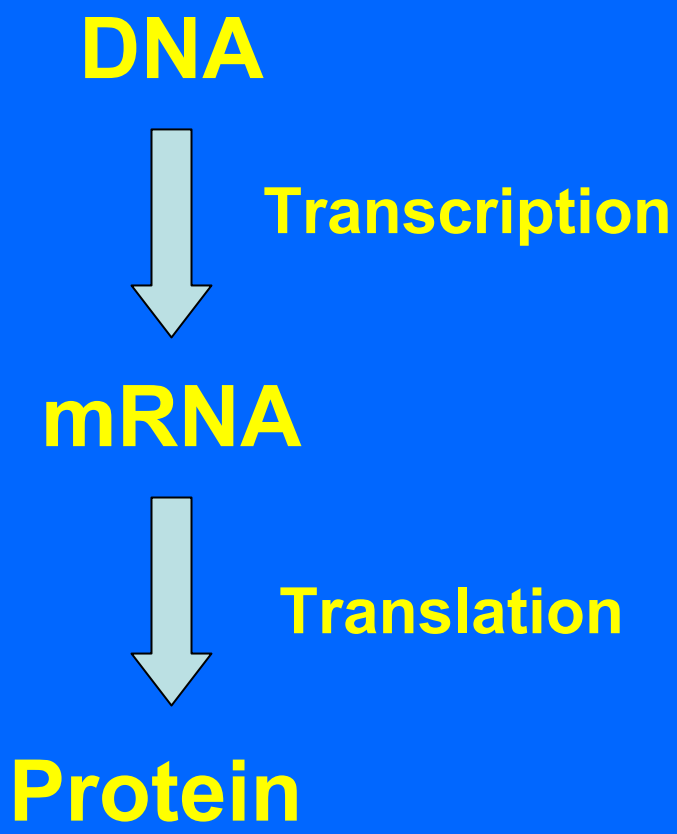
STARS

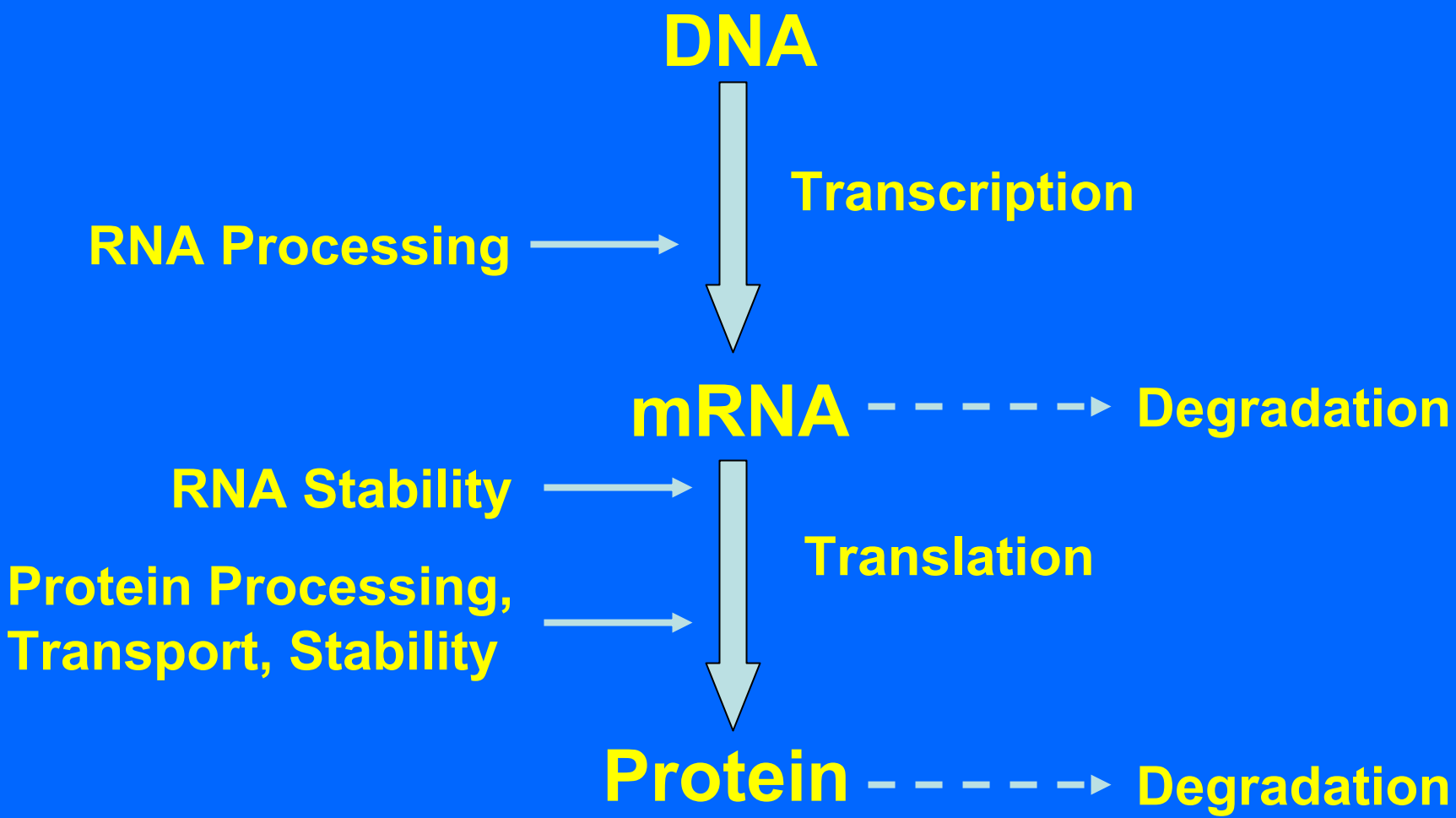
Science Teacher Access to Resources at Southwestern

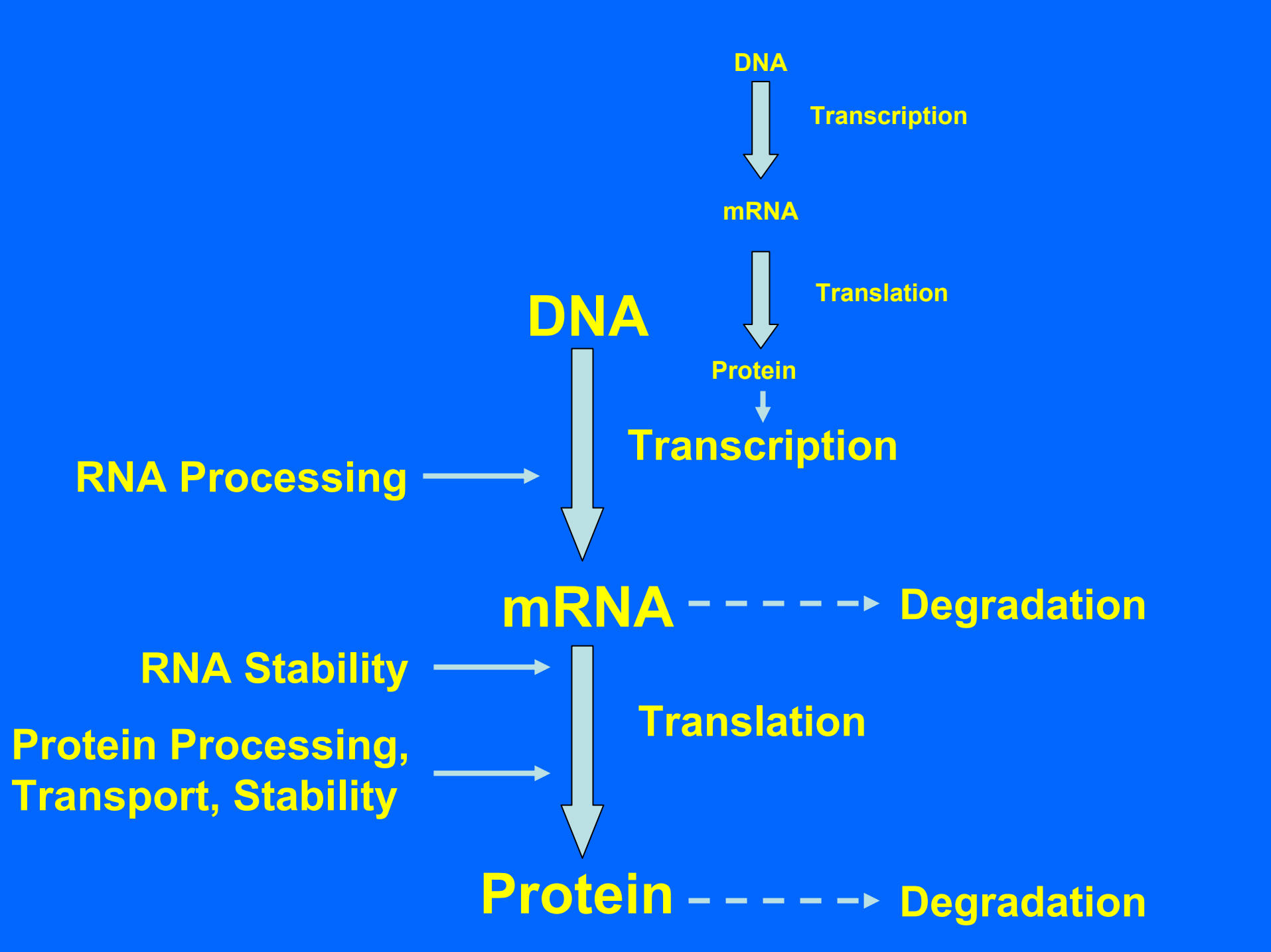
Mini-Symposium

Muscles & Aging: Going, Going, Gone

September 8, 2003

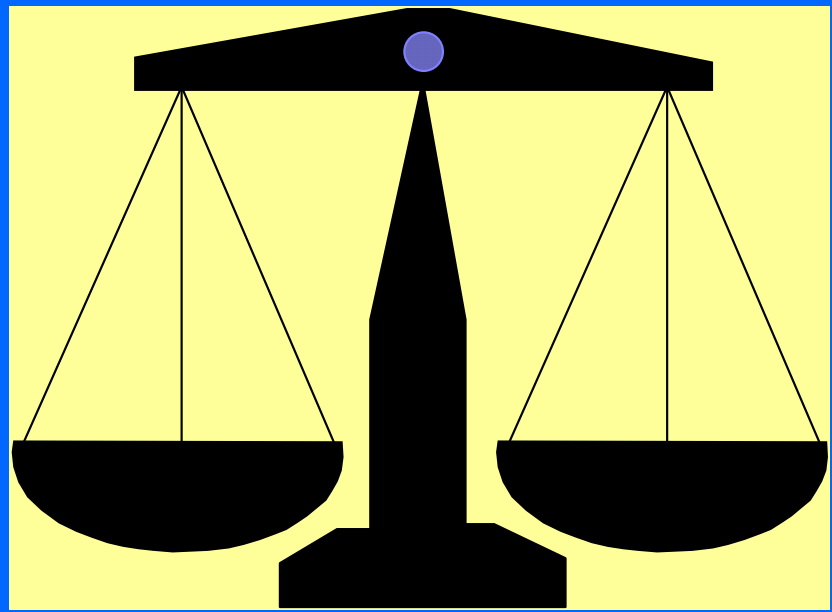

DNA
Transcription
mRNA
Translation
Protein


DNA
Transcription
RNA Processing
mRNA
Degradation
RNA Stability
Translation
Protein Processing,
Transport, Stability
Protein
Degradation


DNA
Transcription
mRNA
Translation
DNA
Protein
Transcription
RNA Processing
mRNA
Degradation
RNA Stability
Translation
Protein Processing,
Transport, Stability
Protein
Degradation

Protein Turnover

Synthesis vs Degradation



Steady State

Synthesis = Degradation

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.

