



THE ENDURING MYSTERY OF HEART DISEASE – ‘THE CLOT THICKENS’

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1

PRESENTATION

- The demonisation of cholesterol
- Contradictions
- Why cholesterol cannot cause cardiovascular disease
- The process of cardiovascular disease

2

ONE HUNDRED AND FIFTY YEARS OF DEMONISING CHOLESTEROL

- First found in gallstones 1769 [Francis Poulltier de la Salle]
- First found in human blood 1833 [M F Boudet]
- First suggested to be arterial plaque 1843 [J Vogel]
- First confirmed to be in arterial plaque 1856 [Rudolf Virchow]
- Atherosclerosis defined 1904 [Felix Marchard]
- Atheroma found to contain 20 x more cholesterol than healthy arteries 1910 [Adolph Windaus]
- Feeding rabbits cholesterol causes atherosclerosis 1913 [Nikolai Anitschkow]
- Anitschkow's work only attracted attention in the West in the 1950s when John Gofman analysed cholesterol and discovered LDL and HDL (so-called good and bad cholesterol).

3

ONE HUNDRED AND FIFTY YEARS OF DEMONISING CHOLESTEROL

- 1958 Editorial on Cardiology's ten Greatest 20th Discoveries: Top three
 - The electrocardiogram
 - Preventive Cardiology and the **Framingham study**
 - **The Lipid Hypothesis**
- Framingham study started 1948 found raised cholesterol to be a key risk factor for CVD
 - Every 1% reduction in cholesterol leads to a 2% reduction in CVD
- Goldstein and Brown discovered the cause of Familial Hypercholesterolaemia (FH) – faulty LDL receptor
- FH associated with 400% increase in CVD risk in young adults
- 1985 Goldstein and Brown win Nobel prize for their work
- 1987 Statins lower LDL and reduce the risk of CVD by up to 40%

4

ONE HUNDRED AND FIFTY YEARS OF DEMONISING CHOLESTEROL

- National Cholesterol Consensus Conference 1984 in the US
- *"It has been established beyond a reasonable doubt that lowering definitely elevated blood cholesterol levels (specifically, blood levels of Low Density Lipoprotein [LDL] Cholesterol will reduce the risk of heart attacks cause by coronary heart disease."* Conclusion of the NIH Consensus panel.
- Definition of high cholesterol lowered from 280mg/dl (7.2mmol/l) to 200mg/dl (5.2mmol/l)
- Cholesterol now like smoking?

5

ONE HUNDRED AND FIFTY YEARS OF DEMONIZING CHOLESTEROL



6

ONE HUNDRED AND FIFTY YEARS OF DEMONISING CHOLESTEROL

- "Photos taken inside clogged city sewer pipes look nearly identical to medical photos of the blood vessels of patients who have spent a lifetime gorging on fried chicken, sausage and bacon. 'It's like your arteries,' said John Parker, environmental compliance inspector with the city's Water and Sewer dept. 'Grease builds up in there. It's gory.'" *Savannah Morning News*.

7

ONE HUNDRED AND FIFTY YEARS OF DEMONISING CHOLESTEROL

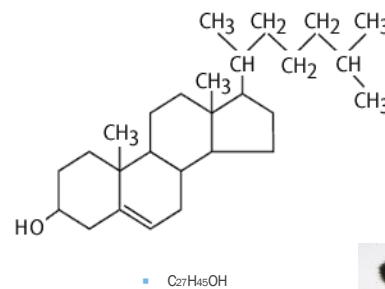


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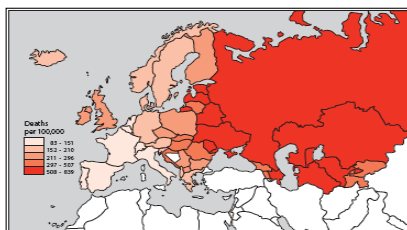
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CHOLESTEROL IS GOOD FOR YOU

