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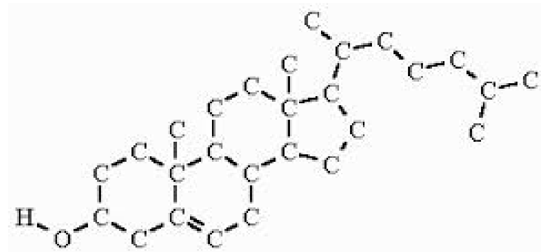
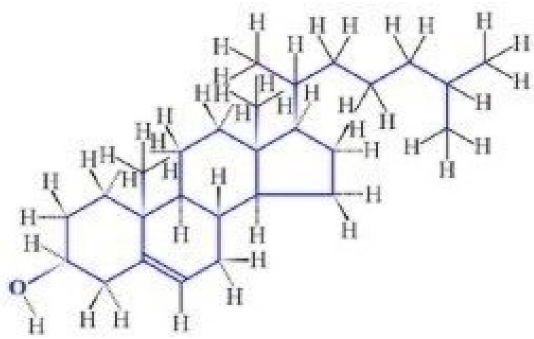
Cholesterol Questions

What is it? Where is it located in the body? What does it do? Where does it come from? How is it transported around the body in the water between cells and blood stream? Can we absorb cholesterol from food? Is cholesterol the correct issue for artery disease? Why the long focus on cholesterol?



Drawing 1: Structure of a Cholesterol molecule, most hydrogens not shown

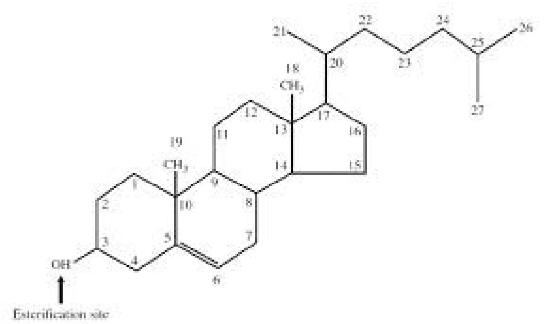
E.g. Many think cholesterol (at least too much of it) is bad and that it comes primarily from food. Neither of these ideas, though widely promoted and believed, are correct understandings.
(Note: All blue underlined text below are relevant internet links.)



Drawing 2: Structure of a Cholesterol molecule, carbons implied; not shown

First, what is cholesterol?

Cholesterol is a fat molecule. Be aware that fat molecules are also commonly called hydrocarbons [because they mostly consist of carbons & hydrogen atoms), oil, grease or (in medical jargon) lipid molecules]. Cholesterol is a very specific fat/lipid molecule, one of many types of fat molecules, a very specific & important one with a very important role for all animal cells on the planet. Repeating, cholesterol, is a very specific fat molecule with a very specific structure and critically important function for all animal cells.



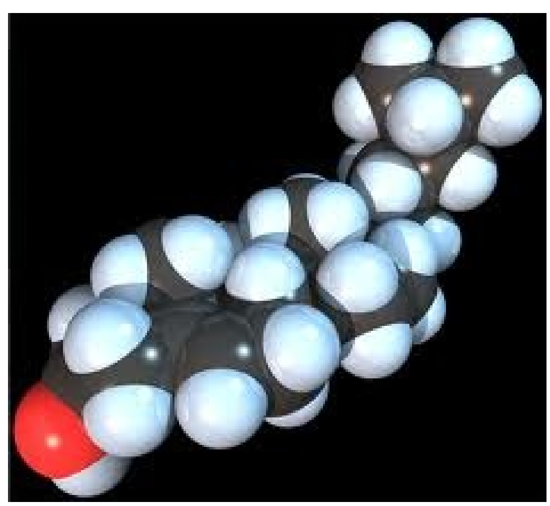
Drawing 3: Structure of a Cholesterol molecule, carbon atoms numbered

So what is the structure of cholesterol?

Please examine the four different drawings of the structure of a single cholesterol molecule at the right: Drawing 1: emphasizes the carbons; hydrogens are not drawn in but "understood to be present". In drawing 2: carbons are "implied" at each corner & the hydrogens are shown. In drawing 3: the carbons are numbered & the hydrogens are again "understood to be present". And in drawing 4: a more spatially correct drawing of cholesterol is depicted; carbon atoms black, hydrogen atoms white, the one oxygen atom red.

