

Free radical damage in cancer and heart disease?

Dr Ross Grant

Penrith SDA Church

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What will be covered
In this session?

Session 2

- The role of free radicals in the development of heart disease and cancer

Top 5 Causes of Death in Australia

Men

Cancer (32%)

Circulatory diseases (32%)

COPD (4%)

Dementia (3%)

Diabetes 1&2 (3%)

Women

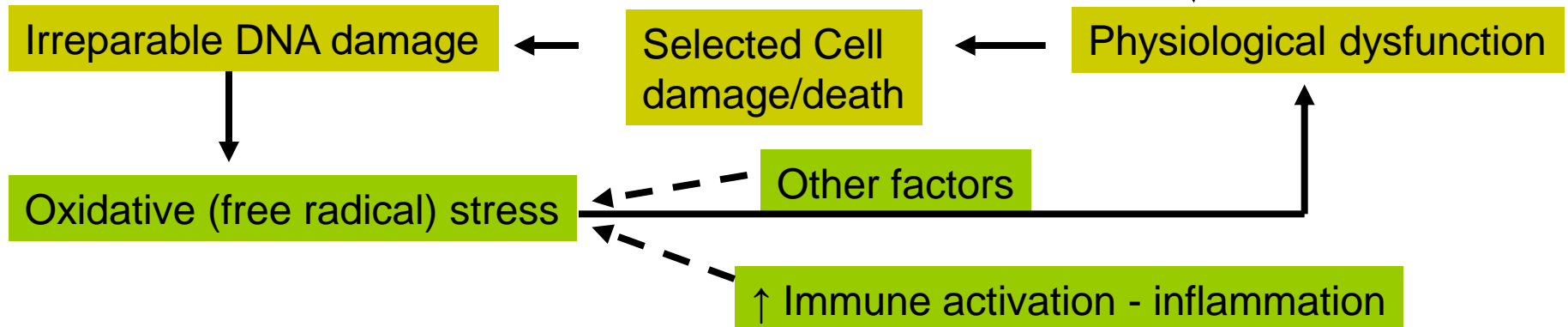
Circulatory diseases (37%)

Cancer (26%)

Dementia (7%)

COPD (3%)

Diabetes 1&2 (3%)



Heart disease: Overview

1. Brief definition of atherosclerosis and heart disease?
2. Link between oxidative stress and development of heart disease.
3. Relationship between high cholesterol, oxidative stress and atherosclerosis

Atherosclerosis

Definition: Atherosclerosis is a disease of the arterial blood vessels (arteries), in which the walls of the blood vessels become thickened and hardened by "plaques."

Also Known As: Arteriosclerosis,
Hardening of the Arteries, Atherosclerotic
Plaque

Plaques are composed of cholesterol and other lipids, inflammatory cells, and calcium deposits.



