

## Atherosclerosis: Its Cause and Its Prevention

I recently spoke at a university hospital and began the presentation by asking the audience to name the atherosclerotic risk factors. Various members of the audience spoke up, and the following was the order in which the risk factors were announced. I wrote them on the flip chart (easel) I used for the presentation: (1) family history, (2) diabetes mellitus, (3) cigarette smoking, (4) high blood pressure, (5) inactivity, (6) overweight, (7) aging, (8) malism, and (9) increased serum cholesterol. I then asked if atherosclerosis was a multifactorial disease or a unifactorial one. The answer universally was multifactorial. I then went down the list of 9 risk factors asking the same question of each, "Does this factor have to be present for atherosclerosis to occur?" The answer for each was "No" except for the last one, namely, hypercholesterolemia. But if that is the case, why was abnormal cholesterol not mentioned as #1 rather than #9? I have experienced the same scenario on many occasions. I believe a strong case can be made for there being a single absolute atherosclerotic risk factor and that atherosclerosis does not occur when that factor is missing.<sup>1</sup> Of course, all of these factors are determined by how they are defined; therefore, the definitions of each are crucial.

Although present in many patients, a family history of cardiovascular disease, however, that is defined, is certainly not necessary. When in medical school, I was taught that atherosclerosis was a degenerative disease, the consequence of living on planet Earth. Certainly that is not the case. Although more common in older people, young adults are not immune to atherosclerotic events. And men do not have a monopoly on plaques. Cardiovascular disease is the most common cause of death in women residing in the Western World. Juvenile diabetes mellitus (type 1) is a genetic problem: type 2 diabetes is a consequence of excessive weight, and cholesterol numbers are virtually never normal (to be defined later) in that situation. Cigarette smoking and/or elevated blood pressures are frequent in some societies where atherosclerotic events are rare. Exercise is quickly nullified by stopping at a fast-food outlet (meaning quick plaques) on the way home from the run. Although most patients with atherosclerotic events are overweight, an increased waist measurement is not a requirement for plaques to form.

### Evidence That Cholesterol Causes Atherosclerosis

If *dyslipidemia* is the cause of atherosclerosis what evidence might be presented to the jury that indeed cholesterol is the villain? In my view, there are 4 facts supporting the proposition that cholesterol is the cause of atherosclerosis.<sup>2</sup>

(1) *Atherosclerosis is easily produced in non-human herbivores (e.g., rabbits, monkeys) by feeding them a high cholesterol (e.g., egg yolks) or high saturated fat (e.g., animal fat) diet.* These studies initially were done by some Russian physiologists beginning nearly 100 years ago.<sup>3,4</sup> And atherosclerosis was not produced in a minority of rabbits fed these diets. No, it was produced in 100% of the animals! Indeed, atherosclerosis is one of the easiest diseases to produce experimentally, but the experimental animal must be an herbivore. It is not possible to produce atherosclerosis in a carnivore, with one exception, and that is in carnivores who have hypothyroidism due to thyroidectomy. The only condition I can think of which is easier to produce experimentally than atherosclerosis is an endocrine deficiency. If the thyroid gland is removed, the consequence is hypothyroidism unless the thyroid hormone is replaced.



In contrast to feeding cholesterol and/or saturated fat, it is not possible to produce atherosclerotic plaques in herbivores by raising the blood pressure chronically or by blowing cigarette smoke in their faces for their entire lifetimes, or by somehow raising their blood glucose levels without simultaneously feeding an atherogenic diet. Few audiences I speak to remember the absolute ease with which atherosclerosis can be produced experimentally.

