Veterans Health Administration
Research & Development
Improving Veterans' Lives — www.research.va.gov

# VA's Impact on Advancing the Nation's Medical Knowledge and Care Practices

**Moderator:**
**Seth Eisen, MD, MSc**
Director, Health Services Research and Development

85 Years of DISCOVERY, INNOVATION, ADVANCEMENT For Veterans
VETERANS AFFAIRS RESEARCH & DEVELOPMENT

Veterans Health Administration
Research & Development
Improving Veterans' Lives — www.research.va.gov

# Stroke Rehabilitation

**Robert L. Ruff, M.D., Ph.D.**
Janis Daly, Ph.D.
Department Veterans Affairs Medical Center in Cleveland
FES Center – A Rehabilitation Research and Development
Center of Excellence

85 Years of DISCOVERY, INNOVATION, & ADVANCEMENT For Veterans
VETERANS AFFAIRS RESEARCH & DEVELOPMENT

# Stroke Rehabilitation

- Stroke is:
  1. The major cause of neurological disability among adults.
  2. The second leading cause of overall adult disability.
  3. Many have residual deficits after stroke.

# Stroke Rehabilitation

- The first stroke leaves about 30% of patients with a functional motor deficit that compromises their activities of daily life.
- Conventional rehabilitation therapy techniques are not sufficient to restore voluntary motor function such as normal gait for many patients following a cerebral infarction.

# Why traditional rehab can fail

1. Stroke survivors cannot volitionally activate muscles rapidly or in the proper timing/sequence for practicing coordinated gait components.

2. Patients continually reinforce abnormal movements during walking.

3. **FES can overcome these issues**.

# Definition of FES (Functional Electrical Stimulation)

- Electrical stimulation of muscle to achieve functional movement of a specific muscle or groups of muscles.
- Rehabilitation technique - enhance recovery of voluntary motor function.
- Neuroprosthesis - replace voluntary motor functions.

# Hypothesis for Application of FES to Improve Gate

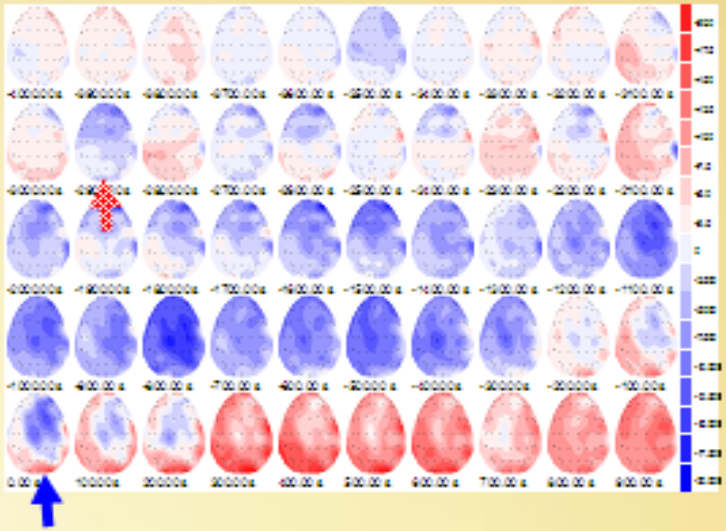
- FES with intramuscular electrodes can augment motor learning after stroke, resulting in recovery of additional **voluntary** motor function and a more normal gait pattern.
- 32 subjects, 2 groups – one treated with BWSTT the other BWSTT + FES.

**Note:**

1. **Time to Action reduced**
2. **Cerebral Activity more focused**

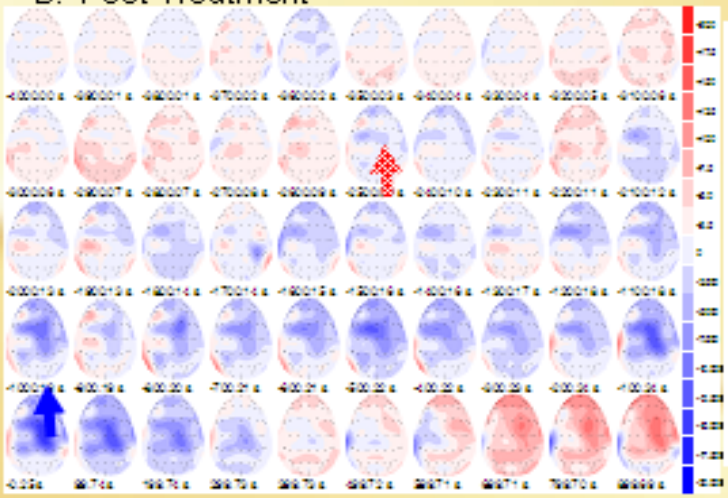
**Figure 4. Pre/Post Treatment Improvement in Cognitive Motor Planning Time and Level of Cognitive Effort.**

A. Pre-Treatment



4a. Pre-Treatment. Long cognitive Planning time (between two arrows, 2900ms). High cognitive effort (dark blue color, high negative potential –15 to –20

B. Post-Treatment



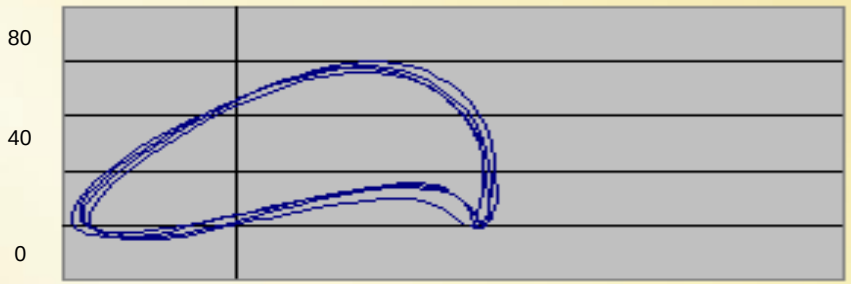
4b. Post-Treatment. Shorter cognitive Planning time (2500ms). Lower cognitive effort level (lighter blue color).

