Cardiovascular Disease: A Single "Drug" Condition?

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Cardiovascular disease is now widely recognized as an inflammatory disorder. This is demonstrated particularly well by the relationship between C-reactive protein and cardiac events. Diets high in fruits and vegetables have been shown to be inhibiting to inflammatory process and protective from cardiovascular disease, even if accompanied with high fat intake. An evolutionary perspective suggests cardiovascular, as well as other chronic diseases involving inflammation, are likely due to chronic deficiencies of phytochemicals and other food compounds. Besides the established nutrients, many other phytochemicals – proposed as conditionally essential nutrients – flavonoids, polyunsaturated fatty acids, carotenoids, etc, regulate the human genome, are anti-inflammatory and are necessary for human health. Many of these nutrients were commonly consumed by our ancestors in the form of plant foods. Consumption of plants delivers nutrients in a phytochemical matrix, which is a form of nutrient delivery that has the favor of evolutionary familiarity due to millions of years of plants playing a primary role in human nutrition. Physiologically active compounds embedded in a phytochemical matrix may be best suited for the prevention, mitigation and in some cases, the treatment of cardiovascular disease.

Physician, political activist and the father of cellular biology, Rudolf Virchow, elucidated the concept of cellular pathology, asserting that cells were the fundamental units of life in the 19th century. While studying the cells involved in cardiovascular disease, Virchow challenged the prevailing view of atherosclerosis as a blood dyscrasia causing localized accumulation of debris in the vessel.[1] Virchow came to the conclusion that atherosclerosis was an inflammatory disorder of the intimal lining.[2]

However, this was quickly forgotten in the early 20th century after a Russian pathologist, Nikolai Anitschkow, fed cholesterol to rabbits. After feeding massive amounts of cholesterol to animals that are natural vegetarians, Anistschkow unsurprisingly found dramatic increases in serum cholesterol followed by a high death rate due to cholesterol-filled atheromas.[3] As a result, a massive advertising campaign against the dangers of fat-containing milk, butter, eggs and meat was launched and the low-fat industry rose out of the campaign.

In the middle of the 20th century, the Framingham Heart Study was initiated and found cigarette smoking and hypertension as risk factors, as well as serum lipid abnormalities, including elevated total serum cholesterol, elevated LDL-cholesterol and low HDL-cholesterol.[4]

Cardiovascular disease has largely been seen as a disease of the vascular tree; proper treatment as opening or bypassing the arterial blockage.[5] This obstruction has primarily been thought to originate due to evaluated levels of lipids. Thus, the prescription frequency of the cholesterol lowering statins has reached an all-time high.[6] Although much of the data supports the lipid hypothesis, there are many incongruities. For example, Sabine et al[7] point out that despite similar consumption levels of dietary choles-

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terol and saturated fat in France and Finland, the coronary heart disease mortality rate in Finland has been at least four times higher than the rate in France. Countries with high intake of saturated fats and cholesterol, but also high intake of plant foods (fruits and vegetables), have lower rates of coronary heart disease mortality.[8] In addition, de Lorgeril et al[8] found that diets high in plant foods and omega-3 fatty acids demonstrated a reduction in all-cause mortality by 30–70%. This is greater than that for any of the secondary prevention trials which used cholesterol lowering as the main goal. These authors went on to state that "…a comprehensive strategy to decrease cardiovascular morbidity and mortality should include primarily a cardioprotective diet," noting reduction in risk of CHD was not associated with differences in total cholesterol. It has been found that 35% of CHD occurs in people with triglyceride levels lower than 200 mg/dL.[9] Additionally, 50% of myocardial infarctions occur in people without any of the four major risk factors (smoking, diabetes mellitus, hypertension and hypercholesterolemia)[10] although this data is considered controversial.[11] Despite the controversy in the origins of heart disease, there has clearly been progress in the prevention and treatment of heart disease.

