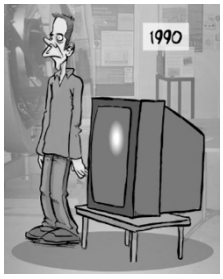
Skeletal muscle plasticity

Muscle reconditioning

Lance Armstrong

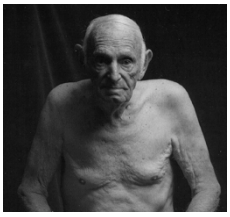
Jay Cutler

Lifestyle changes





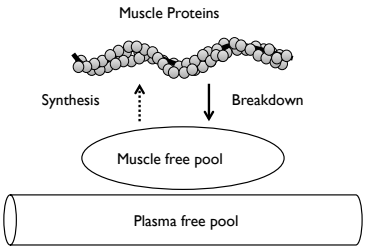
Muscle deconditioning



- sarcopenia
- cancer cachexia
- COPD
- type 2 diabetes
- cardiovascular disease

What regulates muscle maintenance?

## Muscle protein synthesis




Burd *et al.*, *Exerc Sport Sci Rev*, 2013

## Fractional muscle protein synthesis

1-2 % per day

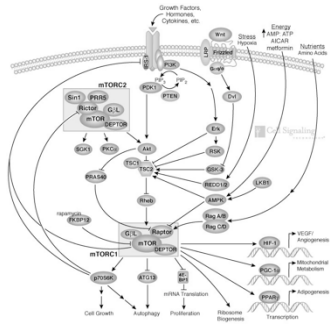
(0.04 – 0.14 %·h$^{-1}$)

## Main anabolic stimuli

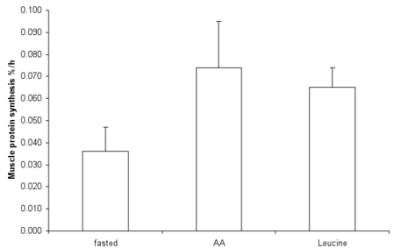
## Nutrition is an anabolic stimulus

## Amino acids

## Amino acids stimulate protein synthesis




## Leucine as a main anabolic signal




Bennet *et al.*, 1989
Smith *et al.*, 1992 and 1998

## Muscle contraction is an anabolic stimulus

## Muscle contraction

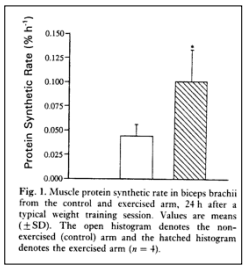
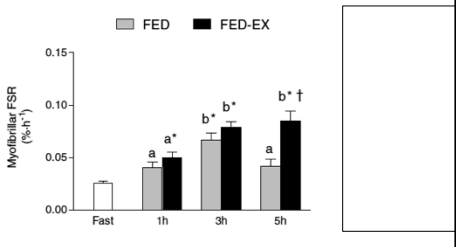



**Fig. 1.** Muscle protein synthetic rate in biceps brachii from the control and exercised arm, 24 h after a typical weight training session. Values are means (±SD). The open histogram denotes the non-exercised (control) arm and the hatched histogram denotes the exercised arm ($n = 4$).

Chesley *et al., 1992*

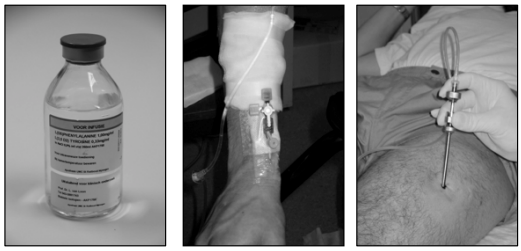
## Interaction between exercise and food intake

## Exercise and nutrition




Moore *et al., J Physiol*, 2009

## Research methods

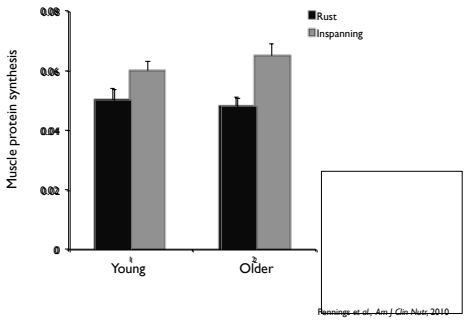


## Intrinsically labeled protein

## Intrinsically labeled protein

van Loon *et al., J Dairy Sci*, 2009, Pennings *et al., J Dairy Sci*, 2010, Burd *et al., Plos One*, 2013

