DANNY LENNON: Today we are indeed talking about cholesterol and lipoproteins, and we're specifically digging into some of the discussions around whether there's actually a benefit maybe to high cholesterol, or at least some detriment to having reduced cholesterol levels, and therefore reduced lipid protein levels. So really, what we're going to try and walk through is this premise that cholesterol is this important molecule in the body, it plays a role in a host of important functions from things like being a precursor to testosterone, cortisol, vitamin D, to playing a role in bile acid synthesis, playing a role in immune function, having a role in the brain or the presence of it in the brain, and things to do with neurotransmitters, and all these other things you've likely heard at some point when someone discusses the importance of this compound cholesterol. To give some example of the types of things you will probably have heard somewhere else, or, if not, many people have heard, there's a couple of examples I'm going to play that are particularly useful for highlighting exactly what I've just said. So yeah, let's get into these.

[Video Being Played] Now, I would not be able to stand here and give this presentation without the LDL cholesterol, which is much maligned because that LDL

cholesterol is supplying cholesterol to my adrenal cortex, giving me the stress hormone cortisol so that I can deal with the stress. The LDL molecule that cardiologists want to wipe from the face of the earth is giving cholesterol to the ovaries, making all women in here look beautiful, and testosterone to men making us look handsome. Now, bile acids are absolutely essential for absorbing fat soluble vitamins, for absorbing fats, and they are cholesterol byproducts, and cholesterol is not a metabolic fuel, we cannot use it for energy. So bile acids constitute the way in which we eliminate cholesterol in our gut. Vitamin D is a cholesterol product.

DANNY LENNON: So that was Dr. Nadir Ali speaking at a previous Low Carb Conference, and Dr. Ali is a low carbohydrate advocate, as you can probably tell from that, but indeed, lectured on a number of occasions about high LDL not necessarily being problematic, and then, as we've just laid out there that cholesterol is important for a number of functions in health. The second example I'm going to play is not because it's that particularly different or I'm not sure you'd have any – think too much of some of the arguments made, but it's because of the size of the audience that these types of messages are reaching. So the second example of this type of rhetoric comes from an appearance on the Joe Rogan Experience from March 26 2021, from Mark Sisson who talks about, again, cholesterol when it's brought up. So we'll play that now.

[Video Being Played] Cholesterol is probably the most important molecule in human body, if you really were to parse it, vitamin D, sex hormones, it's a working molecule on a lot of cell membranes. And to think that we – I mean, the body, it's so important, the body makes like 1300 milligrams a day, regardless of what your cholesterol intake is from food. So in my mind, the notion that we would take this amazing molecule that is basically life giving in many regards and vilify it, and then take drugs to

lower it, which, if you look at the research, and I wasn't planning on going down this path today, but if you look at the research on cholesterol and heart disease over the past 20 years, it's shifted everything away from cholesterol being the proximate cause of heart disease. Cholesterol and saturated fat are not the proximate cause of heart disease, it's oxidation and inflammation. Cholesterol is involved in the repair of damage to the tissue, and, as a result, people get, because of the oxidation and inflammation, there's cholesterol that's in the plaques and things like that. But I think many, many doctors, I'm going to say, the preponderance of doctors now agree that cholesterol isn't the bad guy that people made it out to be. And if you look at other studies, cohorts of people who've had cholesterol of 130 and lower, or 200 and above, the all-cause mortality, you die of everything else at a much greater rate with low cholesterol than you do with high cholesterol. The only difference is the cardiac outcomes, and it's not even deaths, it's just cardiac events is a little bit higher in the higher group.

DANNY LENNON: Okay, so both of those just go to serve as examples of talking about the importance of cholesterol because it does a number of things around the body, and so, therefore, why would we want to reduce it. So this kind of gets us to the two separate but very related points that we're really going to try and discuss here. First, this idea that we should avoid low serum cholesterol, as that can cause harm to our health; and then, second, to take that one step further, elevated levels of cholesterol may not only not be problematic, but could be protective against disease or mortality. And so, if we were to take those two things as a natural consequence of those, we would therefore end up also having to conclude that high levels of Apo B containing lipoproteins, so LDL, VLDL, IDL, etc., are not problematic, as they are simply transporting this important molecule, cholesterol around the body. And then, second to that, we would have to then say dietary

practices that elevate Apo B or LDL particles or LDL cholesterol are not a cause for concern, because, again, these LDL or other atherogenic lipoproteins are simply transporting this important molecule that benefits are health around the body; and beyond that, as it's beneficial for us, then high intakes of saturated fat, for example, are actually health promoting because those increases in cholesterol are not a problem, and, in fact, may be of benefit. And so, with that we get a number of kind of conclusions that we'll come to in a moment, but from what you can tell, does that kind of give a good overview of this idea of cholesterol being an important compound, because it has known functions within the human body?

ALAN FLANAGAN: Yes, that seems to be the high watermark of the claims that will come from that community is to say, this is an important molecule. That means it does all this beneficial stuff, and that means that it can't possibly be doing anything potentially detrimental to health or negative, and it also means that, by implication, there would be negative health implications to deliberately lowering it, because it's so important for all of these functions. So a lot of the way that arguments from that community are posited, it's telling you something without telling you a lot else. Right? It's making a claim about something's importance without really saying how much of it is important, or, where's it required and at what levels, or, how does the body actually process it. And like anything, when we talk about nutrients, if we're going to consider certainly dietary cholesterol, and the idea then flowing from this, which would be argued by that community is you actually want to diet high in saturated fat with dietary cholesterol, because that's going to be good for you because this molecule is good for you. But a fundamental principle of all nutrients is their existence on a bell curve, so yeah, like an insufficiency or deficiency can be detrimental to health, there's generally a range of adequacy, and that differs. I mean, the range of adequacy for iodine might be 150 micrograms to 200

micrograms a day, but vitamin C could be 70 to 90 milligrams a day. And so, these are details that are never discussed really in terms of the community kind of positing what are very kind of general claims that sound like they're kind of well thought through and scientific, but are actually so general as to be practically meaningless as arguments.

DANNY LENNON: Yeah, and I'm going to try and put some of those claims, at least how I can see it from what I can tell of what I'm coming across, some of those claims to you throughout the course of this discussion. And to maybe set some context and maybe just to show people that how this is being framed is not an exaggeration or taken out of context, there's another couple of clips from people who are well known within this space to show that it's not a kind of, oh, slight changes in LDL cholesterol may not be that important, it's actually a real celebration of high LDL. One example is I'll go back to Dr. Nadir Ali, where he kind of concludes that lecture that I just played that previous clip from, by talking about how LDL should be celebrated, and he names actually a number of outcomes by which that can improve health. But I think through the course of this particular podcast, we're going to try and look at in a bit more detail.

[Video Being Played] And this is my conclusion slide which says that should we celebrate a high LDL rather than moan it, especially since most people and these will meet these three criteria. They'll have a higher LDL, they'll have a lower triglycerides, they'll have lower insulin levels, because I'd like to submit to you that this is going to make you live longer, have better cognitive skills, lower infection rate and lower cancer risk. So I really thank you for giving me the opportunity to present here.

