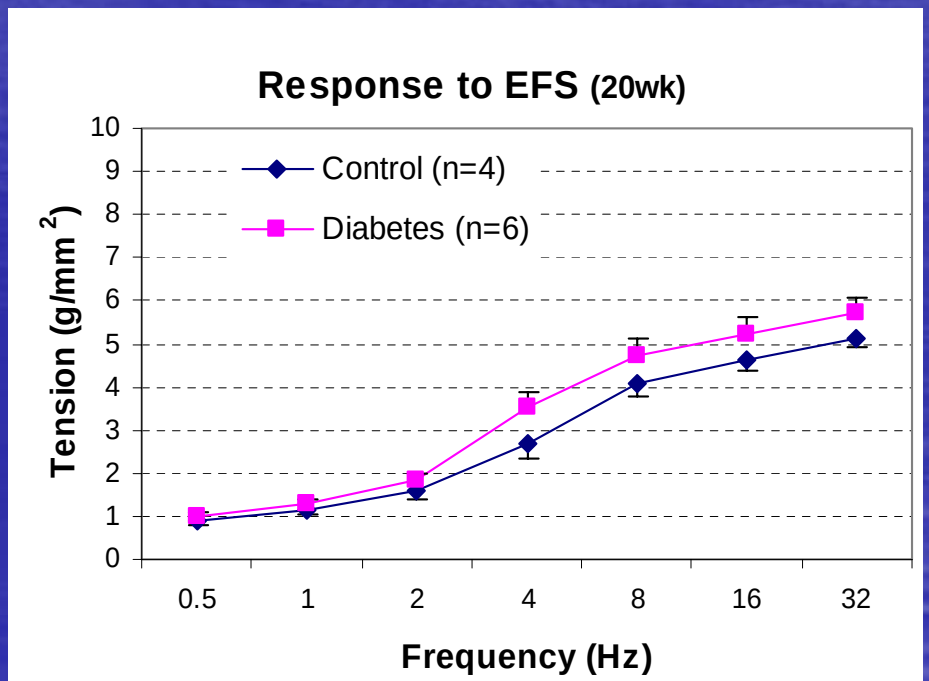

Response to KCl (9wk, n=6)
Tension (g/mm2)
0
1
2
3
4
5
6
30
60
90
120
KCl (mM)
Control
Diabetes-9wk

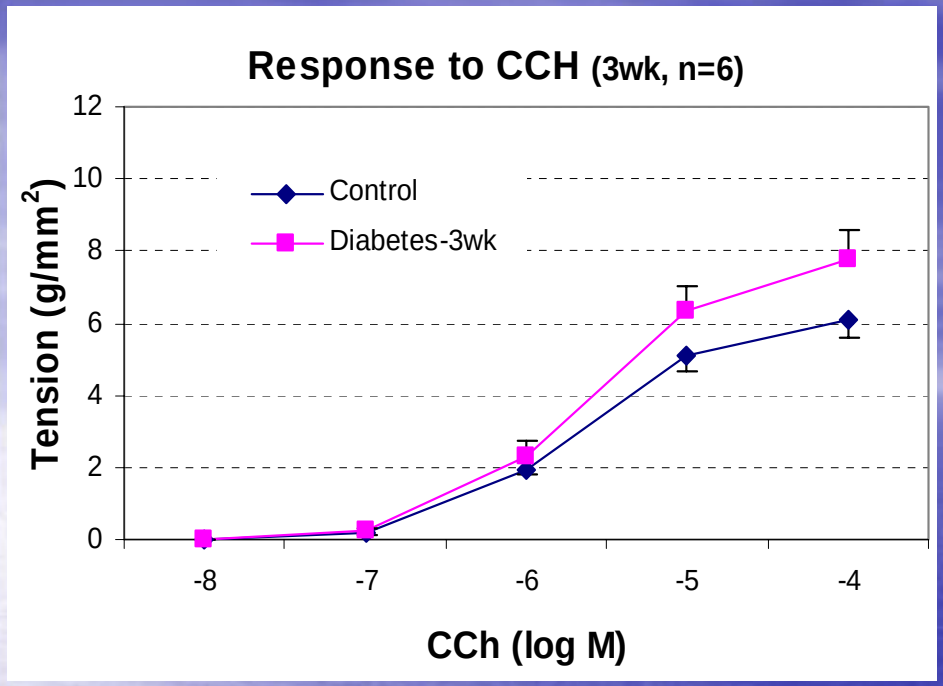

Response to KCl (20wk)
Tension (g/mm 2)
0
1
2
3
4
5
6
30
60
90
120
KCl (mM)
Control (n=4)
Diabetes (n=6)

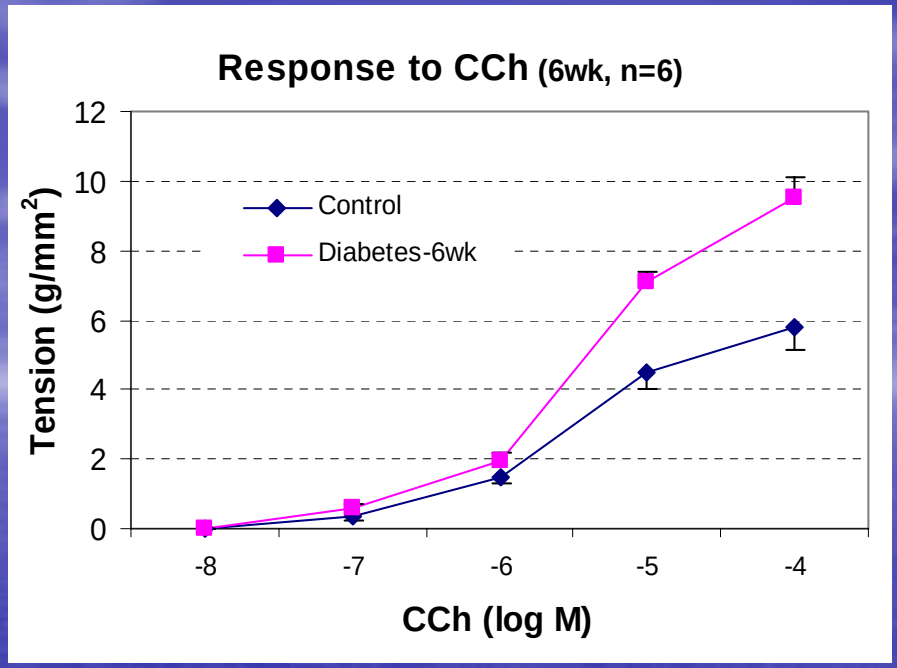

Response to EFS (3wk, n=6)
Tension (g/mm2)
Frequency (Hz)
Control
Diabetes-3wk
0
1
2
3
4
5
6
7
8
9
10
0.5
1
2
4
8
16
32

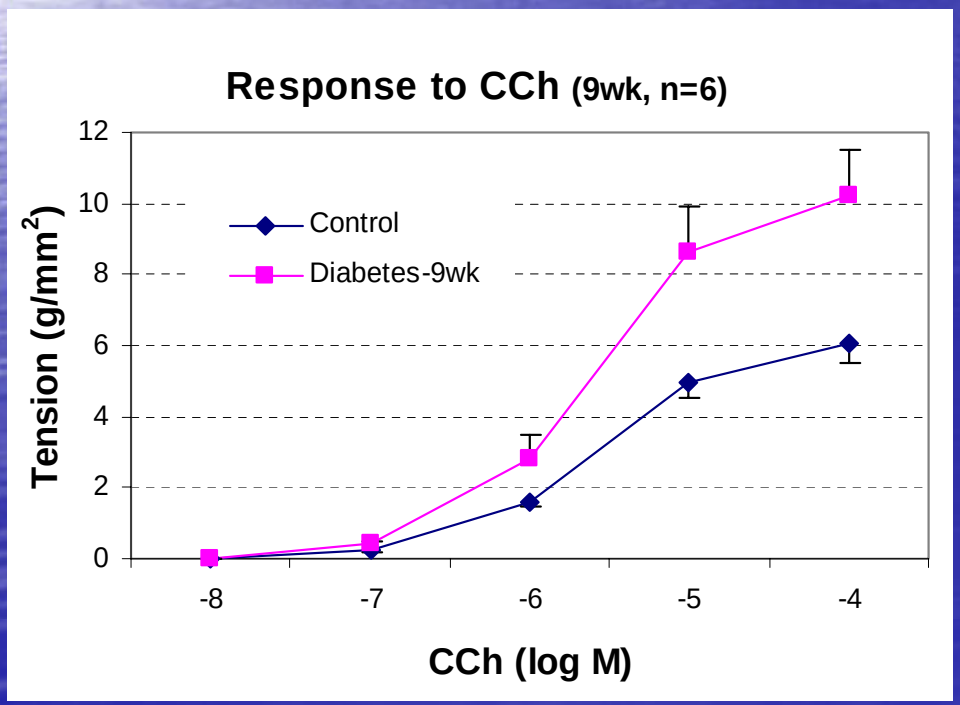

Response to EFS (6wk, n=6)
Tension (g/mm2)
Frequency (Hz)
Control
Diabetes-6wk
0
1
2
3
4
5
6
7
8
9
10
0.5
1
2
4
8
16
32

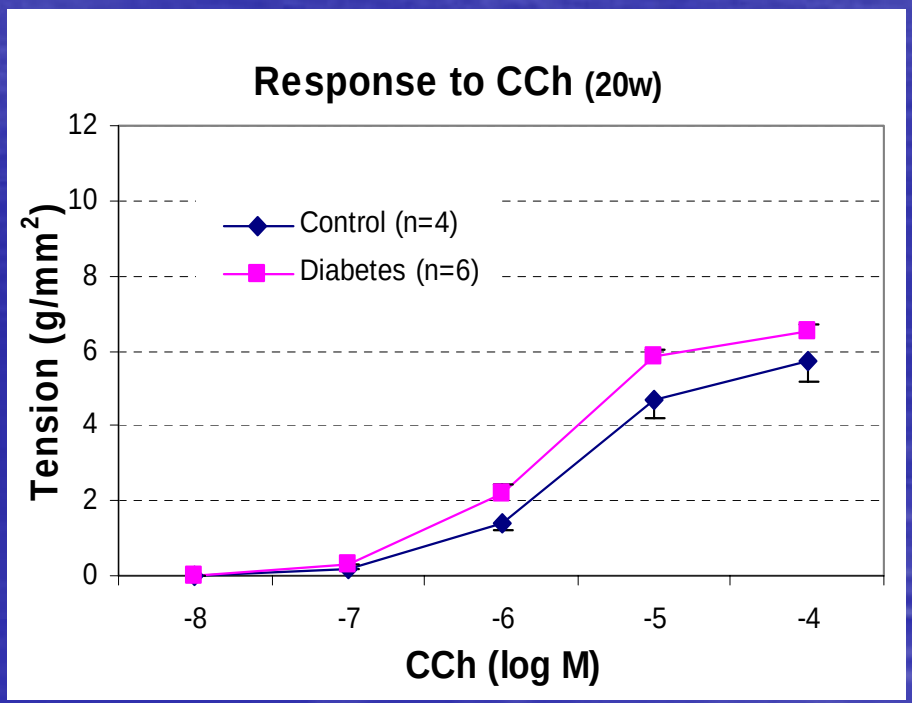

Response to EFS (9wk, n=6)
Tension (g/mm2)
Frequency (Hz)
Control
Diabetes-9wk
0
1
2
3
4
5
6
7
8
9
10
0.5
1
2
4
8
16
32


Response to EFS (20wk)
Tension (g/mm 2)
Frequency (Hz)
Control (n=4)
Diabetes (n=6)
0
1
2
3
4
5
6
7
8
9
10
0.5
1
2
4
8
16
32

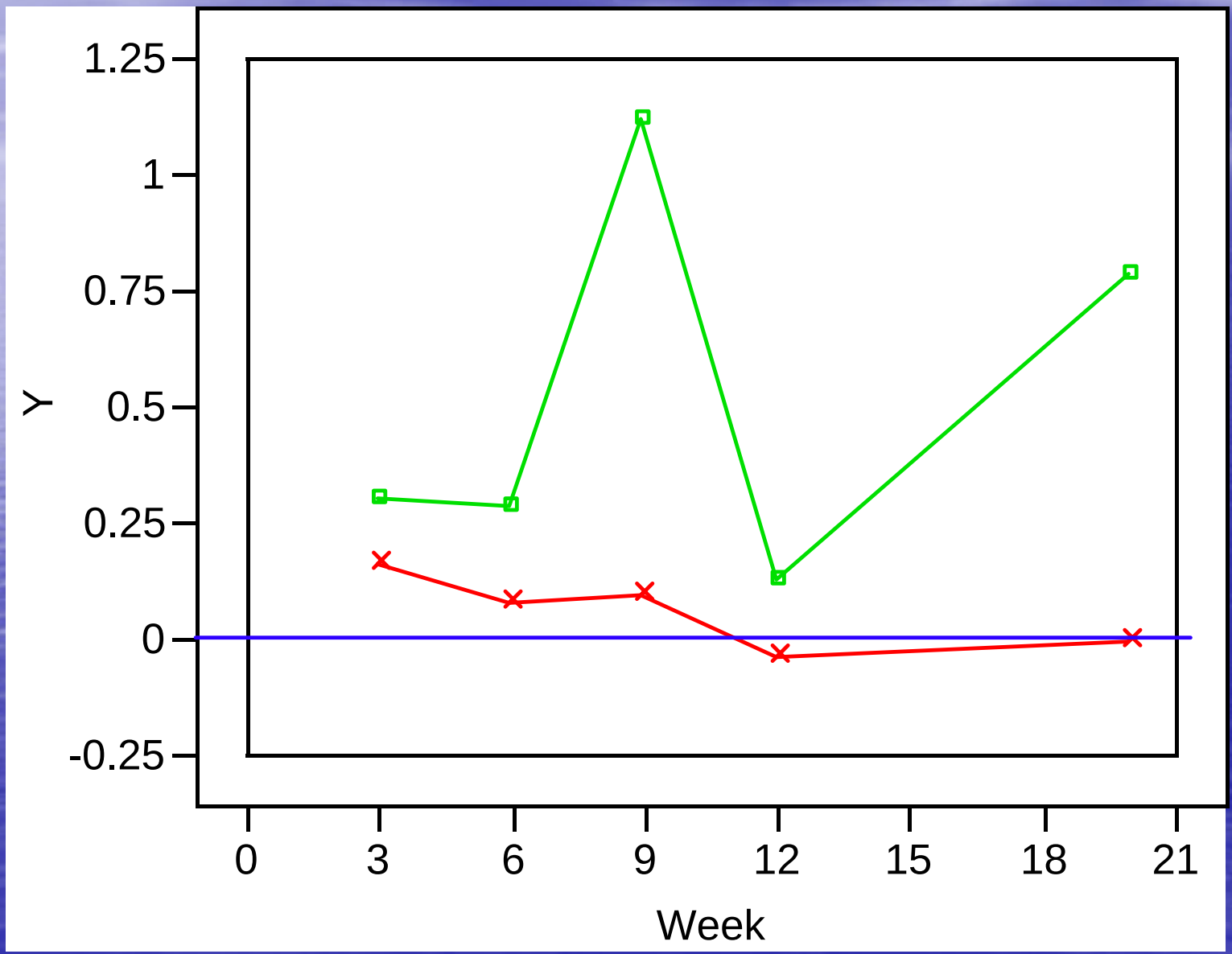

Response to CCH (3wk, n=6)
Tension (g/mm2)
12
10
8
6
4
2
0
Control
Diabetes-3wk
-8
-7
-6
-5
-4
CCh (log M)

