



Australasian  
Research Institute

@ Sydney Adventist Hospital

# Oxidative stress, Ageing & Disease

## How Does lifestyle affect Health?

**Dr Ross Grant**

*Adventist Health Seminar - Perth*

*2010*

## Session 1

- Free radicals and Aging

## Session 2

- Free radicals, heart disease and cancer

## Session 3

- How can you reduce free radical damage, slow aging and the development of lifestyle diseases

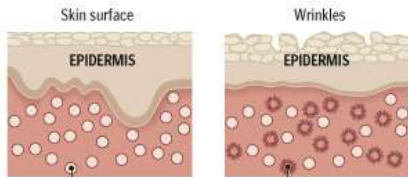
## Session 1.

# Main points

1. Aging results from cumulative cell damage resulting in degeneration
2. Free radicals cause oxidative stress
3. This oxidative stress causes damage to cells that result in aging and disease.

# What happens when we age?

## Skin - Wrinkles



Depleted collagen

## Muscles

decreased muscle fibres



MUSCLE CROSS SECTION FROM A 20-YEAR-OLD

FROM A 60-YEAR-OLD

## Bones

decreased mineral content



NORMAL BONE

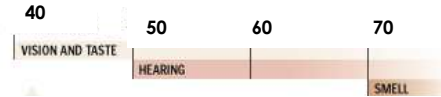
WITH OSTEOPOROSIS

**Joint motion**  
becomes more restricted and flexibility decreases because of changes in tendons and ligaments.

**Cartilage**, which provides cushioning between bones, begins to break down from a lifetime of use. Joints can become inflamed and arthritic.

SOURCES: American Academy of Dermatology, American Academy of Orthopaedic Surgeons, National Eye Institute, National Heart, Lung and Blood Institute, National Institute on Aging, National Institutes of Health, Office of Dietary Supplements, Mayo Clinic, University of Washington Medical Center, iStockphoto

## Aae at which your senses change



## Heart

decreased capacity

## Nerves

decreased number  
Slower transmission

## Stomach

less acid  
B12 absorp. decreased

## Height

decreased by 1 cm  
Every 10yrs after 40



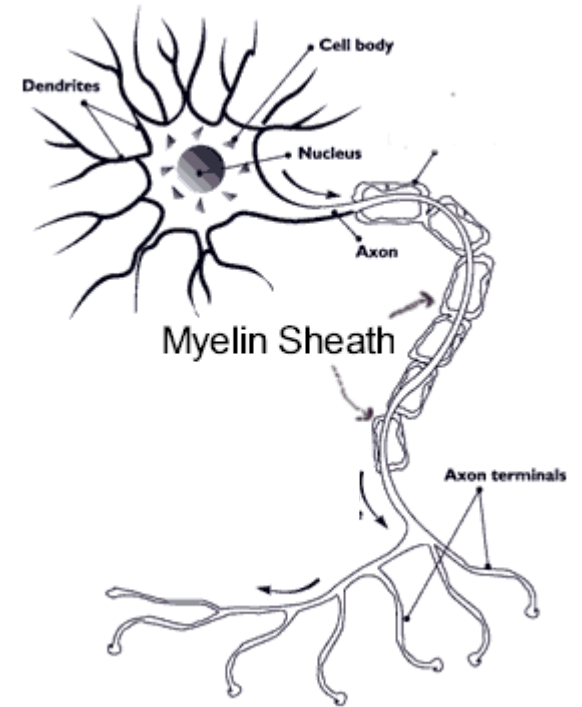
# Why do we age?

# What is the human body?

## Organs

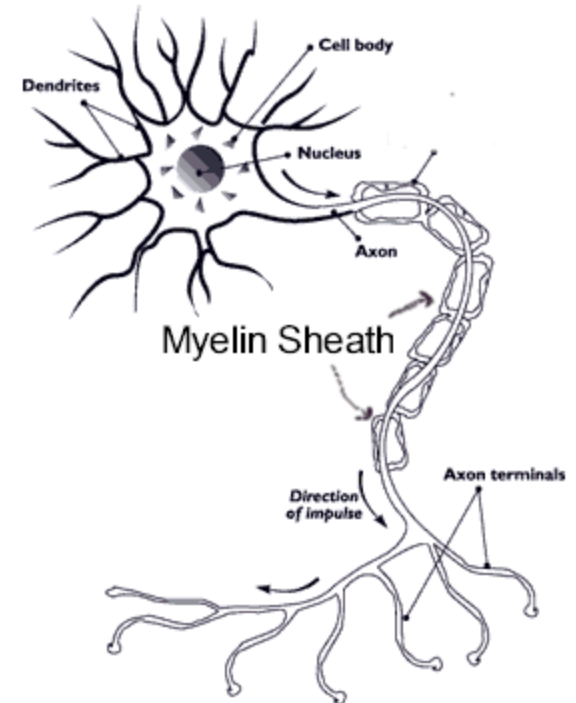
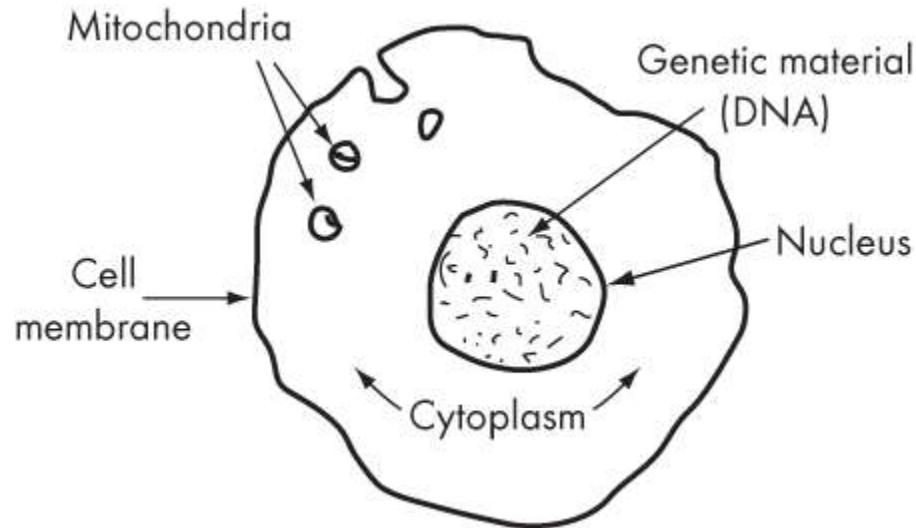


## Cells



## Important point

If we keep our cells healthy our  
body will be healthy!



