

Mechanisms and health effects of marine oils

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This is not the full presentation as presented at the meeting.

It has been edited to preserve confidentiality of new research results, prior to their publication in a scientific journal'

Functional “molecules” from seafood

- n-3 fatty acids:
 - eicosapentaenoic (EPA, 20:5), docosahexenoic acid (DHA, 22:6)
- Peptides/ Proteins:
 - fish protein hydrolysates
 - Angiotensin converting enzyme (ACE) inhibitors
 - Serine protease inhibitors
- Amino acids
 - taurine, lysine, histidine, glutamine
- Vitamins A, D, E and K ...Ubiquinone CoQ10....niacin, B6, B12
- Minerals and trace elements:
 - potassium, calcium, magnesium, zinc, selenium, iodine

..be aware of the risk of over focusing single aspects..

***Greenland Eskimos, on their traditional
diet - lower incidence of CHD***
(Dyerberg et al., 1978)

**Omega-3 protects against atherosclerosis and
thrombosis**

- **Marine mammals and Fish**
- **Visceral organs (liver, kidney, heart)**
- **Raw or minimal processed food**

Differences in morbidity from chronic diseases between Greenland Eskimos and Scandinavians

Eskimos/Scandinavians

Stroke	2/1
Acute Myocardial Infarction	1/10
Psoriasis	1/20
Diabetes	Rare
Bronchial Asthma	1/25
Thyrotoxicosis	Rare
Multiple Sclerosis	0
Epilepsy	2/1
Polyarthrititis	Low

Kromann and Green, ACTA Med Scand 1980, 208, 401.

Traditional refining of marine oils

- Removal of molecules to improve sensory attributes and safety of the oil

May result in:

- The destruction of potent antioxidants and removal of components with potential beneficial effects
- Initiation of a row of chemical reactions; hydrolysis, autoxidation, isomerization, conjugation, polymerization, pyrolysis, and dehydration...

Oxidation rate of fatty acids depends largely on number of double bonds

Fatty acid	Number of double bonds	Induction period (h) 25 C	Rel. rate of oxidation
18:0	-	--	1
18:1	1	82	100
18:2	2	19	1200
18:3	3	1.3	2500
20:5 EPA	5	--	?
22:6 DHA	6	--	?

Effects of marine oils associated with reduction in

- inflammatory reactions
- atherosclerosis
- thrombus formation
- depression
- psoriasis
- inflammatory bowel disease (IBD)
- the activity of platelets

Platelet activity

- Intake of marine oils reduces the activity of platelets (reduce platelet aggregation, adhesion to vessel wall, generation of pro-inflammatory products)
- Important: Platelets are play a central role in thrombosis, atherosclerosis, myocardial infarct (MI), brain infarct (stroke)

General effects of marine oils

- Reduce the production of pro-inflammatory products in several cell-types (e.g. monocytes essential in lesion formation (atherosclerosis), endothelial cells involved in several inflammatory diseases)

Mechanism of atherogenesis -a short review

Different types of cholesterol

-HDL-cholesterol: the **good** cholesterol

-LDL-cholesterol: the **bad** cholesterol

Beneficial effect is to increase HDL-cholesterol and to reduce LDL-cholesterol

HDL-cholesterol can be increased by:

- Physical activity
- Alcohol (redwine is recommended)
- Omega-3 fatty acids (special in whale- and seal oil)

LDL-cholesterol can be reduced by:

- Less intake of saturated fat (pig, lamb, etc)
- Eat fish every day!
- Increased intake of vegetables

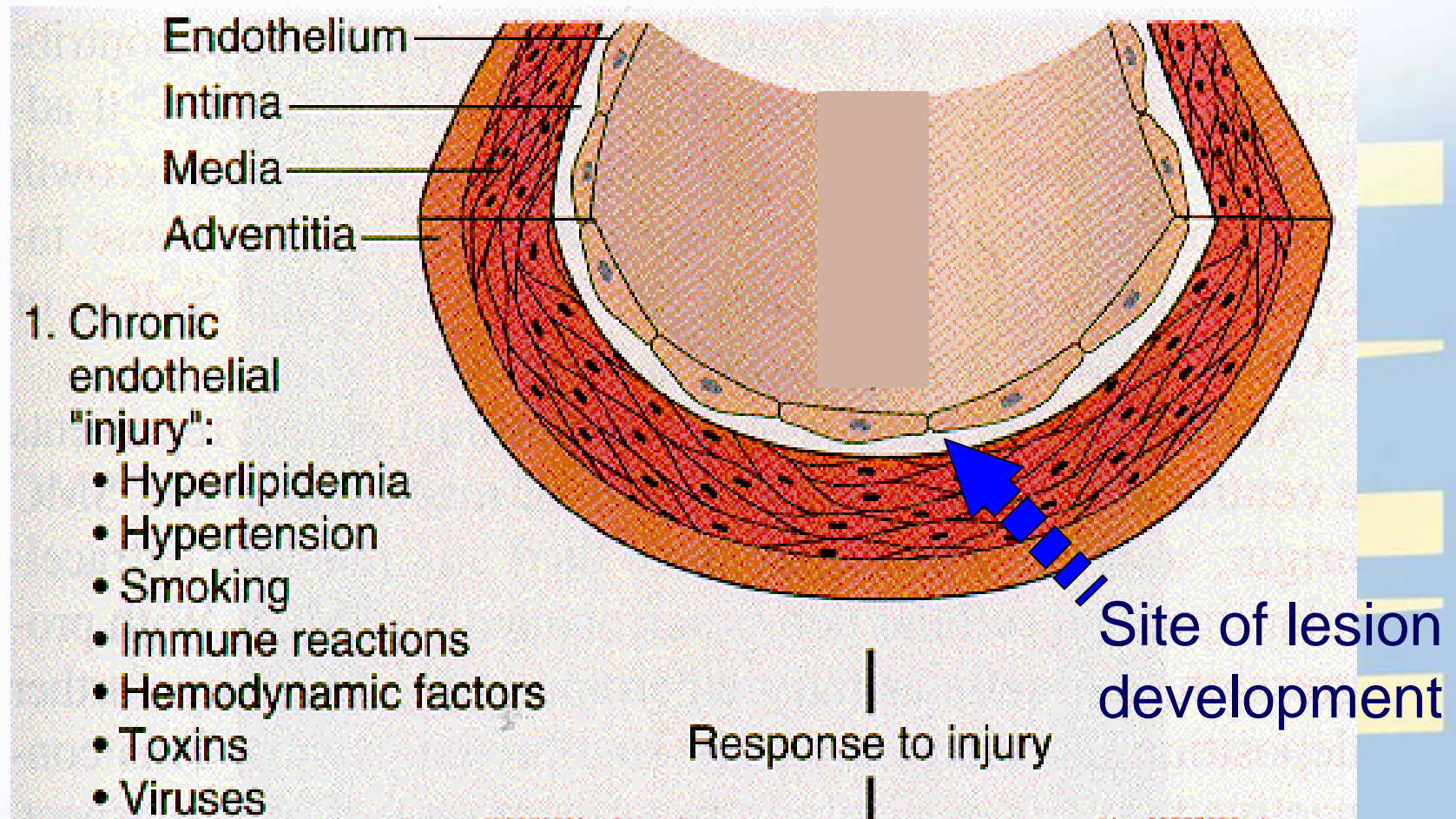
LDL (the major carrier of cholesterol) is diffusing through the endothelium in a passive way into intima

