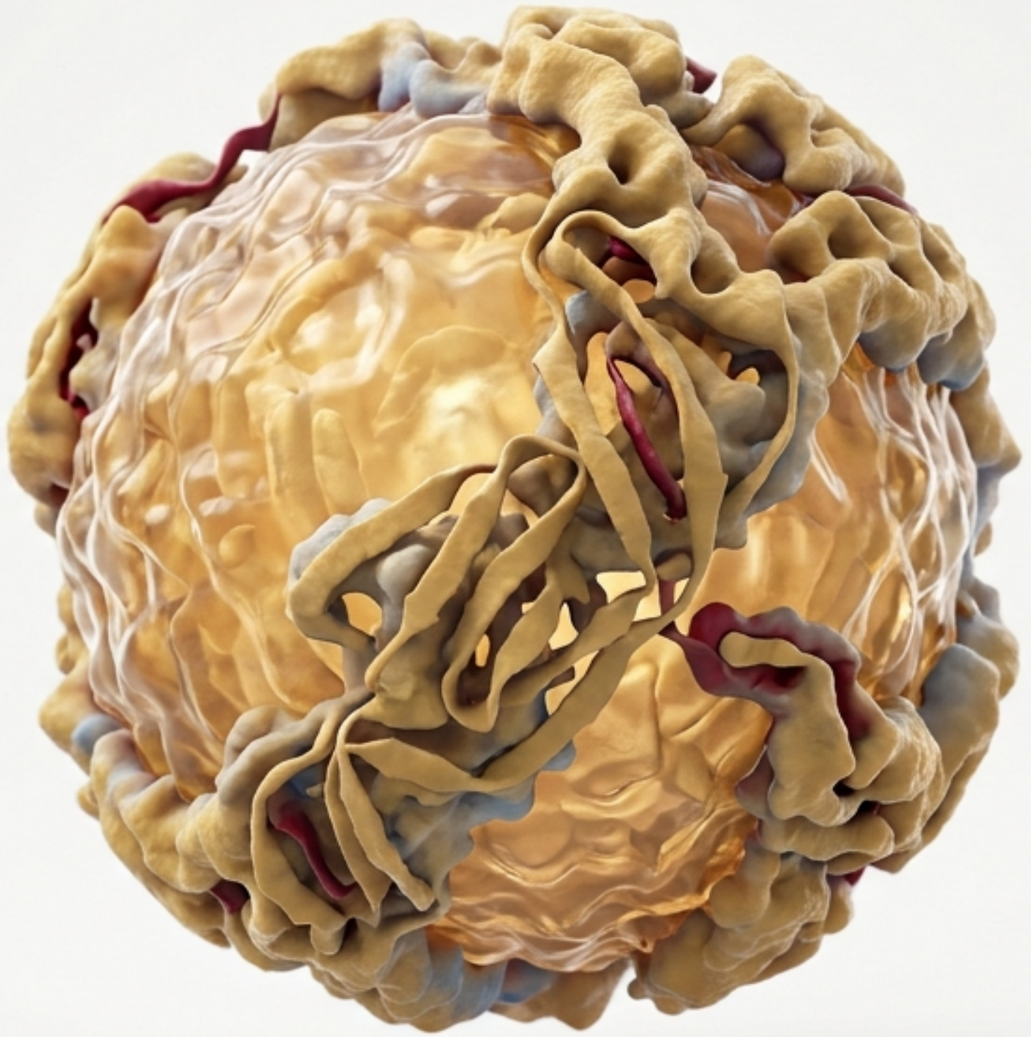
The 5-Gram Paradox

Thermodynamic Exchange, Tissue Needs, and the True Biological Floor of Human Cholesterol



Your Blood Carries the Weight of a Nickel

The average American adult carries about 5.6 grams of cholesterol circulating in their plasma at any given moment.

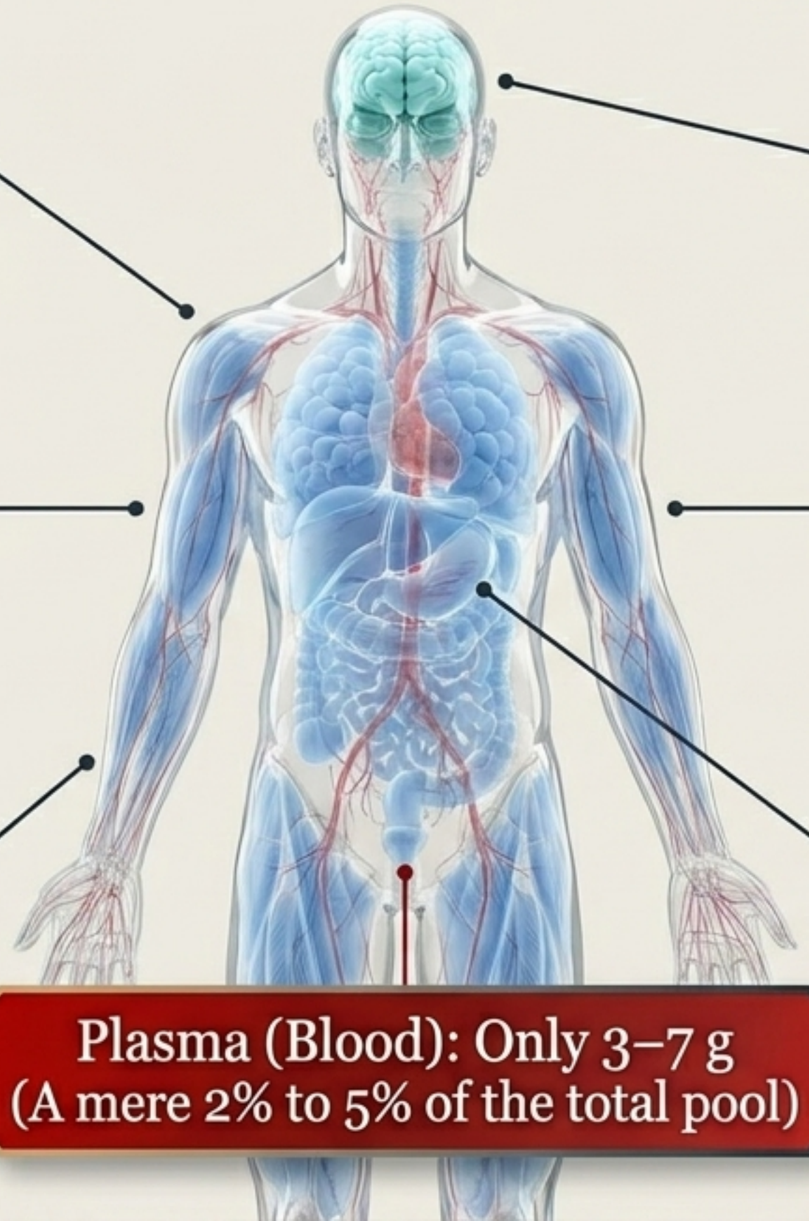
Careful mass-balance modeling reveals a staggering truth: the body's actual transport requirement is less than half of that (1.5 to 2.7 grams).