htt

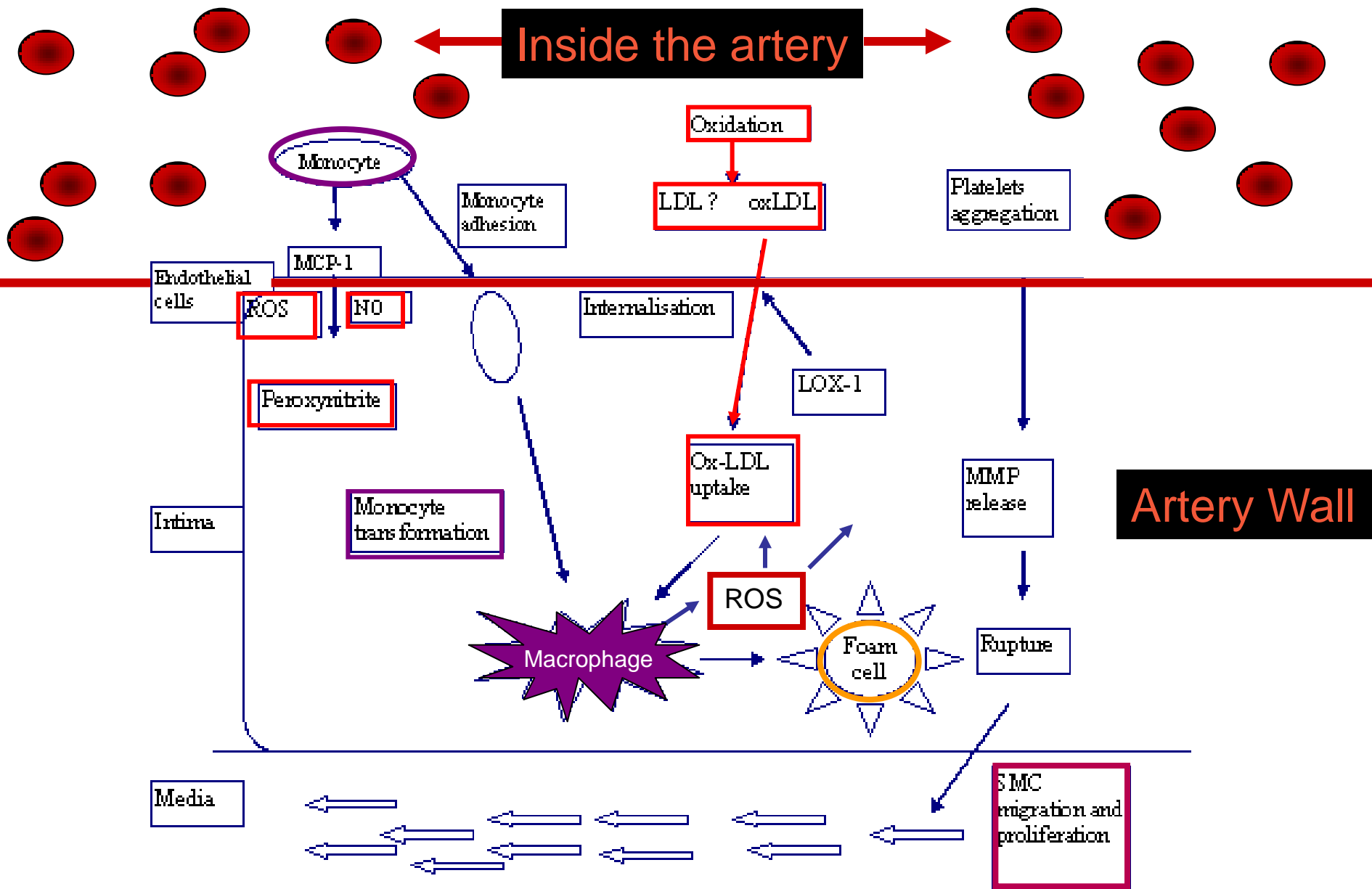
How does the atherosclerotic plaque develop?

What role to Free radicals play?

