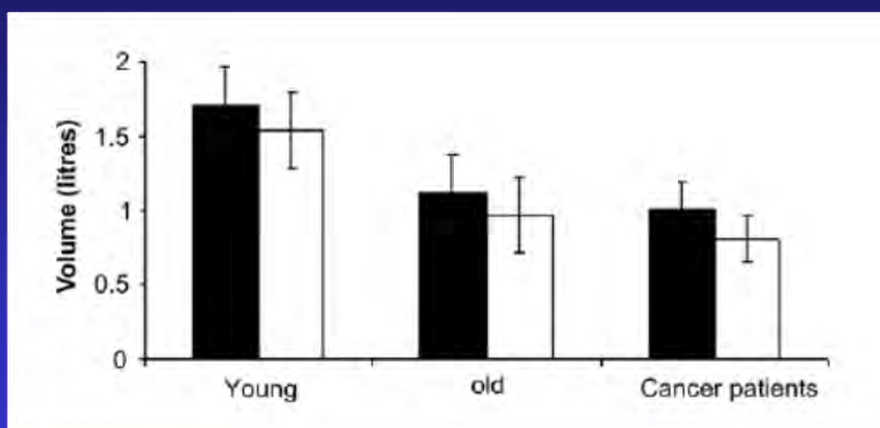


Basic Mechanisms in Cancer Cachexia: more than sarcopenia?

KCH Fearon

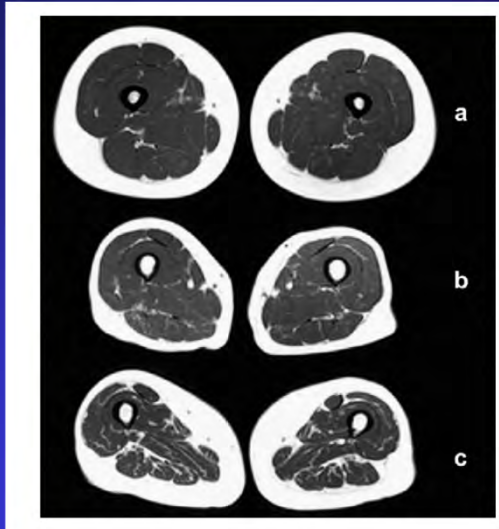
Sarcopenia *Max*?



■ Gross muscle volume
□ K-means muscle volume (fat subtracted)