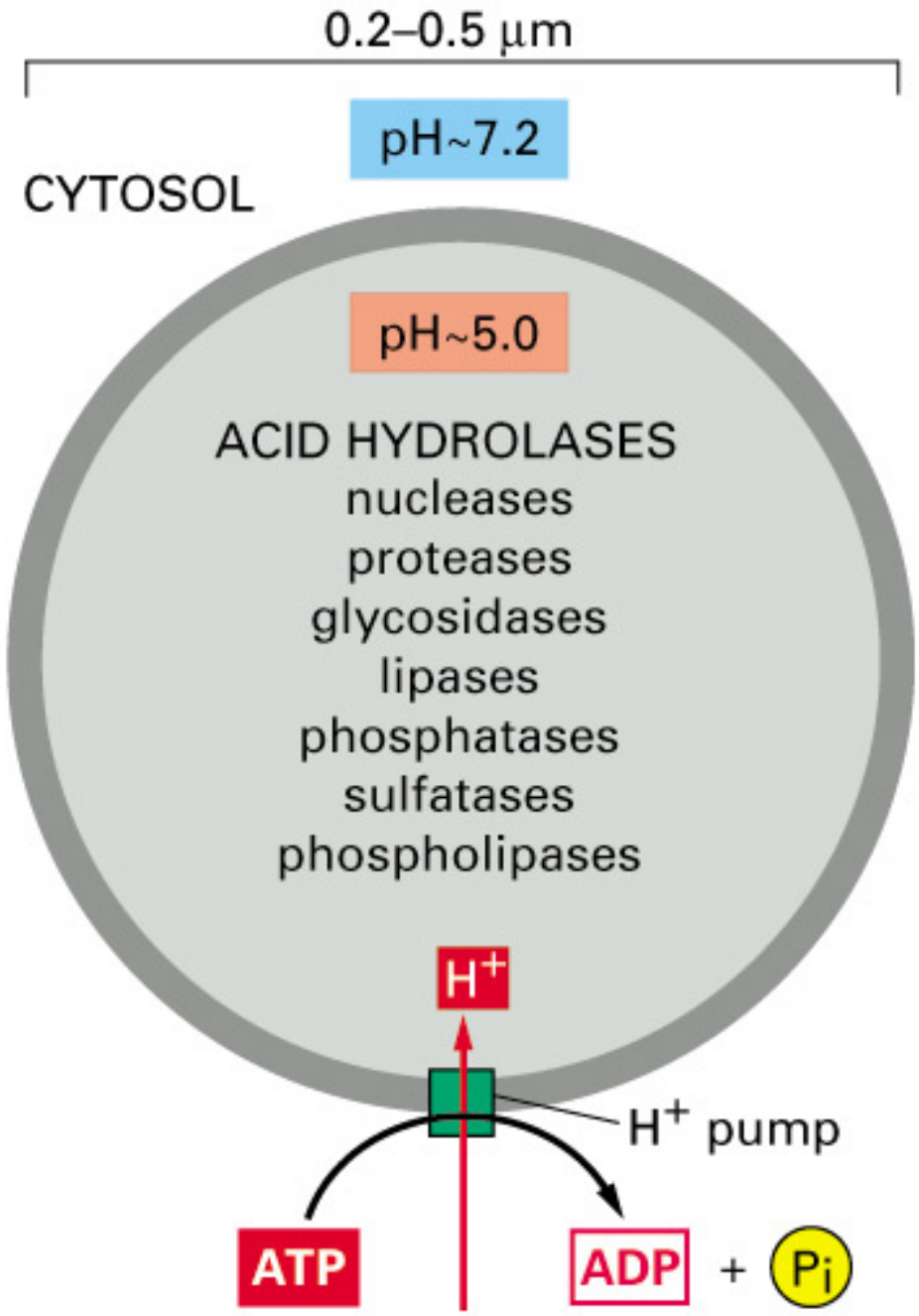
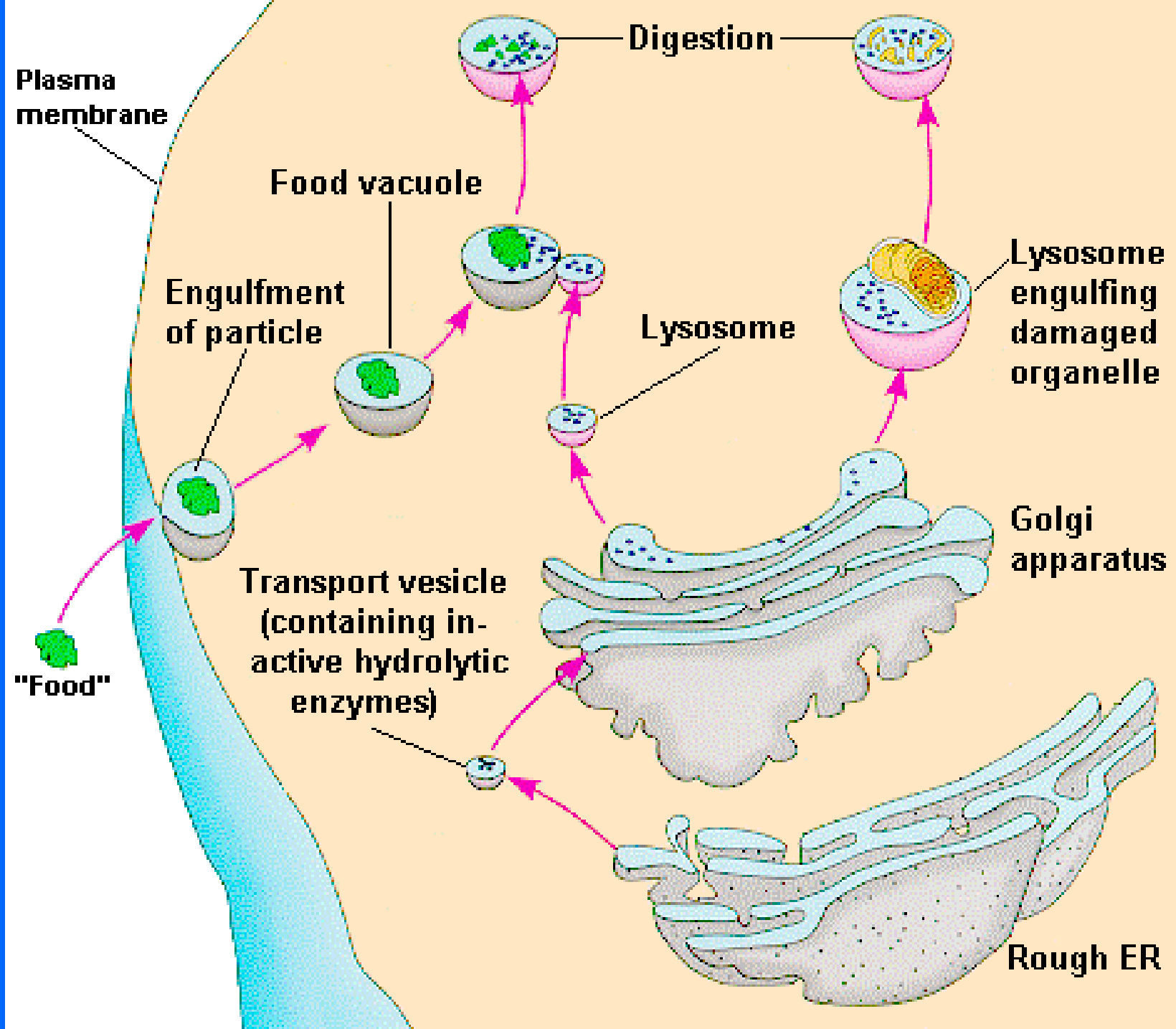


Figure 13–31. Molecular Biology of the Cell, 4th Edition.


Plasma membrane
Digestion
Food vacuole
Engulfment of particle
Lysosome
Lysosome engulfing damaged organelle
Golgi apparatus
Transport vesicle (containing in-active hydrolytic enzymes)
"Food"
Rough ER