(In most depictions, using usual chemistry short-hand, the hydrogens are not shown because carbon atoms in molecules essentially always have 4 bonds & any bonds not shown are assumed to be to hydrogen atoms, a shortcut used for simplicity, though misleading for anyone who does not know the shorthand).

(Per commonly used shortcut notation in organic {carbon} chemistry, each unlabeled intersection of lines is a carbon atom; non-carbon atoms are labeled with the first letter of the atomic name of that atom, e.g. H=hydrogen, O=Oxygen; single lines represent single bonds & double lines represent double bonds, for any carbon without 4 lines, the remaining bonds link to hydrogen atoms.).

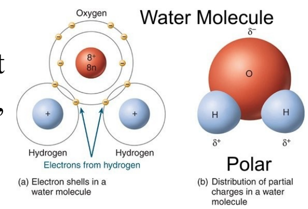


Drawing 4: Spacial model of a Cholesterol molecule; see comment

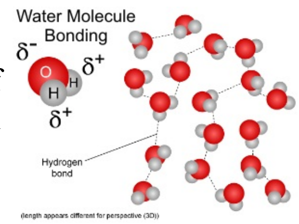
Like all fats, cholesterol is composed of carbon and hydrogen atoms. Unlike other fat molecules, it is not manufactured by plant cells but is manufactured by all animal cells, including all human cells. Notice the 4 ring central structure, three 6-corner hexagon rings and one 5-corner pentagon ring, all built of carbon atoms.

Second, Where is cholesterol located in the body?

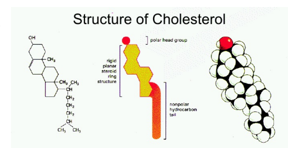
The correct answer is that cholesterol one of the major, about 30%, of the fat molecules from which all animal cell cell membranes, including human cells, are built.



The most abundant molecule within all cells, like the rest of our bodies, is water. If we are slender healthy young males, about **62%** of our entire body is water, **~60%** for women (lower percentage if we have more stored body fat). Of this 62% of our body which is water, on average, about ⅔ of the body water in inside cells, ⅓ outside cells.



Does water have unique properties? Absolutely: They are charged and have what is called a polar structure, positive and negative parts of each molecule. Given this polar structure, water molecules are electrostatically attracted to both other water molecules and/or any other molecules which have charged structures. By comparison, water is not attracted to (i.e. reject) non-charged molecules, such as hydrocarbons, commonly called fats (lipids in medical jargon).

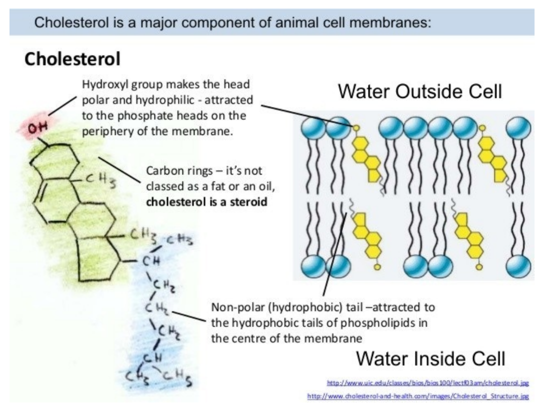


So, for cells, what separates water inside from water outside? After all, if no separation existed, then there would be no cell.

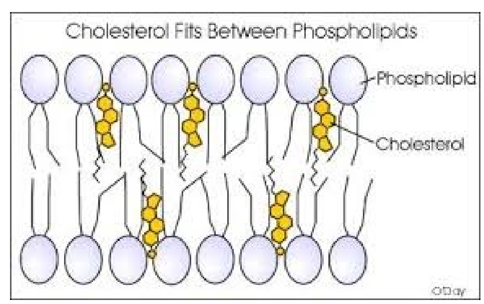
Answer: Thin dividing structures called membranes.

What molecules are the membrane structures build of?

Answer: The membranes are built from molecules which water rejecte & thus will not dissolve in water, yet molecules which have a charged/water-attracting group on one end; called a polar end. The function of membranes is to divide and separate water, first defining the cell itself (separating water inside from water outside) &, for eukaryotic cells, also dividing internal water into many separate internal compartments. These membranes are composed of fat molecules [also called hydrocarbons, oils or (in medical jargon) lipids].