The etiology is now predominantly seen as nutritional, neuroendocrine, oxidative and inflammatory.[5] For example, the development and rupture of plaque in the vasculature are due to processes primarily endocrine and immune in nature, induced over decades by factors including dietary intake and stress. Diet is believed by many to be a root cause in many conditions.[5, 12-17] Diet influences insulin sensitivity, oxidative stress, inflammation, lipid status, methylation, cardiocyte cellular energetics, membrane stability and electrophysiologic dysfunction, which are all important in cardiovascular disease, as well as many other chronic diseases.[5] After an evaluation of 52 countries and almost 30,000 patients, Yusuf[18] has identified the additional risk factors of *decreased consumption of fruits and vegetables*, as well as abdominal obesity, stress and sedentary lifestyle; combined with the original four risk factors - an over 90% population attributable risk for myocardial infarction.

An Anti-inflammatory Diet

One hundred years after Virchow's insight to cardiovascular disease, it appears his hypothesis that cardiovascular disease is an inflammatory process is correct.[19] Cardiovascular disease is now widely accepted as an inflammatory condition.[20] Of the previously mentioned factors in cardiovascular disease; insulin sensitivity, oxidative stress, inflammation, lipid status, methylation, cardiocyte cellular energetics and membrane stability, can all lead to inflammatory process. Inflammation is increasingly being recognized as a precursor to many pathological conditions, including pulmonary disease, arthritis, allergy, Alzheimer's disease and diabetes.[5, 21] Sloop[22] notes atherosclerosis does not result simply from the accumulation of lipids, but that the presenting atherosclerotic lesions represent various stages of chronic inflammation.

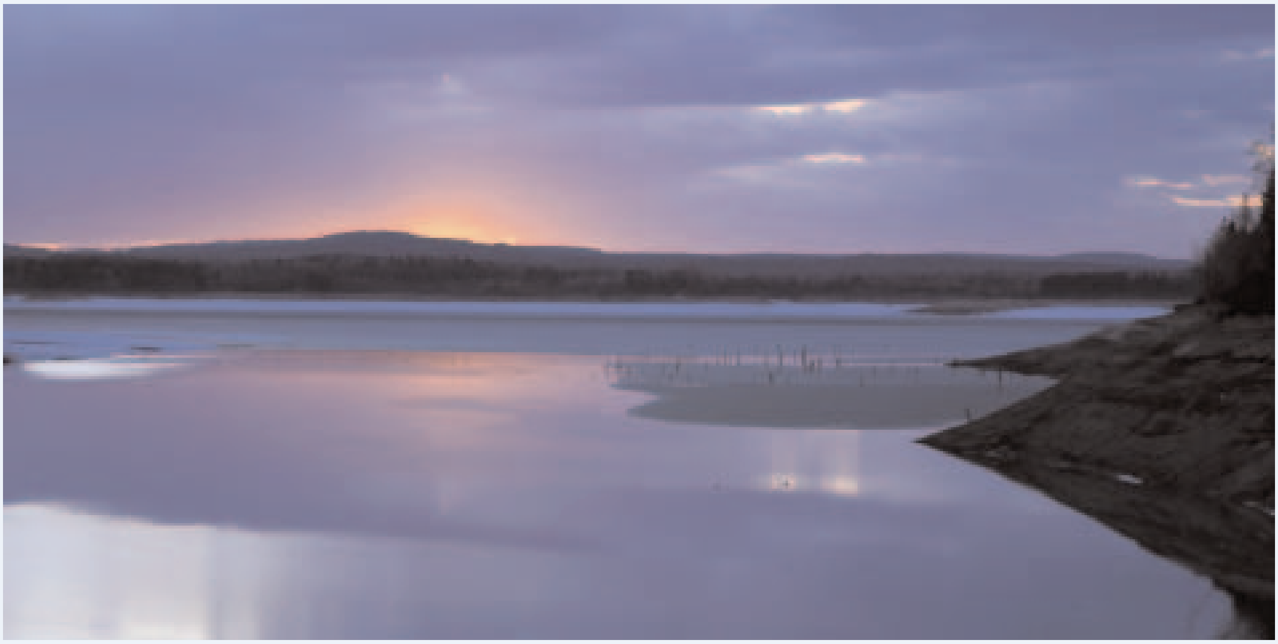
It is highly likely that the inflammatory environment of heart disease and other chronic diseases is due to the reduction in high quality foods in the diet. Phytochemical exposure is crucial for good health.[15] As previously mentioned, countries that have a high intake of saturated fats and cholesterol, but also have a high intake of plant foods (fruits and vegeta-