DANNY LENNON: So there are a number of things that we're going to come back to, so just to put a pin in that for people to remember, we're looking at the claim of elevated LDL will help you live

longer, have better cognitive skills, lower infection rate, and lower cancer risk. They are things that have been directly said, and are things that are not atypical from the type of arguments that we're looking at. The second one, and probably the last kind of clip for now that I want to set up is also again to try and put in context to show where this type of idea of high cholesterol being healthy comes from. And indeed, this gets to a question that I think would be good place for you to open up on this Alan of when we're thinking about how much is actually required for these physiological functions, our friend and quack asylum veteran at this point, Paul Saladino has a podcast episode with Dave Feldman from October of 2020, and it is titled How High Cholesterol Can Be Healthy and Low Cholesterol Could Be Harmful. So that is the exact title, so we're not taking things out of context per se. And to give more context to what is meant by high cholesterol in this context, it's not necessarily just a slight elevation; in this episode, Saladino actually specifically mentions his own lipid measurements, which again, are from that date 6th of October 2020, but as far as I know, he hasn't publicly posted about them ever reducing since then. His measures were an LDL cholesterol value of 533 milligrams per deciliter, or 13.8 millimoles per liter. So as some context, kind of an LDL cholesterol above three millimoles per liter is typically considered high, so we have something four times that amount. And then, he also posts about a LDL particle count, which, depending on which lab you're looking at, you might see an ideal target of less than 1000 animals per liter, high would be more than 1600, very high might be more than 2000 nanomoles per liter. His is at 3283 nanomoles per liter, so extremely high LDL cholesterol and extremely high LDL particle count. Now, I bring all this up because in their discussion, they make this point about cholesterol being seen as conditionally essential, and I think this kind of serves as one of, I suppose, the counterpoint to maybe some of the things that I'm presuming you may get

into. So I'm going to put forth their argument as my kind of first piece about an argument from a side of cholesterol being positive, so this is taken from that particular episode.

[Video Being Played]

I believe that it is conditionally essential, and I know that that's also a controversial idea, because a lot of existing lipidologists would say that your body makes all the cholesterol it needs to. And I think I posit, let me put it this way, I posit that that's somewhat dependent on its existing constituent components resident in the cell. So certainly the cell, if it can, will make cholesterol, if it's absent its availability. But do I think cholesterol might be conditionally essential like some amino acids? I do think that. Definitely.

I think it's very possible, in the podcast with Peter Attia and Tom Dayspring, they make this point to say that if you look at the total body pool of cholesterol, the amount circulating in the lipoproteins is very small; and Tom Dayspring goes as far to say, if you lower your cholesterol down to 40 or 50 milligrams per deciliter, there's still plenty of cholesterol for all your cells. And I kind of like choked a little bit, and I thought, I'm not sure you can say that, especially with the reproducible spike in psychiatric events, suicides, violent homicides, mood disorders, and all sorts of other problems we see when you lower the serum LDL. I'm not convinced your body does have enough cholesterol when you inhibit HMG CoA Reductase, and I would debate Tom Dayspring or Peter to that any day of the week. I'm just not sure that looking at the total pool and saying, oh, there's so much more in the cell membranes than there is in the lipoproteins means anything about how much your body needs and really gives any sort of a safety profile for lowering your serum LDL cholesterol to 40 or 50 milligrams per deciliter, and you might do with a statin and a PCSK9 inhibitor. So I was really disturbed by that comment from Tom, and I think that very – it's very likely that cholesterol is a conditionally

essential nutrient for humans, and that getting in the diet often makes you feel a whole lot better.

DANNY LENNON: So that teases up for the, I suppose, the first point I will put forth of, we know there are things that cholesterol does throughout the body, and we can put forth his argument about being conditionally essential, and therefore, attempts to lower that are going to be problematic for health; and then even if we go a step beyond that, that we can come to a bit later, that actively driving up could be beneficial, but certainly a lower LDL cholesterol or a lower Apo B count is problematic because you are getting less trafficking of cholesterol around the place, and it's this beneficial molecule. So with that, I will leave the stage for you to make your opening comments, but it's kind of based on that initial argument.

ALAN FLANAGAN: Yeah, so it would be really helpful if any of these proponents of this had actually just read the seminal research, and indeed, the development of this research in Goldstein and Brown, who won the Nobel Prize for discovering the LDL receptor through the 1980s, because they make arguments that are now at this point, nearly 40 years old as far as 40 years of data showing why the argument necessarily just doesn't even hold up. I mean, they present a false dilemma fallacy with this idea that because cholesterol is required, lowering it is potentially detrimental, which we'll come back to. In one of their 1986 papers, the one where they, well, it was based on a presentation for them receiving the Nobel Prize, they actually do mention themselves that cholesterol is what they call, the most highly decorated molecule, small molecule in biology. So the reverence for cholesterol is probably not confined just to the low carb kind of ancestral or whatever community, I think, including Goldstein and Brown maybe, is it 13 or 15 scientists have been awarded Nobel prizes,

because of their work in relation to cholesterol. So scientists love the molecule as well.

I think there's a number of ways that we need to potentially think about this. The first is to maybe kind of describe what it is as far as because there's an important distinction we need to make between cholesterol as the molecule, and what it does, and why cells want it, and the lipoproteins that carry cholesterol. And often, if we think back to, for example, the statements that Mark Sisson made on the Joe Rogan clip that you played, that's a really good example of how he conflates LDL cholesterol, like, reducing the circulating levels of cholesterol transported in lipoproteins with the actual importance of the molecule itself. So cholesterol itself is, and again, Goldstein and Brown described it as a Janus-faced molecule. Okay? So it has certain properties that make it very useful in cell membranes, it's very important for cell membranes, and no one would dispute that. And that's because it's insoluble in water. And so, that makes it important for things like membrane fluidity; and within the cell, cholesterol is important for providing the raw material for synthesizing steroid hormones, provides the raw material for bile acids; and again, there's literally no dispute that, as a molecule in the body, cholesterol does important things. What that doesn't tell you is how much we might need and where levels might lie that balance the physiological need of the body for this molecule versus levels that then become involved in pathology, particularly, atherosclerosis and cardiovascular disease. We'll come back to that. But I think for our listeners, it can be helpful to just perhaps give a bit of a simple overview of some of the processes and mechanisms involved.

So we have this molecule, okay? It can be synthesized in other organs and tissues and about roughly around 10% can be synthesized in any given organ, but the majority is synthesized within liver cells. And the liver is

the primary site of regulating cholesterol balance in the body, and that's to do with – that has a relationship with bile acid synthesis and excretion as well, which I'll come back to. But this molecule doesn't like water, scientific term being hydrophobic. And so, because of that, this is where it becomes a two-faced molecule. That's the very property that makes it useful for cell membranes is the very property that makes it really detrimental when it accumulates in places it's not supposed to accumulate, such as the artery wall, because the properties of it, as a waxy and water insoluble molecule mean that it's very hard to mobilize and remove from that place. And there's all these inflammatory and immune responses that result from its retention in the artery that ultimately lead to the buildup of plaque associated with atherosclerosis. So in order to safely transport this molecule around the body, it's packaged as cholesterol esters, so this process of esterification. So it's packaged within the core of lipoproteins, so picture a soccer ball, and imagine that all of it is stuffed in the middle of the soccer ball with triglyceride. So there are triglyceride being carried as well. And it's packaged in that primarily in the liver in very low density lipoproteins, and as the triglyceride from the middle of that soccer ball is broken down and taken up by other tissues, this leaves us with a very more cholesterol rich inside of this soccer ball, which I'm using as an analogy for a lipoprotein. And then we end up with LDL, and that's primarily bringing this two tissues and two cells. Now, because of that nature of cholesterol as not liking water, and then being packaged tightly into the core of these lipoproteins that transport it, it means that it can't just – lipoprotein can't just to arrive at a cell, and cholesterol kind of hops out and goes into the cell. And so, that's where the importance of the LDL receptor comes into play. And the LDL receptor is crucial to understand in all of this, okay? Because it relates to the arguments that are made for this idea that higher might be better.

Cholesterol is regulated really, really tightly, so while packaging cholesterol into the lipoproteins solves the problem that the body has of transporting a molecule that does not like water, can't be transported and doesn't want to be in blood, it also means that we need a mechanism by which that cholesterol can be actually delivered into cells. And so, that's where the LDL receptor comes in. So the LDL receptors' located on the surface of cells, and they bind to a particular type of protein, that's on LDL and other lipoproteins transporting cholesterol, anything that expresses Apo B 100. And we get this binding with Apo B, and that pulls the whole LDL molecule into the cell, and then in the cell then, that cholesterol that's in the core of that lipid protein can be released, broken down, and then the cell can use it then to synthesize the membranes – and this is generally in all kinds of animal mammalian cells, and can also then be used in the cell to synthesize steroid hormones, and can be used then to synthesize bile acids particularly in liver cells, and can be stored as well.