For bacteria & plants, these fats are phospholipid molecules.
For animals, both phospholipids & cholesterol molecules.



Thus our bodies, as well as all life on this plant, are built from fat organized water droplets (called cells). Within each cell are additional complex molecules, including:

- DNA molecules (which store information),
- proteins which are the working molecules within these fat organized water droplets along with
- smaller amounts of various sugar molecules or sugar polymers (e.g. the cellulose of plant cell walls which surround the cell membranes of plant cells making them rigid, thus unable to change shape, unable to move).

The proteins perform a myriad of various specific functions, including what genes do and do not get read. In turn, all proteins are manufactured, or NOT, under both genetic and internal cell controls. Most proteins do very complex tasks inside cells, such as both taking apart other molecules and building complex molecules which the cell needs to function and stay alive.

Some proteins are located in the cell membranes, some are excreted through cell membranes in order to facilitate building structures outside cells, e.g. tendons, ligaments, cartilage, bones, particles which transport fat molecules, etc.

Collectively, all this chemistry is called biochemistry, i.e. the chemistry of all life on this planet. Biochemistry is both fantastically complex and precise, several orders of magnitude more complex than any man regulated chemistry, and much of it remains beyond the understanding of any human, or group of human beings, on this planet. This reality is also one, of many, fundamental reasons why humans do not understand themselves, health or even common disease states.

Each of our cells have an outer membrane forming the outer boundary of each cell, an inner membrane around the nucleus (where the chromosomes & genes are located) and multiple membranes in the space between, called cytoplasm. These additional many membranes separate the intermediate water space, cytoplasm, into multiple complex sub-compartments. These cytoplasm membranes are called endoplasmic reticulum, smooth and rough, vacuoles, Golgi apparatus, mitochondria, etc.

Now back to basic cell structure, i.e. fat organized water droplets, those with membranes built from only phospholipid molecules, called a phospholipid bilayer (as used by bacteria and all plants) can separate water inside from outside, there is a fundamental problem. Phospholipid bilayer membranes are rather stiff and fragile. This is a big problem. Why? Because, for all cells, keeping both water and other molecules (mixed in the water) is crucial to cell life and function. If the membrane tears or suffers a tiny opening (letting both water and other molecules in the water) mix, the cell dies, very rapidly.

So what do bacteria and all plant cells do to protect their stiff fragile membranes? Answer: They build an additional structure outside their membrane, a structure which surrounds the entire cell. This additional structure is far thicker (commonly about 15 times thicker than the phospholipid bilayer, as seen by electron microscopes) and stiffer than the phospholipid bilayer & protects the fragile phospholipid bilayer from mechanical stress.

Because of the thickness and stiffness this extra structure is commonly called a cell wall.
But, is there a downside to this cell wall strategy?
Absolutely!
The cells are unable to rapidly change shape because changing shape requires both tearing down and rebuilding the cell wall, a time consuming process.
This issue is obvious at a gross (non-microscopic) level; Plants don't move (rare specialize exceptions exist).
Plants cannot move because every cell in within its own protective stiff cell wall prison.

Now back to cholesterol molecules. Cholesterol is a specific fat molecule and a large minority of the fat molecules from which all animal (and human) membranes are constructed; typically about 30-35% of the outer membrane fat molecules are cholesterol molecules. The majority of the membrane fat molecules are still phospholipids.
The ratio of cholesterol molecules within any given animal cell membrane varies, generally from a low of 5% up to about 40% of all the fat molecules.

So for cells which all have cholesterol as part of their molecular structure, what difference do the cholesterol molecules make in the properties of each cell's bilipid membrane structure?
Answer: A huge difference. With added cholesterol molecules, the membrane is far more flexible (called fluidity by researchers) and yet does not so easily tear or suffer gaps/holes. This flexibility and resistance to tearing eliminates the need for a cell wall and allows the cells to be able to change shape rapidly, a fundamental characteristic of all animals.
Animals can move & eat the plants which are unable to move.

(Be aware, variations in the structure of the phospholipid and other fat molecules within the membrane also affect membrane properties.)