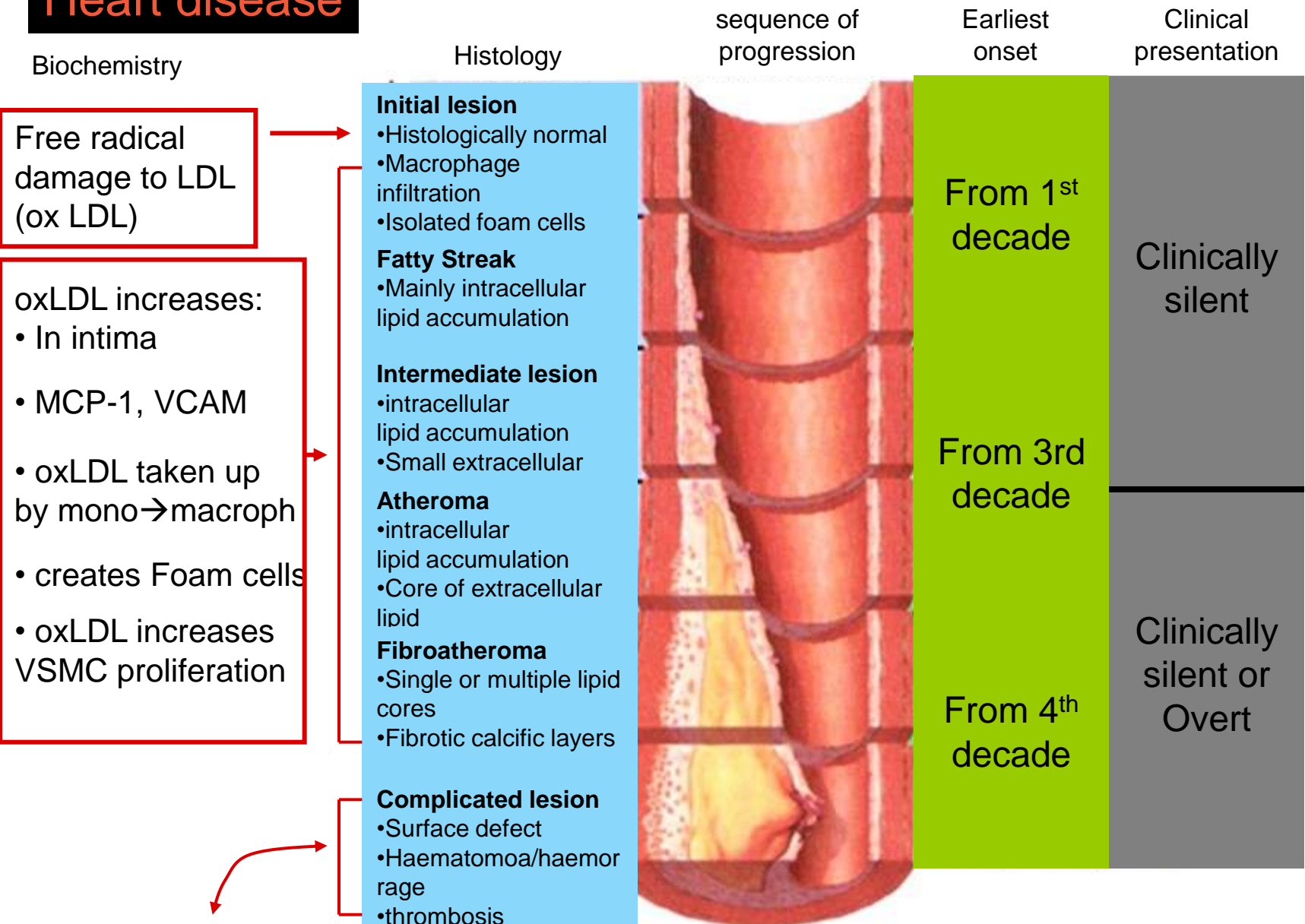


com/nvdam.htm

Plaques can slow the flow of blood through the arteries, If they rupture, the artery can become completely obstructed



Heart disease



oxLDL increases Macrophage activation in atheroma → ROS, metalloproteinases that Degrade matrix, → unstable plaque → rupture of plaque and thrombosis.

Short term effects of high fat on Ox stress and arterial wall function

Tsai W, et al. Clinical Science (2004) 106, 315–319

Study objective: This study was undertaken to investigate the effects of postprandial lipaemia on endothelial dysfunction and oxidative stress.

Study Design: plasma GSH-Px, (antioxidant enzyme), and the urinary excretion of 8-epi-prostaglandin F₂α (8-PGF₂α), a free radical-catalysed product of arachidonic acid, were measured in 16 healthy subjects (mean age, 30±5 years) without major coronary risk factors. High-resolution ultrasound was used to assess the flow-mediated vasodilatation (FMD) of the brachial artery. Blood and urine samples were collected before and 2, 4 and 6 h after a standard high-fat meal (3677 J, containing 50 g of fat).

Results: Serum triglycerides increased and FMD decreased significantly after a high-fat meal. Plasma GSH-Px significantly decreased from 27.2 μg/ml to 25.7 μg/ml 2 h after the meal, and urinary excretion of 8-PGF₂α significantly increased from 1286 pg/mg of creatinine to 2197 pg/mg of creatinine at 4 h

Conclusion: Endothelial dysfunction was observed after consuming a high fat meal and is associated with increased oxidative stress manifested by the depletion of serum antioxidant enzymes and increased excretion of oxidative modification products.

