Skeletal Muscle and Aging: Going, Going, Gone

National Science Teachers Association

53rd National Convention

April 2, 2005

20 yr → 80 yr

(http://www.sarcopenia.com/)

Conditions Leading to Muscle Wasting (Atrophy)

- Limb immobilization (casting)
- Microgravity
- Prolonged bed rest/hindlimb suspension
- Tumor bearing
- Fasting/malnutrition
- Burns
- Infection
- Denervation
- Sarcopenia

Sarcopenia

"No decline with age is more dramatic or potentially more functionally significant that the decline in lean body mass. Why have we not given it more attention? Perhaps it needs a name derived from the Greek. I'll suggest *sarcopenia*."

I. H. Rosenberg, 1989

William J. Evans

Sarcopenia

Sarcopenia is age-related loss of lean muscle mass

Loss of ~40% of muscle mass by 80 years of age

Loss of locomotion due to atrophy of type IIb fibers

Loss of capacity to withstand injuries and diseases

(http://www.sarcopenia.com/)

Sarcopenia

"sarx" – flesh

"penia" – loss or deficiency

Class I

A value of lean body mass 1 to 2 standard deviations below the average value calculated in healthy, young adults.

Class II

A value of lean body mass greater than 2 standard deviations below the average value calculated in healthy, young adults.

Sarcopenia

Physical Consequences

Loss of muscle strength

Decreased mobility and stability

Increased risk of falls and injuries

Decreased reserve of body proteins and energy

Impaired metabolic adaptation and immunological response

Fiscal Consequences

Annual cost of sarcopenia in U.S. = $18.5 billion

- 35% of older adult population has moderate sarcopenia
- 10% of older adult population has severe sarcopenia
- $897 per sarcopenic individual

Annual cost of osteoporotic fractures in U.S. = $16.3 billion

Muscle Functional Characteristics

Muscle Fiber Type

Fast Twitch

- Oxidative (IIa)
- Glycolytic (IIb)
- Rapid shortening
- High power output
- Fatigable (Glycolytic)
- Fatigue resistant (Oxidative)
- Recruited in high intensity contractions

Slow Twitch

- Highly oxidative
- Slow shortening
- Low power output
- Fatigue resistant
- Recruited in all stages of muscle contraction

Muscle Functional Characteristics

Characteristics that determine strength

Fiber cross-sectional area

Fiber number

Fiber type

Ability to maximally recruit fibers

Protein content

Characteristics that change with age

Cross-sectional area decreased

Fiber number decreased

Fast twitch ‘converted’ to slow twitch

Inability to activate all fibers

“Defective” protein

Changes in Skeletal Muscle With Age

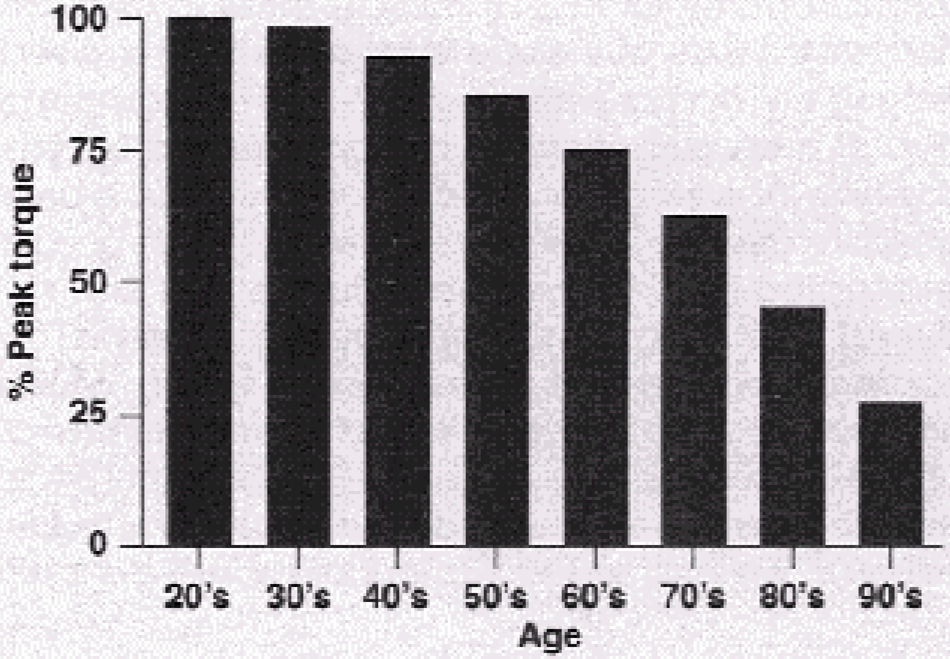

Fig. 3 - *Relative decline with age of peak leg muscle strength. Data were acquired from concentric isokinetic (0.52 rad s⁻¹) knee extension tests performed on 654 men and women aged 20-93 years. Values are expressed relative to the highest (20-30 years) group. Adapted from Lindle et al. (4).*

Strength is not lost uniformly:

- Across different muscles
- Across different types of movements
- Clinical observations: lower body strength declines faster than upper body
- Weightlifter data: relative disuse may be the reason for non-uniform strength loss across muscle groups

Changes in Skeletal Muscle With Age

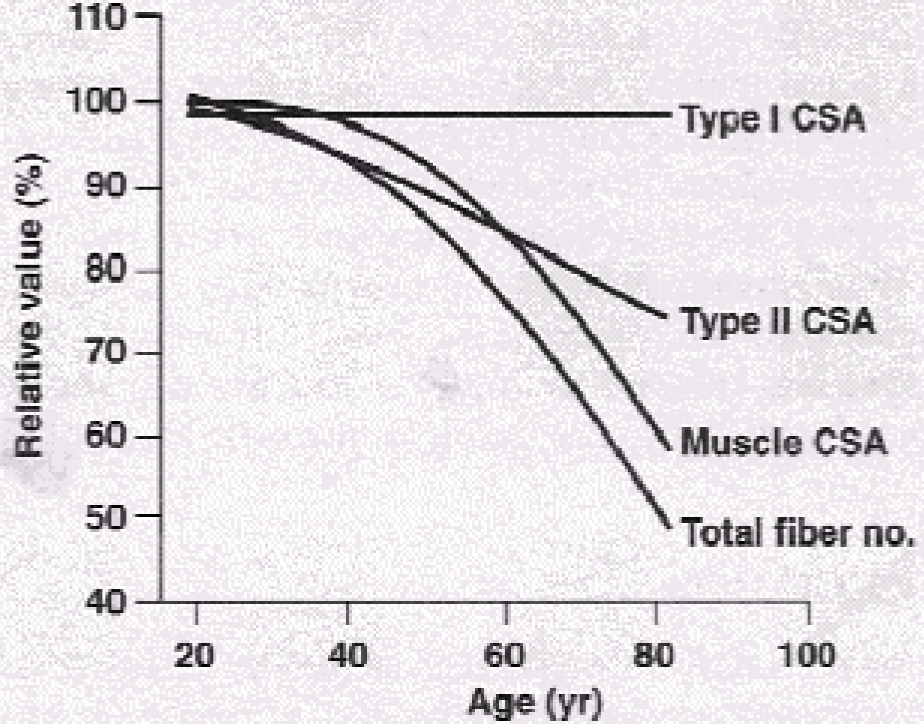

Fig. 2 - *Relative changes in muscle size parameters in humans. Data are summarized from whole vastus lateralis reported by Lexell et al. (18). The decline in total muscle cross-sectional area (CSA) appears to be due to both a reduction in total fiber number and atrophy of type II fibers. The proportion of fiber types was unchanged, but due to the reduced size of type II fibers, the proportion of the total area occupied by type II fibers also declined with aging.*