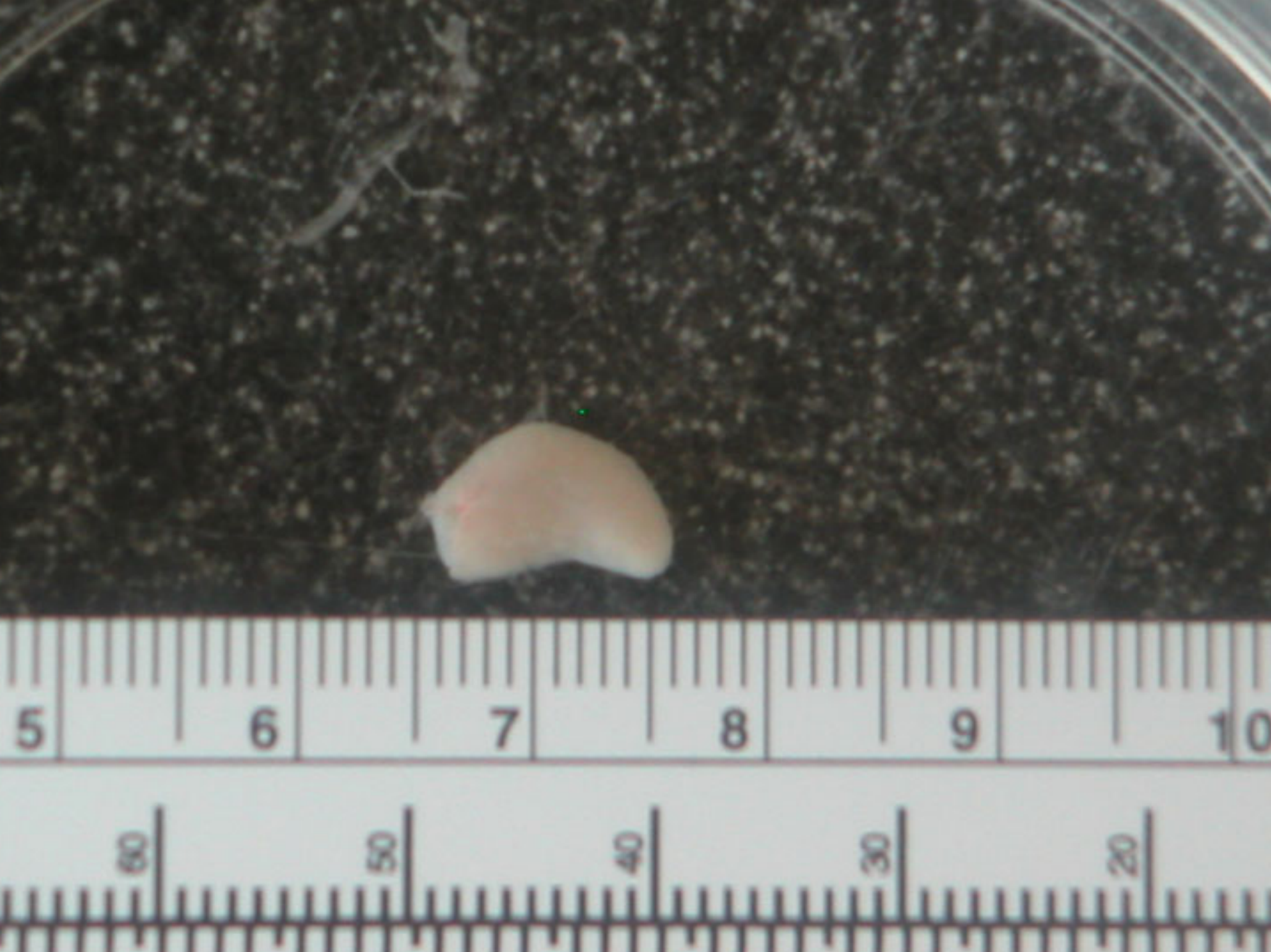

Response to CCh (6wk, n=6)
Tension (g/mm2)
12
10
8
6
4
2
0
Control
Diabetes-6wk
-8
-7
-6
-5
-4
CCh (log M)


Response to CCh (9wk, n=6)
Tension (g/mm2)
12
10
8
6
4
2
0
Control
Diabetes-9wk
-8
-7
-6
-5
-4
CCh (log M)

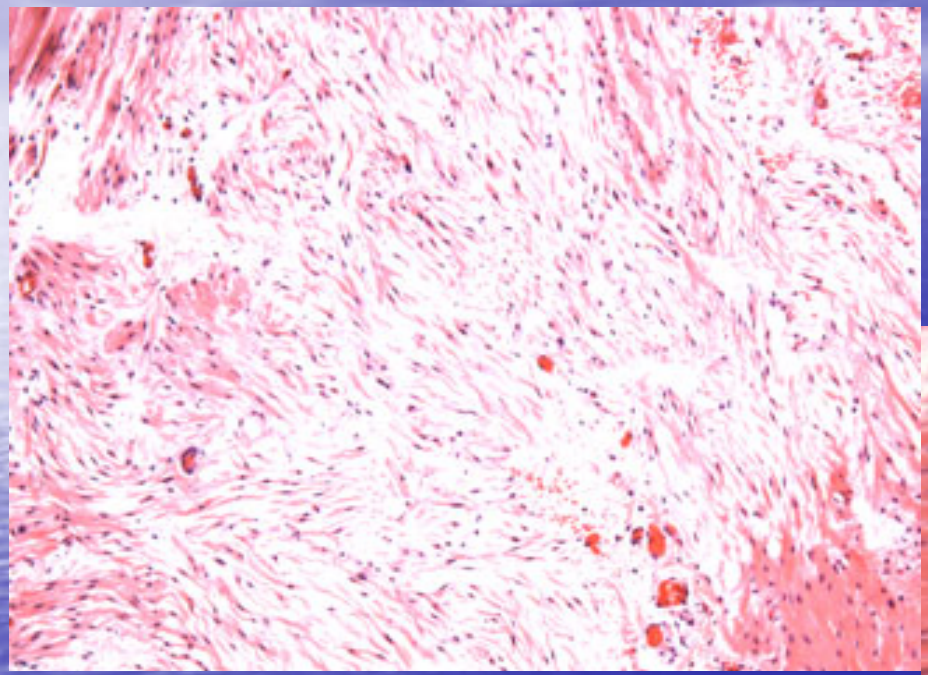

Response to CCh (20w)
Tension (g/mm2)
12
10
8
6
4
2
0
Control (n=4)
Diabetes (n=6)
-8
-7
-6
-5
-4
CCh (log M)

Log DM to Control ED50 and R_{max} Ratios vs. Age

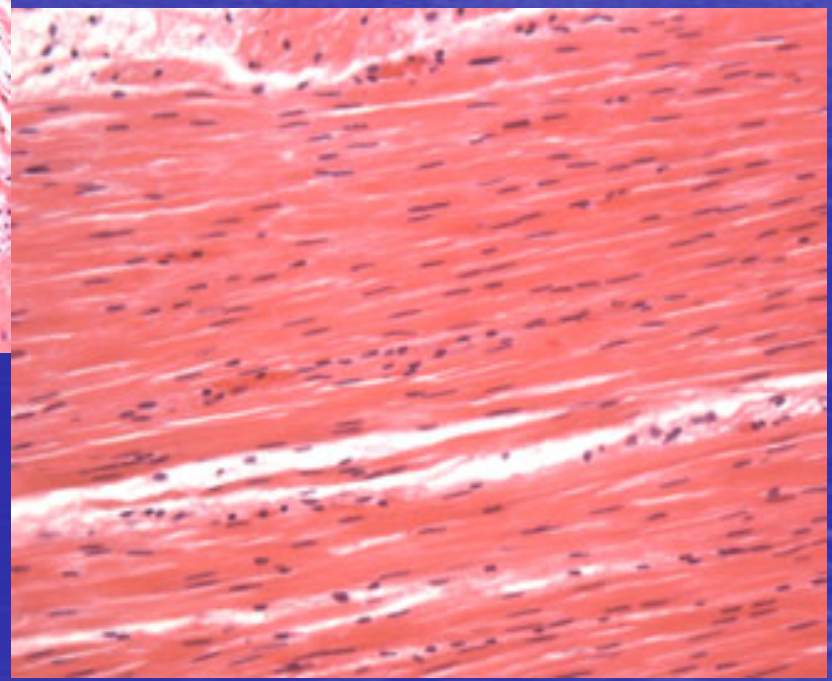



5
6
7
8
9
10
60
50
40
30
20

Gross Changes in Diabetic Bladder

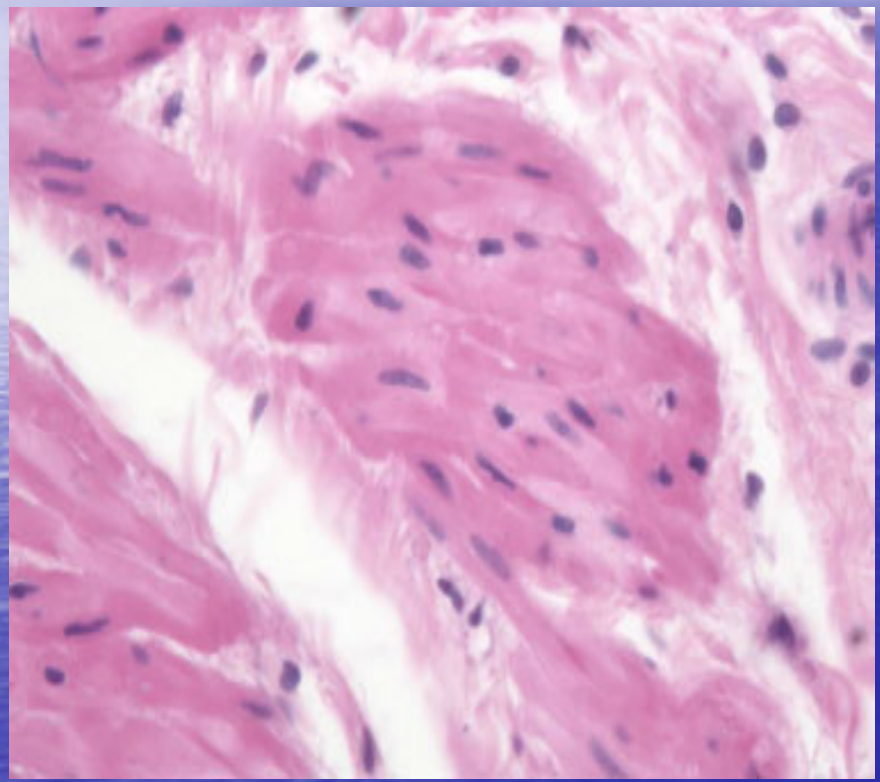


Diabetic

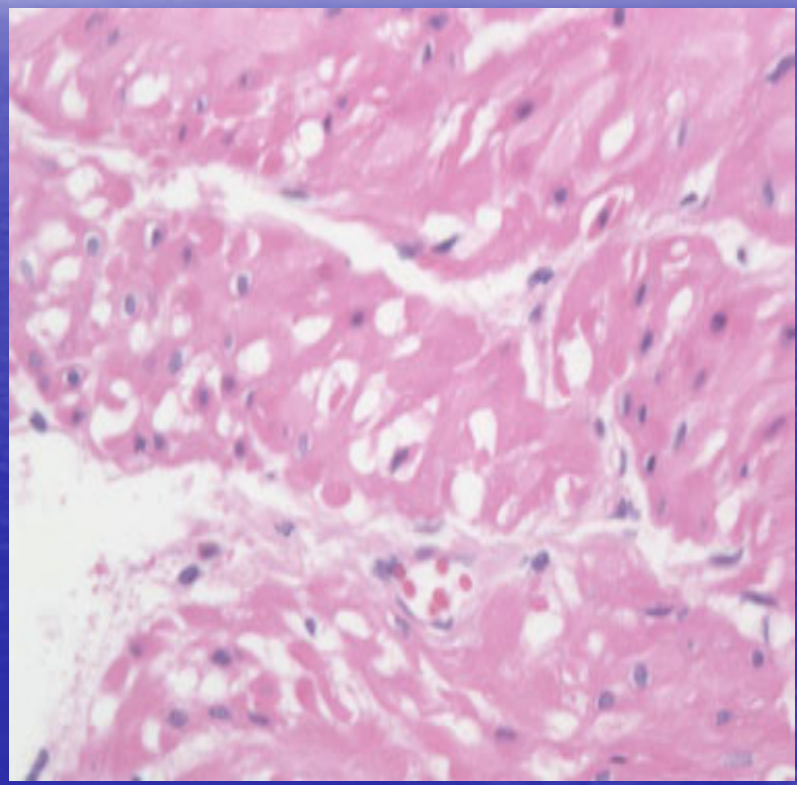


Normal

Cytoplasmic Vacuoles in Muscularis Propria (40X)