Cholesterol, Free radicals and Heart Disease

What are the key points?

1. Free radical damage to the 'bad' cholesterol (LDL) produces ox LDL that initiates a cascade of events leading to the atherosclerotic plaque
2. High cholesterol means there is more 'bad cholesterol' around increasing the possibility it will get damaged by the Free radicals producing ox LDL
3. A high Free radical burden, even with low cholesterol (i.e. < 5 mM) will still produce atherosclerotic heart disease

Cancer: Overview

1. Brief definition of cancer?
2. Link between DNA damage oxidative stress and cancer.

Cancer: what is it?

- An abnormal growth of cells which tend to proliferate in an uncontrolled way and, may metastasize (spread).
- Cancer can involve any tissue of the body and have many different forms in each body area.



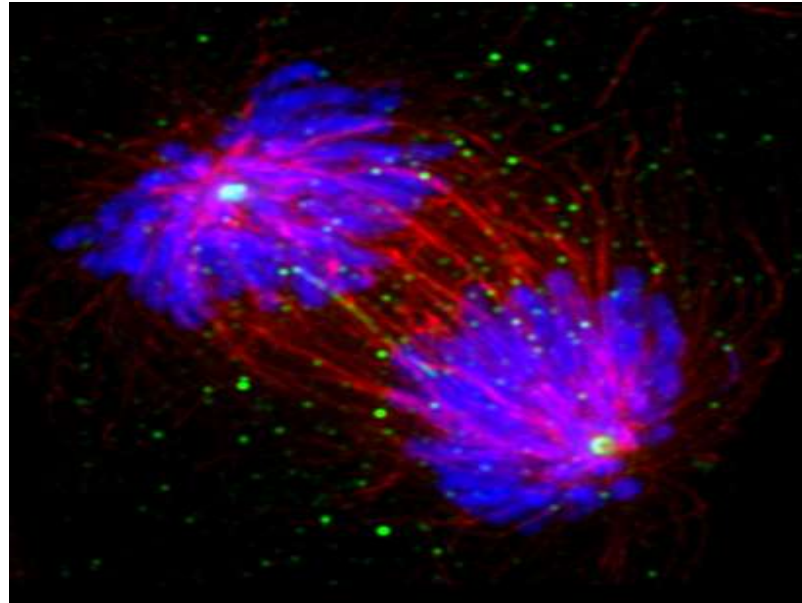
Lung Cancer (SCLC, NSCLC etc)



Skin Cancer (BCC, SCC etc)

Cancer

A cancer can only develop when cell processes controlling cell proliferation (most often involving gene stability and repair) ultimately become dysfunctional or unregulated.



www.dundee.ac.uk/.../images/Cancer%20Cell.jpg

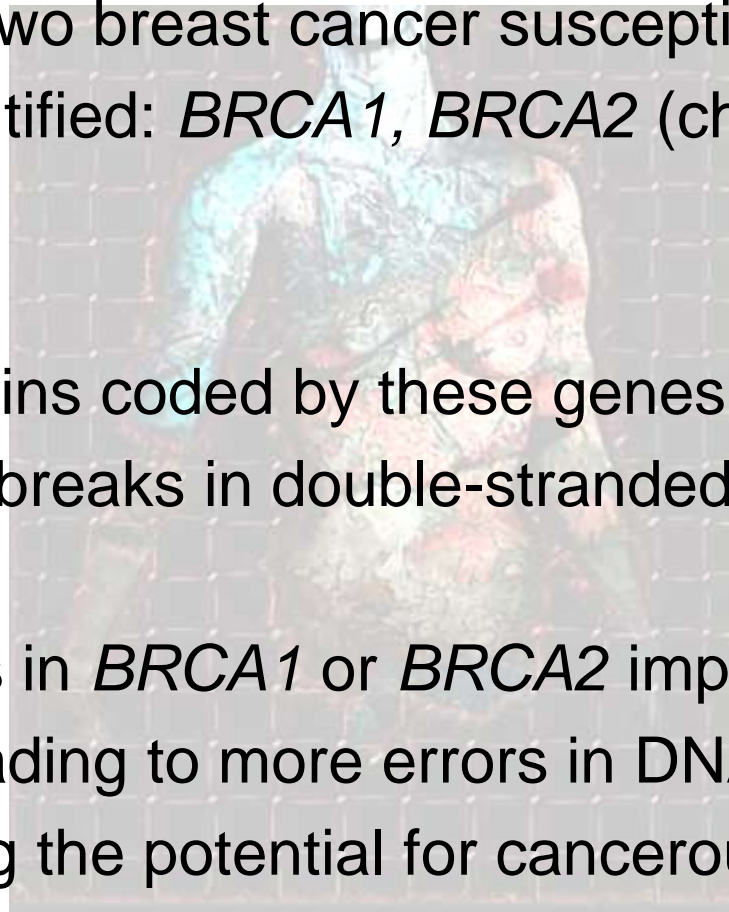
When the DNA is damaged and not repaired properly abnormal cell growth (cancer) can occur.