Muscle Functional Characteristics

Decreased # of fibers

Decreased cross-sectional area of fiber

Total Muscle Force

Fiber type changes: decreased fast twitch to slow twitch ratio

DNA damage: protein quality reduced

Force/Cross-sectional Area

Sarcopenia

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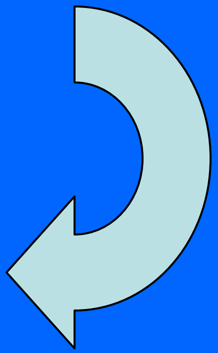
Sarcopenia
Potential Age-Related Causes

- Motor unit remodeling
- Protein synthesis
- Hormonal changes
- Reactive oxygen species and antioxidants
- Inflammation and cytokines
- Mitochondrial mutations
- Protein degradation
- Physical activity

Sarcopenia

"The Vicious Cycle"

Sarcopenia



Inactivity

Sarcopenia

"The Vicious Cycle"

Sarcopenia

"The Vicious Cycle"

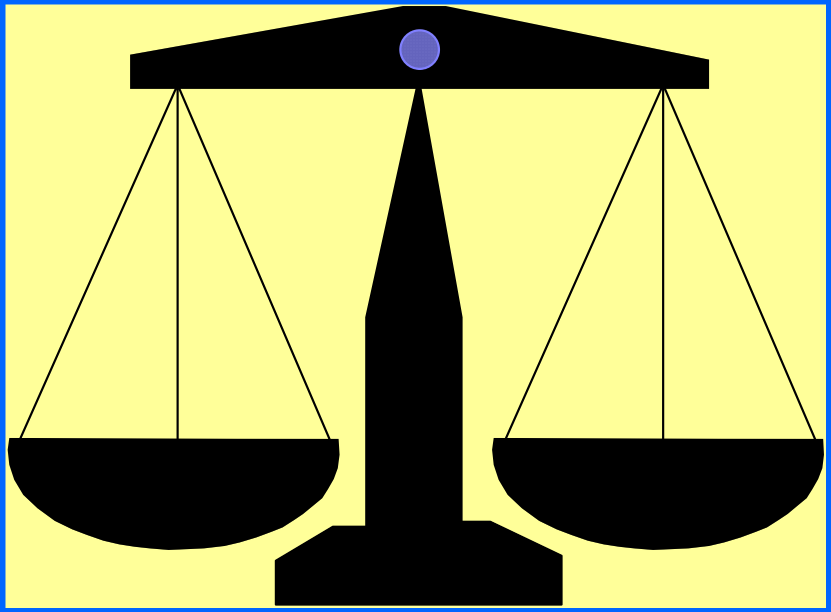
Do we lose muscle mass and therefore become inactive because activity is more difficult?

or

Do we become inactive with age and lose muscle mass as a result?

