

# Chronic Critical Illness

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# Acute Critical Illness

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graph TD; A[Acute Critical Illness] --> B[Recover quickly]; A --> C[Die during acute illness]; A --> D[Require prolonged mechanical ventilation<br/>Elective tracheotomy<br/>Continued high levels of nursing care<br/><u>Become Chronically Critically Ill</u>];
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Recover quickly

Die during  
acute illness

Require prolonged mechanical ventilation  
Elective tracheotomy  
Continued high levels of nursing care  
Become Chronically Critically Ill

# Chronic Critical Illness

- A result of modern critical care:
  - Patients who, in the past, would have died from their acute illnesses no survive but require prolonged life support, as long as months or years after the catastrophic illness
  - Mainly elderly individuals with multiple co-morbid conditions who survive a life-threatening episode of sepsis but end up profoundly debilitated and dependent on mechanical ventilation
  - Require extensive and expensive care

# Who Is Chronically Critically Ill (CCI)?

- Expression first used by Girard and Raffin, 1985
- In various studies referred to as . . .
  - “Difficult to wean patients”
  - “Patients requiring prolonged mechanical ventilation”
  - “Patients with protracted critical illness”
  - “Patients with prolonged critical illness”

# One proposed working Definition of CCI

- Those ICU patients who have an elective tracheotomy performed for failure to wean from mechanical ventilation.
  - Formerly DRG 483, now DRG's 541 and 542
  - A discrete demarcation point in the episode of illness
  - An elective tracheotomy isn't done if a patient is expected to wean with the ET tube or to soon die
  - No specific time requirement, includes clinicians' judgment about patient's long-term prognosis

# Concerns with this definition

- Using DRGs 541 or 542 to define chronic critical illness may introduce bias because of trends towards earlier placement of elective tracheostomies
- Using duration of mechanical ventilation >21 days to define “prolonged mechanical ventilation” identifies a group with higher mortality and higher hospital costs than using DRGs 541 and 542

- Cox, Carson, Lindquist, et al, *Crit Care*, 2007;R9  
(doi:10.1186/cc5667)

# Chronic Critical Illness in the USA

- > 5 Million patients admitted to ICUs in USA each year
- 1/3 require mechanical ventilation
  - Approximately 20% require ventilation > 7 days, 1-2% > 30 days
    - More than 330,000 patients require > 7 days of mechanical ventilation
    - More than 25,000 patients require > 30 days of mechanical ventilation

# Care Environments

- Intensive Care Units
- Post-ICU Respiratory Care Units
- Regular in-hospital nursing units
- Long Term Acute Care (LTAC) Hospitals
  - Freestanding LTAC hospitals
  - Hospital-In-Hospital (specialized LTAC within general hospital)
  - N = 408 (Sept. 2003)
  - Currently 22,000 beds nationally, projected need for 81,000 beds

# Age Distribution

HCUP National Inpatient Sample: Discharges for DRG 483, 1997. Estimated n = 88,000

Age Groups	Number (%)
Age 0 to 21	5,280 (6%)
Age 22 to 49	17,600 (20%)
Age 50 to 64	19,360 (22%)
Age 65 to 74	22,000 (25%)
Age 75 to 84	19,360 (22%)
Age 85 or older	4,400 (5%)

# Estimated costs

Age Groups	LOS (median/mean)	Charges (\$1,000) median (range)
0-21	30/53	120 (.6-2,100)
22-49	30/39	120 (1.2-2,870)
50-64	32/40	131 (0.07-2,220)
65-74	32/40	135 (1.9-2,553)
75-84	32/41	134 (0.3-5,186)
≥ 85	32/40	120 (0.6-977)

National Inpatient Sample: Discharges for DRG 483, 1997

# Survival from Chronic Critical Illness

<u>Study</u>	<u>Hospital Type</u>	<u>Number Patients</u>	<u>Age</u>	<u>Hospital Survival</u>	<u>One Year Survival</u>
Spicher 1987	Acute	250	60	39.6%	28.6%
Gracey 1992	Acute	104	66.3	57.7%	38.7%
Scheinhorn 1997	RWC	1,123	69	71%	37.9%
Carson 1998	LTAC	133	71	50%	23%
Seneff 2000	LTAC	1,702	71	49%	33% 180 days