And the whole point here is that there's quite a large capacity for the LDL receptor to actually uptake LDL, and the cholesterol in it out of the circulation, so it's not in the circulation. But there's two important points as far as, like these levels go, one is that, well, how much, for example, if we're talking about this crucial role LDL has in cell membranes, well, how much cholesterol is actually needed. And it's about 5% of total lipids in a cell membrane. So cholesterol is very important. Yes, not in dispute. Do we need a lot of it? No, not particularly. About 5% of cholesterol in cell membranes is required. And above that threshold, the processes that regulate cholesterol start to kick in, in order to downregulate cholesterol uptake, because the cell's got too much cholesterol at that point. And then, in terms of the LDL receptor itself, so we have – about 5% of the cell membrane is cholesterol levels. Under normal conditions, where people are, you know, they don't have

genetic conditions that affect the LDL receptor or other aspects of cholesterol metabolism, under normal conditions, the cells expressed on a cell surface are less than 10% of the maximum number of LDL receptors that a cell could express, could produce. And the reason for that is because it allows a cell to only uptake the amount of cholesterol that it needs for membrane synthesis and to replace lost cholesterol from membrane turnover. And like I said, 5% of total lipids in a membrane and cell membranes is the threshold above which you get downregulation of LDL receptor transcription. Right? So there's a downregulation of the LDL receptor to prevent more cholesterol kind of coming into the cell.

And so, the whole point about the function and kind of regulation of the LDL receptor, and again, this was clear in Goldstein and Brown, and other groups' research in the 1980s, is that because it has such a high affinity for LDL, it allows the body to maintain low plasma LDL levels, below a threshold that above which atherosclerosis could progress, while also providing sufficient amounts for cholesterol to be delivered to and incorporated into cells to perform all of these. And so, this is the false dilemma fallacy that is presented when these arguments are made that, oh this molecule is really important, so it couldn't be doing all of this kind of negative bad stuff, well, actually, again, identified as early as the 80s was the fact that it's a double edged sword – that the LDL receptor itself, when you look at its functionality, when you look at how much cholesterol is needed for cell membrane function, when you look at how tightly regulated the LDL receptor is, in terms of its feedback, and I'll come to that just round off in a second, and when you look at how high an affinity the LDL receptor has for binding to LDL and getting LDL and its component cholesterol out of circulation, what this points to is a very intricate system of balance in the body, where the LDL receptor allows the body to maintain LDL cholesterol levels under a

threshold at which atherosclerosis can progress, which is, give or take, around 80 milligrams of LDL cholesterol levels in the blood per deciliter, and within a range at which the cells have all and more than enough that they need in order to do all of these important bodily functions, which, again, are not in dispute.

Now, and important in all of this is understanding the kind of feedback loop, because cholesterol levels are regulated by a negative feedback loop involving the LDL receptor. And this is generally regulated at the level of the liver, and so, when liver cholesterol content increases, there's a bunch of signaling processes and proteins that I won't get into to just kind of keep things simple, but basically, when that happens, and the hepatic cellular or cholesterol content increases – cholesterol pool it's sometimes called – you get a downregulation of the LDL receptor, and that results in increased plasma levels of LDL cholesterol. Conversely, when you have the cholesterol content decrease, the opposite occurs, you have an upregulation of the LDL receptor, and you have a decrease in plasma LDL cholesterol. And that's a mechanism, for example, by which statins work, because they inhibit the pathways of synthesis, leading to liver production of cholesterol, it also has certain dietary compounds work. So, for example, some of the allicin compounds in garlic inhibit an enzyme that's actually upstream from HMG CoA Reductase, which is the target for statins called squalene monooxygenase, and so, that's how certain doses of garlic can have lipid lowering effects by inhibiting the pathway of cholesterol synthesis in the liver. And this also then relates to diet, okay, so, again, if you look at this, if there's this argument that we really need this important molecule coming from the diet, and that we need, for example, levels of say saturated fat and cholesterol rich foods, there's two primary pathways in the intestines through which cholesterol might be absorbed from the

diet. But if you actually look at what they primarily do, they tend to re-excrete dietary cholesterol from the lumen back into the intestines. And in liver cells, there is responsible for excreting cholesterol into bile, because those two are intimately linked, the net effect is that, on any given day, ultimately, cholesterol is secreted into bile at rates that match the production of bile salts. And so, ultimately, this is a fine balancing act regulated primarily by the liver, which serves to maintain that, and this applies to, because it means that most cholesterol, if we were to measure cholesterol in the intestine, would not actually be derived from diet. It would still be from internal sources recycled in the liver, and then excreted via bile into the intestines.

And so, what that means ultimately is that the net daily synthesis of cholesterol in the body is always equal to the amount of cholesterol lost in feces through this bile recycling. But again, the idea that we need some sort of large amounts in order to facilitate bile acid secretion or to facilitate bile acid production just isn't the case at all, because it's always regulated quite tightly to the net level of excretion matched to the net level of endogenous synthesis by these negative feedback mechanisms. So it's almost a self-defeating argument based on what we know about how cholesterol balance is maintained and regulated by the liver, to argue that more is needed for, for example, bile acid production, when, in fact, this is a really tightly regulated system that matches that secretion to production, as it relates to both bile salts, bile acids, and cholesterol in the liver.

So I think in sum, the reality is that cholesterol in the body, if we exclude kind of the typical western diet, etc., if we're just talking about mechanistically, the LDL receptor and its negative feedback loop mechanisms, and the mechanisms of cholesterol endogenous production and regulation of balance in the liver, are all designed to maintain or to be able

to maintain LDL cholesterol circulating levels at thresholds under which atherosclerosis can progress, while facilitating more than enough cholesterol production and delivery to cells for all of these important functions.

DANNY LENNON: Yeah, and I think those steps are really important to keep in mind because they are the best way to think through some of these claims. So maybe I'll just recap on essentially what you've laid out there, because I think it's important going forward in this conversation for people to bear that in mind, so you started by saying we have this regulation of cholesterol balance at the liver, we have this molecule cholesterol that is hydrophobic, so it's this water insoluble molecule, whilst that is beneficial for its role within the cell membrane, it also has this potentially problematic aspect of making it harder to remove from plaque in the arterial wall, which we'll probably circle back to. Therefore then to move this molecule around the body, it's packaged within a lipoprotein, we have then VLDL, so very low density lipoproteins contain triglycerides and cholesterol, and as it deposits those triglycerides, it becomes more cholesterol rich, and then, it eventually becomes this low density lipoprotein. The LDL receptor then is what allows cholesterol to be delivered into a cell. These LDL receptors bind to Apo B 100, which is on the surface of this lipoprotein, that allows the lipoprotein to be brought into the cell, cholesterol can be removed and used in the cell as needed. And the number I think you said was about 5% of the cholesterol is needed for cell membranes, if I have that figure correct. And then under normal conditions about only 10% of the maximum capacity of the LDL receptor is expressed, and all that is to go to say that the LDL receptor has this really high affinity for LDL, therefore, that allows us to have enough cholesterol delivered, whilst maintaining low levels of serum LDL particles, and low enough – by low in this context, we mean low enough that atherosclerosis doesn't

rapidly kind of progress. Is that accurate to that point?

ALAN FLANAGAN: Yeah, absolutely. And that if that cholesterol in the cell did get low, then there are mechanisms that kick into place to increase the expression of the LDL receptor, so it goes out and grabs up more cholesterol, and that solves that problem. And conversely, whether from genetics or diet, if there are factors then that have a downregulating effect on the LDL receptor, because they provide too much cholesterol delivered to cells, once over 5% of lipids in the membrane is cholesterol, well, then it will do the opposite, and we'll end up with high LDL cholesterol levels because the cell has gone, now we don't need any more, we've downregulated LDL receptor activity, so it's not pulling LDL and the cholesterol in it out of the circulation.