Breast Cancer

In 1994, two breast cancer susceptibility genes were identified: *BRCA1*, *BRCA2* (chromosome 17,13)

The proteins coded by these genes participate in repairing breaks in double-stranded DNA.

Mutations in *BRCA1* or *BRCA2* impair genetic repair, leading to more errors in DNA replication increasing the potential for cancerous growth.



Colon Cancer

Genes found to be involved in colorectal cancer include: *MSH2* & *MSH6* (chromosome 2) and *MLH1*, (chromosome 3).

Proteins coded by these genes help to repair mistakes made during DNA replication.

If the *MSH2*, *MSH6*, and *MLH1* proteins are mutated and don't work properly, the replication mistakes are not repaired DNA damage accumulates increasing the likelihood of developing cancer (in this case of the colon).

Skin Cancer

- > 33,000 mutations to the genome of COLO-829 melanoma
- the original DNA damage was predominantly on guanine (Fig. 2c).
- substantial evidence that mutagens such as reactive oxygen species predominantly cause damage to guanine which ultimately results in DNA damage (i.e. G.T changes)
- Results from experimental systems suggest that in addition to the direct effects of ultraviolet light other mechanisms of DNA damage are apparent (e.g. by ROS).

lung cancer

- The authors present the complete sequences of a primary lung tumour and adjacent normal tissue.
- Comparing the two genomes, they identified a wide variety of variations, including. 50,000 single nucleotide mutations.

Lee W., etal. Nature (2010) 465; 473-477

“...human diseases including cancer as well as the aging process, have been linked, directly or indirectly, to a condition associated with increased oxidative damage”.