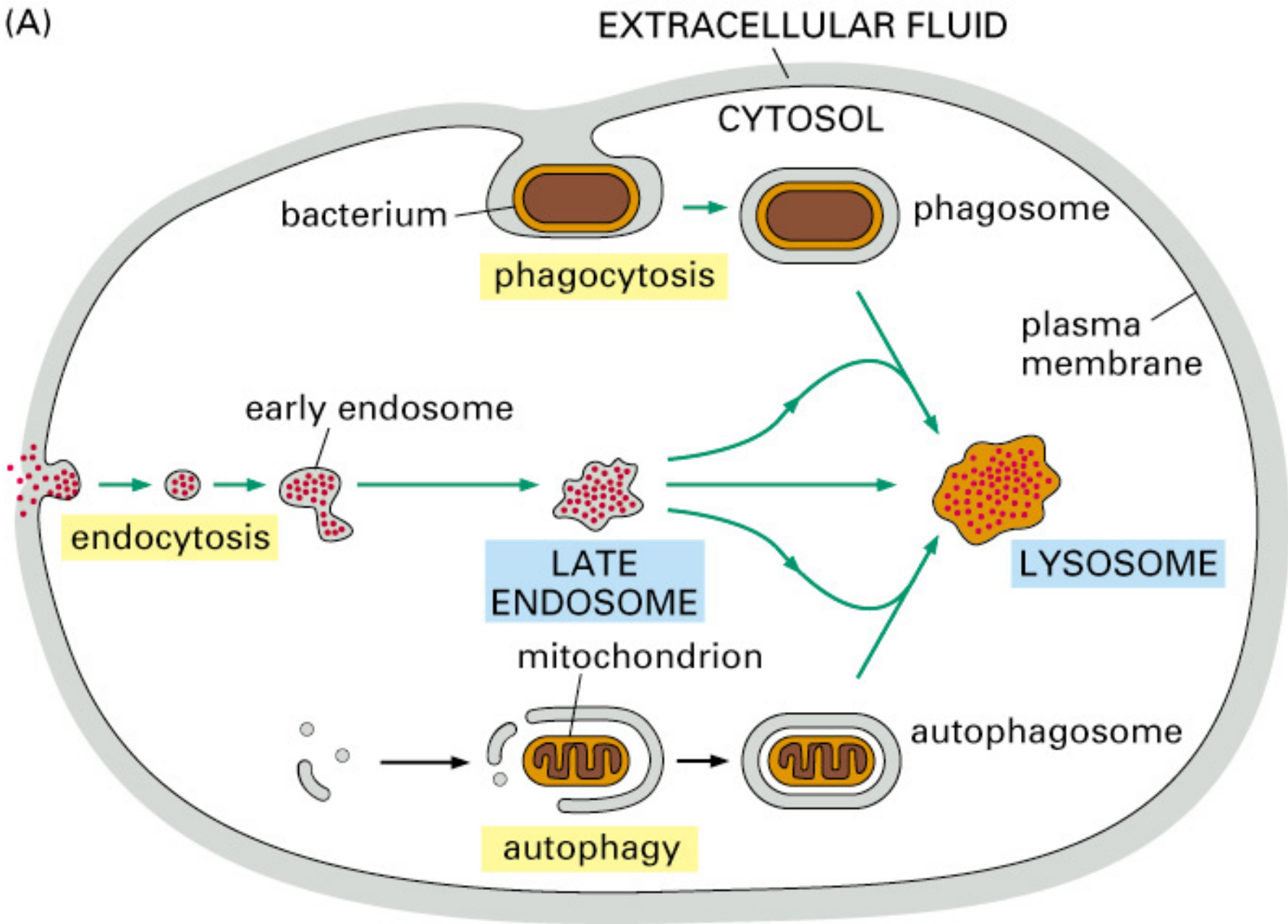


Figure 13–35 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

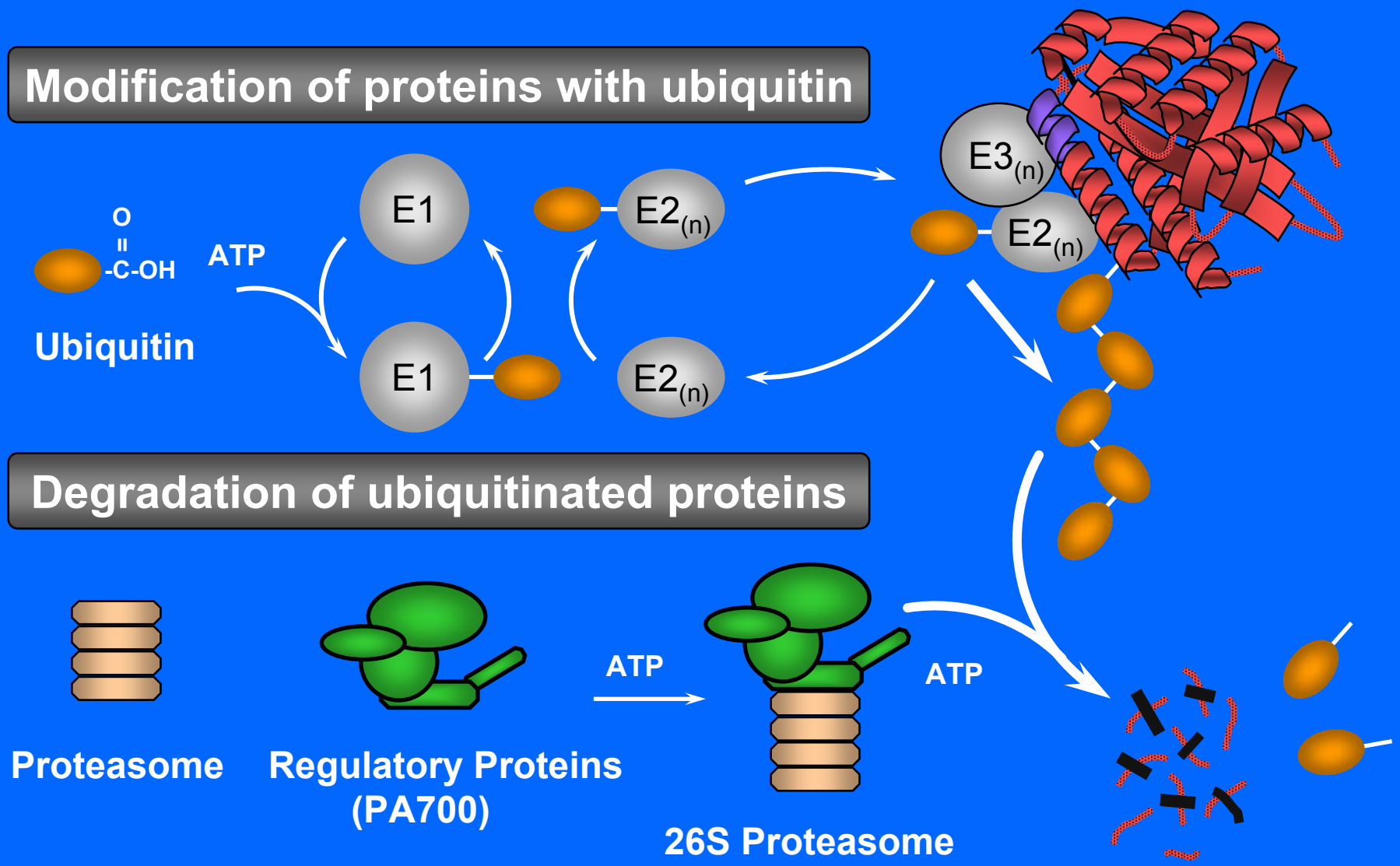
The Calpain System

- 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

Pathways of Intracellular Protein Degradation

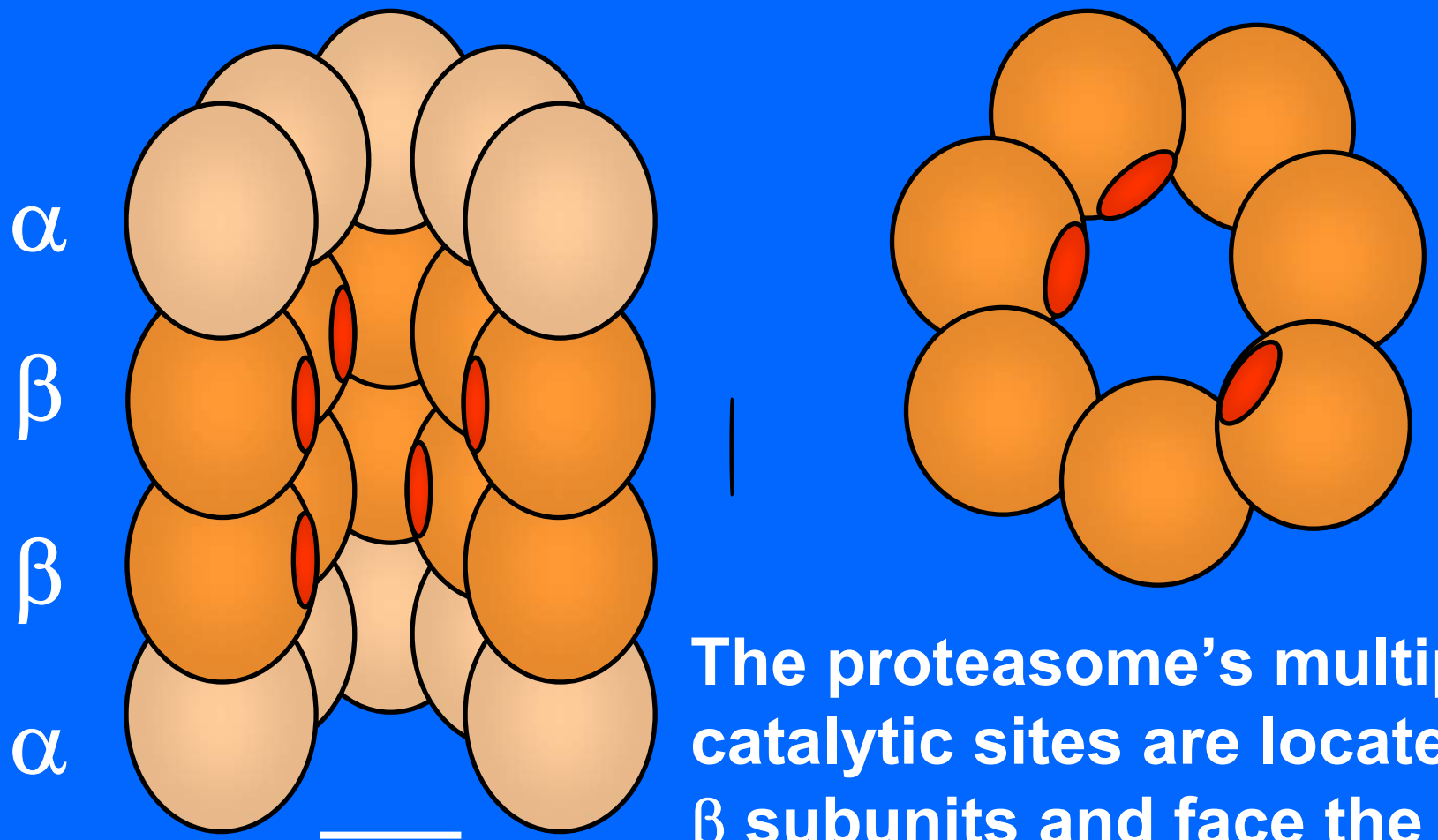
- **Lysosomal Mechanisms (Cathepsins)**
- **The Calpain System**
- **Mitochondrial Proteases**
- **The Ubiquitin-Proteasome Pathway**

The ubiquitin-proteasome pathway of intracellular protein degradation



GND129

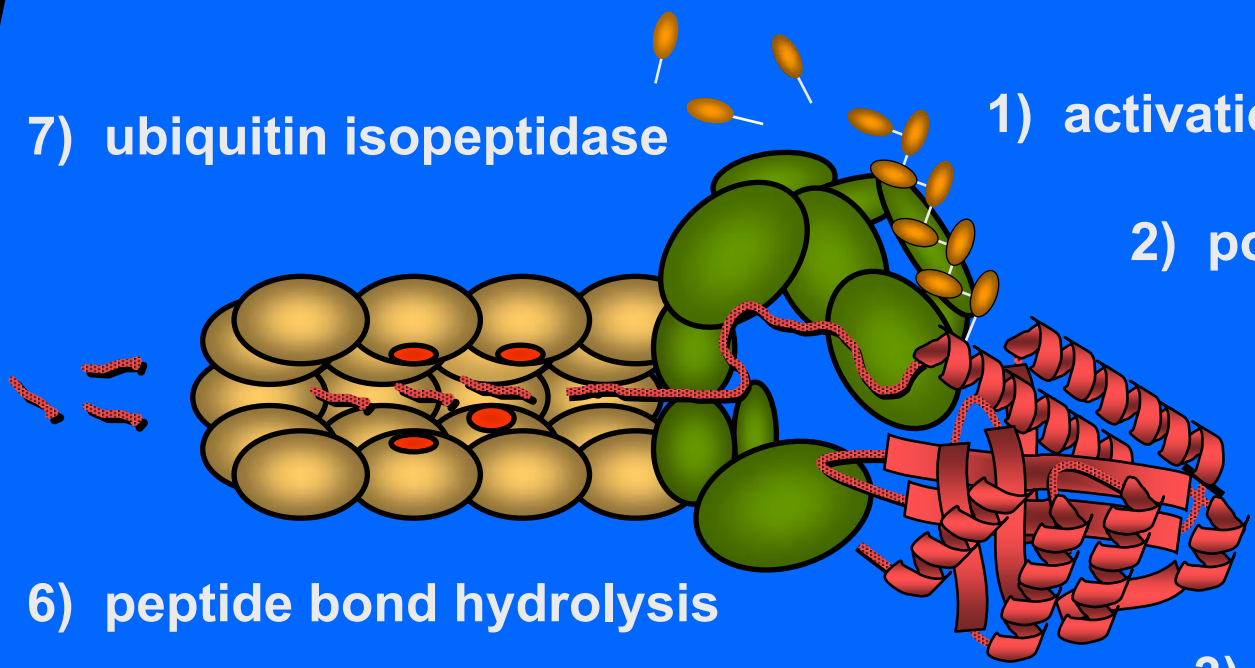
Topology of the proteasome's catalytic sites