# What damages our cells?

## Free radicals from:

Sunlight \*

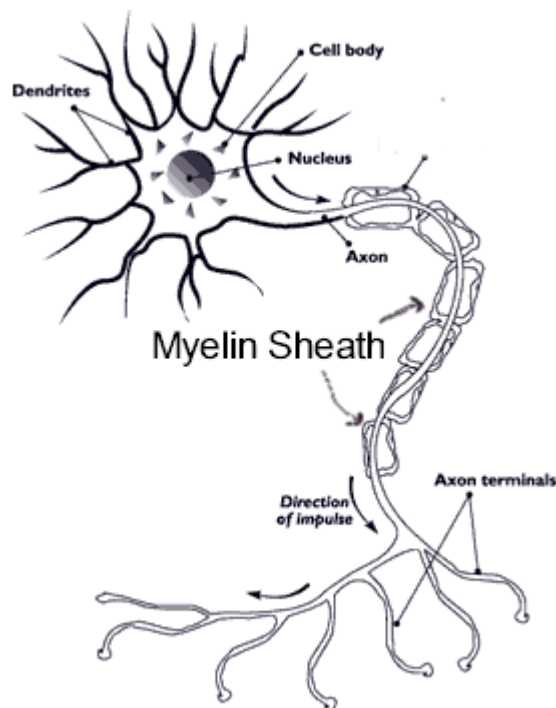
Chemical pollutants \*

Domestic sprays \*

Insecticides \*

Car & factory  
exhaust \*

Body's own  
metabolism



# What Protects our cells?

## Antioxidants

### Free radicals from:

Sunlight \*

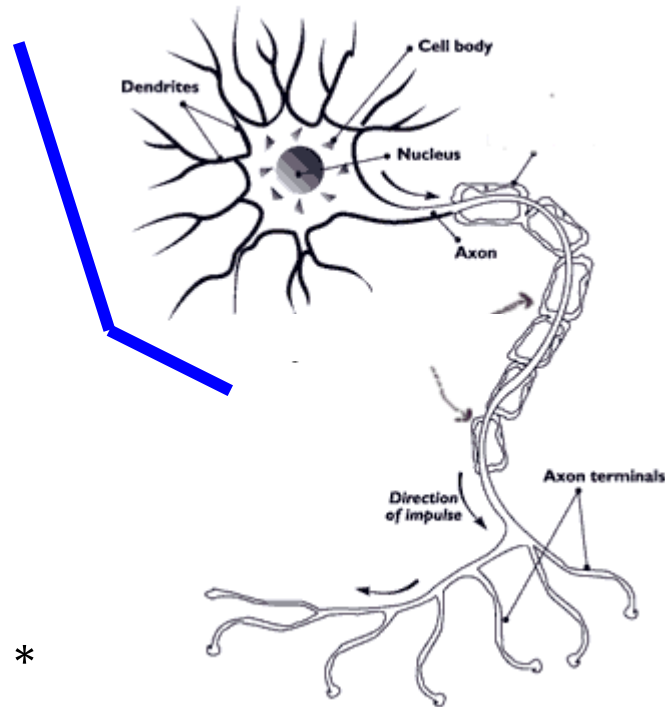
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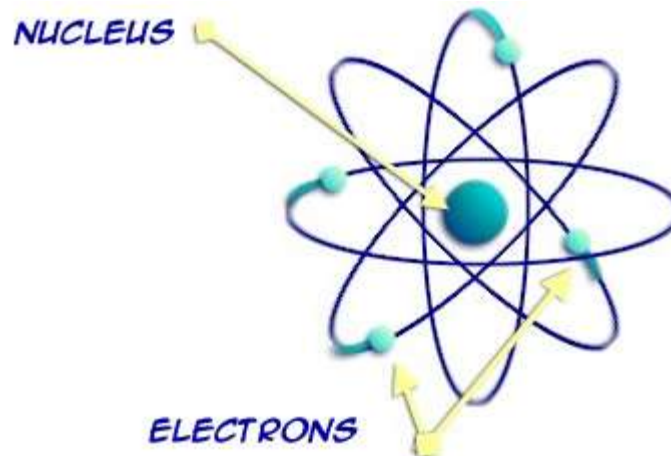
Body\*'s own  
metabolism



# What are Free radicals (oxidative stress)?

Oxidative stress happens in the cell when the level of reactive oxygen molecules (ROS) exceeds the body's capacity to neutralise them (i.e. concentration of ROS exceeds antioxidant capacity)

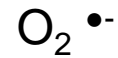
Popular term for ROS (& RNS) are Free radicals.  
ROS/RNS/Free radicals are atoms or molecules with unpaired electrons. The unpaired electrons cause them to be highly reactive.....



# Types of ROS?

## Radicals

Superoxide,



Hydroxyl,



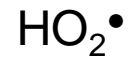
Peroxyl,



Alkoxy,



Hydroperoxyl,



## Non-radicals

Hydrogen peroxide,



Hypochlorous acid,



Ozone,



# Where do Free Radicals Come From?

## **Internal sources:**

Conversion of calories into ATP (body's energy)

Other cell metabolic activities

Immune cells (during inflammation)

## **External:**

Food we eat – AGE's, chemical pollutants

Air/Environmental Pollutants – industrial/motor

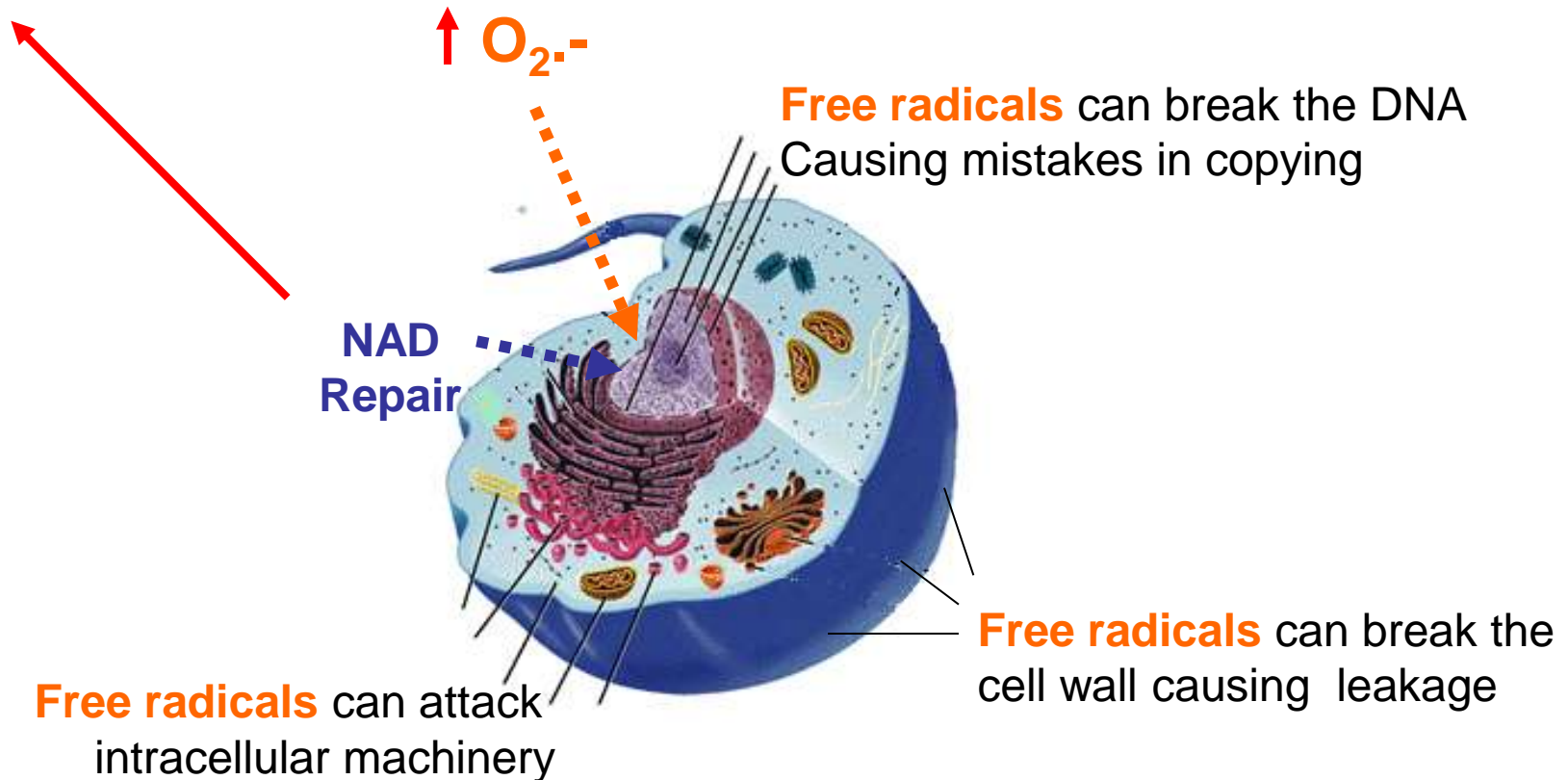
waste, Ionizing radiation: Cosmos, granite etc