To understand this massive biological surplus, we must separate two deeply conflated questions: **What the body needs** vs. **What the blood needs.**

The Two Questions of Modern Cardiology

	Question 1: Does my body need cholesterol?	Question 2: Does my lipid panel reflect that need?
The Reality	YES. Emphatically. It builds cell membranes, synthesizes vitamin D, and forms steroid hormones.	NO. The lipid panel measures the liquid fraction of blood—a transport system, not a whole-body inventory.
The Implication	Without it, eukaryotic life does not exist.	Humans can live entirely healthy lives with LDL cholesterol below 30 mg/dL.

The 150-Gram Human Inventory



Total Body Pool: 120–150 g
(The Master Inventory)

Brain / CNS: ~30–35 g
(23% of total body cholesterol)

Skeletal Muscle: ~25–30 g

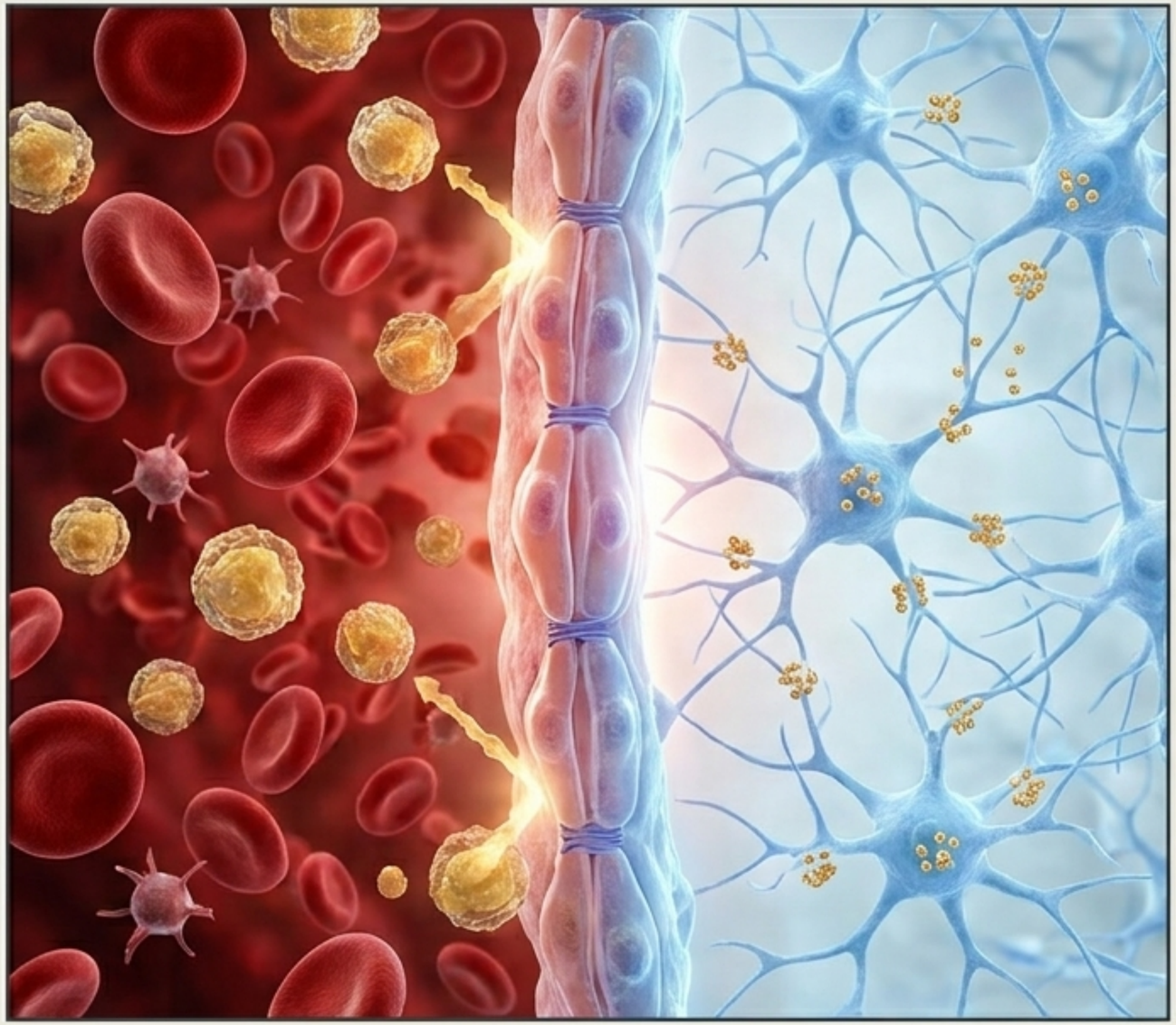
Connective & Adipose:
~25–32 g

Skin: ~12–18 g

Liver: ~4–6 g
(Working stock)

Plasma (Blood): Only 3–7 g
(A mere 2% to 5% of the total pool)

The Brain is an Island



25% of the Supply, 0% from the Blood

The brain contains a quarter of the body's total cholesterol, packed into just 2% of body weight.

Metabolically Isolated

The blood-brain barrier is completely impermeable to lipoprotein cholesterol. Astrocytes produce it locally, shuttling it to neurons via ApoE.

The Exit Route

The only meaningful exit is enzymatic conversion into 24S-hydroxycholesterol, which crosses the BBB to be cleared in plasma.

Clinical Takeaway

Plasma-lowering therapies (Statins, PCSK9i) do not directly deplete brain cholesterol.