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

GND130

Proteolysis by the 26S proteasome



7) ubiquitin isopeptidase

1) activation by gating

2) polyubiquitin chain binding

6) peptide bond hydrolysis

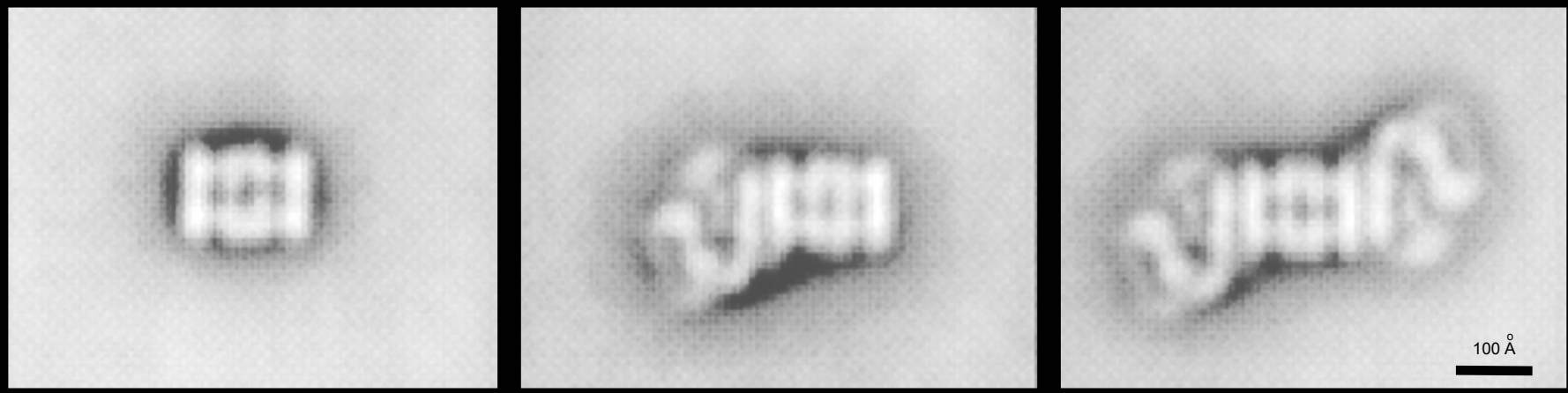
3) ATP hydrolysis

4) substrate unfolding

5) translocation of unfolded polypeptide chain

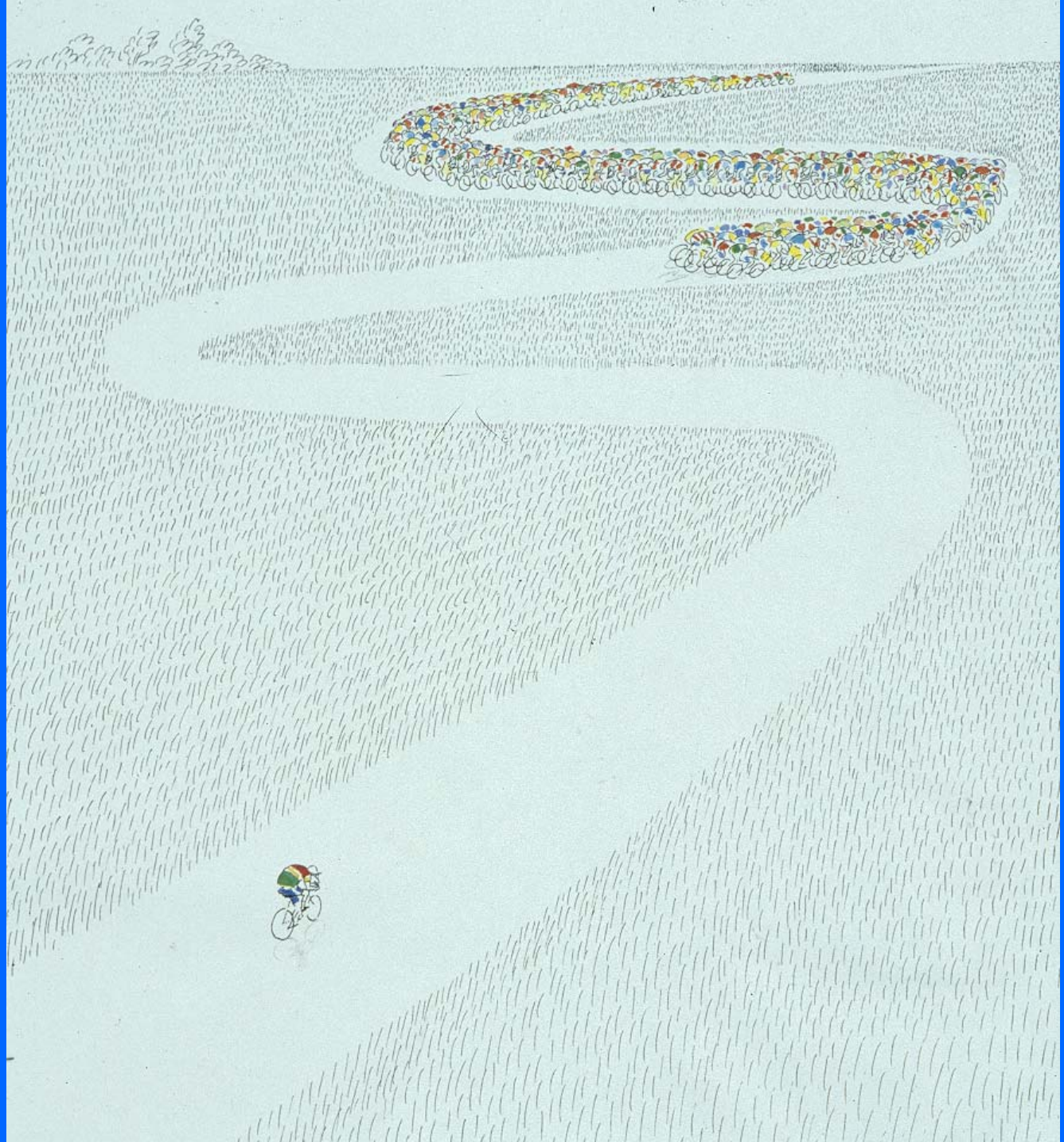
GND133c

Electron microscopy of proteasome-PA700 complexes



Proteasome **Proteasome -PA700**

GND103



Conditions Leading to Muscle Wasting (Atrophy)

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

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/)

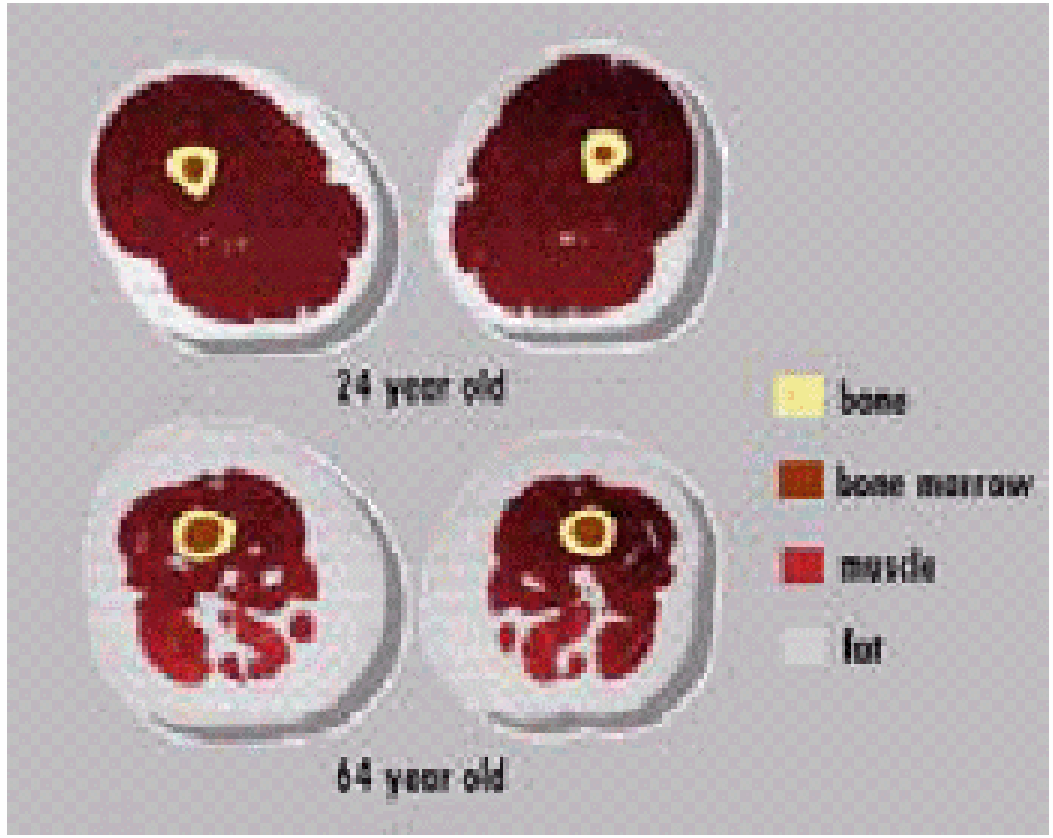
Sarcopenia: What is it?

Sarcopenia: "sarx" - flesh
"penia" - loss

Loss of muscle mass - changes over time...when does it become a disease state?