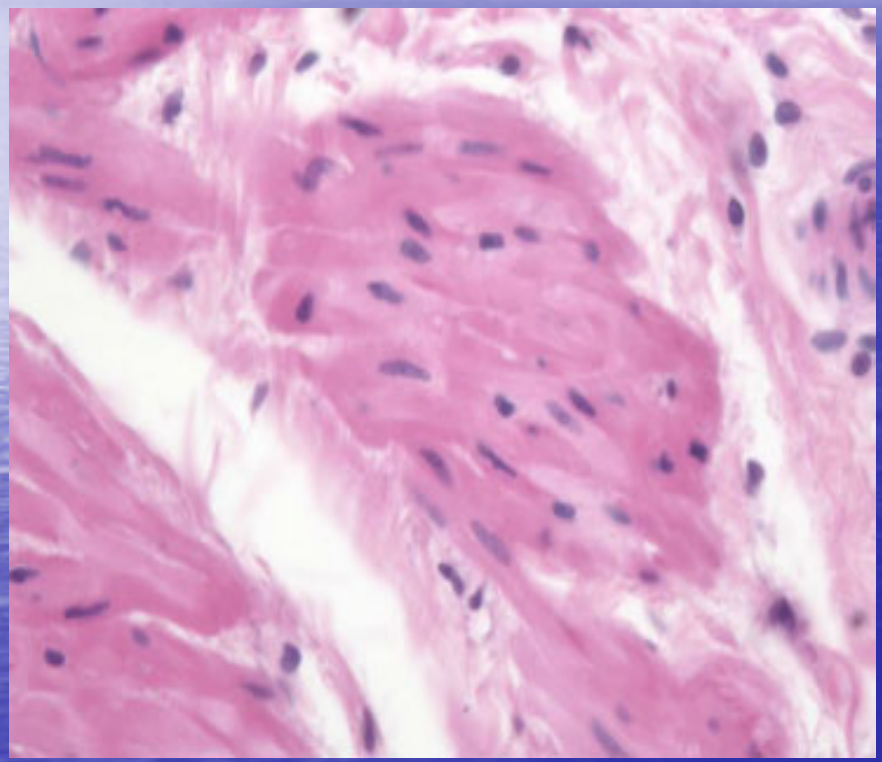


Normal

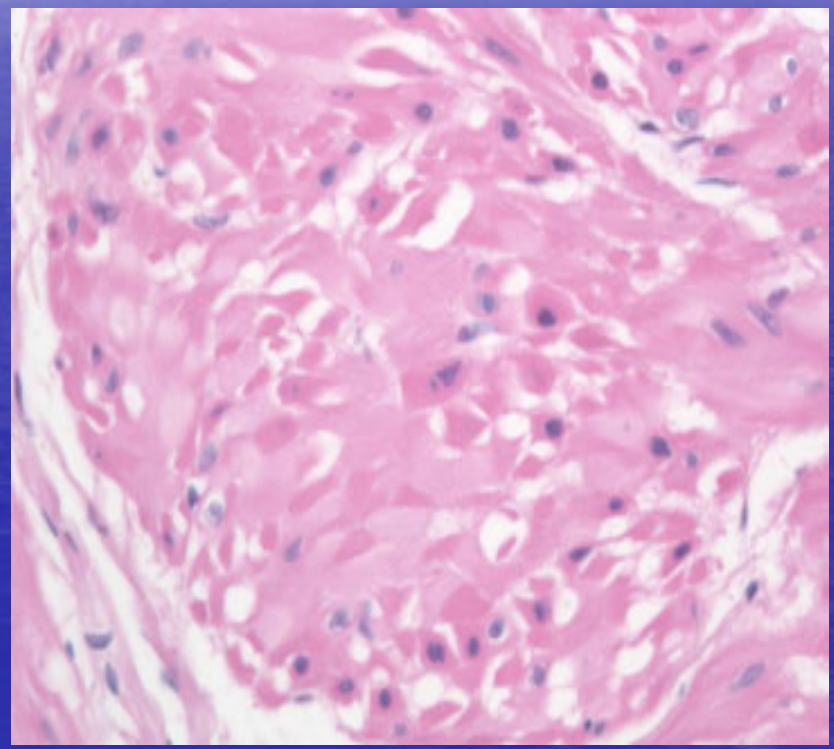


12-week Diabetic

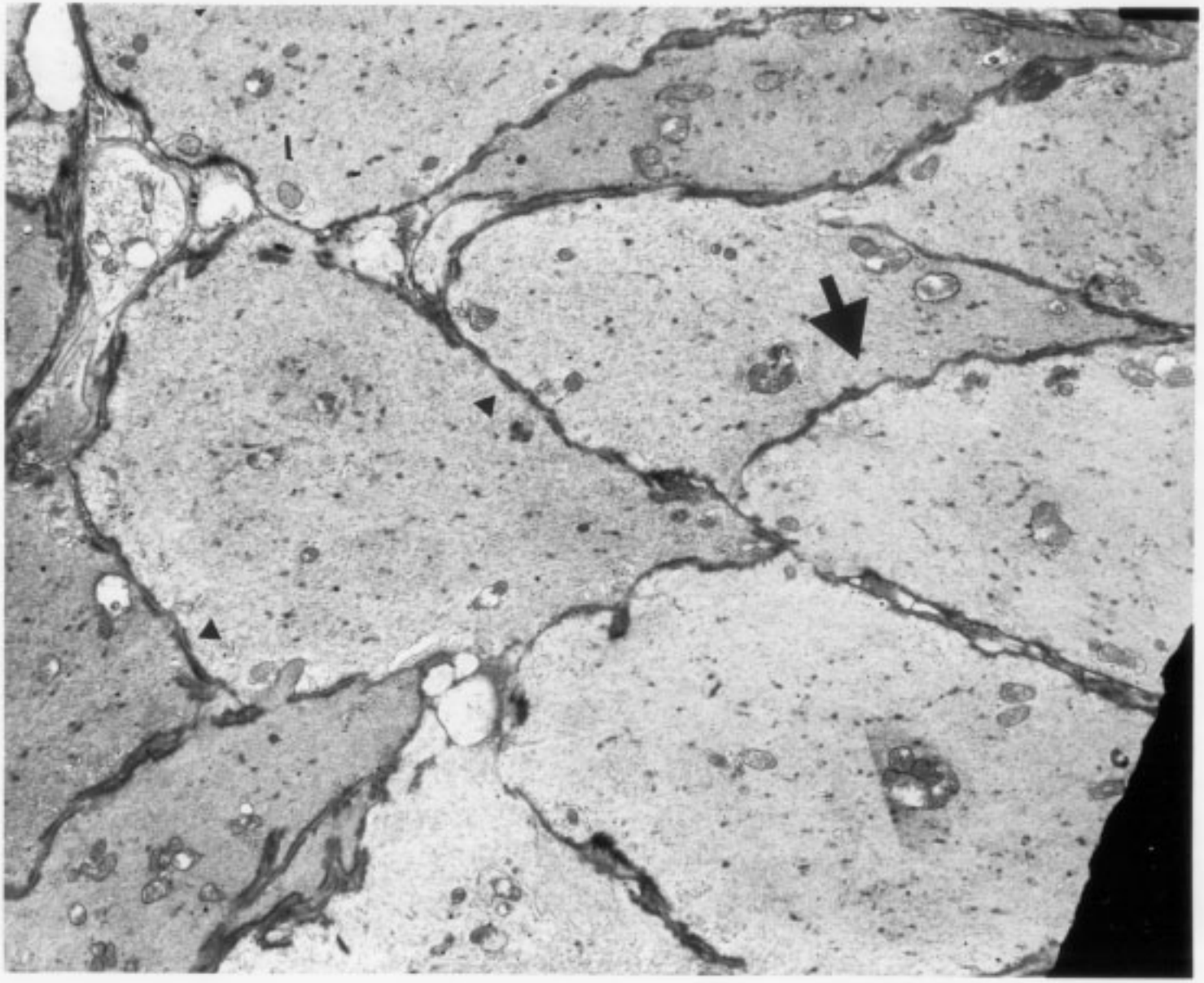
Cytoplasmic Hyaline Globules in Muscularis Propria (40X)

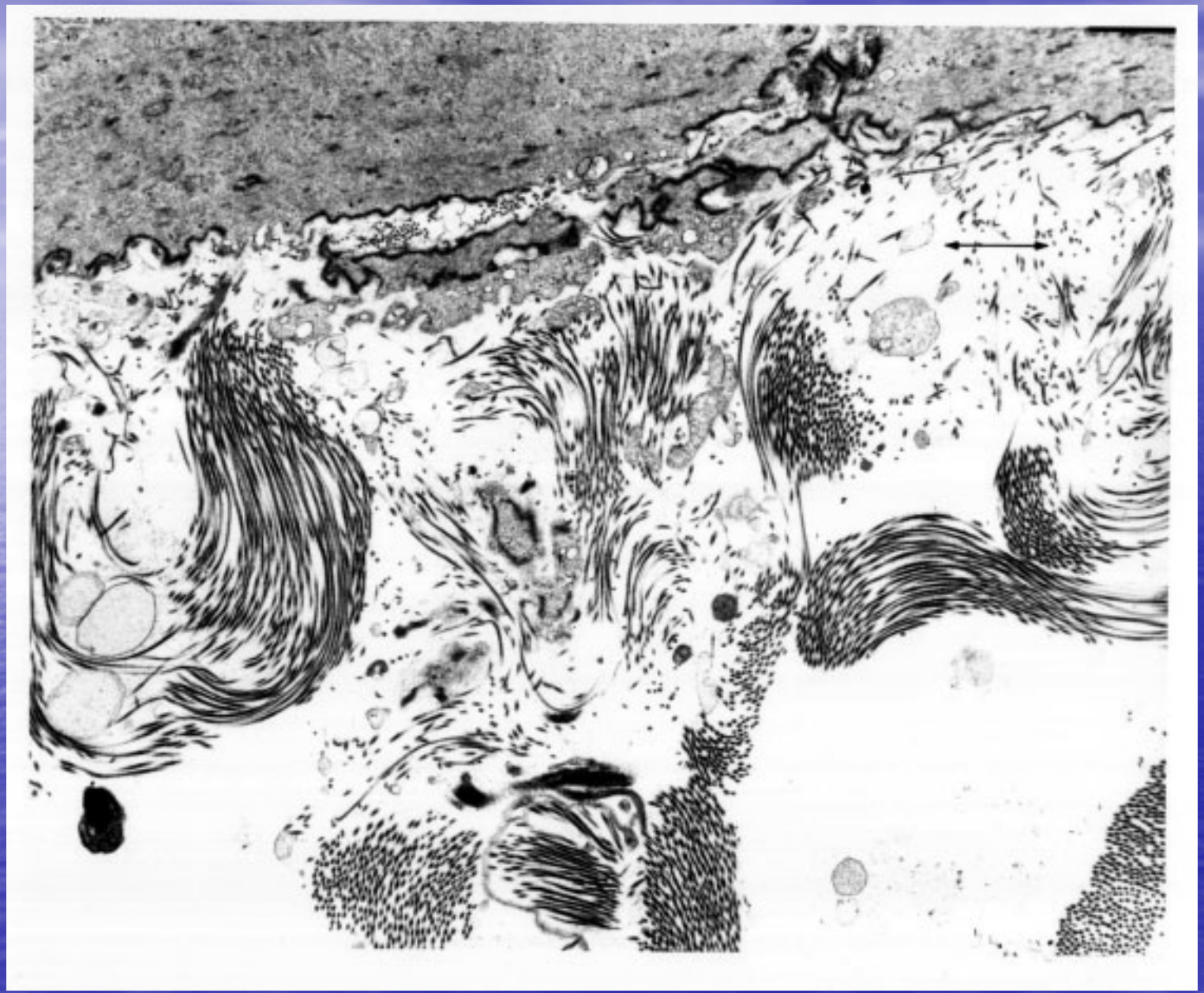


Normal



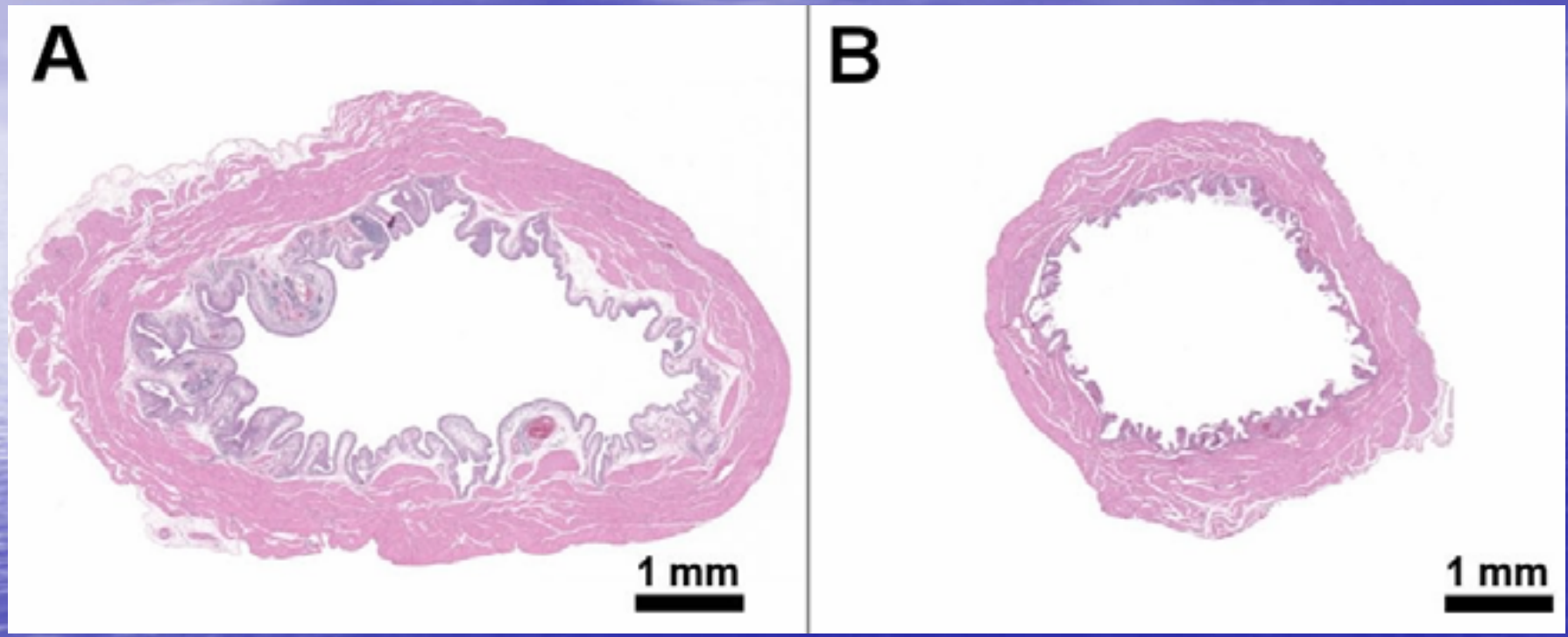
12-week Diabetic





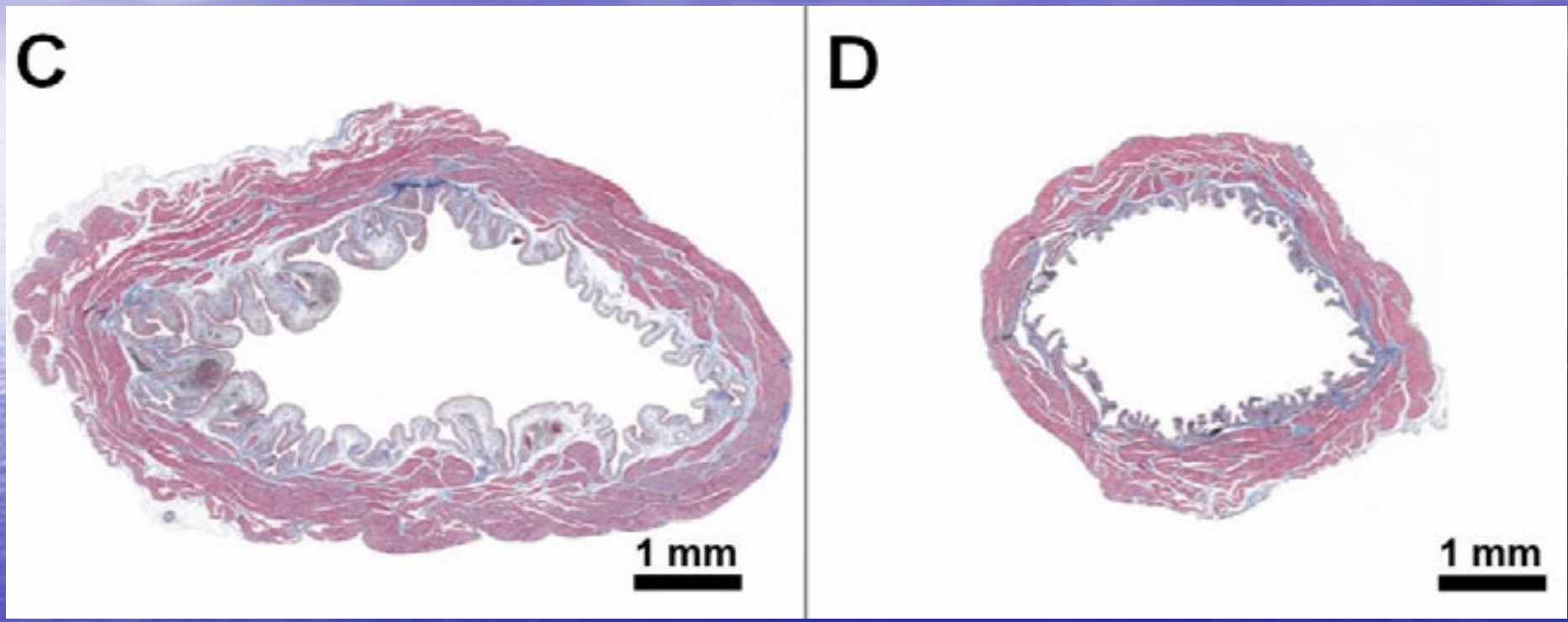
In-Vitro Assays- Morphometric Alterations

Bladder Enlargement



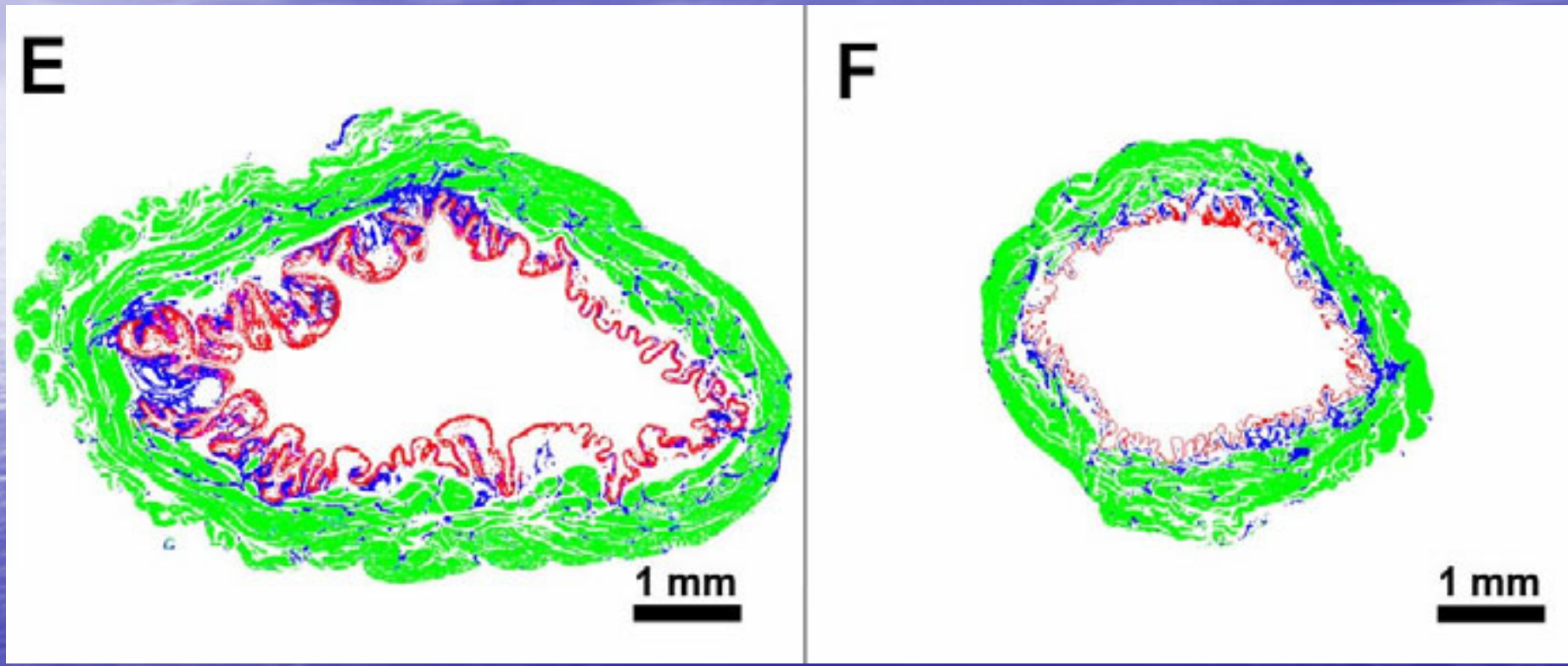
In-Vitro Assays- Morphometric Alterations