DANNY LENNON: And actually one of those genetic examples from that Goldstein and Brown paper is in the context of FH or familial hypercholesterolemia, where in FH cells, you have this, they essentially lack functional LDL receptors. And so, to maintain that normal level of cholesterol, they synthesize more cholesterol, leaving this excess amount of these LDL particles outside the cell, so, in other words, in circulation. And so, when we have these LDL receptors that are deficient, these LDL particles now can build up a number but also circulate for kind of prolonged period, increasing, therefore the risk of them getting into the arteries, and causing atherosclerotic plaque. And so, that kind of highlights not only that genetic example, but maybe gets us on to another concept we might revisit later on in relation to residence time, or how long these particles are hanging about, but certainly, we have this elevation in LDL particle number. The other thing that I was thinking, as you said, that you mentioned, statins, which I know we're going to certainly come back to lipid lowering drugs a bit later on, and its ability there to impact HMG CoA Reductase, but there's also effects statins can potentially

have on LDL receptors as well as I'm aware of, so there's kind of a potentially a double benefit?

ALAN FLANAGAN: Yes, so this is really important, actually, just, I guess, to round off that section, is that every genetic condition associated with profound increases in LDL cholesterol, and therefore cardiovascular disease, both events and mortality, all four of these conditions, there's a couple of types of familial hypercholesterolemia that depends on the exact genetic, whether it's heterozygous or homozygous, so, for example, people with heterozygous FH produce half the number of LDL receptors, someone without the condition. And, as a result, they have two and a half fold higher levels of LDL, and that is associated with a pronounced increase in cardiovascular disease, that often can occur this side of 50 years of age. But that one is a frequency of about one in 500, so it's one of the most common monogenic diseases. But the really awful looking out is homozygous FH, which is about one in 1 million people, they have LDL levels that are six to 10 fold higher, and often, people can have and die from heart attacks in childhood and adolescence with that level. And there's two others as well, and the important point here is that all of these conditions ultimately involve the LDL receptor, and all of the drugs that have been developed to lower LDL cholesterol, and indeed, the dietary interventions that lower LDL cholesterol, all act ultimately through the LDL receptor.

So in the conditions that increase your risk of dying or a cardiovascular event, it's because whatever the condition, it decreases the LDL receptor, or you just don't really have it functioning at all. And all of the genetic conditions on the other side that associate with lower cardiovascular risk over the lifetime, so, for example, you can have a genetic condition that affects PCSK9, and if you have that, if you're lucky enough to have one of them, then you can have almost like a 90% reduction in

your risk of coronary events because the LDL receptor is not inhibited at all, which is what PCSK9 actually does. And all of the drugs and dietary interventions, all act through upregulating the activity of the LDL receptor. So it is the unifying final common mechanism across increased or decreased risk comes back to the activity and expression of the LDL receptor.

DANNY LENNON: So with that, you've mentioned a number of things thus far, around the endogenous production, we've talked about the LDL receptor and its importance there. Some of the aspects I think that we can also get into relate more to some of this cholesterol recycling that we've mentioned, and maybe even the lipid protein remodelling because that tends to be also another counterpoint that could put forward of, okay, there may be this increased LDL, but the actual issue is certain types of lipoproteins, and only if they are either small dense LDL, or maybe only if they're oxidized LDL particles, only then would they be problematic as opposed to just globally a high LDL cholesterol number being problematic. Where should we start moving through some of the mechanisms to try and get some answers to those types of questions?

ALAN FLANAGAN: Yeah, I think that the starting point, the easiest kind of point to departure is something we've discussed in a couple of the statements, and indeed in the kind of written response to Dave Feldman, which is, ultimately, any lipoprotein, of a certain particle size, is capable of penetrating the artery space. Any lipoprotein, less than 70 nanometers diameter is capable of penetrating the artery. So, people could say, well, why the focus on LDL and, indeed, this is often one of the arguments, oh, but it's VLDL remnants or it's chylomicron remnants. Okay. The reason why the focus is on LDL is because it's the primary carrier of cholesterol in the blood. It is far and away, carries the vast majority of cholesterol in terms of what we would call forward cholesterol transport, the

transport of cholesterol to tissues. But there's a couple of lines of evidence that really show how it's the cholesterol content. So yes, the focus is on LDL and LDL is considered causal, because it is the primary carrier of cholesterol in the circulation. But what really points the finger at the cholesterol content of these lipoproteins, this wonder molecule, that, right, is like we've said, it's not that it doesn't do some good stuff, and very important physiological functions; it's just that it's a double-edged sword, and its characteristics that make it beneficial above a certain threshold of circulation also are its, well, our downfall as far as plaque in the arteries.

So if you look at studies that have adjusted for, mutually adjusted for, say, remnant lipoproteins, so this is the cholesterol content in, for example, very low density lipoprotein remnants and chylomicron remnants. So what do we mean by this concept of remnants? Well, remember that we said that cholesterol will be packaged into a lipoprotein, and it will also have triglyceride there. And for chylomicrons, in particular, which are not atherogenic in terms of their baseline size, they have mostly triglyceride and small amounts of cholesterol, and then, VLDL, so chylomicron's dietary intake of fat, and then VLDL synthesized in the liver would have slightly more cholesterol, but also very triglyceride rich. And then as the triglyceride is broken down in those respective VLDL and chylomicrons, you create these more kind of molecules that are carrying more cholesterol, and they're now of a certain size, but they're capable of actually penetrating the artery. But if you were to look at the incidence rates, or the hazard ratio or relative risk of cardiovascular disease with remnant cholesterol and compare it to LDL cholesterol, you'd actually see nearly similar trajectories. And if you actually kind of mutually adjust for both of these factors, remnant cholesterol and LDL cholesterol, you still get similar outcomes, although LDL cholesterol is still a slightly better predictor of certain outcomes like

myocardial infarction. The point is that the elevated blood levels of cholesterol alone, whether in LDL or remnants, is sufficient to drive atherosclerosis once it's above certain thresholds. And then, the second line of evidence comes from some modeling work in Mendelian randomization, which looked at lipoprotein A.

Now, the low carb community have jumped all over lipoprotein A, and we've discussed this before how they're saying, they're happy to say LP little A is causal. And that argument is the most self-defeating argument I've ever seen from that community. It explicitly acknowledges by default of that argument that LDL is itself causal, like, they can't make both arguments. LP little A is effectively an LDL molecule, but it was a Burgess & Colleagues paper from 2018, where they thought, right, what if it's the cholesterol payload into the arteries that's ultimately, and this is where we're looking at this wonder molecule going into the arteries, and becoming less of a wonder molecule when it's there. So if you took per mass 38 milligrams of cholesterol would contain about this 38 milligrams of lipid of low density lipoprotein, of LDL will contain around the same amount of cholesterol as 100 milligrams of lipoprotein A, if you're matching the cholesterol content of both of these mass weights of lipoproteins. What they did was they looked at the effect the risk reduction of lowering LDL by 38 milligrams, and LP little A by 100 milligrams, and it was basically identical, it was identical.

And so, again, this is pointing to the cholesterol content of these lipoproteins being the factor that unifies the atherogenicity of all lipoproteins in circulation that are capable of penetrating the artery, and ultimately, it's the deposition of cholesterol in the artery wall. And in order for that deposition to happen, there has to be sufficient circulation cholesterol levels in lipoproteins above a certain threshold, and that, obviously then, because of the

presence of Apo B, when these molecules go into the artery, because of the presence of Apo B, it binds to proteoglycans in the artery, and then they're retained, they're basically like Velcro, they go in, they get stuck, and then suddenly, this waxy hydrophobic molecule called cholesterol, that's great when it's in cell membranes to about 5% of total lipids, is now deposited in an area where its very properties that made it beneficial in cell membranes when it was out of circulation and stored intracellularly now make it prone to the processes that we know occur after retention of that Apo B containing lipoprotein of which the majority is LDL in the artery, which is the immune and inflammatory and oxidative products, and oxidative processes that then occur following retention of that lipoprotein. So all of this is to point to the cholesterol content of the lipoproteins, the cholesterol payload in the artery wall as the factor, and the reason LDL retains the prime focus is simply because of its role as the primary carrier and the carrier of the majority of cholesterol in circulation.

