

# Hip Fracture – The Final Straw?

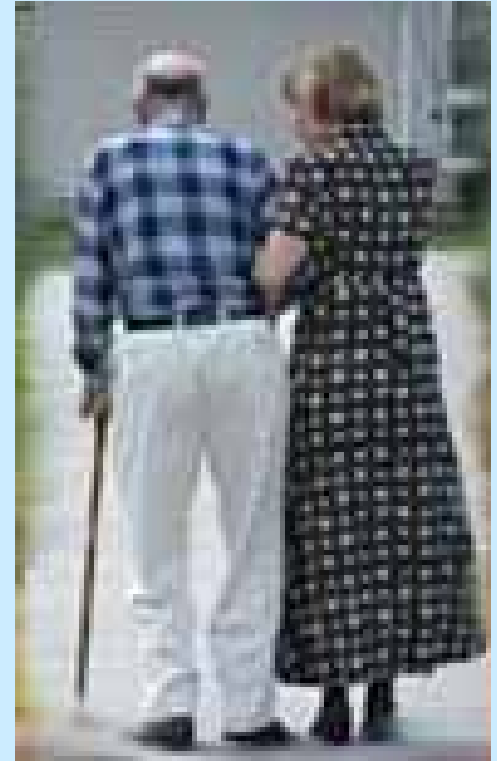


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University**



# Frailty in the Third Age of Man



Ageing = Increasing frailty of an organism with time that reduces the ability to deal with stress, resulting in increased chance of disease and death.



# Ageing and stress

- Risk of physical trauma (Hip-fracture)  
*Wood et al 1992; Khasraghi et al 2003*
- Emotional stress of caring for a partner  
*Kiecolt-Glaser et al 1991; Bauer et al 2000*
- Emotional stress of bereavement  
*Jacobs and Ostfield, 1977; Helsing et al, 1981; Schleifer et al, 1983; Price et al 1997; Phillips et al 2005*
- Effect of social isolation  
*Keller et al 2003*



# Immune Function in Healthy Elderly and Hip-fracture patients

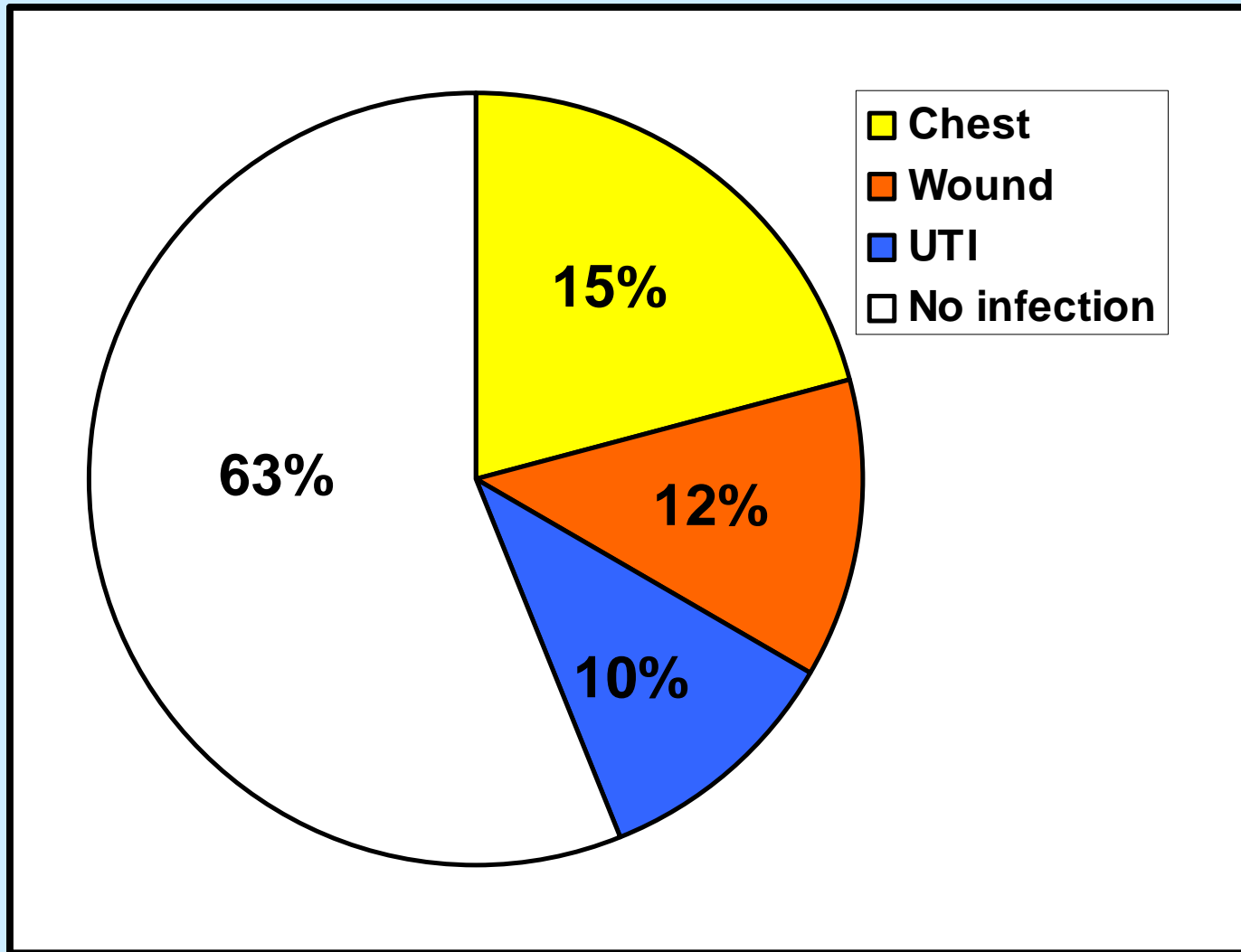
**Subjects: 35 elderly patients (>65 yrs) with fractured neck of femur; 9 young patients (<33yrs) patients with lower limb fractures; 20 healthy age-matched controls**

**Infection rates were monitored and neutrophil function assessed at time of trauma and 6 weeks later.**

**The ratios of serum cortisol:DHEAs were assessed for each group**



# Infections after Hip-Fracture



# Question 1

Why are older people more prone to infections after Trauma (hip-fracture)?