Greig C et al 2010 Clin Nutr

MR image showing loss of muscle mass and fatty infiltration



Young: 23yrs

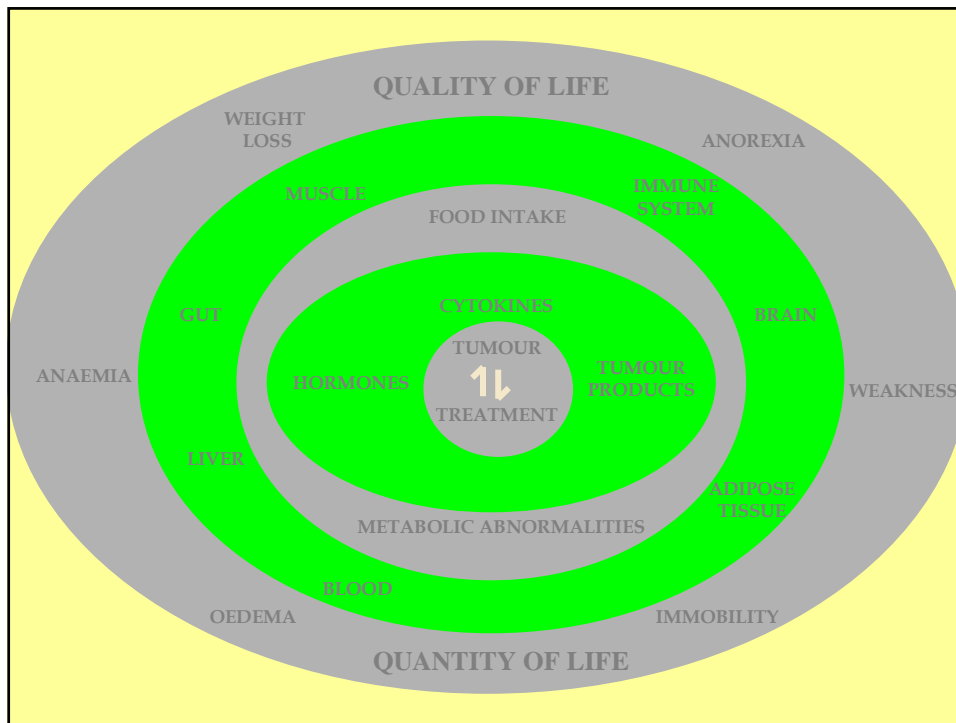
Old: 80yrs

Cancer: 73yrs

Greig C et al 2010 Clin Nutr

The elephant in the room is...



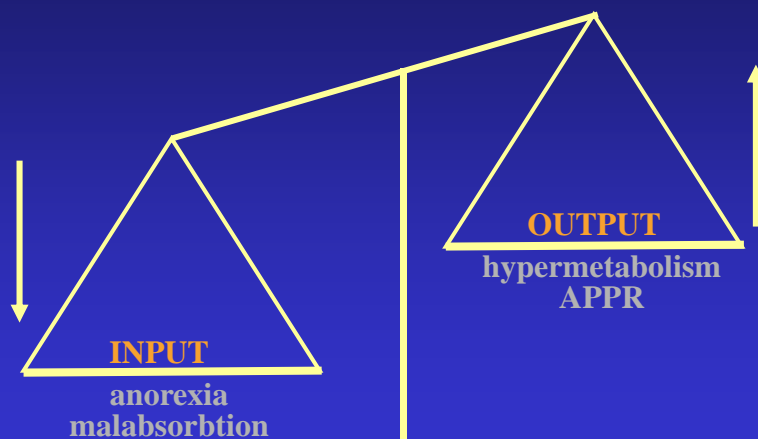


Focus for discussion

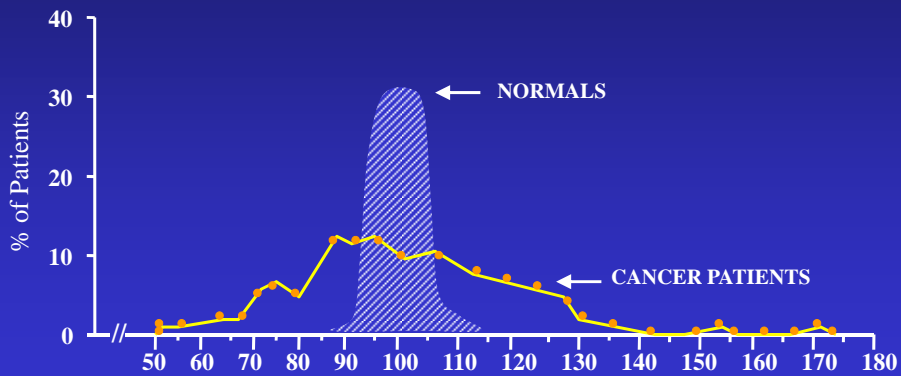
- Energy metabolism
- Liver metabolism
- Adipose tissue