Class I Sarcopenia: -1 to -2 SD below mean for young adults

Class II Sarcopenia: greater than -2 SD below mean for young adults



Muscle Functional Characteristics

Fast Twitch

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

Slow Twitch

- Highly oxidative
- Slow shortening
- Low power output
- Extremely fatigue resistant
- Recruited in all muscle contractions

Changes in Skeletal Muscle With Age

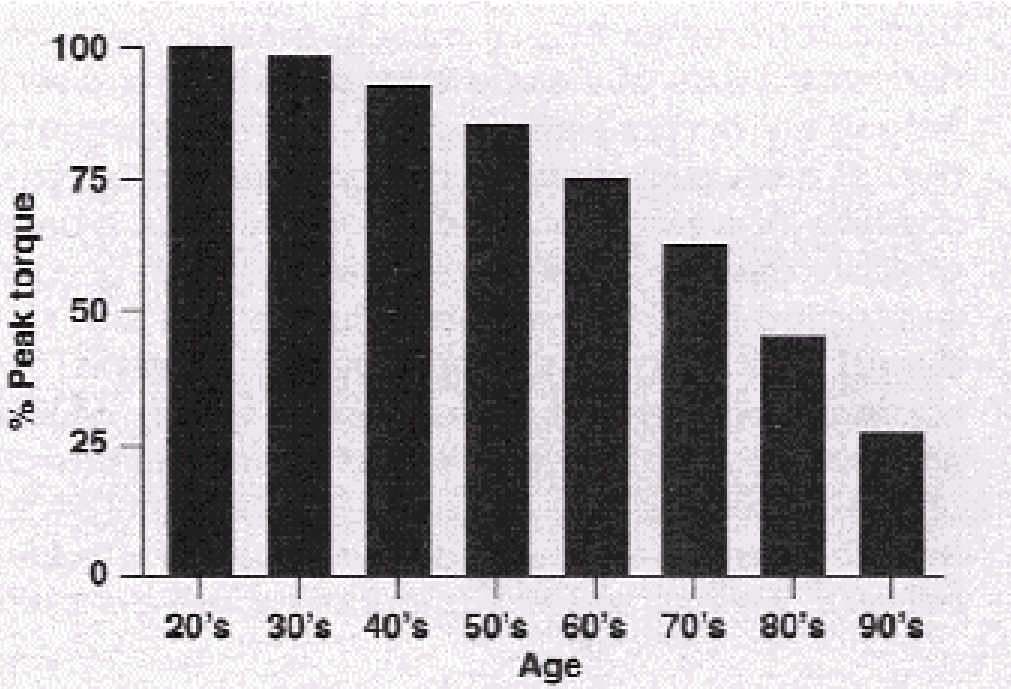


Fig. 3 - *Relative decline with age of peak leg muscle strength. Data were acquired from concentric isokinetic (0.52 rad s^{-1}) knee extension tests performed on 654 men and women aged 20-93 years. Values are expressed relative to the highest (20-30 years) group. Adapted from Lindle et al. (4).*

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

Muscle Functional Characteristics: Changes

- What are the characteristics of muscle that determine strength?
  - Fibre cross sectional area (quantity)
  - Fibre number (quantity)
  - Fibre Type (quality)
  - Ability to maximally recruit fibres (quality)
  - Protein Content (quality)

- How would these change with age to account for reduced muscular strength?
  - Cross sectional area decreased
  - Reduced number of fibres
  - Fast twitch converted to slow twitch
  - Inability to activate all fibres
  - "Defective" protein

Changes in Skeletal Muscle With Age

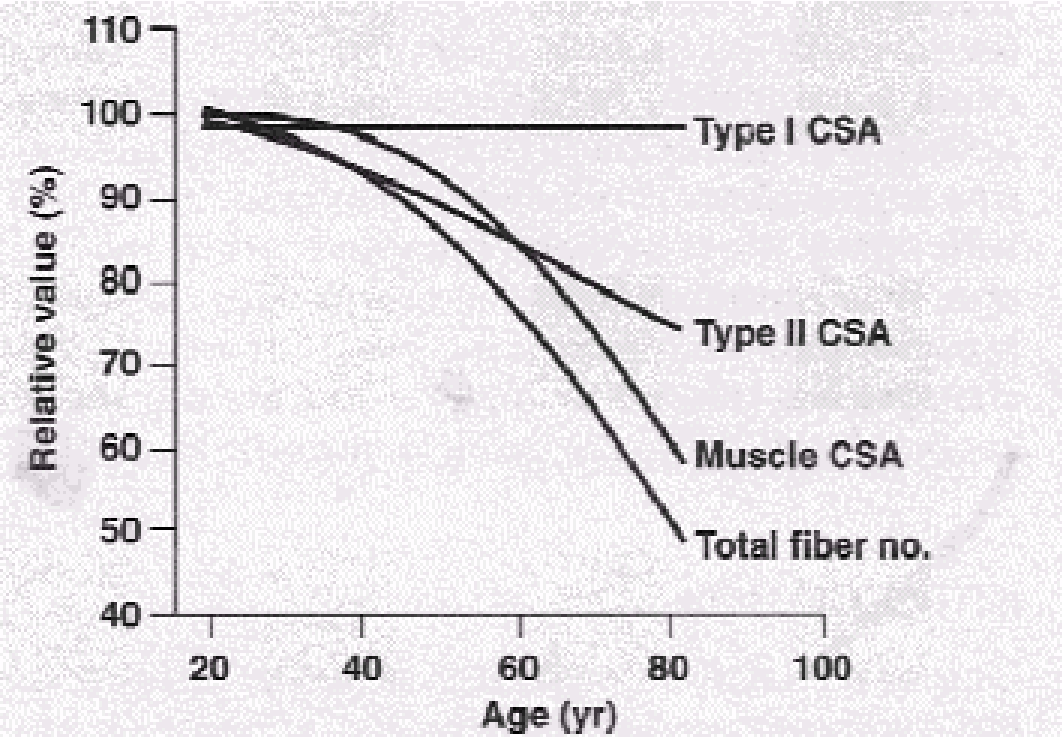
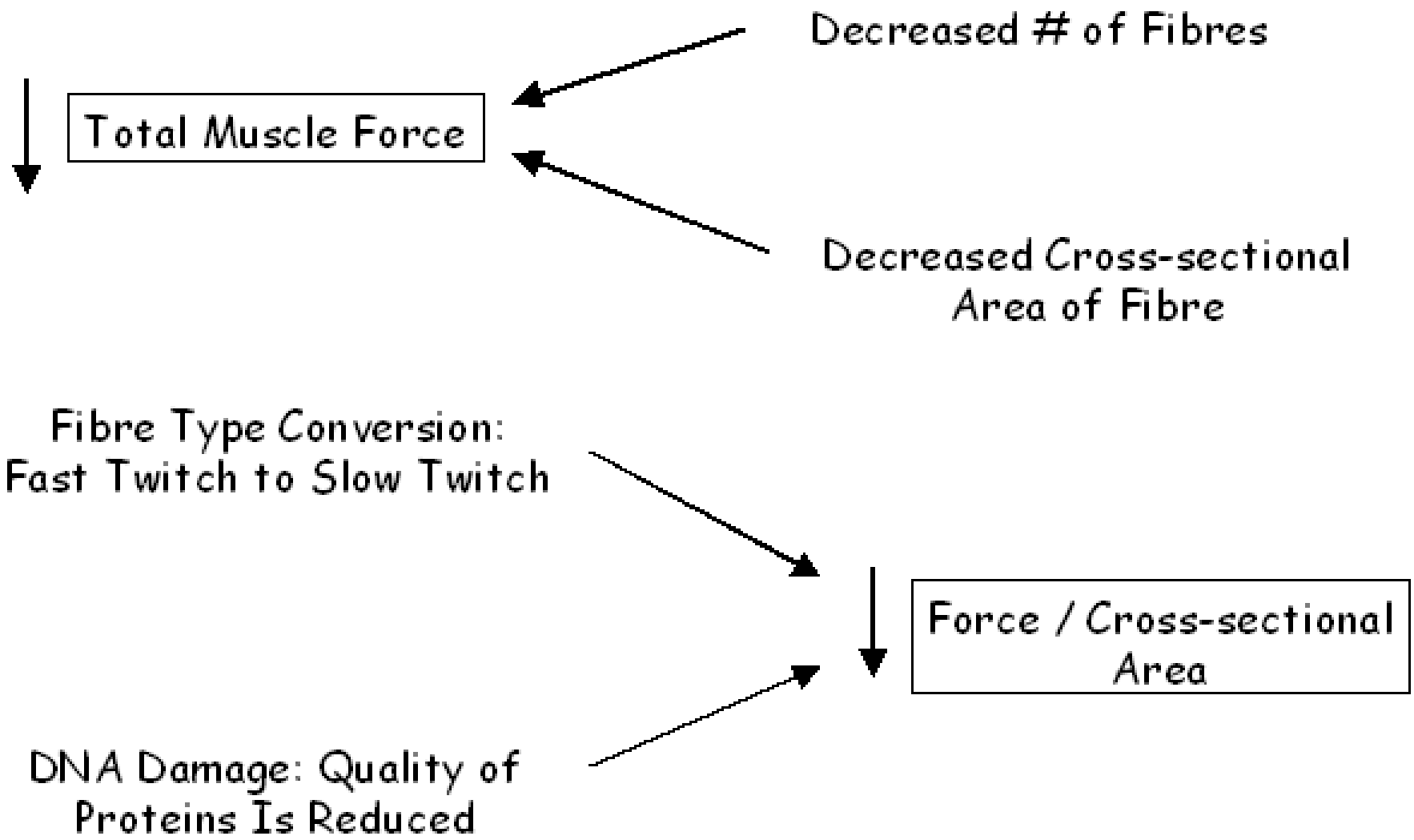


Fig. 2 - *Relative changes in muscle size parameters in humans. Data are summarized from whole vastus lateralis reported by Lexell et al. (18). The decline in total muscle cross-sectional area (CSA) appears to be due to both a reduction in total fiber number and atrophy of type II fibers. The proportion 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: Changes



Reductions in Physical Activity: Sarcopenia – "The Vicious Cycle"

- Do we lose muscle mass and therefore become inactive because activity is more difficult?
- Do we become inactive with age and lose muscle mass as a result?

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

Sarcopenia and Ubiquitin-Proteasome Pathway

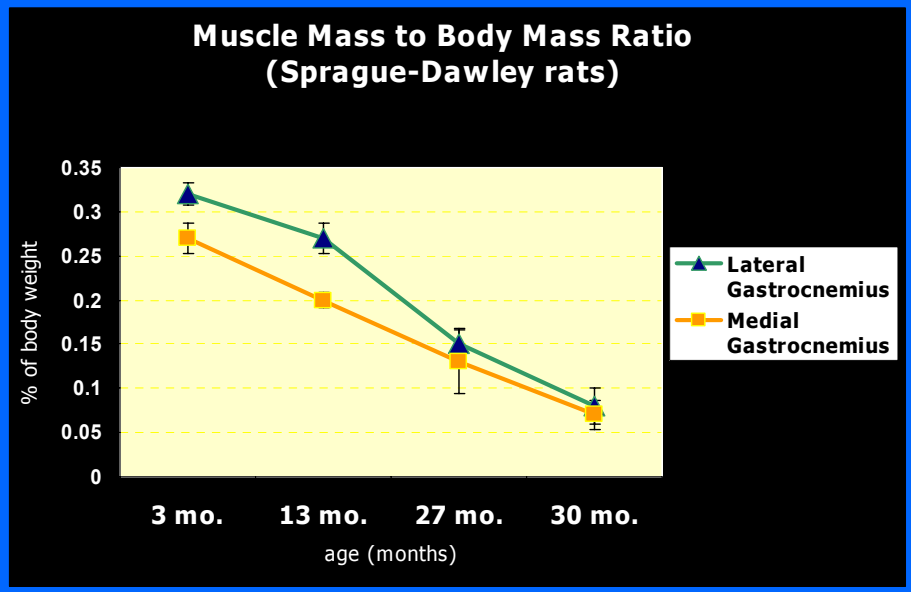
- Proteasome degrades >80% of cellular proteins