# Chronic critical illness: Long-term survival

- Long-term mortality of 162 patients admitted to in-hospital long-term weaning unit at the Cleveland Clinic (2003-2006)<sup>1</sup>
  - 1-year mortality: 57%
  - 2-year mortality: 68%
  - 3-year mortality: 73%
  - 4-year mortality: 76%
  - 5-year mortality: 81%
- 1-year survival related to age<sup>1</sup>:
  - <65 years: 55%
  - 65-74 years: 40%
  - 75-84 years: 29%
- Long-term survivors of chronic critical illness suffer significant functional limitations

1. JK Stoller et al., *Chest*, 2003;124:1892-99; 2. Cox, et al, *Crit Care*, 2007;R9 (doi:10.1186/cc5667)

# Chronic critical illness: Functional status of survivors

- Many who survive CCI live with significant functional impairment
- Activities of Daily Living
  - 3 months: 32% completely dependent in **all** ADLs
  - 6 months: 33% completely dependent in **all** ADLs
- Functional Independence Measure - Motor Score
  - Sum of 13 items, 1-7 scale, maximum dependency = 13
  - Hospital admission:  $75.2 \pm 24.5$
  - RCU discharge:  $18.0 \pm 11.9$  (n = 43)
  - 3 months:  $46.1 \pm 30.5$  (n = 22)
  - 6 months:  $57.4 \pm 34.4$  (n = 19)

*Slide courtesy of J.E. Nelson, MD, JD, The Mount Sinai School of Medicine*

## *Consensus statement*

- Management Of Patients Requiring Prolonged Mechanical Ventilation: Report Of A NAMDRC Consensus Conference

*–Chest 2005;128:393*

# One model for caring for CCI: Mount Sinai Hospital, New York, NY

- Distinct Respiratory Care Unit (RCU): dedicated long-term weaning unit within the acute-care hospital
- Goals of Care:
  - Recovery of lost strength and function
  - Liberation from mechanical ventilation
  - Palliation of symptom burden
  - Minimization of acquired morbidities that may impact on future level of function and quality of life
- A 14 bed "post-ICU" environment specifically for mechanically ventilated patients from the adult ICUs
- Staffed by specialists in pulmonary and critical care medicine, nurses (3:1 ratio), nurse practitioners, respiratory therapists, social worker

# *Emphasizing the "4 R's"*

:

Respiratory

Recovery

Recuperation

Rehabilitation

# Program of care

- Interdisciplinary Care Map
- Protocolized but flexible weaning protocol
- At RCU admission, nutritional/metabolic screens, early tailored metabolic support
- Specific expertise in nutrition/metabolic support, psychiatry, rehabilitation, neurology and wound healing
- Criteria for when to call for help