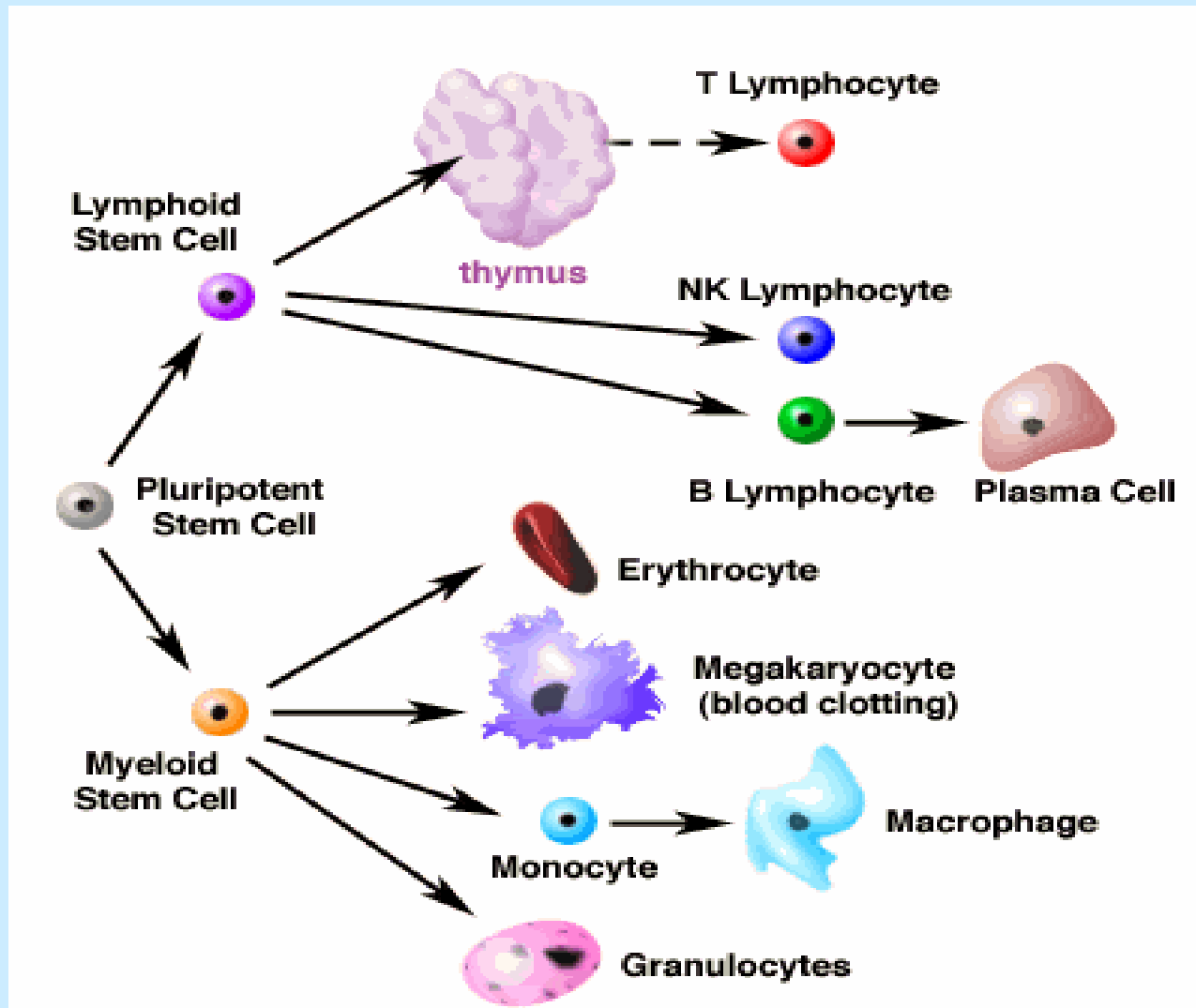
# Age-related increases in infectious diseases

Disease	Change in Elderly subjects	Ref
Gram negative sepsis	50% increase in mortality	1
Bacterial dysentery	3-fold increase in incidence	2
Pneumonia	120-fold increase in mortality	2
GI infections	400-fold increase in mortality	3
Influenza	160-fold increase in mortality	3

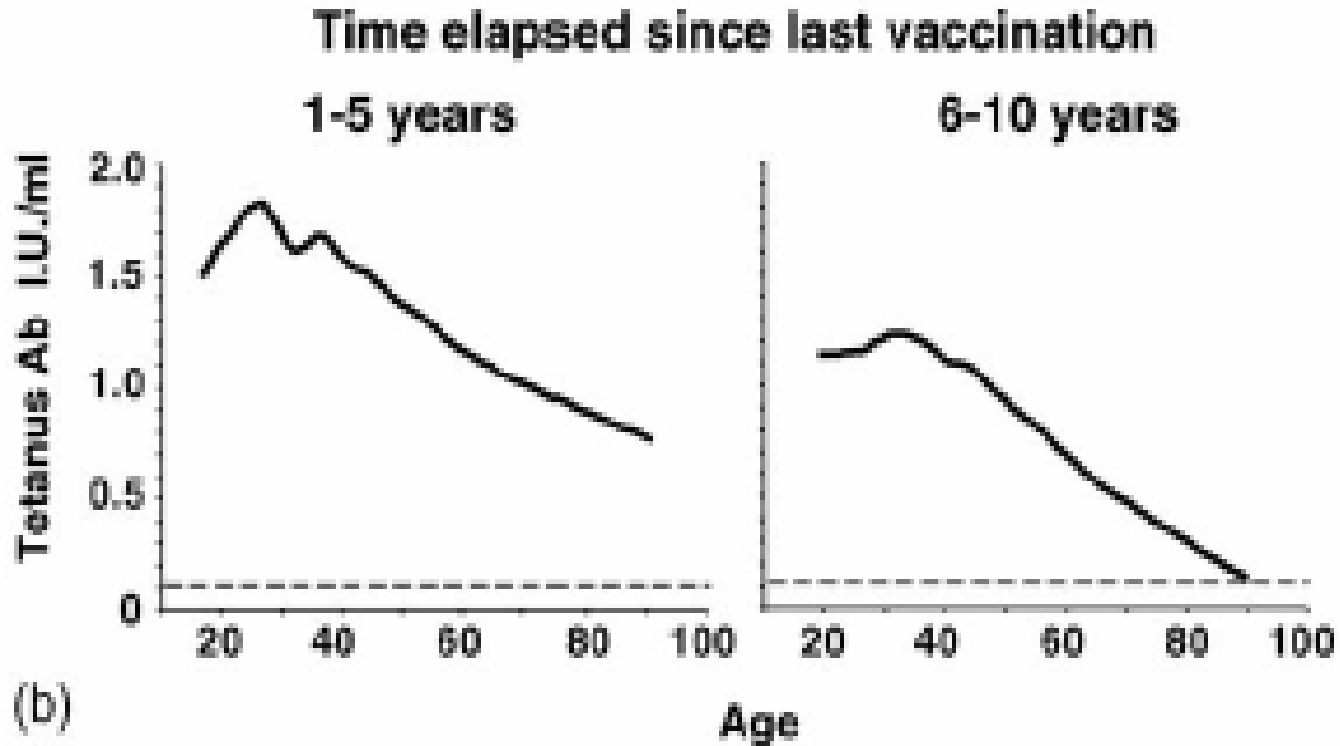
1. Am.J.Med. 39:952, 1965. 2. Rev. Infect. Dis. 2:801, 1980. 3. WHO 1975 World Health Statistical manual.