Now back to answer the question: Where is cholesterol located in the body?
Answer: It is in all the cell membranes of all the cells of our entire body.

Third, what does cholesterol do?

I.e. What role do the cholesterol fat molecules serve within animal cell membranes?
Answer: They allow the phospholipid molecules to slide against one another more freely, than if the cholesterol molecules were not present, but ***without*** the membrane tearing. Indeed, with the addition of cholesterol molecules, the membranes are far more resistant to tearing. Thus animal cell membranes are much more flexible and tolerant of motion and abuse than plant cell membranes. Plant cells (stiff phospholipid membrane with surrounding cell walls), when bent, just break. So cholesterol gives animal cells a big advantage, the cell membranes easily deform, do not require a thick, tough & stiff surrounding cell wall.
Thus in repeat summary, animal cell membranes are more flexible, allowing cells to be able to quickly change shape and animals **to move**.

In addition, all animals use various molecular modifications of cholesterol as both inter (within the cell) and intracellular (between cells) singling molecules. These modified cholesterol singling molecules are called steroids. Some of the common steroids, manufactured by all humans, include cortisol, estrogen, progesterone, testosterone, vitamin D, along with many others.
Men and women both make and use all of these for a variety of signaling purposes, just in different proportions with variations in timing of production and release of how much.

Fourth, where does cholesterol come from?

Since every single animal cell has to have cholesterol to both manufacture and repair cell membranes, do cells just hope to capture some that might happen to be floating by?
Answer: No! This would not be reliable; thus this it is not the correct answer.

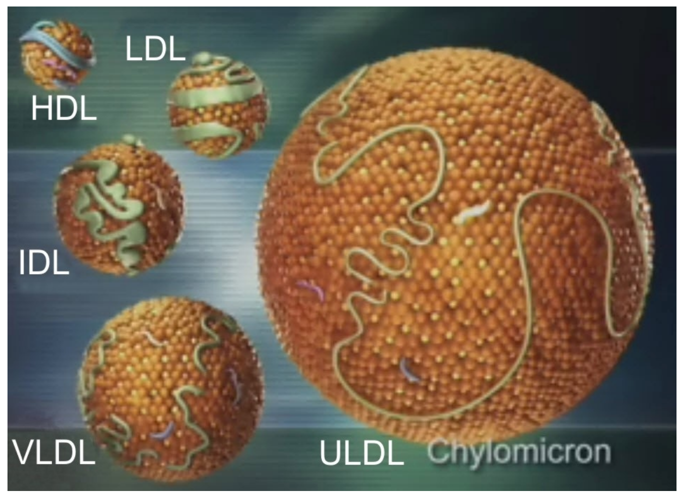
As mentioned above, cells are wizards at chemistry; what they do, constantly, make most man-made chemistry look extremely simplistic. All biochemistry, the chemistry of all living organisms, is totally consistent with all known laws/principles of chemistry. Yet living cells and organisms apply these laws/principles in vastly more sophisticated and precise ways that puts most man-controlled chemistry to shame from both complexity and specificity points of view.

Thus the correct answer to: Where does cholesterol come from? Each and every animal cell manufactures cholesterol, from scratch, staring with 2 carbon atoms at a time and building up the complex molecular structure illustrated on page 1 of this overview. If you will, cells operate like extremely complex tinker toy machines, routinely building complex tinker toys (molecules) out of the molecules and atoms available to them, as needed. Cholesterol is just one of millions of examples.

Fifth: How are cholesterol molecules, and all other fat molecules, transported around the body in the water outside cells, including the blood stream?

To sort this out, lets go back to basics: What is the fluid outside cells, between cells and what is blood composed of?

Answer: Water molecules, H_2O is the most abundant molecule in the body, both within and in between cells and is what blood is built from. But in the case of blood, a fluid tissue, there is more water between cells than in most tissues. Instead of ⅓ water outside, ⅔ water inside, (like other tissues, on average across the entire body) for blood, about 55% of the water is outside the cells, the other 45% inside the cells, called hematocrit (percentage of the blood volume which is Red Blood Cells). Additionally, the water contains a variety of salts, proteins and (of course) cells, both red blood cells and white blood cells; about 1,000 red cells for every white cell.