Bladder Enlargement

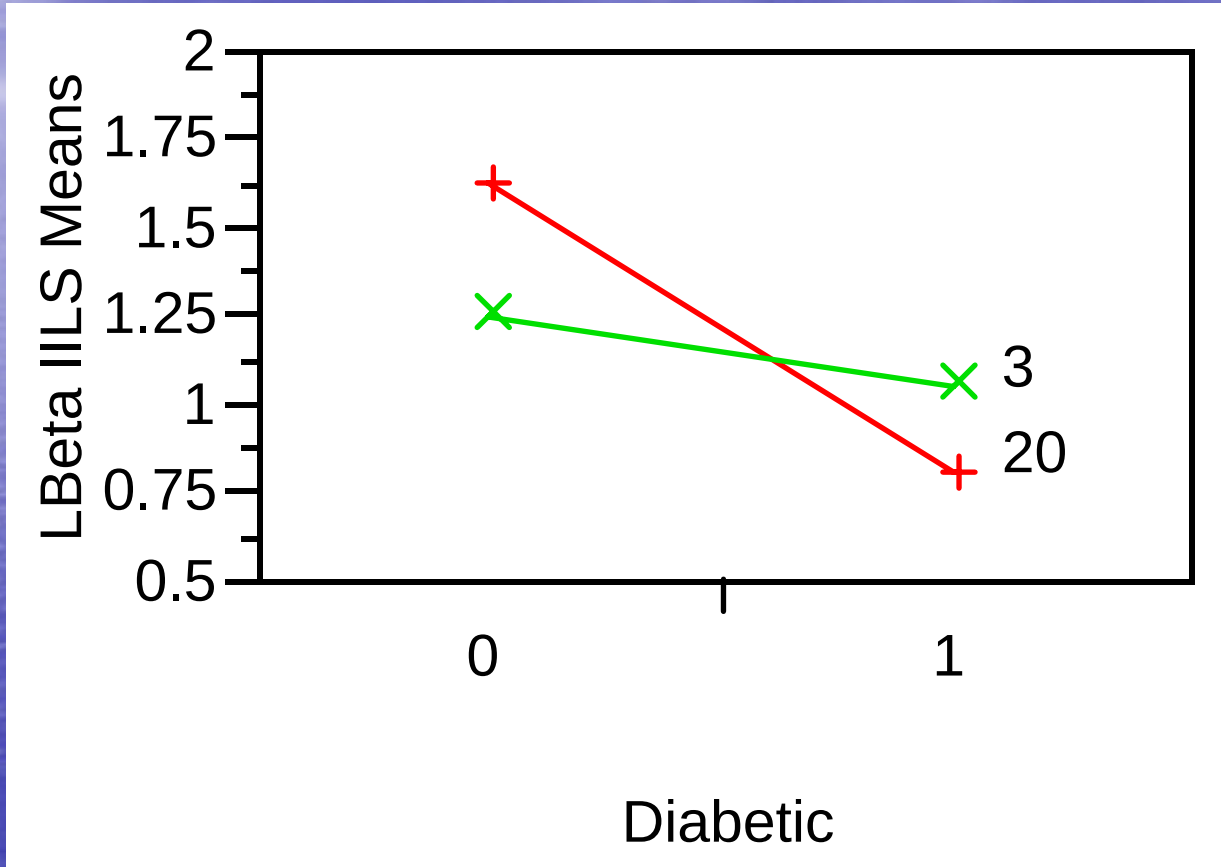


In-Vitro Assays- Morphometric Alterations

Bladder Enlargement



PKC βII: Adjusted Effects of Age and DM (Natural Log Scale)



Time Course of DBD in C57Bl/6

Groups

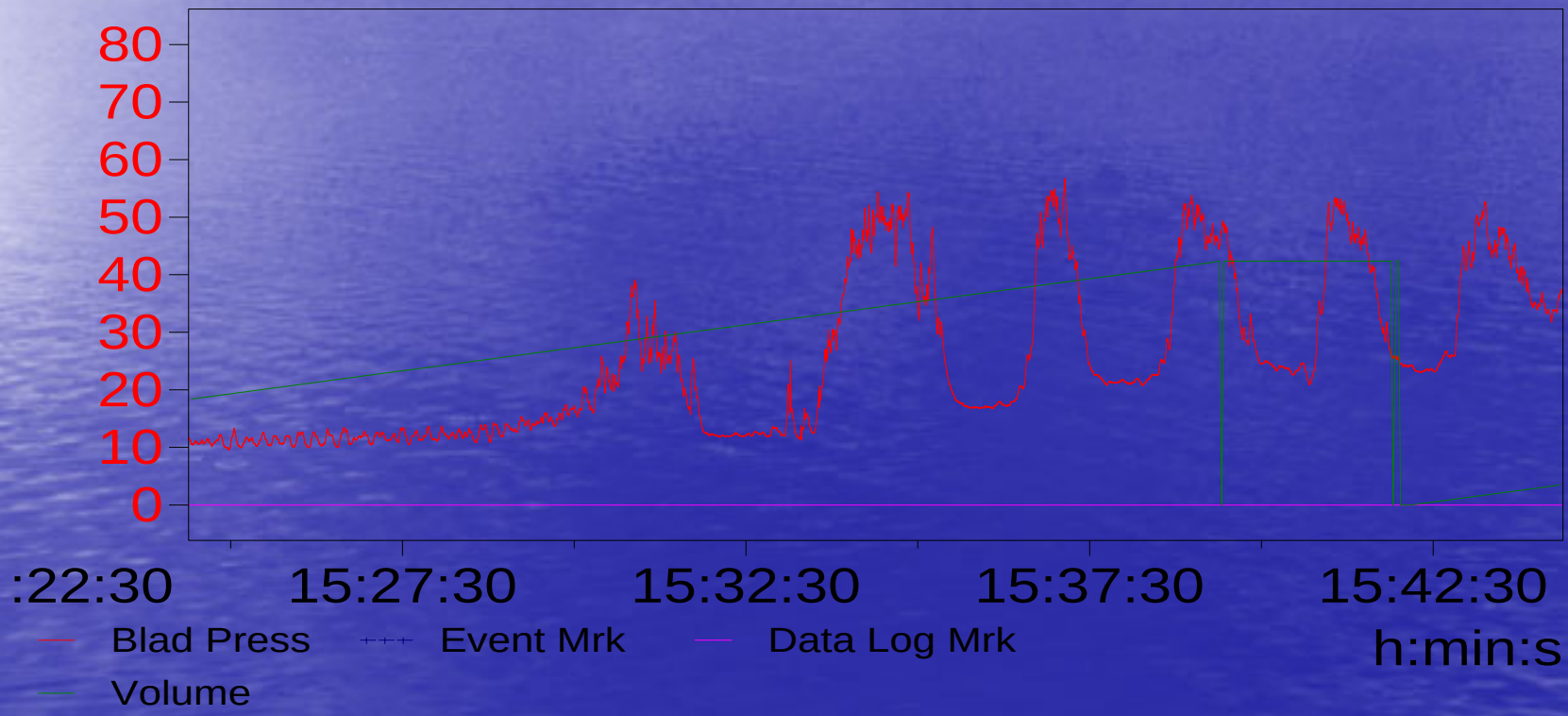
- DM-untreated
- DM-treated
- Diuretic
- Controls

Time points

- 3 weeks
- 9 weeks
- 12 week
- 20 weeks

Time Course of DBD in C57BL/6

Conscious Cystometrogram



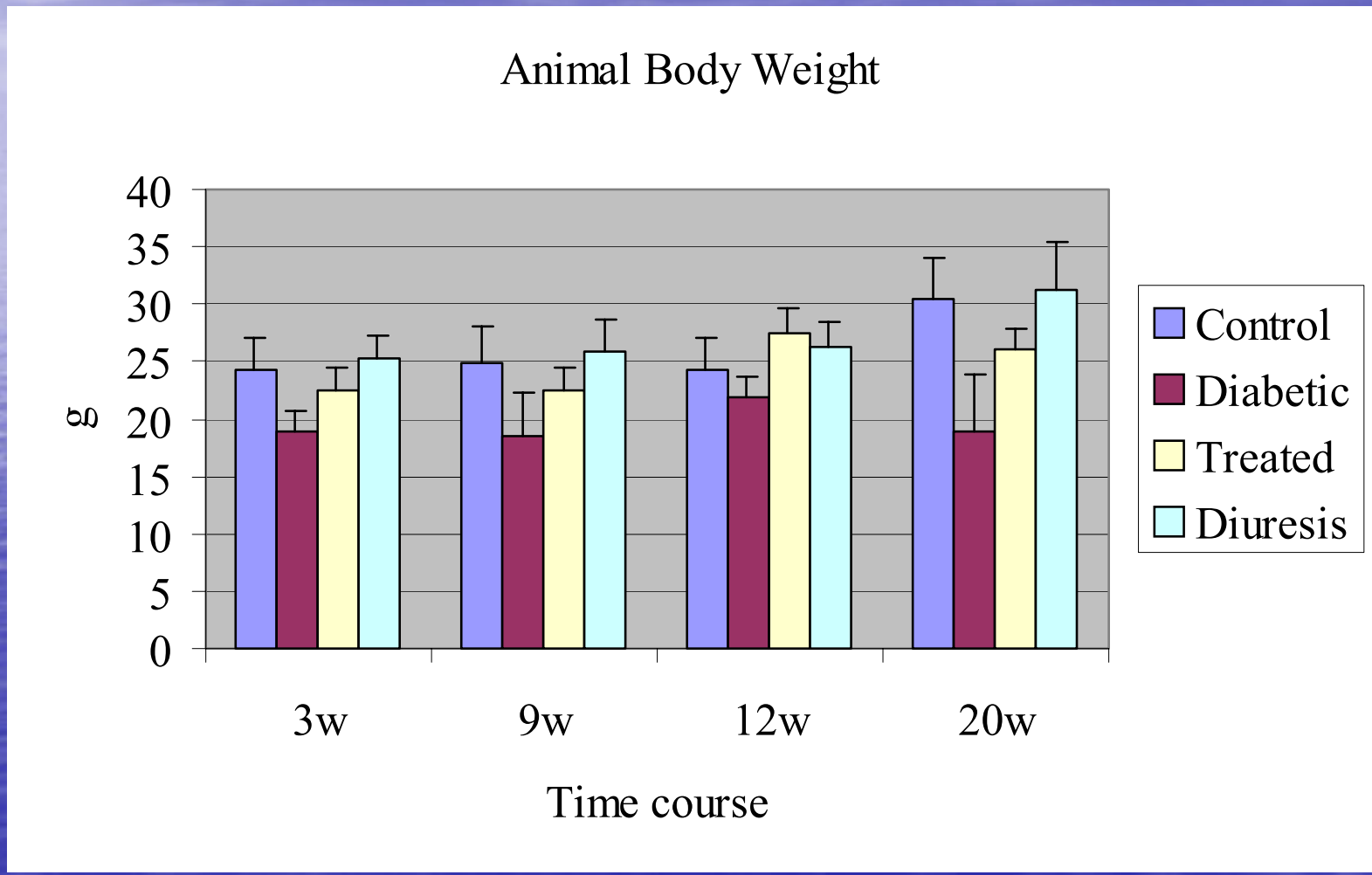
Time Course of DBD in C57BL/6

Blood Glucose

Bladder Glucose (mg/dl)	3-week	9-week	12-week	20-week
Control	107±18.2	118±21.7	106±16.3	110±13.9
Diabetic	356±26.5*	582±44.5*	523±57.9*	591±26.2*
Diabetic Treated	224±17.1*	215±21.0*	293±23.1*	312±30.3*
Diuretic	105±11.4	101±27.3	109±12.5	116±19.2