## Post-prandial muscle protein synthesis



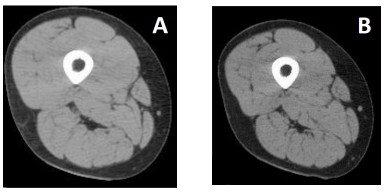

Pennings *et al., Am J Clin Nutr*, 2010

## Muscle mass maintenance

## Muscle disuse atrophy

- falls
- fractures
- immobilisation
- surgery
- hospitalisation
- Illness

## Muscle tissue loss during immobilisation



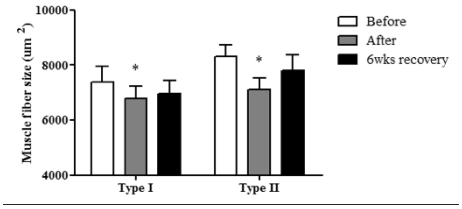

~ 0.5% per day (~100 g/day)

Wall *et al. Nutr Rev,* 2013

## Muscle fiber atrophy


Yasuda et al., *J Appl Physiol, 2005*

## Decline in muscle fiber size

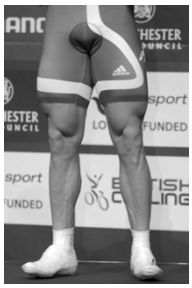



Snijders *et al., Clin Sci,* 2013

## Susceptibility to muscle disuse

Muscle groups of the legs and back are more susceptible to disuse atrophy (LeBlanc *et al.*, 1992)

Postural muscles of the leg are the most susceptible to disuse atrophy (Akima *et al.*, 1997)



## Loss of muscle strength

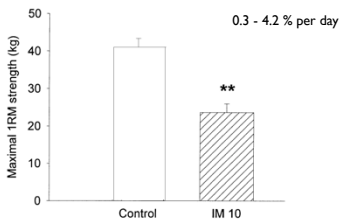



**Figure 2** Maximal 1RM strength measured prior to (control), following 10-day cast immobilization (IM 10). Values are mean ± SEM; ** Significantly different from control, $P < 0.01$.

Thom et al., *Acta Physiol Scand, 2001*

## Loss of muscle strength

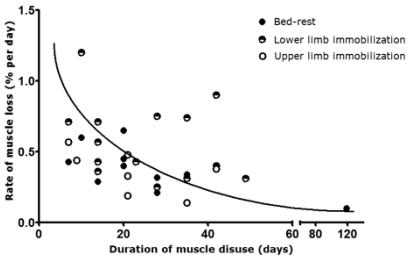
Disuse leads to greater loss of strength when compared to muscle mass: on average ~1.2 % vs 0.5 % per day