ENERGY METABOLISM

Negative Energy Balance

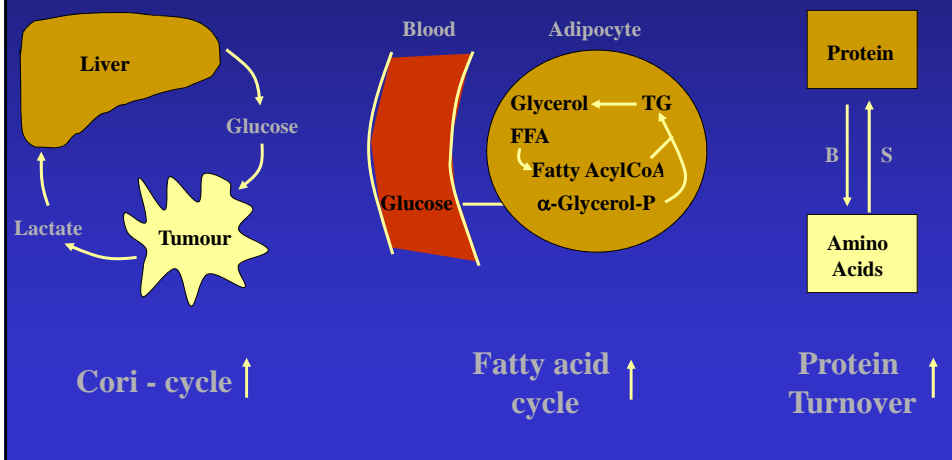


Measured Resting Energy Expenditure as a % of Predicted Energy Expenditure

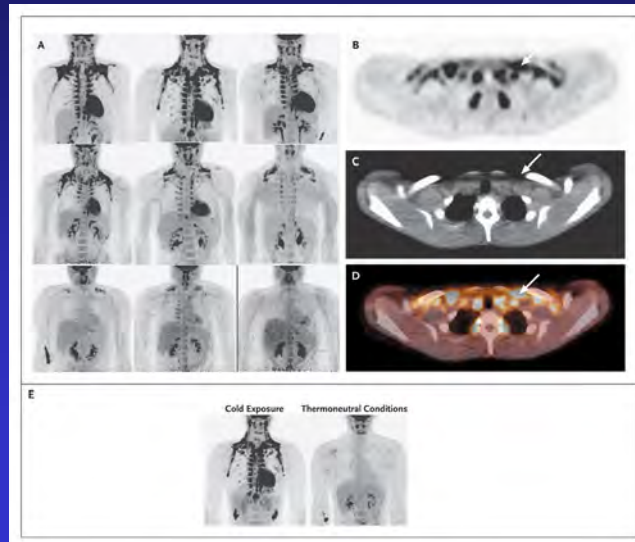


Knox L et al Ann Surg 1983;197:152-62

Aetiology of hypermetabolism in cancer cachexia



Hypermetabolism: Role of UCPs in Brown Fat?



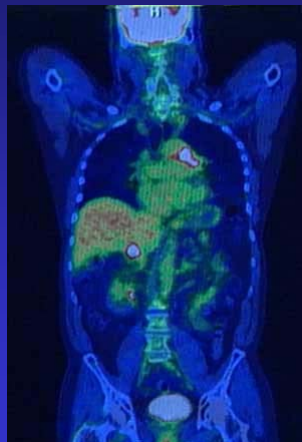
LIVER

Organ oxygen consumption

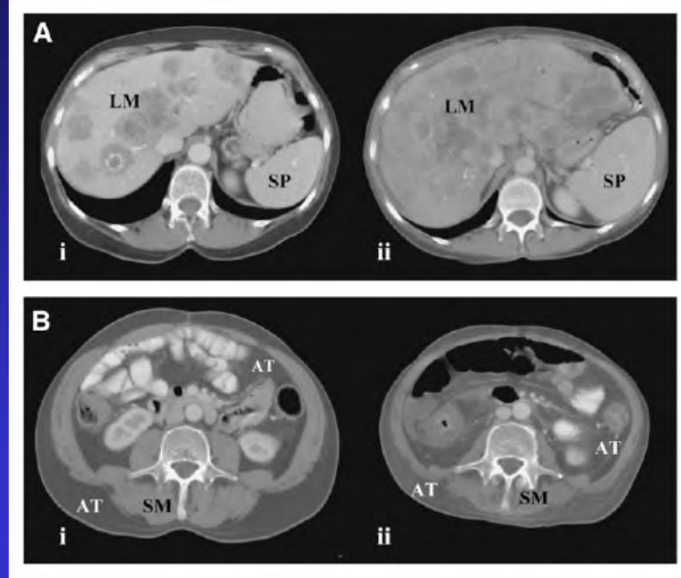
Organ	O ₂ Consumption (ml O ₂ /min per 100g)
Brain	3
Liver*	3
Kidney	5
Skin	0.2
Resting muscle	1
Contracting muscle	50