bles) have lower rates of coronary heart disease mortality.[8] Given that diets high in phytochemicals show a reduction in all-cause mortality by 30–70%, an effect far greater than the cholesterol-lowering strategy used for heart disease,[8] that the effects of diet are even still being debated reveals the politics of the food and medical industry. The debate appears to serve as a corporate generated smoke screen to obscure the influence of nutrition on health and disease. In turn this allows more profits for business reliant on fast-food/junk-food sales and perpetuates the need for a pharmaceutical-centric approach to disease.

Until 500 generations ago, humans consumed foods that were wild and unprocessed.[14] A crucial understanding comes from the recognition that the human genome coevolved with the biochemical input originating from wild plant and animal foods.[23] Attempts to recreate these biochemical signals with isolated nutrients from foods have largely been ineffective. For example, the studies demonstrating the ineffectiveness of antioxidants such as tocopherol, β-carotene and vitamin C[24] in protecting against cardiovascular disease are not surprising. These studies were designed using isolated forms of the therapeutic agent. In one trial, vitamin E was found to significantly increase heart failure and result in a trend towards increasing the ischemic complications from atherosclerosis.[25] Vitamin C has also seen failures in clinical human trials for cardiovascular disease. And, of course, there was the alarming CARET trial on β-carotene that was stopped early due to the finding that cancer rates were going up in smokers in the β-carotene group instead of the expected reduction in cancer rates.[24] Trials such as these clearly demonstrate the relationship between nutrients and disease are in need of reevaluation. People and their genes evolved with whole foods, making it remarkably difficult to identify and demonstrate a single molecules activity in the body.[26] Moreover, these trials should show us the folly of assuming that just because a nutrient is antioxidant or a proven vitamin, doesn't mean it is safe when removed from its coocurring nutrients and associated food factors. Large volumes of data supporting the antioxidant and low toxicology activity of these compounds are best viewed in context: What were the concentrations of particular nutrient and non-nutritive molecules consumed by Paleolithic humans in their whole foods diet?

In some cases, even mixing isolated nutrients in unnatural combinations of antioxidants have failed. For instance, even though men with hypertension have been shown to have low levels of β-carotene and other antioxidants, a combination of vitamin C (120 mg), vitamin E (30 mg), β-carotene (6 mg), selenium (100 μg) and zinc gluconate (20 mg), failed to have any impact, over a 6.5 year period, on the risk of developing hypertension.[27]

It is highly likely that combinations of nutrients embedded in their naturally occurring chemical matrix, rather than individual nutrients or combinations of individual nutrients, are responsible for the efficacious health outcomes noted by diets high in the phytochemicals from fruits and vegetables. Examining fruit and vegetable intake, Esmaillzadeh et al[28] demonstrated that persons in the highest quintile of fruit and vegetable intake had a 34% (95% CI: 20%, 46%) and 30% (95% CI: 16%, 39%) respectively, lower chance of having metabolic syndrome than did those in the lowest quintiles. This relation-



ship also held for C reactive protein plasma concentrations, a measure of systemic inflammatory process and a marker for the risk for cardiovascular events. Both fruit and vegetable intakes were inversely associated with plasma CRP concentrations. Yet, it is difficult to demonstrate such positive effects with isolated vitamins. If an associated nutrient not included in a supplement naturally occurs with the target nutrient in foods, but is the agent responsible for the positive health effect, the reductionist methodology of isolating the nutrient will miss the effects of the associated nutrient, incorrectly determining no positive activity, no activity or detrimental activity.[29]

In support of such phytochemical complexity, Liu[31] proposes that fruits and vegetables, which have thousands of phytochemicals differing in molecular size, polarity and solubility, likely affect bioavailability and distribution of each phytochemical on different macromolecules, subcellular organelles, cells, organs and tissues. He points out that the multi-component nature of fruits and vegetables are responsible for their antioxidant protective effects.