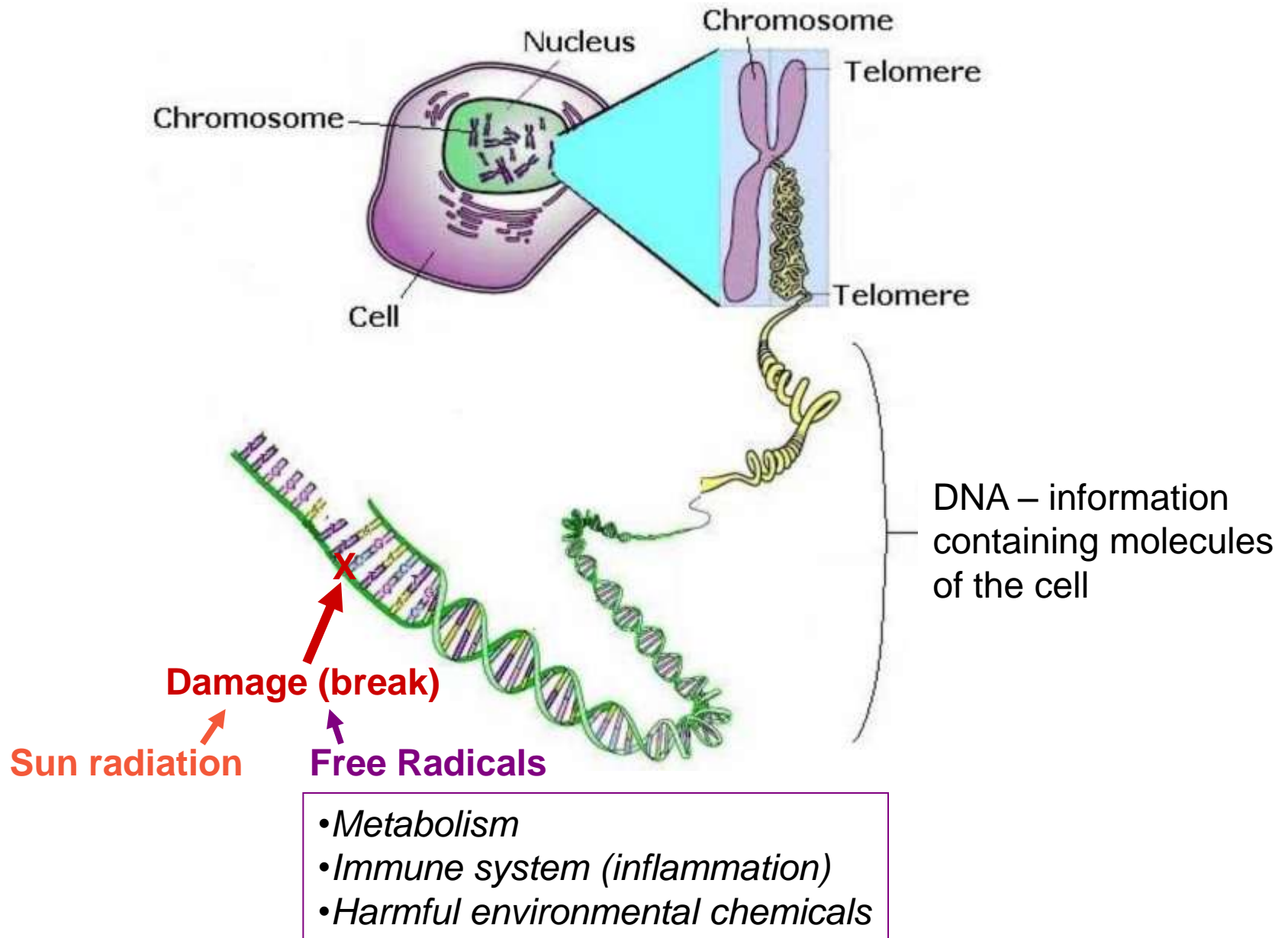
Giustarini D, et al. Critic Rev Clin Lab Sci. 2009; 46(5-6):241-281

Oxidative cell damage

- Estimated that one human cell is exposed to 150,000 hits per day from ROS

Chemico-Biological Interactions. 2006;160:1-40

How can the DNA get damaged?



Session 2.

Main points

- Early stages of atherosclerosis are initiated by free radical damage of low density cholesterol
- High cholesterol will not cause atherosclerosis on its own
- Increased Ox stress in the presence of high cholesterol is the best recipe for development of atherosclerosis
- Cells of the body are constantly exposed to ROS

- Free radical damage to DNA represents the first step in carcinogenesis and aging
- DNA damage can result in:
 - arrest or Induction of transcription or
 - signal transduction pathways,
 - replication errors or
 - genomic instability
- All of these are associated with carcinogenesis

Session 3.

How can you reduce Free Radical damage,
slow Aging and reduce risk of developing
lifestyle diseases?

Session 3.

Main points

1. Impact of calorie restriction on free radical production
2. Effect of high nutrient diet on free radicals
3. Effect of exercise on free radicals

Effect of Calorie restriction on longevity

Rats fed a calorie restricted diet with essential nutrients lived up to twice as long as rats on a normal diet.

McCay and Crowell, 1934

Numerous studies have shown increased lifespan for a variety of animals following calorie restriction from worms to fruit fly to monkeys.