Lack of sufficient antioxidants in the intima, results in the modification of LDL to minimally modified LDL (MM-LDL) through oxidation. Excessive polyunsaturated fatty acids (PUFA) in the LDL makes the oxidation of LDL more likely in the absence of antioxidants.

MM-LDL have chemotactic properties, it mobilizes monocytes from the blood circulation and at the same time upregulate adhesion molecules through activation of endothelial cells whereby monocytes become rolling/adhering to the endothelium and transmigrate into intima.

Atherogenesis

Arterial wall

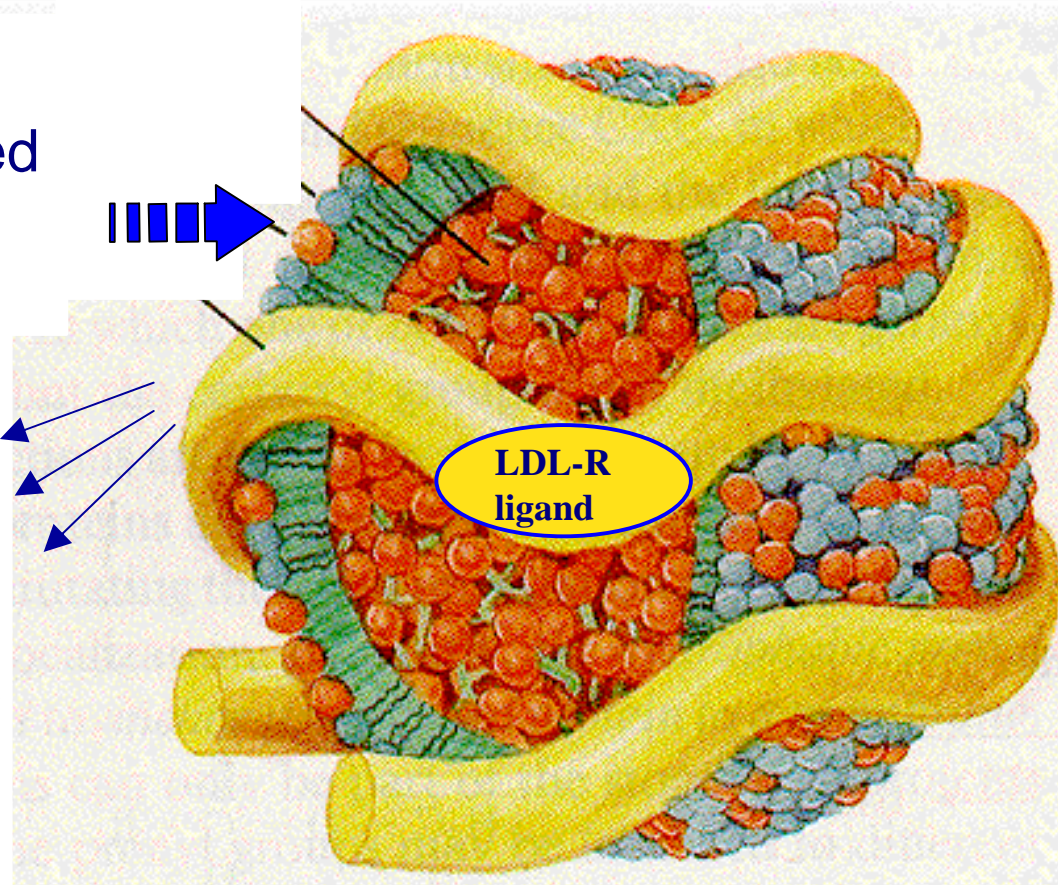


Minimally modified LDL

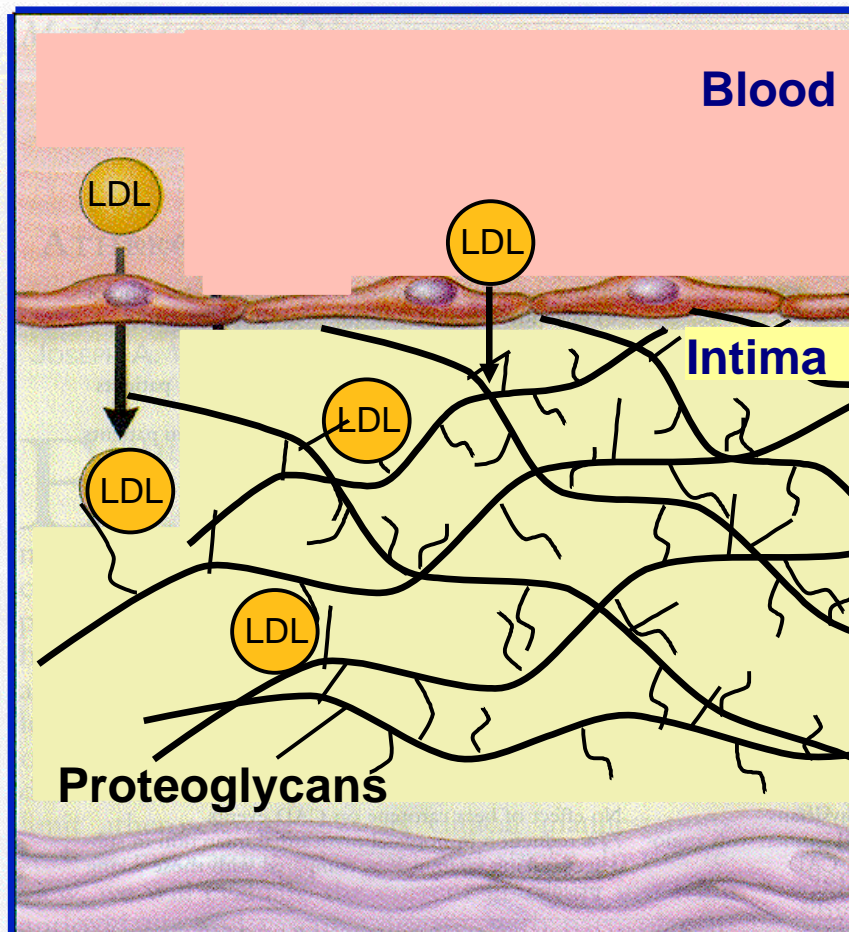
Oxidation of
polyunsaturated
fatty acids in
phospholipid.