Protein Turnover

Synthesis vs Degradation



Steady State

Synthesis = Degradation

Muscle Protein Balance

↓ Physical Activity

↓ Anabolic Hormones
- GH
- Testosterone
- Estrogen

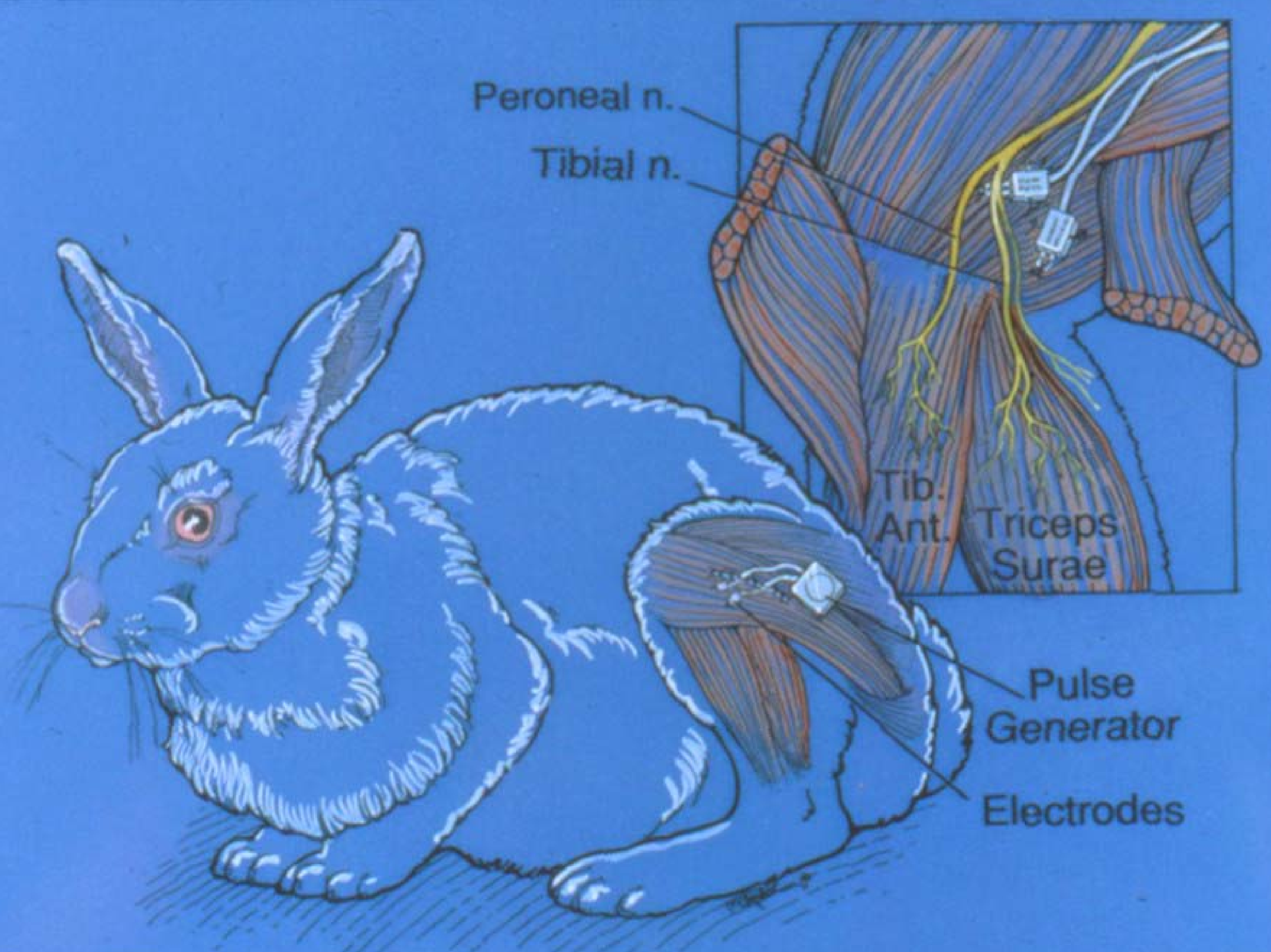
Protein Synthesis : Protein Degradation

↓ Protein Intake

↑ Protein Requirements

↓ α-motor neurons and functional motor units

↑ Catabolic Cytokines
- Interleukin 6


Peroneal n.
Tibial n.
Tib. Ant.
Triceps Surae
Pulse Generator
Electrodes

Pathways of Intracellular Protein Degradation

- **Lysosomal Mechanisms (Cathepsins)**
- **The Calpain System**
- **Mitochondrial Proteases**
- **The Ubiquitin-Proteasome Pathway**

Lysosomal Mechanisms

- Lysosomes digest "food" macromolecules into smaller subunits.
- The lysosome has hydrolytic enzymes to break down polymers into monomers.
- Subunits such as monosaccharides and amino acids are pumped across the lysosomal membrane into the cytoplasm.
- The lysosome is maintained at an acid pH to denature macromolecules, aiding hydrolysis.

The Calpain System

- Calcium-dependent neutral proteases
- Chimeras of a papain-like protease and a calmodulin-like calcium-binding protein
- Muscle-specific form is gene product responsible for limb girdle muscular dystrophy
- May degrade selected proteins during calcium-mediated signal transduction pathways

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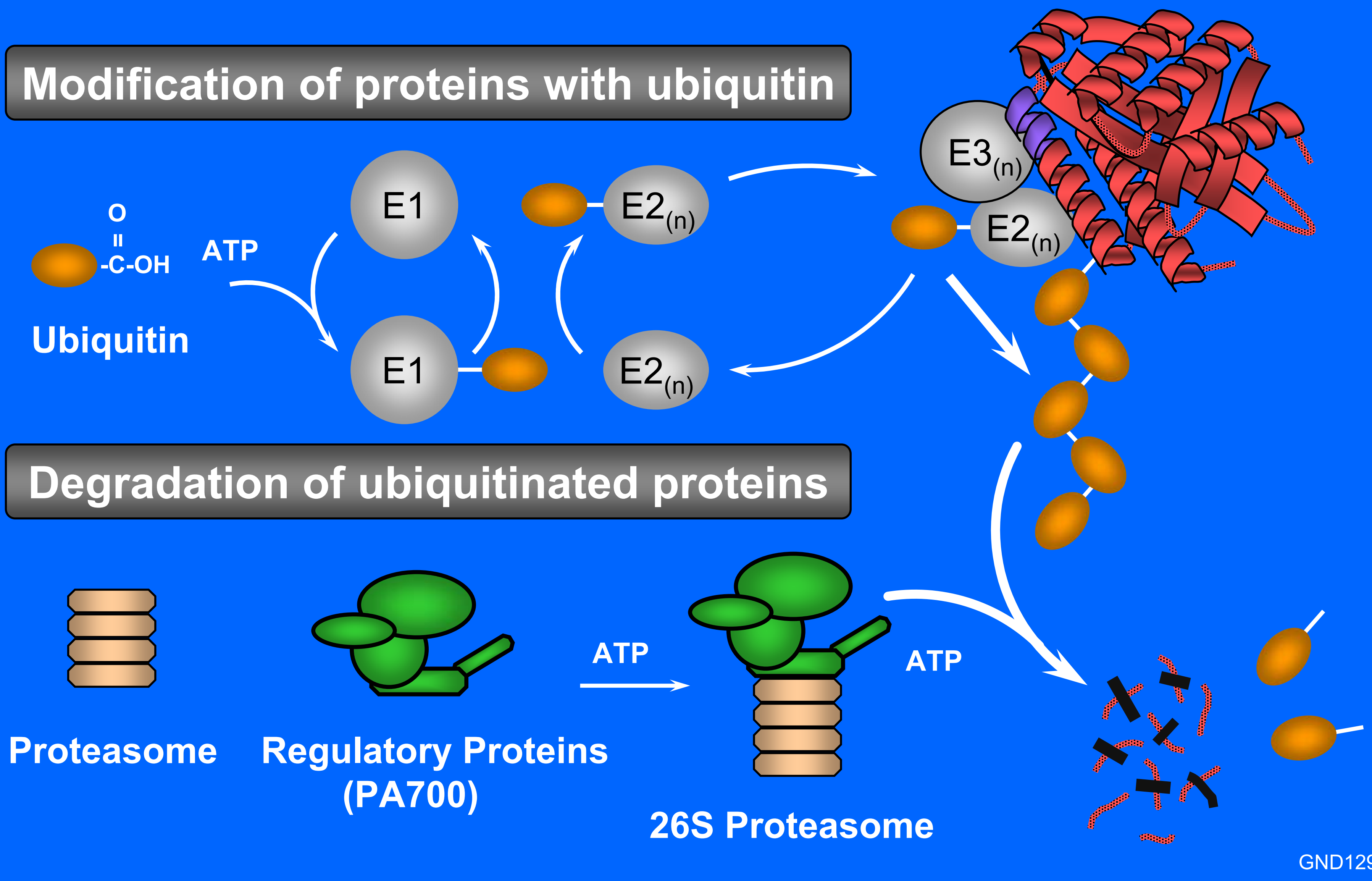
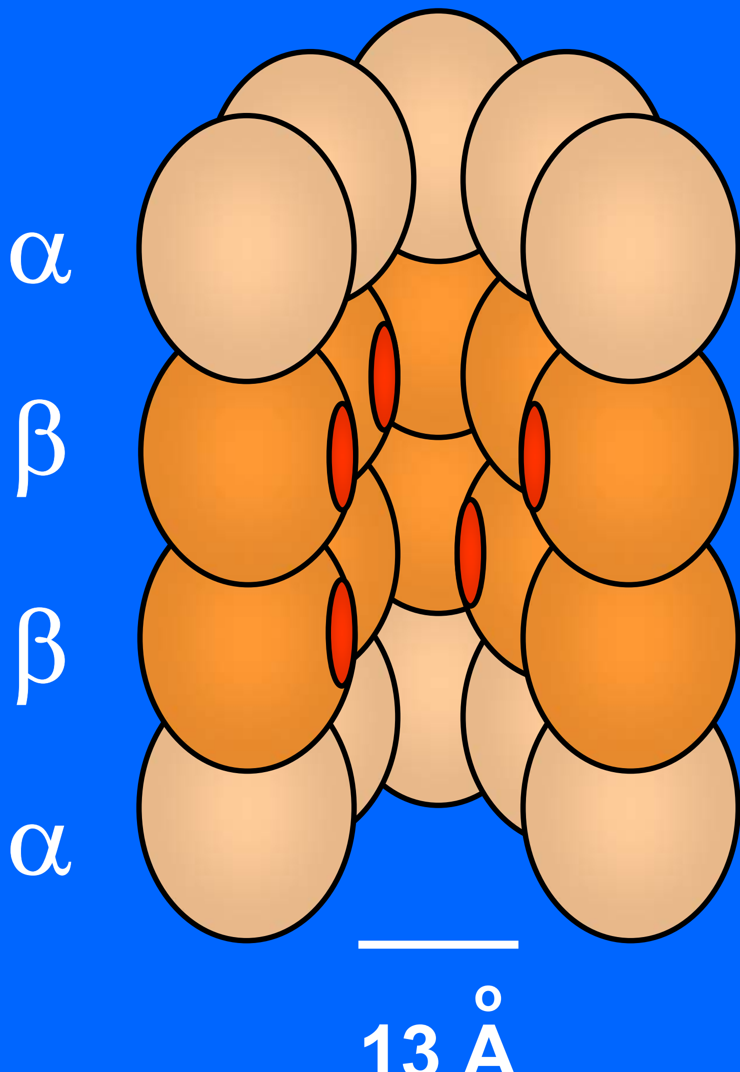
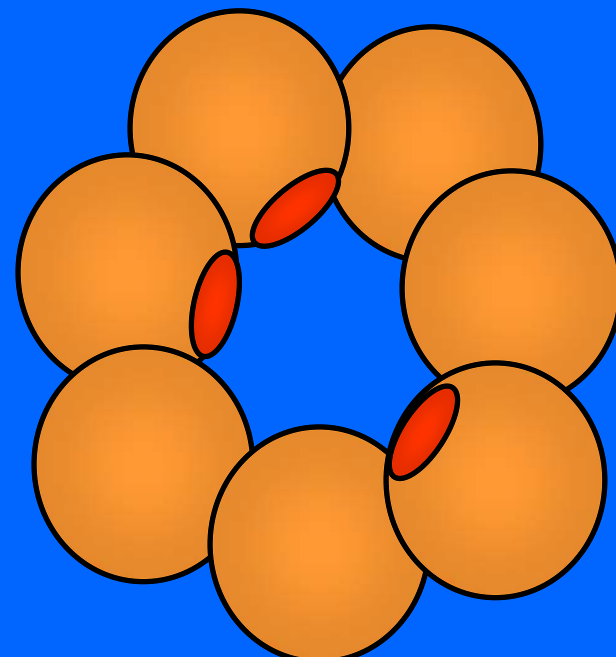
The ubiquitin-proteasome pathway of intracellular protein degradation



