

A STEROID A DAY KEEPS THE DOCTOR AWAY (or Growing Old is Stressful!)



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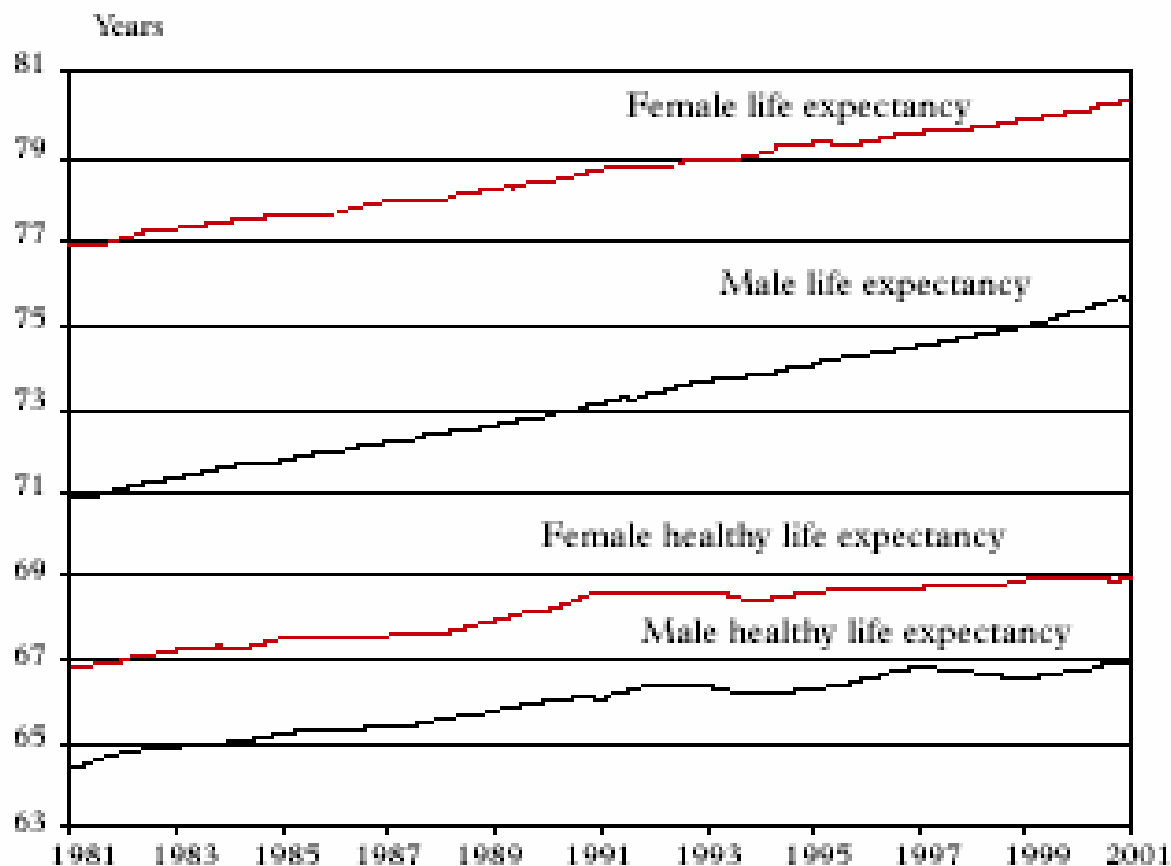


The Third Age of Man



A long life, but a longer death too?

Life Expectancy and Healthy Life Expectancy



Sadly old age is not all morning strolls and afternoon naps.....