* Liver mass=1500g=20% total body oxygen consumption

FDG-PET-CT

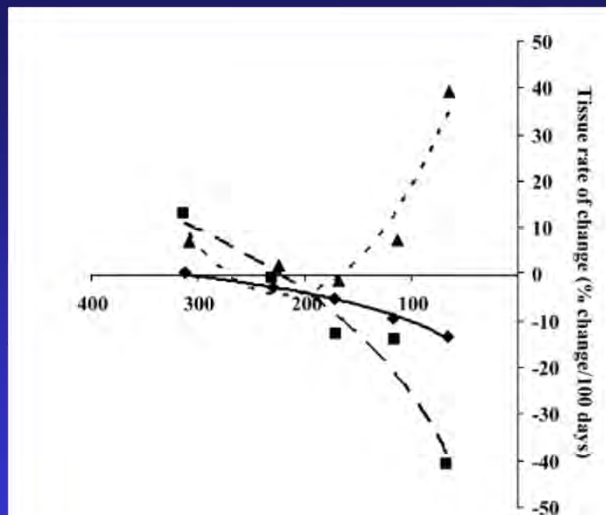


Liver, spleen and tumour growth during last 3 months of life



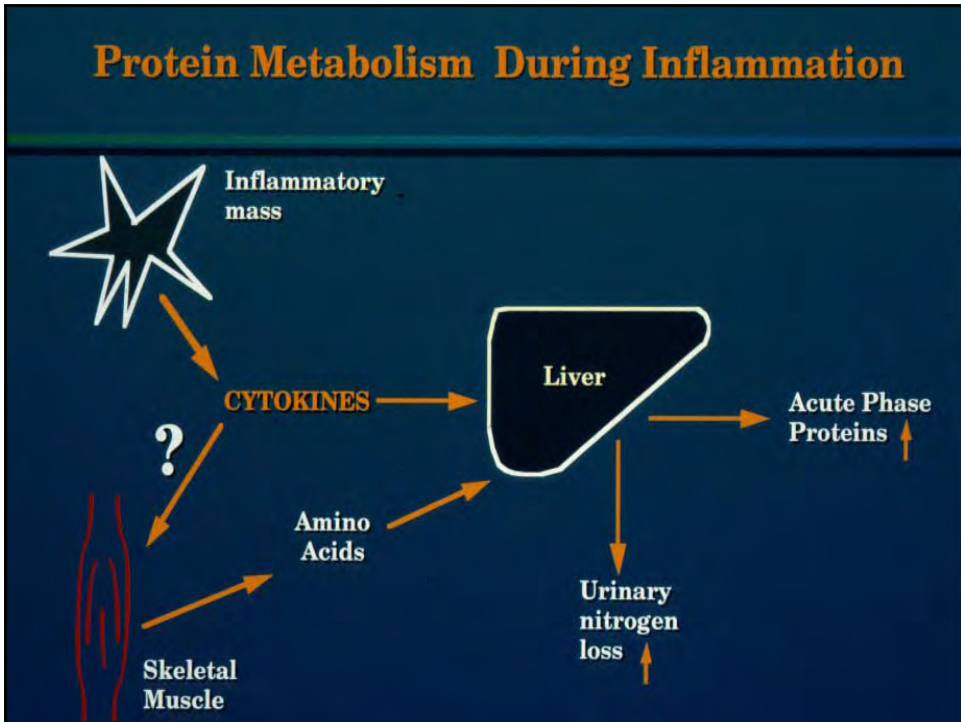
Lieffers JR et al Am J Clin Nutr 2009;89:1173-9