nonionizing radiation: UV from sun

# Greatest source of free radicals are made by the body its' self!

- Normal cell **metabolism** *Endocrine. 2006;29(1):27-32*
  - Conversion of CHO/Fats into energy (ATP)
- Inflammatory immune reactivity *Int Immunopharmacol. 2004 Mar;4(3):327-47*  
*Biogerontology. 2008 ;9(3):153-62*
  - Produced by immune cells for defence against microbes etc.
  - Lack of **sleep** can alter immune response & Ox. stress levels
- Chronic **anxiety** stress *HORMONES 2009, 8(1):7-22*  
*Ann Med. 2009;41(3):224-33*
  - Chronic stimulation of the HPA axis
  - Increases inflammation/free radical production

Greatest source of Free radicals come from conversion of the calories we eat into the energy the cell needs



# High-fat, energy-dense, fast-food–style breakfast results in an increase in oxidative stress in metabolic syndrome

Sridevi Devaraja *et al. Metabolism*. 2008; 57(6): 867–870

## Aim:

to compare the effects of an energy-dense, high-fat, fast-food–style (FFS) meal with an American Heart Association (AHA)–recommended heart-healthy meal on biomarkers of oxidative stress and inflammation in subjects with MetS.

## Subjects:

11 subjects with MetS

## Results:

- Glucose levels increased 2 hours after both FFS and AHA
- HDL (high-density lipoprotein cholesterol) levels decreased only in FFS diet
- Total triglyceride levels significantly increased only in the FFS diet
- Plasma oxidative stress markers (TBARS, MDA and HNE) increased in both dietary groups;
  - but the increase was greater in the FFS.
- Inflammatory markers: increase in IL-1 $\beta$  FFS meal; no change in CRP(HS) or TNF- $\alpha$

## Conclusion:

Consumption of an energy-dense, fatty meal (FFS breakfast) results in increased postprandial oxidative stress compared to a heart-healthy meal (AHA).

# We can also get Free Radicals from what we eat!

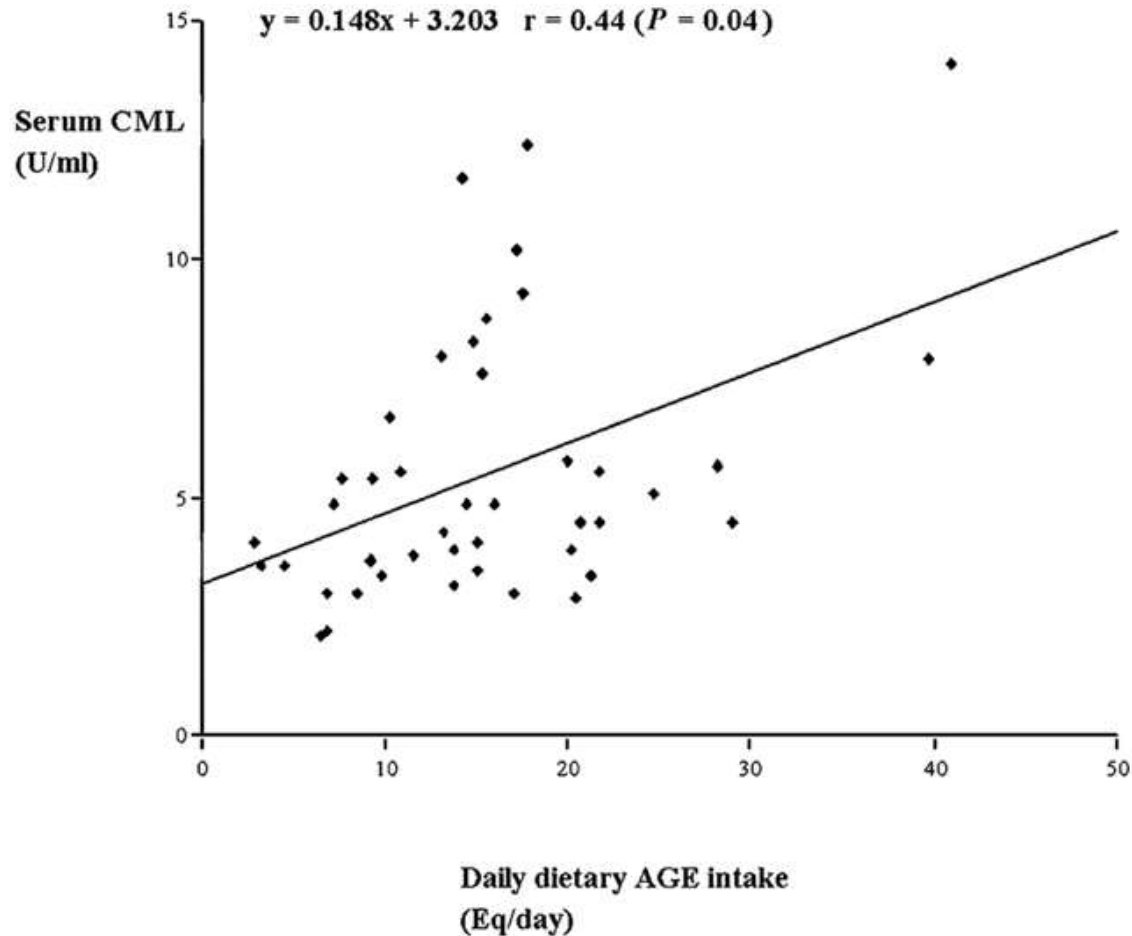


- High levels of sugar (glucose) will produce Advanced Glycation End products (**AGE's**)
- **AGEs** also form during the cooking as the result of the application of heat.

**Deep-Frying** for the brave

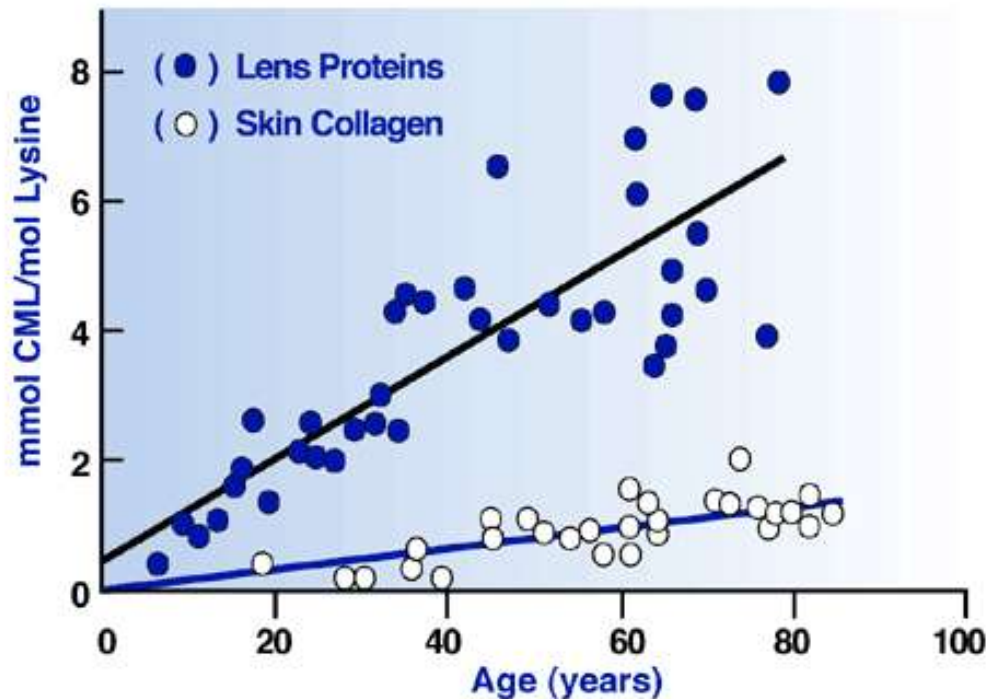


# Dietary AGE's increase serum AGE's



Association between dietary AGEs and serum AGE levels in healthy subjects.