Key: Cognitive Motor Planning Onset → Movement onset

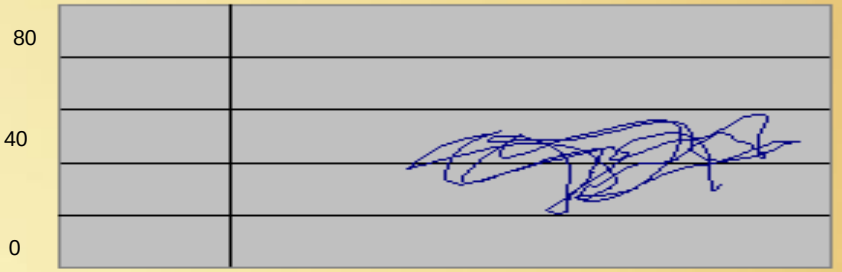
Daly 2006

# Intra-Limb Hip/Knee Angle-Angle Plot
# FES Improves Consistency of Movement

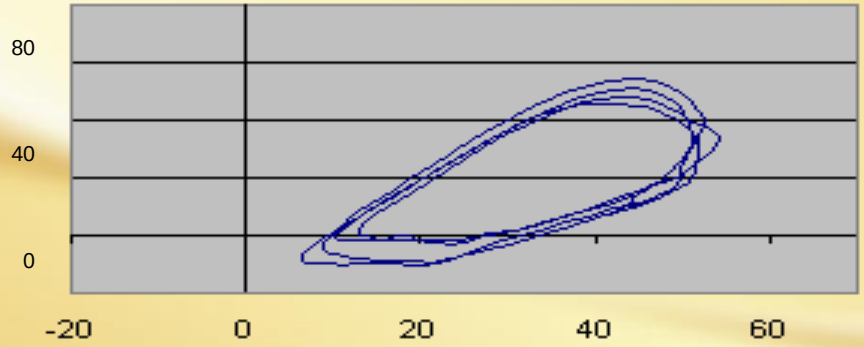
**Control Subject (no Stroke)**




**Stroke Subject Before Treatment**

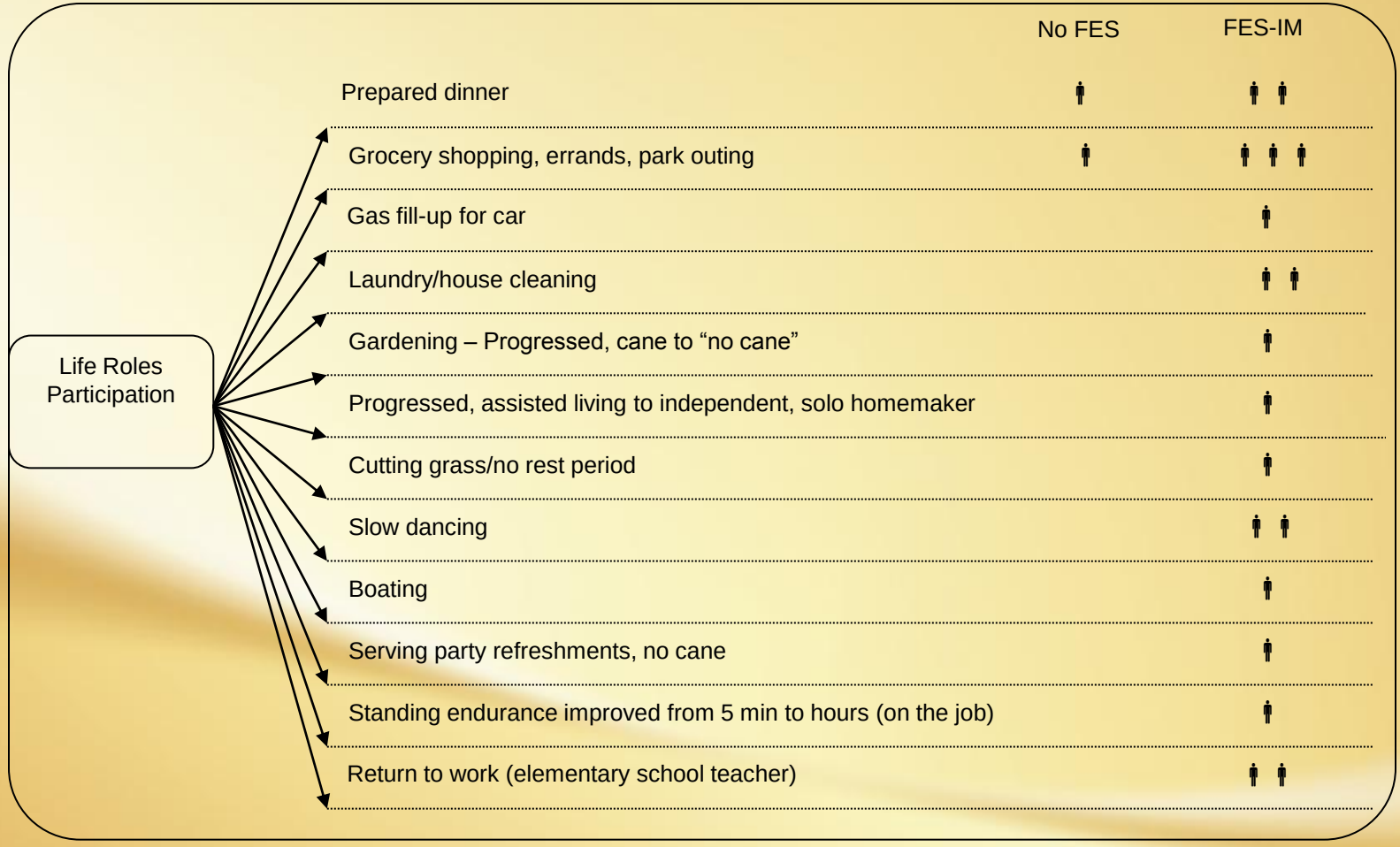



**Stroke Subject after FES-IM Gait Treatment**




Hip Angle (degrees)

# Subjects who received FES did more



# Subject

- Age 69
- Four years prior he had a left hemisphere infarct involving the corona radiata
- He had a right hemiparesis and impaired proprioception on the right
- His wife was not able to manage him at home and hence he was relegated to a nursing home

# Functional State

- Not able to walk alone with cane or walker.
- Fell often due to instability of right lower extremity.

# Note Improved Knee Function Pre- vs Post-Treatment

# Summary

- Rehab enables people to regain function.
- Rehab is an essential part of stroke treatment.
- FES can synergize with other Rehab modalities to enhance recovery.


85 Years of DISCOVERY, INNOVATION, & ADVANCEMENT
For Veterans
VETERANS AFFAIRS RESEARCH & DEVELOPMENT

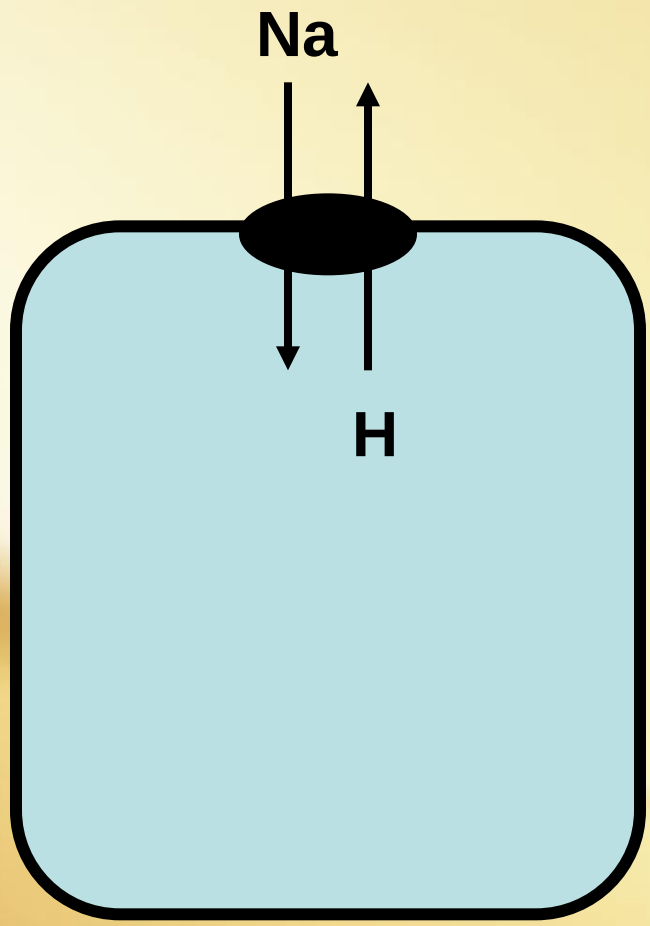
Veterans Health Administration
Research & Development
Improving Veterans' Lives — www.research.va.gov

