Is Ageing a Stressful Experience?

Professor Janet M Lord

Institute for Biomedical Research, Birmingham University
A longer life, but a longer death too?

Life Expectancy and Healthy Life Expectancy

- Female life expectancy
- Male life expectancy
- Female healthy life expectancy
- Male healthy life expectancy

Years: 1981 to 2001

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.
Major Causes of Death by Age

- Injury and poisoning
- Nervous system
- Digestive system
- Mental and behavioural disorders
- Cancers
- Respiratory diseases
- Circulatory diseases

0-14
15-29
30-44
45-64
65-84
85 and over
# Age-related increases in 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>
</tbody>
</table>

Question 1

Why are older people more prone to infections?
Cells of the immune system
Age and vaccination efficacy

Hainz et al (2005)
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)

<table>
<thead>
<tr>
<th></th>
<th>23-35 yrs</th>
<th>&gt;65 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>23-35 yrs</td>
<td>P&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>&gt;65 yrs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Neutrophil Phagocytic receptor expression in the elderly

Effect of Age on CD16 Expression

CD16 expression correlates with phagocytic index

\[ r = 0.875 \]
The problem begins at the beginning!
Question 2

Do these age-related changes impact upon our ability to fight infection or increase our frailty?
We could do longitudinal studies - Low NK activity correlates with increased infection rates and mortality

Ogata et al.  
2001
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
- 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

- Chest: 15%
- Wound: 12%
- UTI: 10%
- No infection: 63%
Ageing suppresses neutrophil Phagocytosis

Butcher et al. Aging Cell (2005)
Trauma suppresses neutrophil bactericidal function in the elderly

Butcher et al. Aging Cell (2005)
Superoxide generation was lower in patients who later developed infection.

Butcher et al. Aging Cell (2005)
Question 3

Why is stress more of a problem with age?
The Hypothalamic-pituitary-adrenal axis

- Hypothalamus
- Pituitary
- ACTH
- Adrenal
- Cortisol
- DHEA
- Immune enhancer
- Immunesuppressor
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± 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

P<0.02

Butcher et al. Aging Cell (2005)
Question 4

Can we do anything about this?
DHEAs primes neutrophils superoxide responses
DHEAs counteracts the suppressive effects of Cortisol

Butcher et al. Aging Cell (2005)
Last question…

Are there other practical ways to improve immunity?
Exercise and vaccination responses

Kohut et al (2005)
Time of flu vaccination affects response (men)

Phillips et al. (unpublished observations)
Lord Group 2007

Stephen Butcher
David Radford
David Lascelles
Keqing Wang

Vijay Killampalli
Emin Kaya Alpar
Wiebke Arlt
Jeremy Tomlinson

“Art is Me, Science is We”
Healthy Ageing – good genes, good diet....but watch out for stressful life events!
Any Questions?