- 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 losing a loved one

Price et al 1997; Phillips et al 2005

- Effect of social isolation

Keller et al 2003



Hip-fractures and Ageing

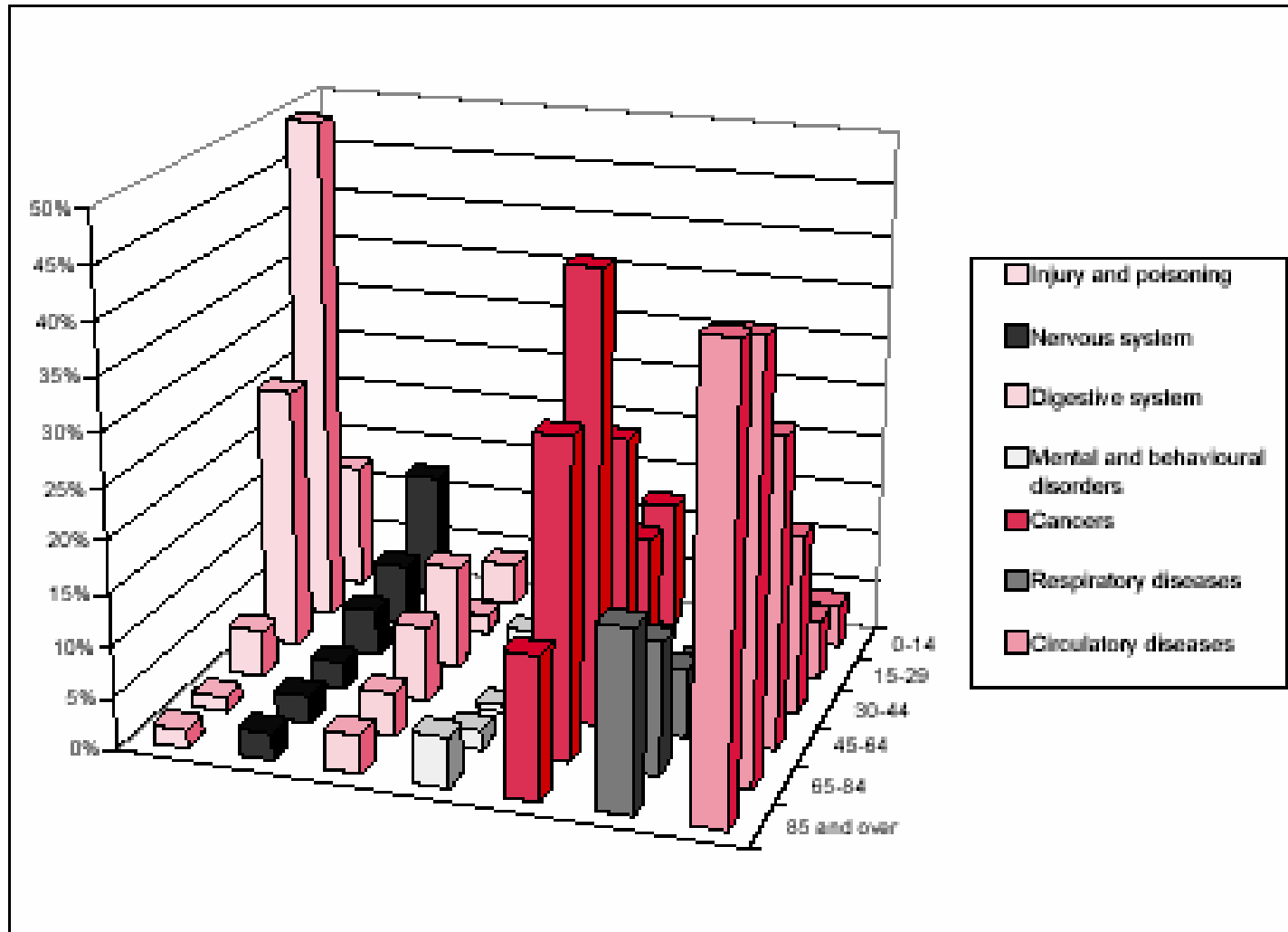
“In the UK, 30% of those over 65 will fall at least once a year, and 40% of those over 75 will fall at least twice a year. Falls are the commonest reason cited for admission to institutional care, and for 40% of admissions to nursing homes or residential homes in the UK the top reason cited is falls.”

“In 1999, there were 647,721 A&E attendances and 204,424 admissions to hospital for fall-related injuries in the UK population aged 60 years or over. The associated cost of these falls to the NHS and Personal Social Services was £908.9 million and 63% of these costs were incurred from falls in those aged 75 years and over”



What no Hip-fractures?

Major Causes of Death by Age



Ageing increases risk of 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

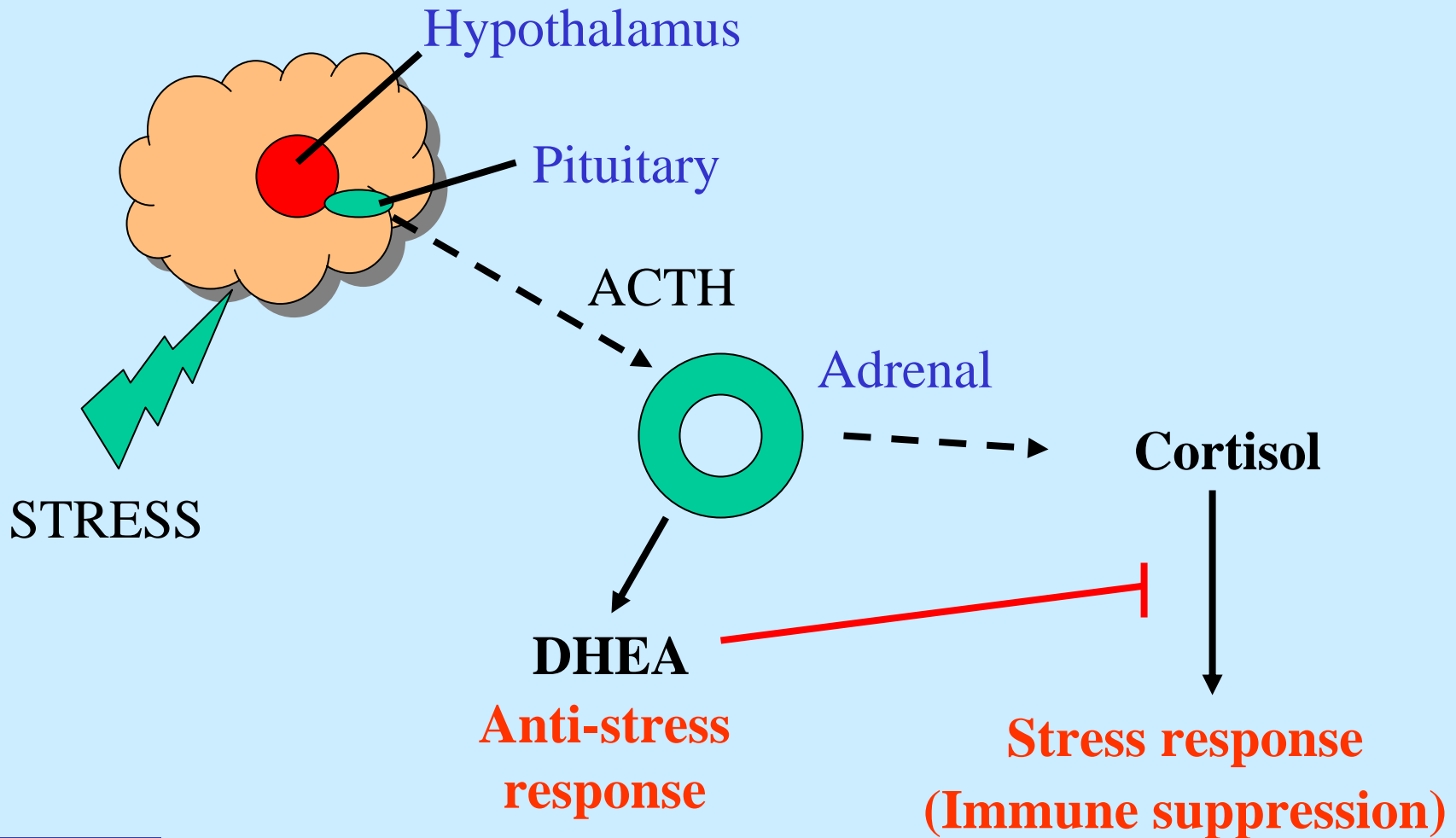
1. Am.J.Med. 39:952, 1965. 2. Rev. Infect. Dis. 2:801, 1980. 3. WHO 1975 World Health Statistical manual.