DANNY LENNON: Yeah, and I want to try and reconcile a couple of things to prevent any confusion on this, because we've just acknowledged here that the cholesterol content or the cholesterol payload here is important, and it's certainly not benign how much of the cholesterol is ending up in the arterial wall. But we've also previously discussed how you can get a refinement of risk when you look at something like Apo B number relative to something like an LDL cholesterol number. And so, maybe just to explain that for people that maybe didn't hear any of those previous conversations, in all those different types of lipoproteins that we've just mentioned, so an LDL, IDL, VLDL, LP little a, and those kind of chylomicron remnants, all of those we consider to be the atherogenic lipoproteins, and those contain an Apolipoprotein B on the lipoprotein itself, so there's one of them on each. And so, by getting an Apo B count, we're essentially counting how many of all these different atherogenic particles there are. So

therefore, the idea being that's a better predictor of risk than, say, LDL cholesterol or an LDL particle number. And so, there's, again, a slight difference there at the LDL cholesterol number, which is the typical LDL-C you see on a standard lipid panel counts up how much cholesterol is contained within all these LDL particles. And then, the LDL particle number would be how many of those particles, and then, therefore, we could think simply of the Apo B as being how many of the total number of these atherogenic lipoproteins are. Therefore, to try and kind of reconcile that, whilst we can acknowledge here the cholesterol payload, the reason why the Apo B is particularly important is if you have way more of these atherogenic lipoproteins in circulation, there's an increased likelihood of them getting into the arterial wall, and then depositing that cholesterol which is still having this negative effect. Is that something that you think kind of clears it up, or is there anything you'd add just to make sure that we're not confusing people with the cholesterol component being important, but also that Apo B, or the number of these lipoproteins has an enhanced risk kind of assessment, compared to, say an LDL cholesterol number?

ALAN FLANAGAN: Yes, and that tends to be this process, like you said, or what would be known as discordance and concordance. And so, this occurs based on Samia Mora's research in about a quarter of the population, so give or take, 25% of people may have discordance between their kind of measured LDL cholesterol, and actually the number of particles that are atherogenic in the circulation, and in those individuals, certainly, a direct measure of Apo B is going to more accurately quantify the risk, and indeed, now, I mean, the recommendations, generally speaking, even in primary care screening seem to be moving, or the recommendations are to move to direct measures of Apo B in order to quantify this. And that's really important, but again, the basic core tenet of the point that we're making remains unchanged that in that

context, you have this cholesterol payload in the arteries from the increasing number of particles.

But that brings us I think just around this point to add nicely to a very common line of argument, which is, oh, it's all about particle size. And there's an excellent Allan Sniderman review from November 2019, which talks about Apo B specifically, but really makes the point that because we know all of these particles under a certain diameter size can penetrate the arteries, what you get with smaller particles is less cholesterol payload, shall we say, per particle, less cholesterol is carried in a smaller particle. In a larger particle, you get more cholesterol carried. So yes, with smaller particles, you might get more net penetration of the arteries, there are more particles in the arteries, and there may be more retained. But the actual net total deposition of cholesterol is a reflection of how much is carried in the first place, and these are smaller particles or less. Conversely, with larger particles, despite the kind of rhetoric of these are fluffy, cuddly particles doing great stuff for your immune system that the low carb community would posit, they carry more cholesterol per particle. So yes, less particles penetrate, yes, less particles retain, but the net effect, overall, kind of pound for pound to use that expression is relatively similar next cholesterol deposition within the arteries. And you can notice this within the actual cardiovascular science literature, not just listening to random engineers that think they're smarter than that whole community is a lot less of a kind of emphasis on particle size. It's acknowledged that it is an important factor in the risk picture, and certainly, one that warrants accurate quantification, so as not to kind of almost misclassify an individual and their potential risk. But ultimately, then the kind of the take home point seems to be to say that really, all atherogenic lipoproteins, all lipoproteins sizes for LDL are equally atherogenic in some respect.

DANNY LENNON: Right. And at certain point, particularly with the types of levels we're talking about, and that those types of extremes, it's just a completely moot point. Right? When you have so much Apo B containing lipoproteins going through circulation, at that point, that's what's driving your risk, it doesn't matter about the size, if you just have so many of these lipoproteins, you're at elevated risk. So with that, I think that maybe sets us up nicely to start discussing some of those outcomes that were discussed a bit earlier, both, or we have kind of like four main things maybe to work through here, the mortality piece, which typically includes cancer, we can look at the infection immune system stuff, we can look at lipid lowering drugs specifically, and then, maybe we'll finish off by looking at the brain. Before getting into those outcomes, is there anything we've left off kind of mechanistic wise that is important, or, can we maybe cover that throughout?

ALAN FLANAGAN: Yeah, I don't think so, so far. I think we've got most bases covered so far.

DANNY LENNON: Cool. Well, let's start with cholesterol and mortality or all-cause mortality, and then we can maybe, as a subset, look at the cancer stuff afterwards. And this is really something that for those of you listening who have read one of our recent sigma statements that was authored by Alan called Low Cholesterol & Increased Mortality Risk, clarifying the confusion, that's available on the website now, and I'll put it in the show notes of this episode as well. This was an issue that we discussed, and this comes from many typical lines that look at maybe either a lack of an association, or maybe even an inverse association between LDL cholesterol levels, and then mortality. One of maybe the best pieces maybe to lead off with because this is probably one of the most, I think, commonly referenced or cited pieces in support of the idea, certainly that I've come across is the 2016 systematic review by Ravnskov and colleagues, and this appeared in BMJ Open, and, as the

name implies, the title of that study was: Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systematic review. So this was like 19 cohort studies they looked at, and reported that there was an inverse association between all-cause mortality and LDL cholesterol in 16 of those cohorts, representing 92% of the total number of participants, leading to the conclusion that, "Since elderly people with high LDL cholesterol live as long or longer than those with low LDL cholesterol, our analysis provides reason to question the validity of the cholesterol hypothesis." And this kind of paper and this conclusion is relatively representative of other points of view, within people of the same persuasion. So maybe we'll maybe first address that, because I think that kind of represents generally other things that we could point to, but was a kind of good focal point for that statement. So maybe let's open up on there.

ALAN FLANAGAN: Yeah, and I mean, that paper is, I mean, it's almost a who's who of quacks from this space. I mean, Uffe Ravnskov is notorious, I mean, I don't even think he has an academic affiliation at this point. David Diamond, Malcolm Kendrick, Aseem Malhotra, it's an all-star lineup, shall we say. And it's commonly cited, I would imagine that, and certainly I've come across it the most whenever this question has come up, and there's a couple of ways that we tried to kind of think about this, and that are best to think about this, I think, as far as, particularly, if we're looking at elderly populations. One is the concept of endogenously lowering LDL, so if you have naturally lower LDL levels, and the other is then lowering LDL through intervention, and with that, particularly, we'd be focused on drugs. And with the former question, naturally, kind of, lower LDL levels, and whether there's an association with risk or whether we're seeing this only in the elderly, a really important factor there is whether there's this kind of risk across the lifespan that you would

see if someone had naturally lower LDL, and this is because, as we've highlighted in other statements, the effect of LDL, like, it's not like your LDL just goes high, and two months later it doesn't... It's a cumulative exposure that builds up over time, and so, you have, depending on the diet and the lifestyle and everything else, potentially from the second decade of life, LDL levels elevated to a threshold at which over time, there is this continual exposure to levels at which atherosclerosis can progress and develop, and further progress and develop with thickening of the arteries, and expansion of plaque. And so, this is really important than because a lot of these studies and this Ravnskov scuff paper in particular that you've referenced to, they don't account for that exposure over the course of the lifespan. They're taking people who were already 60s, and often the kind of the more pronounced apparent lower risk is in people that are over 70, as in, lower risk of mortality with higher cholesterol levels at that point.