- AGE's increase in our tissues as we get older



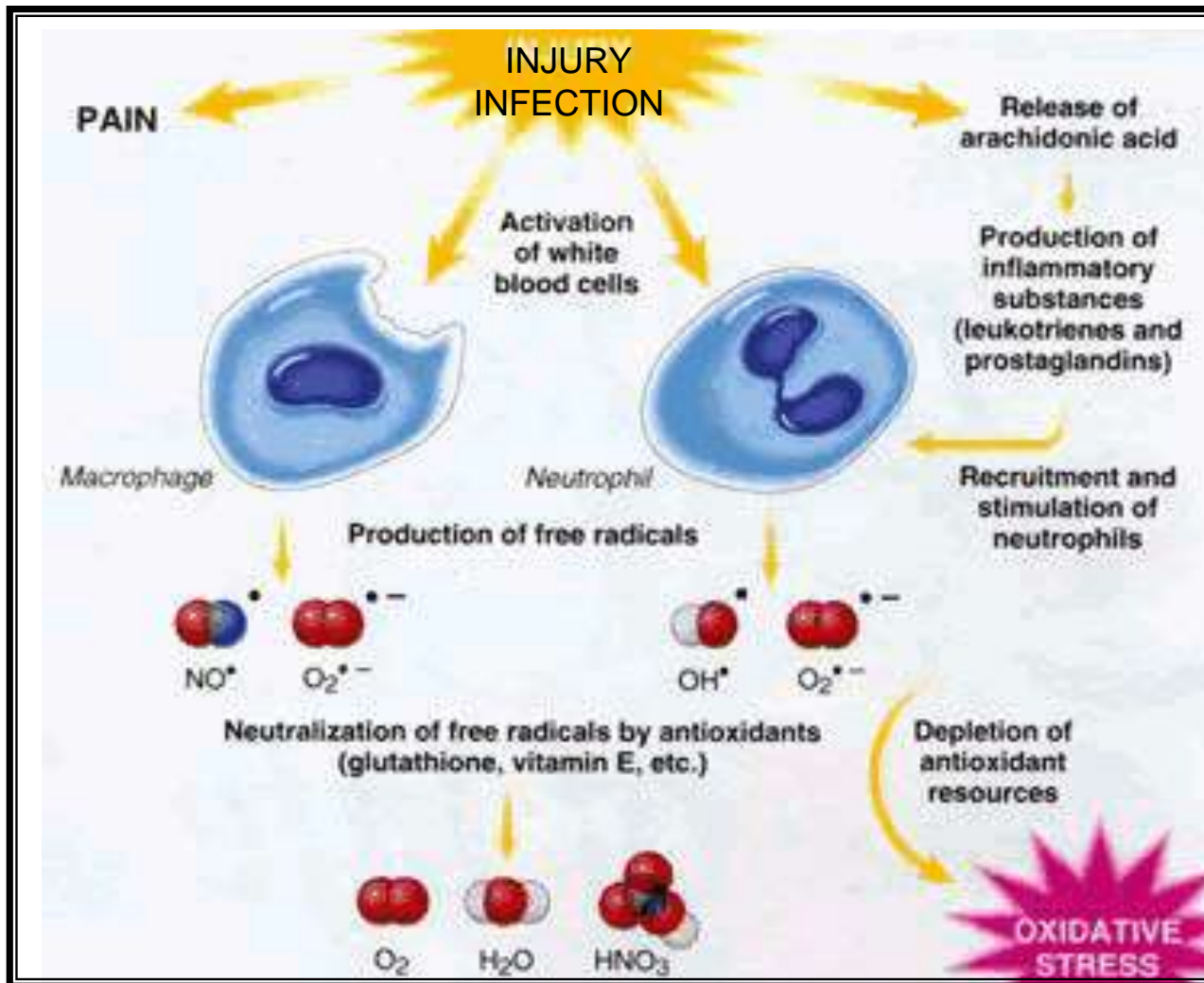
**Fig. 2.** Increased accumulation of AGEs (CML) with age in human lens protein and skin collagen. (Dyer, et al. *The Maillard reaction in vivo*, 1991.)

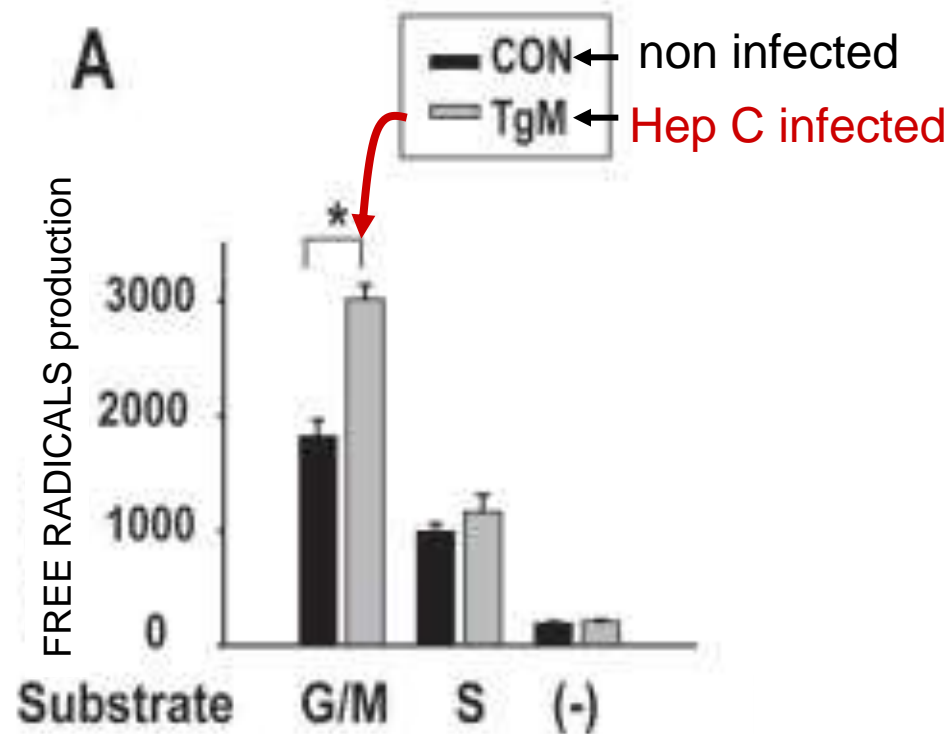
# What do AGE's do?