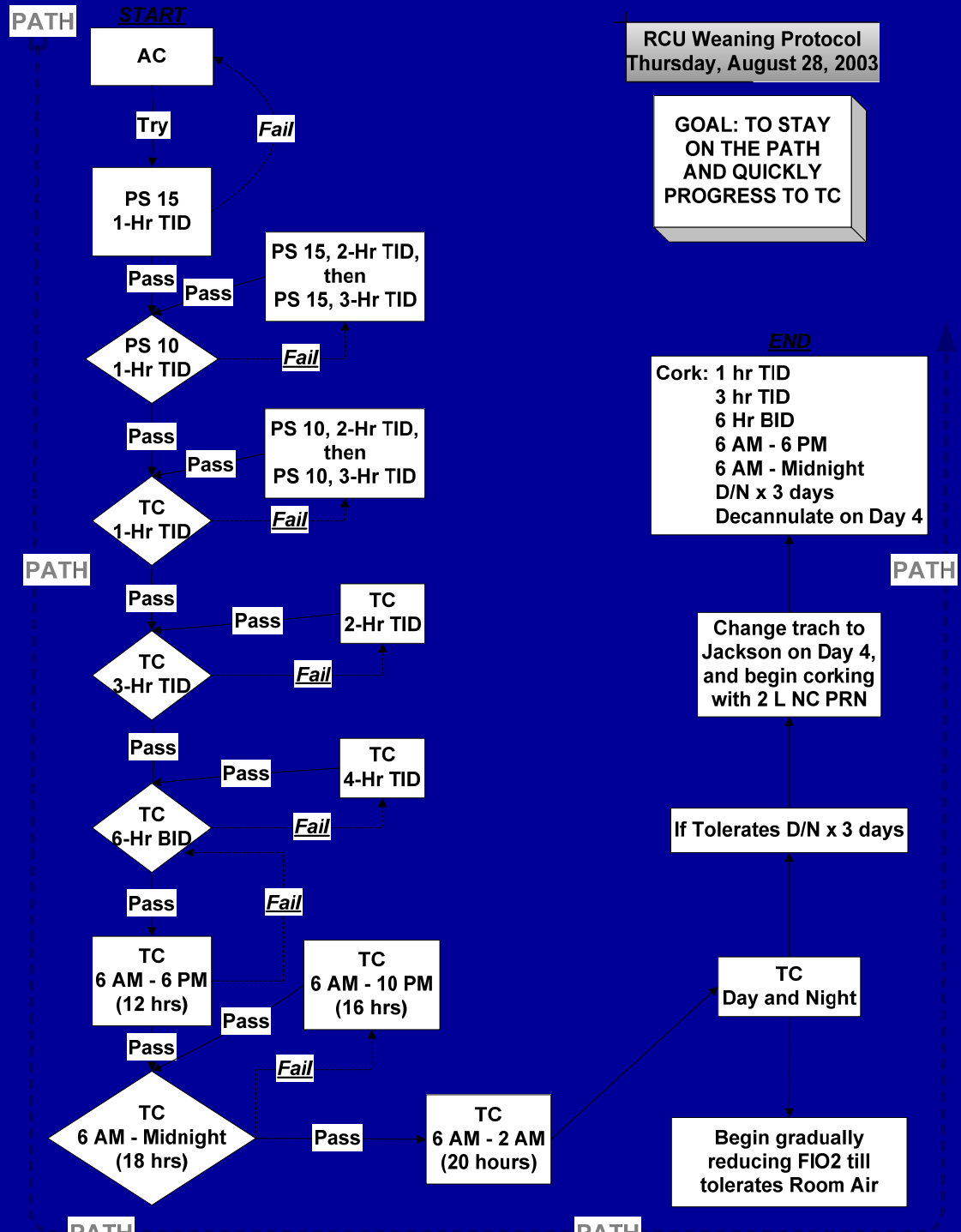
# Respiratory Care Unit Weaning Protocol Mount Sinai Hospital, New York City, USA

Key:

AC= assist control

PS= pressure support

TC= trach-collar



# Family support

- At RCU admission, families receive a booklet that describes prognosis and possible outcomes
- Vital component of recovery and hospital discharge
- Family meeting second week of RCU stay
- N.P.s, social worker and psychiatrist work closely with families to understand expectations, plan for discharge

# Barriers to discharge from RCU

- Pts. are frequently colonized with resistant organisms
- Pressure ulcers
- Pts often need continued life support:
  - Mechanical ventilation
  - Hemodialysis or parenteral nutrition
- Socioeconomic and family issues
- Unrealistic expectations (family and health care professionals)
- Other:
  - No consent for percutaneous gastrostomy tube, iatrogenic complications

# Other weaning protocols

- D. Scheinhorn, et al, *Chest*, 2001;119:236
  - Utilizes Intermittent Mandatory Ventilation (IMV) mode with integrated assessments of spontaneous breathing trials
  - Implemented by respiratory therapists
  - Shorter duration of mechanical ventilation compared to historical control subjects