Is there a link between Ageing,
Stress and Increased
Susceptibility to infection?



The HPA axis – Your Stress Sensor

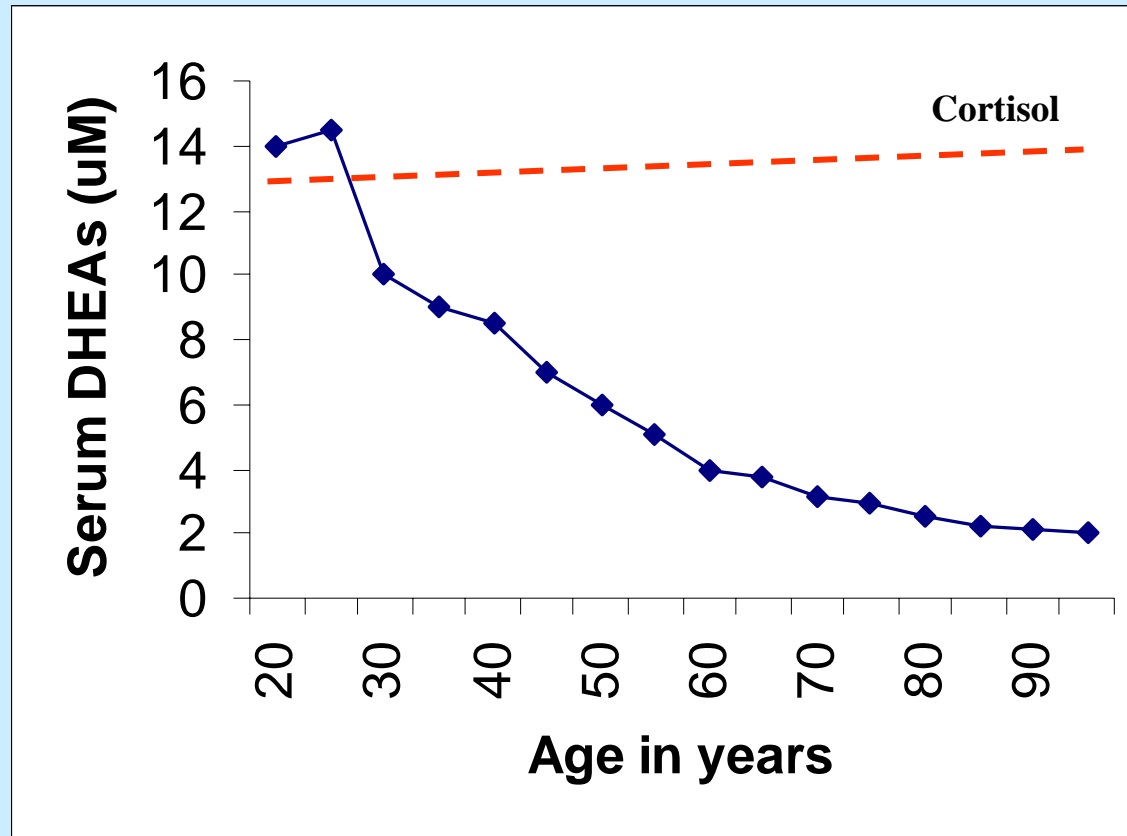


Adrenal Corticosteroids and Immune Function

- **Cortisol - Suppressor**
 - Decreased production of pro-inflammatory molecules
 - Reduced recruitment of inflammatory cells to sites of infection
 - Inhibition of neutrophil (antibacterial) function
 - Induction of death in cells involved in antibody production and anti-viral responses (lymphocytes)
- **DHEA - Enhancer**
 - Increased production of certain pro-inflammatory molecules.
 - Increased function of anti-viral and anti-bacterial cells (CD8, DTH, neutrophils)
 - Decreased death of immune cells
 - Increased production of immune cells in the bone marrow