Oxidized lipids
with biological
effects.

Key factors for
initiation and
progression of
the disease.



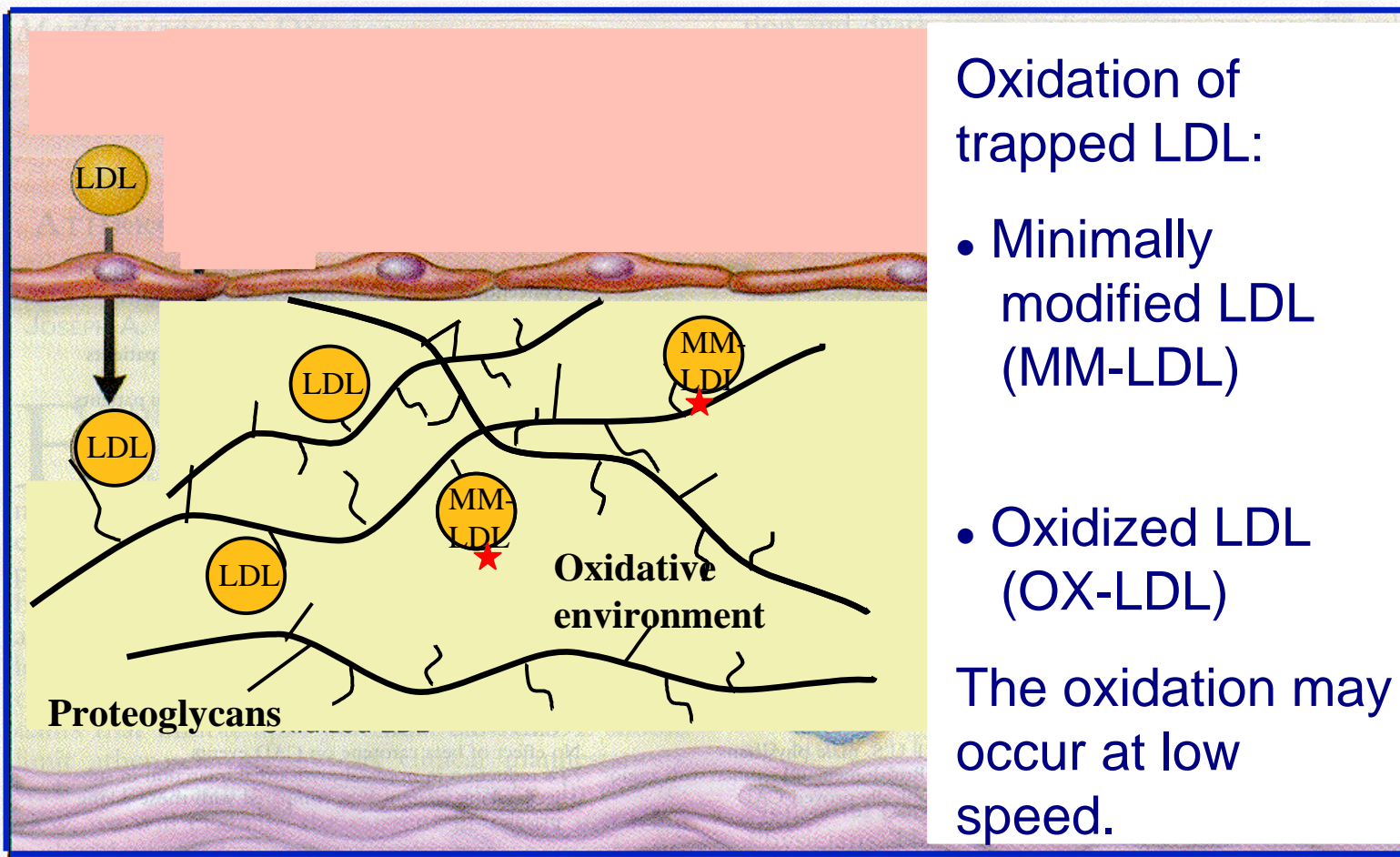
LDL trapment in arterial intima



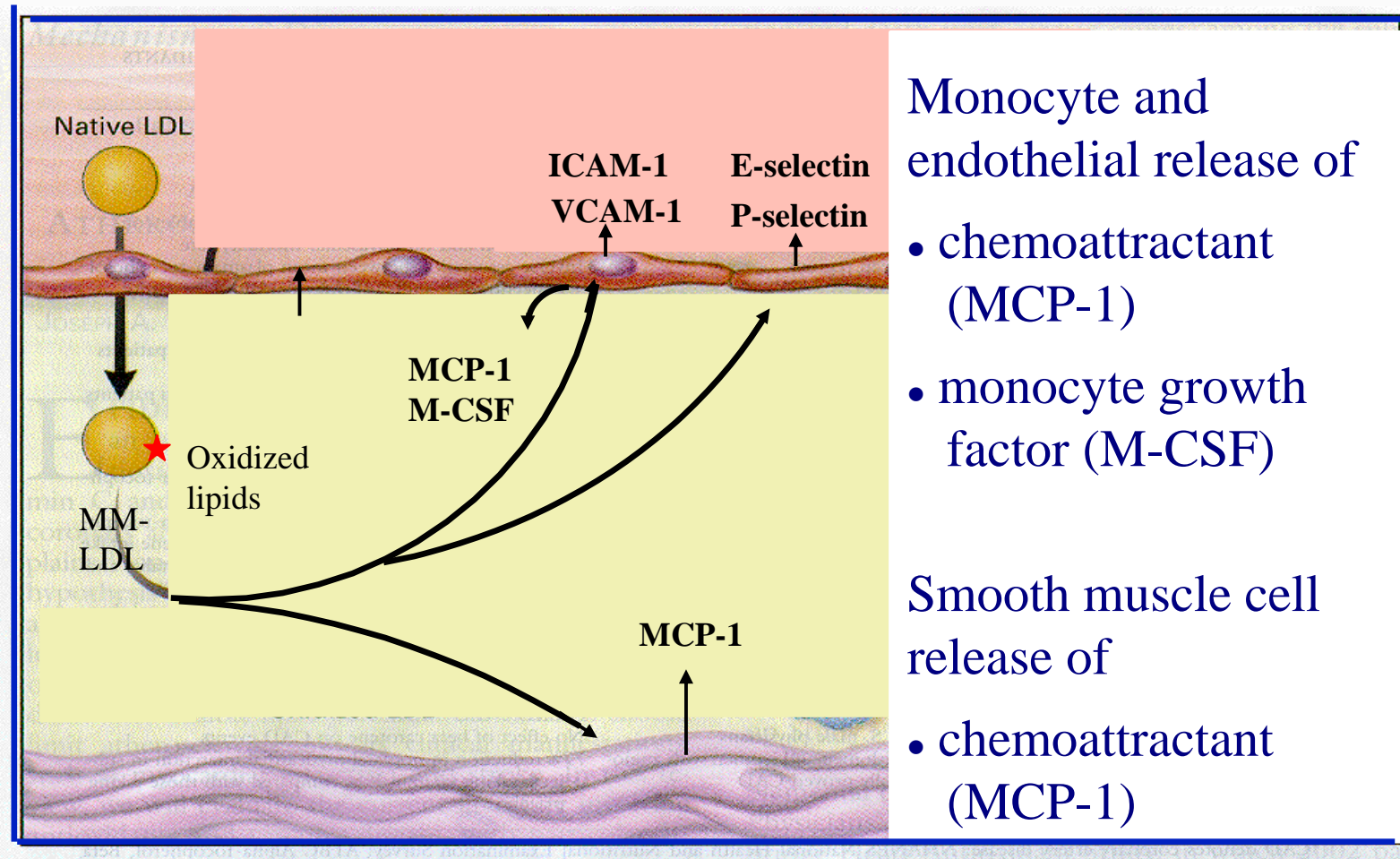
Binding of LDL to PG in arterial intima:

- Long LDL residence time (weeks versus min for other tissue)
- High LDL conc (10-fold higher than in other tissue)