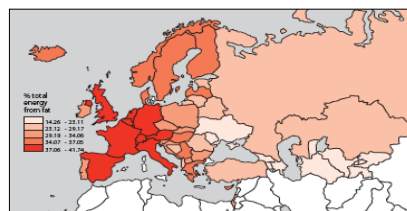


10

Deaths from heart disease



Energy from fat in the diet



<http://www.boninstats.org/uploads/documents/5/SPDE.pdf>

11

CONTRADICTIONS AROUND

COUNTRY	SATURATED FAT INTAKE	CHD DEATHS Per 100/000/yr (men < 65)	CHOLESTEROL LEVELS
Georgia	5.2%	235	5.0mmol/l
Azerbaijan	5.7%	219	5.0mmol/l
Ukraine	7.6%	208	5.1mmol/l
Russia	8.3%	267	5.1mmol/l
Israel	8.6%	44	5.6mmol/l
Spain	10.9%	33	5.6mmol/l
Italy	11.8%	36	5.9mmol/l
UK	13.5%	76	6.0mmol/l
Switzerland	15.3%	32	6.4mmol/l
France	15.5%	24	5.9mmol/l

12

CONTRADICTIONS - JAPAN

- Fat consumption has increased 400% in last fifty years
- Cholesterol levels have increased 3.9mmol/l to 5.1mmol/l
- CHD rate fallen 60%
- Rate of stroke has fallen 7-fold

Ueshima H: 'Explanation for the Japanese Paradox: Prevention of Increase in Coronary Heart Disease and Reduction in Stroke.' J Atherosclerosis and Thrombosis. 2007; 14:278-286

13

CONTRADICTIONS?

- **Evacetrapib** (A drug that you have not heard of, and never will hear of)
- The failure of evacetrapib treatment to produce any clinical benefit despite dramatically elevating serum levels of high-density lipoprotein cholesterol by an average 130% and substantially **dropping levels of low-density lipoprotein cholesterol by a mean 37%** pretty much spells the end of the cholesterol ester transfer protein (CETP) inhibitors as drug candidates
- LDL lowered 37% and **no** effect of CVD
- A classic black swan

<http://www.mdedge.com/ecardiologynews/article/108182/lipid-disorders/accelerate-evacetrapib-clinical-failure-sinks-lipid>

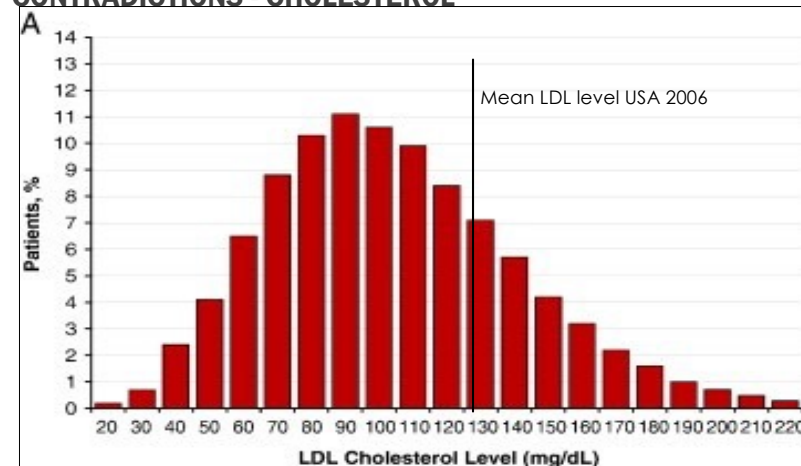
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CONTRADICTIONS - CHOLESTEROL

- ➔ Data from 231,986 hospitalizations from 541 hospitals on admission with MI
- ➔ Mean LDL levels were 104.9mg/dl (This is LDL 2.6mmol/l)

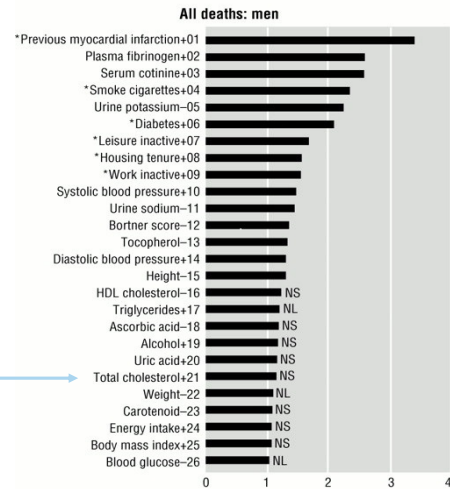
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CONTRADICTIONS - CHOLESTEROL