Topology of the proteasome's catalytic sites





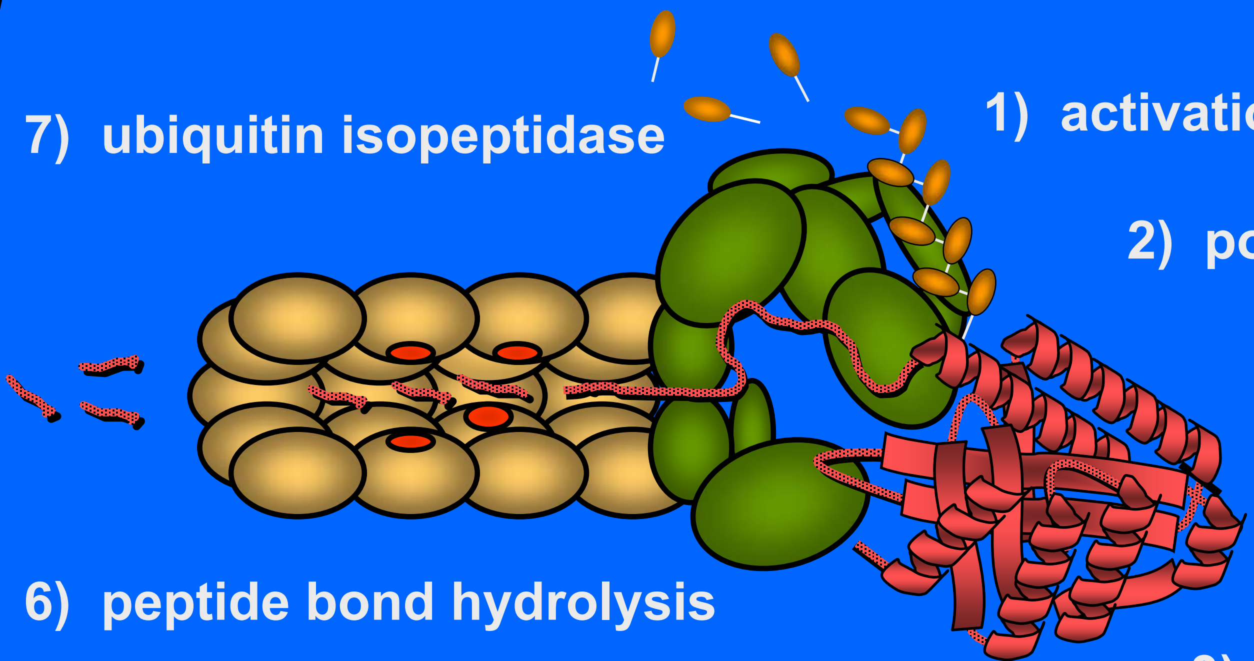
The proteasome's multiple catalytic sites are located on β subunits and face the interior channel