# Kidney Function

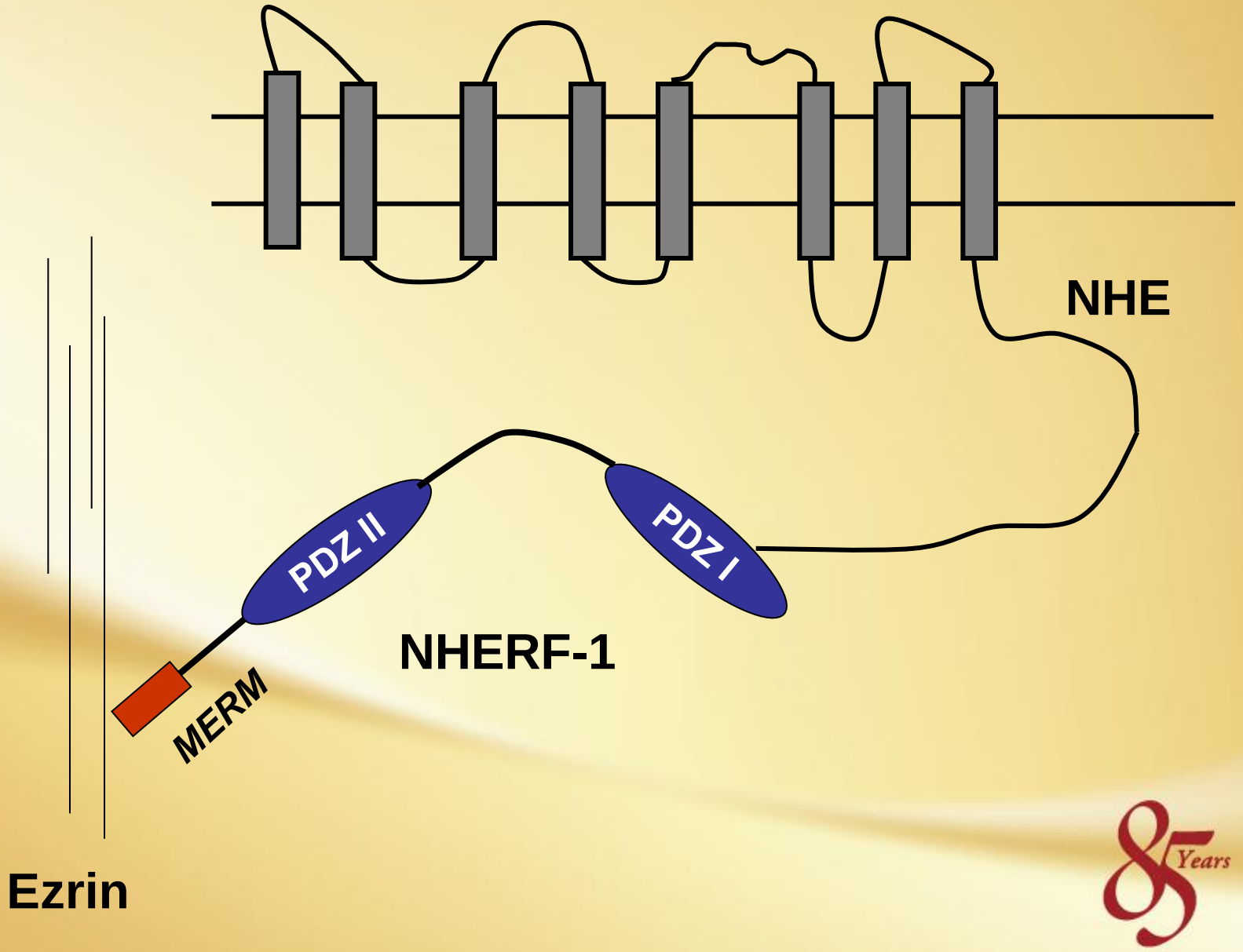
**Edward J. Weinman, MD**

85 Years of DISCOVERY, INNOVATION, ADVANCEMENT For Veterans
VETERANS AFFAIRS RESEARCH & DEVELOPMENT

# Sodium-Hydrogen Exchange (NHE)

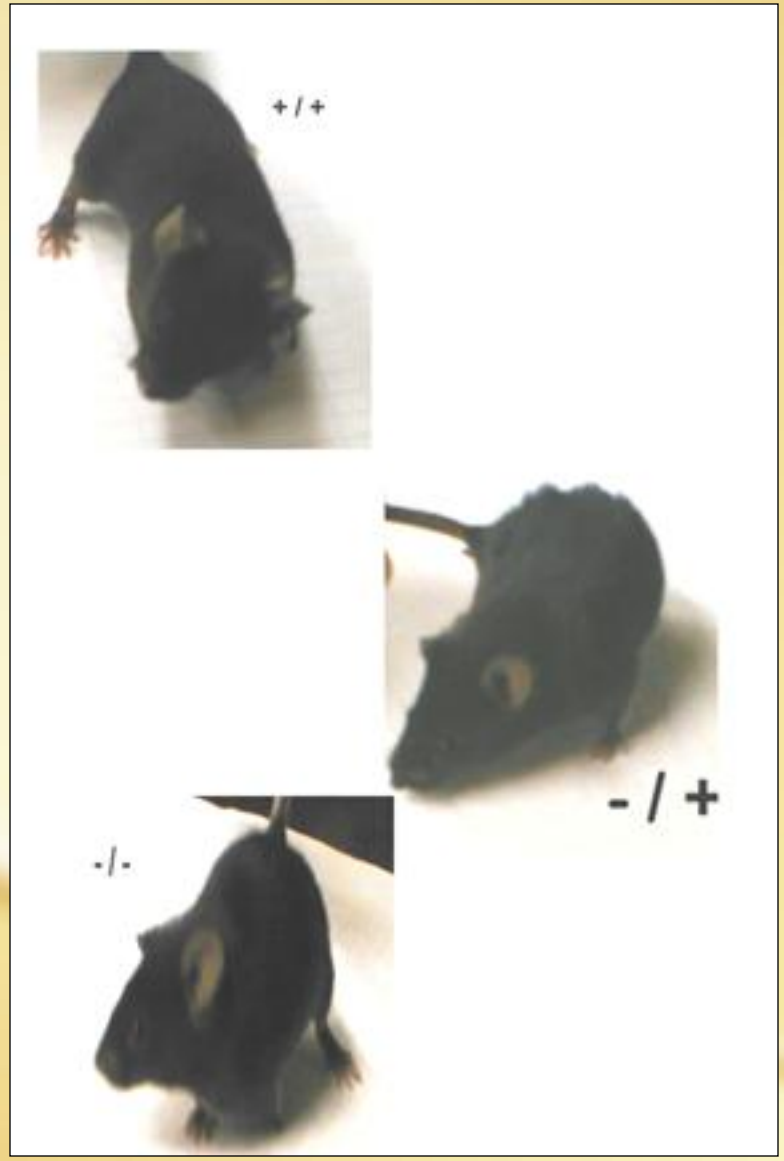



**Hypertension**
**Diabetes Mellitus**
**Cell Growth and Cancer**
**Cell Death (MI, CVA)**

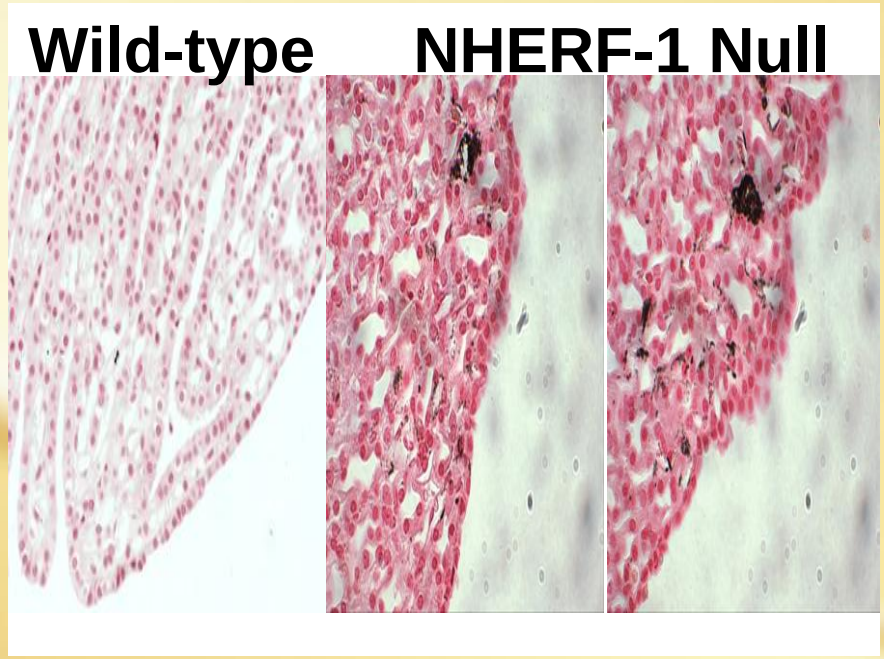

NHE
PDZ II
PDZ I
NHERF-1
MERM
Ezrin

# NHERF Binding Proteins

- **Transporters and Channels**:
  - NHE
  - Npt2a
  - CFTR
- **Hormone Receptors:**
  - β2-Adrenergic Receptor
  - PTH Receptor
  - PDGF Receptor



# Representative Kidneys Stained for Calcium from Wild-Type and NHERF-1 Null Mice



# Mutations in Npt2 Associated with Nephrolithiasis

## Nephrolithiasis and Osteoporosis Associated with Hypophosphatemia Caused by Mutations in the Type 2a Sodium–Phosphate Cotransporter

NEJM 347:983-991, 2002

*Dominique Prié, M.D., Ph.D., Virginie Huart, M.S., Naziha Bakouh, M.S., Gabrielle Planelles, M.D., Ph.D., Olivier Dellis, Ph.D., Bénédicte Gérard, D.Pharm., Philippe Hulin, M.S., François Benqué-Blanchet, D.Pharm., Caroline Silve, M.D., Ph.D., Bernard Grandchamp, M.D., Ph.D., and Gérard Friedlander, M.D., Ph.D.*

# NHERF Associated Diseases

1. Psoriasis
2. Schizophrenia
3. Nerve Deafness
4. Aggressive Estrogen Receptor Positive Breast Cancer
5. Nephrolithiasis


85 Years of DISCOVERY, INNOVATION, & ADVANCEMENT
For Veterans
VETERANS AFFAIRS RESEARCH & DEVELOPMENT

Veterans Health Administration
Research & Development
Improving Veterans' Lives — www.research.va.gov

# The Brain in Liver Disease

## (Why the brain fails, when the liver ails)

**Michael D. Norenberg, MD**

The Bruce Carter Veterans Affairs Medical Center
Depts. Pathology and Biochemistry & Molecular Biology
Miller School of Medicine
University of Miami, Miami FL