16

CONTRADICTIONS - CHOLESTEROL



*Comparison of the prediction by 27 different factors of coronary heart disease and death in men and women of the Scottish heart health study: cohort study. BMJ 1997;315:722

17

CONTRADICTIONS - FAMILIAL HYPERCHOLESTEROLAEMIA

FAMILIAL HYPERCHOLESTEROLEMIA: A GENETIC AND METABOLIC STUDY¹

WILLIAM R. HARLAN, JR.,² JOHN B. GRAHAM,³ AND E. HARVEY ESTES⁴

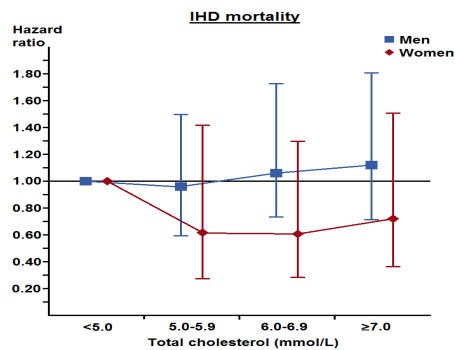
MEDICINE

1966 Vol. 45, No. 2

Our studies provide no evidence that familial hypercholesterolemia appreciably shortens the life of affected individuals, either male or female. On the contrary, they show that high levels of serum cholesterol are clearly compatible with survival into the seventh and eighth decades.

18

CHOLESTEROL - CONTRADICTIONS



<http://online.library.wiley.com/doi/10.1111/j.1365-2214.2011.01726.x/pdf>

19

THE IMPOSSIBILITY OF THE CHOLESTEROL HYPOTHESIS



20

WHAT IS CHOLESTEROL



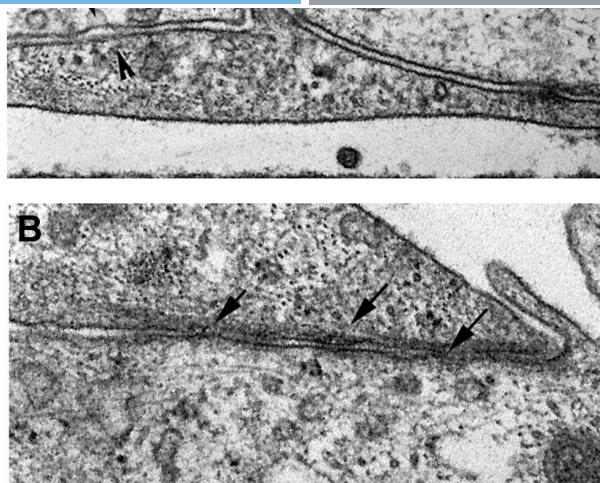
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WHAT IS A LIPOPROTEIN - SCALE



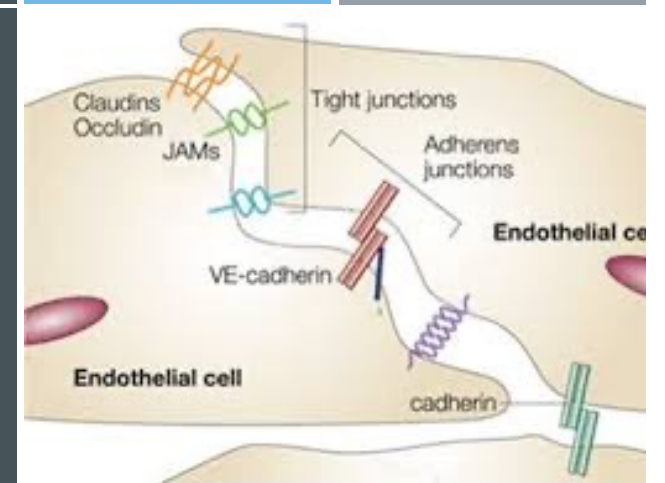
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THE IMPOSSIBILITY OF THE CHOLESTEROL HYPOTHESIS