DHEAs levels decline with Age

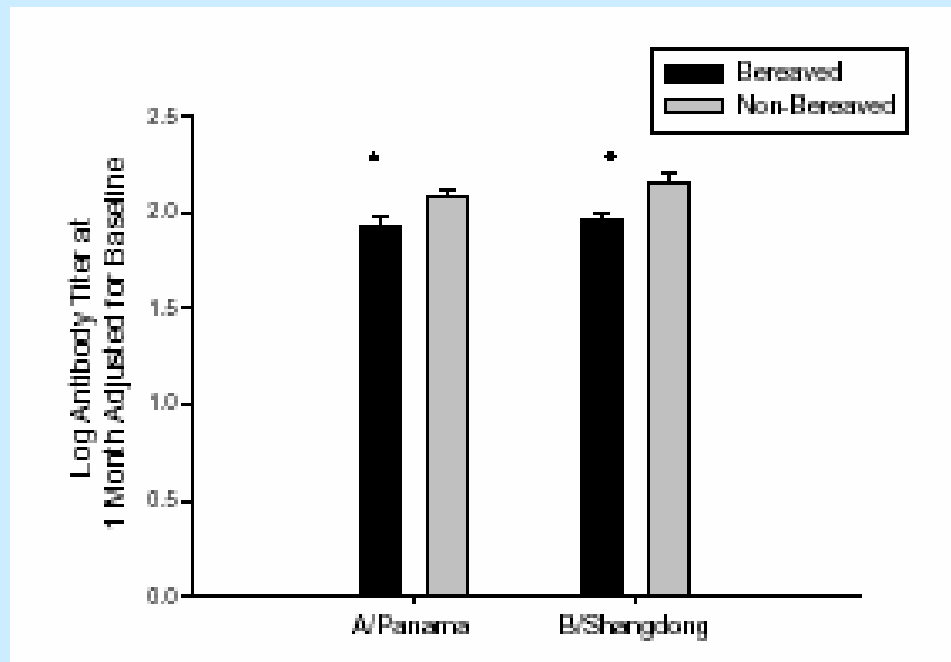


Are the Elderly immune suppressed?

- More susceptible to new infections (SARS, Flu) - T lymphocytes: \uparrow Memory, \downarrow Naïve
- Reactivation of TB
- Poor response to vaccinations (*Jefferson et al [2005] Lancet 366:1165-1174*) – exacerbated by stress



Bereavement decreases vaccination responses



A.C. Phillips et al. *Brain, Behavior, and Immunity* (2005) In press.



Hypothesis

The age related increase in the cortisol:DHEA/s ratio contributes to loss of immune function with age and this will be exacerbated at times of stress.

And if proven.....

Immune status could be restored at times of stress by correcting the cortisol:DHEA ratio (i.e. by oral DHEA supplementation).



Experimental Approaches

- *In vitro* studies of the effect of DHEA on immune cell function (Neutrophils, NK cells)
- Clinical studies of altered cortisol:DHEAs ratio – trauma (hip-fracture) and bereavement



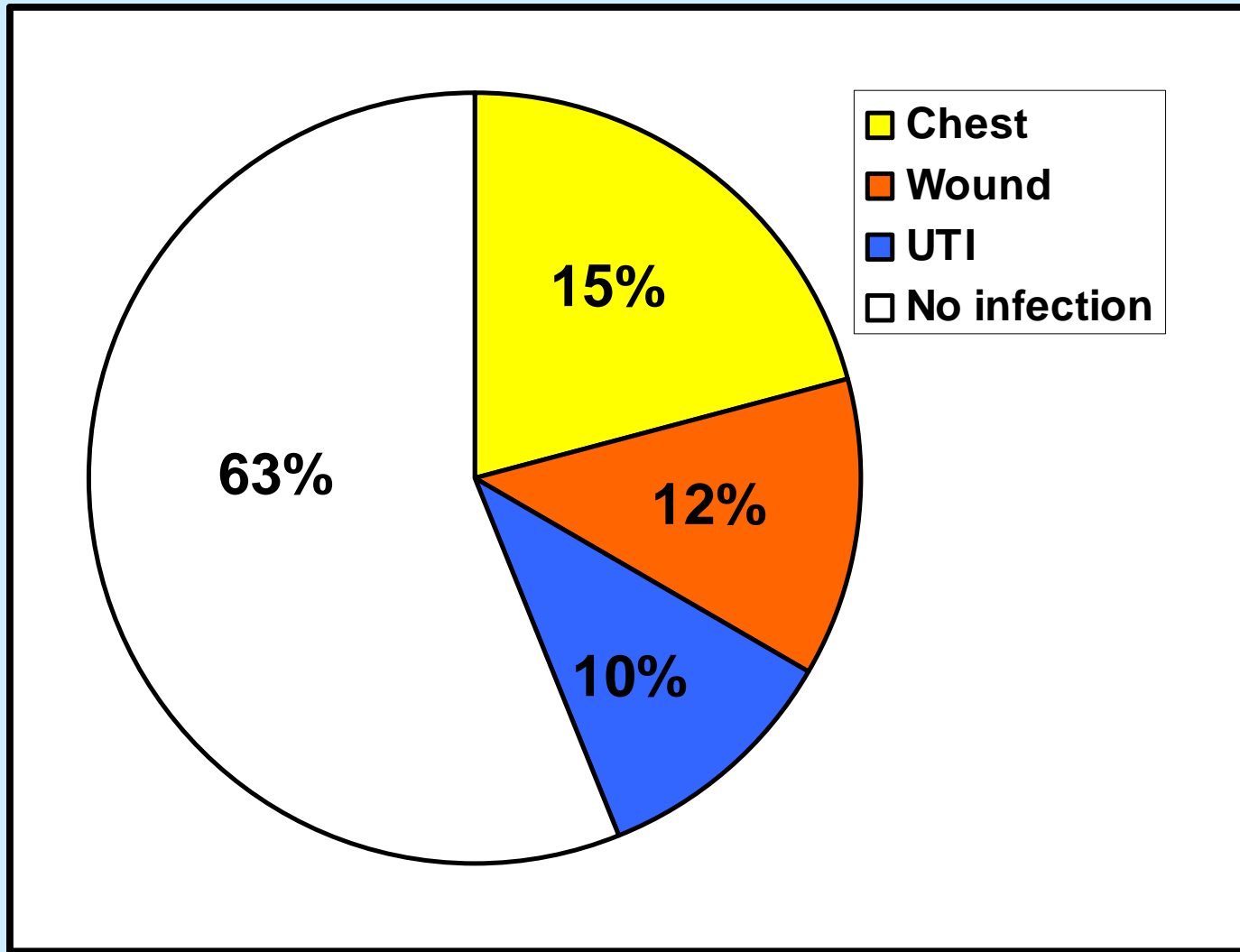
Immune Function in Healthy Elderly and Hip-fracture patients

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

Infection rates were monitored and neutrophil function assessed at time of trauma and 5 weeks later.