Simplified Illustration of Lipoproteins (Submicroscopic Particles)

Since blood is composed of water, and cholesterol is a fat molecule, then cholesterol (and all other fat molecules) can't (i.e. because it is not soluble in water) float around within either the water of the blood stream; or within the water between cells outside the blood stream. Thus blood, by itself could not carry and transport cholesterol molecules any more than it can any other fat molecule.

So how do animals solve this dilemma of moving insoluble fat around in the water outside cells? In fact, not just around in the blood but around the entire body throughout all the water spaces between cells; both the smaller volume of blood-plasma-water and the larger volume of water outside cells and outside the bloodstream?

Answer, all animals manufacture proteins specifically designed to carry fat molecules, including cholesterol fat molecules. The role of these proteins is to function as sub-microscopic sized suitcases which electrostatically attract water (on their outer surface), thus are water soluble and can easily mix into blood and move around the body in the water outside all cells. These complex protein particles (80-100 proteins per particle) carry fat molecules (thousands to tens of thousands of fat molecules per particle) hidden within. Thus these are fat carrying proteins, traditionally called lipoproteins, i.e. lipid (fat) carrying proteins.

What fat molecules do these particles carry?
Answer: All fat molecules; no fat molecules are soluble in water and can thus cannot move through water on their own.

How do the lipoprotein particles interact with cells all around the body?
Answer: The lipoprotein particles interact with specific proteins which cells can expose on their surface ←click on link to see a fairly accurate video commissioned by the Genzyme company. These cell surface proteins interact with the fat carrying proteins and determine if fat will be removed from the lipoproteins or added into the lipoproteins; a topic of greater detail beyond this introduction.

Thus the answer to: How is cholesterol transported in the blood stream? Like all fat molecules it is packaged and carried within lipoprotein particles. The cholesterol and all other fat molecules are just passive passengers, being removed, transported and transferred to wherever the lipoproteins and interacting cell surface proteins take them.

Are the lipoprotein particles simple, made up of just one or a few proteins?
Answer: No. They are quite complex, submicroscopic particles, smaller that all cells and made up of about 80 to 100 different proteins for every single particle.

Have all these proteins being identified and has the role of each of these proteins been defined? Again, No. While some of the proteins have been identified, not all have and the interacting controls and function remain poorly understood. What the various roles of all these various proteins play in the life and function of each particle remain topics of ongoing research efforts.
This vehicle we all drive, for a lifetime, commonly called a body, is just too complex for researchers and doctors to fully understand, i.e. the location of the **Real** Hi-Tech as mind over matter creatures.

Is cholesterol the only fat molecule being transported by the lipoprotein particles?
Answer: Of course not. All the other fat molecules being transported are also there, inside each of the lipoprotein particles.

So, bigger picture, what are the dominant fat molecules being transported within the lipoprotein particles?
Answer: Triglycerides dominate, the phospholipids and cholesterol (cell membrane building block proteins) are typically next, plus a variety of smaller amounts of all the other fat molecules (beyond the topic of this overview).

Is the ratio of fat molecules within each particle, of a given size and structure, constant and predictable?
Answer: You probably already guessed it; No! The function and contents can vary widely due to many physiologic variables, most only partially understood.

How many different fat carrying proteins, i.e. lipoproteins, are there?
Answer: You probably already guessed it; a bunch. From research dating back to the 1930s, the

lipoproteins are generally divided into 5 groups: ULDL (aka Chylomicrons), VLDL, IDL, LDL and HDL. In all cases, the last L is an abbreviation for lipoprotein.

What do the other letters stand for?
Answers:
ULD = ultra low density (compared to water), historically called Chylomicrons, the only particles, which if really huge, as occasionally happens, on can barely see little round colorless balls under a ver high power light microscope, oil-immersion lens over a thin glass slip covering the solution below.
VLD = very low density (compared to water), smaller than the ULD particles
ID = intermediate density (compared to water), smaller than the VLD particles
LD = low density (compared to water), smaller than the VL particles
HD = high density (compared to water), even smaller than the VL particles

Notice the constant use of the term density. Density of what?
Answer: The density of the surrounding water, the reference for relative density of each group of particles.