# Cells of the immune system



# Age and vaccination efficacy



# Meet the Neutrophil

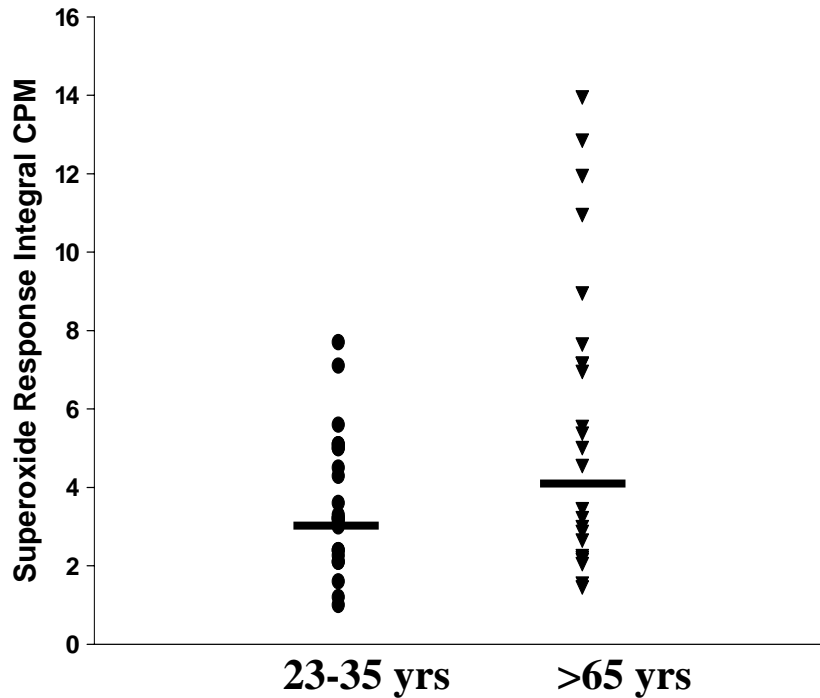
## OXIDATIVE BURST

Neutrophils kill microbes by producing reactive oxygen species, demonstrated here with the dye nitroblue tetrazolium (NBT)

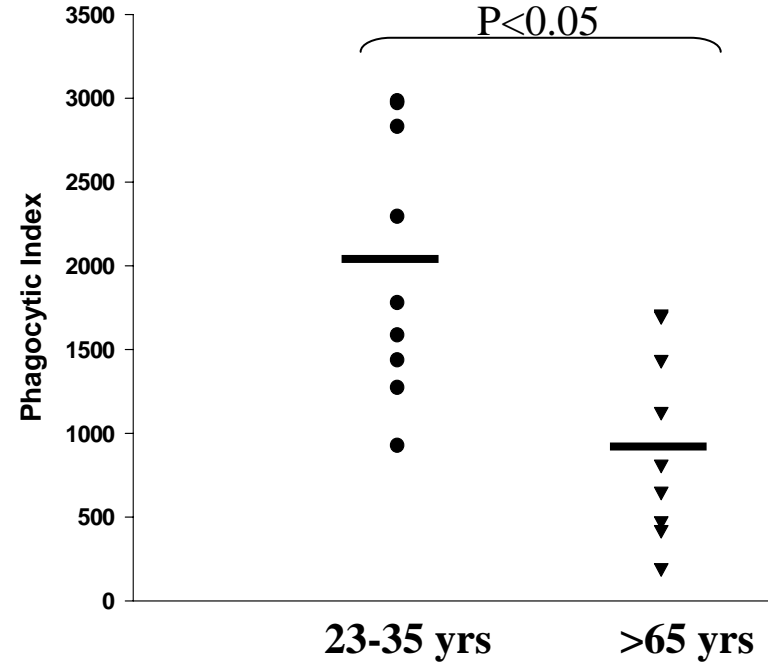


# Effect of Age on Superoxide generation and phagocytosis

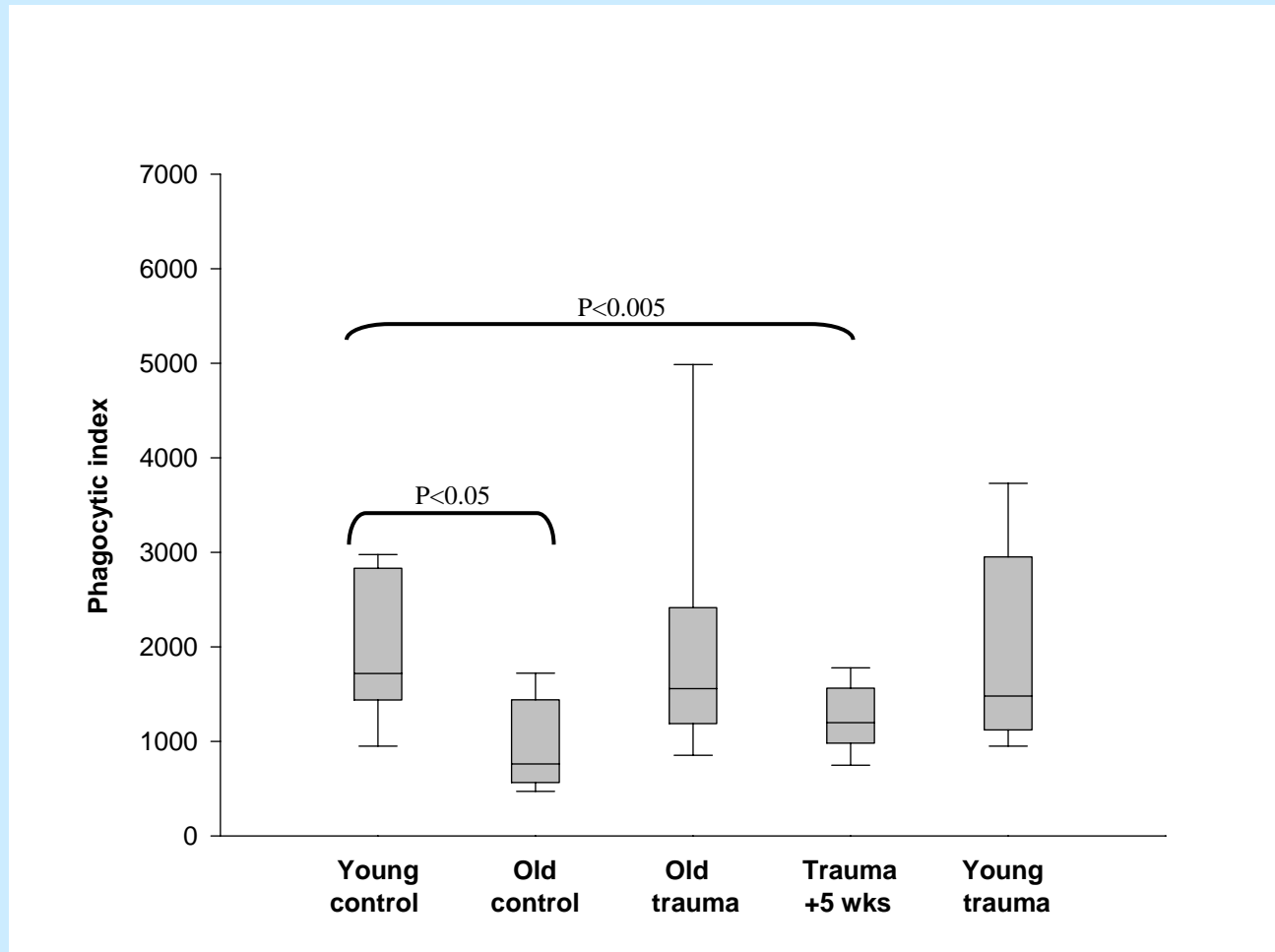
Superoxide Generation  
(n=20)