The Biology  
of Chronic  
Critical  
Illness

Admitted to RCU

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graph TD; A[Admitted to RCU] --> B[Improvement & recovery]; A --> C[No recovery from acute illness]; B --> D["Liberation from Ventilator  
Improvement in Albumin  
Participate in Physical Rx"]; D --> E["Discharge to Rehabilitation  
or Home"]; C --> F["Repeated Septic Episodes  
Remain Ventilator  
Dependent"]; F --> G["Die or Discharge to SNF  
on Ventilator"];
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Improvement &  
recovery

No recovery from acute  
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Liberation from Ventilator  
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Participate in Physical Rx

Repeated Septic Episodes  
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Discharge to Rehabilitation  
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# Common physiologic disturbances in CCI

- Disruption in anterior pituitary hormones secretion
- Bone hyperresorption
- Male hypogonadism
- Psychiatric disorders
- "Immune exhaustion"
- Severe symptom burden
- Bone marrow suppression
- Specific wasting syndrome leading to adult kwashiorkor-like malnutrition
- Critical illness polyneuropathy
- Pressure ulcers
- Recurrent infections

# Fundamental question: Is there a specific syndrome of CCI?

- Syndrome: a combination of signs and/or symptoms that forms a distinct clinical picture indicative of a particular disorder
  - *Concise Medical Dictionary*, 2000, Oxford University Press
- Syndrome of CCI:
  - Follows an acute critical illness, usually with at least one episode of sepsis
  - Metabolic, endocrine, physiologic and immunologic abnormalities
  - Continued requirement for mechanical ventilation
  - Continued need for high level nursing care
  - Weeks to months

# Care of patient with CCI at the Mount Sinai Hospital

- Extensive evaluation of nutritional and metabolic status on admission to the RCU
  - Complete blood count, serum chemistries, pro-thrombin time
  - Capillary glucose measurement q6 hours
  - Hemoglobin A1C
  - Homocysteine level
  - Ammonia
  - Pre-albumin
  - 24-hour urine for urea nitrogen
  - TSH, free T4
  - Intact PTH, 25-hydroxy-vitamin D, 1,25-dihydroxy-vitamin
- Optional
  - Testosterone, total and bioavailable, prostate specific antigen
  - Methylmalonic acid
  - Iron studies
  - Morning serum cortisol, 24-hour urine cortisol
  - Co-syntropin stimulation test (1 mcg or 250 mcg)
  - Anti-thyroid antibodies

Adapted from: Mechanick JI.  
*Curr Opin Clin Nutr Metab Care* 2005;  
8:33-39.

# Nutritional Pharmacology In CCI Patients:

## Some supplements to consider

Agent	Effect	Dose	Comment
Calcitriol	↑calcium absorption from GI tract	0.25-0.5 mcg qDAY (IV or enterally)	Must monitor serum Ca, PO <sub>4</sub>
Carnitine	Fatty acid oxidation	1 gm enterally t.i.d.	Consider for patients on valproate or with diminished gluconeogenesis
Pamidronate	Decrease bone resorption	90 mg IV ONCE	May cause fever Avoid in patients with low Vitamin D
Vitamin D	Treatment of nutritional deficiency	50,000 units enterally once a week	Can take >1 month to replete stores
Zinc sulfate	May aid wound healing	220 mg enterally b.i.d.	Can induce copper deficiency, anemia

Adapted from: Mechanick JI. *Curr Opin Clin Nutr Metab Care* 2005; 8:33-39

# Critical illness and endocrine dysfunction

- Acute and chronic critical illness result in endocrine and metabolic abnormalities
- The following slides summarize some of these abnormalities and when they occur during the course of critical illness

Hormone,	Acute	Chronic
<b>Somatotrophic Axis</b>		
Pulsatile GH	Increased	Decreased
GH Binding Protein	Decreased	Increased
IGF-I	Decreased	Very Decreased
<b>Thyrotrophic Axis</b>		
Pulsatile TSH	Increased/No change	Decreased
T4	Increased/No change	Decreased
T3	Decreased	Very Decreased
rT3	Increased	Increased/No change

Hormone	Acute	Chronic
<b>Gonadotrophic Axis</b>		
Pulsatile LH	Increased/No change	Decreased
Testosterone	Decreased	Very Decreased
<b>Pituitary-adrenocortical Axis</b>		
ACTH	Increased	Decreased
Cortisol	Very Increased	Inc/No Change/Dec
<b>Lactotropic Axis</b>		
Pulsatile Prolactin	Increased	Decreased

Van den Berghe G. *Frontiers in Neuroendocrinology* 2002; 23:370-91.