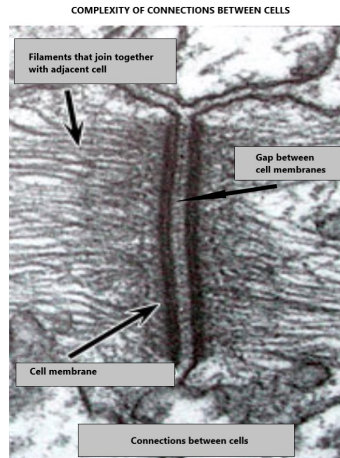
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THE IMPOSSIBILITY OF THE CHOLESTEROL HYPOTHESIS



24

THE IMPOSSIBILITY OF THE CHOLESTEROL HYPOTHESIS

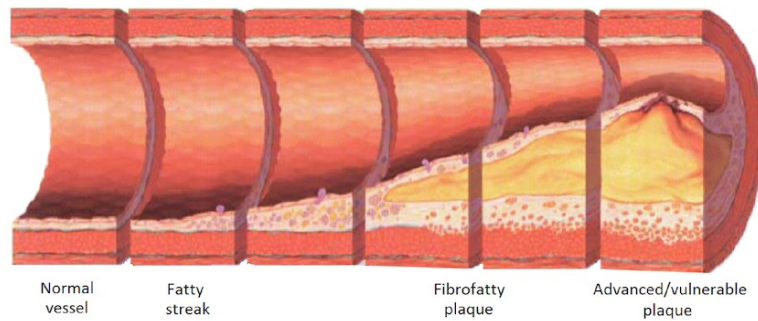


25

START AGAIN –
WHAT IS GOING
ON?



26



Atherosclerosis

27

START AGAIN

- Only in large arteries
- Never in veins
- Almost never in the lungs (pulmonary circulation)
- SLAD

28

Q-RISK 3

- Age
- Sex
- Smoking
- Diabetes
- Total cholesterol/HDL ratio
- Raised blood pressure.
- Variation in two blood pressure readings
- BMI
- Chronic kidney disease
- Rheumatoid arthritis
- Systemic Lupus Erythematosus (SLE)
- History of migraines
- Severe mental illness
- On atypical antipsychotic medication
- Using steroid tablets
- Atrial fibrillation
- Diagnosis of erectile dysfunction
- Angina, or heart attack in first degree relative under the age of 60
- Ethnicity
- Postcode

29

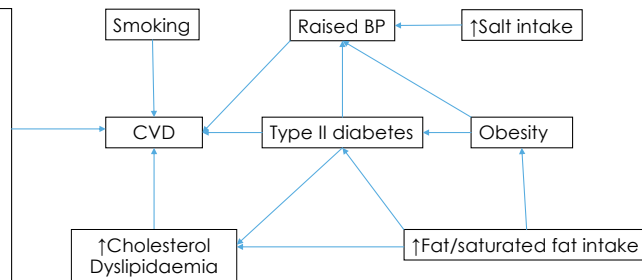
PILE OF STONES

'Science is built up of facts, as a house is built of stones; but an accumulation of facts is no more a science than a heap of stones is a house.' **Henri Poincaré**

30

THE RISE OF PREVENTATIVE MEDICINE (UK QRISK3)

Ethnicity
Atrial Fibrillation
Age
Sex
Rh Arthritis
CKD
Post-Code
Family History
SLE
Severe mental illness
Atypical antipsychotic
Taking steroid tablet
Erectile dysfunction



31

THROMBOGENIC HYPOTHESIS

'Rokitansky proposed that the disease is the result of an excessive intimal deposition of blood components (blood clots) including fibrin. He maintained that localized thickening, atheromatous changes and calcification of the arterial wall are due to the repeated deposition of blood elements and their subsequent metamorphosis and degeneration on the lining membrane of the vascular wall.'