Impairments in neuromuscular recruitment

Skeletal muscle quantity ***and*** quality

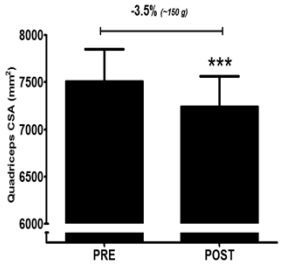
Wall and van Loon., *Nutr Rev,* 2013

## Loss of muscle during immobilisation



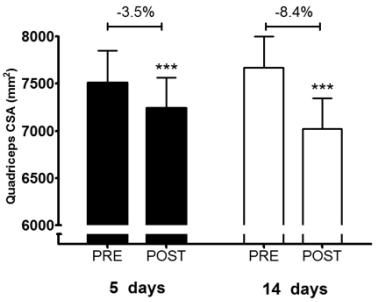

Wall and van Loon, *Nutr Rev*, 2013

## Short term muscle disuse (5 days)



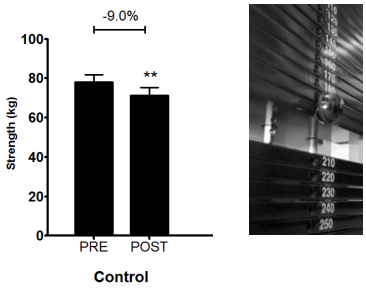

Wall *et al. Acta Physiol. Scand.*, 2013

## Short term muscle disuse



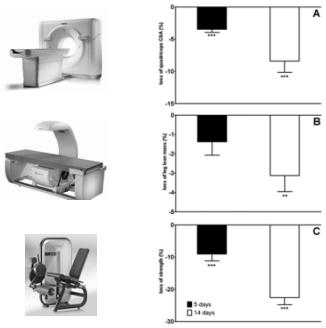

Wall *et al. Acta Physiol. Scand.*, 2013

## Short term muscle disuse



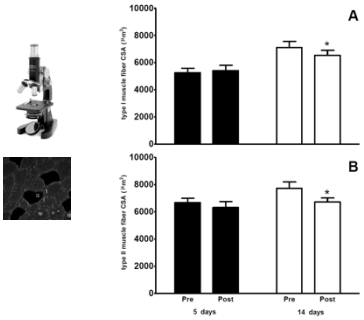

Wall *et al. Acta Physiol. Scand.*, 2013

## Short term muscle disuse atrophy



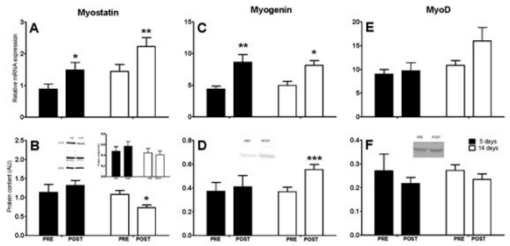

Wall *et al. Acta Physiol. Scand.*, 2013

## Short term muscle disuse




Wall *et al. Acta Physiol. Scand.*, 2013

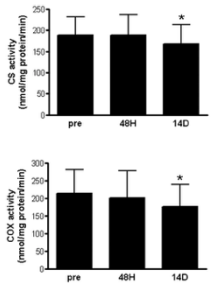
## Short term muscle disuse




Wall *et al. Acta Physiol. Scand.*, 2013

## Metabolic consequences

## Loss of muscle oxidative capacity

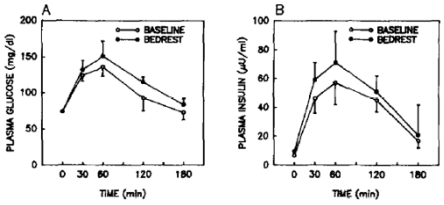



Disuse leads to a coordinated decline in metabolic rate, mitochondrial content/ activity, and subsequent declines in oxidative capacity

Abadi et al., *PLoS One, 2009*

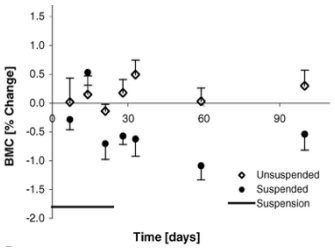
## Loss of insulin sensitivity

Bed-rest increases whole body and skeletal muscle insulin resistance



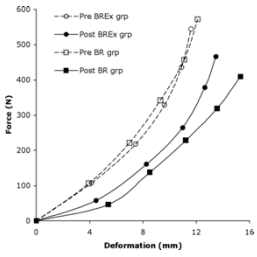

Stuart et al., *Metabolism, 1988*

## Decline in bone mineral content




Riltweger et al., *J Physiol, 2006*

## Decline in tendon function



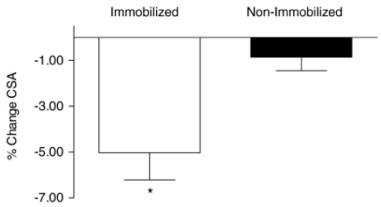

Disuse does not alter tendon cross sectional area, but does effect tendon function

Reeves et al., *J Appl Physiol*, 2005

Christensen *et al., J Appl Physiol*, 2008

What causes disuse atrophy?