# Wasting syndrome of chronic critical illness

- Possible endocrine abnormalities:
- Growth hormone-insulin-like-growth factor-1 axis
  - Normal physiology: diurnal peaks of circulating growth hormone (GH) levels, approx. 6 am and 9 pm each day
  - Acute phase of critical illness: higher circulating GH levels with loss of diurnal variation and more frequent peaks, peripheral tissue resistance to GH
  - Chronic critical illness: lower circulating GH levels with loss of diurnal variation, peripheral tissues regain response to GH
- G. van den Berghe, *Crit Care Clin*, 2002

# Wasting Syndrome: Male Hypotestosteronemia

- 30 consecutive CCI men, median age 73 yrs
- **Total testosterone** by radioimmunoassay after purification by column chromatography
- **Bioavailable testosterone** (non-sex hormone binding globulin [SHBG] bound testosterone), by separation of the SHBG bound steroid from the albumin bound and free steroid with ammonium sulfate

# Wasting Syndrome: Male Hypotestosteronemia

- Total testosterone =  $104 \pm 96$  ng/dl
- Bioavailable testosterone (bioT) =  
 $19 \pm 20$  ng/dl ( $16 \pm 9\%$  of total testosterone)
- BioT levels averaged  $11 \pm 11\%$  of levels found in age-matched normal men
- 29/30 (96%) men had bioT levels well below the lower limit of normal for their age range.
- *However, it is uncertain whether supplementing testosterone leads to improved clinical outcomes*

# Hypothalamic-Pituitary-Adrenal Axis

- Acute critical illness
  - CRH, cytokines and NE stimulate ACTH
  - Hypercortisolism
    - Diverts fuels to vital organs and suppresses anabolism
    - Mutes inflammatory cascade to protect from overstimulation
- Chronic critical illness
  - Endothelin possibly maintains hypercortisolism
  - ANP/substance P inhibit ACTH?
  - Prolonged endogenous hypercortisolism may impair wound healing and cause myopathy.
  - This mechanism eventually fails!

# Hypothalamic-Pituitary-Adrenal Axis: “adrenal exhaustion”

- 20-fold increase (25-40%) of adrenal insufficiency in critically ill patients > age 50 > 14 days in ICU
- “Adrenal Exhaustion Syndrome”
  - Marik & Zaloga. *Chest* 2002; 122:1784-96
  - Acquired in the ICU
  - Probably due to a prolonged inflammatory response, with chronic secretion of systemic cytokines and other HPA suppressive substances
- Hypercortisolism + decreased DHEAS + decreased Prolactin = possible susceptibility for infections

# “Immune Exhaustion”

- At RCU admission, 8 of 22 patients had low *in vitro* response by peripheral lymphocytes to Candida Antigen (LSA assay)
- 5/8 (63%) of 8 low responders died; 1/14 (7%) above normal responders died.
- Initial pro-inflammatory phase in acute sepsis replaced by anti-inflammatory features:
  - Decreased monocyte function
  - Suppression of proinflammatory cytokines (TNF, IL-1, IL-8)
  - Enhanced anti-inflammatory cytokines (TGF-beta, IL-1ra, IL-10)
  - Lymphocyte apoptosis