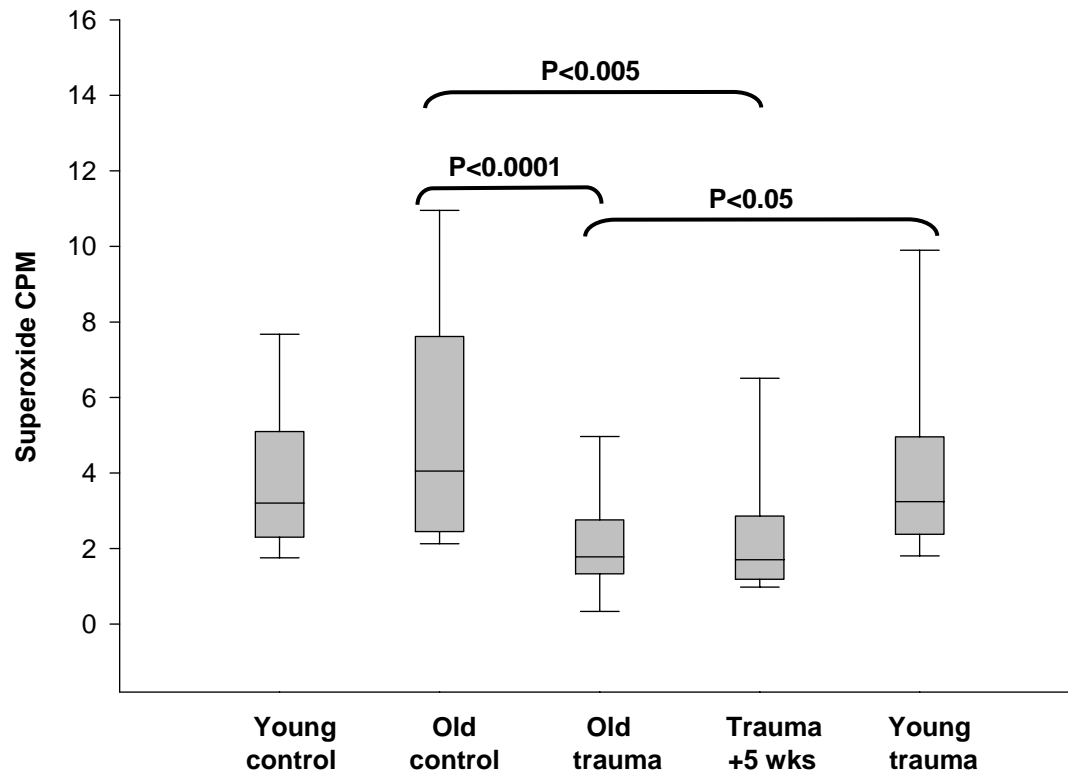
Phagocytosis  
(n=20)



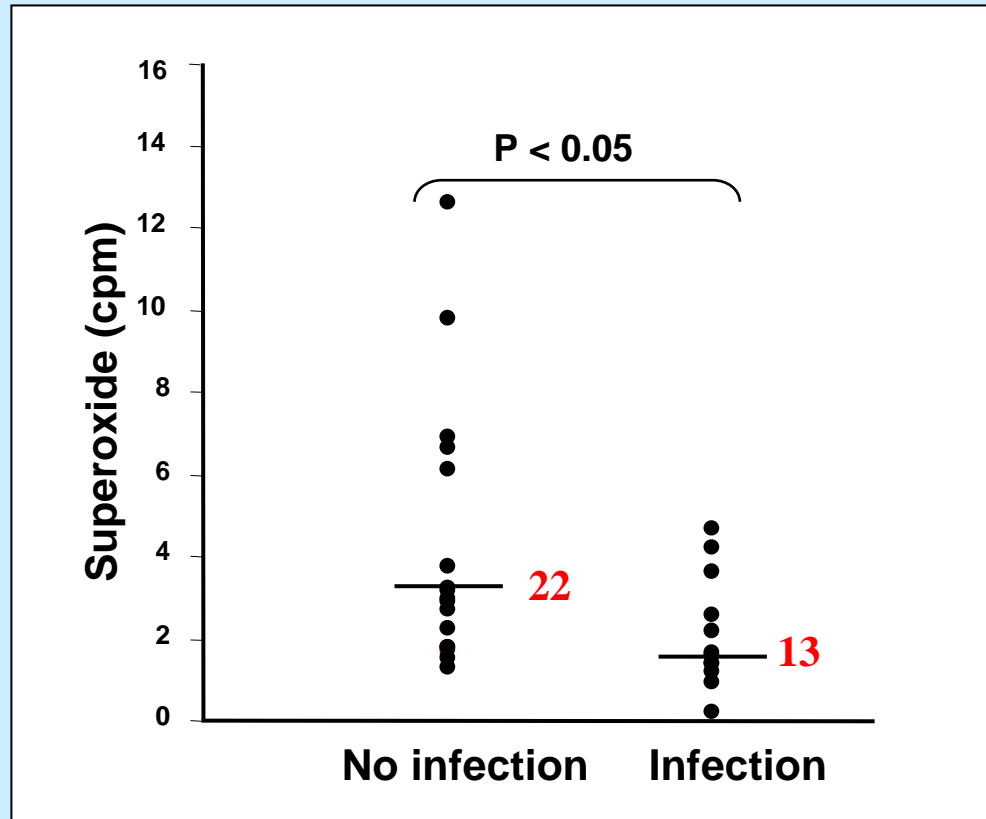
# Trauma does not affect neutrophil Phagocytosis