85 Years of DISCOVERY, INNOVATION, ADVANCEMENT For Veterans
VETERANS AFFAIRS RESEARCH & DEVELOPMENT

# The Brain in Liver Disease

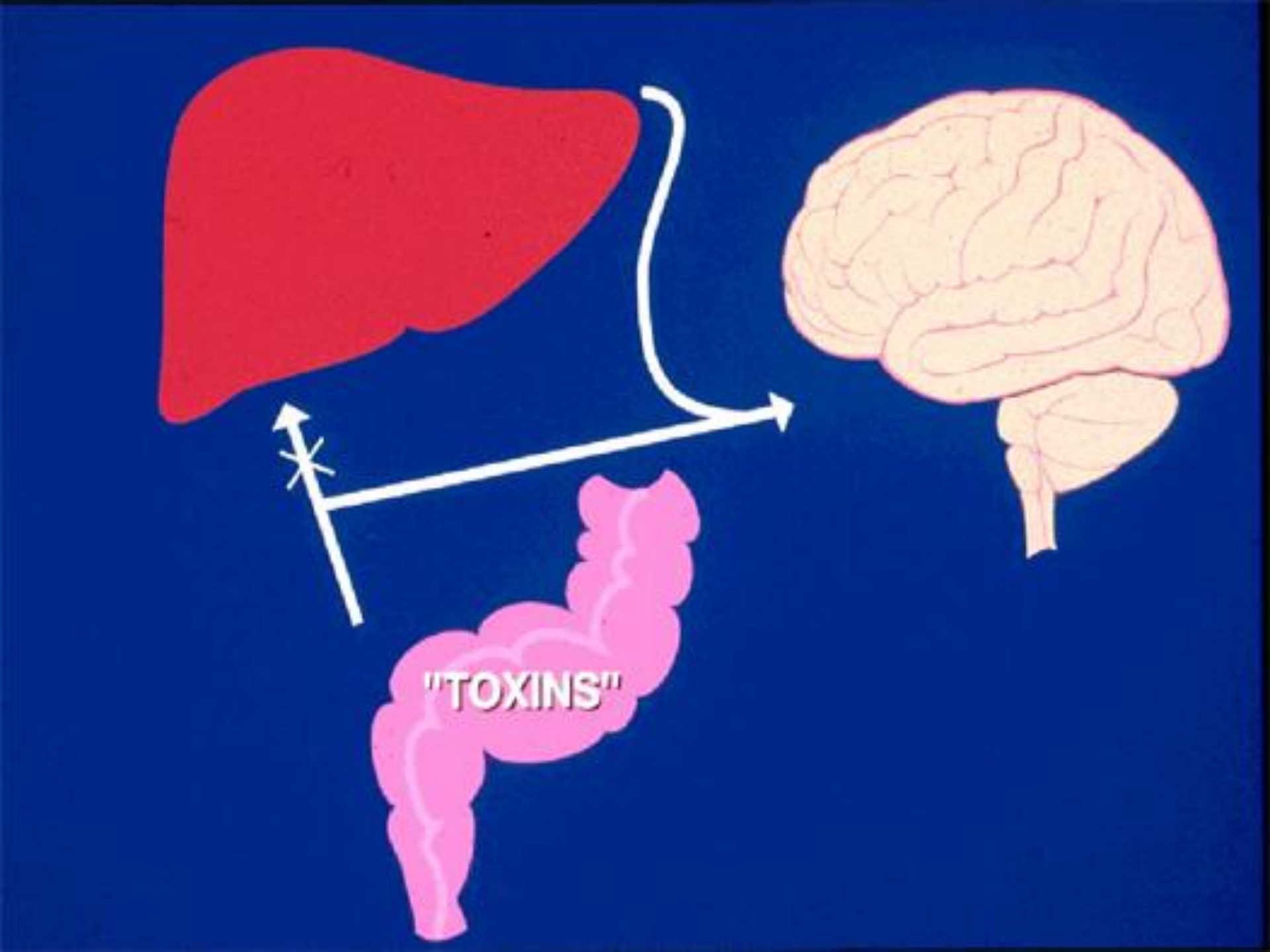
- **Hepatic encephalopathy**

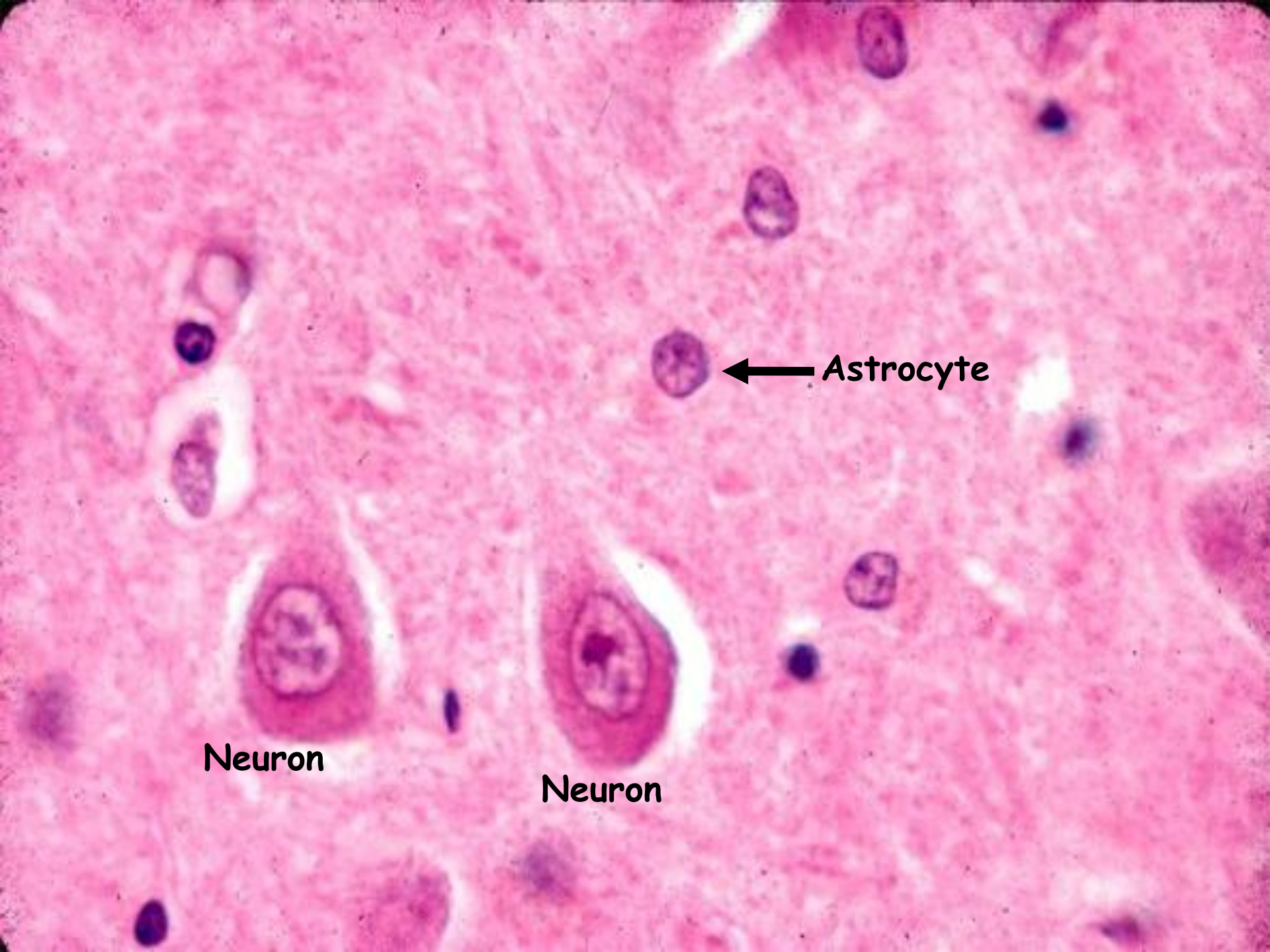
**Chronic**

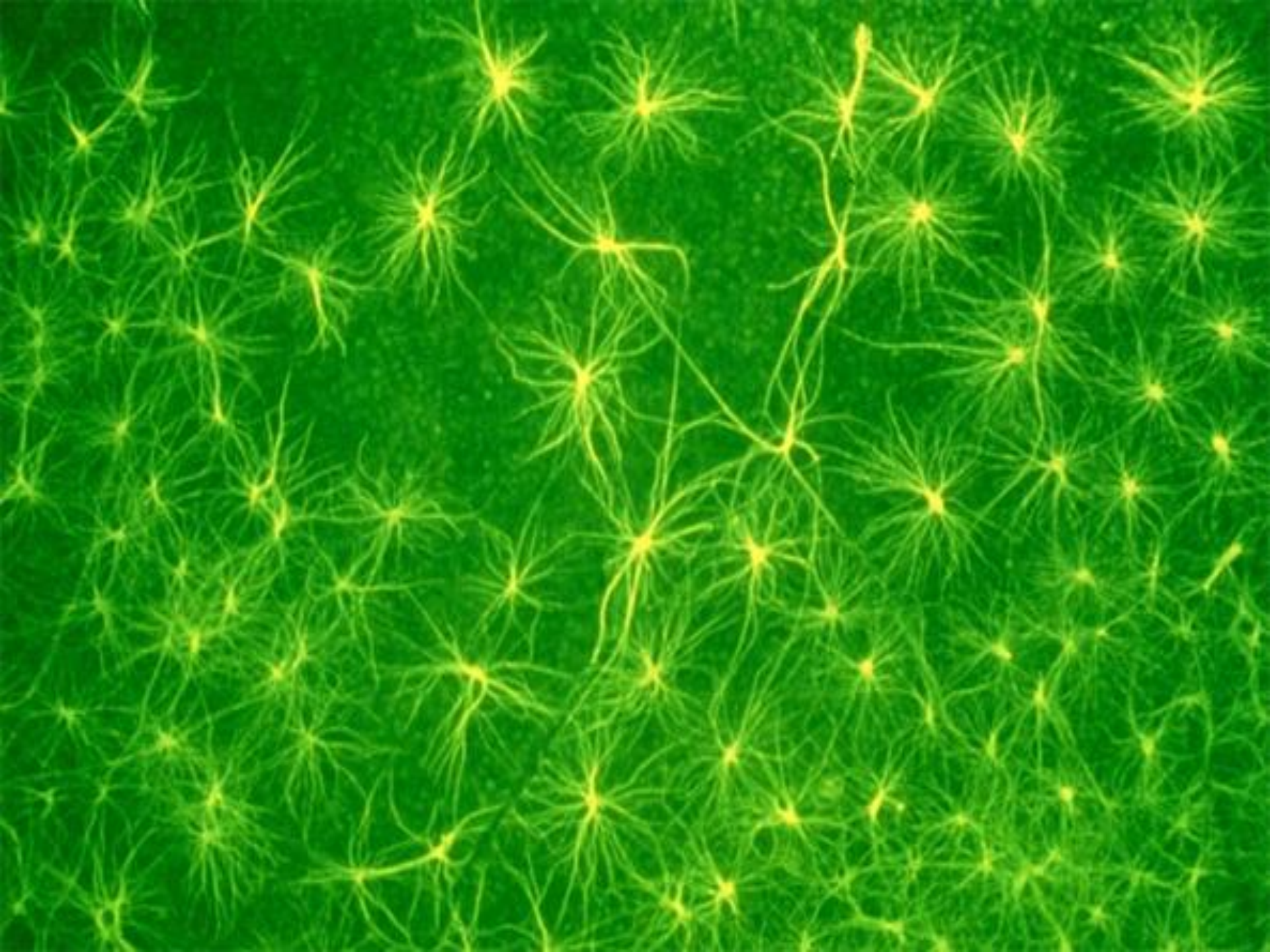
- Altered mood, behavior, personality; confusion, and decreased cognitive abilities
- Usually occurs in the setting of cirrhosis
- Important socio-economic impact

