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A plant-based diet and animal protein: questioning dietary fat and considering animal protein as the main cause of heart disease

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Dietary 'fat' (e.g., oils, triglycerides, cholesterol) has long been considered a major risk factor for cardiovascular and related diseases. As reviewed elsewhere,[1,2] Vogel in 1847[3] identified cholesterol as a major component of the atherosclerotic lesion, a precursor of cardiovascular disease. Later, in 1913–1914,[2,4,5] experimental animal research showed that dietary fat (including cholesterol) increased atherosclerotic lesions in the aorta. According to Kritchevsky, writing in 1983,[2] so fixated were these early researchers on the hypothesis that dietary fat caused atherosclerosis that decades were to pass without considering the contributions of other dietary components to this disease. Now, after three more decades, most researchers (and the public) still believe that the chief dietary component linked to heart disease is the amount and type of fat, especially cholesterol and saturated fat.

Highly publicized diet and health policy reports have made specific recommendations on fat as a means to decrease cardiovascular and related diseases,[6–8] although the U.S. dietary guidelines recently relaxed its recommended limit on cholesterol consumption, but for questionable reasons.[9] Over 50 years ago, Kritchevsky, a prominent researcher on cardiovascular disease called attention to the "strong tendency in both popular and scientific press to correlate dietary fat and especially dietary cholesterol with coronary heart disease."[10] He mentioned the weakness of some of the evidence at that time but, still today, the association of fat and heart disease is a popular belief.

Research during most of the last century has investigated ever smaller components of fat. They include beta-lipoproteins, low-density lipoproteins, high density lipoproteins, apolipoprotein,[11] phospholipids, triglycerides, troponin proteins and various types of fatty acids distinguished by the saturation of their double bonds with hydrogen.[12] Similarly, cardiovascular disease is now described by sub-types of disease, including coronary heart disease, myocardial infarction, heart arrhythmia, rheumatic heart disease, congenital heart disease, valvular heart disease, aortic aneurysms, venous thrombosis, angina pectoris, stroke, atrial fibrillation, hypertensive heart disease, ischemic heart disease, peripheral heart disease, atherosclerosis and arteriosclerosis, just to name a few.

The practice of dividing a complex disease and its causes into smaller and smaller parts reflects the inexorable stream of science to understand how disease is caused and how it progresses. For some, it reflects great advances in medicine. But investigation of ever smaller parts of a complex disease, although helpful, runs a risk of becoming too narrowly focused, too reductionist, less relevant and more confusing. It also leads to a risk of ineffective protocols for disease treatment and management. And it obscures an understanding of nutrition's contribution to the cardiovascular disease—especially the nutrition provided by whole foods. The nutritional contribution to heart disease, from disease initiation to disease treatment, is a highly dynamic process that has seldom been acknowledged and understood. This is a serious oversight, for which we have paid a huge, incalculable price that can no longer be tolerated.

After dietary cholesterol was found to 'cause' heart disease, many key 'discoveries' have shaped the subsequent conversation. One of the more significant, first reported in 1952,[13] showed that, in addition to amount of dietary fat (i.e., mostly triglycerides) affecting plasma cholesterol and disease risk, so too does the type of fat. Vegetable 'fats', mostly unsaturated fats and liquid at room temperature reportedly decreased plasma cholesterol[13] whereas animal fats, mostly saturated and solid at room temperature, reportedly increased plasma cholesterol.[12] If, however, the unsaturated oils of plant-based foods were hydrogenated, making them solid at room temperature (as in the making of oleomargarine that forms trans fats), then these newly hydrogenated fats act like saturated fats. Unfortunately, the

marketplace mostly ignored this inconvenient truth by claiming that, simply because of the vegetable origin of oleomargarine, it still retains its ability to decrease plasma cholesterol. Consumers therefore responded to this deception by unwittingly increasing their consumption of vegetable-sourced fats, but this meant including trans, saturated fats, not unsaturated, fats in their diets. Thus arose the simplistic, false impression that plant-sourced oils (either as fats or oils) are healthier, mostly because their whole food form was thought to decrease plasma cholesterol and, presumably heart disease.