# Trauma suppresses neutrophil bactericidal function in the elderly



# Superoxide generation was lower in patients who later developed infection

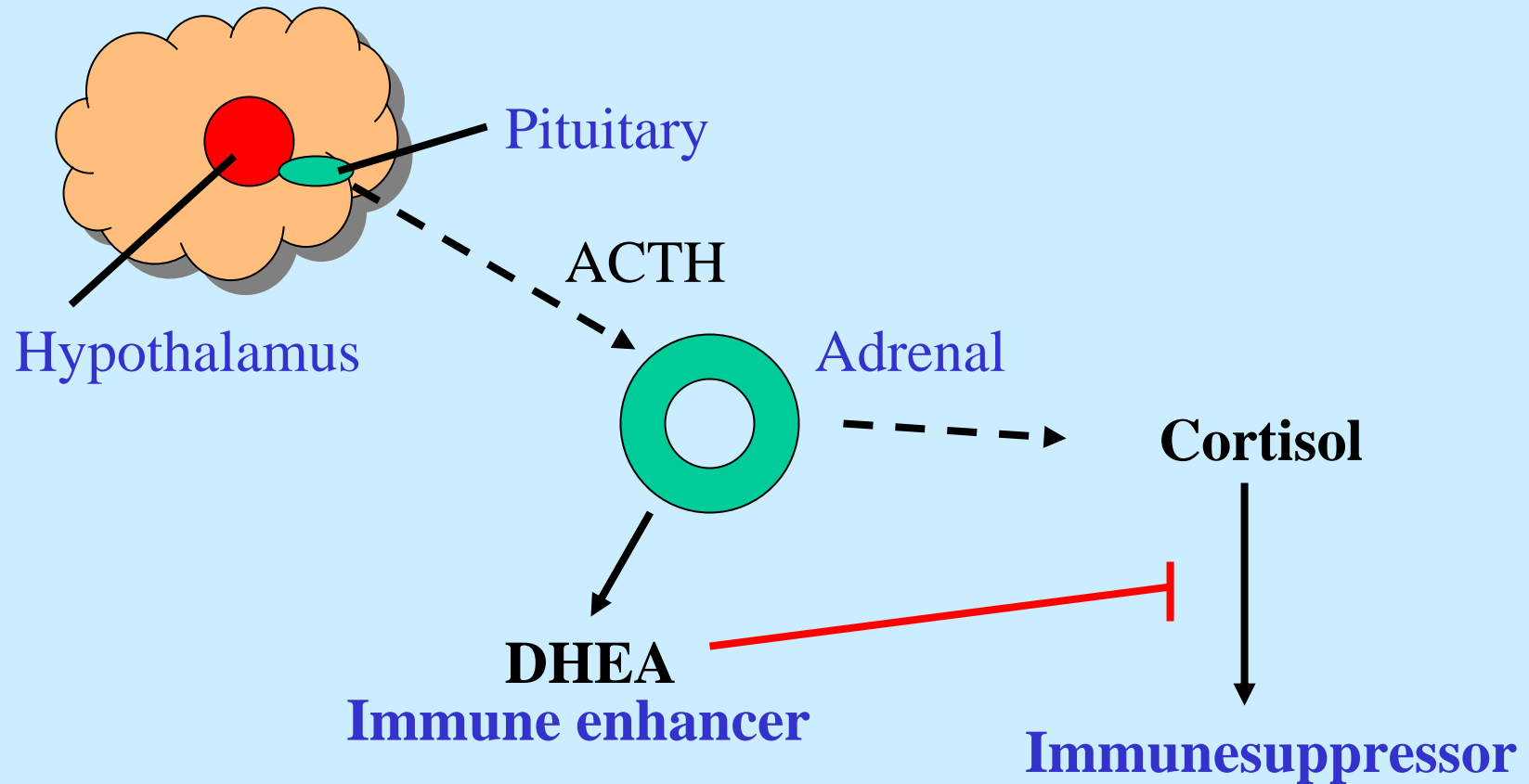


# Question 2

Why is stress more of a problem with age?



# The Hypothalamic-pituitary-adrenal axis

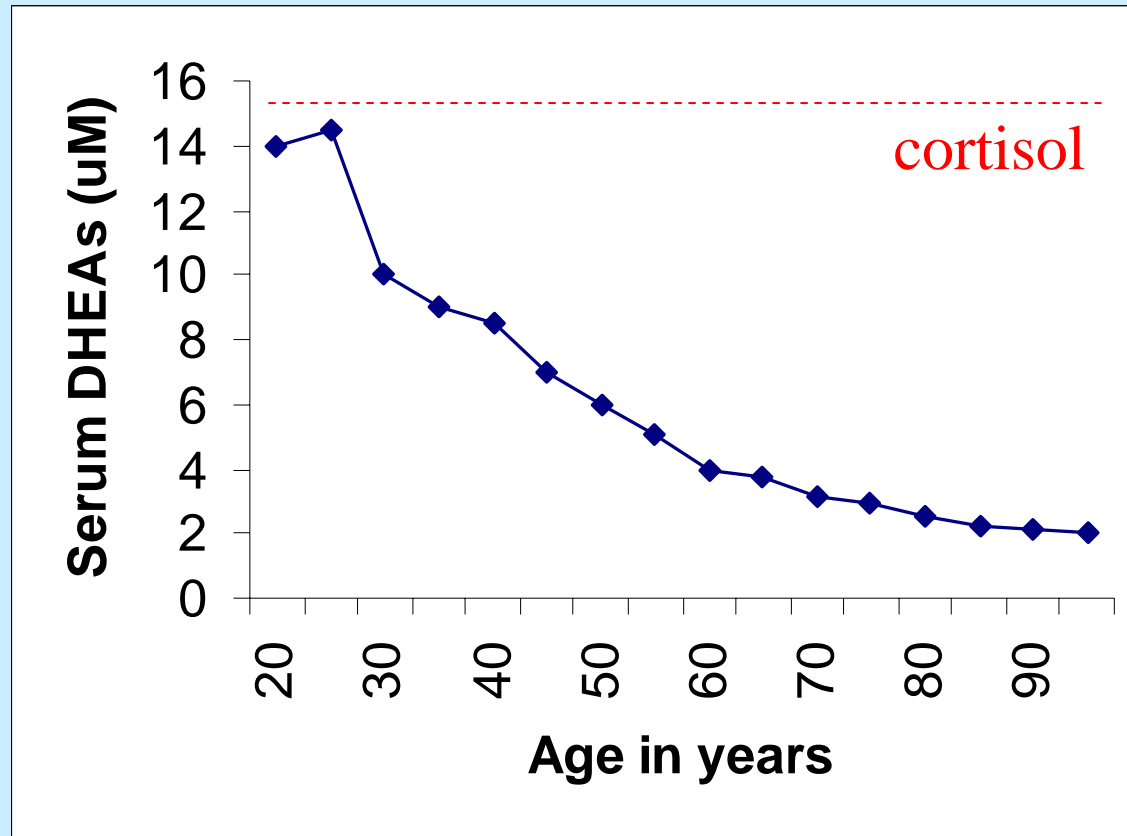


# Adrenal Corticosteroids and Immune Function

- Cortisol
  - Decreased production of pro-inflammatory molecules (IL-1, TNF, GM-CSF, IL-2, IL-3, IL-4, IL-5, IL-8, NO, prostaglandins, leukotrienes)
  - Reduced extravasation of inflammatory cells
  - Induction of apoptosis in lymphocytes and eosinophils
  - Inhibition of neutrophil function
- DHEA/s
  - Increased cytokine production (IL-2, IL-3, IFN-gamma)
  - Increased T cell function (CD8, DTH)
  - Decreased apoptosis of PBMC
  - Increased myelopoiesis and lymphogenesis