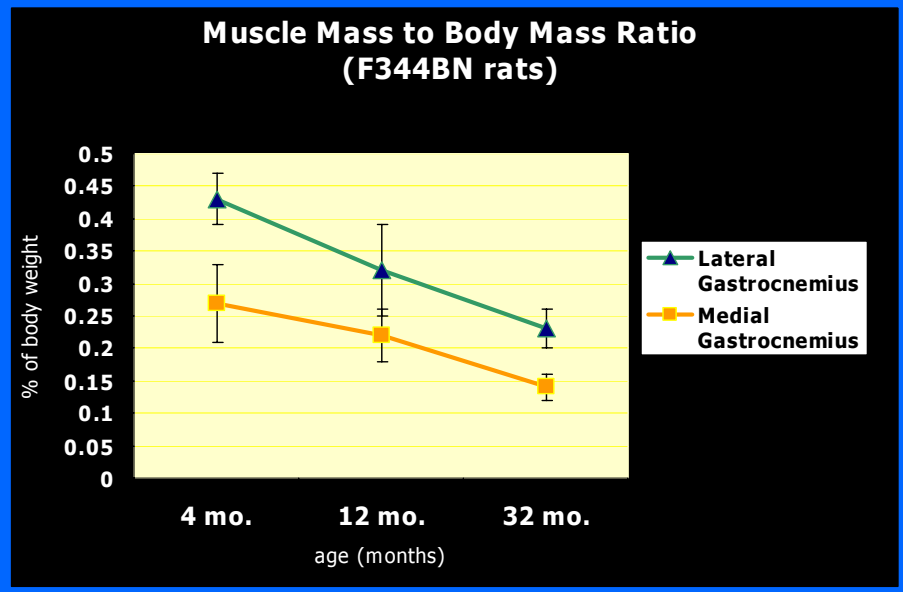
- Proteasome is the major player in a variety of atrophies

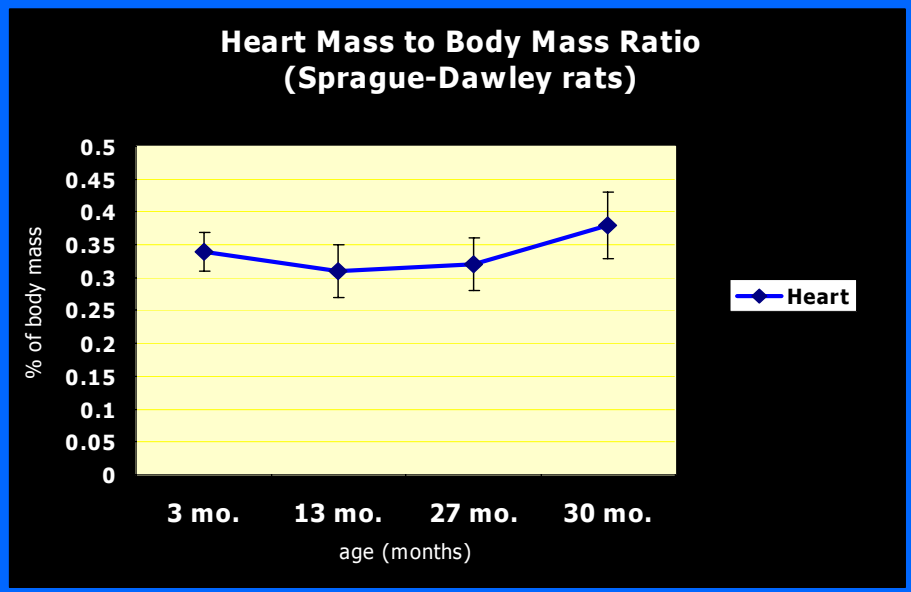
- Myofibrillar proteins are proteasome substrates

- Proteasome degrades oxidized, damaged, & denatured proteins

Change in Lean Muscle Mass with Age

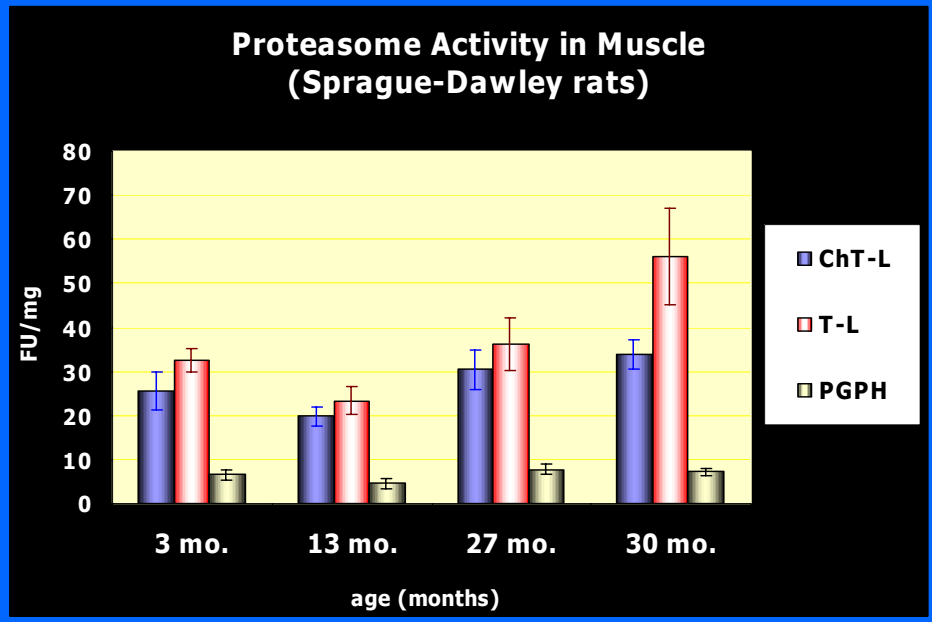


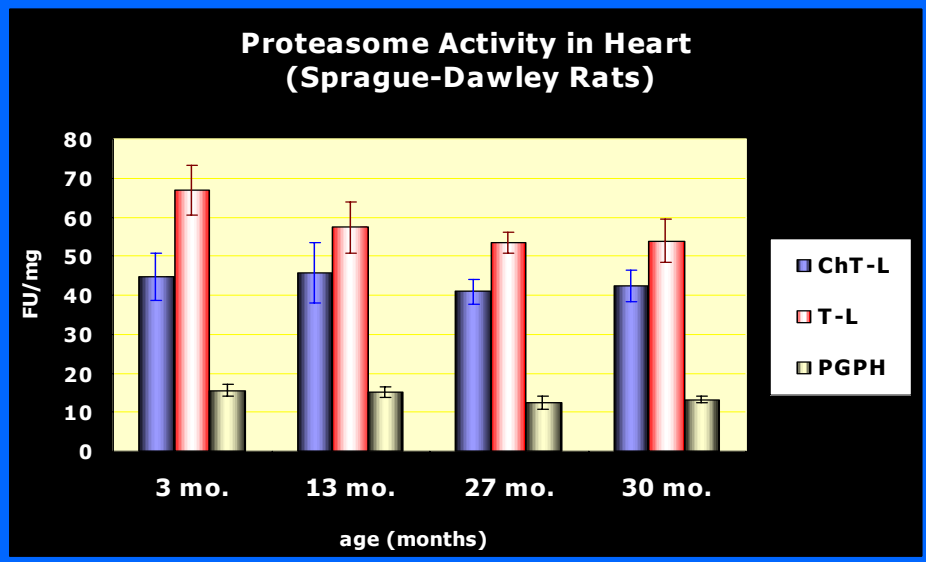




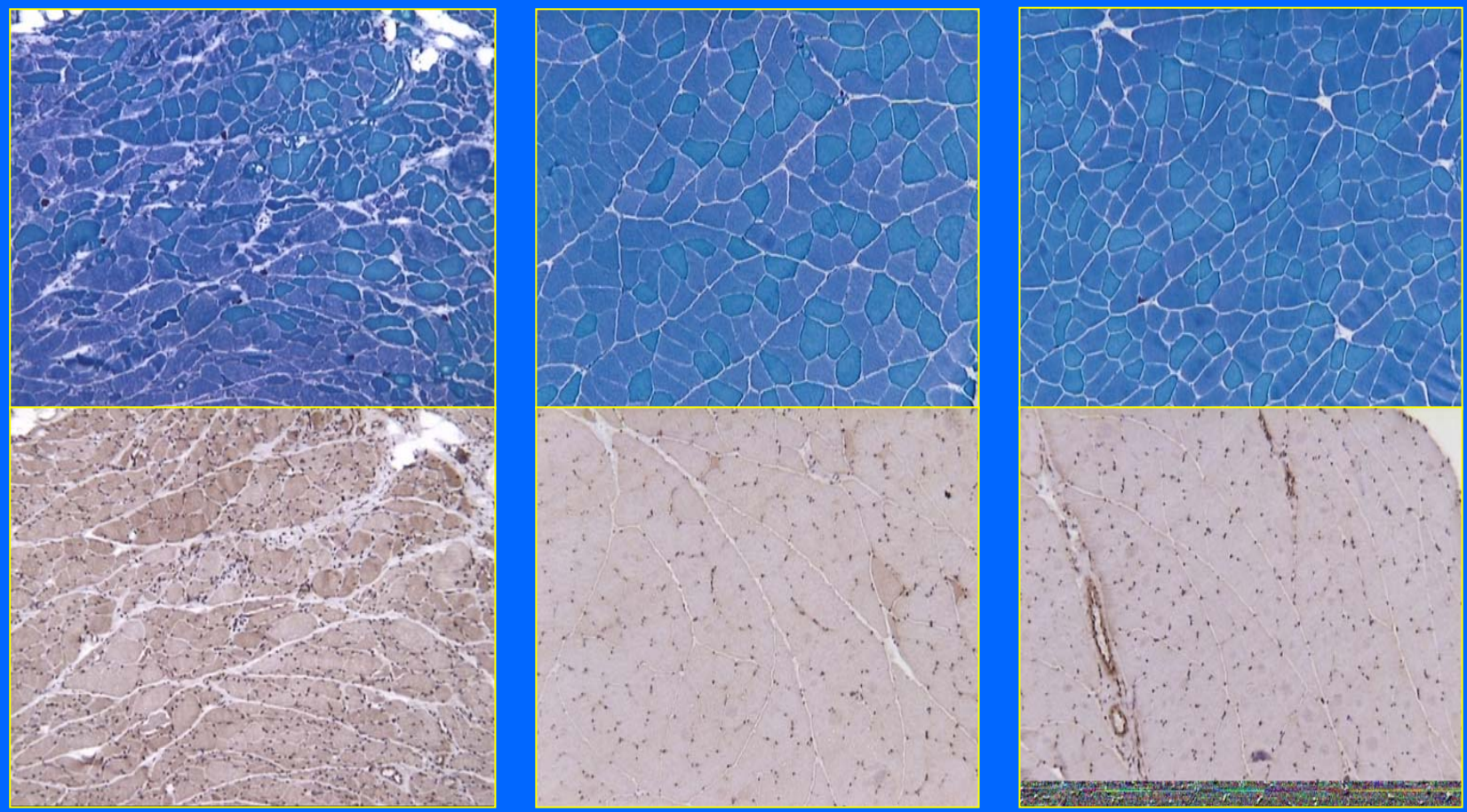
$$\frac{\text{Muscle mass (g)}}{\text{Body mass (g)}} \times 100 = \%\ \text{Body mass}$$