Ancel Keys, initially famous for his 'K' rations used by soldiers during World War II, was a prominent researcher during the 1950s–1990s. He is also well known for his Seven Countries Study[14] and his assertion that saturated fat increases plasma cholesterol,[15] therefore implicating a detrimental effect of animal-based foods on heart disease. He introduced the Mediterranean diet that he described as "mainly vegetarian".[16] This dietary practice, which was common to southern Italy and other countries of similar latitude bordering on the Mediterranean Sea, included the consumption of generous amounts of "greens" that Keys associated with "very low" rates of heart disease, being a "medical rarity" in Crete. He investigated the effect of diet on serum cholesterol,[17–21] and concluded that the "major villains in the diet that are responsible for raising the concentration of cholesterol in the blood serum are saturated fatty acids in the fat of meat and dairy products".[16] Assuming that serum cholesterol was a cause of heart disease and that it originated from a diet high in saturated fat, he recommended use of "diet before resorting to drugs" as a means to control this disease, a belief of Keys that is ignored by popular critics of his work.[22,23] Keys also said in 1995,[16] more than two decades ago, that the Mediterranean diet had already shifted "far from the … pattern" that existed when he did his research and went on to say that "unhappily, the current changes in Mediterranean countries [more meat and dairy] tend to destroy the health virtues of the diet".

The Framingham Study was another study that greatly influenced the conversation on diet and heart disease during these past few decades. This longitudinal study, now following three generations of families since its beginning in 1948,[24,25] initiated the concepts of 'risk factor',[24,26,27] and 'multivariable risk'[27] when studying the etiology of this disease. After more than 50 years, the Framingham study had identified several modifiable risk factors for coronary heart disease, including high systolic blood pressure, high serum cholesterol, smoking, obesity, diabetes, male gender, older age, sedentary lifestyle and several electrocardiographic abnormalities.[26,27] The study also introduced the idea that profiles of risk factors, not single risk factors, cause 'heart' disease. Although this observation on multivariable risk factors promoted a more rational discussion of the dietary causes of heart disease, many people still focus on individual risk factors as if they act independently, perhaps in an additive manner.

During these last 75 years, an enormous amount of clinical, epidemiological and laboratory follow-up research has promoted, directly and indirectly, the idea that 'fat' is a (if not 'the') cause of cardiovascular disease. As one indication of the quantity of this research, a PubMed search, using the key words 'dietary cholesterol', 'saturated fat and cardiovascular disease', 'dietary cholesterol and heart disease' and 'dietary fat and heart disease' yielded 33,530, 39,598, 5039 and 8224 publications, respectively. In turn, this torrent of information has encouraged the development of many widely publicized diet and health recommendations for heart disease, cancer and related chronic degenerative diseases.[9,28–31] Similarly, the World Health Organization[32] along with many country reports have subscribed to these same conclusions and recommendations. All of these reports have featured a major role for dietary fat, especially saturated fat, in the causation of heart disease.

This continual emphasis on fat as major cause of heart disease has led to claims of health benefits for foods low in fat, like lean cuts of meat, low or non-fat dairy products and cholesterol-free products. There is little or no evidence that such 'low-fat' products are healthier because of the singular[4,33] absence of cholesterol or saturated fat, although their presence certainly is a good indicator of the type of food in the package. However impressive or unimpressive the evidence on fat 'causation' of heart disease has become over these past 50–75 years, it mostly arose from population-based studies that do not translate into estimates of disease risk for individuals[26,34,35] because of the familiar precaution that correlation does not mean causation.

This mistaken inference of the independent effects of dietary fat and/or cholesterol on serum cholesterol and heart disease also suggested the use of cholesterol lowering drugs, like statins. A recent finding on a risk assessment model of the American College of Cardiology/American Heart Association (ACC/AHA) however shows that assuming a 7.5% risk of a cardiovascular event per 10-year interval, 56 primary prevention patients would need to be treated with statins to prevent one cardiovascular event.[36] This finding could mean the need for more precision in estimating risk and treating individual would-be patients—a very reductionist strategy—but such an interpretation avoids the larger question of whether our insistence on precise knowledge

and targeted drug therapy promotes a good research strategy for understanding and controlling heart disease. I can easily envision going astray and causing unintended side effects by chasing hypothetically precise causal, mechanistic and treatment pathways for heart disease (like other complex diseases) within infinitely complex networks of pathways. Again, the larger and more important context is ignored. Is it possible that nutrition, when properly understood as a fact of nature, can steer us in a more realistic direction to control this disease?