Also notice that as size goes down, density goes up and visa versa? Why so?
Answer: Back to basics: Lipoprotein particles are composed of a thin protein shell with lots of fat molecules packed inside. As lipoprotein particles pick up more fat molecules, what happens to their size? They get larger. And how does the density of protein and fat molecules compare to the density of water?
Answer: Protein molecules are generally more dense than water, mix and sink. Fat molecules are less dense than water and float. Thus the larger the particle, the more fat, the more it floats in water. Indeed this is precisely the basis for how these complex particles were first characterized and how they were named.

Given the focus on LDL (Low Density Lipoprotein) particles as being the most important of the 5 groups of Lipoprotein particles in term of driving artery disease, first identified by research published August 1950 and repeatedly verified ever since, how many of the various fat molecules are present within a single LDL particle?
Answer: 3,000 to 6,000 fat (lipid molecules) are typically present within a single LDL particle.

Are the percentage of different fat molecules always the same?
Answer: No. This percentage varies, rather widely, over time and often widely between people. As a crude approximation, for a single LDL particle, there may be anywhere for several hundred to several thousand cholesterol molecules combined with several thousand to several hundred triglyceride plus phospholipid and other fat molecules. This wide variation is the reason that LDL-C values (only an estimation, not even measured) and LDL particle measurements are commonly very different.

When the two values are not in agreement, which one matches artery disease progression and outcome data?
Answer: It is always the LDL particle concentration, never the LDL-C estimation, even if it were

measured (rarely done clinically because more expensive and no added value).

LDL-C is only a calculated ESTIMATE of how many cholesterol molecules are present within one tenth liter of blood plasma (abbreviated dL; meaning a tenth of a liter).
First, it is never measured from the person's blood.
Second, even if it were measured, would it reveal how many LDL particles are present within that volume of plasma? No!
So why was it promoted, starting with the US government, so-called National Institutes of Health & National Cholesterol Education Program Committee, starting in the early 1970's?
Answer: Money &, in theory, good enough to help recognize those with the very highest rates of artery disease progression.
Problems: Has never been the correct issue and highly misleading for the vast majority of people.

For a given lab, both the cholesterol molecule and triglyceride content per LDL particle can be estimated from commonly done lab. However, doing the calculation is a little tedious and does essentially nothing to add to clinical information regarding disease effect, thus this is rarely done. Just pay attention to the LDL particle concentration (Not Cholesterol), in concert with the other lipoprotein particle concentrations and be aware the vast majority of clinical labs do NOT have the capability to measure LDL particles (back to both money & usual low technology issues).

Sixth: Can we absorb cholesterol from food?

Answer, yes, but typically very little. Food is only a limited source, at most. Indeed, if an animal eats only plants, then there is no intake of cholesterol because plants do not make cholesterol. This is one key reason all animal make cholesterol from scratch. A relatively healthy adult human of about 150 lbs typically manufactures about 1 gm (1,000 mg) of cholesterol each day, however this rate of production does vary from person to person, sometimes markedly. Thus, to stay in balance, the human also excretes about 1 gm of cholesterol per day. The primary route of excretion is the liver, removing cholesterol from the blood and excreting it into the bile and in turn into the intestines. The average person absorbs about 50% of the free, non-esterified cholesterol from the intestines, back to the liver and into the blood stream. The 50% that is not absorbed exits as part of the stool and amounts to about 1 gm/day, thus keeping the system in balance. Again, there values are group averages for people considered young, lean, active and healthy. These values actually vary, at times quite widely, from individual to individual.

What if a person is also eating food which comes from animals. Then there will be additional cholesterol entering the intestines, however much of the cholesterol in food is broken down by the fat digestion proteins (called lipases) or is esterified. Esterified cholesterol is rejected by the intestinal brush border protein system which binds and controls cholesterol absorption from the intestines, i.e. not absorbed. Thus, even if a person eats a very high animal based food diet, the cholesterol intake from food pales compared to the internal recycling and has minimal effect on blood/body cholesterol content. Personally, in my 30 years as a physician, I have never seen anyone successfully lower their serum cholesterol by adopting a low cholesterol diet. On the other hand, because low cholesterol foods is usually translated to mean higher intake carbohydrates, many increase both their triglyceride and cholesterol levels but choosing such foods, sometimes quite dramatically. Excess carb intake, beyond the small amounts which can be quickly burned, are rapidly converted by the liver cells into triglyceride and other fats for storage, thus driving both higher blood fat concentrations and obesity.