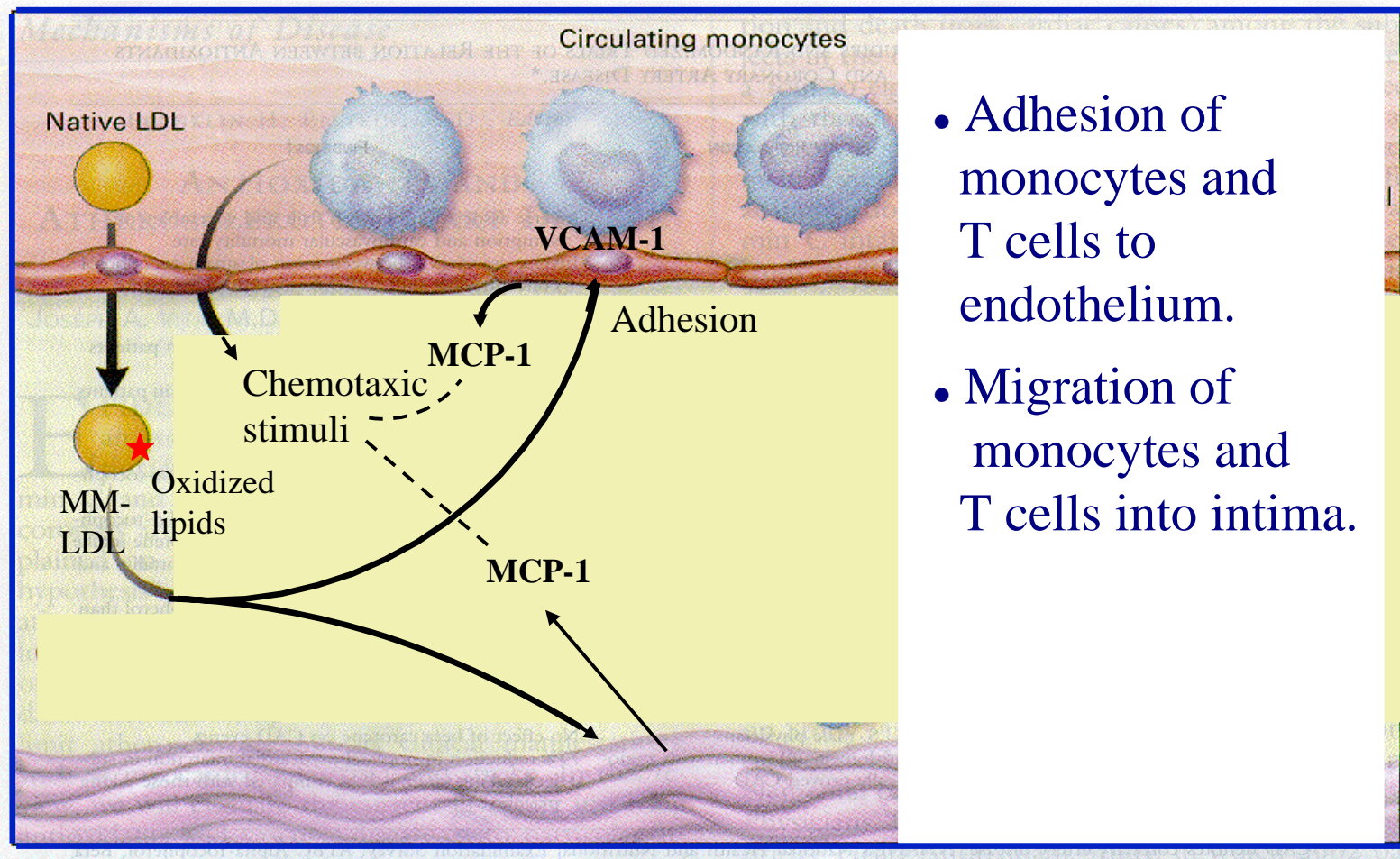
LDL oxidation



Effects of minimally modified LDL

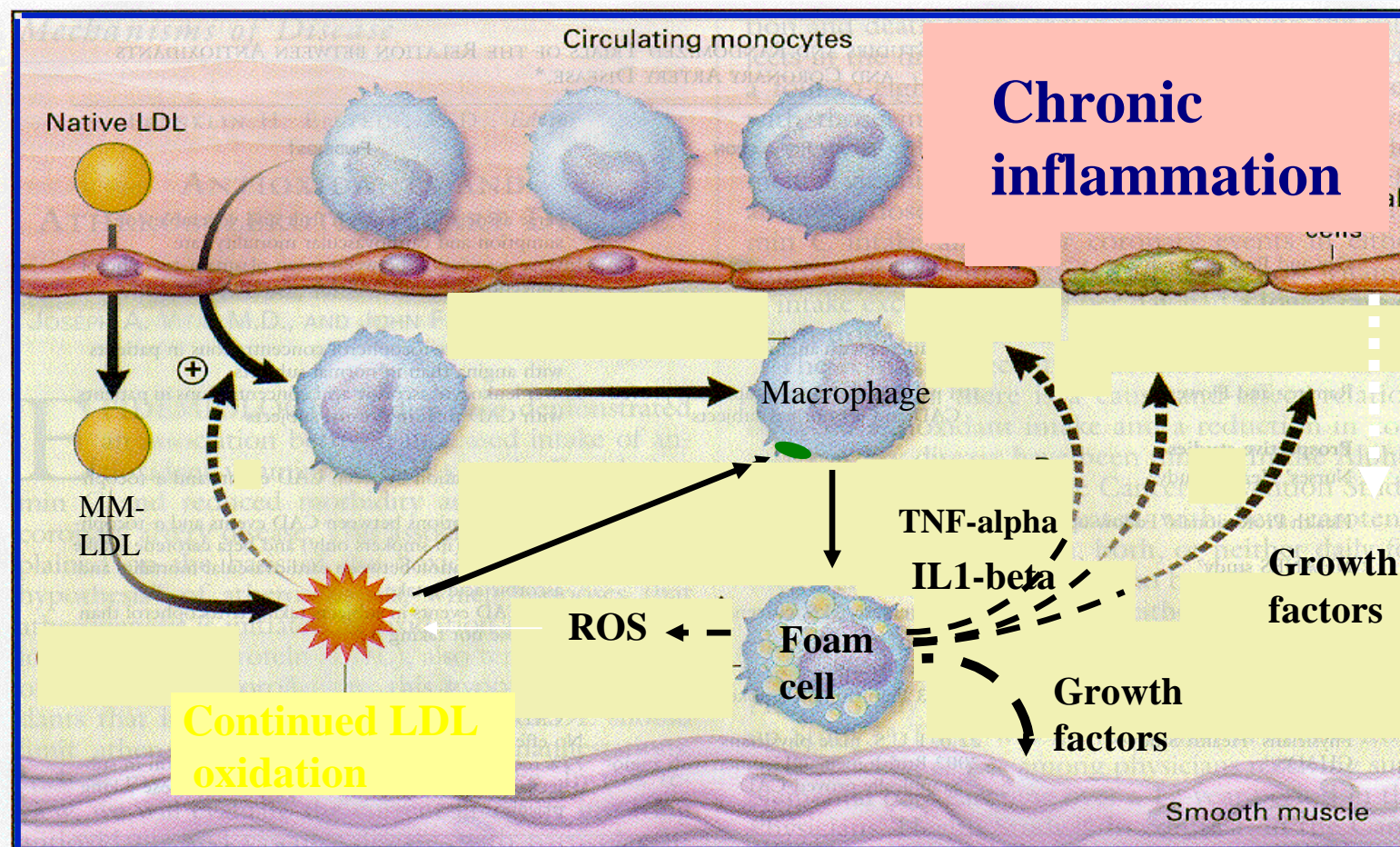


Effects of minimally modified LDL



Effects of foam cells

Continued influx of activated inflammatory cells leads to more advanced lesions.



- **omega-3 fatty acids are also incorporated in LDL-particles**
- **particles are thereby more susceptible for oxidation**
- **prevention of the oxidation may prevent foam cell formation in the intima**

Antioxidants: reduce lesion formation in animal models

Mechanisms:

- » **Inhibit prostaglandin metabolism**
- » **Inhibit lipoxygenase pathway leading to e.g. leukotriene B4**
- » **Neutralizes oxygen metabolites**

Combination of omega-3 fatty acids and antioxidants are reducing pro-inflammatory products in cell membranes

- Incorporation of omega-3 fatty acids in the cell membrane causes a reduction in the availability of arachidonic acid
 - and thereby reduced formation of pro-inflammatory leukotrienes and prostaglandins
- omega-3 fatty acids are converted into leukotrienes and prostaglandins which have just a small part of the pro-inflammatory effect as compared to the products derived from arachidonic acid