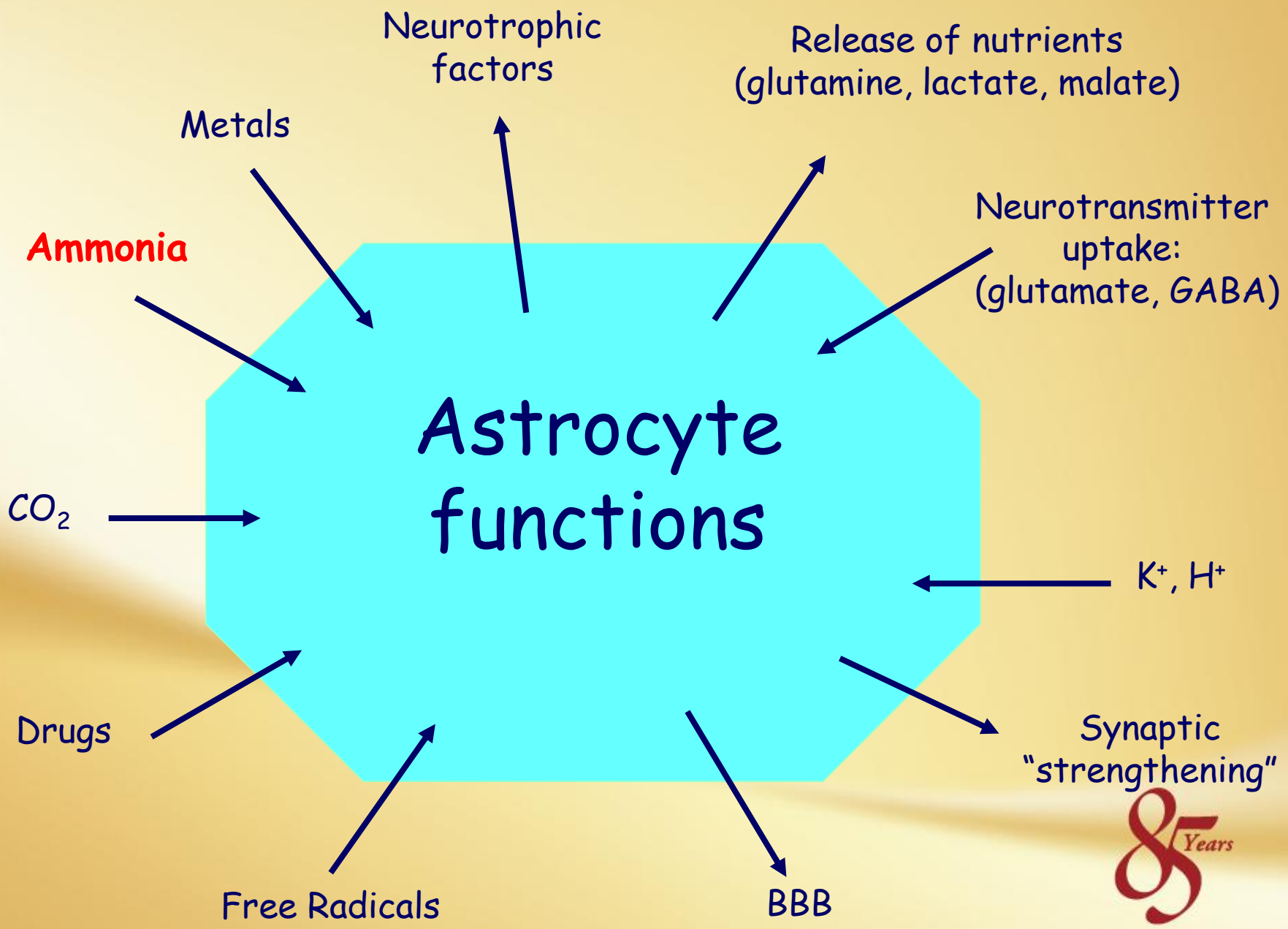
**Acute**

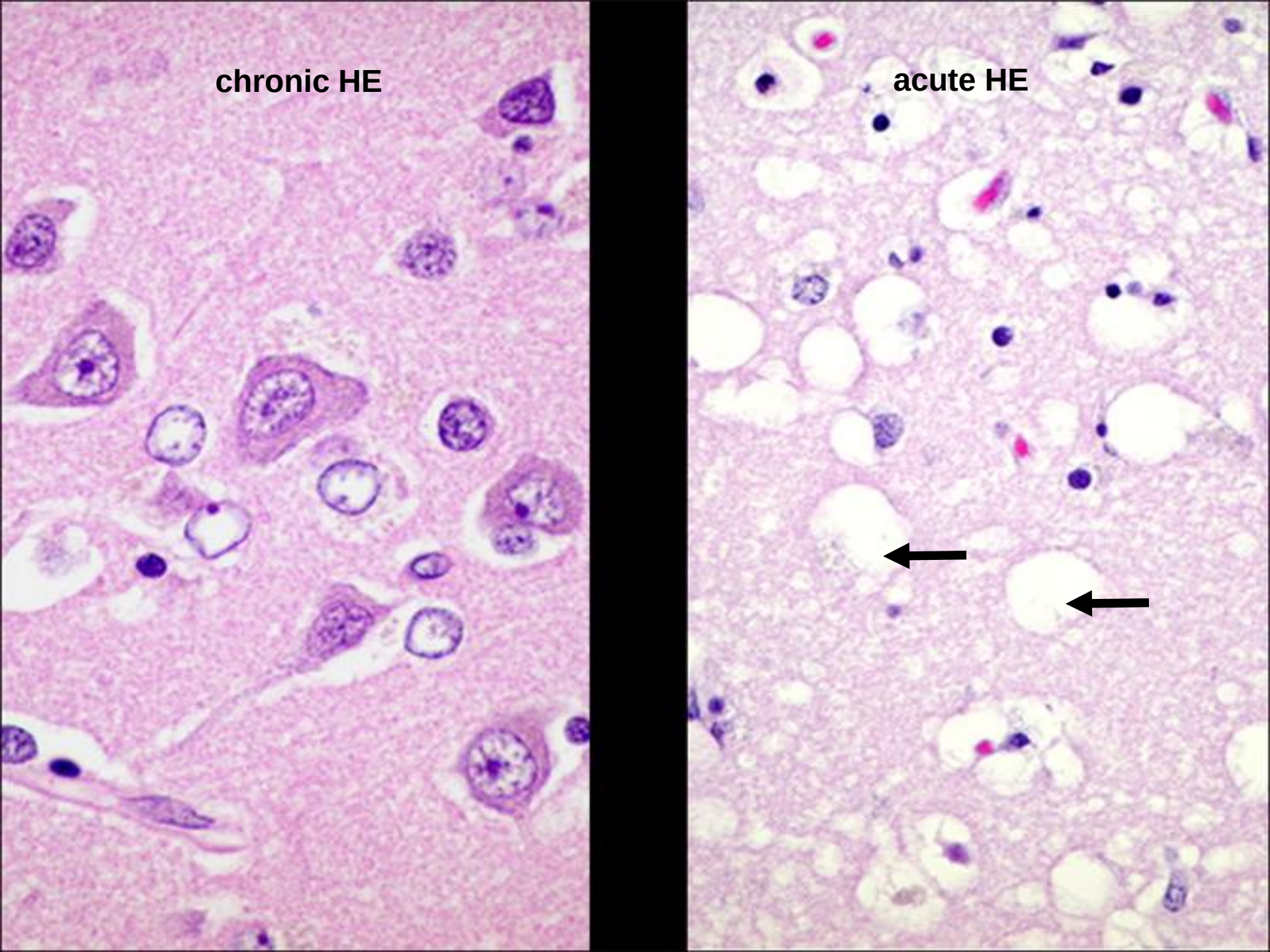
- Rapid onset of seizures and coma
- Usually after viral hepatitis; acetaminophen toxicity and other liver toxins; end-stage cirrhosis
- Often lethal


"TOXINS"


Astrocyte
Neuron
Neuron




Neurotrophic factors
Release of nutrients (glutamine, lactate, malate)
Metals
Neurotransmitter uptake: (glutamate, GABA)
Ammonia
Astrocyte functions
$CO_2$
$K^+$, $H^+$
Drugs
Synaptic "strengthening"
Free Radicals
BBB


chronic HE
acute HE

**Normal** **Acute HE**

# Events Triggered by Ammonia

- Evidence of oxidative stress (OS)
- Mitochondrial permeability transition
- Mitogen-activated protein kinases
- NF-kappaB (inflammation)
- NKCC (ion transporter)
- Aquaporin-4 levels (water channel)

# Potential Therapies

- Interference with ammonia metabolism: histidine
- OS: antioxidants
- mPT: cyclosporin
- MAPKs: inhibitors
- NF-kappaB: BAY 11-7082
- NKCC: bumetanide

# Central Pontine Myelinolysis


85 Years of DISCOVERY, INNOVATION, & ADVANCEMENT
For Veterans
VETERANS AFFAIRS RESEARCH & DEVELOPMENT

Veterans Health Administration
Research & Development
Improving Veterans' Lives — www.research.va.gov

# Effect of CPAP on GWI Symptoms

**Mohammad M. Amin, MD**
Pulmonary, Critical Care and Sleep Division
Assistant Professor, Stony Brook University
Staff physician, VAMC, Northport NY

85 Years of DISCOVERY, INNOVATION, & ADVANCEMENT For Veterans
VETERANS AFFAIRS RESEARCH & DEVELOPMENT

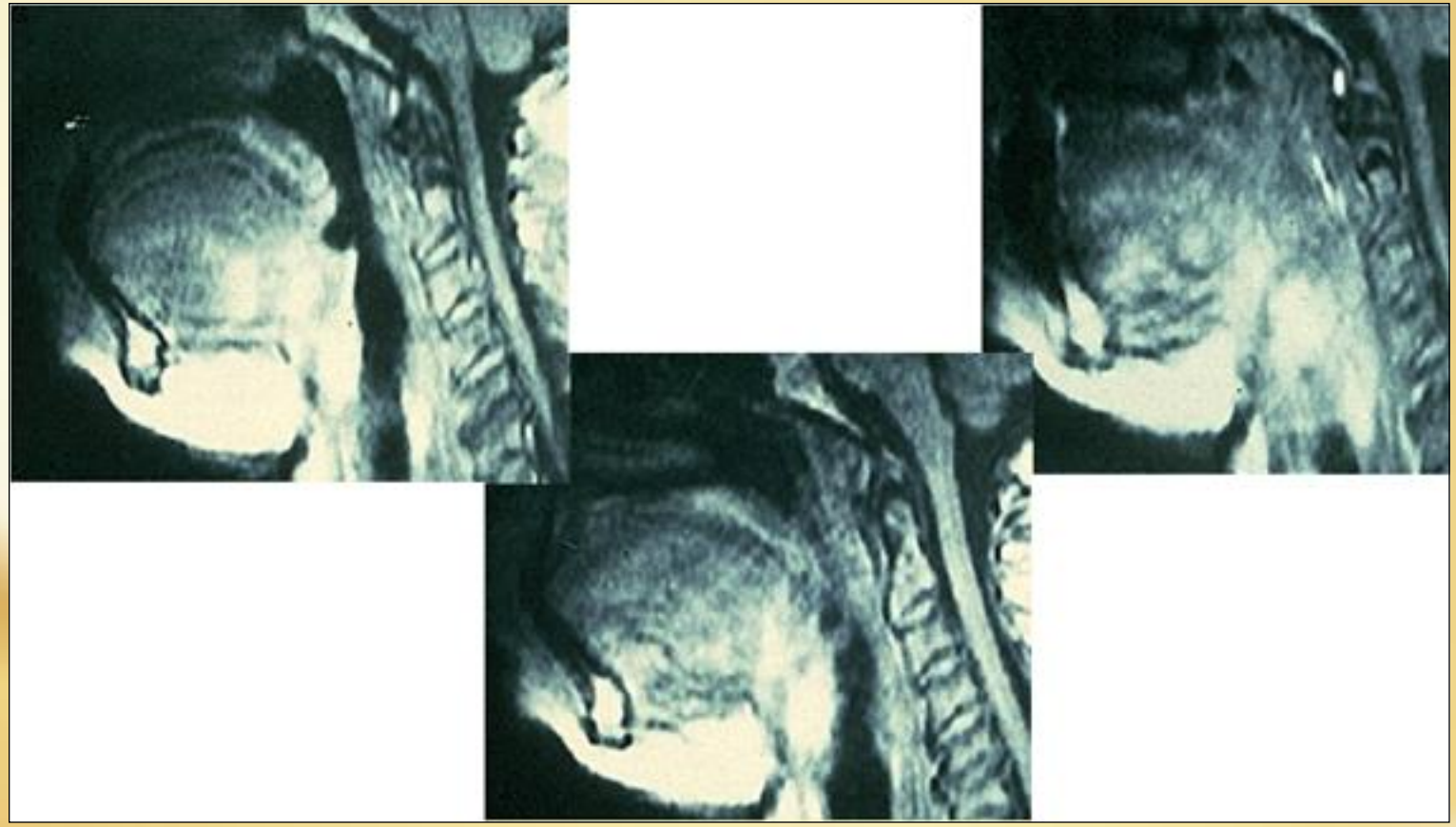
# Background

- Veterans of the first Gulf War experience the symptoms of the *functional somatic syndromes*, including: headaches, widespread pain, cognitive difficulties, fatigue and gastrointestinal complaints.
- My involvement with this research began with the recognition that pharyngeal collapse during sleep plays a role in the symptoms of the functional somatic syndromes.