## Muscle disuse following immobilisation




Glover et al. *J Physiol*, 2008

## Basal muscle protein synthesis

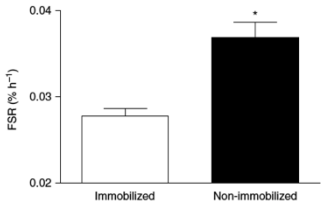



**Figure 4. Pooled (from both low and high infused groups) resting fasted myofibrillar protein fractional synthetic rate (FSR)**
*Significantly different from immobilized ($P < 0.001$).

Glover et al., *J. Physiol.*, 2008

Gibson et al., *Clin Sci*, 1987

## Muscle protein synthesis

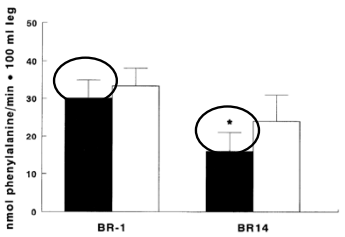



Fig. 2. Skeletal muscle protein synthesis (PS; solid bars) and breakdown (PB; open bars) before (BR −1) and after (BR 14) bed rest. *$P <$ 0.03 vs. BR −1.

Ferrando et al., *Am J Physiol, 1996*

## Muscle protein breakdown

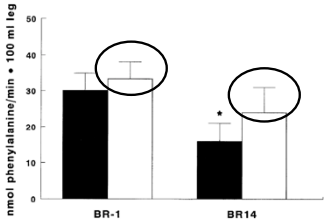
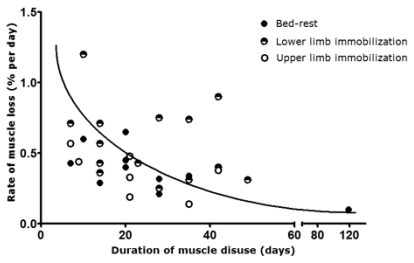



Fig. 2. Skeletal muscle protein synthesis (PS; solid bars) and breakdown (PB; open bars) before (BR −1) and after (BR 14) bed rest. *$P <$ 0.03 vs. BR −1.

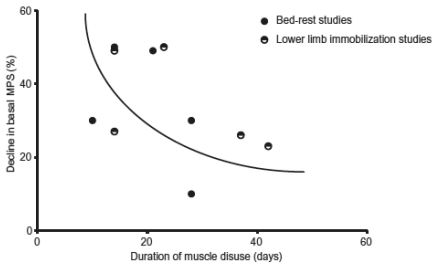
Ferrando et al., *Am J Physiol, 1996*

## Loss of muscle during immobilisation



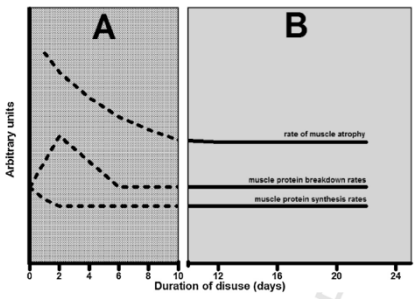

Wall and van Loon, *Nutr Rev*, 2013

## Basal muscle protein synthesis




Wall and van Loon et al., *Nutr Rev, 2012*

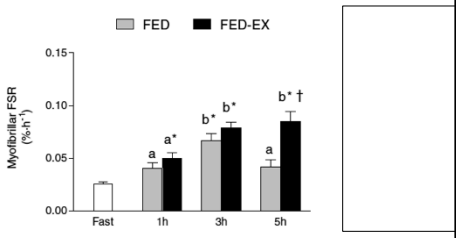
## Disuse atrophy




Wall *et al., Ageing Res Rev,* 2013

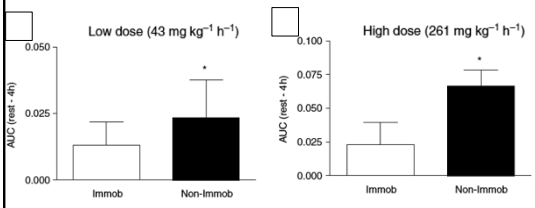
## Anabolic resistance

## Exercise and nutrition




Moore *et al., J Physiol,* 2009

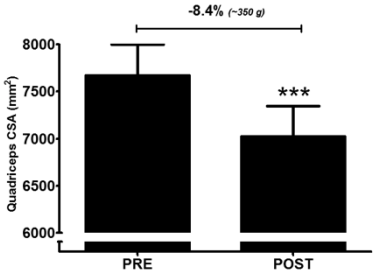
## Post-prandial muscle protein synthesis