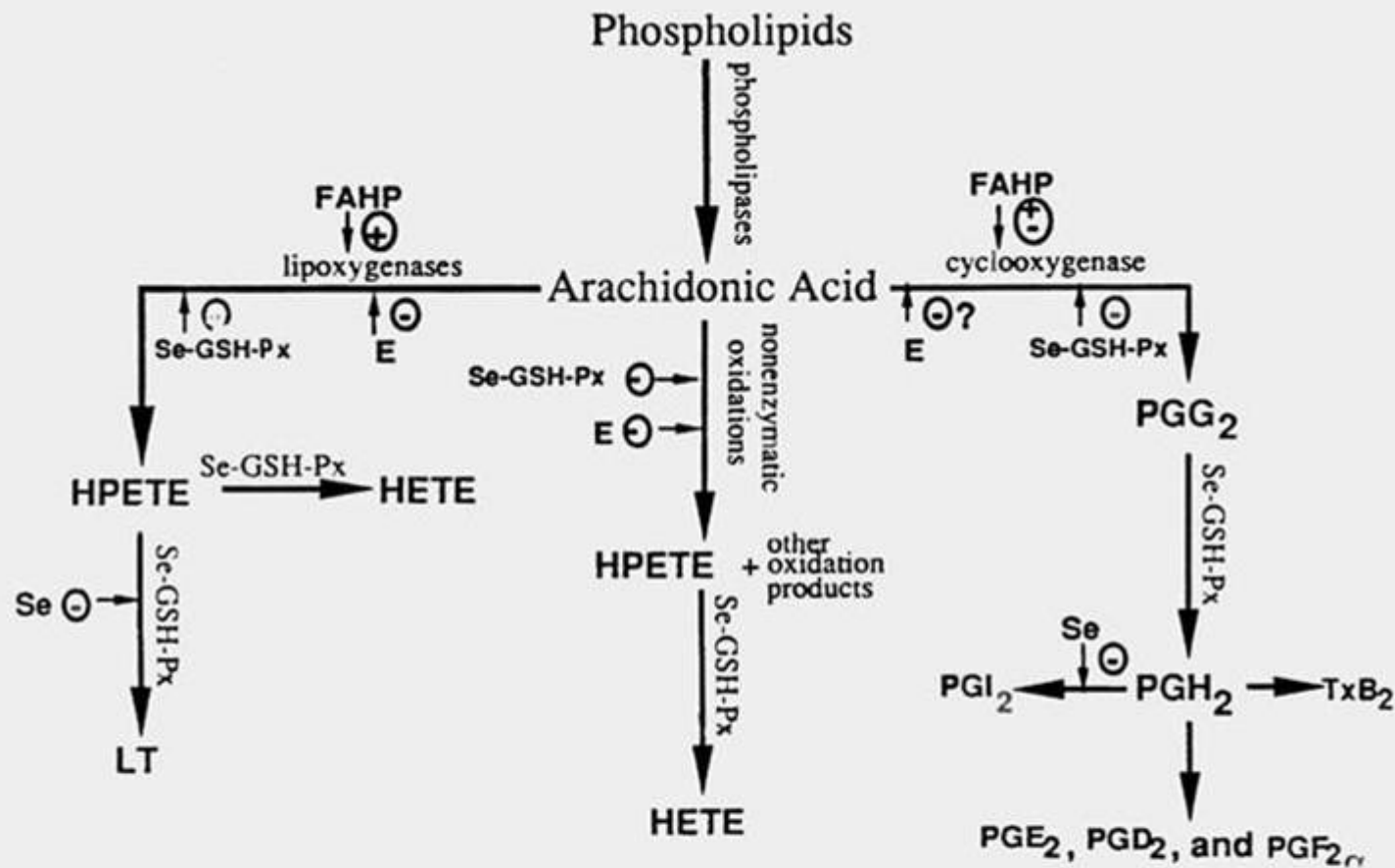


FIGURE 2. The proposed role of vitamin E and selenium in the arachidonic acid cascade. FAHP, fatty acid hydroperoxide; Se, selenium; Se-GSH-Px, selenium-dependent glutathione peroxidase; \ominus , inhibition; \oplus , activation; $\ominus?$, controversial reports; \oplus , activates at low concentration, inhibits at high concentration.

Foam cell formation

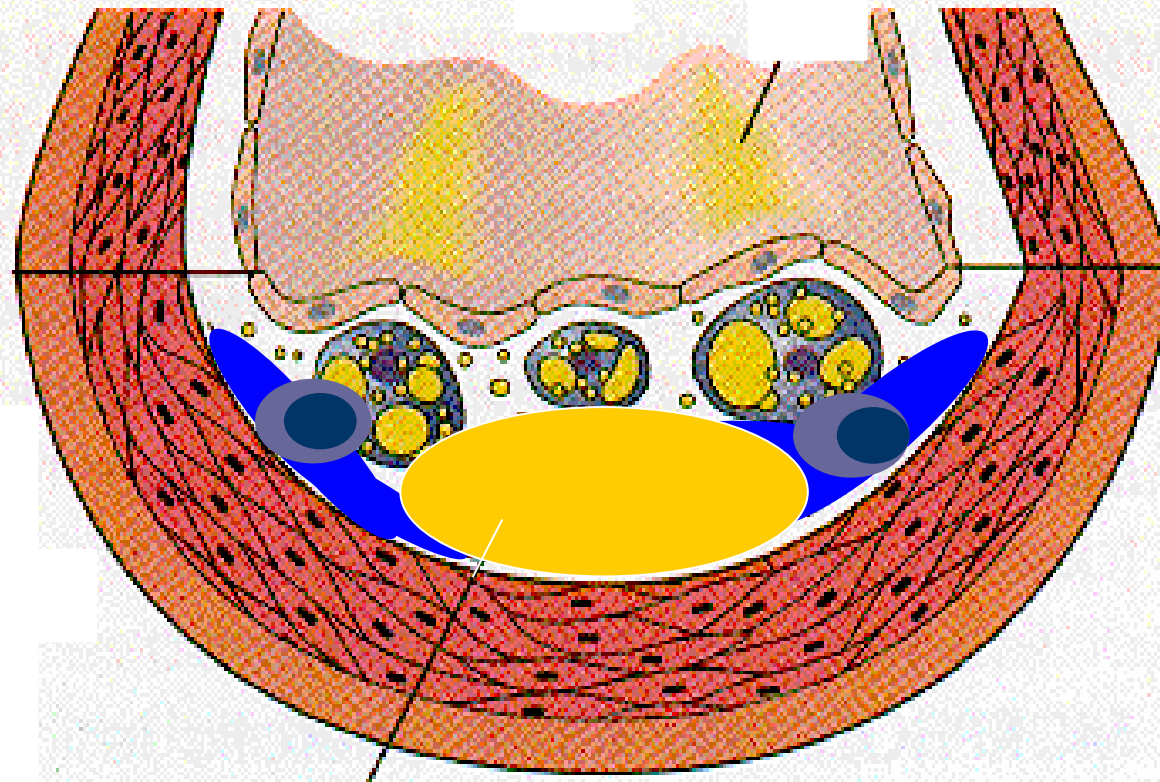
- Through receptors on the macrophages, oxidized LDL is taken up, whereby the macrophage cell is converted into a foam cell rich in fat which assembles just beneath the endothelium and which is seen as a yellow lesion, the beginning of the development of atherosclerosis.