- Increase Free radical stress in the body
- Increased protein cross-linking making it stiff, non-functional and hard to remove (e.g. collagen)
- Accelerate atherosclerosis (trapping lipid in blood vessel wall)



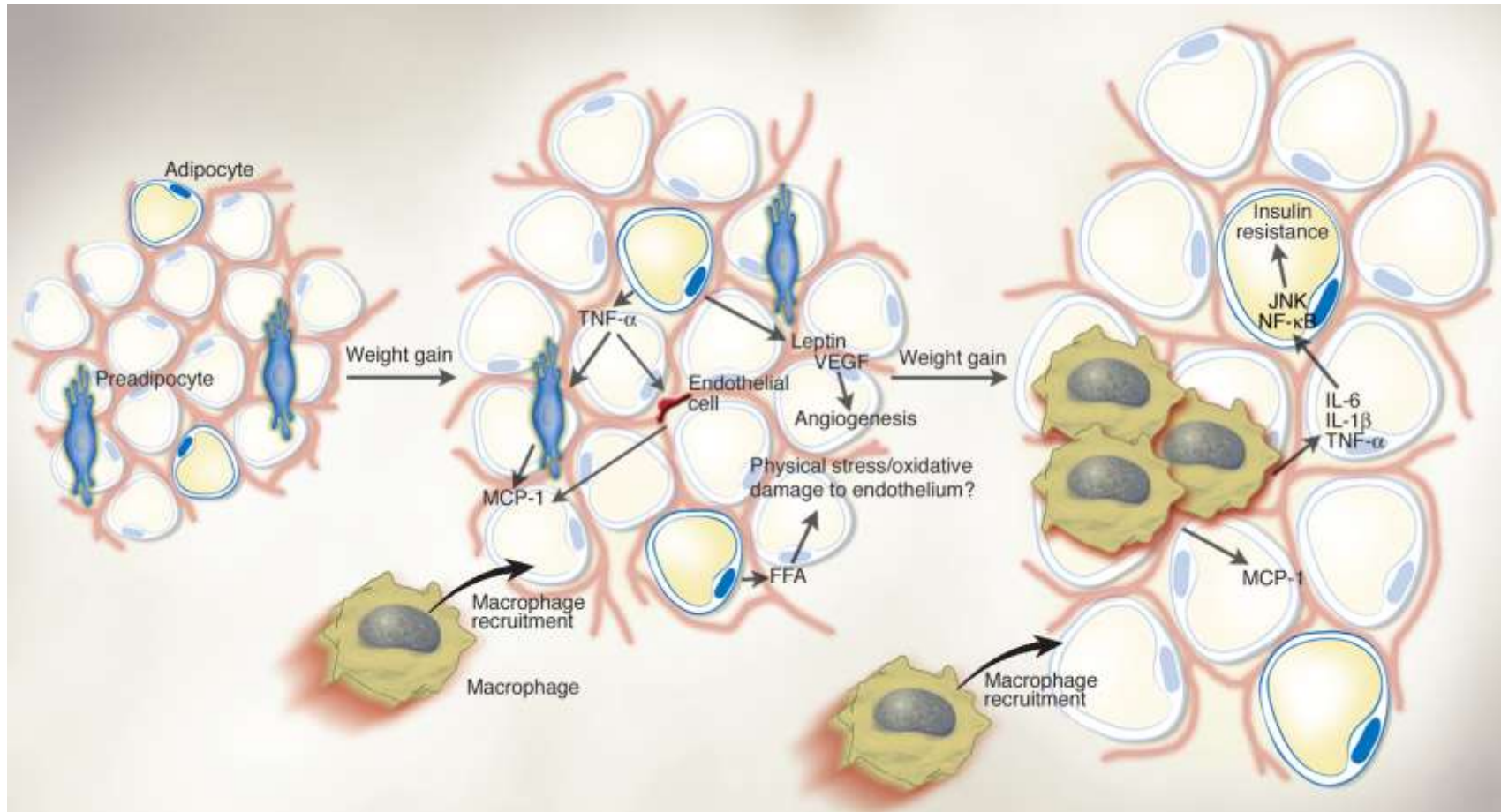
# Free radicals can also be produced by the immune system!





**FREE RADICAL production in isolated mitochondria.** A, ROS production was measured by the change in DCF fluorescence under conditions of state 4 respiration. \*,  $p < 0.05$ ; \*\*,  $p < 0.01$ ), G/M, glutamate and malate; S, succinate; (-), no substrate.

# Weight gain increases inflammation



Adipose (fat) tissue is characterized by inflammation (1) and progressive infiltration by macrophages as obesity develops

# Effect of Aging on OX stress levels and DNA damage

(only selected data shown)