Although presently it is commonly stated that "atherosclerosis is an inflammatory disease," I am unconvinced that inflammation or infection actually play a role in the production of atherosclerotic plaques.<sup>5-8</sup> Inflammatory cells are infrequent in plaques of coronary arteries studied at necropsy or in endarterectomy specimens. When present, the few mononuclear cells, even giant cells, appear to be a reaction to the deposits of lipid (pultaceous debris) present in the plaque. "Inflammation" appears to be a surrogate for elevation of serum C-reactive protein or various cytokines (interleukins-1 and-6, tumor necrosis factor, etc.), not for inflammatory cells in plaques. Thus, it is a definition situation, and the morphologic definition of inflammation is not applicable.

(2) *Cholesterol is present in the plaques.* Several studies in the 1930s nicely demonstrated that experimentally produced plaques in herbivores were similar to plaques in humans.<sup>9,10</sup>

(3) *Populations with relatively high serum cholesterol levels compared to populations with relatively low serum cholesterol levels have a much higher frequency of atherosclerotic events, a much higher frequency of dying from these events, and a much greater quantity ("burden") of*

plaque in their arteries. This factor was nicely supplied by the 7-Countries study<sup>11</sup> and the Framingham study among others.<sup>12,13</sup>

(4) Lowering serum total cholesterol and low-density lipoprotein (LDL) cholesterol levels decrease first and repeat atherosclerotic events.<sup>14–31</sup> Additionally, plaque size may decrease.<sup>32–34</sup>

In my view, the connection between cholesterol elevation and atherosclerotic plaques is clear and well established.<sup>2</sup> Atherosclerosis is a cholesterol problem! If one has elevated cholesterol and also has an elevated blood pressure, or smokes cigarettes, or has an elevated blood sugar, these additional factors serve to amplify the cholesterol damage but they by themselves do not produce arterial plaques! Societies with a high frequency of systemic hypertension or a high frequency of cigarette smoking but low serum cholesterol levels rarely get atherosclerosis.

### Differences Between Herbivores and Carnivores

Because humans get atherosclerosis, and atherosclerosis is a disease only of herbivores, humans also must be herbivores.<sup>35</sup> Most humans, of course, eat flesh, but that act does not make us carnivores. Carnivores and herbivores have different characteristics. (1) The *teeth* of carnivores are sharp; those of herbivores, flat (humans have some sharp teeth but most are flat for grinding the fruits, vegetables, and grains we are built to eat). (2) The *intestinal tract* of carnivores is short (about 3 times body length); that of herbivores, long (about 12 times body length). (Since I am 6 feet tall my intestinal tract should be about 60 feet long. As a consequence if I eat bovine muscle [steak], it could take 5 days to course through those 20 yards.) (3) *Body cooling* for carnivores is done by panting because they have no ability to sweat; although herbivores also can pant, they cool their bodies mainly by sweating. (4) *Drinking fluids* is by lapping them for the carnivore; it is by sipping them for the herbivore. (5) *Vitamin C* is made by the carnivore's own body; herbivores obtain their ascorbic acid only from their diet. Thus, although most human beings think we are carnivores or at least conduct their lives as if we were, basically humans are herbivores. If we could decrease our flesh intake to as few as 5 to 7 meals a week our health would improve substantially.

### Conditions Uncommon in Human Non-Flesh Eaters

Some extremely common conditions in the Western World are relatively uncommon in purely or predominately vegetarian-fruit eating societies.<sup>36–39</sup> These include: (1) *severe atherosclerosis* and its devastating consequences (heart attacks, brain attacks, etc.)<sup>40,41</sup>; (2) *systemic hypertension*: in societies who eat not enough salt for it to be measurable, the systemic arterial blood pressure is usually about 90/60 mm Hg, a level near what it is at birth, but a level in the Western World often associated with shock<sup>42–48</sup>; (3) *stroke*<sup>49</sup>; (4) *obesity*<sup>50</sup>; (5) *diabetes mellitus*<sup>51–53</sup>; (6) *some common cancers* (colon, breast, prostate gland)<sup>54–69</sup>; (7) *constipation, cholecystitis, gallstones, appendicitis, diverticulosis, hemorrhoids, inguinal hernia, varicose veins*<sup>70,71</sup>; (8) *renal stones*<sup>72</sup>; (9) *osteoporosis* and *osteoarthritis*<sup>73–76</sup>; (10) *salmonellosis* and *trichinosis*; and (11) *cataracts and macular degeneration*.<sup>77,78</sup>