Proteolysis by the 26S proteasome

7) ubiquitin isopeptidase

1) activation by gating

2) polyubiquitin chain binding



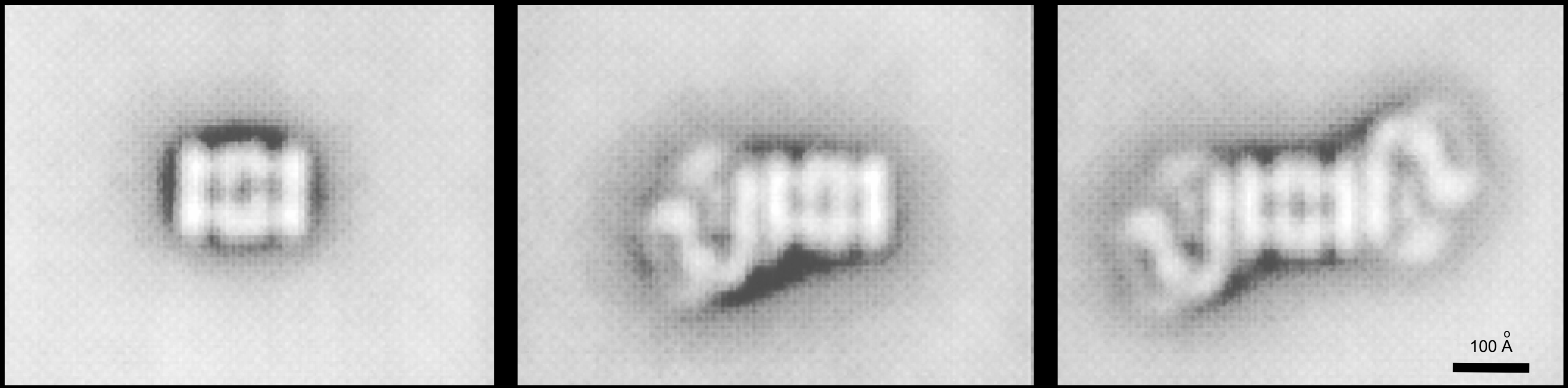
6) peptide bond hydrolysis

3) ATP hydrolysis

4) substrate unfolding

5) translocation of unfolded polypeptide chain

Electron microscopy of proteasome-PA700 complexes



Proteasome **Proteasome -PA700**

GND103

Sarcopenia and Ubiquitin-Proteasome Pathway

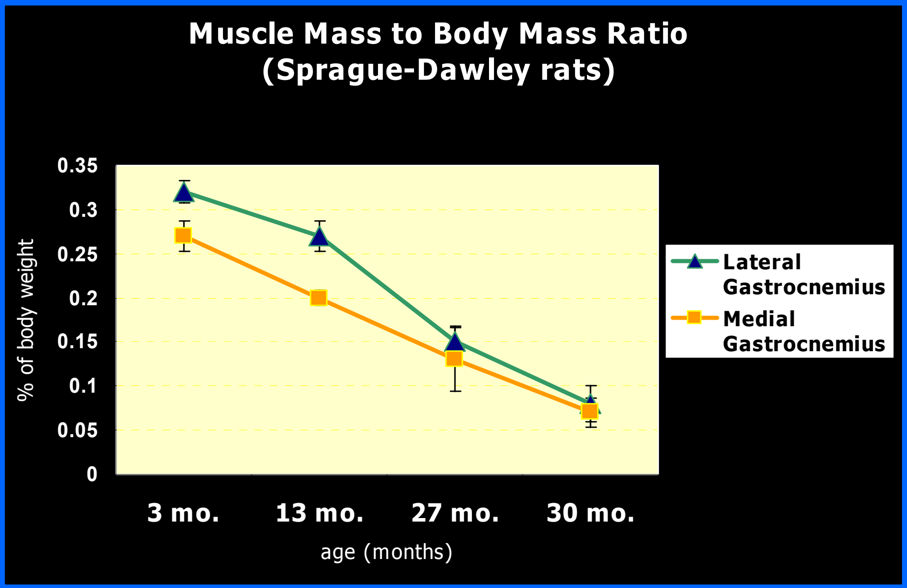
- Proteasome degrades >80% of cellular proteins

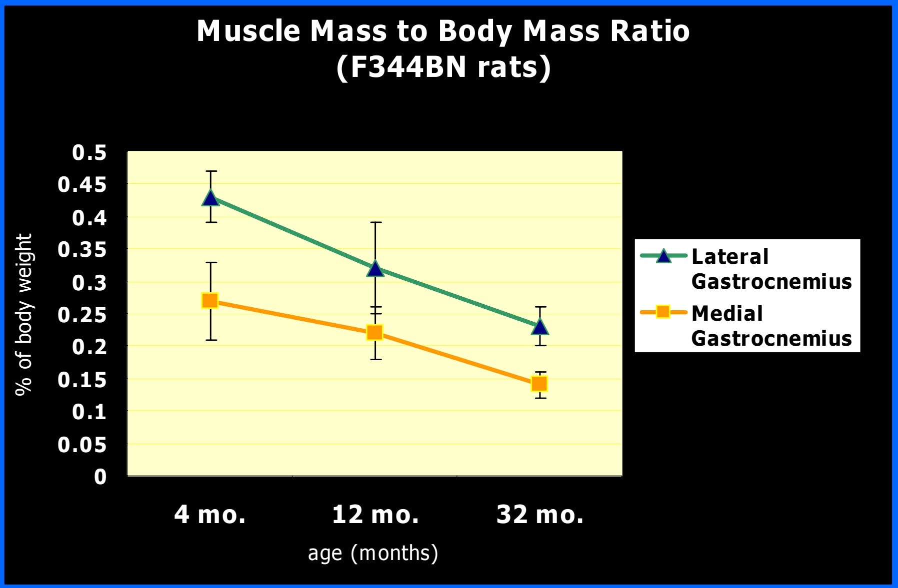
- Proteasome is the major player in a variety of atrophies

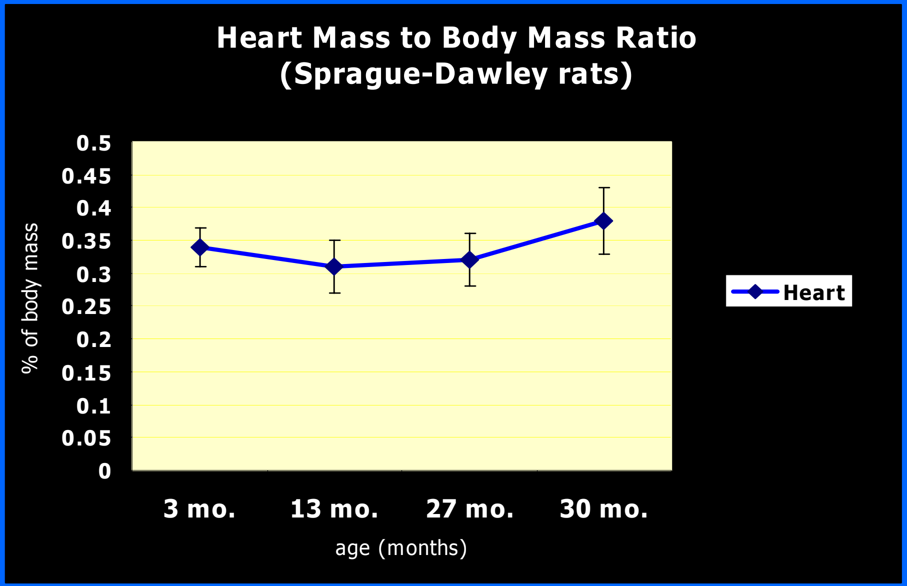
- Myofibrillar proteins are proteasome substrates