So there's two issues that arise with these later studies. One is that if we look at research, Mendelian randomization studies for people with genetic exposure to low LDL levels, so we're not talking about FH here, we're talking about mutations in the HMG CoA Reductase enzyme activity, so they have lower synthesis of cholesterol in the liver, or, we're talking about people with PCSK9 mutations, and they have they have a hugely lower LDL cholesterol level, AND they have it from birth, because it's a genetic defect. And there are also other genetic mutations in some of the pathways associated with intestinal absorption and regulation of cholesterol at the level of the gut. Hands down PCSK9 mutations win the genetic lottery as far as lowering LDL, and then lowering your risk across the lifespan of cardiovascular disease, and it's quite profound, the risk reduction. On average, if you look at the HMG CoA Reductase mutations or some of the gut ones, you can have a greater than half a risk reduction, like, over 50% risk reduction with some of these

genetic conditions. And there's no evidence of any sort of adverse outcomes over the course of the lifespan, or certainly some of the health outcomes that would be claimed by people in this community for having low LDL levels. And some of these conditions, you might actually have levels, particularly with PCSK9 mutations of sitting around the kind of 40-50 milligram per deciliter mark. So is there a risk of mortality, if you have low cholesterol levels for your entire life? No, absolutely not. There's actually just no evidence for that, and indeed, your cardiovascular risk specifically is profoundly reduced.

So that then makes us look more to what factors could be at play in the over 60s, or in this kind of elderly age group. One is that you have a survivorship bias. There are people because you're studying a population, higher risk individuals have already died, and they're not involved in the cohort. You have another factor at play, which is the actual use of drugs themselves. So we know that if you're intervening in people later in life, six-seven decades with statins, for example, then atherosclerosis is already quite advanced because of this concept we've discussed of this cumulative exposure over time. So they already have quite advanced atherosclerotic plaque developed already. So you don't tend to get the net benefit, ultimately, from intervening. You still do get a risk reduction, but it's not to the same magnitude. But the point is that many of these patients in these studies have multiple comorbidities, and they're on multiple medications. And their LDL cholesterol may not come down to the same magnitude as if you started treating someone in their 40s. So compared to others, it may still appear to be higher, but they're still on drugs that are into prolonging life.

So these are factors, but whether it's survivorship bias, whether it's the fact that there's this burden of comorbidities, and they're high risk individuals anyway in this age

group, whether it's the fact that they're being treated, even though it hasn't made much of a dent in their LDL cholesterol levels, the drugs are still having an effect on prolonging life. And one way to kind of then kind of resolve this in this age group is to also look at Mendelian randomization studies that actually look across the lifespan. So we've discussed genetic predisposition to lower LDL across the lifespan does not increase your all-cause mortality risk, and lowers your cardiovascular disease risk. And we've discussed how there are these various confounding factors in these cohort studies where people are 60-70 years old at baseline. So if you look at Mendelian randomization studies that have stratified people according to their level of LDL, into say, lower, medium, and high LDL categories, and you then stratify them by decade of life, under 50, 50 to 60, 60 to 70, all the way to over 90, then across every single decade of life that you've broken this down to, high LDL genetic score is associated with higher all-cause mortality risk. This isn't even cardiovascular. This is the darling all-cause mortality. And so, you still see this across the lifespan, when we're factoring out these confoundings because this is genetic exposure to higher versus lower LDL levels. Then as your genetic LDL score increases, so does risk of all-cause mortality in every decade of life, for the most part, 50, 50 to 60, 60 to 70, 70 to 80, and 80 to 90.

So this study and this line of research really shows that people with genetic predispositions for longevity, because this is often the claim is that, like, oh, well, you want high LDL, because it's going to make you live longer, based on these cohort studies, well, actually no, the associations with longevity in the Mendelian randomization work is actually with lower LDL cholesterol levels, because of their genetic predisposition than the general population. So all in all, there’s a couple of lines of evidence that we can come at to take issue with and, in effect, refuse the veracity of the evidence that suggests that higher LDL is protective. And

that leads us then to the question of, well, in this age group, okay, because a pushback could be fine, you've got your genetic studies that say low LDL over the course of the lifespan is beneficial, but what if it's just low LDL in your elderly years, in your 50s and 60s, that maybe you just don't want it low at that point, because all of these other benefits. One big issue, and this research goes back to the 80s as well, is this concept of the unsuspected sickness phenomenon. And this is where there is a lowering of LDL cholesterol as a metabolic consequence of an underlying latent disease, i.e., a disease process that has not yet been diagnosed. And this is most associated with cancer as an outcome, and gives rise to most of the claims in evidence that there's some relationship between low LDL and cancer. And so, there's a few ways of teasing that out, and we've discussed it more thoroughly in the statement. One is that you eliminate early follow-up, so that means that people have the underlying disease already, then you get rid of the, say, first four years of follow-up, or two years of follow-up, and that kind of excludes these people who could have already had the disease nearly close to diagnosis, but not diagnosis at the time they started the study. And in a lot of studies that will abolish the association between low LDL and cancer risk, and then other studies have actually looked at the kind of temporal relationship between how far out from a diagnosis LDL can lower as a metabolic consequence to cancer in its relationship to kind of underlying latent disease, and one study, in particular, that we cited looked at cancer incidence and mortality over 18 to 20 years, and found, yes, this relationship between low cholesterol levels and cancer was strongest within this first two years of follow up. So this really suggested this effect of underlying latent disease, and most of those associations attenuate or abolished once this kind of concept of this unsuspected sickness phenomenon is factored in. So this suggests that this association is primarily one of reverse causality.

DANNY LENNON: A number of things there that's worth tracking back over, so there you not only address the cholesterol and all-cause mortality, but then it also sets the stage for this kind of subset of looking particularly at cancer, and I think in the statement, you kind of started with, we do indeed have this associational work from work in the 80s, where we see this association between low LDL cholesterol and subsequent cancer risk, which is what a lot of people end up hanging their hat on. But once that's investigated, we can see that there's this unsuspected sickness phenomenon, where we have, essentially, undiagnosed latent disease, so when you get rid of that first two years of follow-up, you start to see these things dissipate away. And related to the cancer and the unsuspected sickness phenomenon is also in relation to other types of illnesses and infections. And so, maybe to actually serve as a good way to show people the type of argument that we were just discussing that you put forth the counter evidence to, I wanted to play this particular clip that people will be familiar with if they did indeed read the statement, but I think it perfectly outlines the type of claim that is made. But I also think it does a really good job of highlighting how convincing this can be, if someone's coming across this for the first time. So this is Dr. Aseem Malhotra discussing this impact on infections, immunity, cancer, etc., and particularly making reference to people in that older age group.

[Video Being Played] So over 60 LDL there was no correlation with heart disease, so the higher LDL, no correlation. What was also interesting we found is that the higher LDL over 60, statistically, you were more likely to live longer. So it seemed to be protective against an early death, and one of the reasons for that is, which is not something commonly discussed, is that LDL cholesterol has a likely role in the immune system. Older people are more vulnerable to dying from infections, and it seems there's probably some protective mechanism from that

perspective, and that's why it may be protective, but certainly there's no correlation with heart disease. The next question is: should we be lowering LDL? Well, I did another systematic review published in BMJ evidence based medicine last year, and it was me and two other cardiologists, and what we did is we looked at all the drug trials, forget about diet for a second, drugs are very potent lowering (agents) of LDL cholesterol. Diet can have a very small effect, but actually drugs lower them much better. So if the drug effect is very, very large, or certainly negligible, then we can almost completely exclude the diet. And what we found was the traditional sort of mantra coming out from scientists, and let's be honest, I think, most of them are well intentioned, but they are funded. Most people that put guidance on cholesterol, who determined guidance for doctors have got huge financial ties with the drug industry that manufacture drugs that lower cholesterol, so there's a huge bias there. But if you look at all of the evidence, lowering LDL cholesterol, bad cholesterol with drugs, even varies dramatically 40 or 50%, there was no clear correlation in reducing heart attacks and strokes. So basically, what I would say is, for the overall majority of people, well, in fact, everybody, my view is focusing on lowering LDL cholesterol, so called bad cholesterol is a complete and total waste of time, both from drugs and from diet, absolute waste of time. And I can easily back that up in any forum, and with any scientist, and anywhere around the world, I would easily be able to back that up with very good strong evidence and explain it.