Thus, if a person takes in more cholesterol molecules, does that mean that cholesterol levels in the blood will rise greatly? The answer is no, the effect is typically minimal, though it does vary from person to person. The reason that intake, or lack of it, does not typically have a large impact on blood cholesterol is that all living creatures exhibit multiple automated adjustment behaviors which compensate for externally imposed influences. These adjustment behaviors are collectively referred to as homeostasis, a characteristic exhibited by all living creatures, single cell up organisms up to and including 30-40 trillion cell organisms such as human beings.

In the case of varying body and blood level cholesterol concentrations, when it goes up, individuals tend to absorb a little less and the big control is that they slow down production. In cholesterol body and blood level cholesterol concentrations fall, then absorption and especially production goes up. This is why low cholesterol diets typically have a minimal effect, if any. Indeed it is rather silly (though used to be widely and foolishly promoted) to think that changing cholesterol intake would have much effect; despite the long known basic principle of homeostasis.

At the same time, do not think food choices have not have an effect? Actually, they do. The big effect is an indirect one and tends to be powerfully reflected in body build. High stored body fat tends to correlate with high blood fat, including blood cholesterol values; fat is being shipped around the body in high quantities. Conversely, higher muscle mass and lower relative body fat tends to correlate with lower blood fat values, including cholesterol. For many people (especially if relatively sedentary), high carbohydrate (not fat) intake, beyond what is burned with the next few hours, drives increased conversion of the excess carbohydrate into storage as additional body fat, thus compounds lipoprotein driven problems, regardless the cholesterol concentrations.

However, as always, there are big individual variances in the specifics, presumably encoded both (a) within our genes and (b) how we each individually control and express our genetic blueprints, a huge issue.

Seventh: Why the long focus on cholesterol?

As you may be starting to understand, cholesterol has NEVER been the correct issue with respect to arterial disease progression/regression? This fact has been known since at least 1950, at least in research circles. Then why has cholesterol continued to be promoted?
Answer: The usual human reasons: Time, Effort, Money.

In the 1970s, after decades of verifying that lipoproteins were the correct and dominant issue in driving/stopping/potentially reversing arterial disease, people at the NIH started to promoted that physicians start doing a bit more about reducing arterial disease events, after people had demonstrated they clearly had advanced disease. But, how much did performing a lipoprotein assay by the means long used in research labs cost? About $5,000 US dollars per single blood sample. So did the people at the NIH promote that physicians should convince the people who came to see them, even after a heart attack, stroke or other obvious arterial disease events, have a $5,000 blood test? Answer: No. So what did the do instead? Answer: Guess at the particles by measuring one of the fat molecules being carried by the lipoprotein particles.

Next, so what fat should they have picked; what fat did they pick? How about a fat molecule that comes from both food and internal production, triglyceride molecules?
Answer: No.
Why? Since they come for both outside and inside, what the person has eaten over the last month, even day, becomes a big confounding issue. So triglyceride measurements are out to start with.

So what would be a better, even if still misleading, but at least less expensive alternative. Answer: your guessed it Cholesterol.

Is cholesterol the correct issue for artery disease?

Answer: No.
Then why so long promoted?

Answer: As above, because it was, and still is, less expensive to measure/estimate as a way to ***estimate*** the number LDL, HDL and other lipoprotein particles. However, using cholesterol to estimate these complex fat transport protein particles is also notoriously inaccurate because these protein particles carry large number of all fat molecules, hundreds to hundreds of thousands per particle, and the percentage which are cholesterol is quite variable from person to person and time to time.

But even if it is not the correct issue, isn’t it good enough?
Answer: No, assuming one cares about avoiding arterial disease during one’s lifetime.

But isn’t spending less money on tests of value?
Answer: Yes, perhaps, but what if it results in much a higher incidence of heart attacks, strokes, circulation problems all over one’s body, which is not only very expensive to treat and impossible to undo.

But doesn’t angioplasty, stents and bypass surgery treat the problems of artery disease?

Answer: Actually No! These procedures are only treatments for some of the symptoms, at high cost and high risk while also further complicating the disease. Like nearly all medical treatments, they are only that: treatments, largely not about the disease, but only some of the symptoms of very advanced, finally obvious disease.