Cachexia: a viscerally driven syndrome

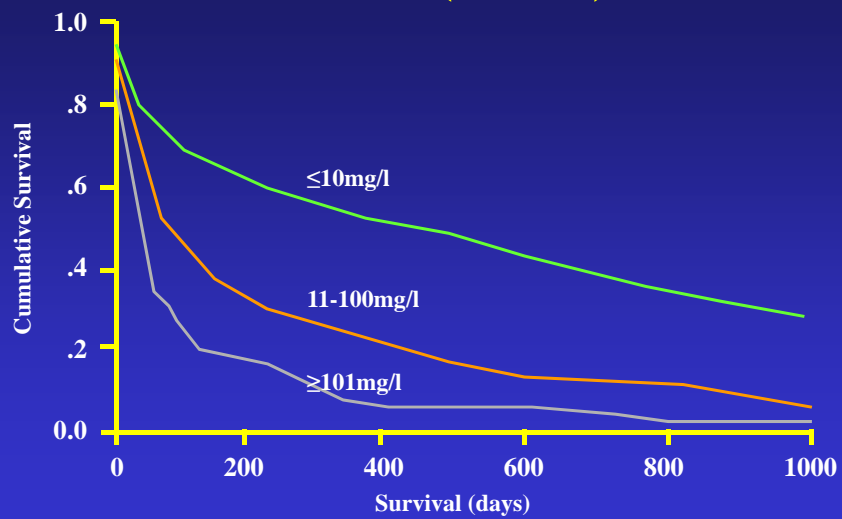


Change in liver mass will increase REE by 200Kcal/d

Lieffers JR et al Am J Clin Nutr 2009;89:1173-9



Cancer Specific Survival in Advanced Cancer (n=772)



McMillan et al, Nutrition and Cancer, 2001, 41; 64-51

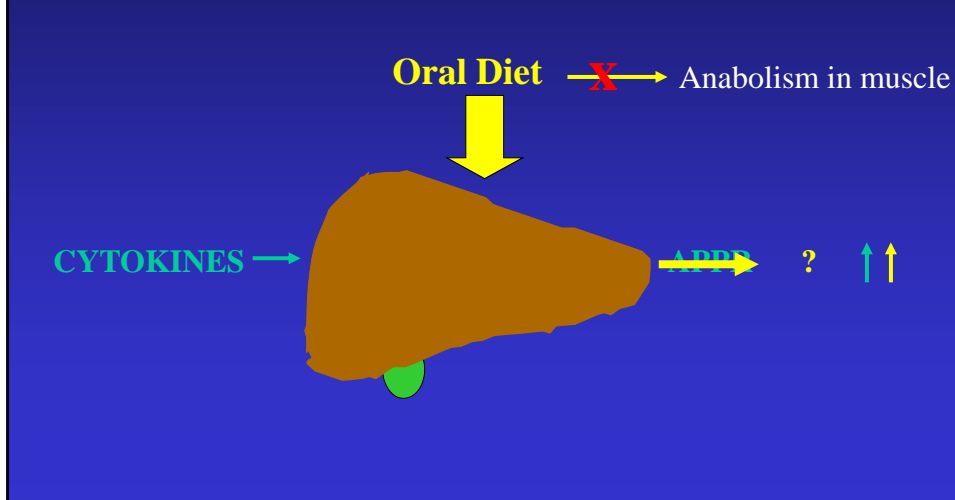
The APPR : a double edged sword?