# DHEAs levels decline with Age - Adrenopause



**Cortisol:DHEAS ratio - Young = 0.09; Elderly = 0.17**



# Cortisol:DHEAs is increased in Elderly hip-fracture patients

Young trauma

Elderly trauma

$0.087 \pm 0.01$

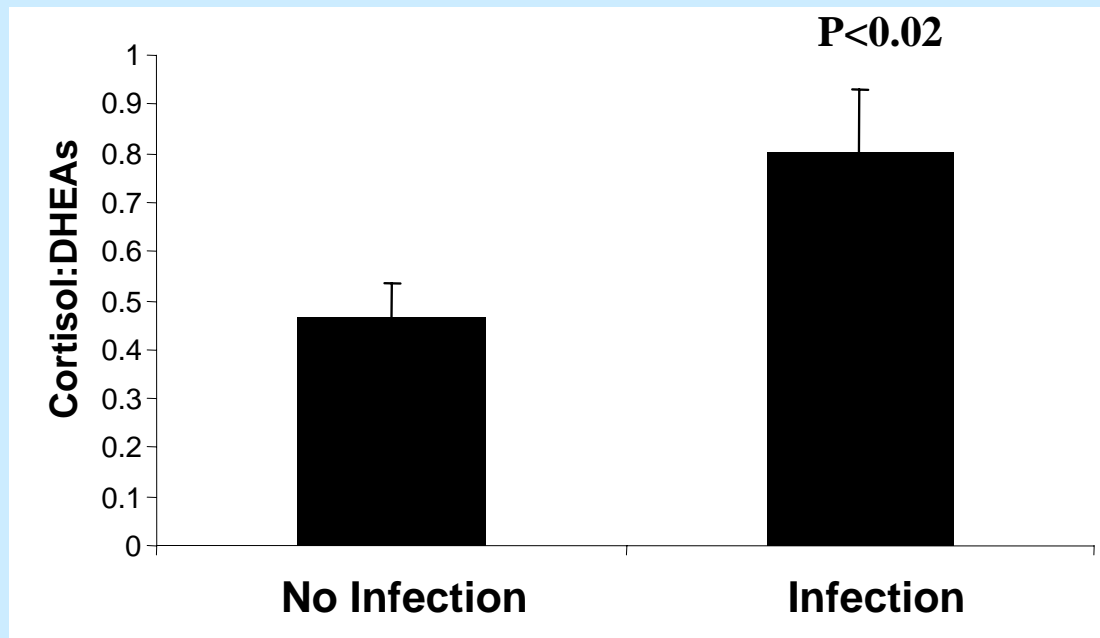
$0.562 \pm 0.06$

$p < 0.0001$

[Healthy young =  $0.094 \pm 0.01$ ; Healthy elderly =  $0.176 \pm 0.03$ ]



# Cortisol:DHEAs is higher in patients who developed infection

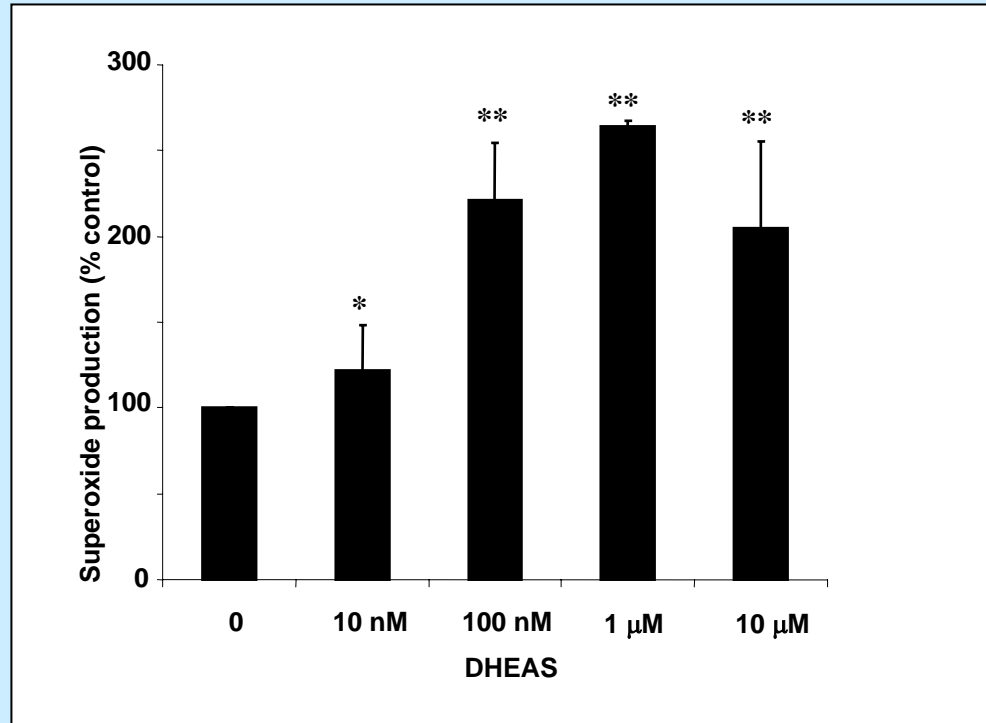


# Question 3

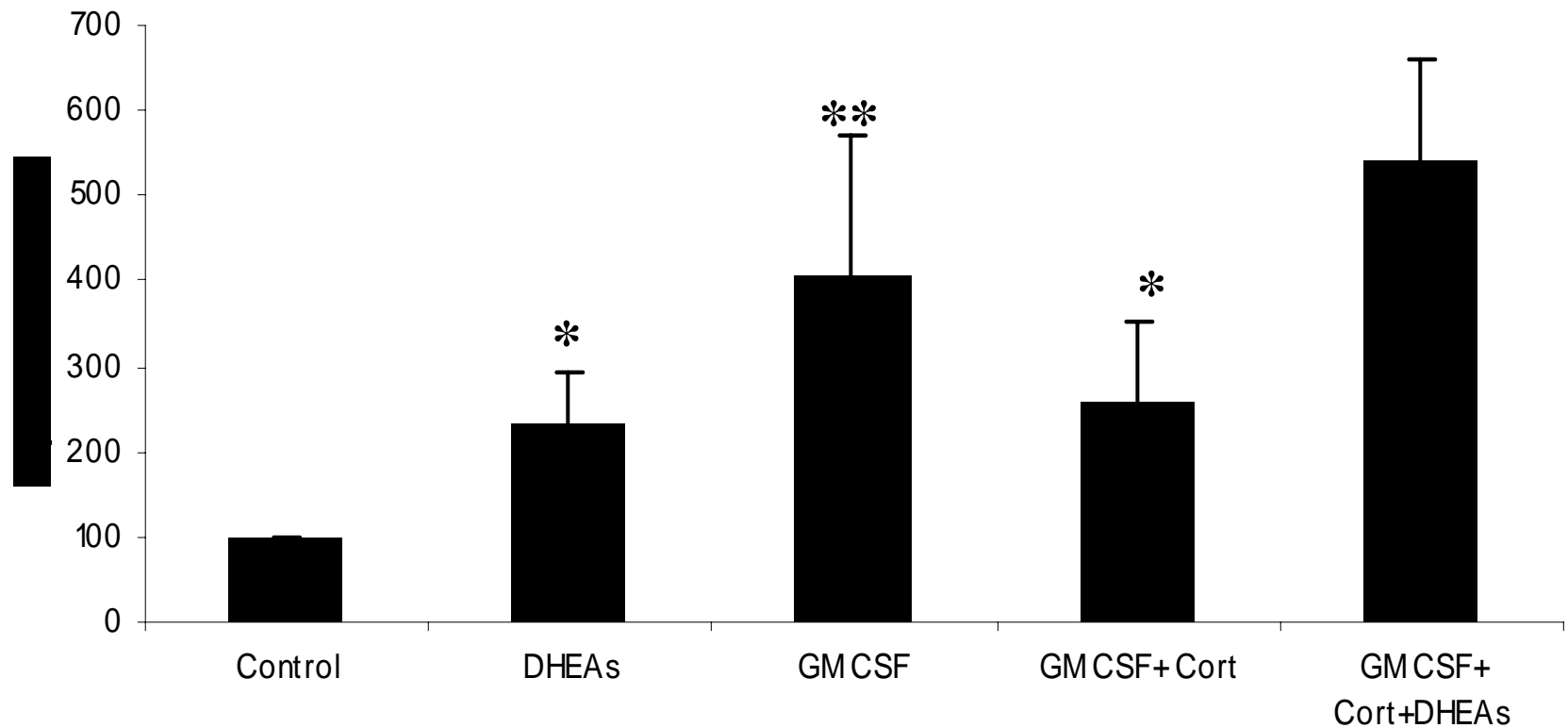
Can we do anything about this?