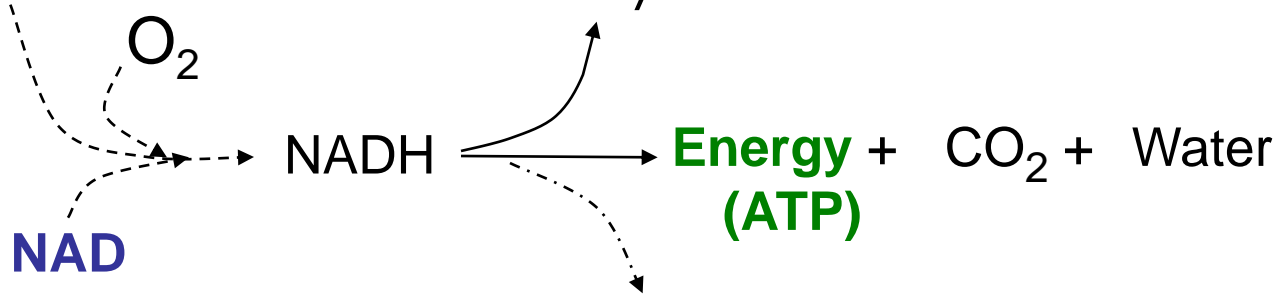
A 20% reduction in calorie intake in a Japanese population produced an ~40% reduction in death rate for heart disease, stroke and cancer.

Nutr Health 1992;8:97-105

A large number of studies have shown improvement in cardiovascular and other health markers in people following a nutritionally balanced calorie restricted diet.

**EATing less
calories will
significantly
reduce free radical
production**

Sugar/Fats



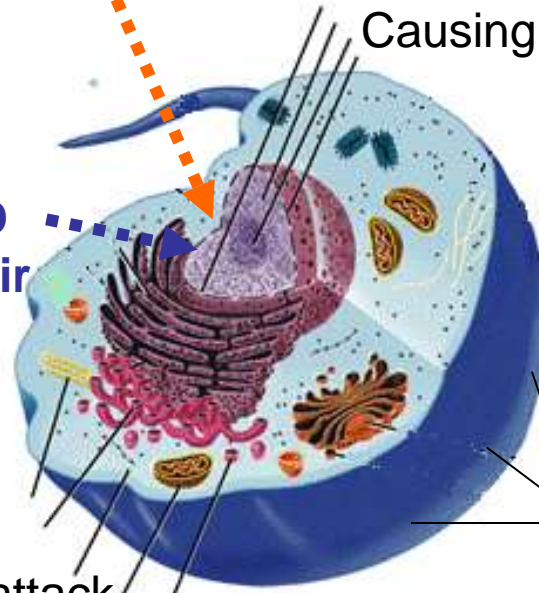
$\uparrow O_2 \cdot^-$

Free radicals can break the DNA
Causing mistakes in copying

NAD Repair

Free radicals can attack
intracellular machinery

Free radicals can break the
cell wall causing leakage



Hungry for life: How the arcuate nucleus and neuropeptide Y may play a critical role in mediating the benefits of calorie restriction.

[Minor RK](#), [Chang JW](#), [de Cabo R](#).

Mol Cell Endocrinol. 2008 Nov 11.

- Laboratory studies consistently demonstrate extended lifespan in animals on calorie restriction (CR), where total caloric intake is reduced by 10-40% but adequate nutrition is otherwise maintained. CR has been further shown to delay the onset and severity of chronic diseases associated with aging such as cancer, and to extend the functional health span of important faculties like cognition.



	% Daily Value*
at 13g	40%
ed Fat 5g	70%
rol 30mg	20%
60mg	28%
31g	19%

Exercise

increases the
body's capacity to
neutralise Free
radicals

How does the body handle free radicals?

1. Tries to detoxify or nullify the radicals using antioxidants:

Endogenous

- Glutathione
- Catalase (H₂O₂)
- Superoxide dismutase



Exercise increases
activity of Antioxidant
enzymes

Exogenous (from food)

1. Vitamins A, E, C
2. Polyphenols

Exercise

- Reduces the stress response
- Reduces desire for food
- Gives a little endorphin ‘high’
- Promotes mitochondrial activity in fat and muscle cells.
- This increases metabolic rate, decreases circulating triglyceride and insulin resistance
- Increases activity of antioxidant enzymes

How does the body handle free radicals?