- Proteasome degrades oxidized, damaged, & denatured proteins

Change in Lean Muscle Mass with Age

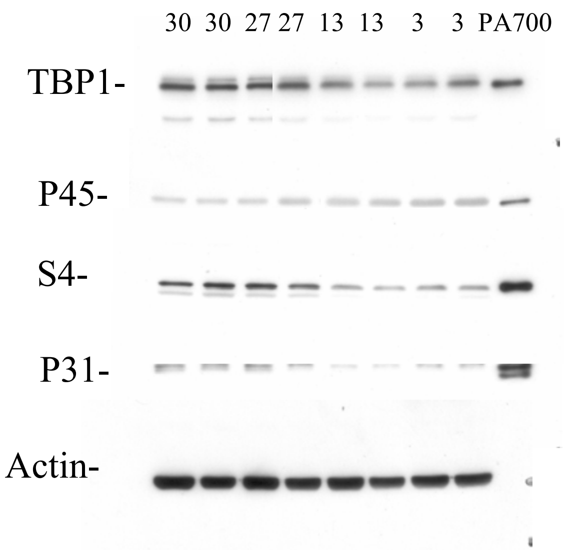


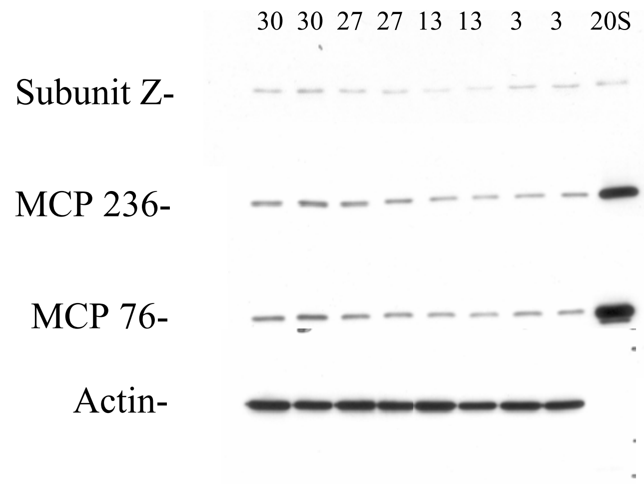


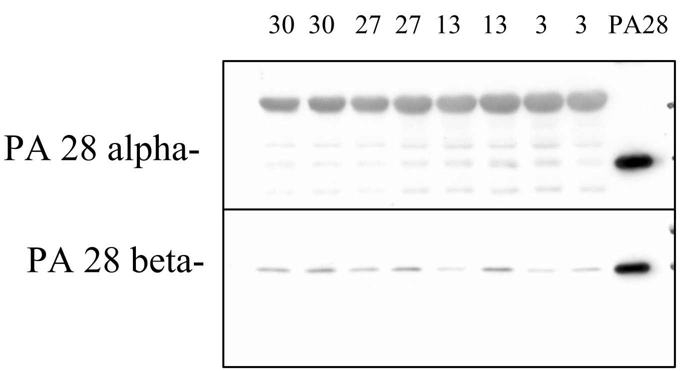


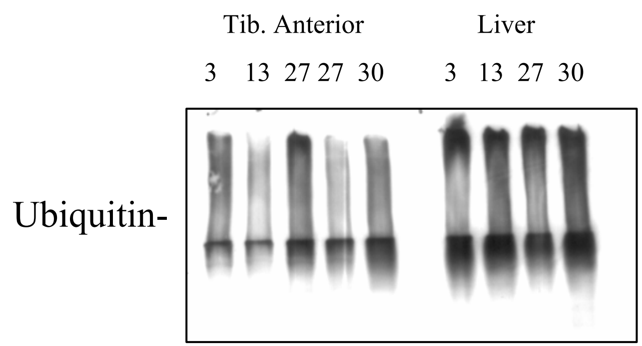
$$\frac{\text{Muscle mass (g)}}{\text{Body mass (g)}} \times 100 = \text{\% Body mass}$$