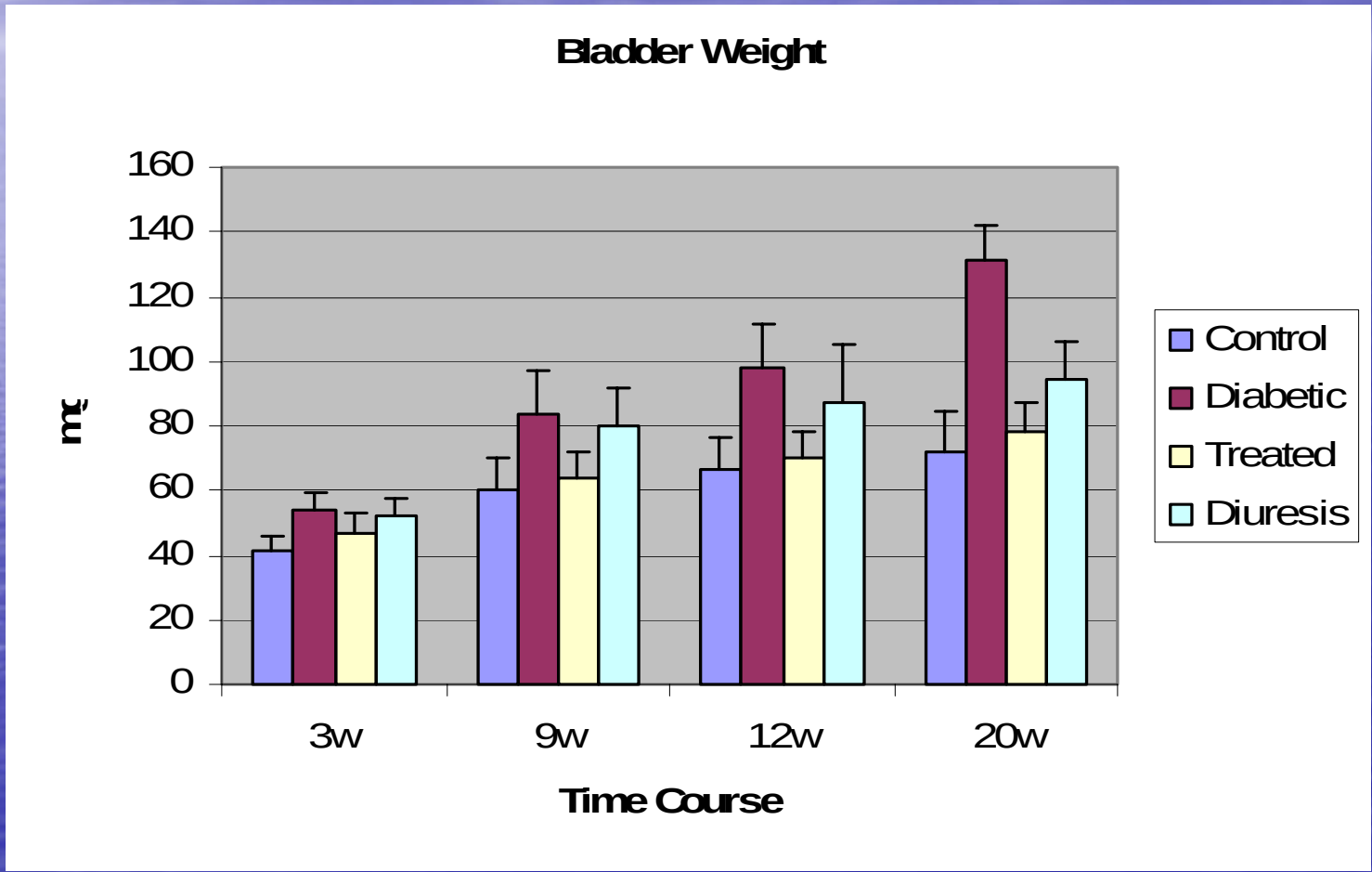
Time Course of DBD in C57BL/6

Body weight



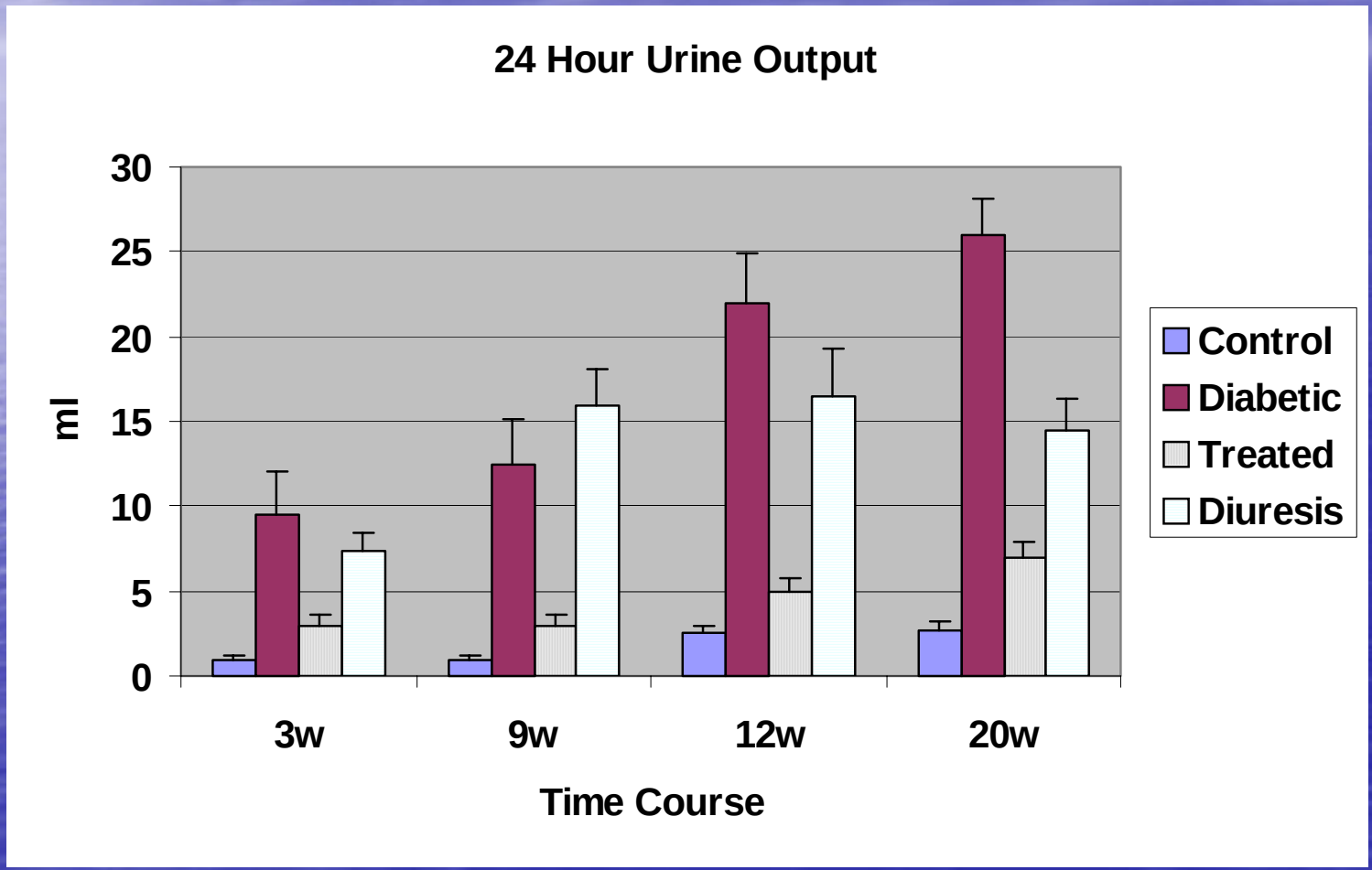
Time Course of DBD in C57BL/6

Bladder Weight



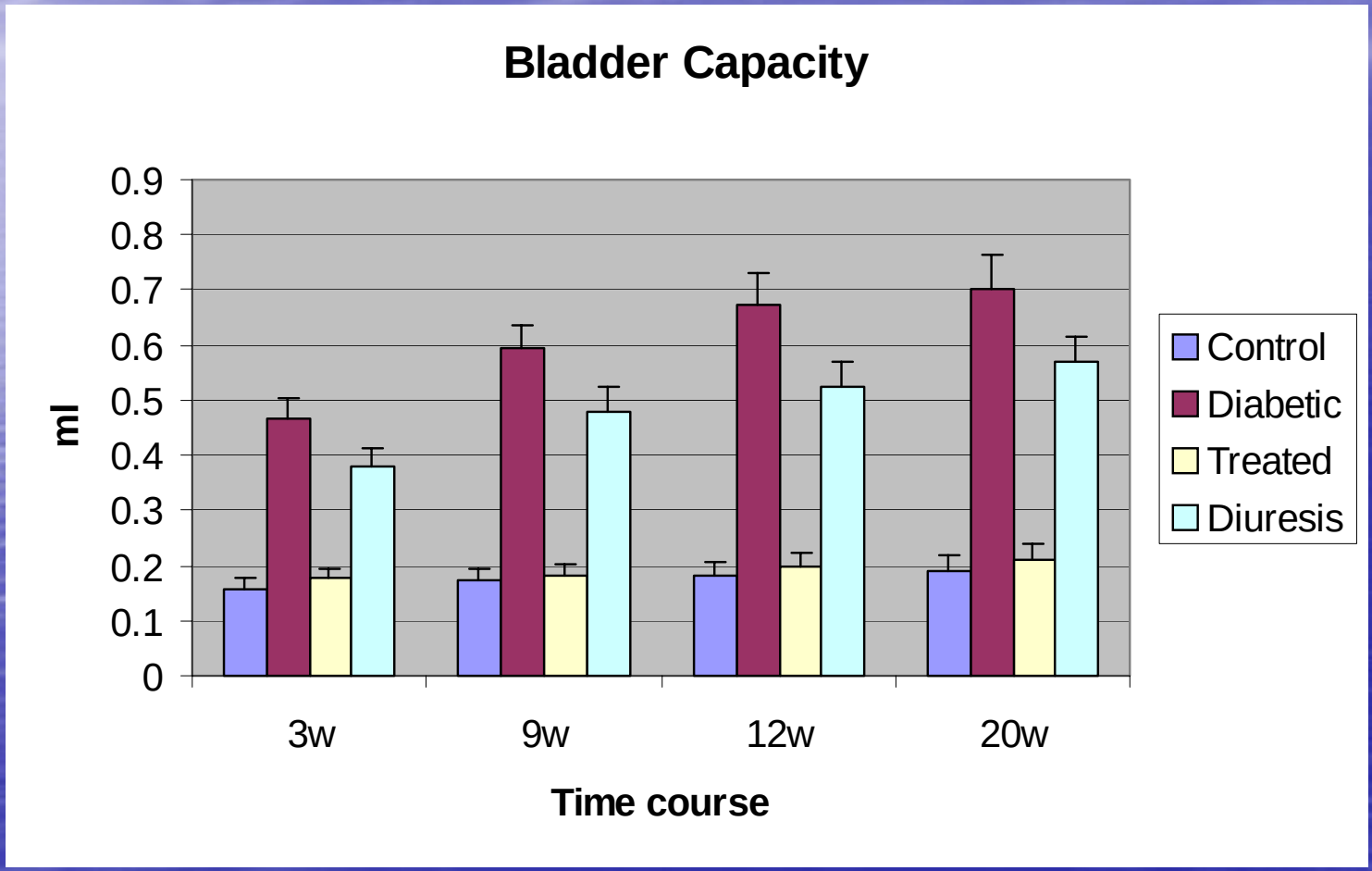
Time Course of DBD in C57BL/6

24 Urine Output



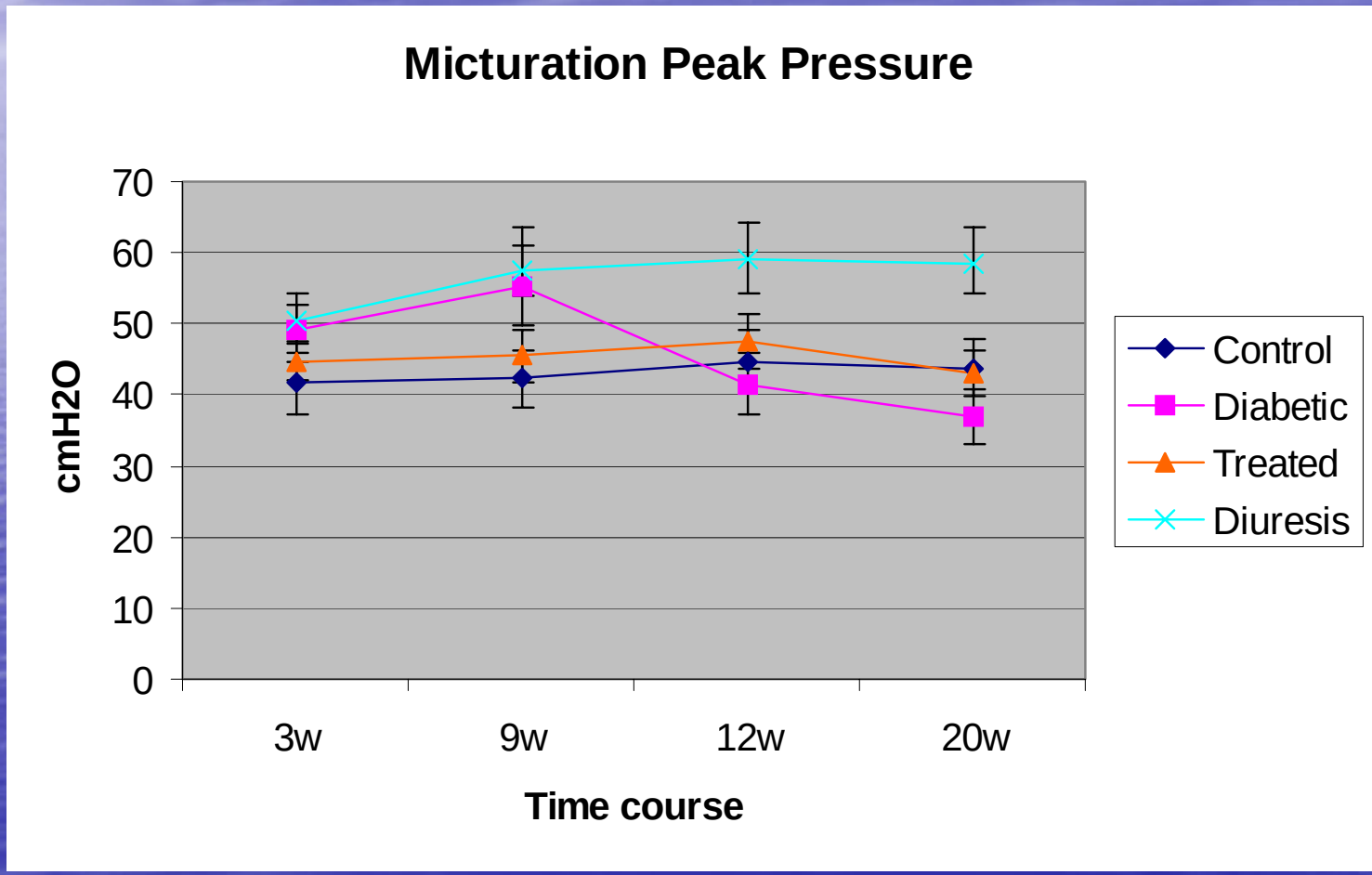
Time Course of DBD in C57BL/6

Bladder Capacity



Time Course of DBD in C57BL/6

Voiding Pressure



Time Course of DBD in C57Bl

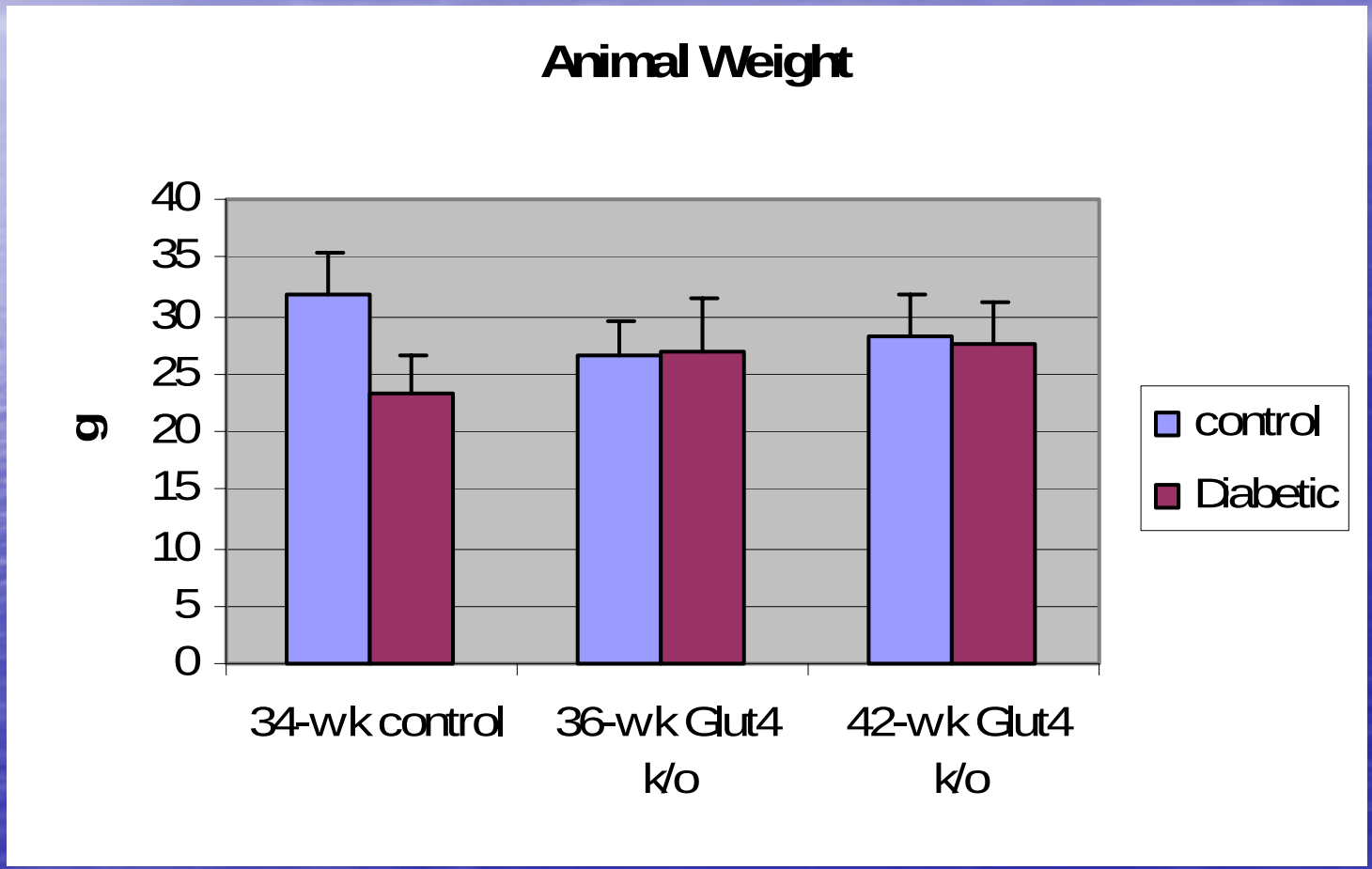
Conclusions

- DBD is different from Diuretic induced dysfunction
- Transition of bladder from hyperactive to hypoactive status between 9-12 weeks post STZ-induced DM