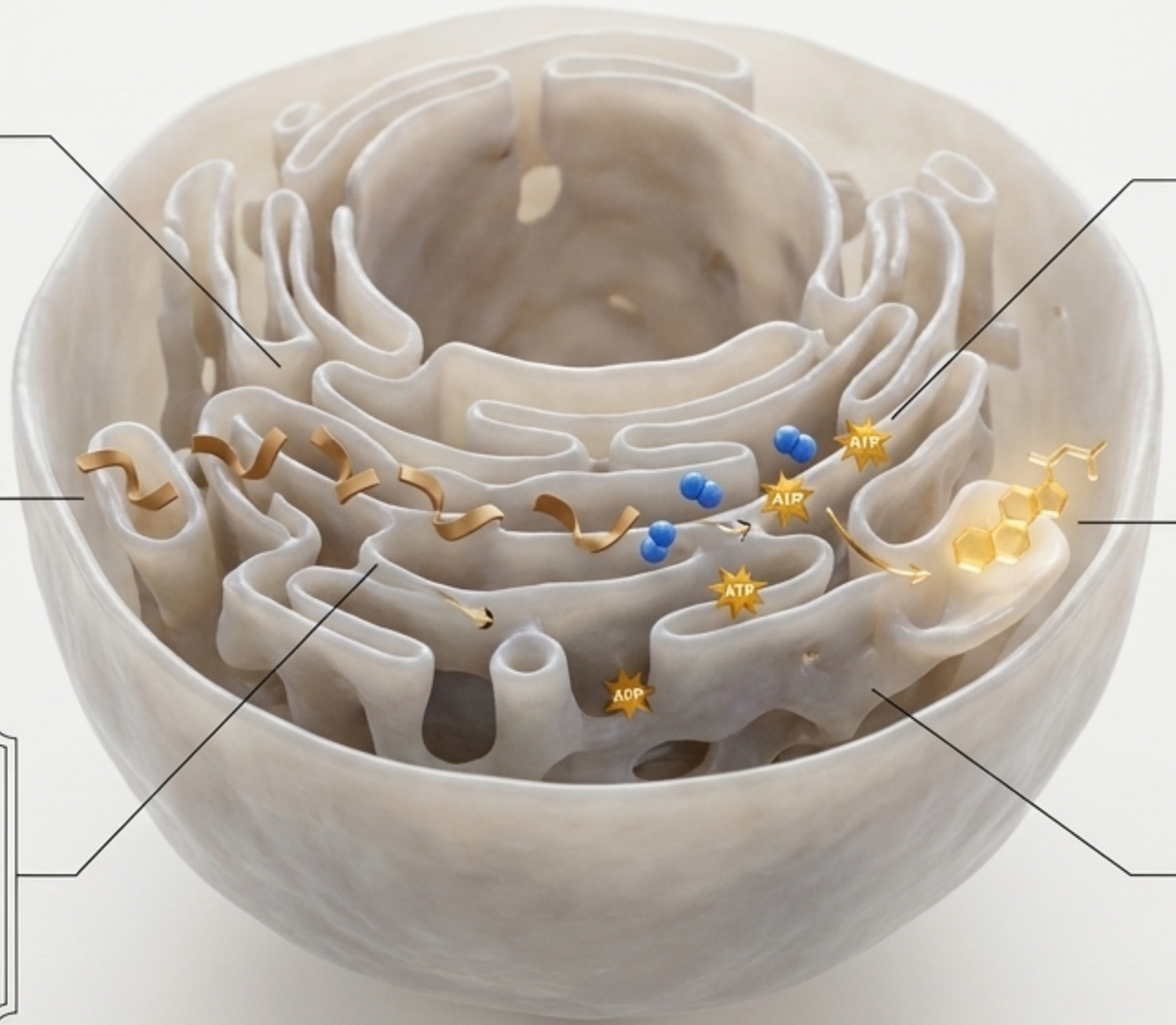
Every Cell is a Factory

The Mevalonate Pathway.

Almost every nucleated cell in the human body can synthesize its own cholesterol.

The Energetic Tax

Producing a single cholesterol molecule requires an immense biological cost: 11 molecules of oxygen and ~100 ATP equivalents.



The Regulation.

SREBP2/SCAP/Insig sensors in the ER strictly monitor the accessible plasma membrane pool to suppress synthesis when full.

The Math.

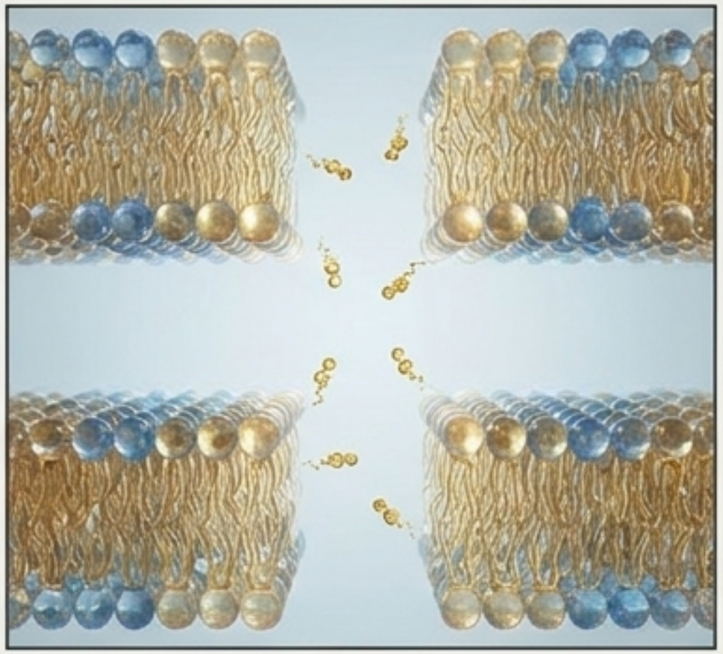
Whole-body synthesis runs at ~700 mg/day (10 mg/kg/day). The liver contributes only ~10%. Tissues make the other 90%.

If Tissues Make Their Own, What is the Blood For?

01. Energy Highway

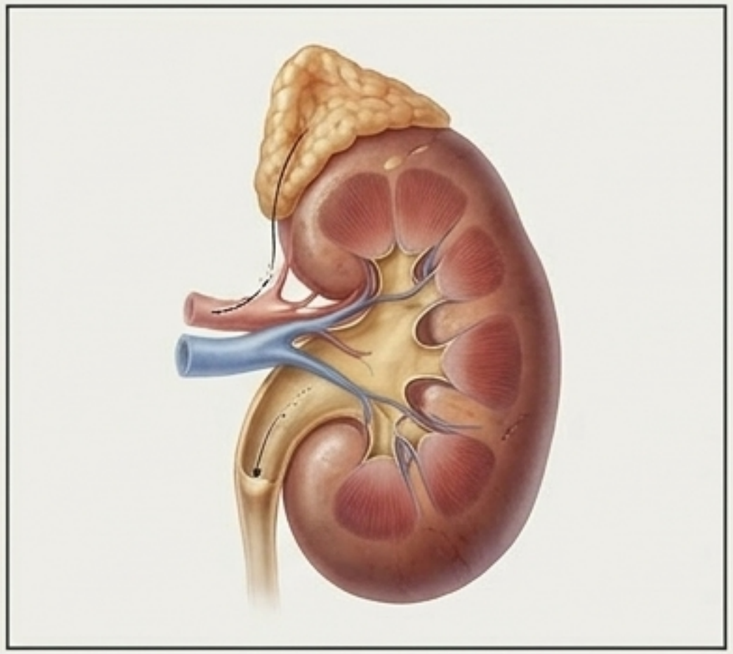
VLDL particles distribute triglycerides (fat) for energy. LDL (fat) for energy. LDL is a kinetic byproduct of this energy delivery.

02. Thermodynamic Buffer



Thermodynamic Buffer
Maintaining chemical equilibrium and uniform sterol activity across all cell membranes via spontaneous exchange.