### Cholesterol Numbers Needed to Prevent and Arrest Atherosclerotic Plaques

The guidelines for cholesterol modifying therapy published in 1988, 1993, and 2001, and modified subsequently, brought some rationale into the arena of who should and who should not be treated with “life-style changes” and/or lipid-lowering drugs or both.<sup>79–83</sup> These guidelines, however, were based exclusively on the concept of “decreasing risk” of events, not decreasing the formation of plaques. Because atherosclerosis is rarely genetic in origin (1 in 500),<sup>84</sup> and because the pharmaceutical industry has provided us with truly miracle drugs for lowering serum LDL cholesterol levels, it is time to switch gears from the concept of decreasing risk of atherosclerotic events to actual prevention of atherosclerotic plaques.<sup>85</sup> To make this change the guideline-recommended numbers must be lowered substantially.

According to the published guidelines, initiation of lipid-modifying drug therapy should be based on the serum LDL cholesterol level and the presence or absence of other atherosclerotic risk factors.<sup>79–82</sup> Lipid-lowering drug therapy is recommended in persons with only 1 or no non-LDL cholesterol risk factors if the LDL cholesterol is >190 mg/dl with a goal of <160 mg/dl. But, the most common LDL cholesterol number in people with heart attacks is about 140 mg/dl so this recommendation is not “preventive.” If >1 non-LDL-cholesterol risk factor is present then the LDL cholesterol drug-treatment number is >160 mg/dl with the goal of <130 mg/dl. If a patient has a coronary event, however (or is at high risk of an atherosclerotic event, such as having diabetes mellitus or a previous non-coronary atherosclerotic event), the LDL cholesterol goal is <100 mg/dl (with an “option” of <70 mg/dl).<sup>83</sup> If it is useful for the LDL cholesterol to be <100 mg/dl after a heart attack, surely it must be useful for the LDL cholesterol to be <100 mg/dl before a heart attack! Therefore, in my view, the goal for all populations—not just those with heart or brain attacks or diabetes mellitus or non-coronary atherosclerotic events—needs to be LDL cholesterol <100 mg/dl and ideally <70 mg/dl. If such a goal was created, the great scourge of the Western World would be essentially eliminated, “primary” and “secondary” prevention would be the same, and >100 million Americans—rather than the present 13 million—would need to be on a statin drug with or without ezetimibe or be pure vegetation-fruit eaters.

Thus, although not clearly established at this time, to prevent atherosclerotic plaques, the serum LDL cholesterol needs to be <70 mg/dl, the serum total cholesterol certainly <150 mg/dl, and the high-density lipoprotein (HDL) cholesterol >20 mg/dl. The latter—surely a surprise to most readers—is in patients with a serum total cholesterol level of about 130 mg/dl, and a LDL cholesterol level about 60 mg/dl. Exactly what HDL cholesterol level is required to prevent plaques is unclear at this time, but clearly if the LDL cholesterol is very low (e.g., 50 mg/dl) then a low HDL cholesterol—as long as it is >20 mg/dl—appears not to be dangerous. Ideal may be equal serum HDL and LDL cholesterol levels or a HDL cho-

Table 1

Statins and their equivalent efficacious doses, their effects on total (TC) and low-density lipoprotein (LDL) cholesterol, and effect on LDL cholesterol by ezetimibe alone and in combination with a statin