# Pharyngeal Collapse with Inspiratory Flow Limitation

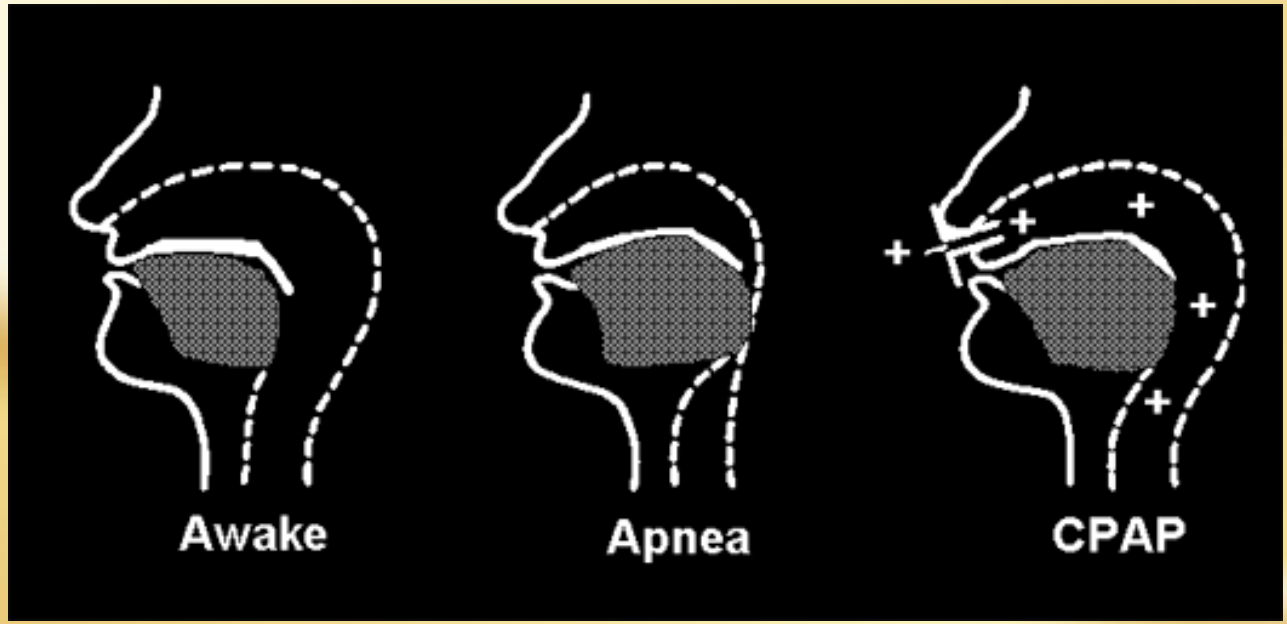

**Veteran with GWI**

# Obstructive Sleep Apnea



# Obstructive Sleep Apnea

Nasal Continuous Positive Airway Pressure (nasal CPAP)



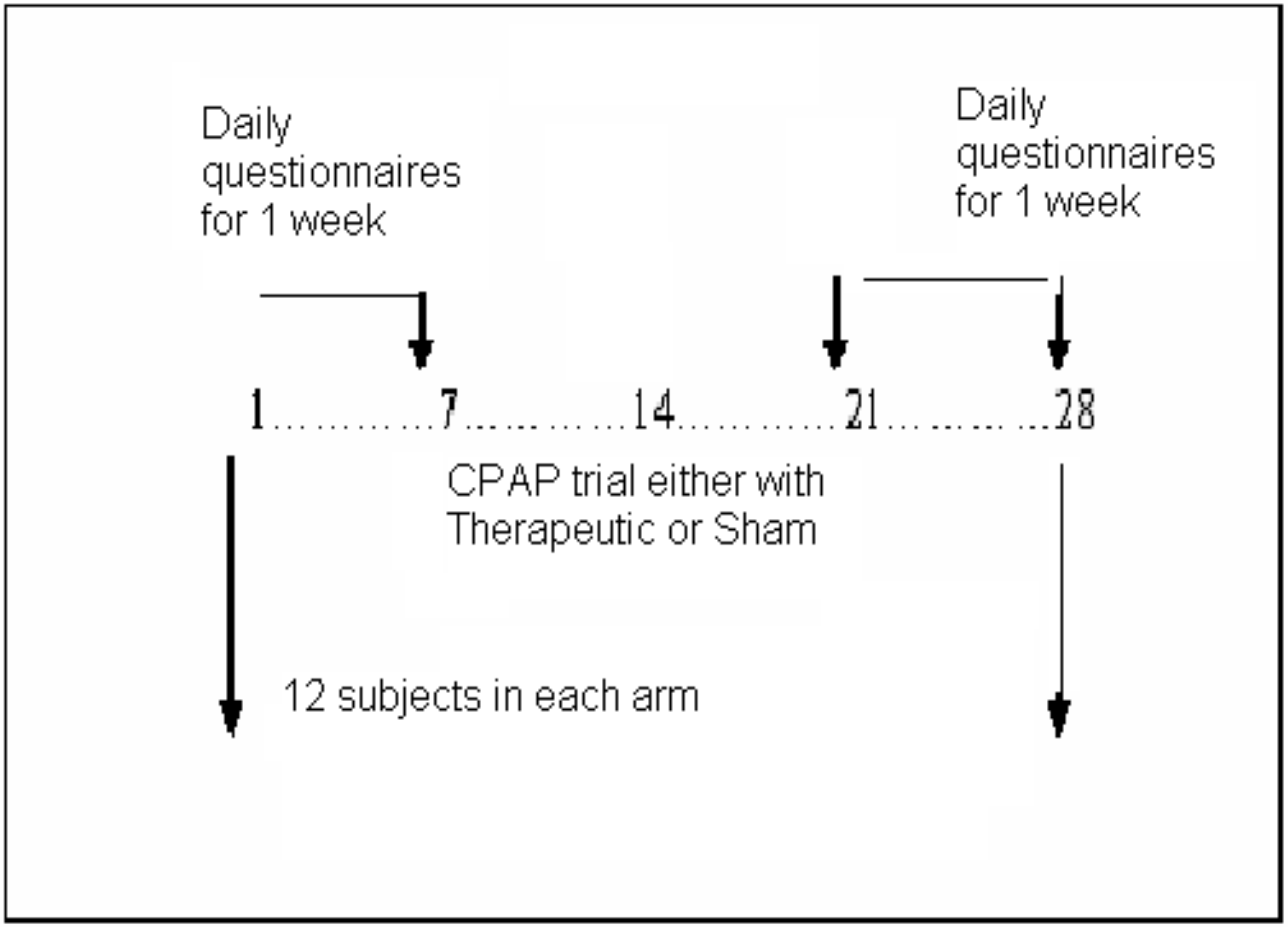
- *Hypothesis* : GWI veterans have Inspiratory Flow Limitation (IFL) during sleep and its correction will result in an improvement of sleep complaints and other functional symptoms.

***Objectives*:**

1. GWI veterans have increased IFL compared to asymptomatic Gulf War veterans ( cross sectional study)
2. Relief of IFL results in improvement of GWI Veteran's symptoms (longitudinal study)

# Study Protocol

1. Initial enrollment and verification of GWI status.
2. First FNSS
3. Second FNSS with supra-glottic catheter to measure effort and pneumotachography to measure flow / CPAP titration.
4. Randomization to receive either therapeutic CPAP or sham CPAP for three weeks.
5. Third FNSS on their assigned CPAP.


Daily questionnaires for 1 week
Daily questionnaires for 1 week
1
7
14
21
28
CPAP trial either with Therapeutic or Sham
12 subjects in each arm

# Recruitment

- By advertisement, Veterans must have been deployed to the theater of operations between 8/90 and 8/91 and have the following 3 symptoms beginning after 8/90, lasting at least 6 months and present at the time of screening.

- All 3 symptoms must be unexplained by any clearly defined organic illness and intentionally sleep complaints were not screened and not part of inclusion criteria.