# DHEAs primes neutrophils superoxide responses



# DHEAs counteracts the suppressive effects of Cortisol



**Mild trauma:**

Cortisol increase



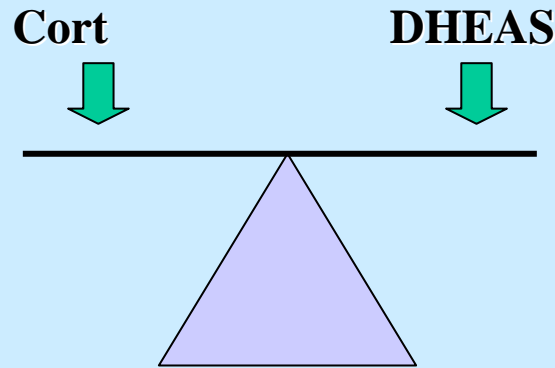
Immune system down-regulation

DHEAS increase

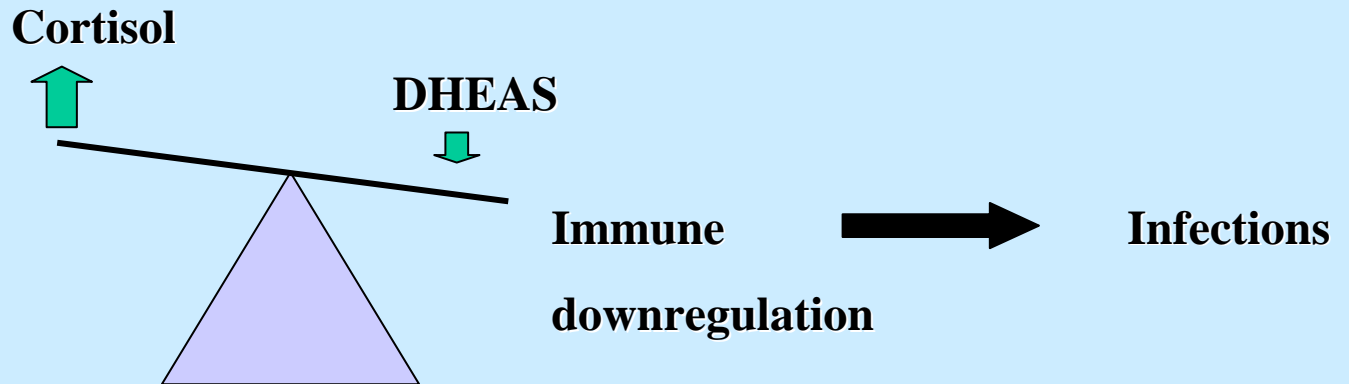


Immune system up-regulation

**Young**

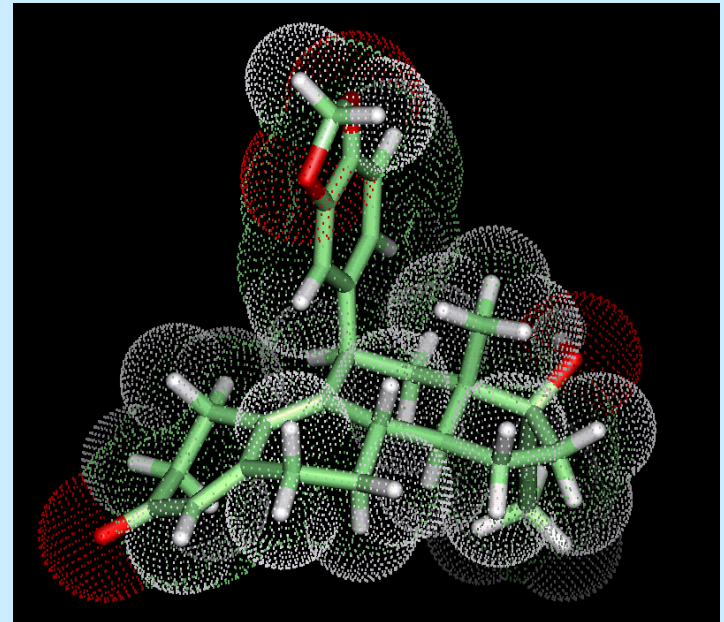


**Elderly**

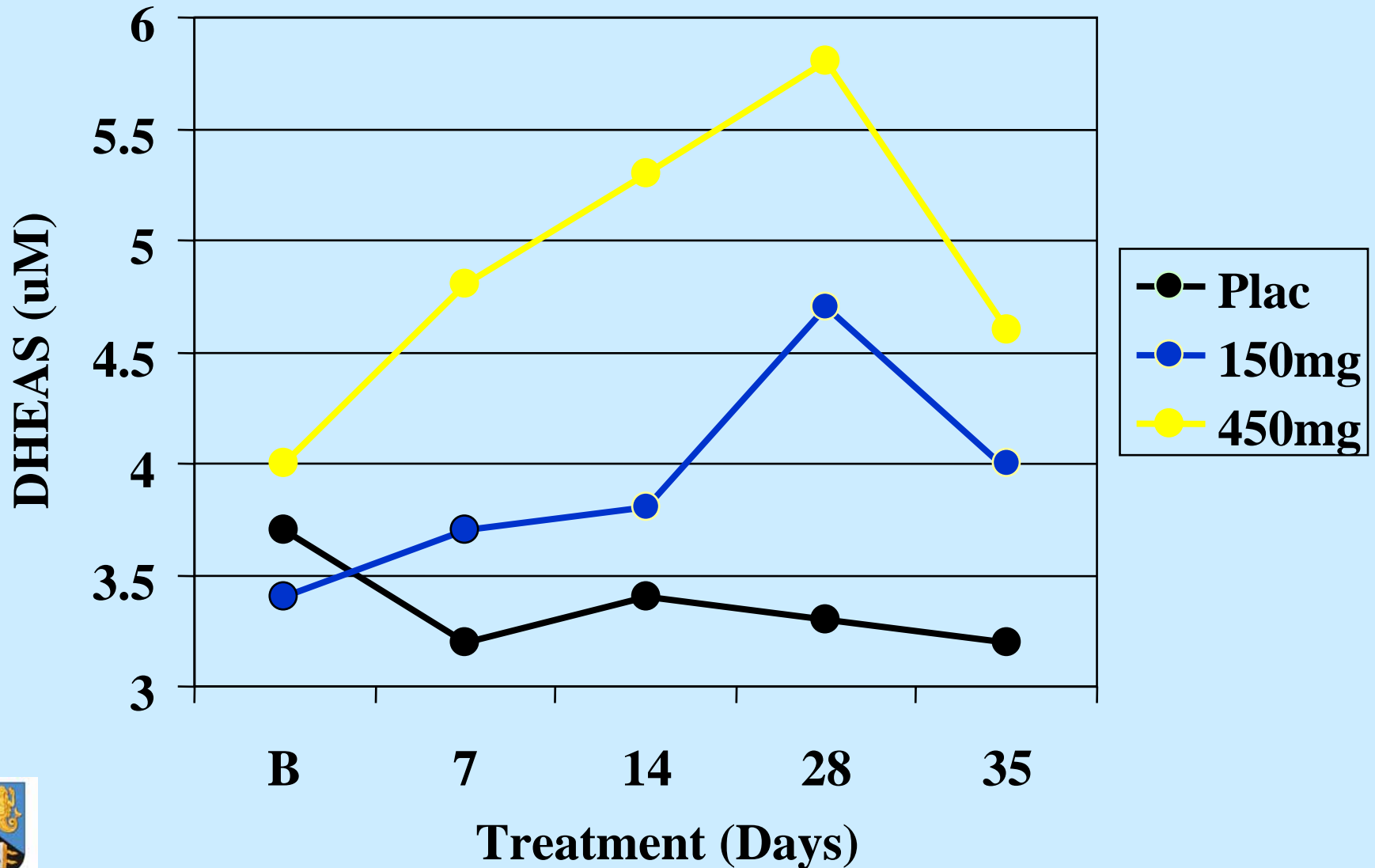


# Improving immunity after hip fractures in the elderly

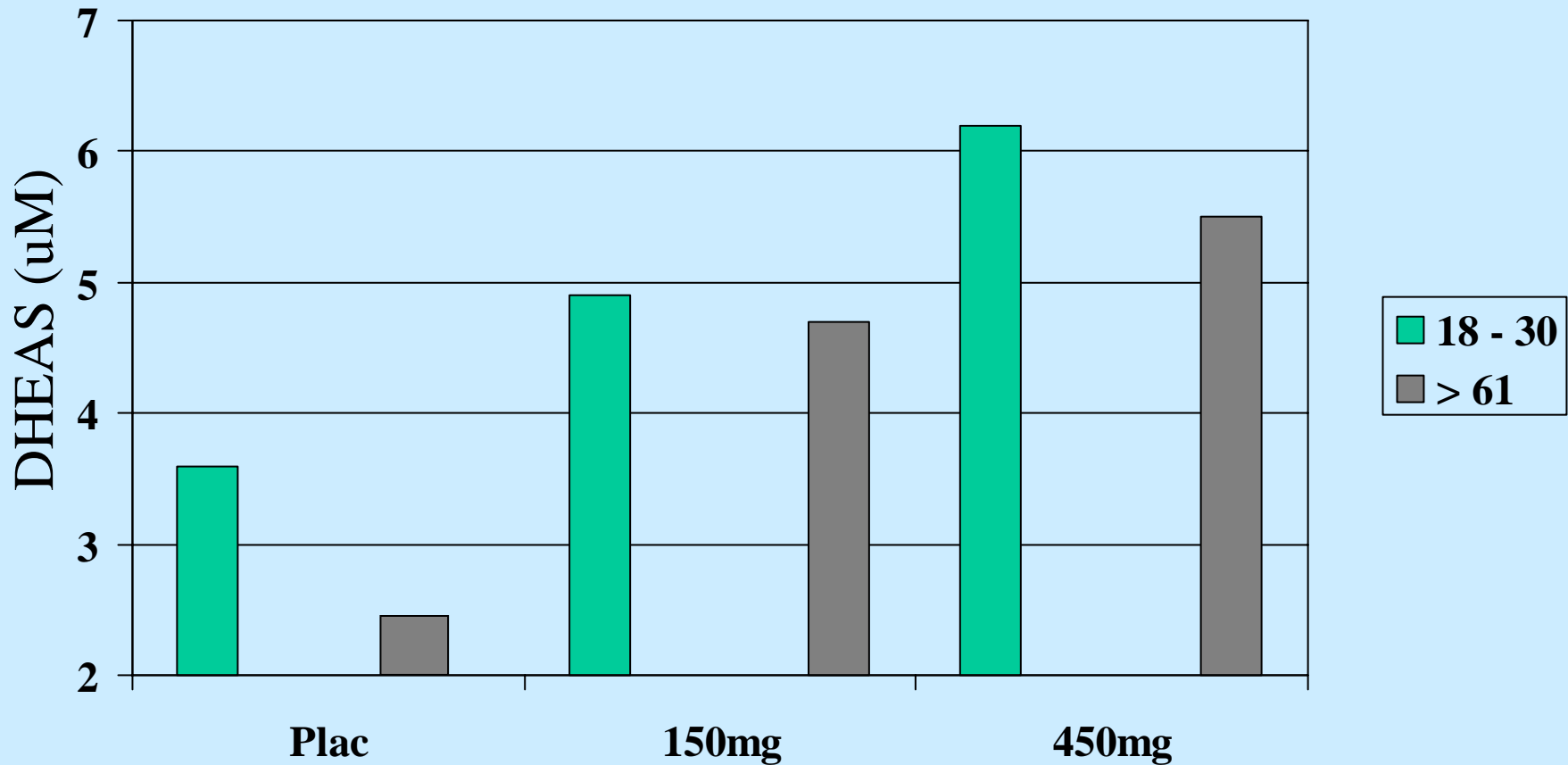
- DHEAS supplementation
- Or blocking cortisol



# The anti-glucoocorticoid also raises DHEAS levels



# Older subjects can also raise DHEAS levels



# Lord Group 2007



**“Art is Me, Science is We”**

Stephen Butcher

David Radford

David Lascelles

Keqing Wang

Vijay Killampalli

Emin Kaya Alpar

Wiebke Arlt

Jeremy Tomlinson



**Healthy Ageing – good genes,  
good diet...but watch out for  
slips and trips!**