Advanced lesion

Lipid core formation

AHA
lesion
type IV

Atheroma



Extracellular
lipid core

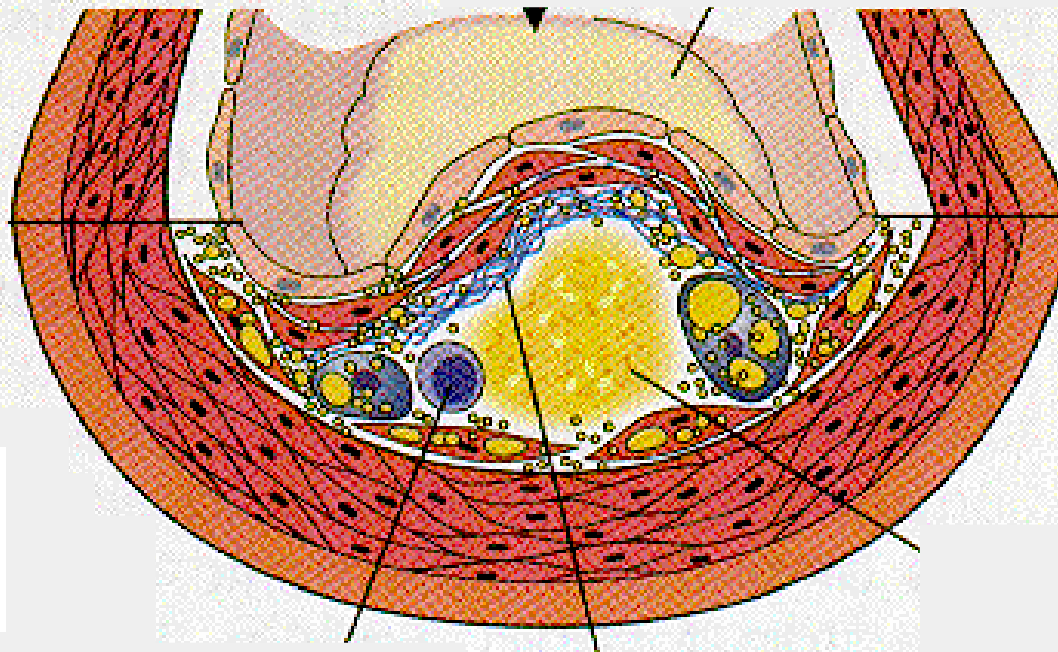
cholesterol
cholesterol ester

Advanced lesions

Intimal smooth muscles cause marked expansion of the intimal lesion due to

- proliferation
- collagen synthesis
- fibrous cap formation

Fibro- atheroma



AHA lesion
type Va

Although the mechanism of atherogenesis is quite complex, several of the reaction steps have been clarified through knock out studies in mice (transgene mice)

(Østerud and Bjørklid, Physiological Reviews 2003).

Lesion formation

Antioxidants have been shown to reduce lesion formation in animal models (Aviram M, Fuhrman B. Ann N Y Acad Sci. 2002;957:146-61. Review).

Knock out mice and evidence of important mediators of lesion:

- Inhibition of the LTB₄ receptor in transgenic mice predisposed for atherosclerosis, reduced lesion formation by about 70 % (Aiello et al. Arterioscler Thromb Vasc Biol. 2002;22:443-9).
- Inhibition of the TxB₂ receptor in transgenic mice predisposed for atherosclerosis, reduced lesion formation by about 70 % (Cayatte et al. Arterioscler Thromb Vasc Biol. 2000;20:1724-8)

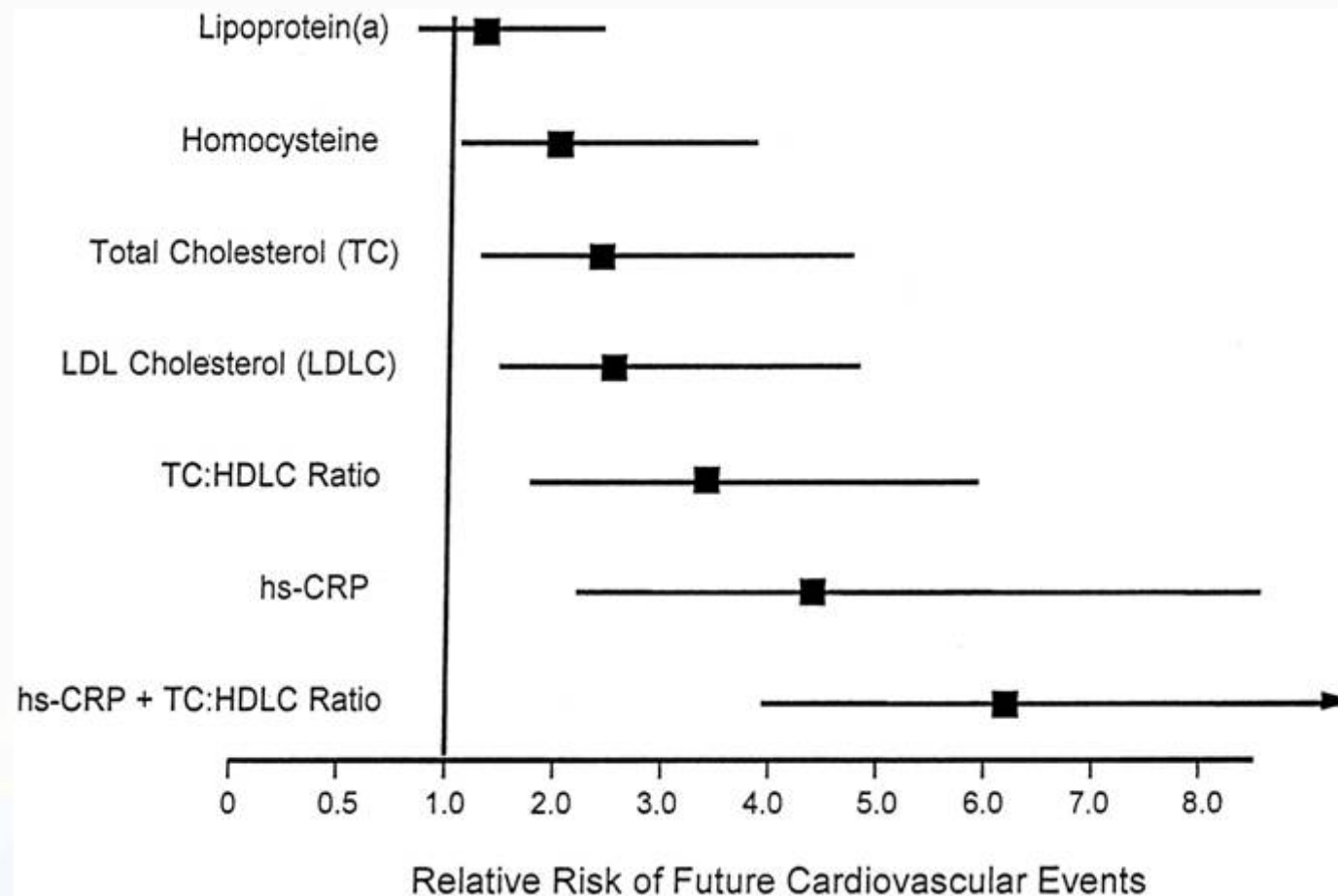
Hypersensitive CRP (hsCRP)