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

Infections after Hip-Fracture



Infecting Species in Hip-Fracture Patients

Chest	Urinary Tract	Wound
Streptococcus pneumoniae 3	MRSA 2	Proteus species 2
Coag -ve staphylococcus 3	Staph. aureus 2	Coliforms 2
MRSA 3	Coliforms 1	Serratia species 1
Morecella cateralis 1	Vancomycin resistant enterococci 1	E.coli 1
Pseudomonas 1		
Candida species 1		

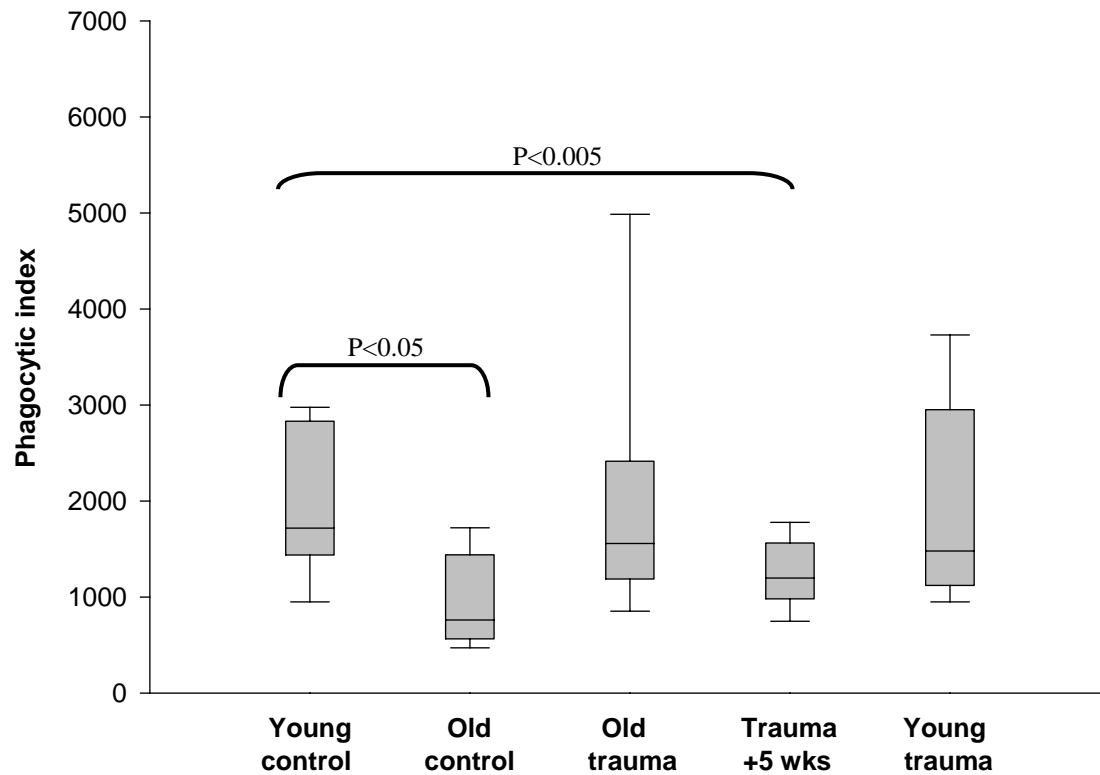
Neutrophil killing power

OXIDATIVE BURST

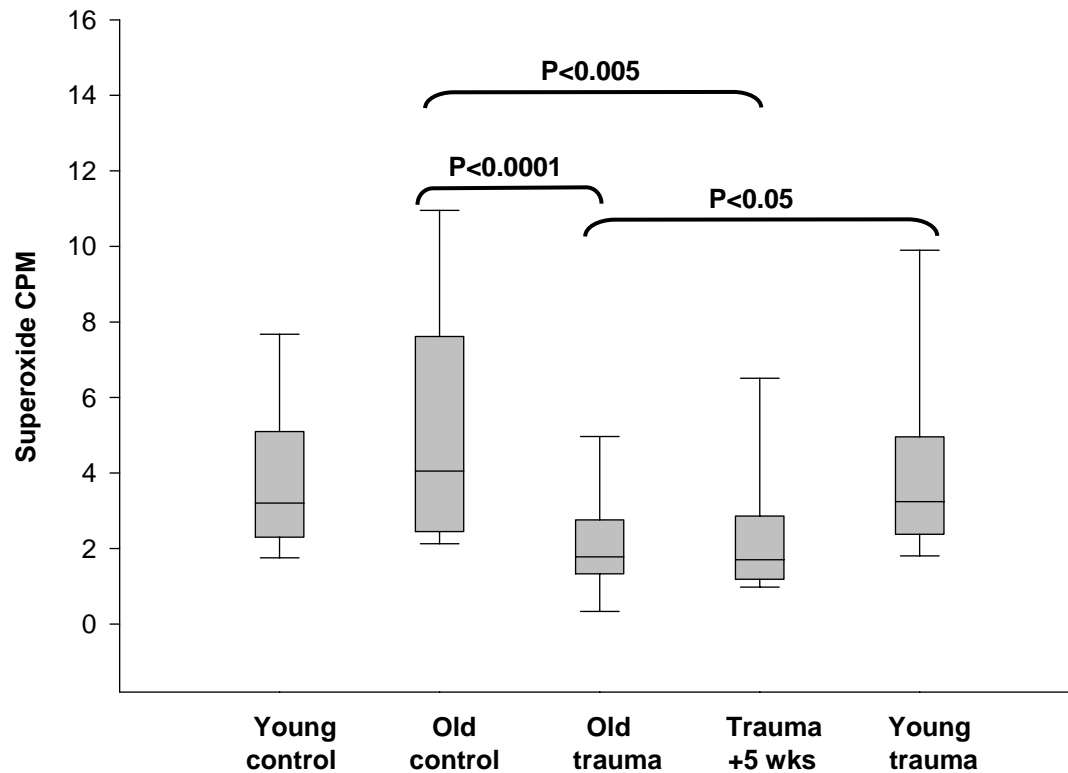
Neutrophils kill microbes by producing reactive oxygen species, demonstrated here with the dye nitroblue tetrazolium (NBT)