Proteasome Activity





Sarcopenia at the Cellular Level (Sprague-Dawley Rats)




24 FITNESS

Exercise

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

National Institute on Aging

www.nia.nih.gov/exercisebook

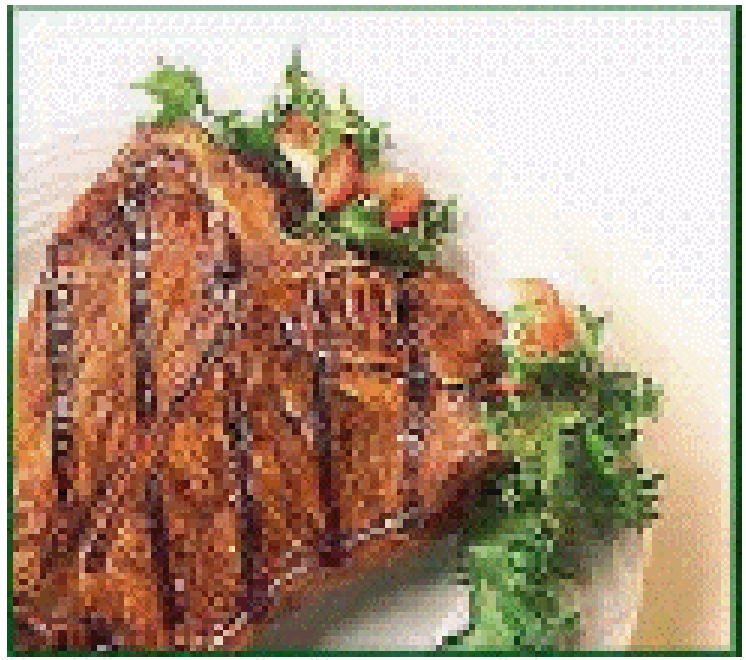
American College of Sports Medicine

www.acsm.org

Protein Balance and Aging: Dietary Protein

Protein Intake:

- 0.8 g/kg/day is young adult RDA
- 1.25 g/kg/day is older person's RDA
- 50% of men and women over 60 yrs eat less than RDA
- ~35% of men and women over 60 yrs eat less than 0.8 g/kg/day
- ~ 15% eat less than 75% of 0.8 g/kg/day



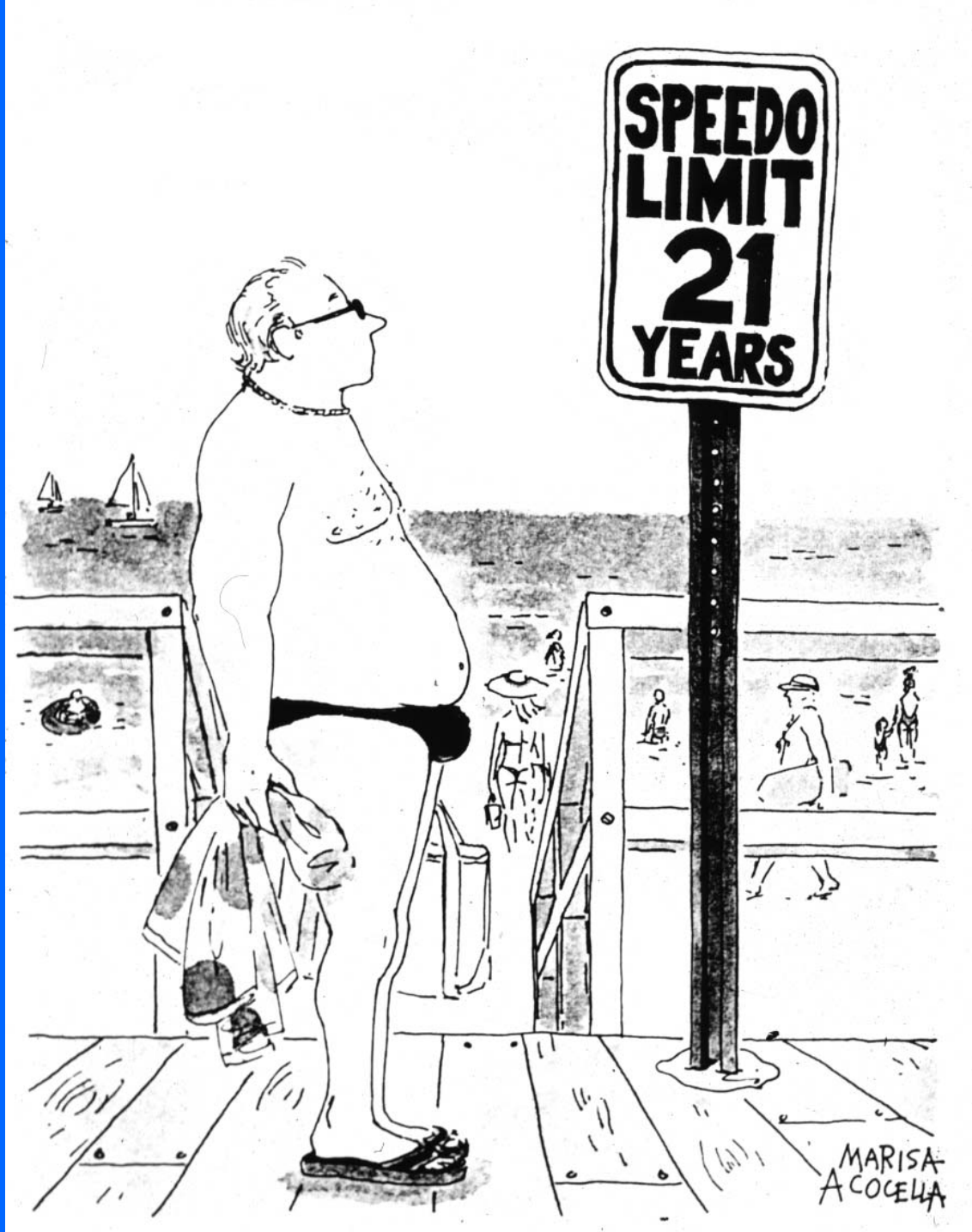
Indicators for Exercise and Diet Interventions