# Results of Treatment Trial

All of the 18 GWI Veterans who qualified for the study demonstrated pharyngeal collapse during sleep

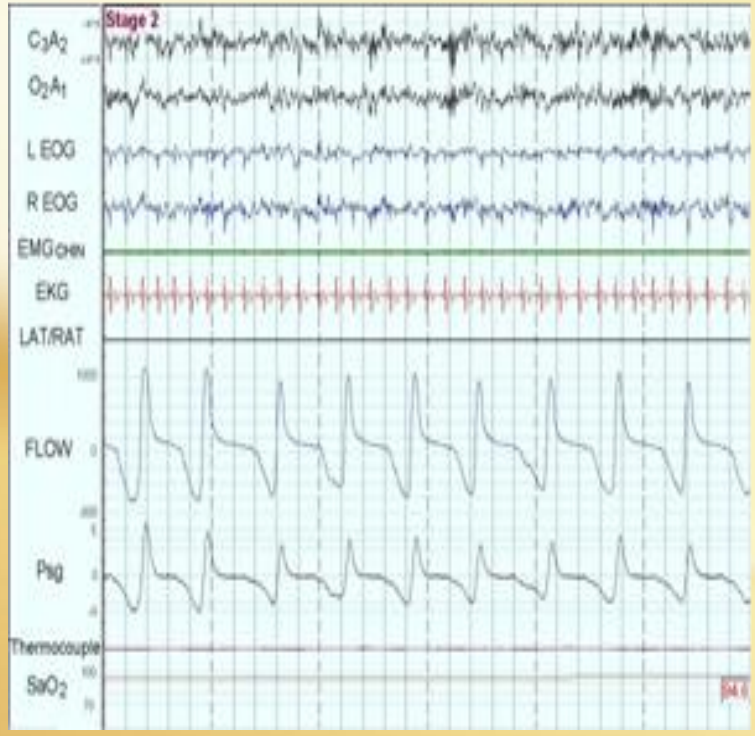
After 3 weeks on therapeutic CPAP participants experienced:

- A 37 % improvement of pain VAS score (p=0.002)
- A 49 % improvement of Fatigue Severity Scale score (p=0.0002)
- A 44% improvement of cognitive VAS score (p=0.014)
- A 43% improvement of PSQI score (p=0.007)

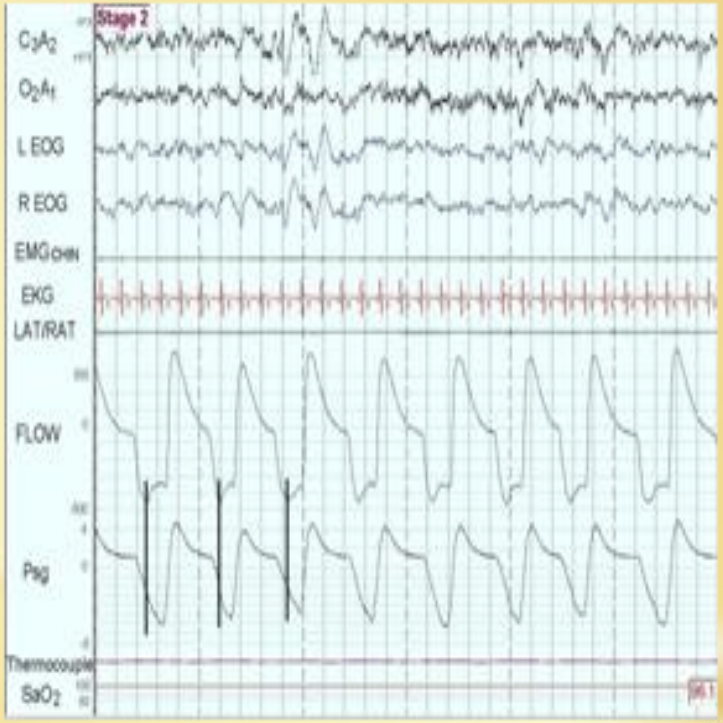
The p-values are compared to the sham group who generally experienced mild worsening of symptoms.

# Control Group

Recruited 11 healthy controls Gulf War Veterans without symptoms of GWI and compare their upper airway dynamics to the18 Veterans with GWI. The two samples were matched for age and BMI.  All of the participants were registered in the Gulf War Veterans Registry.




**Control**




**GWI Participant**

85 Years

# Conclusion

- Our findings in this pilot study suggest that pharyngeal collapse during sleep is common among Veterans with GWI and contributes to their symptoms.
- GWI Veterans may benefit of long term utilization of CPAP, we need a large scale VA cooperative study to supports results of this pilot study.
- Acknowledgement to DVA Career Development Award


85 Years of DISCOVERY, INNOVATION, & ADVANCEMENT
For Veterans
VETERANS AFFAIRS RESEARCH & DEVELOPMENT

Veterans Health Administration
Research & Development
Improving Veterans' Lives — www.research.va.gov

# From Research to Clinic: Computer Support for Evidence-Based Care

**Mary K. Goldstein, MD, MSc**
Director, Geriatrics Research Education & Clinical Center
VA Palo Alto Health Care System
and Professor of Medicine, Stanford University

85 Years of DISCOVERY, INNOVATION, ADVANCEMENT For Veterans
VETERANS AFFAIRS RESEARCH & DEVELOPMENT

# Veterans Deserve the Best

- Clinicians want to
  - Keep up with the latest research
  - Have patient data readily available
  - Have tools to visualize complex clinical information

- Patients are complex:
  - Many diagnoses
  - Many medications
- Medical Literature is huge
- Link information technology with clinical care
  - Information highly tailored to the patient being seen
  - Presented quickly to the clinician within the workflow

# Hypertension is Common

85 Years

85 Years

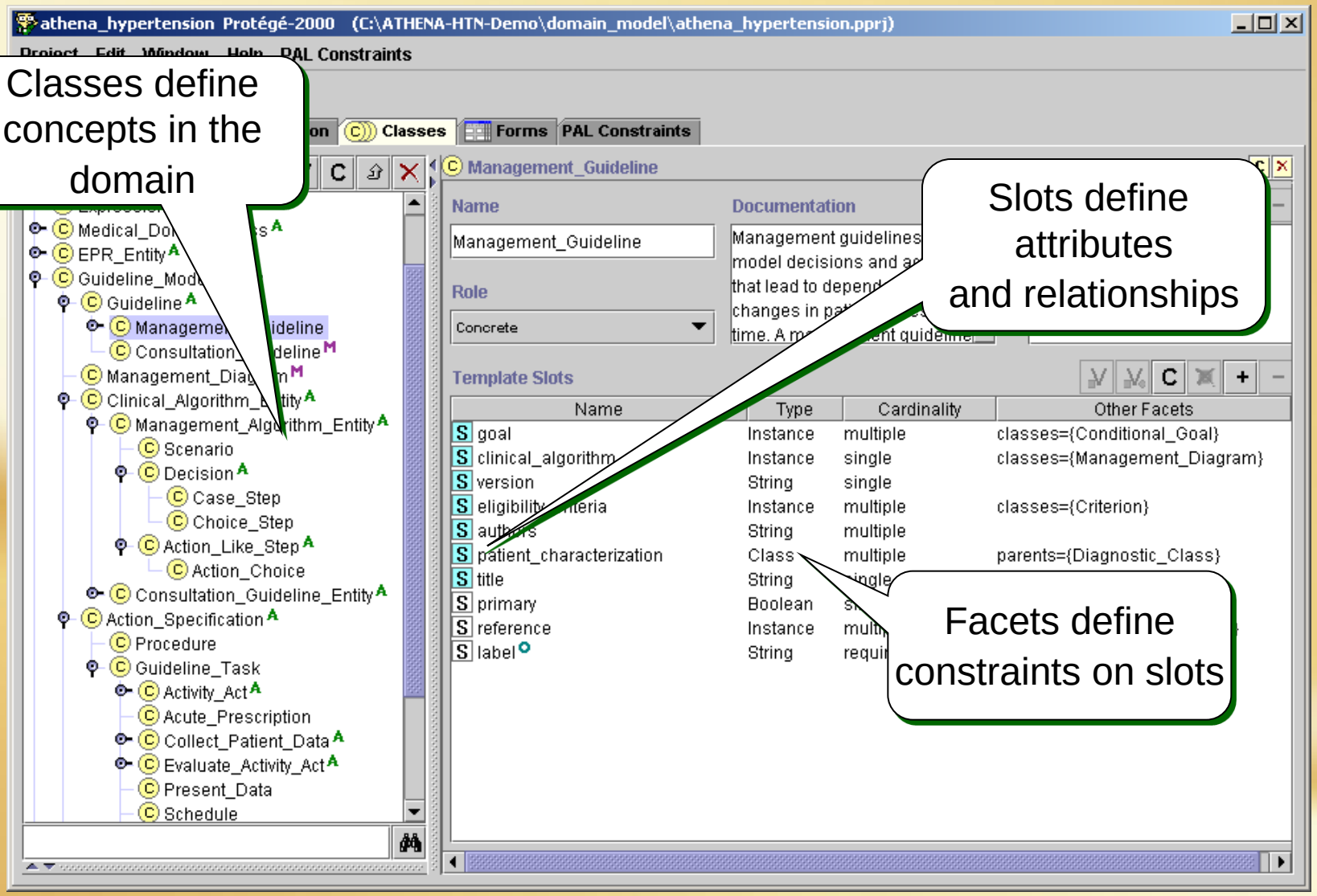
# Clinical Decision Support (CDS)

Research goals:

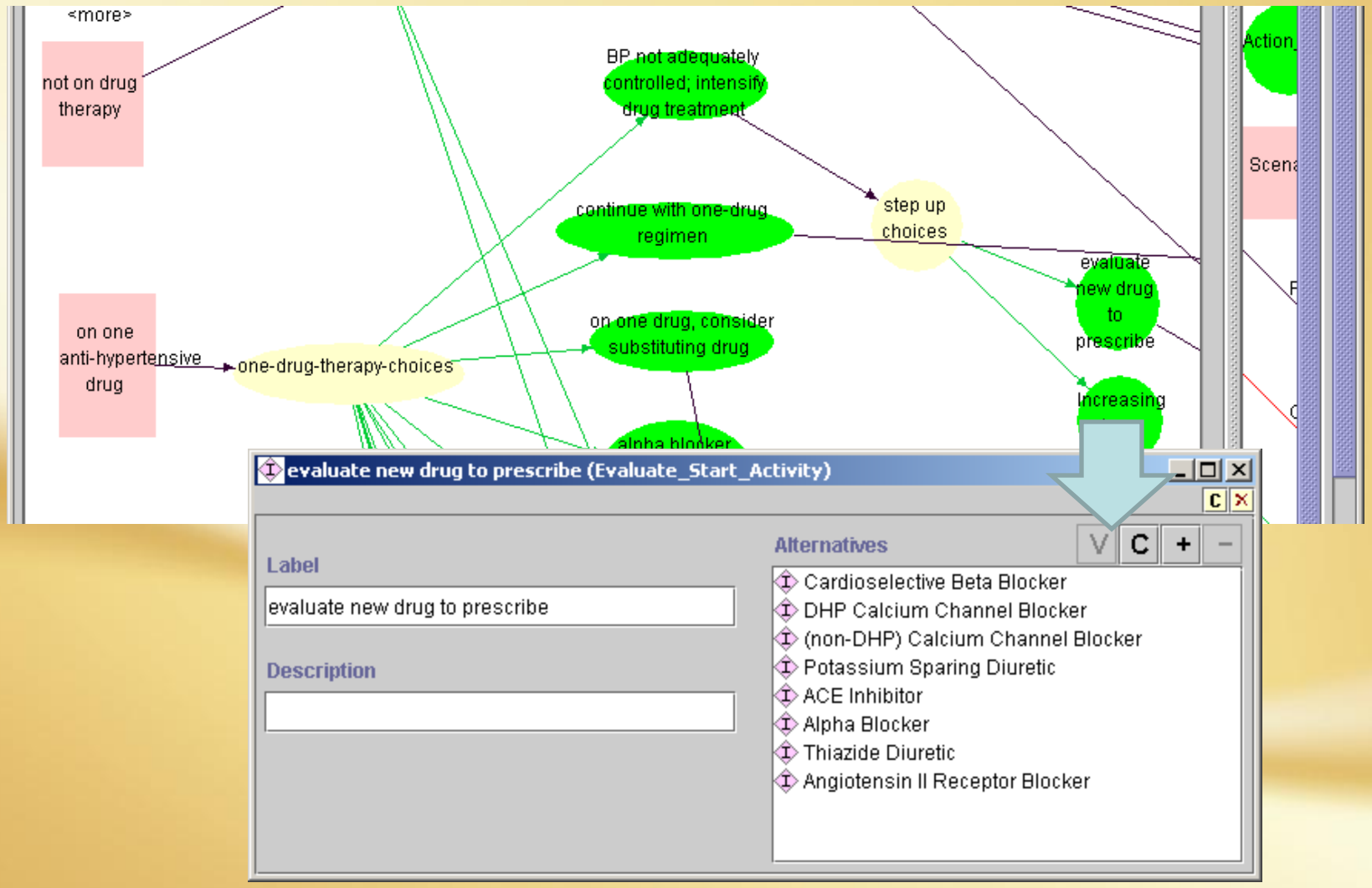
- Rapidly present pertinent information about individual patients to the clinician
- Rapidly provide evidence-based advice
- Account for clinical complexity

