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?

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?
Ageing increases risk of infectious diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Change in Elderly subjects</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram negative sepsis</td>
<td>50% increase in mortality</td>
<td>1</td>
</tr>
<tr>
<td>Bacterial dysentery</td>
<td>3-fold increase in incidence</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>120-fold increase in mortality</td>
<td>2</td>
</tr>
<tr>
<td>GI infections</td>
<td>400-fold increase in mortality</td>
<td>3</td>
</tr>
<tr>
<td>Influenza</td>
<td>160-fold increase in mortality</td>
<td>3</td>
</tr>
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Is there a link between Ageing, Stress and Increased Susceptibility to infection?
The HPA axis – Your Stress Sensor

Hypothalamus → Pituitary → Adrenal → Cortisol

STRESS → DHEA → Anti-stress response

Stress response (Immune suppression)
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

![Graph showing the decline of DHEAs levels with age, compared to cortisol levels.](image)
Are the Elderly immune suppressed?

- More susceptible to new infections (SARS, Flu) - T lymphocytes: ↑Memory, ↓Naïve
- Reactivation of TB
- Poor response to vaccinations (Jefferson et al [2005] Lancet 366:1165-1174) – exacerbated by stress
Bereavement decreases vaccination responses

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

- Chest: 15%
- Wound: 12%
- UTI: 10%
- No infection: 63%
## Infecting Species in Hip-Fracture Patients

<table>
<thead>
<tr>
<th>Chest</th>
<th>Urinary Tract</th>
<th>Wound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae</td>
<td>MRSA</td>
<td>Proteus species</td>
</tr>
<tr>
<td>Coag –ve staphylococcus</td>
<td>Staph. aureus</td>
<td>Coliforms</td>
</tr>
<tr>
<td>MRSA</td>
<td>Coliforms</td>
<td>Serratia species</td>
</tr>
<tr>
<td>Morecella cateralis</td>
<td>Vancomycin resistant enterococci</td>
<td>E.coli</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida species</td>
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</table>
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

![Graph showing the effect of ageing on neutrophil phagocytosis](image)

- **Young control**
- **Old control**
- **Old trauma**
- **Trauma +5 wks**
- **Young trauma**

The graph illustrates that neutrophil phagocytosis decreases with ageing, as indicated by the lower phagocytosis index in old compared to young individuals. The differences are statistically significant:

- Young control vs. Old control: *P* < 0.05
- Young control vs. Old trauma: *P* < 0.005
Trauma suppresses neutrophil bactericidal function in the elderly
Superoxide generation is lower in infected patients

![Graph showing superoxide generation in infected and non-infected patients]

P < 0.05
Did the cortisol:DHEA ratio alter with trauma?
Cortisol:DHEAs is increased in Elderly hip-fracture patients

Young trauma       Elderly trauma

0.087± 0.01        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

![Graph showing cortisol:DHEAs comparison between no infection and infection with p-value P<0.02]
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 \textit{in vitro}

• DHEA supplementation in elderly hip fracture patients (and the bereaved) may reduce post-traumatic infections
“Art is Me, Science is We”
Acknowledgements

Steve Butcher  Wiebke Arlt
Dave Radford  Jeremy Tomlinson
Hema Chahal  Vijay Killampalli
Keqing Wang  Wellcome Trust Clinical Trials Unit
David Lascelles  PPP Foundation

BBSRC
THANK YOU – take care, falls are dangerous!