50-70% decline in myofibrillar FSR during amino acid infusion

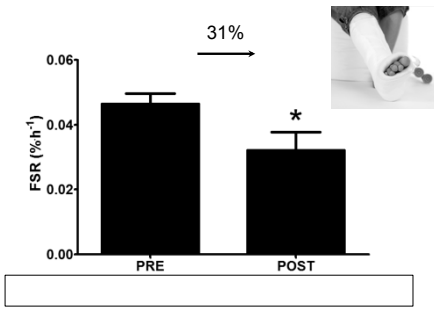
Glover *et al. J Physiol, 2008*

## Muscle disuse following immobilisation




Wall *et al. J Clin Endocrinol Metab,* 2013

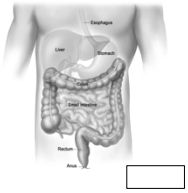
## Anabolic resistance to protein intake




Wall *et al. J Clin Endocrinol Metab,* 2013

## Anabolic resistance

- protein digestion
- amino acid absorption
- plasma amino acid availability
- hormonal response
- postprandial perfusion
- muscle protein signaling proteins
- myofibrillar protein synthesis



Burd *et al., Exerc Sport Sci Rev,* 2013

## Attenuating muscle disuse atrophy

## Nutritional strategies

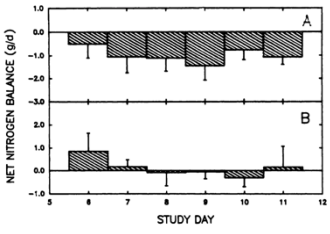
## Maintaining energy balance

Negative energy balance:
3 fold greater loss of muscle tissue during disuse

Biolo *et al. Am J Clin Nutr,* 2007

## Maintenance of dietary protein intake

Protein intake
0.6 g / kg body weight / day vs 1.0 g / kg body weight / day

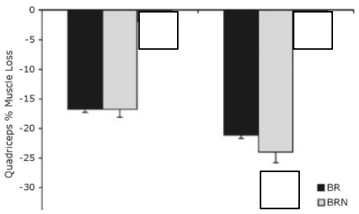



Stuart *et al. Am J Clin Nutr,* 1990

## Increasing dietary protein intake

Protein intake

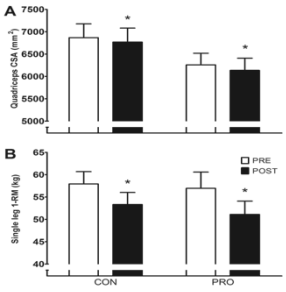
1.0 g/kg/d vs 1.6 g/kg/d




No effect of the high protein diet

Trappe *et al. Acta Physiol, 2007*

## Protein supplementation during short term disuse

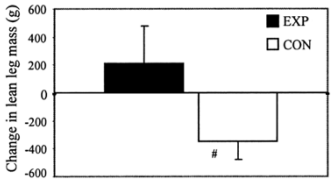



*Dirks et al., J. Nutr.*, 2014

## Amino acid supplementation

Protein intake

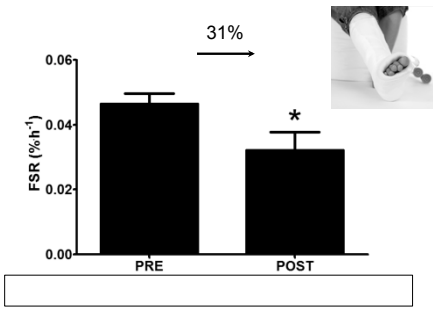
Normal diet with (EXP group) or without (CON group) 3 × daily essential amino acid supplements (16.5 g each) - (~0.7 vs 1.3 g /kg/d)