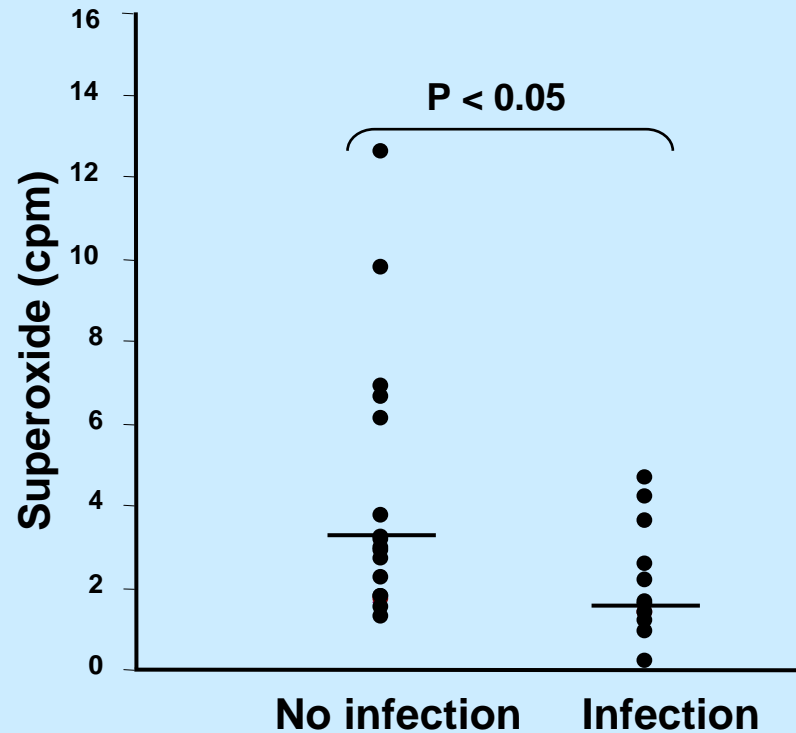
Ageing suppresses neutrophil Phagocytosis



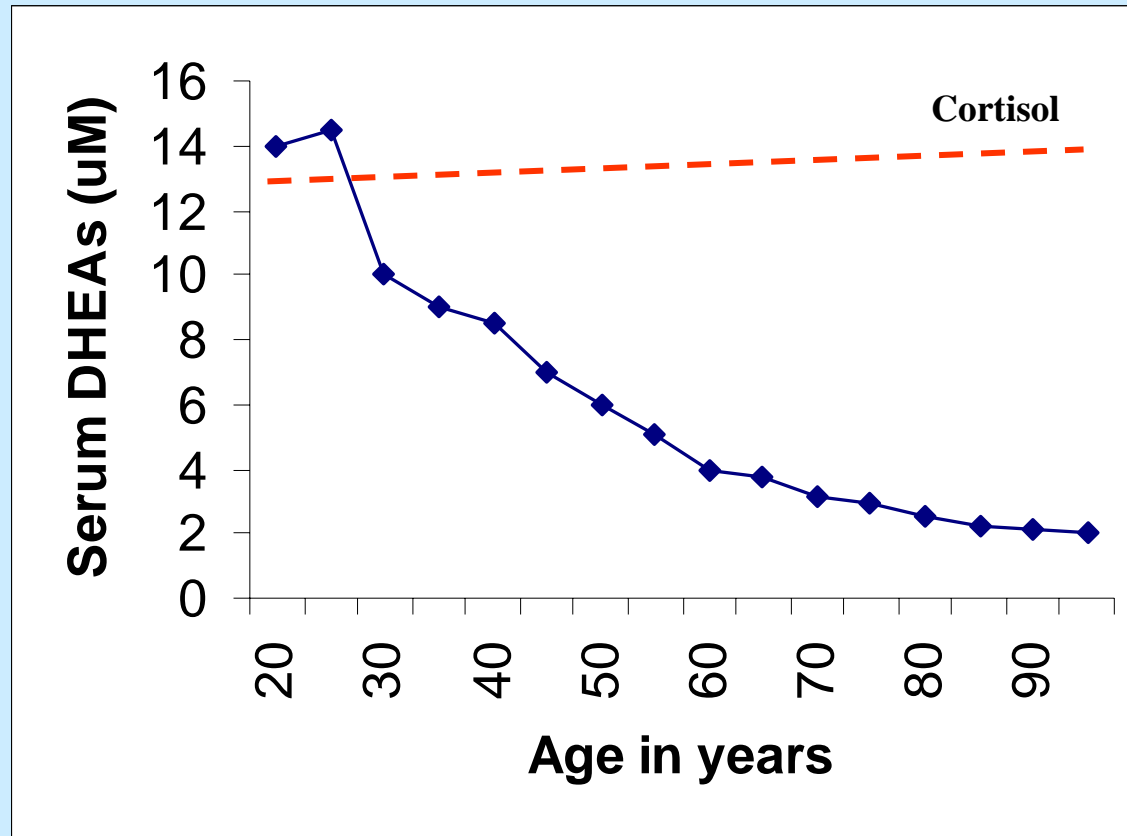
Trauma suppresses neutrophil bactericidal function in the elderly



Superoxide generation is lower in infected patients



Did the cortisol:DHEA ratio alter with trauma?