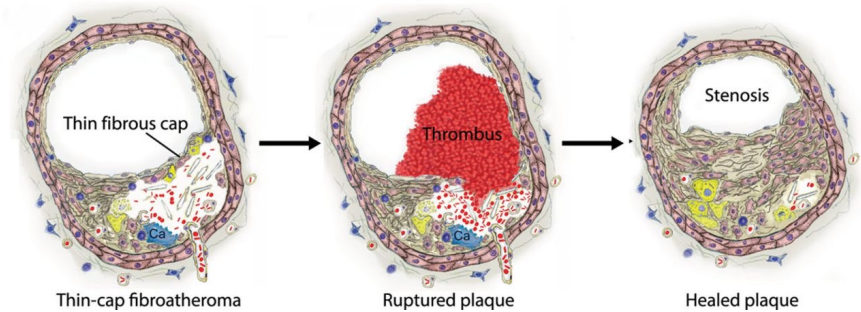
32

THROMBOGENIC HYPOTHESIS

- *'After many years of neglect, the role of thrombosis in myocardial infarction is being reassessed. It is increasingly clear that all aspects of the haemostatic [blood clotting] system are involved: not only in the acute occlusive event, but also in all stages of atherosclerotic plaque development from the initiation of atherogenesis to the expansion and growth of large plaques.'* **Elsbeth Smith**

33

PLAQUE PROGRESSION



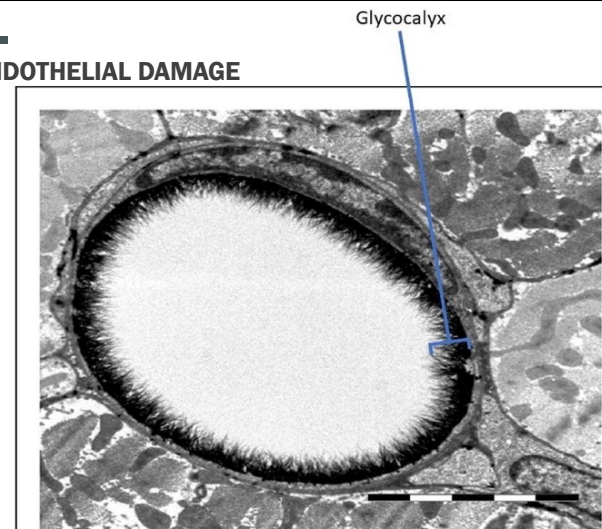
34

THREE STAGE PROCESS

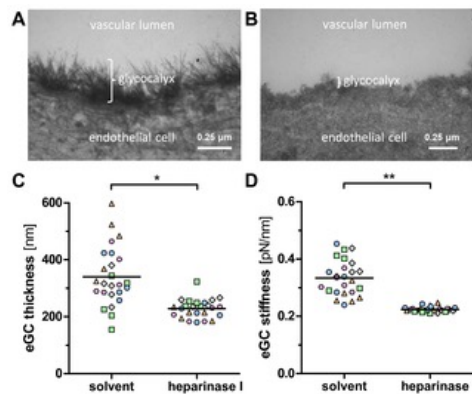
- Damage the endothelium
- Clot forms
- Repair systems go to work

35

ENDOTHELIAL DAMAGE



36



ENDOTHELIAL DAMAGE

THE PROCESS

- Smoking
- 'All these processes lead to endothelial dysfunction. Direct physical effects of smoke compounds and produced reactive oxygen species (ROS) lead to endothelial cell loss by apoptosis or necrosis' *
- Wood smoke
- Air pollution
- Coal mining etc.