Chronic inflammatory reactions with an enhanced level of hsCRP may be a better indicator of future MI

Subjects with hsCRP values just below 5 are much more prone to have MI than one with 0.5 suggesting that long time inflammatory reactions may be priming cellular activation reactions involved in the development of atherosclerosis.

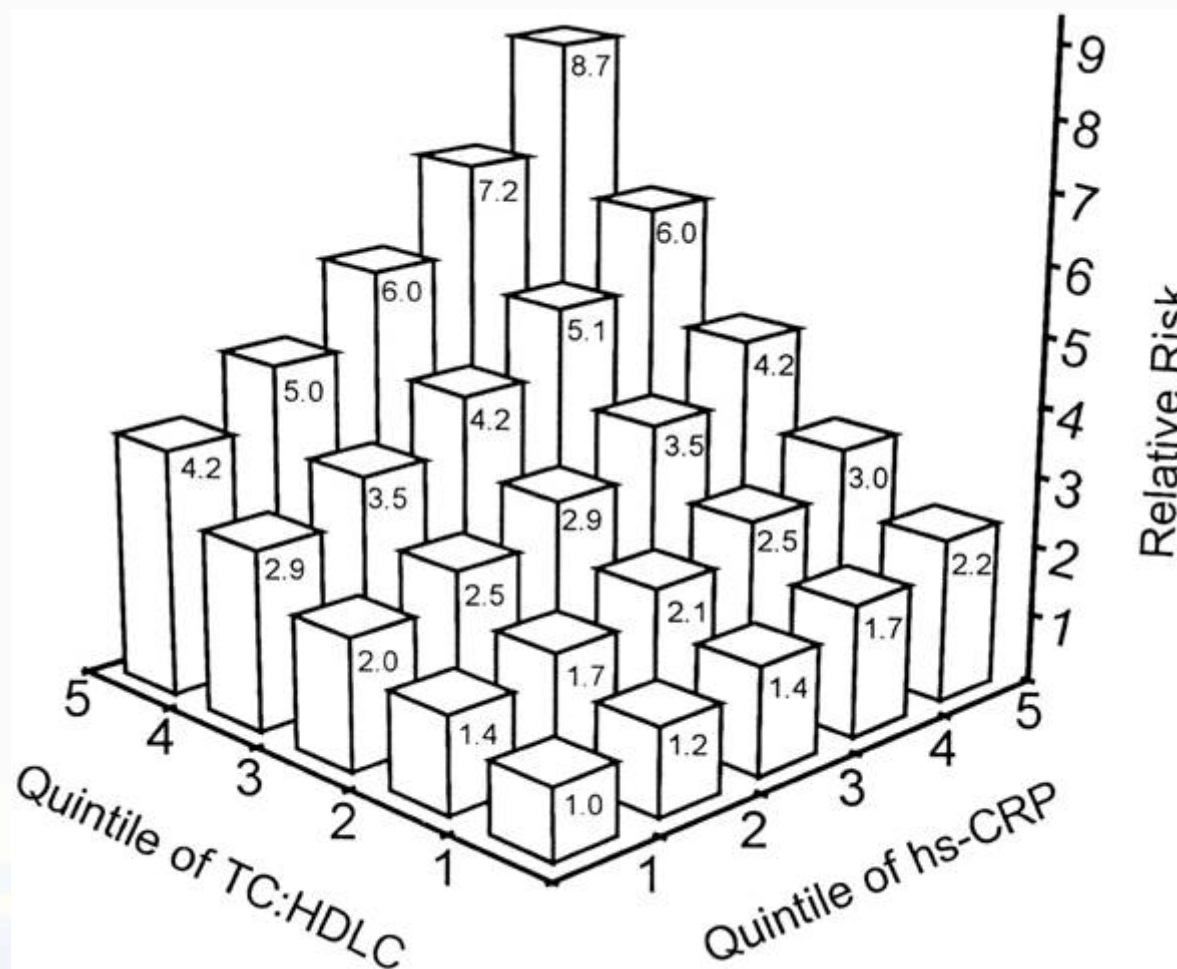
Using the ratio of Total cholesterol over HDL-cholesterol (the good cholesterol) combined with hsCRP, it gives a very strong prediction of future MI as shown on the next two slides.

Direct comparison of magnitude of relative risk of future cardiovascular events associated with HSCRP (hs-CRP), cholesterol levels, lipoprotein(a), and homocysteine among healthy women



Ridker, P. M. *Circulation* 2001;103:1813-1818

Interactive effects of CRP and lipid testing as determinants of cardiovascular risk. hs-CRP indicates high-sensitivity CRP assay; TC, total cholesterol



Ridker, P. M. Circulation 2001;103:1813-1818

OliVita has all the positive effects of omega-3 fatty acids; but even more important, excessive antioxidants/anti-inflammatory products; that together with the omega-3 fatty acids, prevent inflammatory reactions associated with the development of atherosclerosis and other inflammatory diseases as psoriasis, auto-immune diseases, and inflammatory bowel disease (e.g. Crohn's disease).

Eskimo advice - for obvious reasons this may not be perceived as an alternative....

"Every day you should eat something from each of the five basic food groups; fried blubber, boiled blubber, stewed blubber, baked blubber and raw blubber"



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A better life with seafood...



www.seafoodplus.org