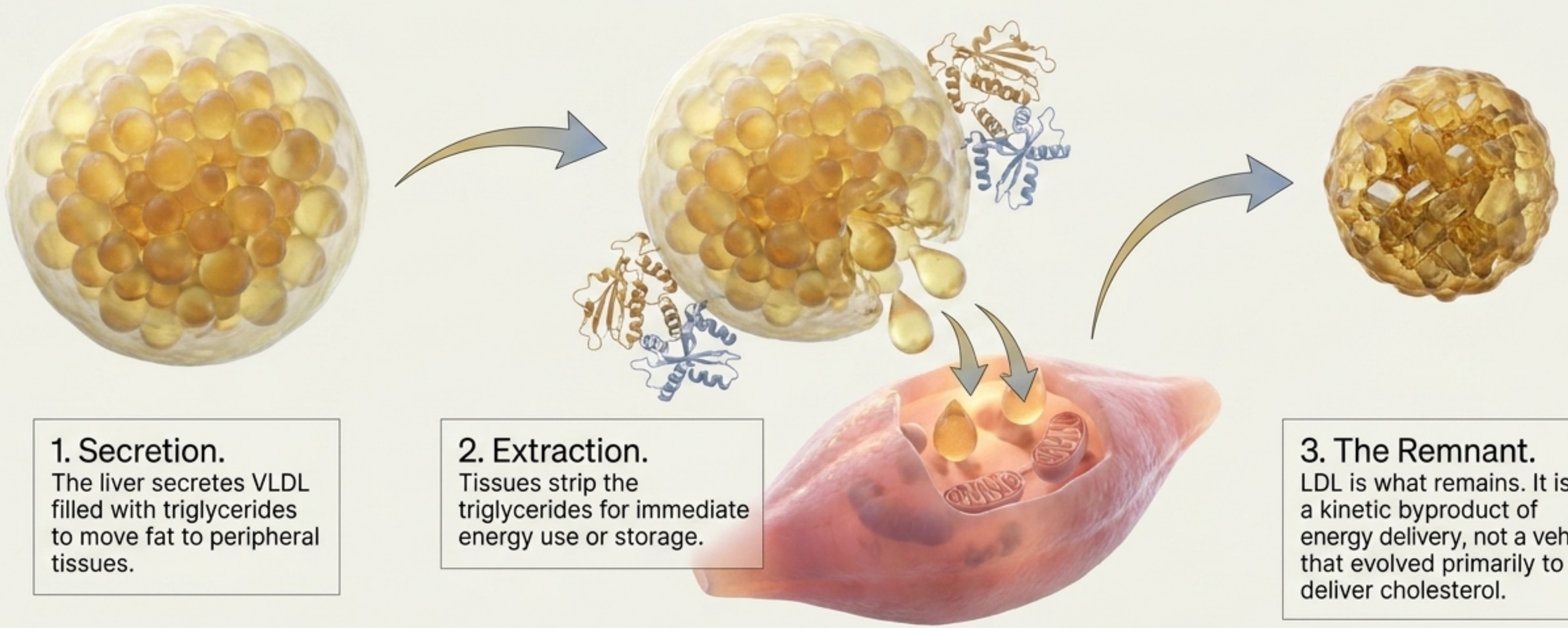
03. Niche Delivery



Providing raw exogenous materials to a small subset of high-demand tissues (adrenals, gonads) for steroid hormone synthesis.

Function 01: Energy Transport Byproduct

Lifespan of a Lipid



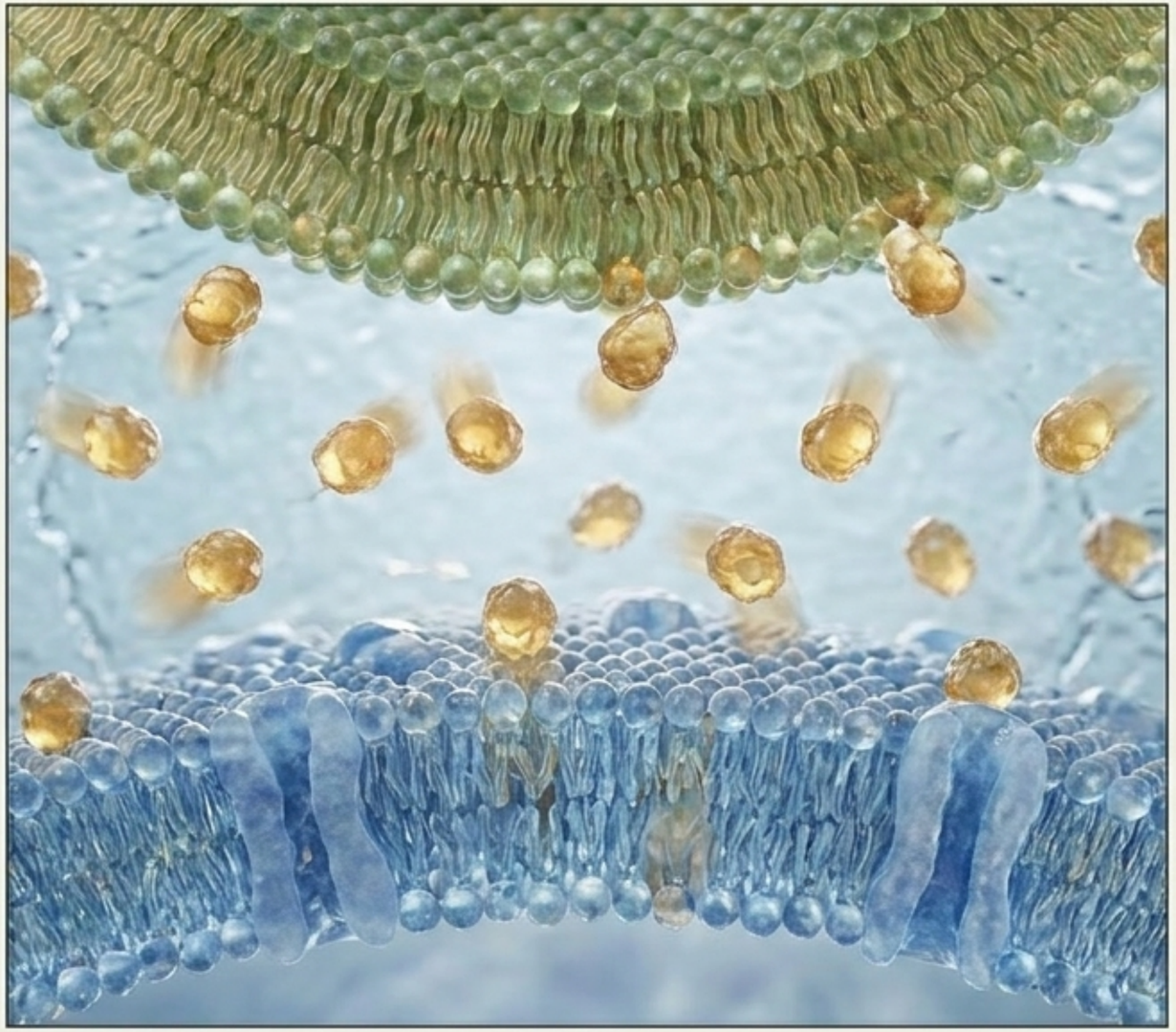
1. Secretion.
The liver secretes VLDL filled with triglycerides to move fat to peripheral tissues.