**ATHENA-Hypertension (HTN)**

# ATHENA-Hypertension:
## Building the “Knowledge Base”



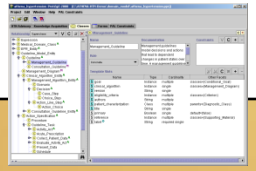
# From Clinical Scenarios to Treatment Recommendations



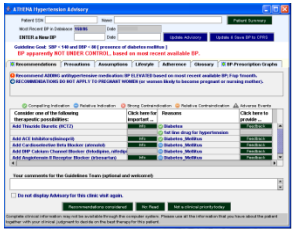
# Combining Patient Data with Clinical Knowledge

Individual Patient
Clinical Information

Clinical Knowledge in
ATHENA- HTN



Information Display for
Clinicians about
Individual Patient

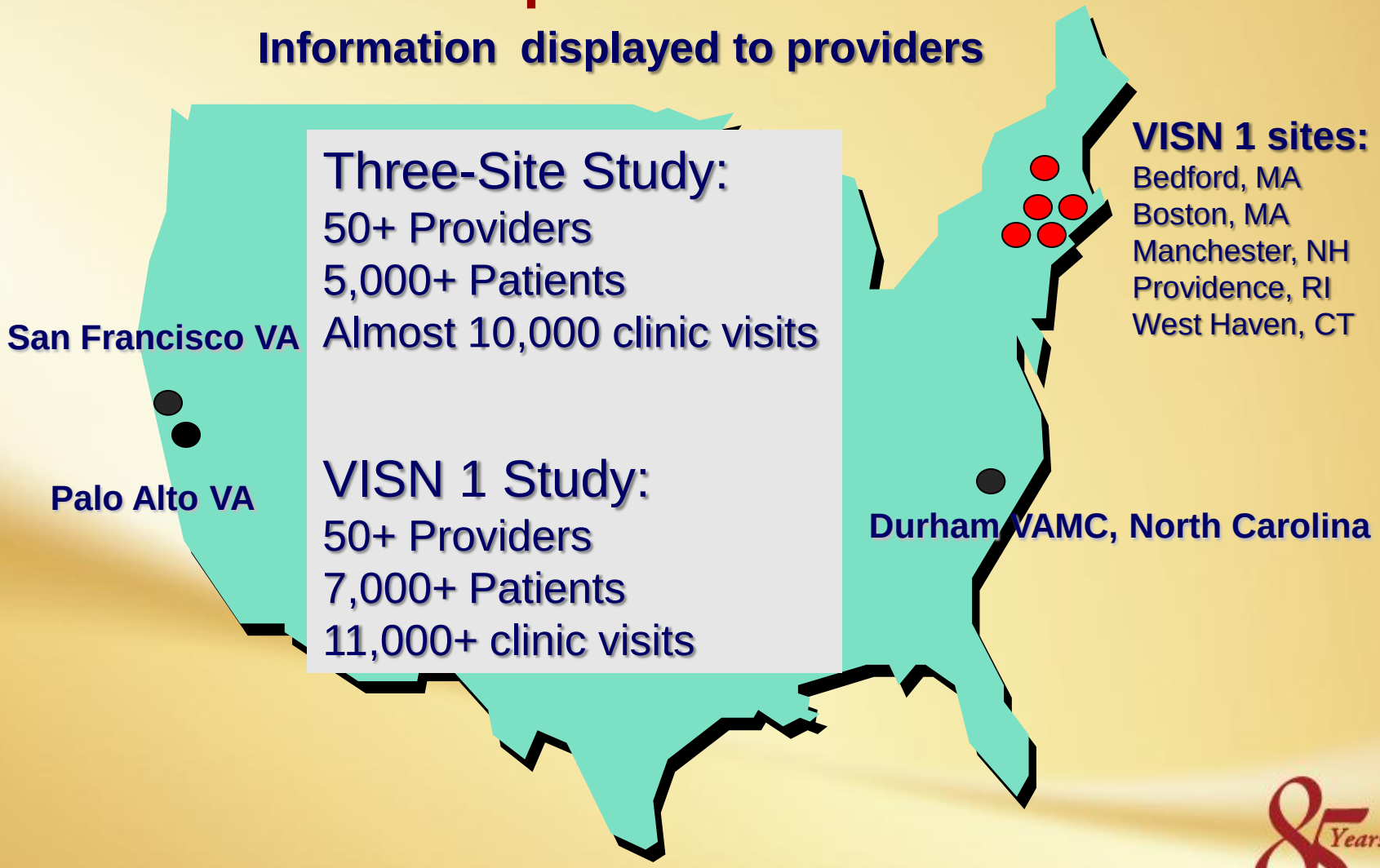


JAMIA 2002, 2004


ATHENA Hypertension Advisory
Patient SSN
Name:
Patient Summary
Most Recent BP in Database
Date
ENTER a New BP
Date
Update Advisory
Update & Save BP to EPRS
Guideline Goal: SBP < 140 and DBP < 90 [ presence of diabetes mellitus ]
BP apparently NOT UNDER CONTROL, based on most recent available BP.
Recommendations
Precautions
Assumptions
Lifestyle
Adherence
Glossary
BP Prescription Graphs
Recommend ADDING antihypertensive medication: BP ELEVATED based on most recent available BP; 7 sig. 9 months.
RECOMMENDATIONS DO NOT APPLY TO PREGNANT WOMEN (or women likely to become pregnant or nursing mother).
Compelling Indication
Relative Indication
Strong Contraindication
Relative Contraindication
Adverse Events
Consider one of the following therapeutic possibilities:
Click here for important ...
Reasons
Click here to provide ...
Add Thiazide Diuretic (HCTZ)
Diabetes
1st line drug for hypertension
Add ACE Inhibitors(lisinopril)
Diabetes_Mellitus
Add Cardioselective Beta Blocker (atenolol)
Diabetes_Mellitus
Add DHP Calcium Channel Blocker (felodipine, nifedip
Diabetes_Mellitus
Add Angiotensin II Receptor Blocker (irbesartan)
Diabetes_Mellitus
Your comments for the Guidelines Team (optional and welcome!)
Do not display Advisory for this clinic visit again.
Recommendations considered
No Read
Not a clinical priority today
Complete clinical information may not be available through the computer system. Please use all the information that you have about the patient together with your clinical judgment to decide on the best therapy for this patient.

# ATHENA-HTN Implementation

## Information displayed to providers



# Clinician Response to ATHENA-HTN

- Use ATHENA-HTN extensively.
  - Speaks to usability and usefulness.
- Report ATHENA-Hypertension makes a difference in their medication prescribing.
- ATHENA-Hypertension continues to improve, based on user comments.

# Acknowledgments


- Support: VA Health Services Research & Development (HSR&D) and National Library of Medicine (NLM)
- Brian Hoffman, MD co-principal investigator
- Collaborators Eugene Oddone MD, Hayden Bosworth PhD
- Stanford BioMedical Informatics Research (BMIR) EON Group: Mark Musen, Samson Tu, Ravi Shankar, Martin O'Connor, Aneel Advani
- ATHENA Group at VA Palo Alto: Bob Coleman, Susana Martins, Grace Yeh, Dallas Chambers, Dan Wang
- Former Trainees: Albert Chan, S. Nicki Hastings, Herb Szeto, Melissa Fischer, Michael Steinmann, Steve Lai, Nancy Lin
- Other collaborators/advisors: Lars Osterberg, Howard Strasberg, Michael Shlipak, Paul Heidenreich, Michael Gould, Paul Conlin, Denise Hynes, James Schlosser, and others
- VISN Collaborative MAVERIC staff and other VISN 1 Colleagues
- VA OI&T (formerly IRMS)
- Statisticians: Phil Lavori and Alex Sox-Harris (3-site study); Tyson Holmes (VISN 1 collaborative)
- ….And many others who have contributed to projects


# Future Directions

- Add More Disease Guidelines
  - Diabetes, chronic kidney disease, heart failure
- Add clinical information from free-text portions of the electronic health record

## Summary

**Improve health care for Veterans**


85 Years of DISCOVERY, INNOVATION, & ADVANCEMENT
For Veterans
VETERANS AFFAIRS RESEARCH & DEVELOPMENT