Rosuvastatin Crestor <sup>®</sup>	Statin (mg)					Fluvastatin Lescol <sup>®</sup>	↓ TC <sup>‡</sup>	↓ LDL <sup>‡</sup>	↓ LDL by Ezetimibe 10 mg	Total LDL ↓ by Statin + Ezetimibe 10 mg <sup>‡</sup>
	Atorvastatin Lipitor <sup>®</sup>	Simvastatin Zocor <sup>®</sup>	Lovastatin Mevacor <sup>®</sup>	Pravastatin Pravacol <sup>®</sup>						
1.25*	5	10	20	20	40	22%	27%	18%	45%	
2.5 <sup>†</sup>	10	20	40	40	80	27%	34%	18%	52%	
5	20	40	80	80	—	32%	41%	14%	55%	
10	40	80	—	—	—	37%	48%	12%	60%	
20	80	—	—	—	—	42%	55%	10%	65%	
40	—	—	—	—	—	47%	60%	10%	70%	

\* Not available.

<sup>†</sup> The 2.5-mg tablet is available in Japan but not in other countries.

<sup>‡</sup> These reductions are  $\pm 3\%$ .

lesterol greater than LDL cholesterol. In summary, the recommended guideline numbers—particularly those for primary prevention—are those for decreasing the risk of atherosclerosis events, not for preventing formation of atherosclerotic plaques.

### The Rule of 5 and the Rule of 7 in Lipid-Lowering Therapy and the Goal for All

The statin drugs, in my view, are the best cardiovascular drugs ever created, in that they have the greatest potential to prevent atherosclerotic plaques and their complications, and they also have the greatest potential to arrest plaque formation, and therefore, to prevent additional atherosclerotic events. The statin drugs are to atherosclerosis what penicillin was to infectious diseases.<sup>86</sup> Despite their being truly miracle drugs, they are terribly underutilized and underdosed.

The average serum LDL cholesterol level in American adults is about 130 mg/dl. Therefore, if we want to prevent plaque formation in the USA, most of us will need a 50% LDL cholesterol reduction! As shown in Table 1, that goal can be achieved by 3 doses of statin monotherapy (rosuvastatin 20 and 40 mg daily or atorvastatin 80 mg daily) or by adding ezetimibe 10 mg to all statin doses except the lowest level of recommended statin doses.<sup>87</sup> Because titration is often neglected, starting the dose from the beginning that achieves the preventive goal (LDL cholesterol <70 mg/dl) appears reasonable. Most American adults have life insurance, which, in actuality, is death insurance. The insured pays for the policy, dies, and then someone else gets the money. The statin drugs—with or without ezetimibe—represent true life insurance. The taker of the drug lives longer and is able to provide for his/her family longer. They are safe.<sup>88–105</sup> (Myopathy occurs 1 in 10,000 persons.) The risk of taking the drug is far less than the atherosclerotic consequences that might occur from not taking the drug! Of course, a vegetarian-fruit diet is the least expensive and safest means of achieving the plaque-preventing LDL goal, but few in the Western World are willing to live on the herbivore diet<sup>106,107</sup> If we did so, however, we would prevent the daily killing in the USA of 100,000 cows, of 300,000 pigs, and of 15 to 20 million chickens!

### Conclusion

Thanks to the pharmaceutical industry, we now have the armamentarium to change our cardiovascular health. We will not do so by waiting to treat our serum LDL cholesterol levels until an atherosclerotic event occurs or by using guidelines such as LDL cholesterol >190 or >160 mg/dl before lipid-lowering drug therapy is initiated. The blowing up of balloons or the placing of stents in our arteries or the performing of bypass operations (with all of their damaging incisions [e.g., median sternotomy]) can be prevented or their need enormously reduced if the statin drugs  $\pm$  ezetimibe are utilized in proper doses to produce serum LDL cholesterol levels low enough where atherosclerotic plaques do not form. Life insurance policies are often purchased by individuals in their 20s. Statin drugs  $\pm$  ezetimibe can be started at the same time because they—along with antihypertensive drugs—represent true life insurance. And to smoke cigarettes or to eat excess calories or not to put on a seatbelt in an automobile or airplane or to ride a motorcycle or not to control our cholesterol numbers is simply not to use our brain as it was intended to be used!

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