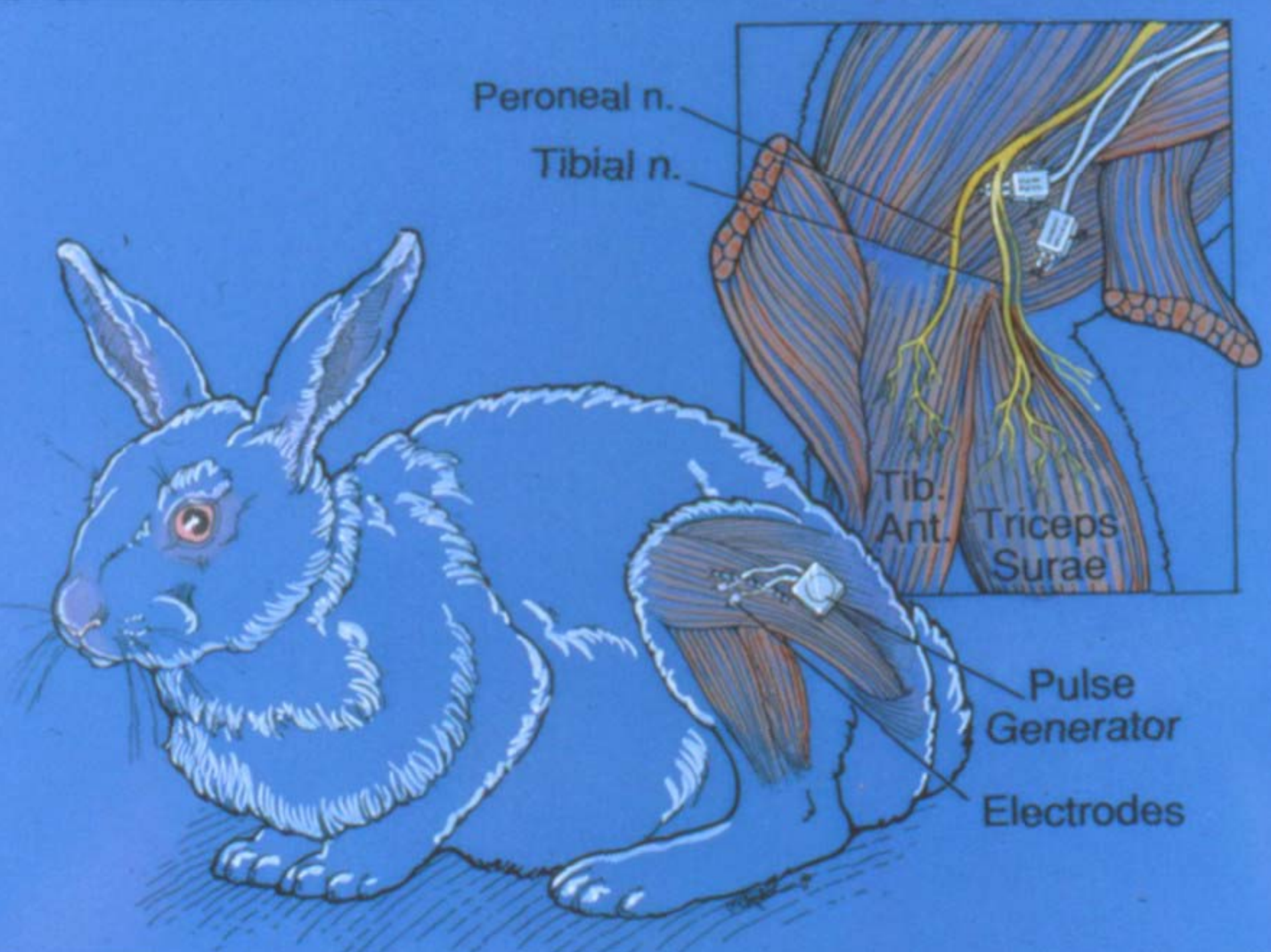
Protein Synthesis : Protein Degradation

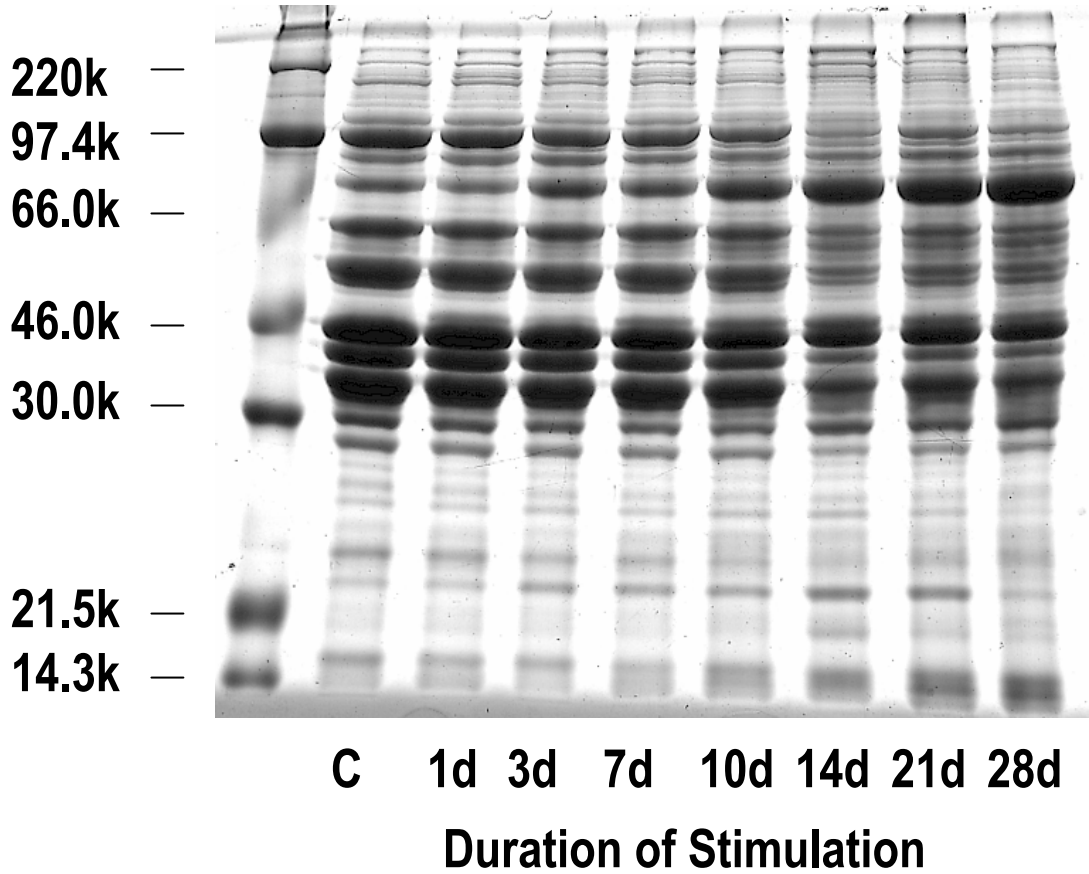
Strength Training

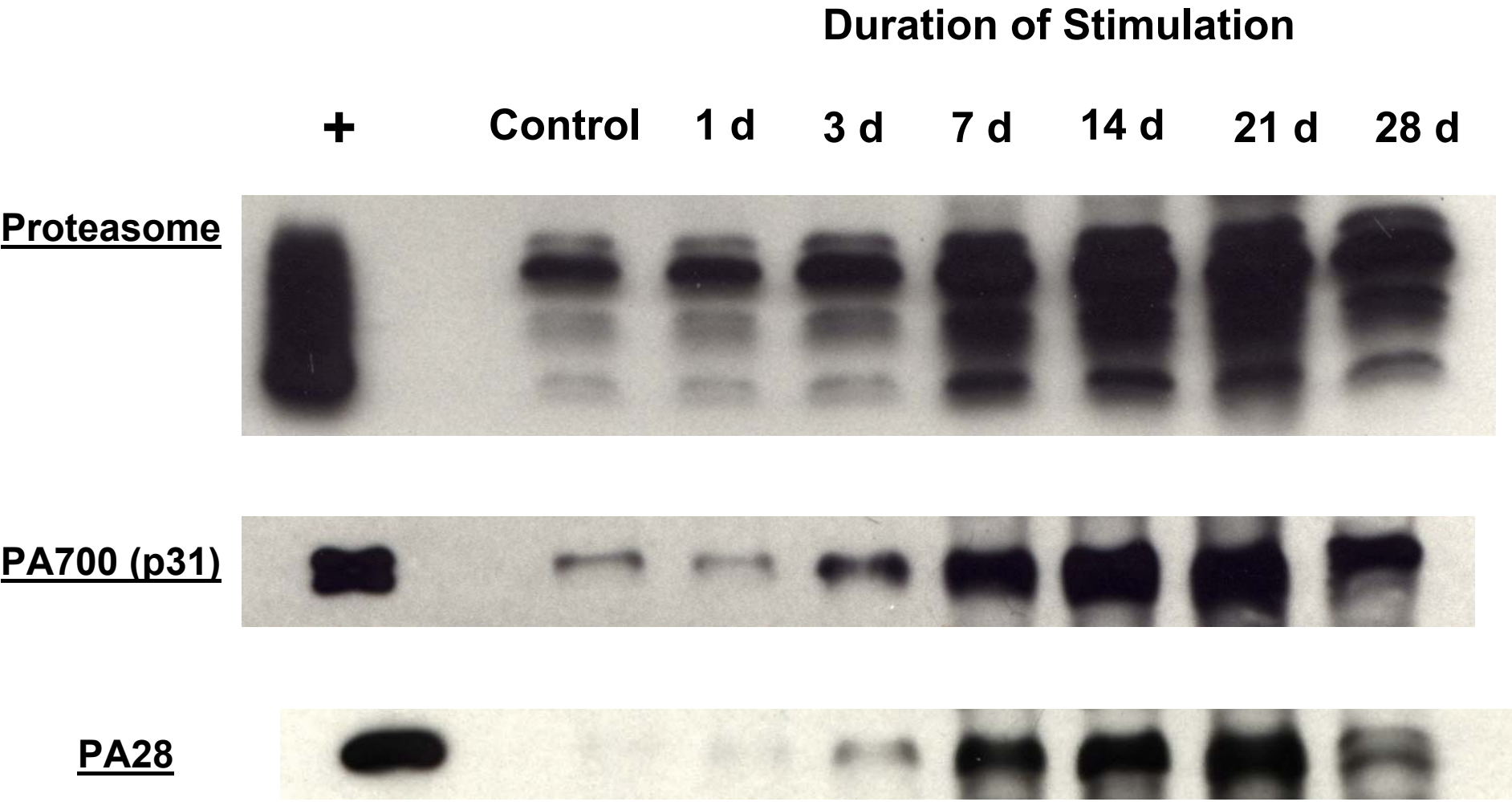
Nutrition (Protein intake)

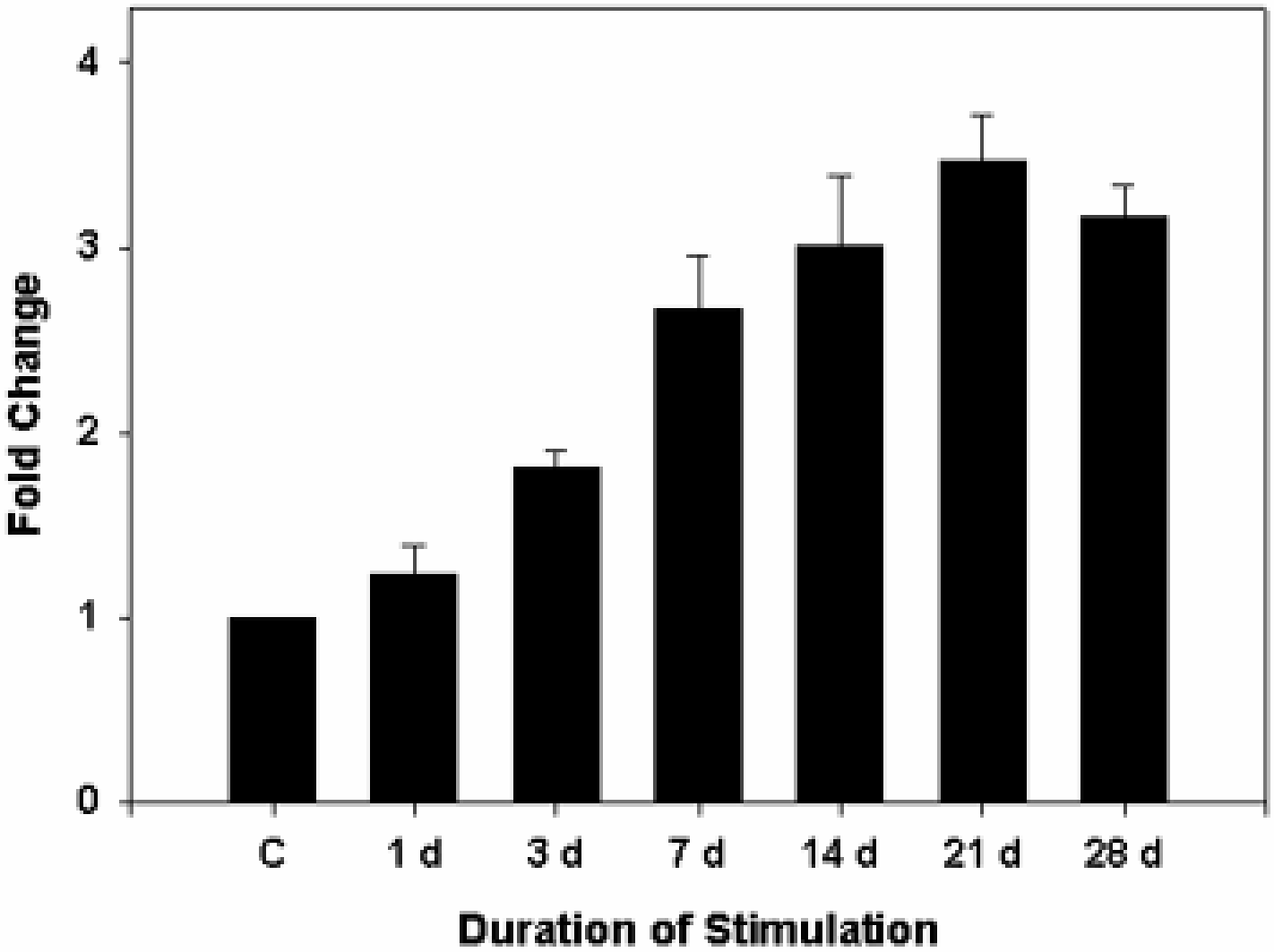
- Capacity of the muscle protein synthesis machinery is preserved until very old age (We can make muscle in old age)
- Significant gains in muscle mass (metabolic and strength benefits)
- Important gains in mobility and balance (improve quality of life and reduce risk of debilitating falls)


SPEEDO
LIMIT
21
YEARS
MARISA
ACOCELLA


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


220k
97.4k
66.0k
46.0k
30.0k
21.5k
14.3k
C
1d
3d
7d
10d
14d
21d
28d
Duration of Stimulation


Duration of Stimulation
+
Control
1 d
3 d
7 d
14 d
21 d
28 d
Proteasome
PA700 (p31)
PA28


Fold Change
0
1
2
3
4
C
1 d
3 d
7 d
14 d
21 d
28 d
Duration of Stimulation

Effect of contractile activity on ^{14}C casein degradation

	- Ub/ATP	**+ Ub/ATP**	**+ Ub/ATP/Lac**
Control	3.1	7.2	2.9
Stimulated	6.7	13.8	5.0