2. Extraction.
Tissues strip the triglycerides for immediate energy use or storage.

3. The Remnant.
LDL is what remains. It is a kinetic byproduct of energy delivery, not a vehicle that evolved primarily to deliver cholesterol.

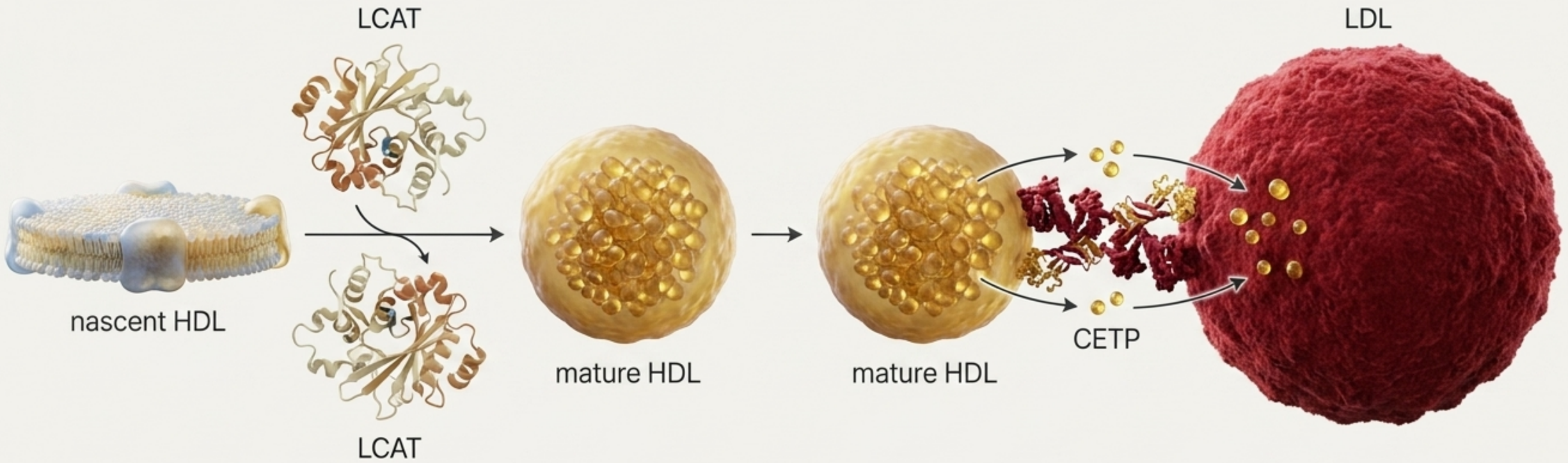
Function 02: The Kinetic Chemical-Potential Buffer

Free cholesterol on the surface of every lipoprotein is in continuous, spontaneous equilibrium with the cell membranes it encounters.



This passive aqueous diffusion smooths out moment-to-moment variations. It operates without receptors or energy or energy, ensuring uniform thermodynamic activity of cholesterol across all extracellular lipid surfaces.

Function 03: Maturation & Exchange Engines

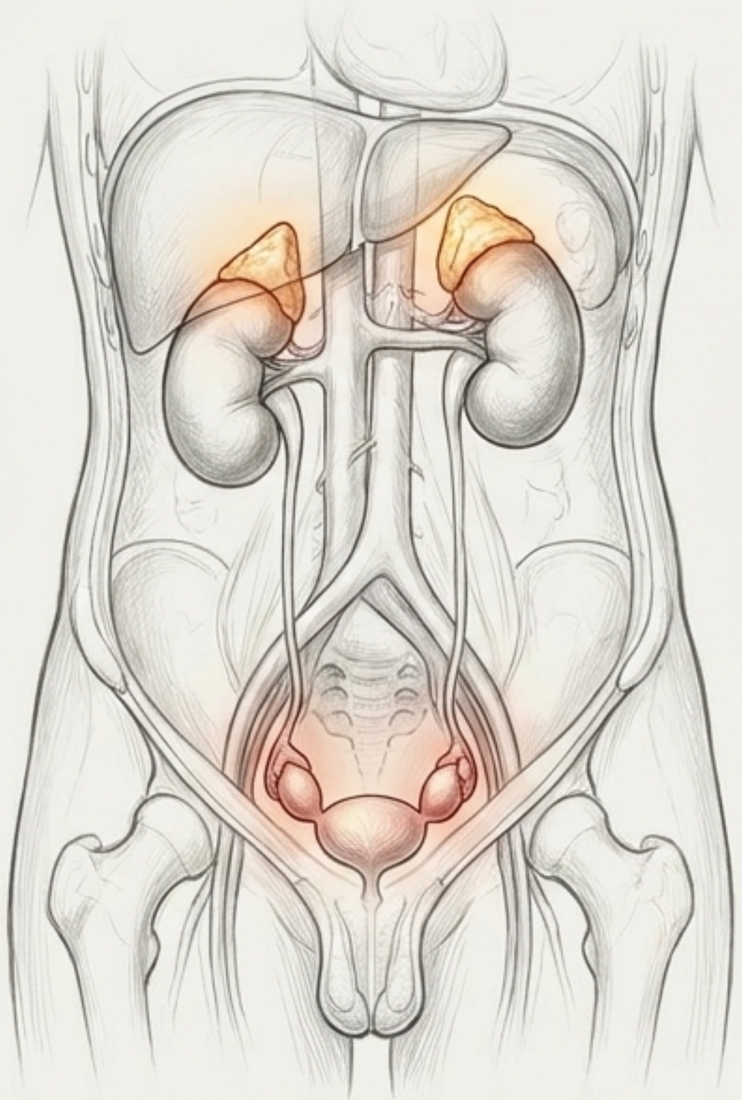


LCAT (Lecithin-cholesterol acyltransferase):
The compactor. It esterifies surface free cholesterol, forcing it into the hydrophobic core and maturing HDL into a sphere.

CETP (Cholesteryl ester transfer protein):
The trader. It shuttles esterified cholesterol from HDL to ApoB-containing particles (like LDL) in exchange for triglycerides.

The Result: LDL becomes enriched with cholesterol that has cycled through peripheral cells and HDL.

The Daily Delivery Quota



The Reality: Only a few specialized tissues have exogenous demands that exceed their local mevalonate pathway capacity under baseline conditions.

Adrenal Steroidogenesis:	~30–60 mg/day (Driven by LDLR and SR-B1 pathways to produce cortisol and aldosterone).
Gonadal Needs:	< 10 mg/day.

Total Net Obligate Demand:
For a nonpregnant adult, the total net demand drawn from the bloodstream is approximately 50 mg per day. (A tiny fraction of the 700 mg the body synthesizes daily).

The Structural Requirement

The Blueprint:
Before the blood can deliver any cholesterol, the transport vehicles themselves require surface free cholesterol just to physically hold together.

The Physics:
Free cholesterol (FC) intercalates between phospholipid chains, reducing permeability and providing mechanical stability to the liquid-ordered monolayer.