Many beneficial phytochemicals and associated food factors embedded within the phytochemical matrix that surround constituents, such as vitamins and minerals, are proving to play an important role in cell biology.[32] For instance, choline, inositol, ubiquinone (coenzyme Q10), carnitine and α-lipoic acid found in foods - but also endogenously produced by the body and therefore not considered essential nutrients - clearly play a crucial role in cellular processes.[32] The endogenous production of these nutrients is not always sufficient. Thus, additional intake may be necessary for optimizing health status.[32,33] For instance, the acute phase response to inflammation, trauma, infection and chronic disease, lowers the levels of non-essential nutrients such as the carotenoids, including α-carotene, β-carotene and lycopene.[34] Research demonstrates that nutrient supplementation can compensate for dietary deficiencies, metabolic abnormalities and treat disease processes.[32, 35, 36] Therefore, these "non-essential" nutrients would best be considered conditionally essential nutrients and likely contribute to the biochemical milieu necessary for good health. A close examination of our ancestors' diet shows that large amounts of phytochemicals, many of them potentially regulating inflammatory response, were a routine and important part of the diet (Table I).[37] Isolated constituents cannot recreate the biochemical milieu generated by the phytochemical ingestion that "shaped" the human genome.

Considering the human genome is essentially unaltered since well before the agricultural revolution some ten thousand years ago,[14, 32, 38] it is reasonable to suggest that modern humans have similar nutritive requirements as our ancestors.[32] Given that dietary chemicals, the majority being of plant origin, either directly or indirectly alter the expression of genomic information and that the progression from a healthy phenotype to a chronic disease phenotype must occur by changes in an individual's genomic expression,[14] it is obvious nutritional input is a major culprit in chronic diseases in general, and this includes cardiovascular disease.[16, 17] The facts are incontrovertible: A large number of compounds found in food can modulate gene expression.[32, 39, 40] Diet is a decisive source of the signals invoking gene activity that construct and regulate the body.[32] For example, of the 4,000 flavonoids known to occur in the diet, many modulate gene expression.[32, 41] The polyunsaturated fatty acids (PUFAs), either from plants, fish or the lower concentrations found in meats, also demonstrate modulation of gene expression.[40] Additionally, flavonoids,[42-45] PUFAs,[46-48] carotenoids[32, 49] and many other phytochemicals have anti-inflammatory activity as well.[50, 51]

Keith and Zimmerman[52] astutely suggest that many genes might need complementary action to modify disease processes. In other words, single agents may not be sufficient to effectively modulate gene expression. The historical recurring exchange of molecular information between the secondary

Table I: Makeup of the Hunter-Gatherer Diet
From [30] O'Keefe and Cordain

• Lean protein	• Vitamins
• Polyunsaturated fats (especially ω-3)	• Minerals
• Monounsaturated fats	• Antioxidants
• Fiber	• Other beneficial phytochemicals

metabolites of plants and humans is believed to have promoted human adaptation through genomic alterations and DNA repair.[53-56] Particular phytochemicals, such as alkaloids, glycosides, phenolics, uncommon proteins, unusual free amino acids, sterols, essential oils, terpenes and resins, are capable of altering the metabolism and potentially improving the biological fitness of humans.[53, 57] A case in point are the flavonoids, which have demonstrated the ability to repair DNA transcriptional errors.[56] Rather disturbingly, the foods found in many grocery stores, and as such make up the majority of the food baskets of common people, are chillingly void of their original phytochemical content. For example, of the 12 micronutrients and B vitamins plentiful in wheat grain, 70-90% have been removed by modern processing methods (vitamins B1, B2, B3, B5, B6, folic acid, E and the minerals iron, zinc, copper, manganese and selenium)!58 With poor phytochemical input, metabolic adaptability decreases, deficiencies develop and rather than immediate and visible symptoms of deficiency, there appears to be chronic DNA damage which eventually surfaces as chronic degenerative conditions such as heart disease and cancer.[59, 60]