Cortisol:DHEAs is increased in Elderly hip-fracture patients

Young trauma

0.087 ± 0.01

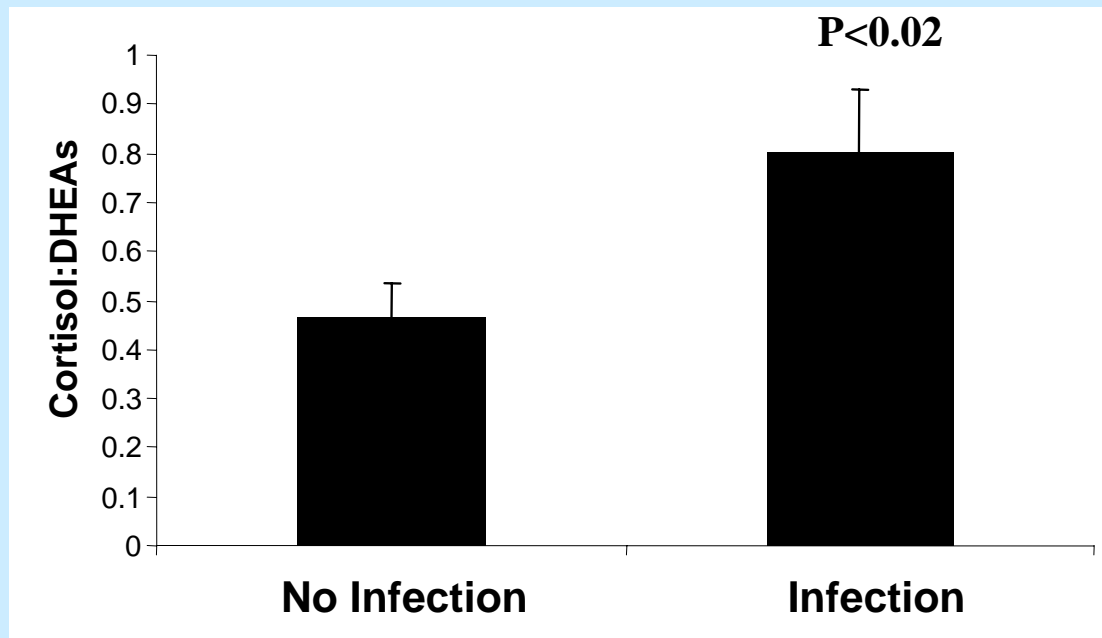
Elderly trauma

0.562 ± 0.06

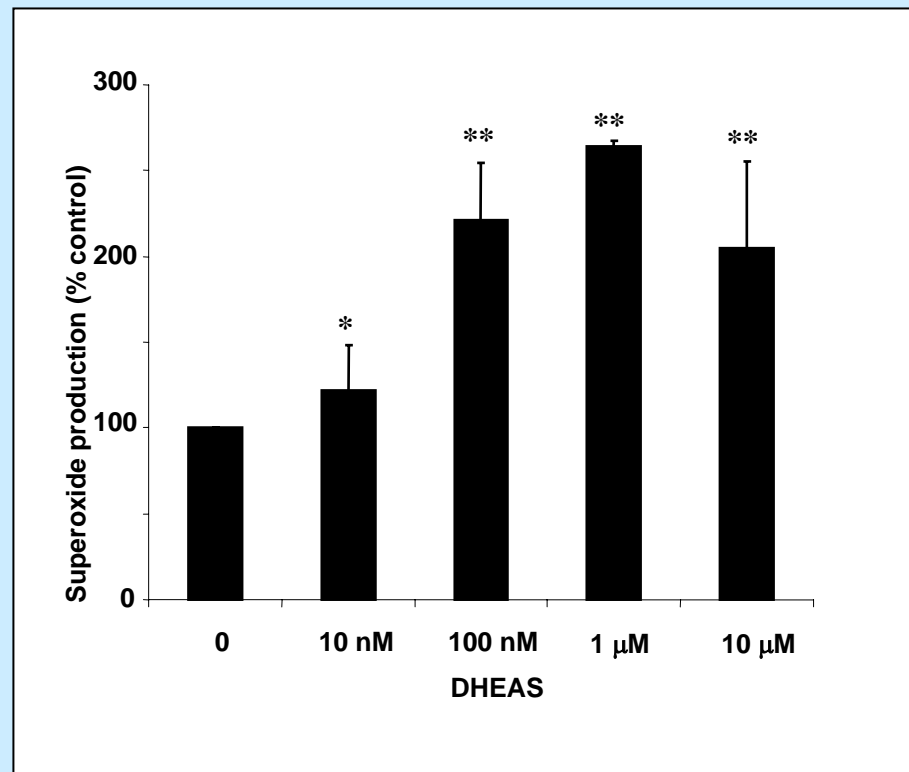
$p < 0.0001$

[Healthy young = 0.094 ± 0.01 ; Healthy elderly = 0.176 ± 0.03]