Loss of lean tissue and energy reserves

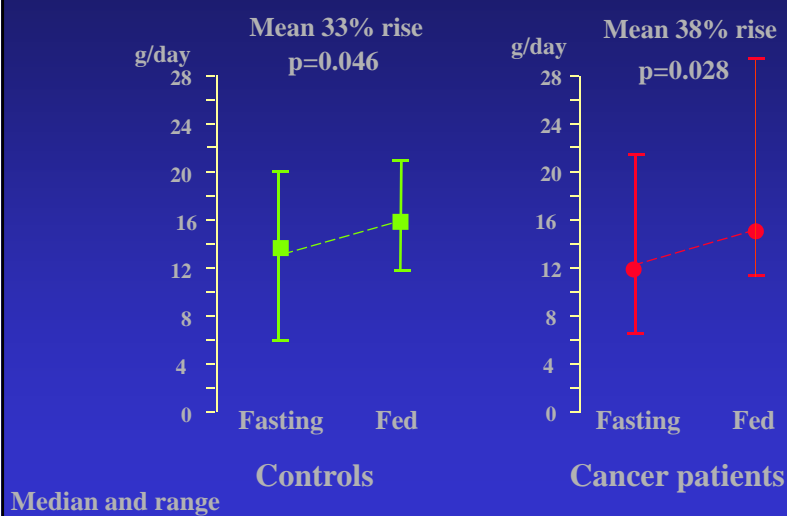


Circulatory proteins valuable in healing, repair and during infection

Effects of inflammation on post-prandial visceral protein synthesis

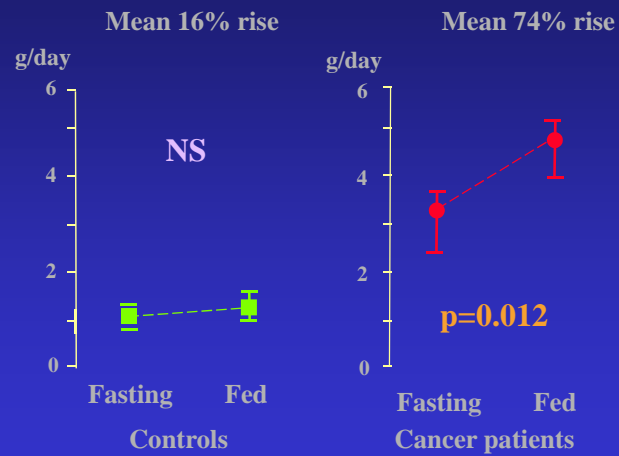


Albumin synthesis (Total synthetic rate)



Barber et al 2000, Am J Physiol End Metab, 279, E707-14

Fibrinogen synthesis (Total synthetic rate)

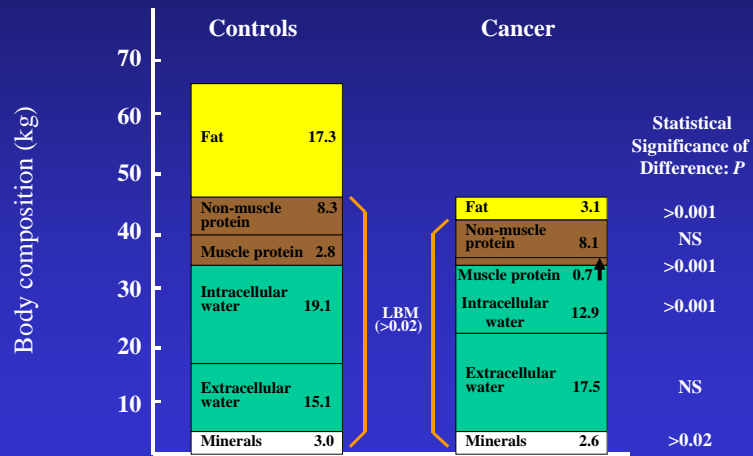


Median and interquartile range.