Endogenous Expression of Proteasomal Subunits

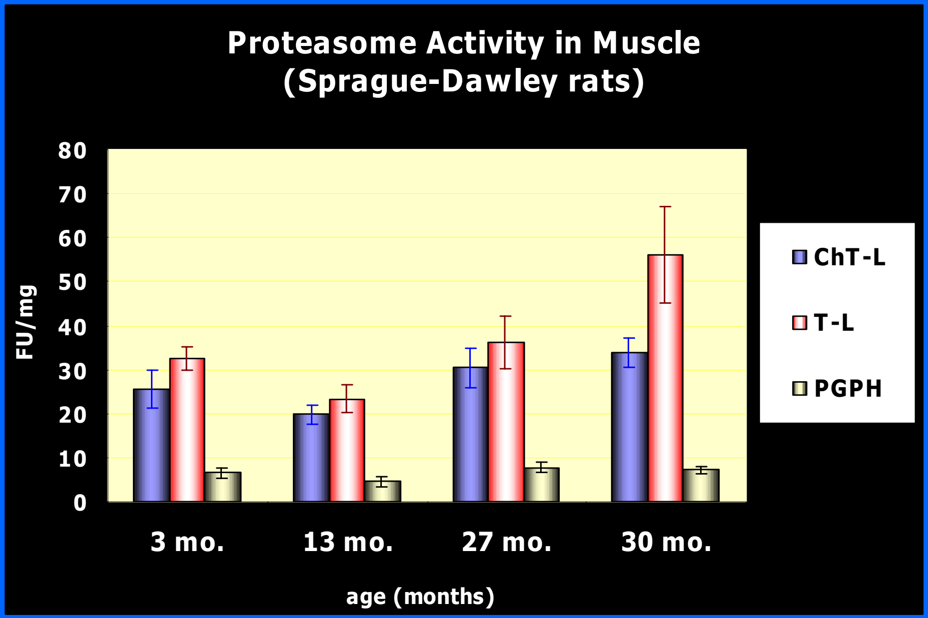


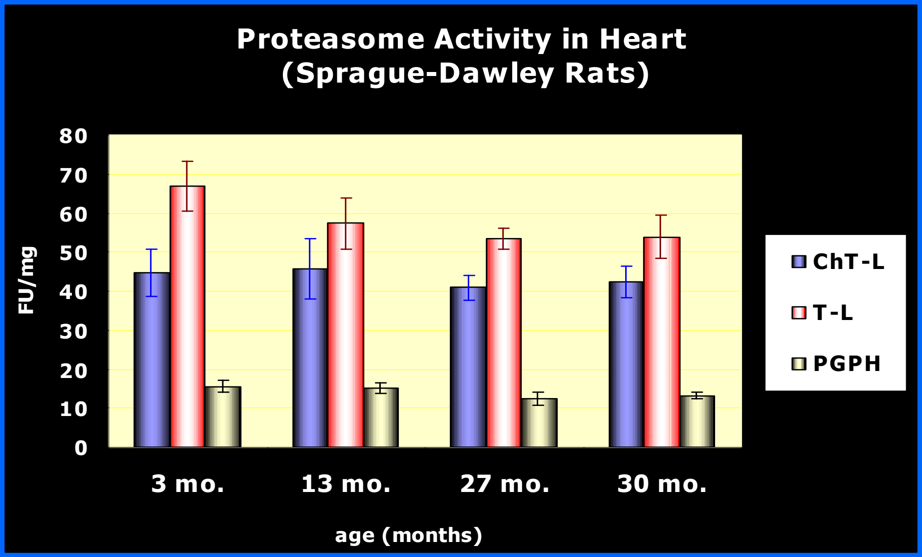






Proteasome Activity



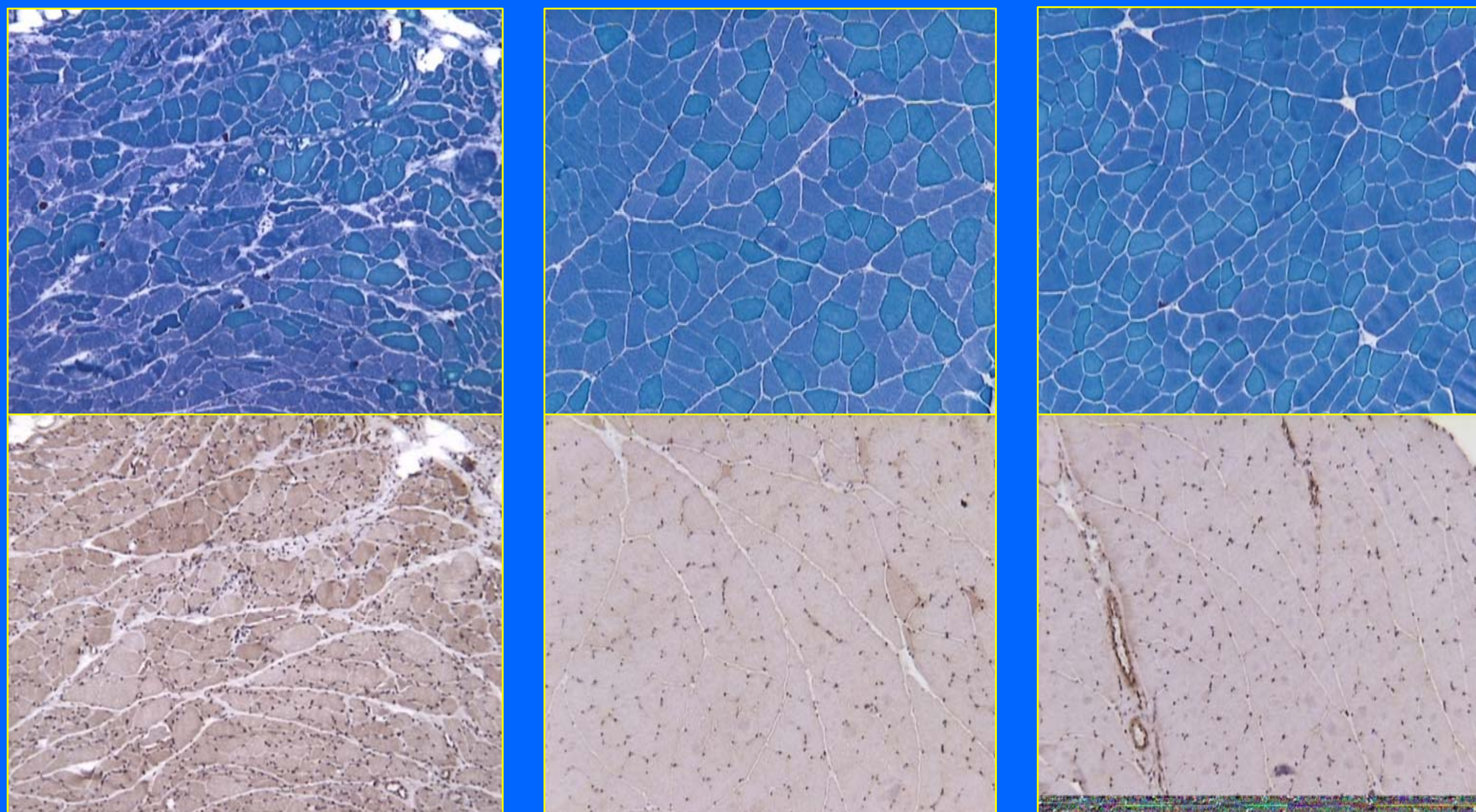


Sarcopenia at the Cellular Level (Sprague-Dawley Rats)