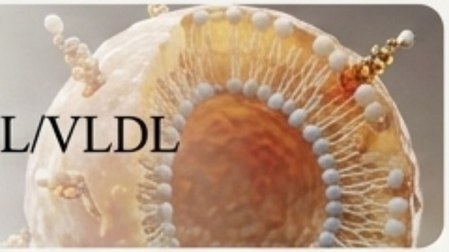
The Physics:
Free cholesterol (FC) intercalates between phospholipid chains, reducing water permeability and monolayer.

The Math: Summed across all circulating particle classes at typical counts, the blood requires ~25 to 30 mg/dL of structural surface free cholesterol simply to maintain the integrity of the fleet.

Calculating the Body's True Circulating Requirement

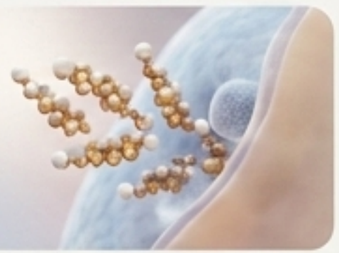
1. Structural Integrity

Surface Free Cholesterol for LDL/HDL/VLDL fleet (~45-55 mg/dL plasma FC total)



2. Delivery Buffer

Meeting the ~50 mg/day obligate exogenous tissue demand



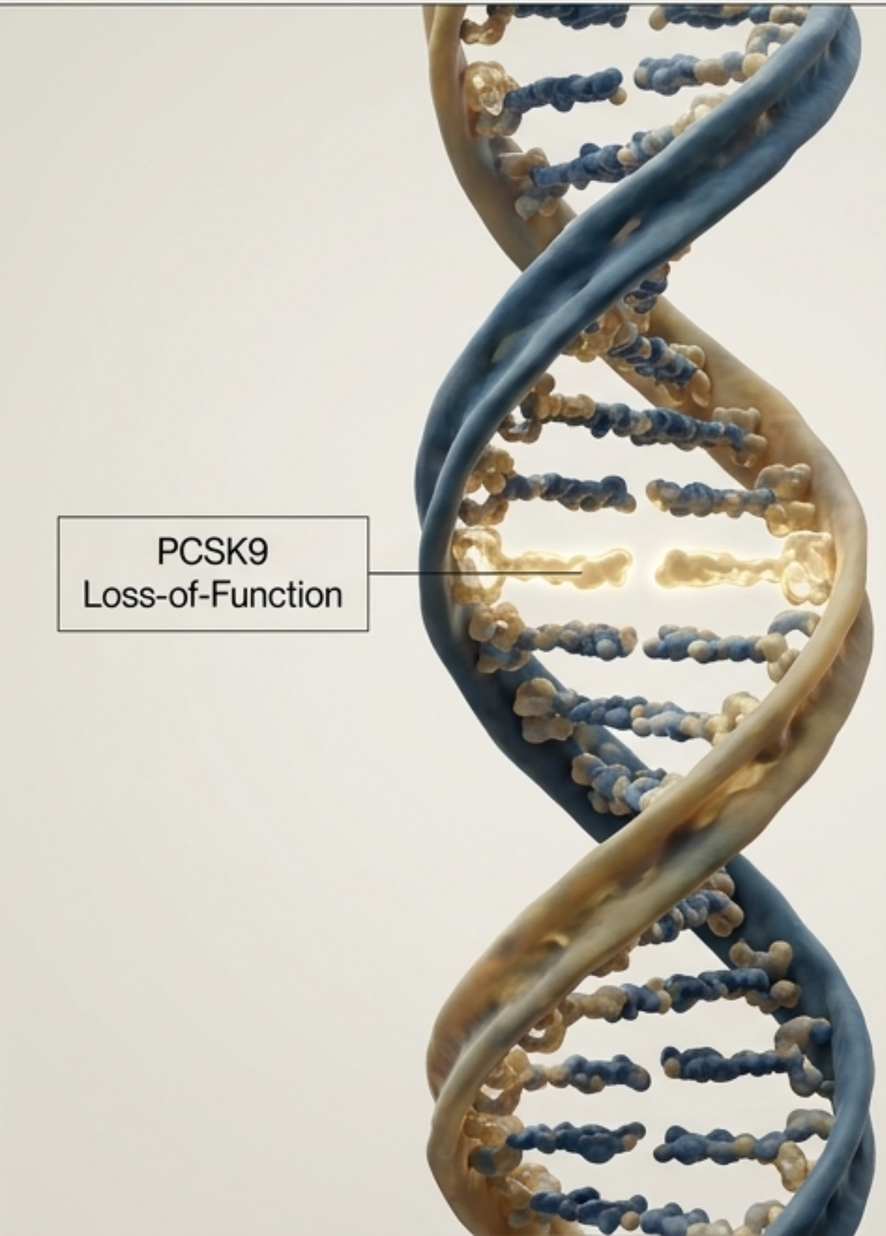
3. Core Cargo

Cholesteryl esters required for receptor-mediated delivery

The Modeled Floor: 50 to 90 mg/dL Total Cholesterol

Note: In absolute mass, this means only 1.5 to 2.7 grams of cholesterol is required to sustain transport across the entire 3-liter plasma volume.

Real Humans Live at the Model's Floor



The Genetic Case:
PCSK9 loss-of-function homozygotes (discovered via the Dallas Heart Study). These individuals clear plasma LDL aggressively their entire lives.

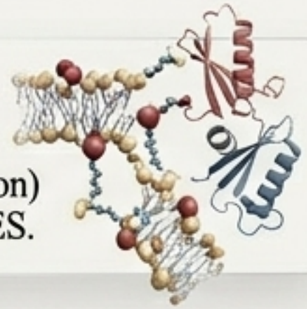
Lifelong Blood Levels:
LDL-C of 14 to 29 mg/dL.
Total Cholesterol of 50 to 80 mg/dL.

Health Status: Normal cognition. Normal fertility. Normal steroidogenesis. Zero observed abnormalities.

Conclusion: The calculated 50-90 mg/dL floor isn't just theoretical math; it is a proven, biologically viable human baseline.