Barber et al 2000, Am J Physiol End Metab, 279, E707-14

FAT

Body composition in cancer cachexia



Fearon and Preston, 1990

THE NEW ENGLAND JOURNAL of MEDICINE

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Cancer Cachexia and Fat–Muscle Physiology

Kenneth C.H. Fearon, M.D.

N ENGL J MED 365:6 NEJM.ORG AUGUST 11, 2011

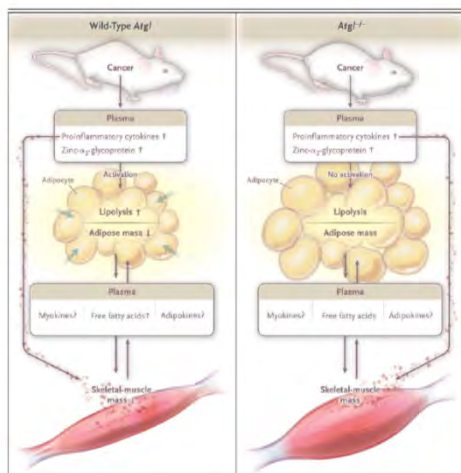
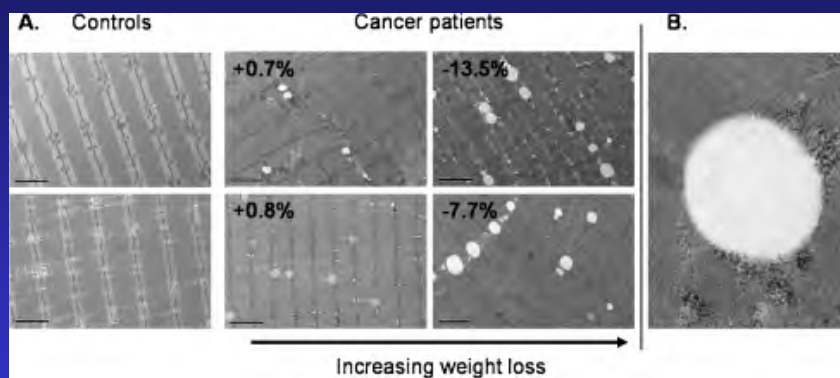


Figure 1. Model of Cachexia and Lipolysis in Tumor-Bearing Mice with Wild-Type *Atg1* or *Atg1*^{-/-}.
 In tumor-bearing mice with the wild-type gene for adipose triglyceride lipase (*Atg1*, also known as *Atgl*), a variety of circulating mediators, including cytokines (tumor necrosis factor α and interleukin-6) and zinc- α_2 -glycoprotein, activate *Atg1*, which triggers lipolysis, resulting in net mobilization of white adipose tissue and an increase in plasma levels of free fatty acids. Concomitantly, cachexia — the process of protein catabolism, apoptosis, and muscle atrophy — begins and may be modulated by cross-talk between muscle and adipose tissue mediated by free fatty acids or by various adipokines or myokines. In tumor-bearing mice in which the *Atg1*^{-/-} gene has been ablated, the same pattern of mediator release fails to activate lipolysis, plasma levels of free fatty acids remain normal, and both white adipose tissue mass and skeletal-muscle mass are maintained. The mechanism through which skeletal-muscle mass is maintained in the presence of the systemic mediators is unknown but may involve muscle-adipose cross-talk through free fatty acids, myokines, or adipokines. Alternatively, the maintenance of skeletal-muscle mass may be a direct consequence of autonomous lipolysis in defective tissue.