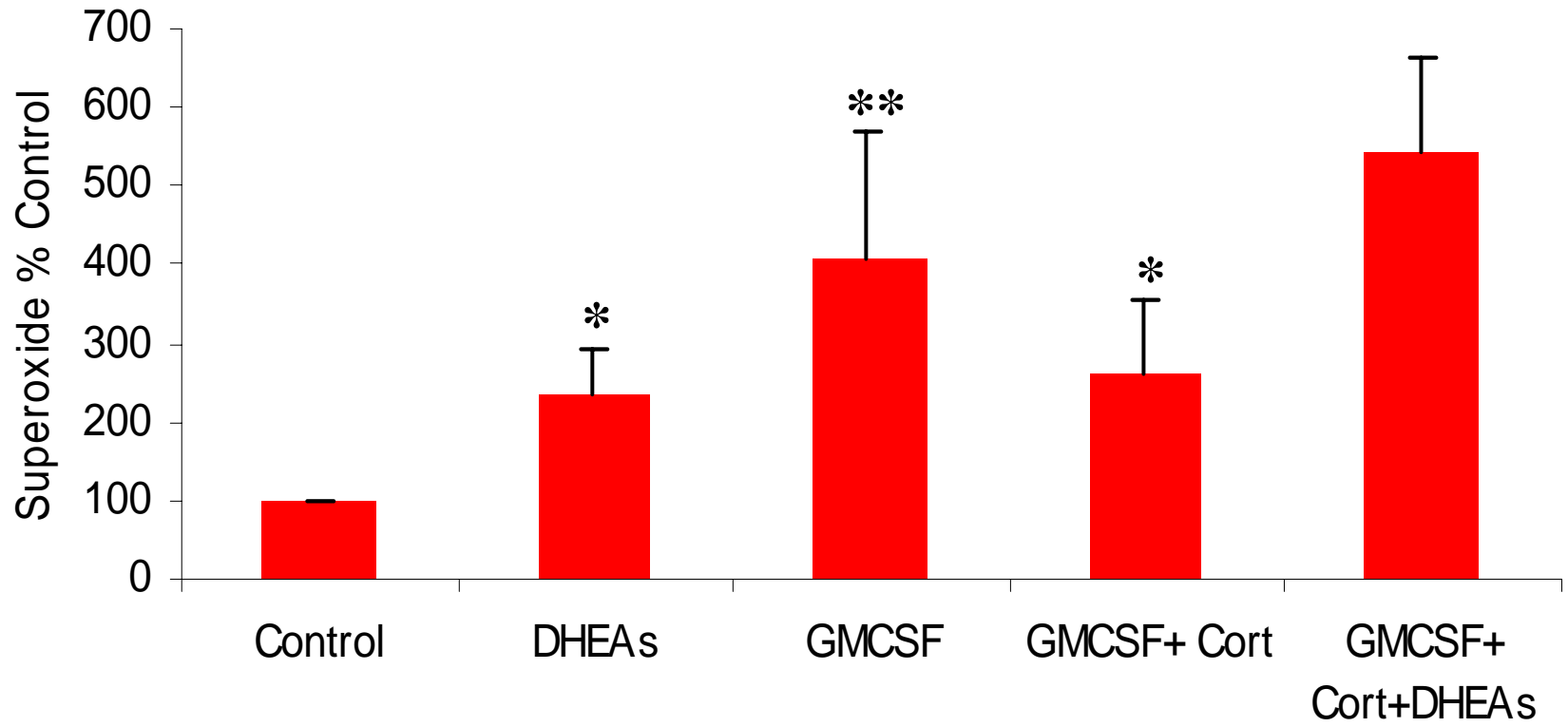
Cortisol:DHEAs is higher in patients who developed infection



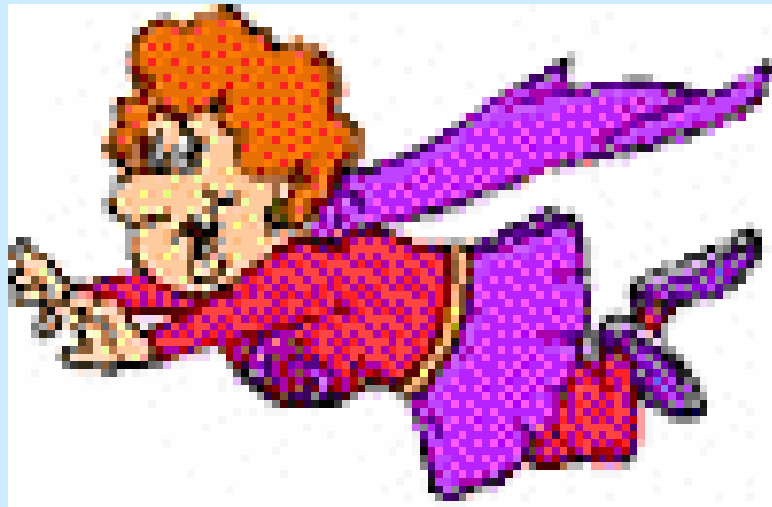
DHEAs primes neutrophils superoxide responses



DHEAs can counteract the suppressive effects of Cortisol



....So will DHEA supplementation improve immunity in Elderly Hip-fracture patients or the bereaved?



Conclusions

- **Elderly trauma patients have an enhanced cortisol:DHEAs ratio and a high incidence of bacterial infection**
- **Neutrophil phagocytic function declines with age and trauma additionally reduces superoxide generation**
- **DHEAs can enhance neutrophil superoxide generation *in vitro***
- **DHEA supplementation in elderly hip fracture patients (and the bereaved) may reduce post-traumatic infections**

Lord Group 2005



“Art is Me, Science is We”

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THANK YOU –take care, falls
are dangerous!