AMDCC Collaborative studies

Total Body Glut4/ko-C57Bl/6- University of MI

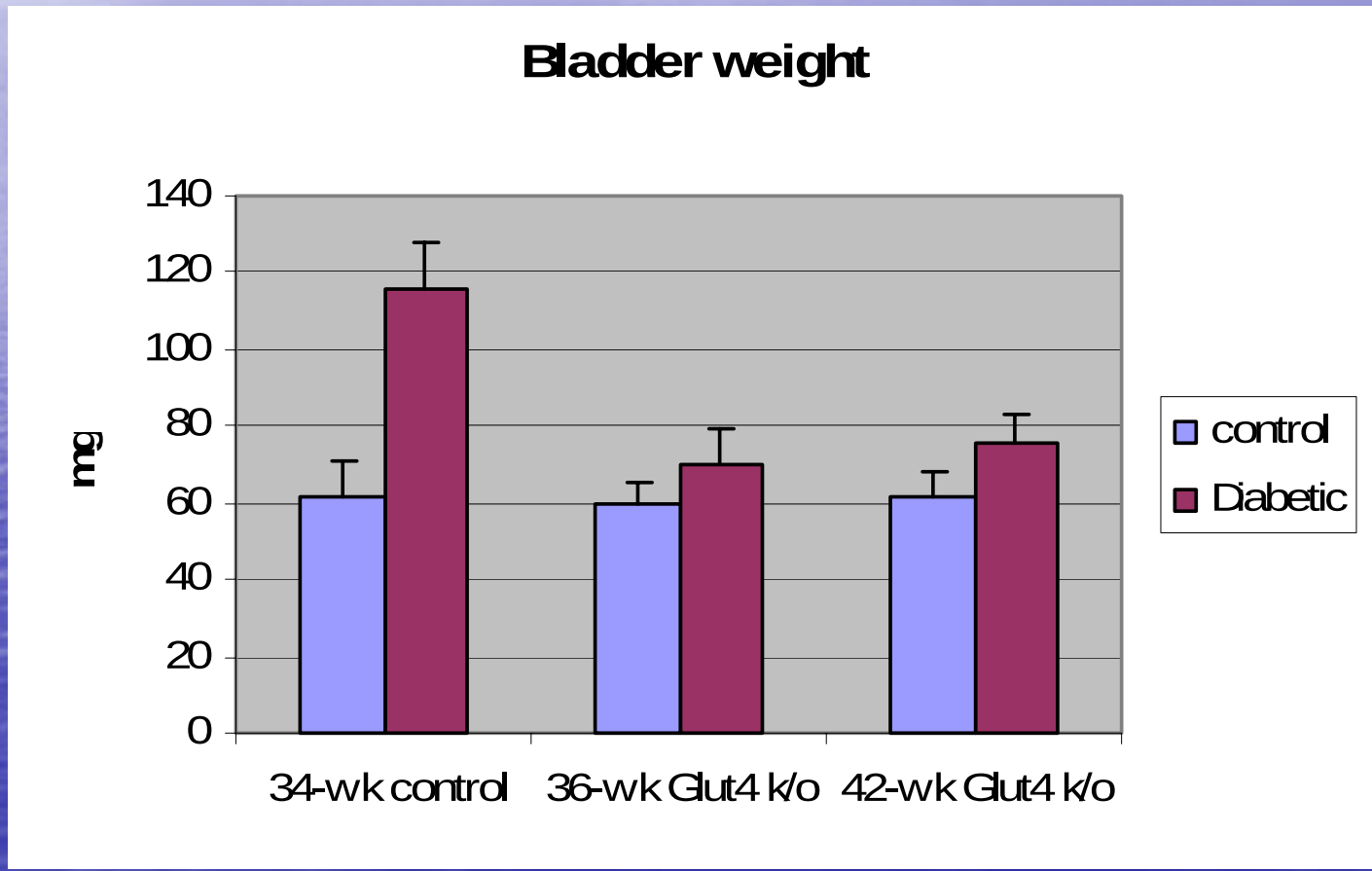
Animal weight



AMDCC Collaborative studies

Total Body Glut4/ko-C57Bl/6- University of MI

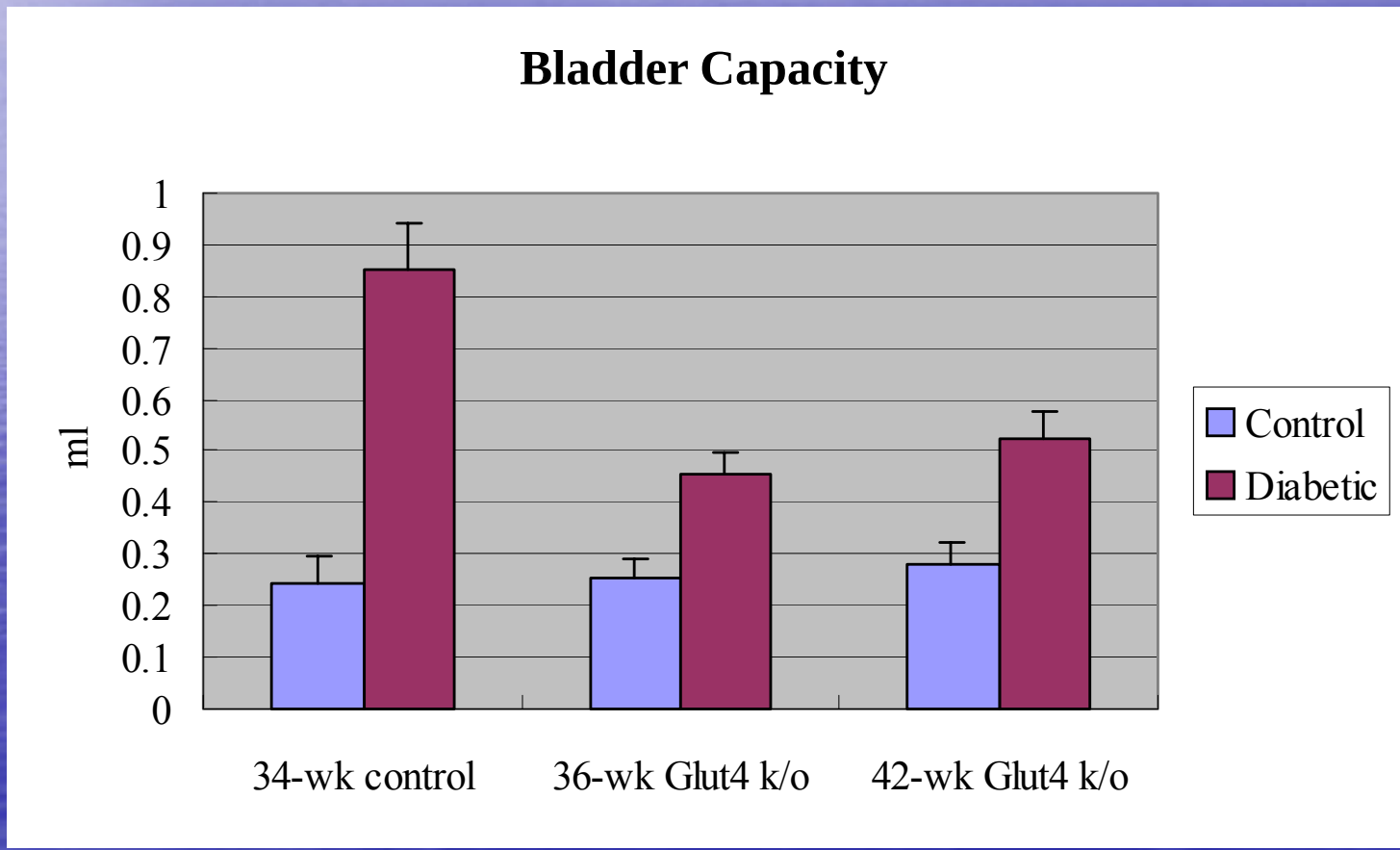
Bladder weight



AMDCC Collaborative studies

Total Body Glut4/ko-C57Bl/6- University of MI

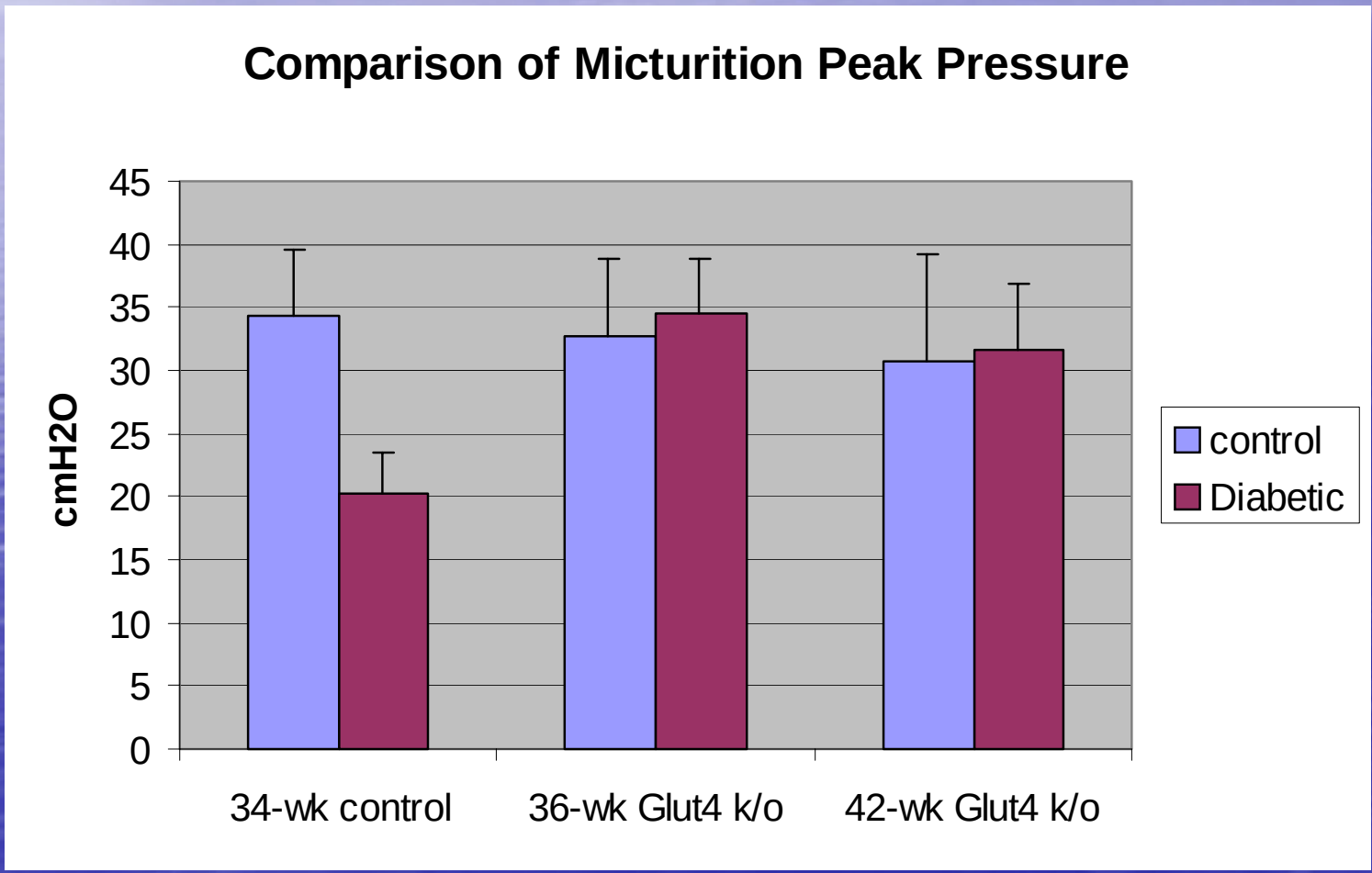
Bladder Capacity

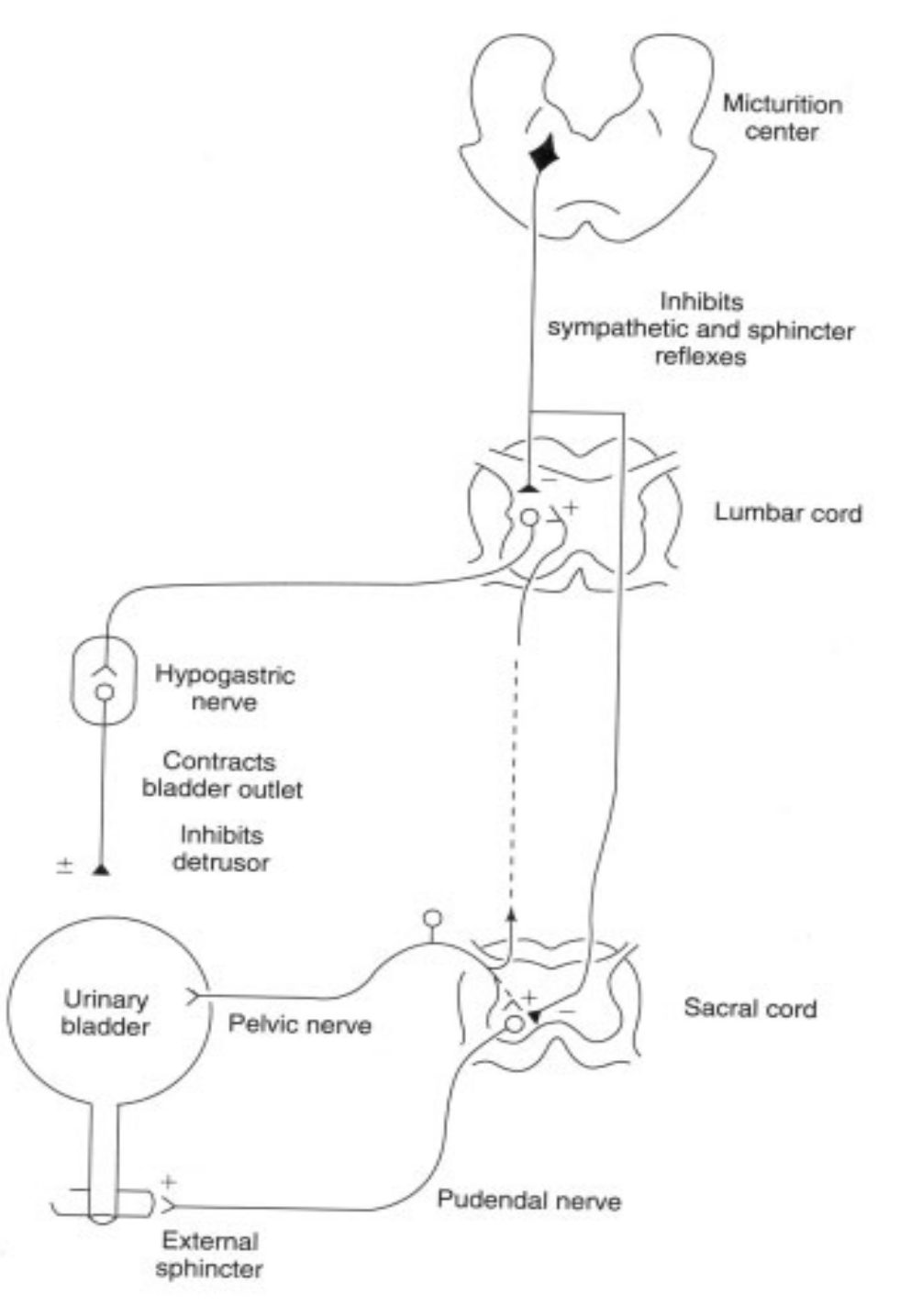


AMDCC Collaborative studies

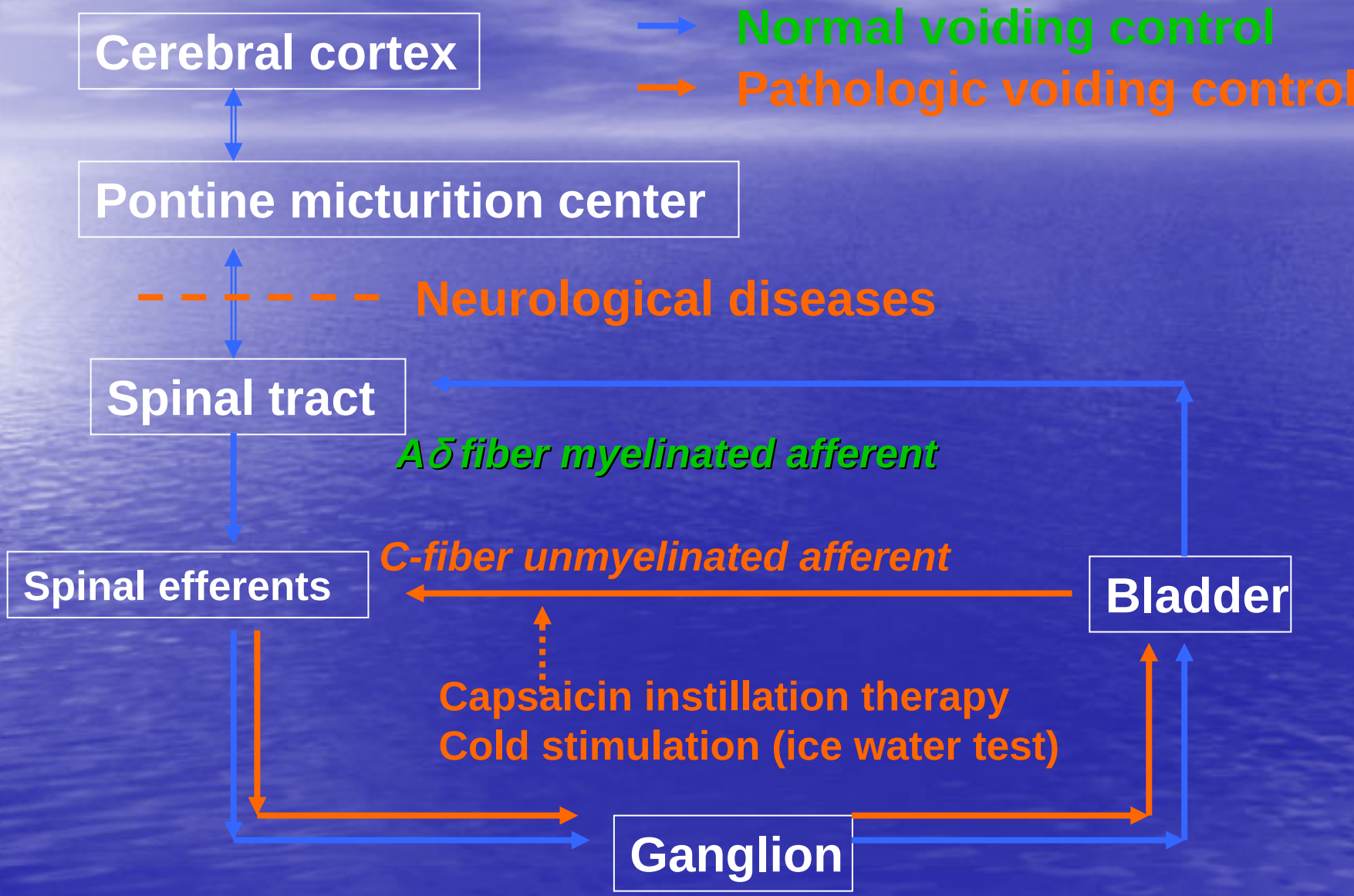
Total Body Glut4/ko-C57Bl/6- University of MI

Voiding Pressure




Micturition center
Inhibits sympathetic and sphincter reflexes
Lumbar cord
Hypogastric nerve
Contracts bladder outlet
Inhibits detrusor
Urinary bladder
Pelvic nerve
Sacral cord
Pudendal nerve
External sphincter