Bounding the Safe Range from Above

1. The Trials:
FOURIER
(with Open-Label Extension)
& ODYSSEY OUTCOMES.



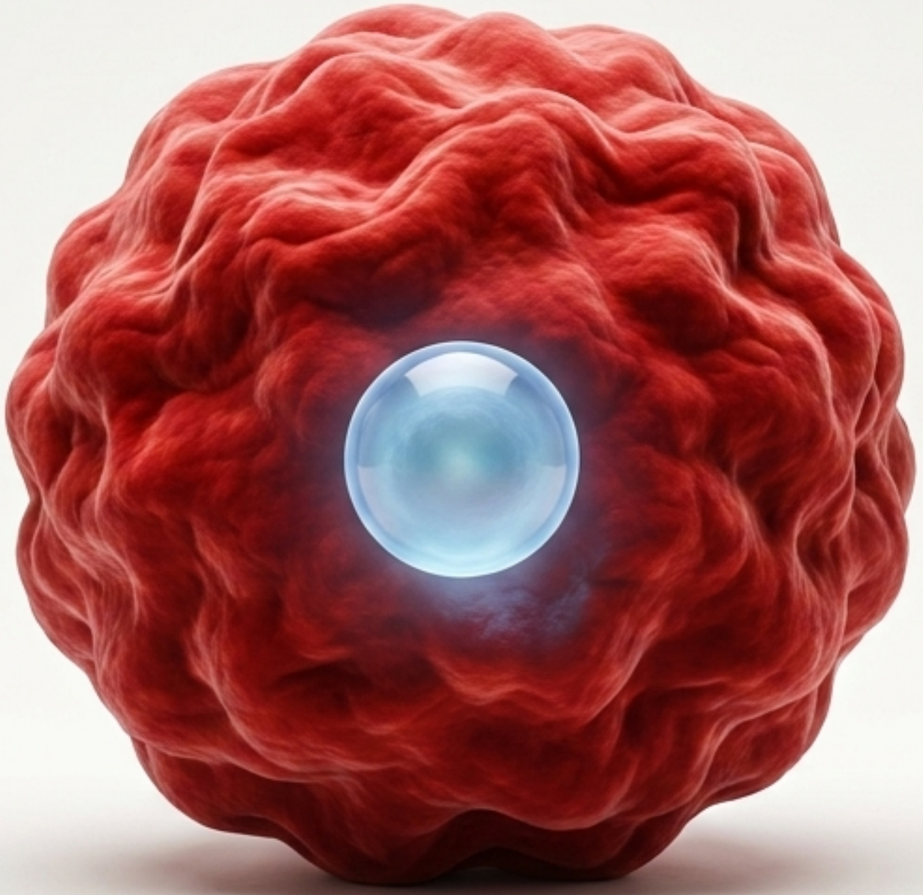
2. The Scale:
> 46,000 combined patients.

3. The Exposure:
Median on-treatment LDL-C of ~30 mg/dL, maintained for up to 8.4 years of cumulative exposure.

The Verdict: Zero signal of adrenal insufficiency, hypogonadism, hemorrhagic stroke, or cognitive decline.
Humans tolerate profound, pharmacologically induced lipid-lowering without tissue starvation.
The model is empirically validated.

The Modern Excess

The Reality: If the body only requires **50 to 90 mg/dL** of total cholesterol to sustain transport and tissue demands... why is the U.S. adult average **188 mg/dL**?

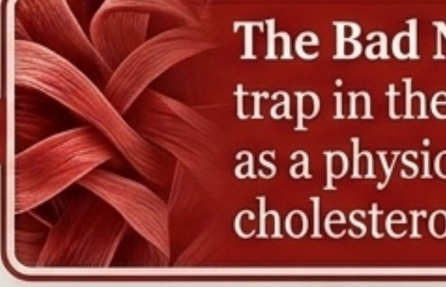


The Gap: Modern population averages exceed the true physiological requirement by a factor of **two- to four-fold**.

The Crucial Question: Is this massive, 5.6-gram circulating surplus harmless?

Metabolically Tolerated ≠ Biologically Neutral

Atherogenic Risk /Plaque Formation
Atherogenic Risk / Plaque Formation



The Bad News: It sets a deadly, mechanical trap in the arterial wall over time. Cholesterol as a physiological need is entirely separate from cholesterol as a cardiovascular risk.

The Good News: Excess plasma cholesterol does not poison tissues, cause cells to malfunction, or cause organs to fail. From a purely metabolic standpoint, the surplus is tolerated.

Physiological Need / Tissue Toxicity

The Cost of Exposure

The Mechanism

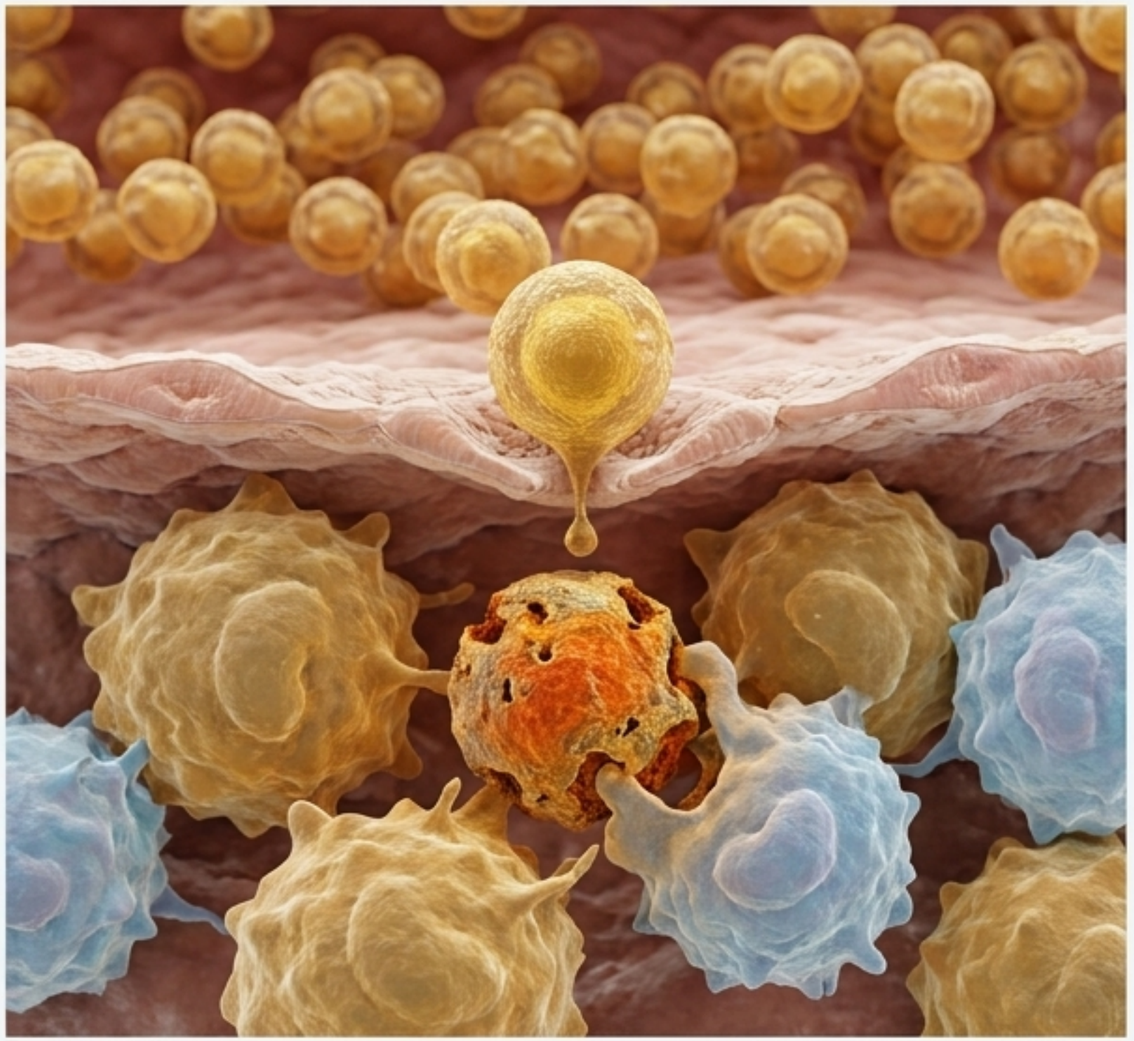
Every additional ApoB-containing particle in the bloodstream carries a probability of entering the arterial wall, becoming retained, oxidizing, and seeding an atherosclerotic plaque.