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*Supervisor* Dr Ross Grant



School of Medical Sciences  
Faculty of Medicine, UNSW

# Wistar Rats as an Attractive Model for Aging

Rat (months)	Human (years)
3	20
6	25
9	30
12	40
18	65
24	>80



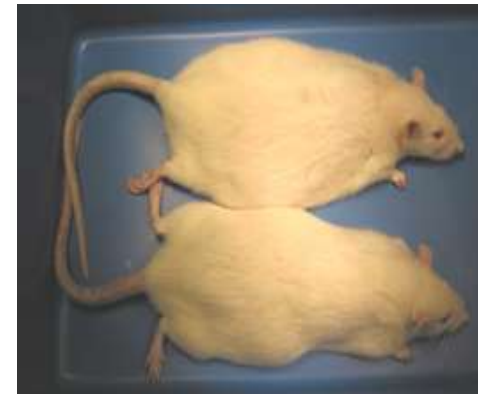
20 Y Human



3 M Wistar Rat

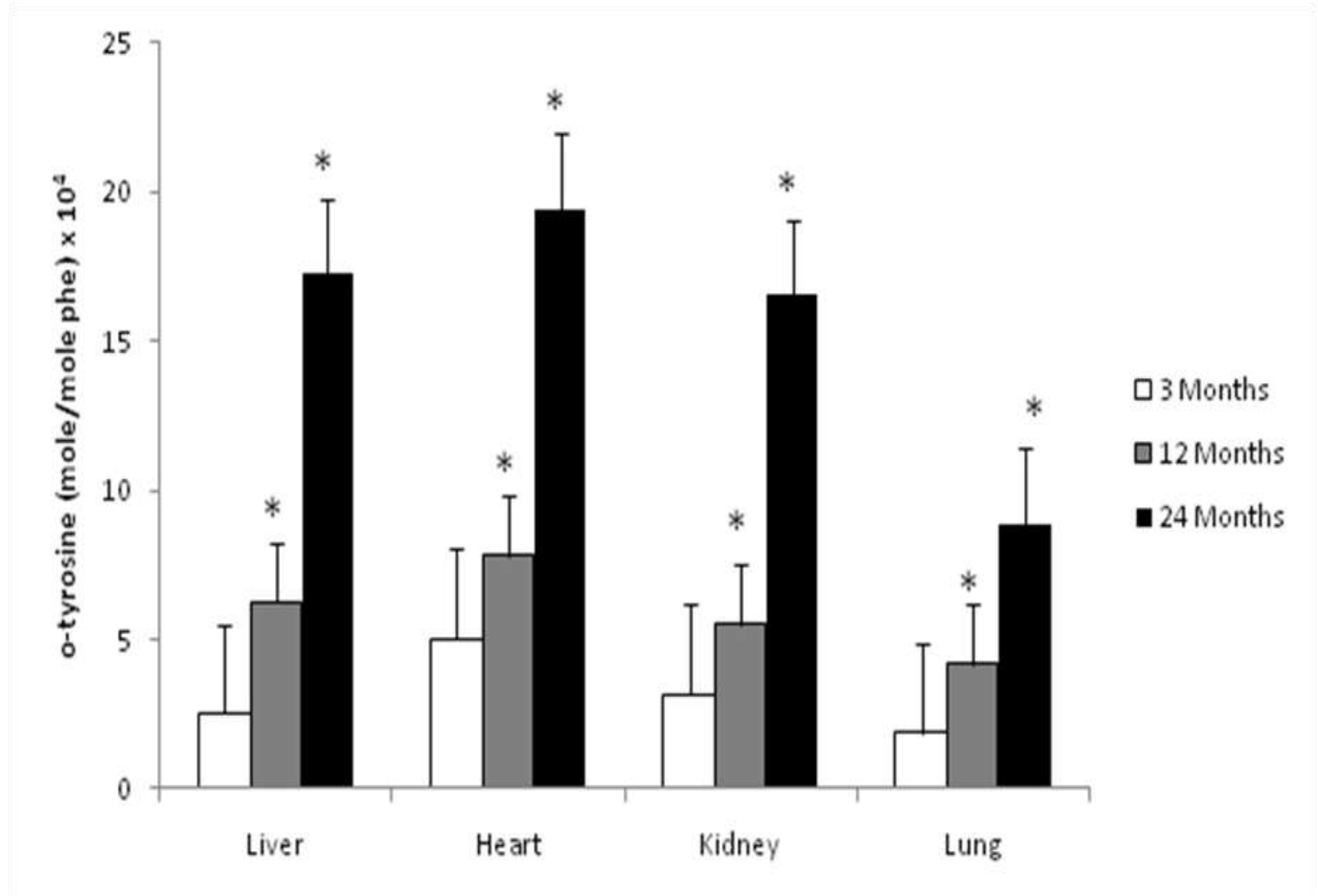


80 Y Human



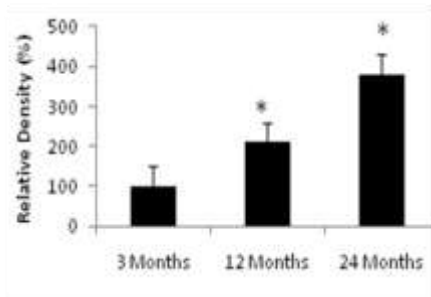
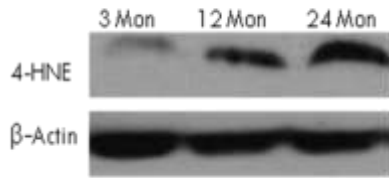
24 M Wistar Rats

# Accumulation of Ox stress damaged proteins with age

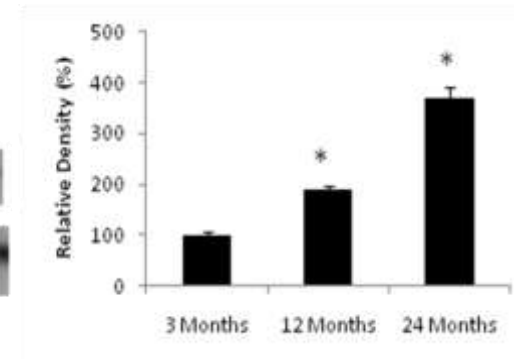
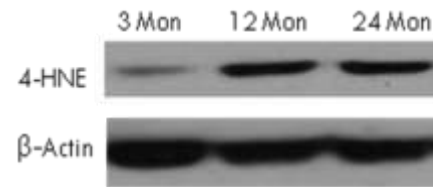


# Accumulation of Ox stress damaged Lipids (fats) with age

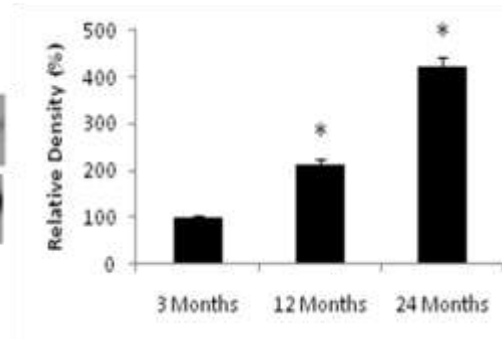
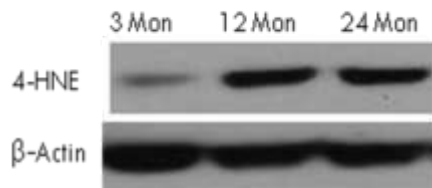
## Liver



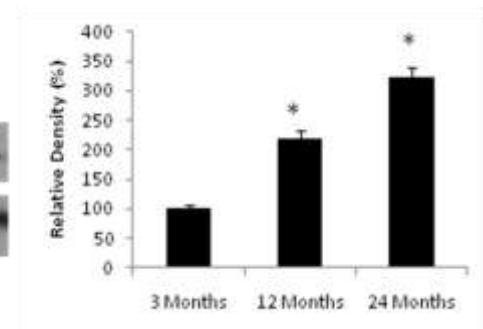
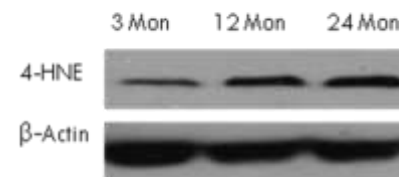
## Heart