Autonomic Nervous System of the Lower Urinary Tract

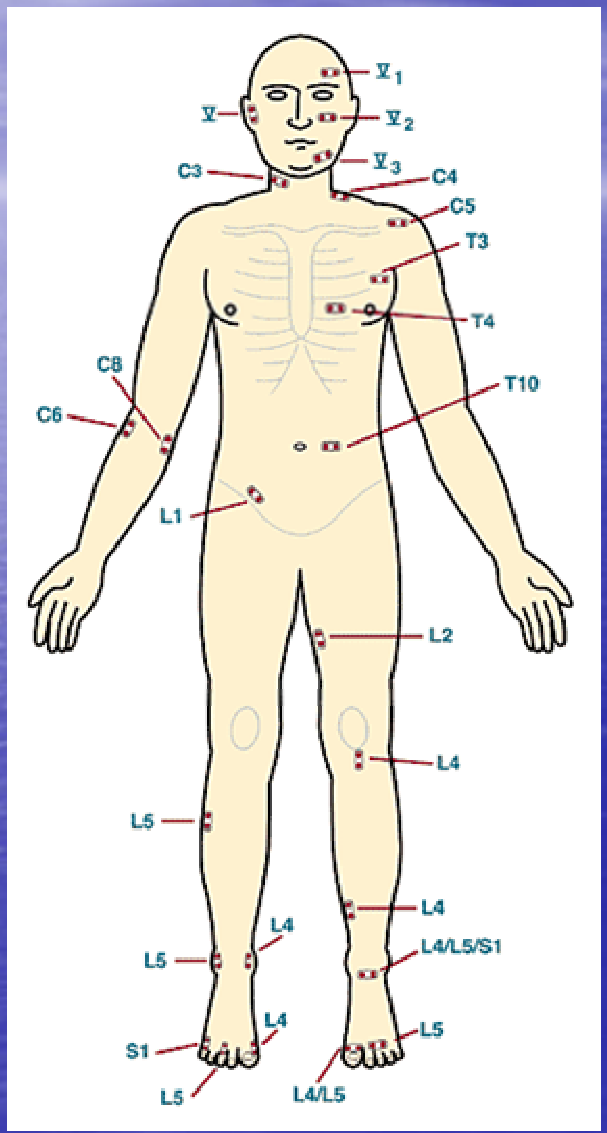


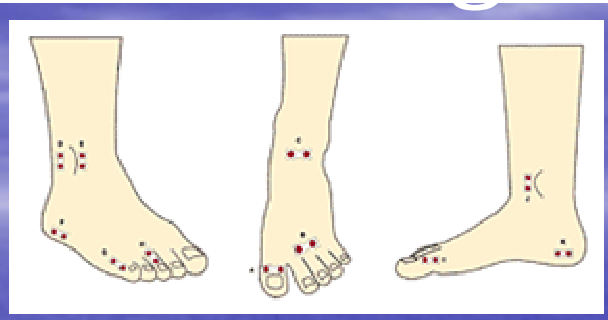
Assessment of the Bladder Sensation

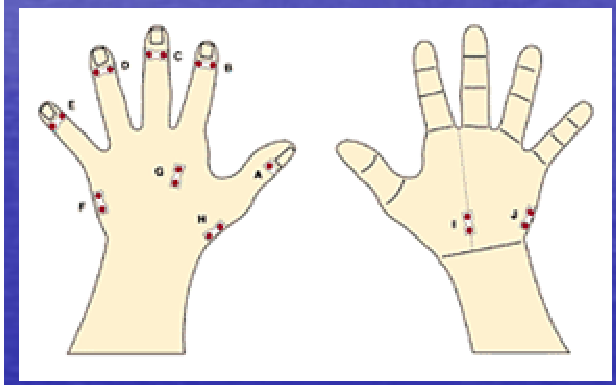
- Targeted Afferent autonomic fibers:
  - C –fibers
  - Aδ fibers

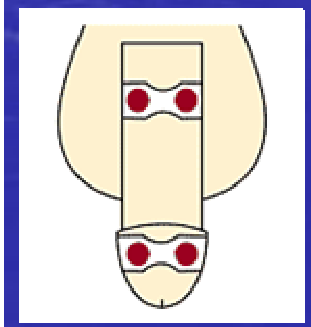

NEUROMETER® CPT/C

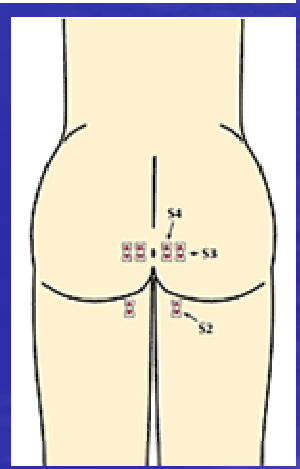
Neurometer skin testing site



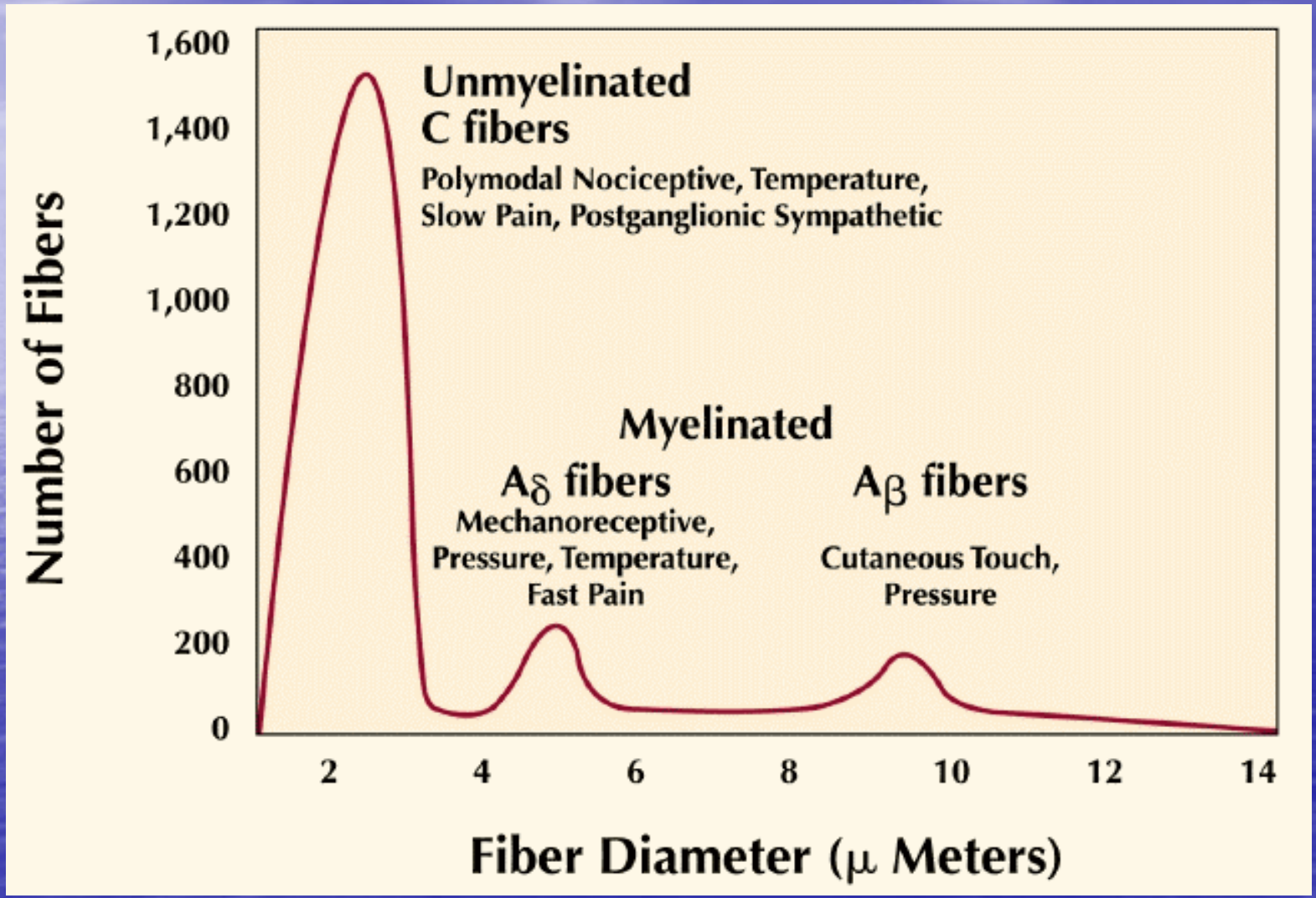








Sensory nerve fiber composition chart

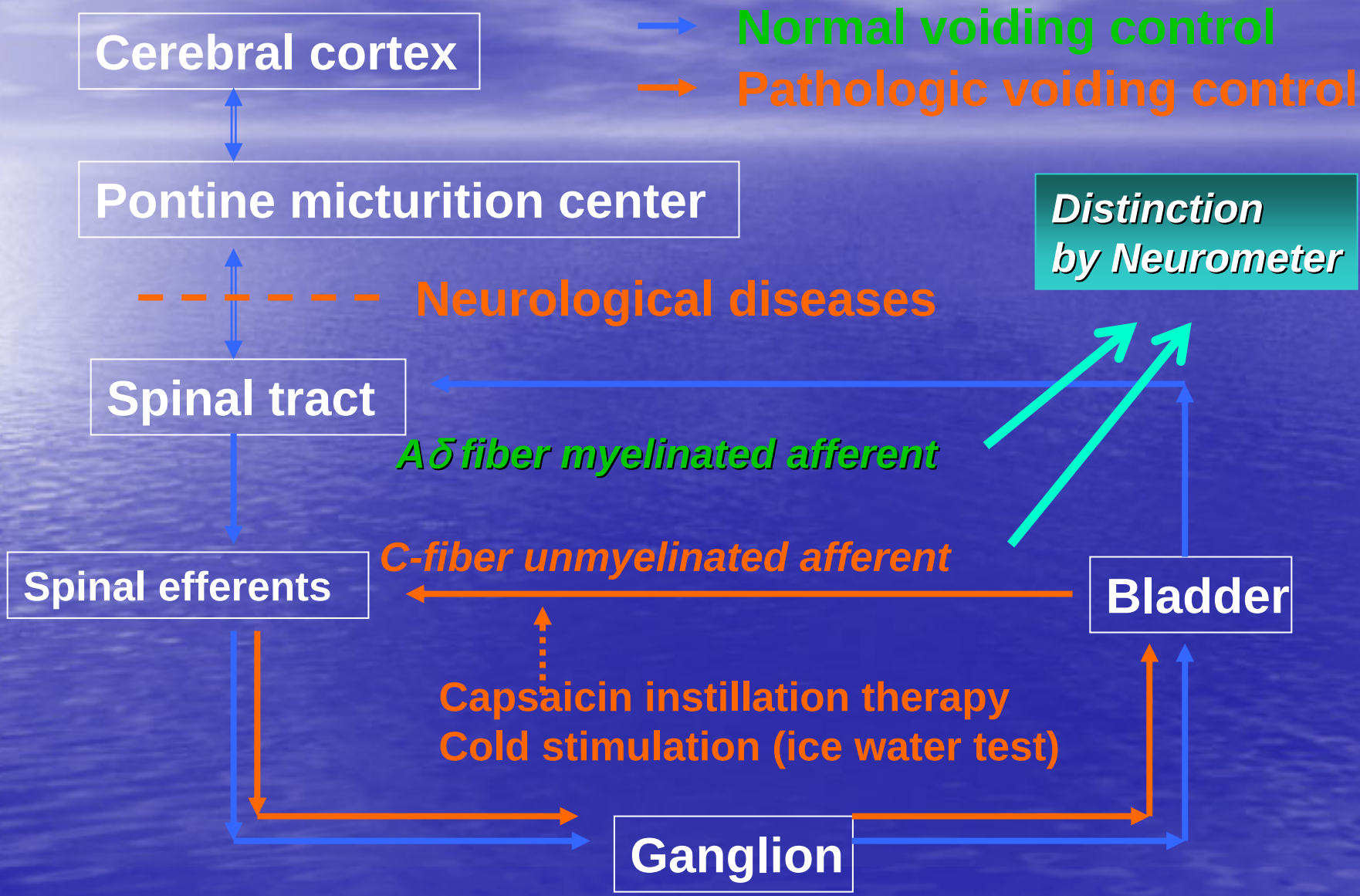


Neurometer as a Quantitative Sensory Testing

- Is c/w Nerve Conduction Studies
- Bypasses the receptor
- Needs to be standardized against other QST

American Association of Electrodiagnostic Medicine: Neurometer CPT: Muscle and Nerve 1999. 22: 523-531

Diagram of the central reflex pathways



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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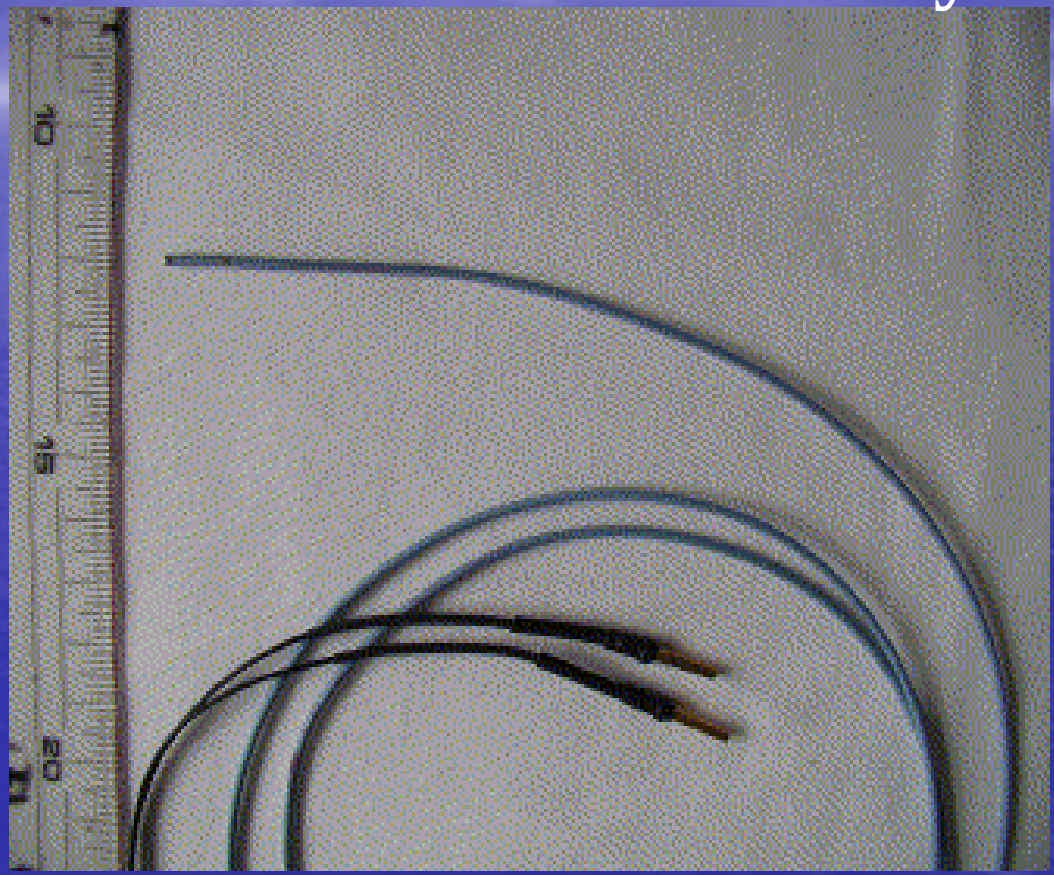
Accepted 13 August 2003