# Bone Hyperresorption

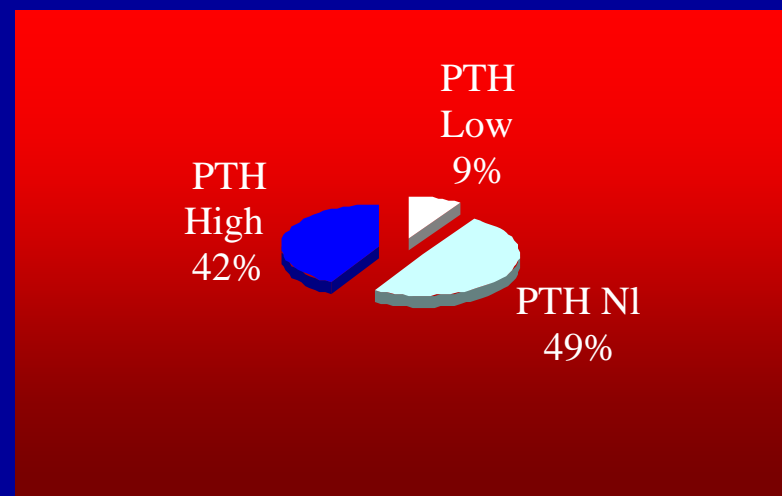
- CCI pts are at risk for accelerated bone loss due to:
  - Vitamin D deficiency
  - Prolonged immobility
- Identification and treatment of bone loss may prevent debilitating fractures after recovery

# Bone hyperresorption: Laboratory evaluation

- 24-hr urine within 48 hours of RCU admission
- Urine N-telopeptide (NTx) measured, Osteomark<sup>®</sup> assay
- Serum Intact PTH, 25-vitamin D, 1,25-vitamin D
- Elevated serum intact PTH level diagnostic of physiologically significant vitamin D deficiency
- Elevated Urine NTx = Abnormal Bone Resorption
- *If* NTx elevated, then:
  - Low PTH = Immobilization
  - High PTH = Vitamin D deficiency
  - Normal PTH = Both

# Prevalence of bone hyperresorption in CCI

- 49 CCI patients
- Median age 73 yrs, M/F = 28/21
- 22 Medical, 27 Surgical
- Median ICU LOS = 20 days
- Post-tracheotomy till RCU transfer = 7 days
- *92% of population found to have Abnormal Bone Resorption*



Distribution of PTH levels among Subjects with high urine NTx

# Treatment of bone hyperresorption

- 157 CCI patients, 19 months, retrospective review
- 131 (83%) pts had ↑ urine NTx
- 55 pts:
  - ↑ NTx levels at RCU admission
  - Treated with either calcitriol alone (n = 44) or calcitriol + pamidronate (n = 11)
  - NTxs remeasured after treatment
- All pts received calcitriol (1,25-dihydroxyvitamin D<sub>3</sub>) 0.25 mcg/day enterally (Rocaltrol<sup>®</sup>) or IV (Calcijex<sup>®</sup>)
- At endocrinologist's discretion, pamidronate, 30 mg IVSS qD x 3 consecutive days given (~ \$532)
- Indications for pamidronate:
  - Elevated PTH + hypercalciuria
  - Very elevated urine NTx suggesting severe bone hyperresorption

# Response to Treatment

	Calcitriol	Calcitriol + Pamidronate
Urine NTX Pre Rx	187 ± 146	329 ± 238
Urine NTX Post Rx	178 ± 123	100 ± 85
<i>p</i> value	NS	< 0.01
PTH Pre Rx	93 ± 145	36 ± 29
PTH Post Rx	40 ± 28	53 ± 51
<i>p</i> value	0.02	NS

NTX Units = BCE/mmol Cr; PTH Units = pg/mL

# Pathogenesis of CCI: Hypothetical model

- Unremitting or repeated episodes of physiologic stress result in changes in the homeostatic set-points of various neuro-endocrine axes (hypothalamic-pituitary-adrenal, hypothalamic-pituitary-thyroid, etc.), which eventually result in tissue dysfunction and organ damage, and eventually in the syndrome of CCI
  - Mechanick, *Curr Opin Clin Nutr Metab Care*, 2005;8:33-9

# Important Future Questions

- Can we identify patients shortly after ICU admission into those at low and high risk for becoming CCI?
  - Epidemiologically
  - Biologically?
- What should the research agenda be in this area?
- How do cultural and social values contribute to the growing number of CCI patients?
- How does the financing of the health care delivery system contribute?
- Is this primarily an phenomenon in the USA?

*Critical Care Clinics,*  
Volume 18, Number 3  
(July 2002)

For further, in-depth reading