DANNY LENNON: So there you go. If anyone listening is a lipidologist or works in academia with lipidologist, please extend the invite to them that Dr. Malhotra will debate them anytime.

ALAN FLANAGAN: Yeah, this is, for context, anyone, the paper he referred to that they published last year was referred to as “an extraordinary deception” because of their methodology, yeah, it was a joke of a paper that was absolutely torn apart

by various respondents in the science media center. And actually, when you took the exact same data that they used, and used it in an intellectually honest and statistically robust way, it showed exactly what we would expect to see from statin interventions, which is a risk reduction.

So yeah, so that argument then brings us like everything we were just discussing relates to, you know, we started out this part of the conversation with this idea of distinguishing between naturally endogenously lower LDL cholesterol, like, is there a risk there at any stage of the lifespan, particularly, in the elderly. If there is this apparent association in the elderly, what might explain it? And then there's the second question of exogenously lower LDL – so deliberately intervening to lower LDL to reduce cardiovascular disease risk. Now, this can be broken down into two kind of component parts of the arguments, and it will tend to be by the likes of Malhotra et al. One is the just the question of whether intervening to lower LDL reduces cardiovascular risk. The second, because you might get the odd person in that community that might acknowledge there's a lower cardiovascular risk, but will then say, but there's a tradeoff that's too much of a compromise, because if we lower that mortality risk from cardiovascular disease, because we've lowered this super molecule, we then increase their risk of death from other diseases.

Okay, there's an enormous body of evidence that at this point from statin interventions, and from non-statin interventions, really shows this just not to be the case. So, one that we mentioned in the statement was a meta-analysis of 28 statin trials, looking at both cardiovascular and non-cardiovascular mortality in the elderly, and if you looked at the benefit to lowering cardiovascular disease, it was absolutely present. But there was no competing offset increase in risk for non-cardiovascular mortality or for all-cause

mortality. And so, this is present in the statin interventions, you know, when they were looking at cancer incidence, for example, or deaths from cancer, per 38 milligram reduction in LDL cholesterol, or, if you're in the UK, one millimole per liter, just nothing, just no association whatsoever. And actually, if you factored in everything, rather than we're talking about specific cancer and cardiovascular mortality risk, if you looked at the metric that they love to cite, which is all-cause mortality, it was 9% lower. So a modest reduction, but a major factor here, and the magnitude of a factor, as we kind of alluded to, just in the previous segment was that the magnitude of your risk reduction relates to the age of intervention, and the average age of participants at baseline in a lot of the mega trials, the statin interventions is 63. And so, you don't necessarily always get the same magnitude of risk reduction as you would, if you intervened in, say, someone's 40s. So the earlier you intervene and get LDL lower, the greater the magnitude of the risk reduction. And that allows people like Malhotra to play some kind of statistical gymnastics to try and show that there isn't necessarily that much of a benefit to lowering LDL in the elderly. Well, it's not that there isn't that much of a benefit, it's a reflection of the advanced nature of the disease at that point in the intervention.

And then there's also obviously we need to consider now the body of drugs that are available. So we've discussed statin interventions, there's also been analyses of RCTs of non-statin trials. So these are other drugs that use, for example, PCSK9 inhibitors or Ezetimibe, so bile acid sequestrants that inhibit cholesterol absorption at the level of the gut. But what was really interesting about these analyses was these drugs have been used in the context of participants, many of whom have already achieved low LDL levels of baseline. So this comes back to the whole idea that you don't want to lower it more, you don't want to lower to, like as Saladino said at the start, 40 to

50 milligrams. Well, actually, these are people with baseline levels of LDL, a give or take about 70 milligrams per deciliter, and they're lowered too often in these trials where drugs are added to statin therapy, 90 milligrams per deciliter. And we can discuss how low some of these big mega trials have gone, when we discuss that kind of how low can you go concept in a minute. But there was absolutely no association with cancer risk or with any other serious events, whether that was kind of diabetes or stroke, or even myalgia which is kind of like muscle pain that is often a reported side effect. And so, these are drugs that all, like we said before, they act through the same mechanism, in terms of cardiovascular risk reduction. The benefit to cardiovascular risk reduction is very clear, the reason it might not seem as pronounced in people 60 plus or even 70 plus is because their arteries are already full of plaque and they are high risk patients anyway. And pharmacological lowering of LDL, with any of these drugs does not increase any other health risks, either cancer or all-cause mortality.

DANNY LENNON: So from that I can presume you disagree with this statement?

ALAN FLANAGAN: I would say that the statins are probably the greatest hoax ever perpetrated on the American public in terms of medicine.

DANNY LENNON: Agree or disagree?

ALAN FLANAGAN: That's, god, they love it, don't they, like, the hoax...

DANNY LENNON: The greatest hoax.

ALAN FLANAGAN: The greatest hoax, yeah, along – he mentioned Ancel Keys somewhere in that episode, definitely.

DANNY LENNON: Of course, yeah.

ALAN FLANAGAN: It's so painful...

DANNY LENNON: While we're on statins, if we were to maybe paint the most generous picture of someone to come along and say, okay, statins or LDL cholesterol lowering per se, I don't think is that bad, but what I have heard is that using a statin in primary prevention isn't going to really reduce my individual risk that much, and any medication can come with side effects. And so, therefore, I'm not really sold on the idea of using it. That's another type of point that's commonly put forward, if you're not really going to benefit the vast majority of people, particularly, in primary prevention, and yet, you're inducing some type of risk, because any medical intervention has a risk. What do you tend to make of those types of claims?

ALAN FLANAGAN: I mean, you know, God, we see some similar arguments with COVID, don't we, as far as, like, well, I'm kind of low risk and I'm healthy, and I've had COVID, and I've got antibodies. So I'm not, you know, there are grains of legitimacy in these discussions. Right? And a lot of it relates to particularly for cardiovascular disease and statins, a lot of it relates to how we currently compute risk. But there is a slow shift in this, and one of the one of the biggest factors with this is that the levels that we've kind of, certainly, to date, defined as "normal" may not necessarily be optimal or ideal, as far as kind of risk reduction goes. And all things being considered, there's also the level of walking – it's not the drug per se, what really we need to focus on is actually what's the magnitude of achieved LDL reduction. And so, yes, there can be a variation in the magnitude of LDL reduction and apparent kind of inconsistencies or certainly an apparent lack of magnitude of benefit, and, in kind of my opinion and interpretation, tends to relate to that magnitude of risk reduction. The sooner though that someone gets that level lower, the better, and that seems to be just gathering more strength as a paradigm. So if someone was saying, well, I don't really think I'm going to benefit for primary prevention, the question

would be, well, you may not benefit necessarily, if there's only, you know, if your levels are lowered from like 140 to 120 or whatever or to even a 100. And you may not necessarily see a benefit if you're starting at 40, and your follow-up at 45. So really, it's trying to reframe the kind of paradigm by which we think of this cumulative exposure over time, and the levels at which atherosclerosis can progress, and both of those factors, a clearer picture emerges that with reductions to levels of certainly under 80 milligrams per deciliter, atherosclerosis can be kind of arrested, and indeed can start to regress in the artery; and the earlier that that's achieved in life, the greater the magnitude of risk reduction is. So there are reasons why there may be that apparent lack of benefit in primary prevention, but the cumulative weight of evidence now really does point to sooner better than later as far as intervening and certain thresholds of low being better than kind of some of the more kind of, I guess, gray area levels of “normal” that we've currently defined levels of LDL as.