Electrode for Neurometer

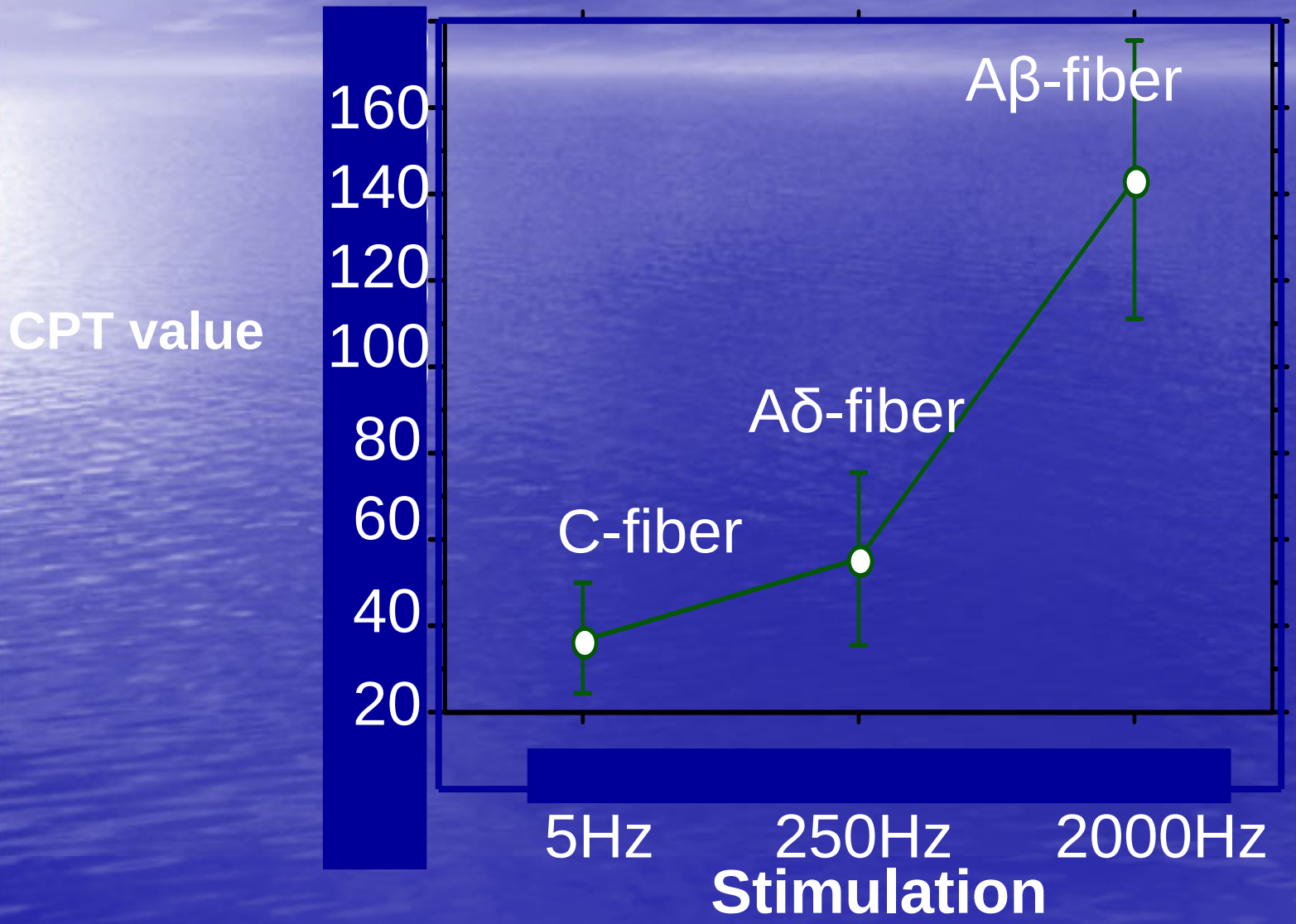
For Skin Sensory

For bladder Sensory

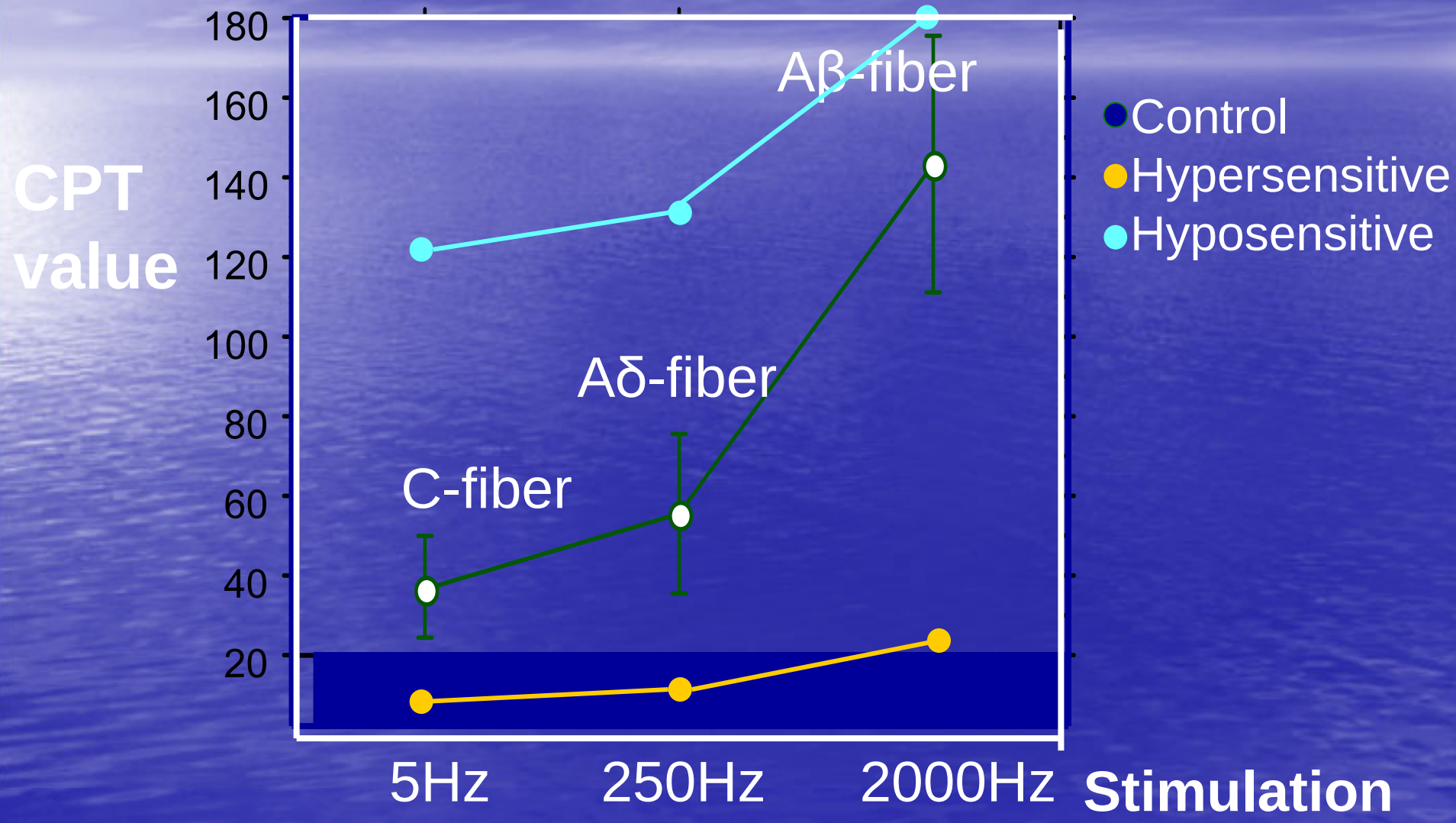


Intravesical electrode (right): 1.67 mm (5fr.) in diameter (inserted through end-hole catheter) Another dispersion electrode is on the lower abdominal skin.

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



Result (Ukimura 2004)

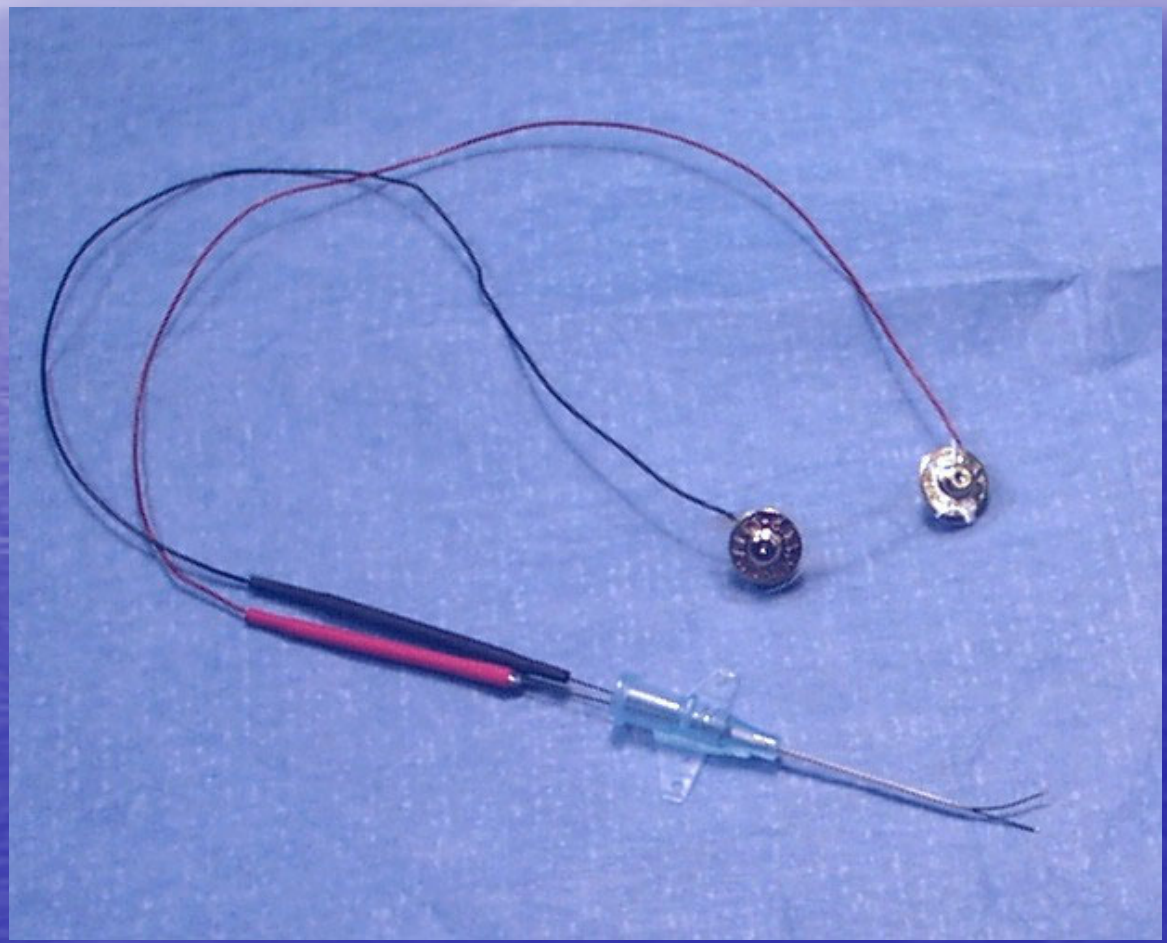
- In 8 patients with detrusor hyperreflexia due to incomplete spinal cord injury (supra-sacral lesion)
- 5Hz (c-fiber)
  - 4.0±1.9 (P<0.01) vs. 26.2±17.7 in control
- 250Hz (A-delta-fiber)
  - 15.3±15.6 (P<0.01) vs. 50.5±28.7 in control

Result (Ukimura 2004)

- In the 11 neurogenic bladders determined to be underactive (including 6 post pelvic surgery, post infra-sacral level spinal cord injury and 5 diabetes patients)
- 5Hz (c-fiber)
  - 98.0±97.1 ($P<0.05$) vs. 26.2±17.7 in control
- 250Hz (A-delta-fiber)
  - 86.4±47.3 ($P=0.07$) vs. 50.5±28.7 in control

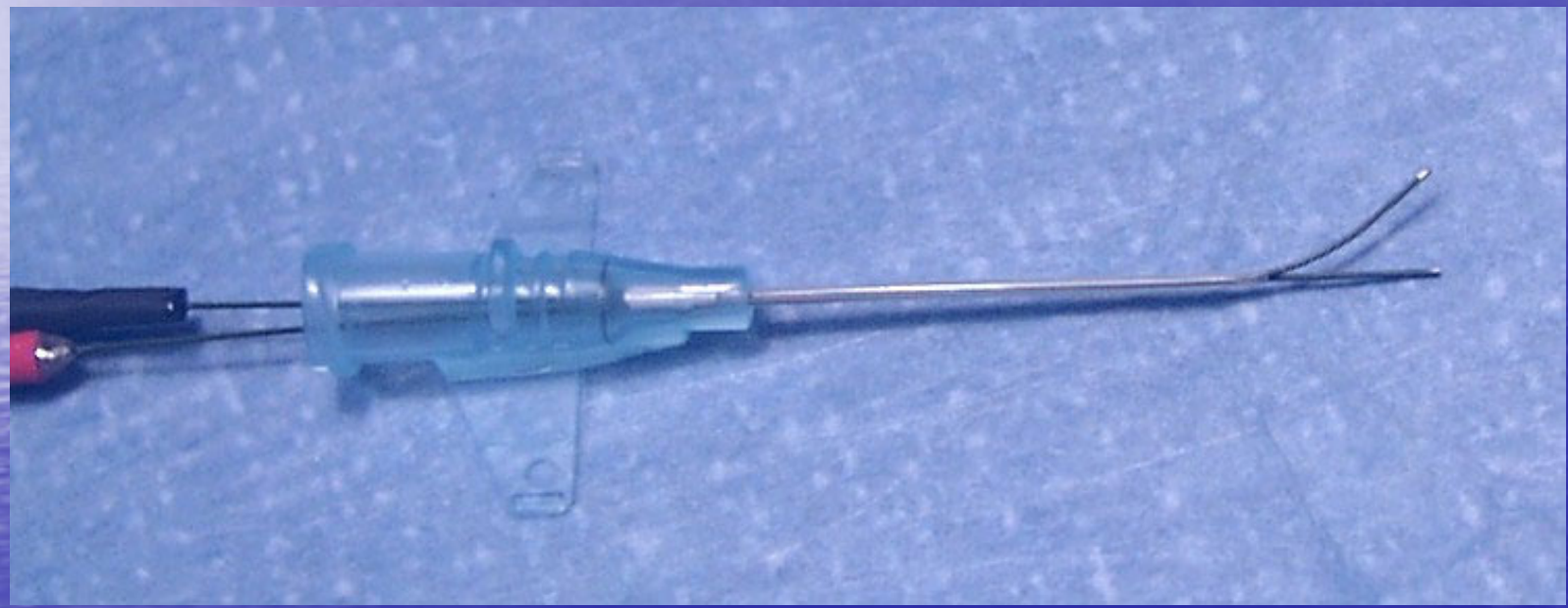
Osamu Ukimura, M.D. Ph.D.

TransUrethral Afferent Current Preception Threshold (TUR-ACT) in rat/mouse



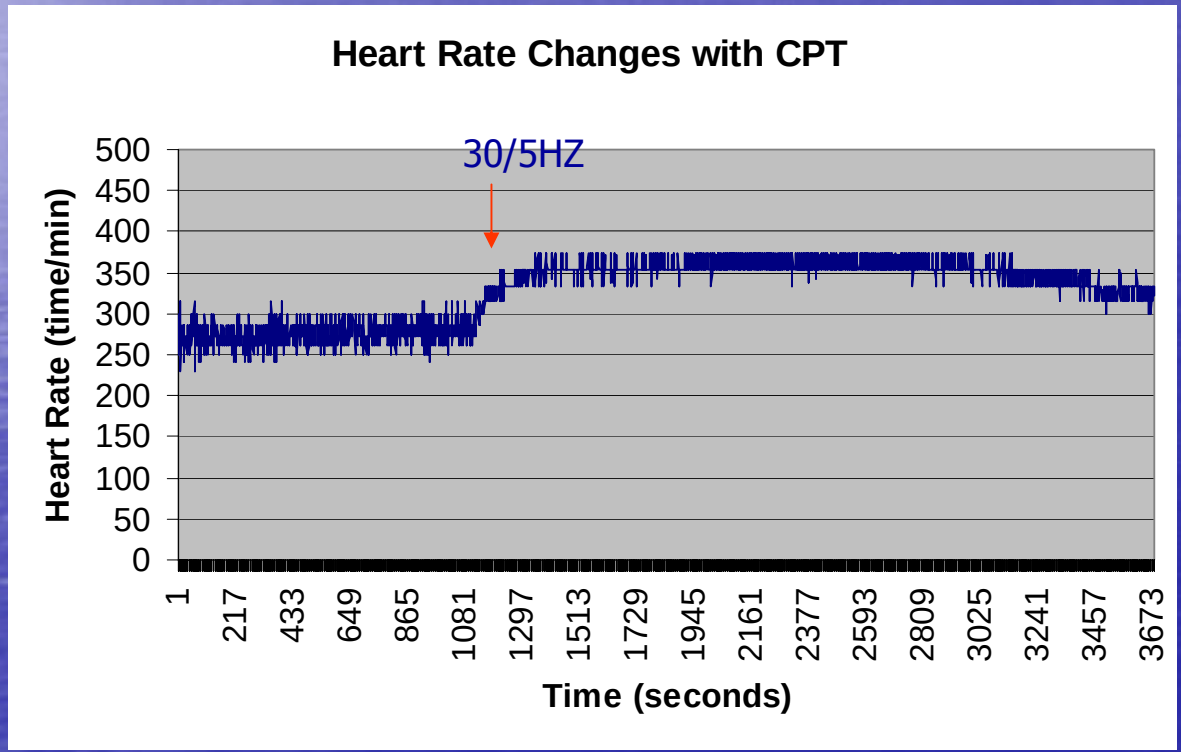
Daneshgari 2004

TransUrethral Afferent Current Perception Threshold (TUR-ACT) in rat/mouse



Daneshgari 2004

Alterations of HR in response to CPT Measurments SD WT-Rat



Measurement of CPT values in small animal models of diabetes

- Measurement of BP and HR as the ANS response
- Measurement of abdominal rectus muscle as a somatic pain response (vesicomotor) independent of ANS (Timothy Ness, M.D., Ph.D. UAB)

RFA

- RFA-HD-04-018: "MEASUREMENT TOOLS FOR ALTERED AUTONOMIC FUNCTION IN SPINAL CORD INJURY AND DIABETES

AMDCC and Uropathy