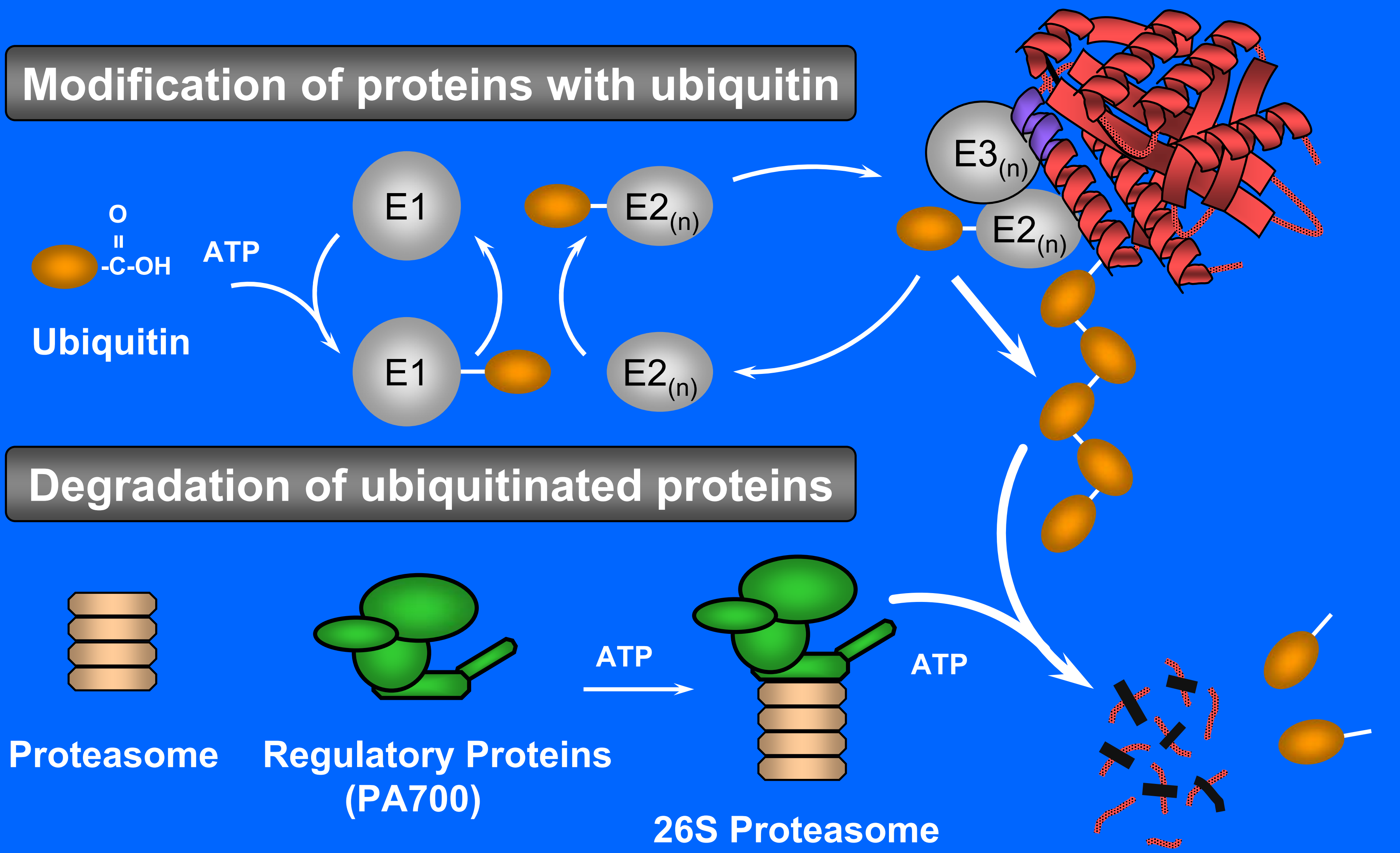
30 month | **13 month** | **3 month**

ATPase (metachromatic stain)

S4



The ubiquitin-proteasome pathway of intracellular protein degradation



GND129

Micro-array Analysis

↓

"Atrogenes"

↓

E3 Ubiquitin Ligases

MAFbx1

MuRF1

Exercise

- **Strength Exercises**
- **Endurance Exercises**
- **Balance Exercises**
- **Stretching Exercises**

National Institute on Aging

www.nia.nih.gov/exercisebook

American College of Sports Medicine

www.acsm.org


FITNESS

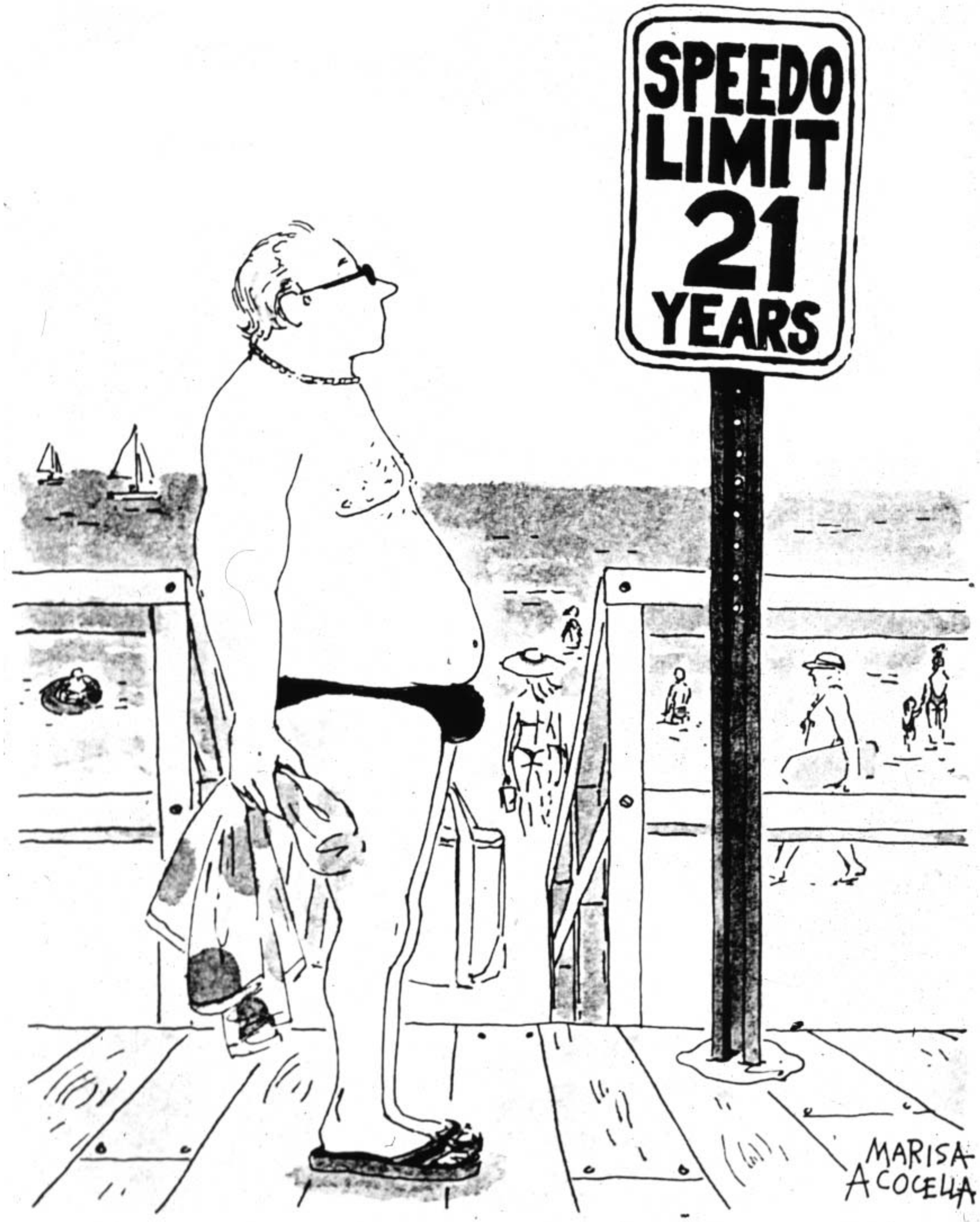
Indicators for Exercise and Diet Interventions

↑ Protein Synthesis : Protein Degradation

Strength Training

↑ Nutrition (Protein intake)

- Capacity of the muscle protein synthesis machinery is preserved until very old age (We can make muscle in old age)
- Significant gains in muscle mass (metabolic and strength benefits)
- Important gains in mobility and balance (improve quality of life and reduce risk of debilitating falls)


SPEEDO
LIMIT
21
YEARS
MARISA
ACOCELLA

http://www.utsouthwestern.edu/stars