DANNY LENNON: Yeah, that cumulative lifetime exposure is, like you say, thinking of it in terms of the interaction between the absolute levels achieved, but by the magnitude of the amount of time over the life course that you have these lower levels. And so, therefore, based on and we'll probably come to this question of how low can you go, but on the premise that there likely doesn't seem to be an amount where we're seeing really much problem with going very, very low, it seems likely that it'd be hard to take a position of going very low with your Apo B containing lipoproteins over a longer period of time is going to reduce your risk, and the lower and longer as a combination those things are, then the greater risk reduction.

ALAN FLANAGAN: Yeah, absolutely.

DANNY LENNON: While you mentioned COVID just to – and also it fits in with our piece around infection, because the unsuspected sickness phenomenon

that you mentioned in relation to the Malhotra clip, but we also discussed with Austin Baraki on our recent podcast episode, and one of the things he talked about was that impact of infection on a variety of parameters, including LDL cholesterol. But as a beautiful way to knit those all together with your mention of COVID, this is the last thing I have for us.

[Video Being Played] If we're talking about COVID, it appears that high cholesterol, higher cholesterol is protective for infections like COVID.

DANNY LENNON: And so, that, of course, is going to be the case. So with that, do we have to round up anything there on lipids that we didn't get to – are you kind of happy with where we're at there?

ALAN FLANAGAN: Yeah.

DANNY LENNON: I should say lipid lowering drugs.

ALAN FLANAGAN: Yeah, lipid lowering drugs, I think we're, yeah, I think we're pretty good with.

DANNY LENNON: Excellent. Okay, so we'll start wrapping this up. We're kind of in the homestretch now. We won't take too much longer. I think the last thing that we had planned to mention, because it does come up, is around cholesterol and the brain, and this comes from a variety of different claims that are put forth and, of those, I tend to see it be something along the lines of to do with cholesterol within the brain, and we know it's going to have some degree of function within there; and then people will go from that point to say, if you have very low levels of say, serum cholesterol, they may even point to certain dietary patterns, like I often see people point to a vegan diet as problematic for brain function because of very low cholesterol levels that are achieved, and starting making connections with the fact that we see cholesterol within the brain, and therefore, there's a problem with very low levels of LDL. And, of course, earlier, we had that example from Paul Saladino, where he makes this claim

around when you lower your serum LDL, you see spikes in psychiatric events, suicides, violent homicides, and mood disorders, which I'm not sure what he's basing that on, but in relation to that just a general concept, we don't want to spend too much time on this. But any of those claims that get brought up around cholesterol, and it's kind of rolling the brain, where does the evidence come down on that?

ALAN FLANAGAN: Yeah, I just wonder whether, yeah, again, whether any of the actual evidence is being engaged in, so yes, cholesterol is in the brain; no, we don't want it particularly in high amounts; we've talked about the membrane thresholds for cholesterol. There's evidence for cholesterol, disordered cholesterol metabolism related directly to the amyloidogenic pathway in the brain, i.e., the pathway that results in the production of amyloid beta, the protein that builds up in plaque in Alzheimer's and dementia. The links between the head and the heart are quite striking both mechanistically, and in terms of potential benefit, and primarily, the brain as we've discussed before, is polyunsaturated fatty acids, and, in particular, DHA is very high in brain phospholipids. And there's mechanistic support for a role in phospholipid membranes that are enriched with DHA diverting the precursor protein for amyloid beta, down what they call the alpha-secretase pathway. So there's two pathways here, there's the alpha and gamma secretase pathway. So the alpha-secretase pathway is good. If you've got amyloid precursor protein, APP, you want to diverse it down there, because it reduces beta amyloid levels. On the other hand, this gamma-secretase pathway is amyloidogenic, and substrate processed through that pathway will result in the accumulation of amyloid beta protein, and cholesterol is involved in that, and cholesterol promotes the substrate binding to gamma-secretase pathway, when it goes over this threshold of associated with benefits in membrane and ultimately actually results in kind of membrane thickness per se. And so,

again, this is potentially one of the benefits to kind of mechanistically to DHA in the brain is that it might suppress that pathway, in particular, but it certainly appears that the role of cholesterol in this. And it relates to these, like I said, these membrane levels, so when you get these reductions in these membrane plasma allergens, as they're called, it inhibits cholesterol metabolism, and then you get increases in free cholesterol that actually inhibit the non-amyloidogenic pathway. So when you have increased membrane levels of free cholesterol, remember, we don't necessarily want that, that actually inhibits the processing of amyloid precursor protein and substrates through the non-plaque buildup pathway. Elevated free cholesterol actually then diverts to amyloid beta processing.

So if there is a role for higher cholesterol in the brain, it's probably implicated in the pathogenesis of neurodegenerative disease, and not really serving any protective function. And again, although we're talking about kind of certain brain specific mechanisms, the idea that there is a benefit to cholesterol in the brain, just doesn't appear to have any evidence, and this is, in fact, supported by statin interventions, and Brendon Stubbs, actually, who you had on there, was involved with his group of meta researchers a couple of years ago publishing a meta-analysis of statin intervention trials and dementia. And so, you do see a significant reduction in dementia and Alzheimer's risk from lipid lowering therapies, and that is possibly because there's the potential for cholesterol when it's, shall we say, kind of, in excessive requirements to do as much damage to the brain as to the arteries.

DANNY LENNON: So yeah, counter to a lot of the points that people may be hearing, and I wonder how many of those statin trials are reporting high numbers of violent homicides among the participants in the intervention arm, I look forward to seeing that data. We're just up on 90 minutes, so I think we'll kind of start closing

this out here. With that, maybe we'll just end with the conclusion to the two kind of main questions we've been just discussing today, which are, essentially, two sides of the same coin, or, two different sides of the same coin: Does low serum cholesterol cause a harm to health? And then, therefore, does high cholesterol level lead to health benefit? And I think we've kind of put forward, or, you have put forward the case against those propositions, and hopefully, people find your arguments compelling. And, if not, maybe they think it's statins are still a hoax, but I think you have done your best to put forth the arguments that you see fit, so if there's anything you want to add before we leave people go?

ALAN FLANAGAN: I think just to put some cold, hard numbers on this, because it comes back to this whole trope of like, the body needs cholesterol, bro. It's like, yeah, it does, again, no one has disputed that, just to put some cold, hard numbers on this for people. The LDL receptor itself becomes saturated at about point 0.06 millimole per liter, or 2.5 milligram per deciliter of available cholesterol. Right? So that means that the actual physiological maximum for total circulating cholesterol that could be required is about 25 milligrams, and any more than that could be surplus to actual requirements. And as Goldstein and Brown did look at, when is actual tissue, if this molecule is so important for all this growth and development, when is actually the highest tissue requirement for energy and substrate, in any given human's life? It's during the phase of infancy and early development. And mean cholesterol levels in that life stage, when we're going through our most rapid period of growth and tissue growth and development is 28 to 32 milligrams. And that covers the basis for the most kind of dramatic phase of tissue cellular requirements for substrates under our lifespan. And then, we also have evidence that under levels of give or take around 80 milligrams per deciliter, the evidence for atherosclerosis is pretty much absent. So for the cold, hard numbers, for all of

the kind of hysteria that like, oh, levels of LDL at low levels, the body needs more than that, there's categorically little to no evidence to support that there's any physiological requirement for more than the levels that I've just outlined. And to just reiterate the point about this molecule, as any paper from the kind of seminal researchers in this area from the 80s would highlight is that it exists in this balance, it is both true that cholesterol is a really important molecule that we need to do all of this stuff, and it is equally true that it is atherogenic and causes plaque in the arteries at certain thresholds. And the mechanisms that the body has developed have developed so that we can have both sufficient levels for the requirements that cholesterol is important for, without actually developing levels of atherosclerosis. And that is consistent with what we would see in kind of unacculturated or hunter-gatherer populations where their levels of atherosclerosis are virtually nil.

DANNY LENNON: Perfect. I think that does us, and I think that is an excellent way to summarize and end this episode.