Effective at maintaining muscle mass during bed-rest

Paddon-Jones *et al. J Clin Endocrinol Metab*, 2004

## Anabolic resistance to protein intake




Wall *et al. J Clin Endocrinol Metab*, 2013

## Post-prandial protein synthesis


- source of protein


- amount of protein


- macronutrients


- timing


- food compounds

## Exercise strategies

## Bed rest and physical activity

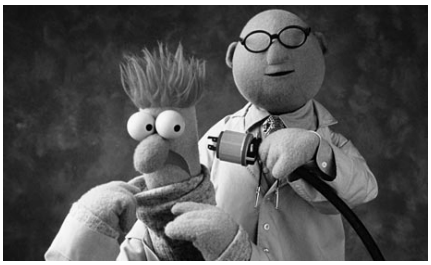
Unique Bed Loom Gives Invalids Fun and Exercise

KEEPING young patients entertained while exercising their muscles at the same time is the purpose of the invalid's weaving loom pictured at the left. The invention of Margaret Gleave, a nurse at the James Whitcomb Riley Hospital for Children, in Indianapolis, Ind., the loom is operated by youngsters suffering from leg and hip diseases to help them exercise their afflicted limbs. The invention won a fifty-dollar prize for the nurse.

Taking this kind of medicine is fun—and good for the patient, too

Akima, *Acta Physiol Scand*, 2001
Oates *et al. Muscle Nerve*, 2010

## Neuromuscular electrical stimulation

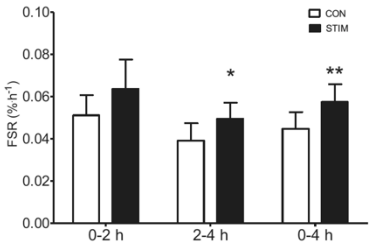


Wall *et al. Am J Physiol*, 2012

## Neuromuscular electrical stimulation

Wall *et al. Am J Physiol*, 2012

## Neuromuscular electrical stimulation

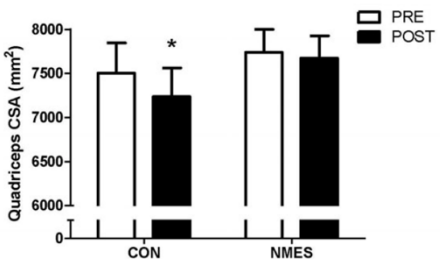



Wall *et al. Am J Physiol*, 2012

## NMES as an anabolic stimulus

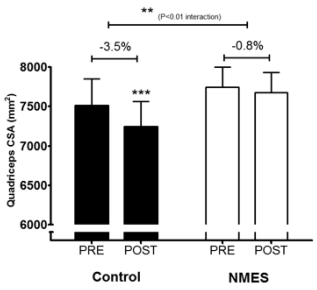
Dirks *et al., Acta Physiol Scand., in press*

## NMES to prevent disuse atrophy



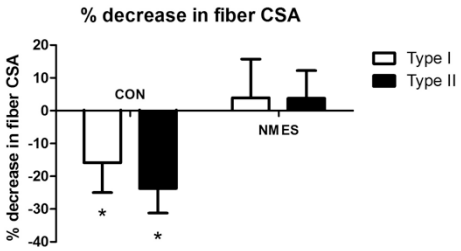

Dirks *et al., Acta Physiol*, 2013

## Neuromuscular electrical stimulation




Wall *et al. unpublished*

## NMES during coma

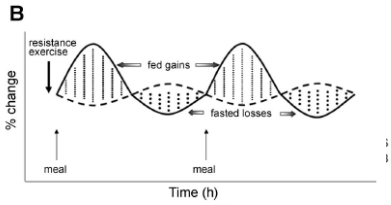



Dirks *et al.*, unpublished

## NMES and nutritional intervention

Combining NMES with appropriate timing of food intake should augment the post-prandial muscle protein synthetic response

## Prolonged nutritional intervention




Burd *et al., J Appl Physiol*, 2008

## Conclusions

Even short-term muscle disuse leads to a substantial loss of both muscle mass and strength

The loss of muscle mass is attributed to a decline in basal muscle protein synthesis rate and impairments in the post-prandial muscle protein synthetic response

Interventions should target anabolic resistance by providing greater nutritional stimuli and/or re-introducing some level of physical activity.

## Clinical relevance

## Bedrest and disuse atrophy

## Hospital admission

Short periods of bedrest following disease or injury contribute substantially to the loss of muscle mass with aging

Wall *et al.*, *Aging Res. Rev.*, 2013