<https://www.abajournal.com/dol/10.1161/ajph.113.300156>

THE PROCESS - LEAD

- New estimates suggest that 256,000 premature deaths from cardiovascular disease -- including 185,000 deaths from ischemic heart disease -- in the USA may be linked to historical lead exposure in middle-aged and older adults

Low-level lead exposure and mortality in US adults: a population-based cohort study. *The Lancet Public Health*, 2018 DOI: [10.1016/S2468-2667\(18\)30025-2](https://doi.org/10.1016/S2468-2667(18)30025-2)

THE PROCESS - LEAD

- '...the data discussed in this review point to the involvement of the cardiovascular system as a major target of long-term toxicity (of lead), ranging from endothelial dysfunction to pro-coagulative transformation of RBC (Red Blood Cells). Taken together, these effects expose all organs and systems to increased thrombotic risk.'

<https://www.mdpi.com/1422-0067/22/12/6604>

THE PROCESS



41

THE PROCESS – SICKLE CELL DISEASE

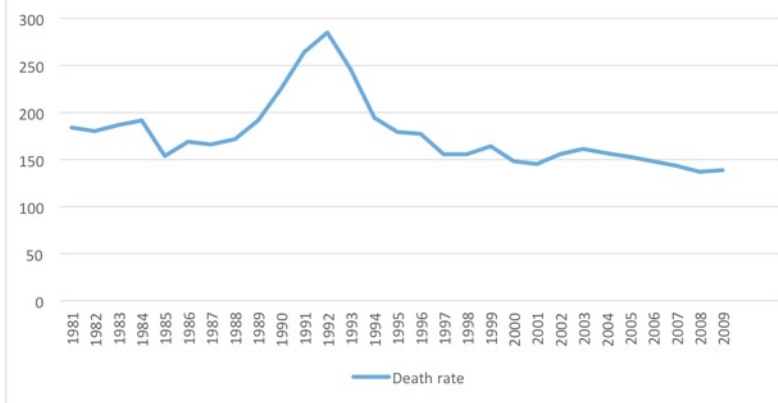
- A recent study of spleens resected from Sickle Cell Disease (SCD) patients... has shown that there were **consistent vascular lesions affecting large arteries**. The same finding was also shown in studies of brains from SCD patients who developed cerebrovascular accidents (strokes). **These lesions were attributed to the rigidity of sickled erythrocytes causing mechanical injury to the endothelial cells.**
- ...contributing to **large vessel endothelial injury, vascular intimal hyperplasia and thrombosis**

<https://www.sciencedirect.com/science/article/pii/S1533316707000192>

42

THE PROCESS – STRESS/STRAIN

Death rate men under 65 per 100,000 Lithuania



43

THE PROCESS – STRESS/STRAIN

- 'An unfavourable pattern of psychosocial risk factors for CHD: **job strain, social isolation, depression and vital exhaustion characterised Vilnius men, who also showed an attenuated cortisol response to the laboratory stress test**. This stress response has earlier been shown in states of chronic stress; loss of dynamic capacity to respond to new demands may be a predisposing factor for disease **Vilnius men had more peripheral atherosclerosis; thicker intima media, more and larger plaques and greater (arterial) stiffness.**'

<https://www.dissertations.se/dissertation/44356583/>

44

THE PROCESS - DIABETES

- Loss of Endothelial Glycocalyx During Acute Hyperglycaemia Coincides With Endothelial Dysfunction and Coagulation Activation In Vivo.'
- *'Hyperglycaemia is associated with increased susceptibility to atherothrombotic stimuli. The glycocalyx, a layer of proteoglycans covering the endothelium, is involved in the protective capacity of the vessel wall.'*

<https://diabetes.diabetesjournals.org/content/55/2/480>

45

THE PROCESS

- Endothelial damage
- Clot formation
- Repair

46

THE PROCESS - REPAIR

- *Cardiovascular Adverse Events in Patients With Cancer Treated With Bevacizumab: A Meta-Analysis of More Than 20 000 Patients.'*
- *'Treatment with bevacizumab increases the risk of arterial adverse events, particularly cardiac and cerebral ischemia, venous adverse events, bleeding, and arterial hypertension. This risk is additionally increased with high doses of bevacizumab.'*

<https://www.ahajournals.org/doi/10.1161/JAHA.117.006278>

47

THE PROCESS - REPAIR (AVASTIN)

- Increased risk of stroke = **1,129%**
- Increased risk of heart attack = **416%**

48