Let us now return to those first cited reports[2,4] that dietary cholesterol caused preliminary fatty lesions in rabbits that presumably led to heart disease. Still earlier evidence in 1909[2] had shown that animal-based protein increased plasma cholesterol. Following this and other research for the next decade or so, Clarkson and Newburgh in 1926,[37] reviewed these studies and concluded that the "…elevation of blood cholesterol in the diet …[is]… directly referable to the excess of protein in the diet and not to its cholesterol content." In 1941 rabbit experiments, casein was 5-fold more atherogenic than soy protein over a 6-month feeding period[38]—a huge differential that has since been strangely ignored. In experimental animal studies in other laboratories, it was reported that casein simultaneously and substantially increased both plasma cholesterol and atherosclerosis,[39] lactalbumin (another cow milk protein) increased atherosclerosis more than 2-fold over corn and wheat protein,[40] and for casein and soy protein crossover studies, a quick response (within one day) was observed when diets were switched. Serum cholesterol increased with casein and decreased with soy protein.[41,42] Generalizing these effects to other animal and plant-based proteins is reasonable because all 12 kinds of animal protein elevated cholesterol levels in experimental rabbits when compared with 11 kinds of plant protein, with no overlap.[43]

In addition to the findings of these experimental animal studies, supportive evidence also was forthcoming from human studies. In a 1961 epidemiological survey of dietary practices and heart disease mortality among 24 countries done by Connor and Connor,[44] cholesterol consumption, an indicator for animal protein-based foods, was highly correlated with heart disease (r = 0.83, P < 0.01).[44] In a later 1972 study,[45] they confirmed this finding by showing that the highest correlation of dietary nutritional factors with coronary heart disease was for animal protein (r = 0.78), even more than total fat (r = 0.68) and animal fat (r = 0.63). There was an inverse correlation between vegetable protein and coronary heart disease (r = –0.40).

In 1957, Yerushalmy and Hilleboe[35] wrote a brilliant expose on the limitations of interpreting epidemiological studies, curiously using as an example the rising interest in dietary fat at that time as a cause of heart disease. They noted that, in 1953, Keys[46] was careful to suggest (but not conclude) that dietary fat was associated with heart disease. In 1954, Leitner,[47] referring to the Keys' data, upped the ante by saying that the correlation between fat and heart disease mortality was "strong, if not convincing". In 1955,[48] Keys was more assertive, saying that there was a "remarkable relationship" between heart disease mortality and the proportion of fat intake in the national diet. The idea that dietary fat causes heart disease was maturing and becoming more established. However, Yerushalmy and Hilleboe,[35] after discussing the merit of determining specific causes of disease from epidemiological data, went on to show that the correlation of percent dietary fat with heart disease among 22 countries was neither "specific for fat", nor "proven", nor "valid", nor statistically significant (although it was direct). In contrast, the correlation of animal protein with heart disease was strong and statistically significant (P < 0.02), although not proven to be sufficiently specific.

The validity of the observation, first made more than a century ago but supported many times since, that animal protein is a more significant cause of heart disease than fat (cholesterol, total and saturated fat) casts a very different light on our present day understanding of the diet-heart disease relationship. Two questions thus become pertinent. Why has this evidence been ignored for so long? And, second, is an animal protein effect on heart disease biologically plausible?

One way that might help to explain the reason for choosing fat instead of animal protein as the principle cause of heart disease is to consider a parallel case of diets' link to cancers that geographically co-exist with heart disease. Dietary fat strongly correlates with breast and other cancers[6,49–51] but, similar to heart disease, these correlations occur for total and saturated fats, not for unsaturated fat,[52] thus favoring an association of these cancers with animal-based foods. Also, among these countries, dietary fat and animal protein consumption are highly correlated,[53] thus the observed association of these cancers with dietary fat could just as easily be an association with animal protein. Indeed, in a survey of 37 countries, the correlations of animal protein and saturated fat with breast and colon cancer exceeded those with socio-economic factors that typically characterize Western societies.[54] Similarly, in rural China, affluent cancers are much less common than in the U.S.[53] In these areas, dietary animal protein consumption is only about 10% that in the U.S. and mean plasma cholesterol [a surrogate for more animal and less plant protein consumption and the variable that is mainly correlated with this ag-

gregate group of cancers and other affluent diseases ($P < 0.001$)] is only 127 mg/dL.[54] This is an impressive finding in an environment with such low statistical sensitivity.