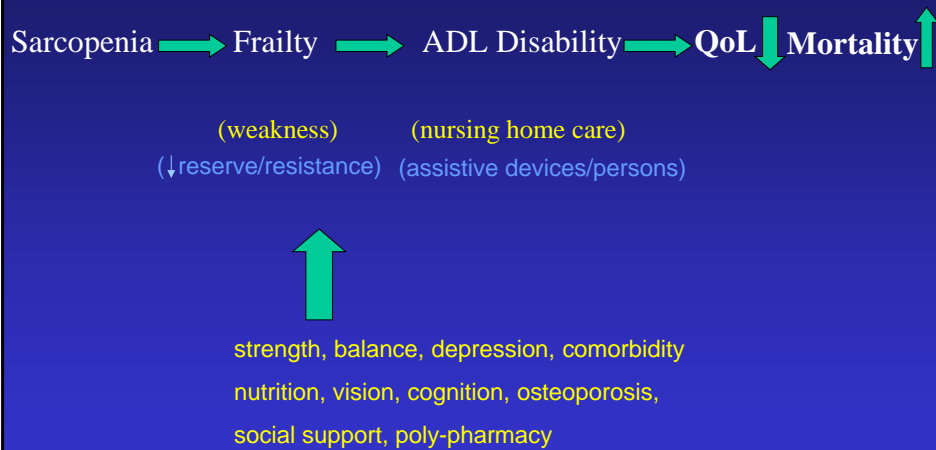
Derived from: Das S K et al Science 2011

Intramyocellular lipid droplet accumulation in cancer cachexia

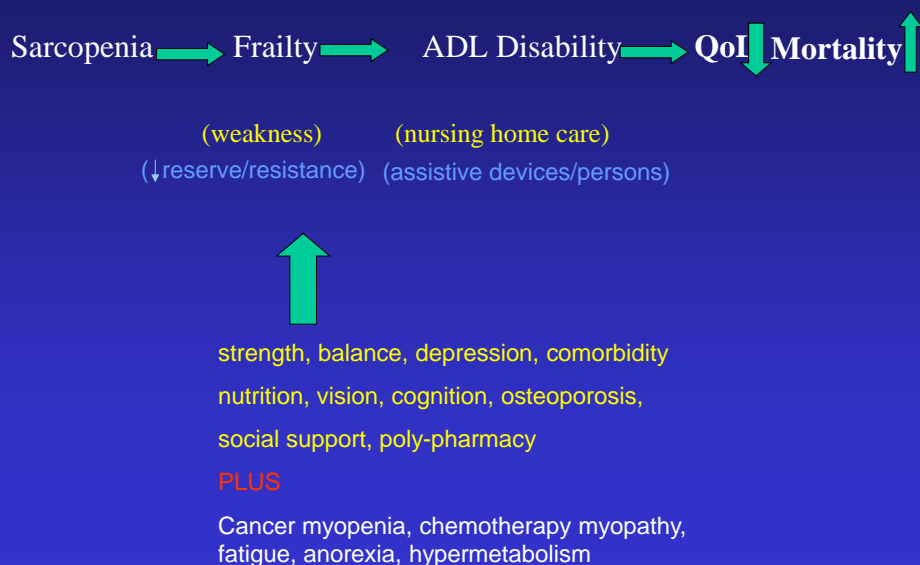


Stephens N A et al J Cachexia, Sarcopenia Muscle 2011

Impact of age-related sarcopenia

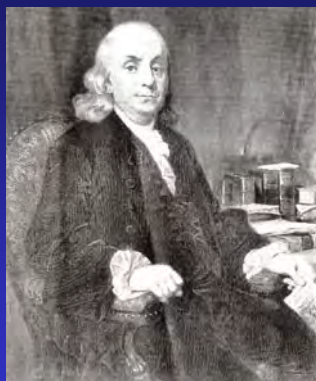


Impact of cancer beyond sarcopenia



Summary

- Cachexia is multifactorial: it has unique features but can occur in parallel with starvation and sarcopenia of the elderly
- Altered hepatic metabolism and systemic inflammation are key features
- Fat-muscle physiology is likely to be of growing importance



Persons of good sense seldom fall into dispute except lawyers, university men and men of all sorts that have been bred at Edinburgh.

BENJAMIN FRANKLIN 1706 - 1790