ESC European Society of Cardiology

European Heart Journal (2021) **42**, 4781–4790
doi:10.1093/eurheartj/ehab438

CARDIOPULSE

Global Spotlights

The changing *Nature* of atherosclerosis: what we thought we knew, what we think we know, and what we have to learn

Peter Libby *

Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 77 Avenue Louis Pasteur, Boston, MA 02115, USA

When the science journal *Nature* asked me to provide an Insight Review on Inflammation in Atherosclerosis in 2002,[1] the field had already matured to a point that we had strong experimental evidence and some human biomarker data that suggested the operation of inflammatory pathways in atherosclerosis (*Figure 1*). Yet, there was then considerable skepticism regarding this concept in many quarters. We possessed convincing evidence that low-density lipoprotein (LDL) was causal in atherosclerosis. We had great enthusiasm for the statin class of drugs which targeted LDL and reduced events. We had reason to suspect that pleiotropic effects of statins could lower inflammation, but a direct anti-inflammatory therapy that did not alter lipids was far from a reality. We were generally excited by the notion that raising high-density lipoproteins (HDL) would confer cardiovascular benefit, based on strong observational epidemiology and extensive in vitro data. Most discounted a causal contribution of triglyceride-rich lipoproteins to atherosclerosis outcomes, as adjustment for HDL, the putative protective factor, attenuated the relationship between triglycerides and cardiovascular events. The dénouement of that chapter, recounted in the current review, taught us humility and reminds us of the pitfalls of observational studies. We were in the throes of working out the cellular and molecular mechanisms of the formation of the thin-capped fibroatheroma, the so-called 'vulnerable plaque' responsible for plaque rupture, thrombosis, and many myocardial infarctions. We had no anti-diabetic medications that could reduce cardiovascular events, a source of considerable frustration to clinicians. The idea of a 'precision' allocation of therapies that targeted inflammation was purely theoretical.

How things have changed in the almost two ensuing decades! When invited to contribute another review about atherosclerosis, I chose to focus on *The Changing Landscape of Atherosclerosis*.[2] My mentor, Dr Eugene Braunwald, taught me when I was a student to keep my eyes on a moving target. This advice has informed many of my choices in research. It contributed to my reluctance to accept received notions without critical examination and to my striving to pursue new ideas even if they were unpopular. My Northern California upbringing and involvement in the civil rights and Free Speech Movements as a student in Berkeley in the 1960s also contributed to my contrarian streak, I must confess. Another aspect colors my approach to research and thinking about the disease: I stay close to patients and strive to remain abreast of the clinical as well as the scientific literature. I have always practiced both inpatient and ambulatory cardiovascular medicine and recently started a new 'CHIP clinic' where I see patients with clonal hematopoiesis to counsel them regarding cardiovascular risk. Having clinical activity close to my laboratory interests enriches in both directions, fosters new ideas, and spurs me to keep trying to solve clinically important questions. It reminds me that people are not just big mice without fur.

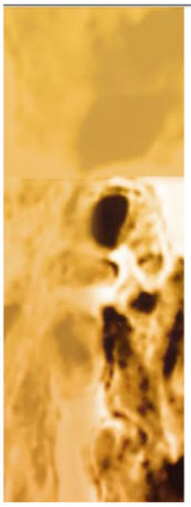
Table 1 shown here from the current *Nature* review juxtaposes some of the 'then and now' precepts. I had originally entitled these rubrics 'Point' and 'Counterpoint', but I was asked to change this. (Was I trying to work in "counterpoint" in subtle homage to J.S. Bach, whose work I revere?[3])

Of course, with strict word limitations, one cannot be encyclopedic, and I could not reference many who have contributed so decisively to the field. I took a deliberately provocative stance, for purposes of argument, and apologize if I have not presented a sufficiently nuanced view. Perhaps anti-oxidant therapies would show clinical benefit if started earlier? Maybe a functional subclass of HDL will prove able to confer athero-protection?

The advances of the last two decades provide some grounds for satisfaction, but the things we got wrong, and the unfinished stories should keep us humble and motivated to dig ever deeper. How many of the arguments I present today will seem antique or even erroneous 20 years hence?