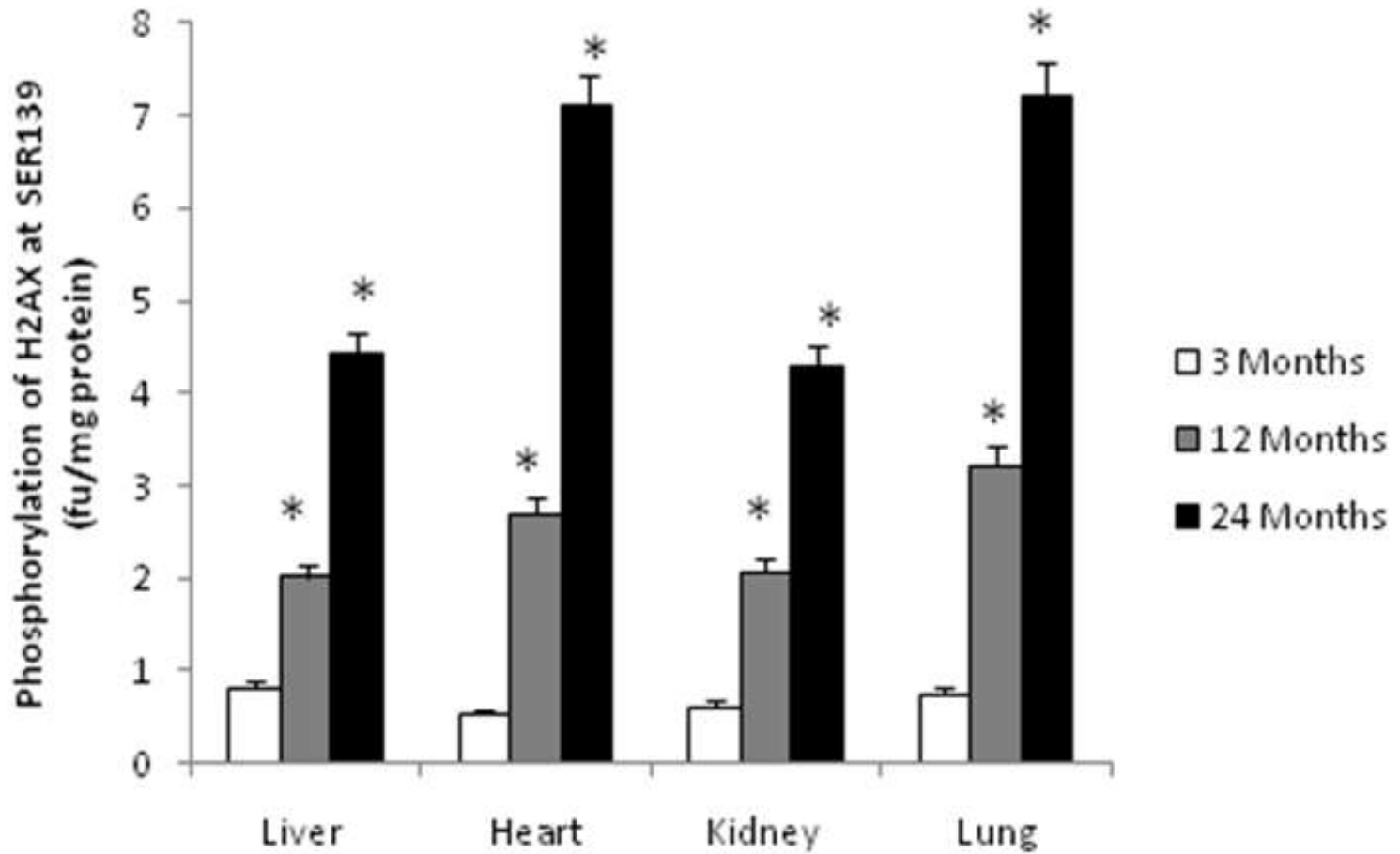
## Kidney



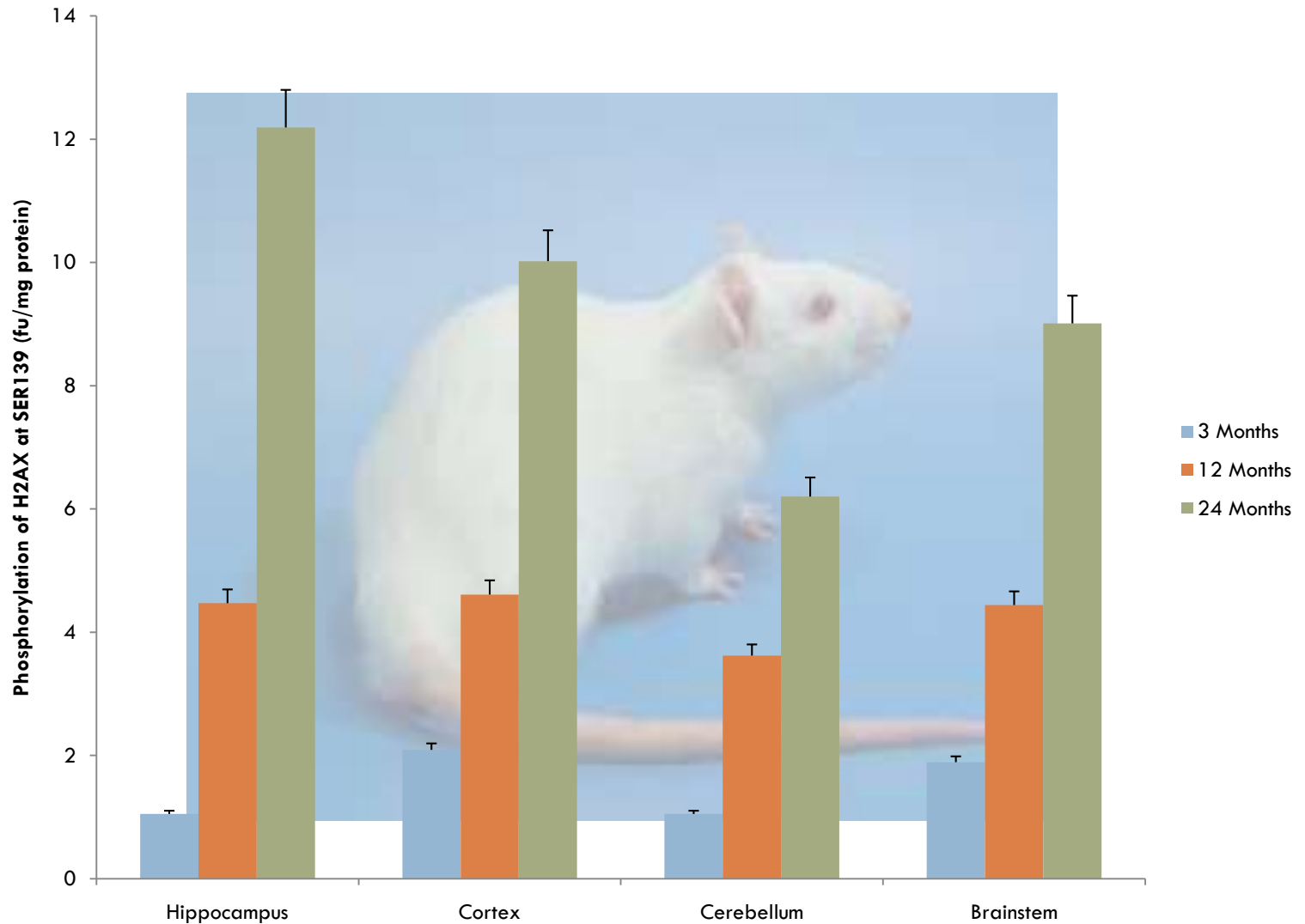
## Lung



# Accumulation of Ox stress damaged DNA with age

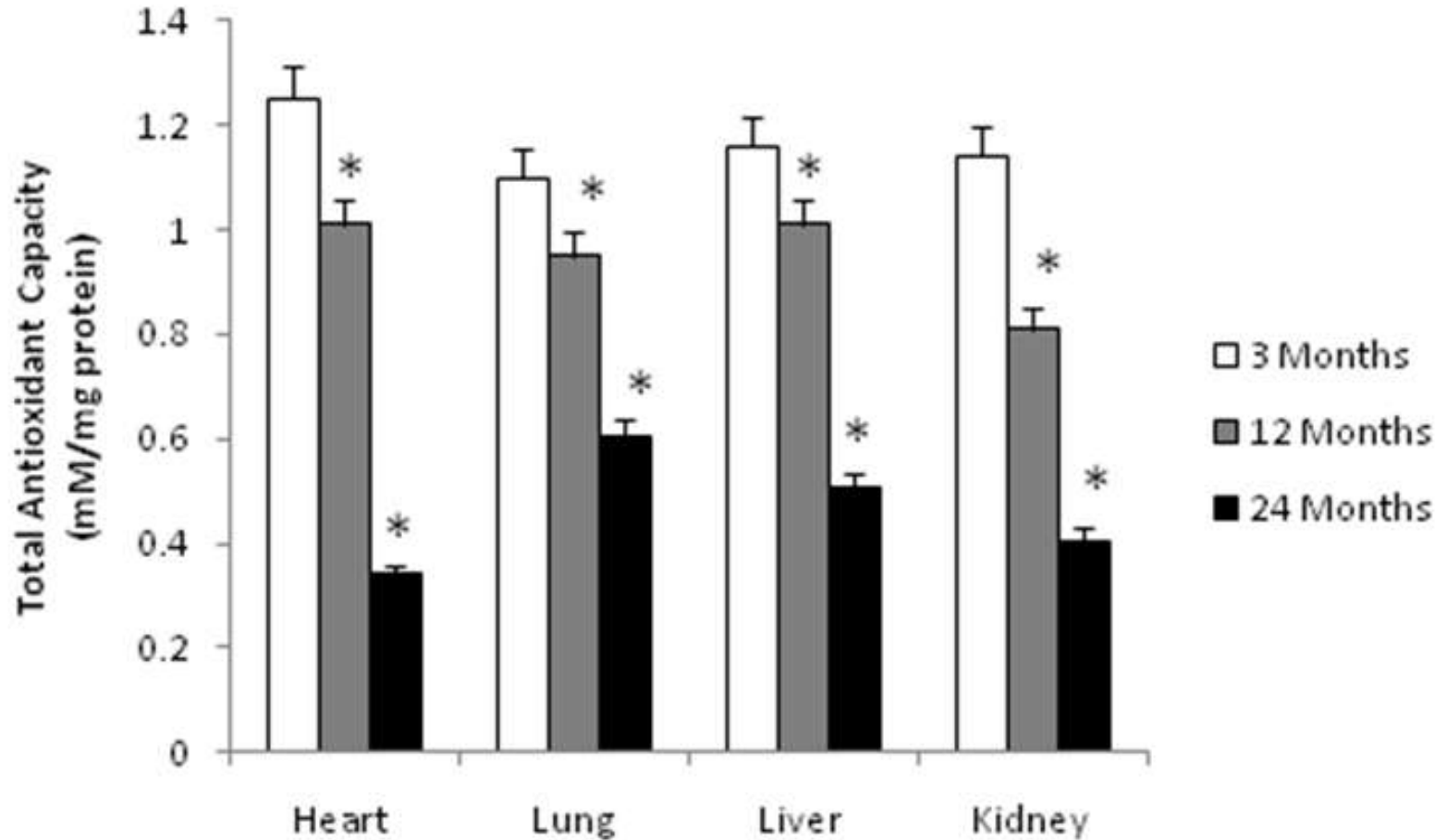


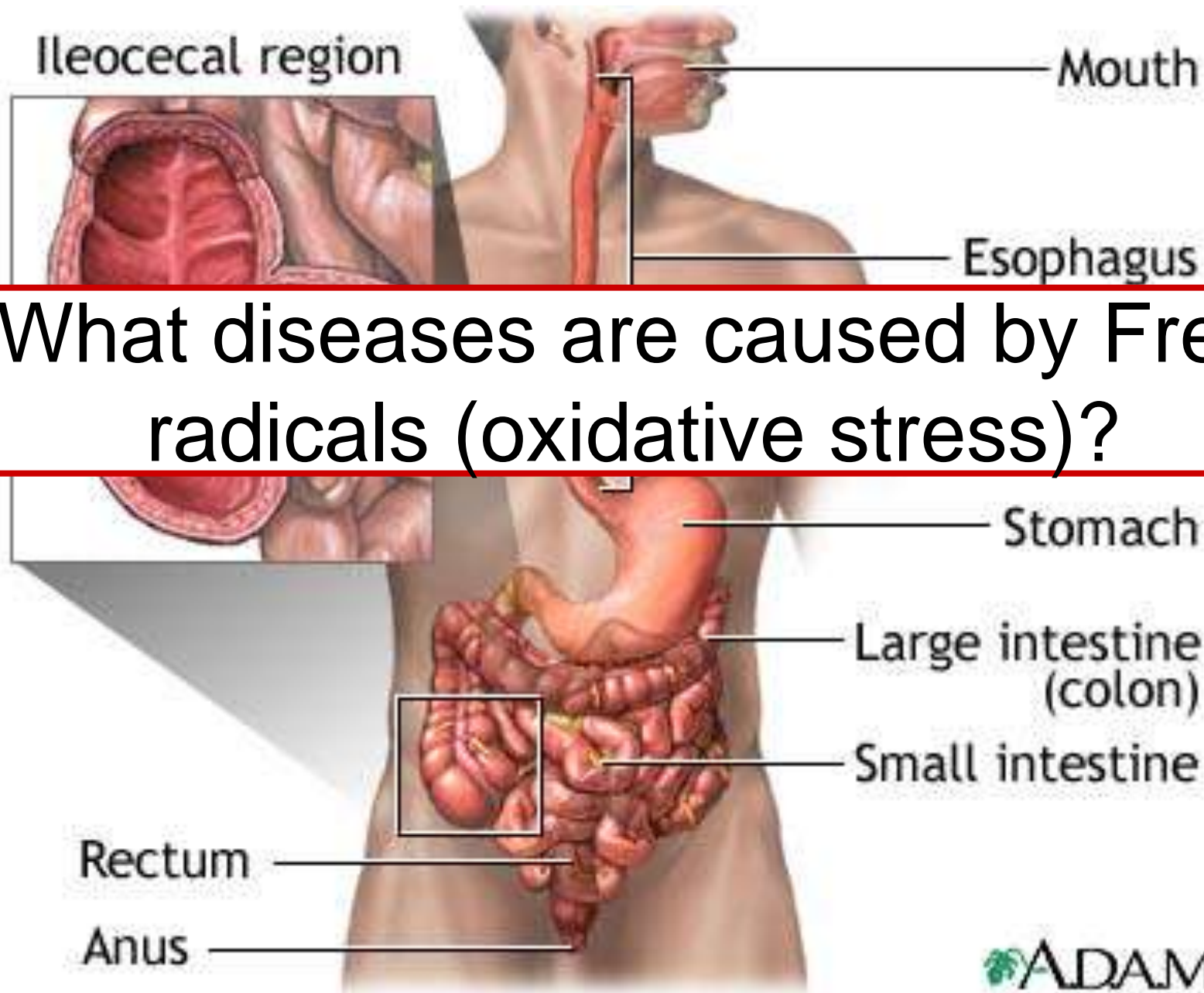
# Accumulation of Ox stress damaged DNA with age in **Brain cells**



*Brady, Ling & Grant, (2009) Pub in preparation..*

# Total Antioxidant capacity decreases with age





What diseases are caused by Free radicals (oxidative stress)?

# Top 5 Causes of Death in Australia

## Men

Cancer (32%)

Circulatory diseases (32%)