If, therefore, it is more correct to suggest that heart disease is more a function of animal protein than fat, then we are led to the second question: whether an association of animal protein with heart disease is biologically plausible. There is very little or no empirical evidence on this effect because it was never a question of interest as the evidence on animal protein was largely ignored. Nonetheless, there are ample mechanisms that could account for an animal protein effect. For example, the production of reaction oxygen species (ROS) and reactive nitrogen species (RNS) could be more than a sufficient mechanistic explanation. The American Heart Association[55] agrees that these molecules, although used by many normal cellular processes, also can lead to "extensive tissue dysfunction and injury" that have already been implicated in "many cardiovascular diseases." Although AHA points out that "there is no conclusive evidence that ROS/RNS are fundamentally involved in the pathogenesis of cardiovascular disease in humans," because no antioxidants are effective therapies." In my opinion, this is not an adequate explanation because several antioxidants, when taken in pill form (supplements), have been shown not to behave as they do in food,[56–60] either having no effect or, in some cases, having an opposite effect. It should also be noted that a high animal protein diet readily increases the activity of the P450 oxidase enzyme,[61,62] which could be a regular source of ROS in addition to the mitochondrial electron transfer powerhouse.[63]

This question of biological plausibility for an adverse effect of animal protein has been more systematically investigated in cancer development. On the promotion of breast cancer, animal protein may elevate growth hormone, circulating estrogens,[64] ornithine decarboxylase activity and cell proliferation in mammary tissue,[65] ROS[66] and enzymatic activation of chemical carcinogens through the drug metabolizing enzyme system.[67] In laboratory animal experimentation, liver tumor growth increases as dietary protein (casein) is increased and decreases as casein is decreased. The plant proteins in soy and wheat had no such effects on tumor growth. That is, cancer development is likely to be turned on-off-on-off by nutritional means when animal protein is fed above general protein requirements. In a series of studies designed to search for the responsible cellular mechanism for tumor formation by animal protein, ten such candidate mechanisms were identified—eight requiring genetic up-regulation and two requiring down-regulation—but all directed to the promotion of tumor development.

There is little doubt that there is an abundance of mechanisms that could directly account for initiation and promotion of atherosclerosis by animal protein. But a direct effect of animal protein—however impressive it may be—could be less relevant when compared with the effect produced by the distortion of the diet produced by adding animal-based foods. When more animal protein-based food is included in the diet, there is less plant-based food, a rarely considered trade-off. In addition to providing an abundance of cardioprotective plant-based substances, these foods also have an effect on very important and carefully balanced metabolic systems, for example, pro-oxidation/anti-oxidation and omega-6 pro-inflammation/omega-3 anti-inflammation systems.

In examining nutritional effects on the development of cardiovascular diseases, one must recognize the totality or 'wholeness' effect, as in a whole food plant-based dietary lifestyle. The comprehensiveness of evidence now available suggests that there is no other protocol—dietary or non-dietary—that offers the same health benefits. Perhaps the best testimonial for this whole food effect is its reversal of coronary heart disease during its advanced stages of development.[68–71] The most recent of these studies[71] included 196 patients, 177 who complied with the dietary advice. In 2–7 years, only one of the patients who complied suffered an event; in contrast, 62% of the non-compliant patients suffered an event. I am not aware of a single other cardio-therapy protocol that approximates such spectacular results.

And finally, the incentive to ignore for so many years the evidence that animal protein is more significant than fat in the development of heart disease may be explained in various ways. I suspect that there was a very subtle but powerful reluctance to challenge the perceived nutritional worthiness of animal-based food that had existed since the identification of protein in 1839 when it was proclaimed that it was the "stuff of life itself" and the basis for civilized peoples. Placing the onus on fat as the cause of heart disease offered the opportunity to remove the offending agent from food but still retain the essential essence of the food. However, removing animal protein from these products was not possible without sacrificing the consumption of animal foods as an entire class. Thus, a huge and highly successful market was created for lean cuts of meat and low-fat and non-fat milk products.

Admittedly the choice was exceptionally difficult but the cost of not doing so for these past 100 years seem to be unfathomable. Although some of these costs can be estimated economically, it is the costs of lives lost and suffered that is the most difficult challenge to fathom. But this conversation must begin for there are still more costs, such as the envi-

ronmental impact, which are even more ominous. This conversation can begin simply by addressing the question of which dietary factor is more significant in causing cardiovascular disease, fat or animal-based protein?

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