I was very flattered when the editors of the Newsletter of the ESC Working Group on Atherosclerosis and Vascular Biology reached out to me to tell me that they had selected an article that I had published as the paper of the month. They asked me to write a brief commentary. I was happy to do so.[4] Accordingly, I penned something a bit personal about how our cherished notions rise or fall over time

* Corresponding author. Tel: +1 617 525 4383, Fax: +1 617525 4400, Email: plibby@bwh.harvard.edu



insight review articles

Inflammation in atherosclerosis

Peter Libby

Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts 02115, USA (e-mail: plibby@rics.bwh.harvard.edu)

Abundant data link hypercholesterolaemia to atherogenesis. However, only recently have we appreciated that inflammatory mechanisms couple dyslipidaemia to atheroma formation. Leukocyte recruitment and expression of pro-inflammatory cytokines characterize early atherogenesis, and malfunction of inflammatory mediators mutes atheroma formation in mice. Moreover, inflammatory pathways promote thrombosis, a late and dreaded complication of atherosclerosis responsible for myocardial infarctions and most strokes. The new appreciation of the role of inflammation in atherosclerosis provides a mechanistic framework for understanding the clinical benefits of lipid-lowering therapies. Identifying the triggers for inflammation and unravelling the details of inflammatory pathways may eventually furnish new therapeutic targets.

Figure 1 Atherosclerosis insight in *Nature* 20 years ago.[1]

Table 1 Changing views on atherosclerosis

Past	Present
Atherosclerosis predominantly affects developed countries	Developing countries now bear the greatest burden of atherosclerosis
Coronary thrombosis affects primarily middle-aged white men	Women, younger individuals, individuals from a range of ethnic backgrounds, and the very old suffer increasingly from acute coronary syndromes
Atherosclerosis is a lipid storage disease	Inflammation links dyslipidaemia and other risk factors to atherogenesis
Oxidized LDL drives atherosclerosis	Native or aggregated LDL drives atherogenesis
HDL cholesterol protects against atherosclerosis	TGRL participates causally in atherosclerosis
Thin-capped fibroatheromata are vulnerable plaques	The 'vulnerable plaque' is a misnomer; superficial erosion is an increasing cause of arterial thrombosis
Atherosclerosis is an inevitable, steady, and degenerative accompaniment to ageing	Atherosclerosis evolves episodically and can regress, and lifestyle and medical measures can modulate the process

TGRL, triglyceride-rich lipoproteins.

depending on emerging evidence contrasting my published views from almost two decades ago to reflections of the field of atherosclerosis today. As the topic may interest readers of the *European Heart Journal* beyond the Vascular Biology Working Group, I am pleased that the editors of CardioPulse were interested in a version of this brief personal perspective.

Funding

P.L. receives funding support from the National Heart, Lung, and Blood Institute (1R01HL134892), the American Heart Association (18CSA34080399), the RRM Charitable Fund, and the Simard Fund.

Conflict of interest: P.L. is an unpaid consultant to, or involved in clinical trials for Amgen, AstraZeneca, Baim Institute, Beren Therapeutics, Esperion Therapeutics, Genentech, Kancera, Kowa Pharmaceuticals, Medimmune, Merck, Norvo Nordisk, Novartis, Pfizer, and Sanofi-Regeneron. P.L. is a member of scientific advisory board for Amgen, Caristo, Cartesian, Corvidia Therapeutics, CSL Behring, DalCor Pharmaceuticals, Dewpoint, Kowa Pharmaceuticals, Olatec Therapeutics, Medimmune, Novartis, PlaqueTec, and XBiotech, Inc. P.L.'s laboratory has received research funding in the last 2 years from Novartis. P.L. is on the Board of Directors of XBiotech, Inc. P.L. has a financial interest in Xbiotech, a company developing therapeutic human antibodies. P.L.'s interests were reviewed and are managed by Brigham and Women's Hospital and Partners HealthCare in accordance with their conflict-of-interest policies.

Data availability

No new data were generated or analysed in support of this research.

References

1. Libby P. Inflammation in atherosclerosis. *Nature* 2002;**420**:868–874.
2. Libby P. The changing landscape of atherosclerosis. *Nature* 2021;**592**:524–533.
3. Libby P. Johann Sebastian Bach: A healer in his time. *Circ Res* 2019;**124**:1303–1308.
4. Libby P, The changing landscape of atherosclerosis Commented by the ESC WG on Atherosclerosis and Vascular Biology – June Newsletter. *Working Group on Atherosclerosis and Vascular Biology*; 2021.