The Math of Risk

Mendelian randomization proves a log-linear danger. Lifetime risk tracks exact cumulative ApoB particle exposure.

No Free Pass

There is no ‘threshold’ where risk vanishes. The modern surplus contributes proportionally to arterial exposure, year after year, decade after decade.

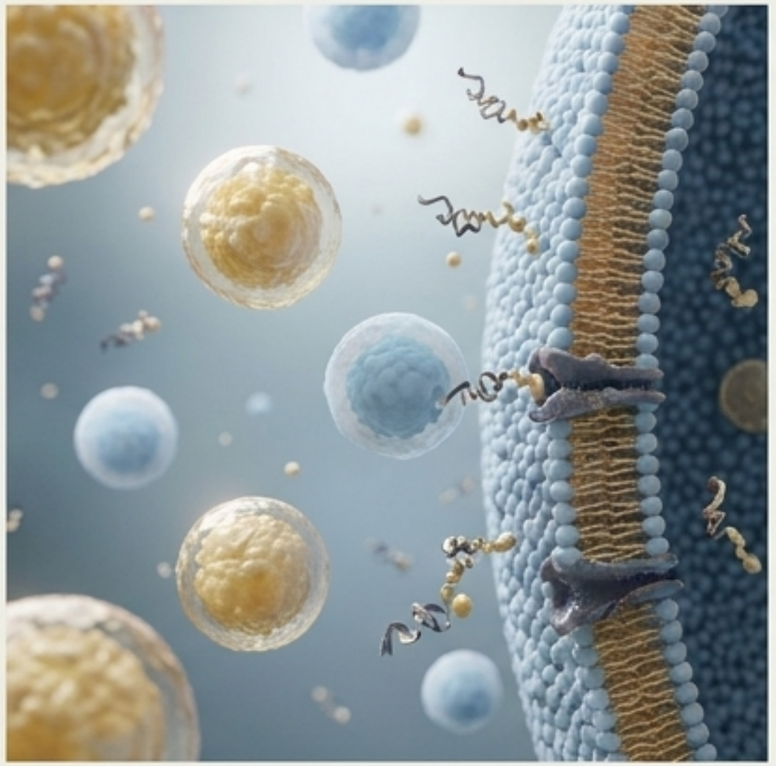


The Three Truths of Human Cholesterol

1. The Structural Pool (150g).

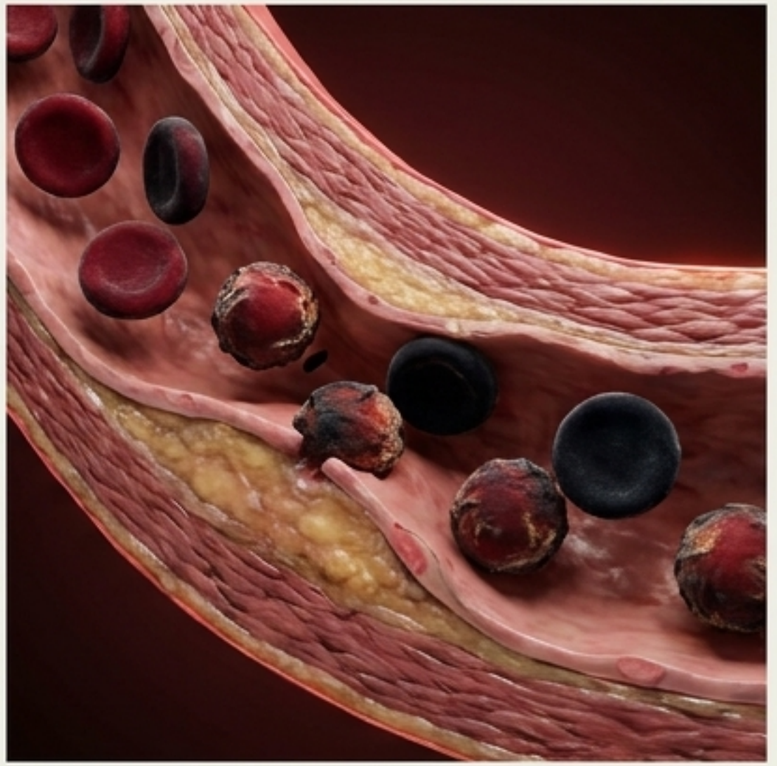
Cholesterol is vital. Tissues mostly manufacture their own at massive energetic cost. The brain is totally isolated.

2. The Transport System (1.5–2.7g).

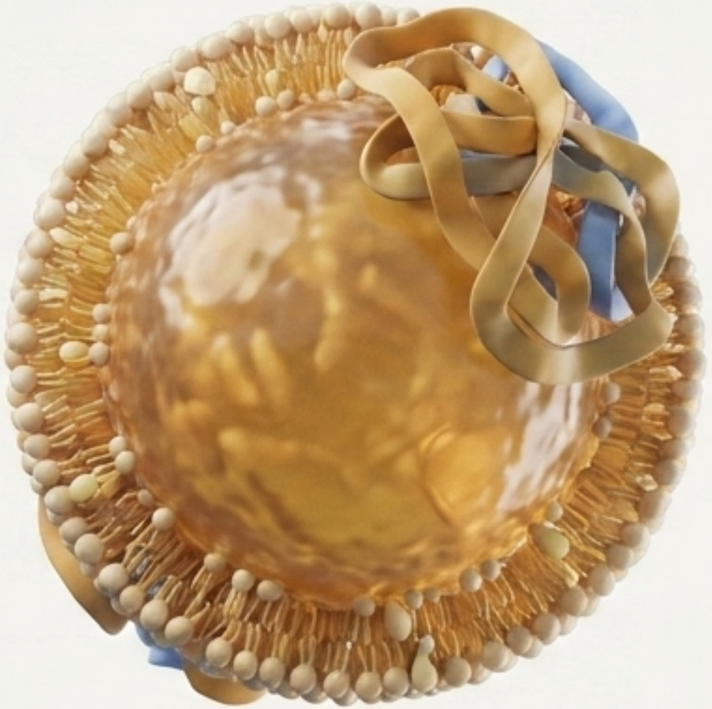


A kinetic buffer and energy byproduct requiring only 50–90 mg/dL to function perfectly and meet niche endocrine demands.

3. The Atherogenic Exposure.



A cumulative, mechanical risk driven entirely by excess ApoB particles crashing into the arterial wall over a lifetime.



Your body needs cholesterol. Your blood mostly doesn’t need to carry as much of it as it does.

Holding both of these truths together is the foundation of modern preventive cardiology.