COPD (4%)

Dementia (3%)

Diabetes 1&2 (3%)

## Women

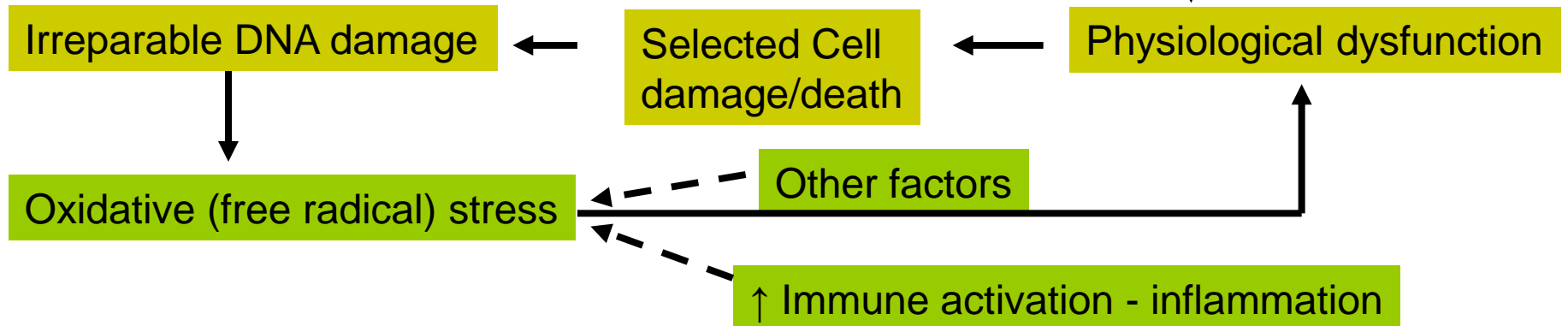
Circulatory diseases (37%)

Cancer (26%)

Dementia (7%)

COPD (3%)

Diabetes 1&2 (3%)



# Summary: Session 1.

1. Free radicals are rogue chemicals produced mainly by the body, but can originate from the diet
2. Free radicals cause damage to cells and organs
3. Free radical damage accumulates as we age leading to diseases such as heart disease, cancer, and dementia.

# Session 2.

Free radical damage in cancer  
and heart disease: How does it  
happen?