1. Tries to detoxify or nullify the radicals using antioxidants:

Endogenous

- Glutathione peroxidase (Glutathione-GSSG)
- Catalase (H_2O_2)
- Superoxide dismutase

Exogenous (from food)

1. Vitamins A, E, C
2. Flavonoids, polyphenols etc

Eating **food** with the right nutrients will help here

Comment on Meat Vs Vegetarian

	Vege meal ¹	Traditional Meat meal ¹
Saturated fat	13 g	25 g
Unsat Fat	22 g	9 g
Omega-3 (ALA)	2.2 g	0.4 g
Cholesterol	213 mg	388 mg
Fibre	43 g	20 g
Polyphenols	<i>Large amounts</i>	<i>minimal</i>

¹ Reid et al. Meeting the NRV's on a Vegetarian Diet; Vegetarian Interest Group (2008)

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² Arts, I.C. and P.C. Hollman, "Am J Clin Nut. **81** Suppl: p. 317S-325S (2005)

Research indicates that **polyphenols** may have antioxidant characteristics with potential health benefits and may reduce the risk of cardiovascular disease and cancer².

Functional components; Polyphenols *etc*

Flavonoids		
Anthocyanidins	berries, cherries, red grapes	cellular antioxidant defences; may contribute to maintenance of brain function
Flavanols—Catechins, Epicatechins, Procyanidins	tea, cocoa, chocolate, apples, grapes	may contribute to maintenance of heart health
Flavanones	citrus foods	neutralize free radicals which may damage cells; bolster cellular antioxidant defences
Flavonols	onions, apples, tea, broccoli	neutralize free radicals which may damage cells; bolster cellular antioxidant defences
Proanthocyanidins	cranberries, cocoa, apples, strawberries, grapes, wine, peanuts, cinnamon	may contribute to maintenance of urinary tract health and heart health
Isothiocyanates		
Sulforaphane	cauliflower, broccoli, broccoli sprouts, cabbage, kale, horseradish	may enhance detoxification of undesirable compounds and bolster cellular antioxidant defences
Phenols		
Caffeic acid, Ferulic acid	apples, pears, citrus fruits, some vegetables	may bolster cellular antioxidant defences; may contribute to maintenance of healthy vision and heart health

So what **else** can we do to live longer, healthier lives and slow down the aging process?



www.bio-pro.de/en/life/magazin/02104/index.html

Exercise and EAT MORE nutrient-rich foods

Summary of anti-aging strategies

Age enhancing (DNA damaging)	Anti aging (DNA preservation) <i>Behaviour strategy</i>	Anti aging (DNA preservation) <i>Food strategy</i>
<i>Environment Free Rads</i> -car/industrial fumes -Chemical sprays	Reduce exposure Exercise	Increase vege foods
<i>Excess Sun exposure</i>	Reduce exposure Exercise	Increase vege foods
<i>Biological Free Rads</i> -cell metabolism -immune activity	Eat less Get plenty of sleep Exercise	Reduce high energy food Increase vege foods
<i>Anxiety (HPA activation)</i>	Faith (1Peter 5:7) Exercise Relaxation strategies	Reduce caffeine Intake

Conclusion

What can be done to minimise DNA damage, aging and the chances of getting diseases such as cancer?

1. Decrease exposure to harmful 'Free Radicals'
 - *Don't eat too much high calorie or crispy foods (AGE's)*
2. Increase the body's ability to neutralise the 'Free radicals'
 - *Exercise (increases body's natural antioxidants)*
 - *Eating foods containing antiox. (fresh fruit and veges)*
3. Increase the body's capacity to repair the DNA
 - *Eat foods with high nutritional value (whole grains, fruit, veges)*

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3. Increase the body's capacity to repair the DNA

- *Eat foods with high nutritional value (whole grains, fruit, veges)*

- Pure air
- Sunlight
- Abstemiousness (no tobacco, coffee, tea or alcohol)
- Rest
- Exercise
- Proper diet (low calorie, vegetable-rich)
- Use of water
- Trust in GOD

E.G. White MH 1905