Chemical Complexity as a Necessary Component of Health

The dietary requirements of Paleolithic humans are essentially identical to modern day humans, and in most cases our genetic ancestors ate large quantities of plant foods.[61] Thus, many of the non-essential compounds - which this author has suggested might best be considered conditionally essential nutrients are, as discussed above, necessary. More importantly, the food context in which nutrients are taken is most likely as important as the nutrients themselves. The biochemical environment the human genome originally coevolved with was largely generated through the consumption of plants, nutrients or therapeutic agents embedded in a phytochemical matrix. Quite likely the cellular environment of humans is dependent on this long-standing relationship with chemical complexity, due to the ingestion of large amounts of leaves, roots, seeds etc, to the point that isolated nutrients may induce substantially different cellular physiological responses than ingestion of a phytochemical matrix.[23, 57, 62] Rather than nutrients or drugs being introduced as isolates, an evolutionary viewpoint would suggest that recreating the biochemical milieu in which the human genome evolved would be sensible.[57] Using this viewpoint, we arrive at the conclusion that both processed foods and tablets of isolated constituents, with only chemicals that have been "proven" to be necessary, is foolish at best. At worst, it may be detrimental to human health. Isolated nutrients derive from the same reductionist model utilized to generate pharmaceuticals. Given that prescribed drugs have become one of the leading causes of death,[63-65] this seems an unwise model to mimic. Furthermore, the prevalence of coronary heart disease[66] and hypertension[67] exceeds, or at least is unchanged from, what it was 20 years ago.[38] The drugging strategy currently used is clearly in need of reevaluation.

Though rather confounding, the bulk of research utilizes isolated agents; pharmaceuticals, nutrients or phytochemicals that perturb a single target. Although these studies are necessary for several reasons, McCarty[68] comments that clinical strategies based on single therapeutic molecules do not meet the goals of dealing with chronic disease. Moreover, McCarty goes on to suggest that the likelihood of a single chemical having a "magic bullet" effect is rare. Many isolated chemicals target a single biochemical site and this may not target the dominant abnormality or redundancy in cell signaling.[26] Aggarwal[21] has suggested chronic multifactorial disorders require therapeutic agents able to perturb multiple biochemical sites and pathways.

Conclusion

The established nutrients, and the many other "conditionally essential" nutrients – flavonoids, choline, ubiquinone, carotenoids, etc. - are known to have anti-inflammatory activity. Many of these compounds also modulate the human genome and are necessary for human health. Additionally, chronic deficiencies of the conditionally essential nutrients slowly and insidiously develop into chronic diseases, such as cardiovascular disease. Given that diets high in plant foods and omega-3 fatty acids demonstrate a reduction in all-cause mortality by 30–70% and that diets high in plant foods are preventive to the development of cardiovascular disease, it is probable that cardiovascular disease is a chronic deficiency of phytochemicals; nutritive and non-nutritive.

Essential nutrients were predominantly consumed by our ancestors via plants – a whole food form. Thus, nutrients, and bioactive non-nutrients, were delivered in a complex phytochemical matrix. The human genome has evolved with this chemical complexity due to millions of years of evolution. This strongly suggests that in preventing, mitigating and in some instances, treating cardiovascular disease, a superior strategy may be delivering physiologically active compounds in a whole-food like mixture.

The Phytochemical Matrix of *Allium sativum* (Garlic)

from Dr. Duke's Phytochemical and Ethnobotanical Database

Cholesterol lowering agents	Blood pressure lowering agents	Cholesterol lowering agents	Blood pressure lowering agents	Cholesterol lowering agents
2-vinyl-4h-1,3-dithiin	diallyl-disulfide	2-vinyl-4h-1,3-dithiin	diallyl-disulfide	2-vinyl-4h-1,3-dithiin
adenosine	diallyl-sulfide	adenosine	diallyl-sulfide	adenosine
ajoene	diallyl-trisulfide	ajoene	diallyl-trisulfide	ajoene
allicin	inulin	allicin	inulin	allicin
alliin	lignin	alliin	lignin	alliin
campesterol	methyl-ajoene	campesterol	methyl-ajoene	campesterol
	nicotinic-acid		nicotinic-acid	

Anti-inflammatory agents

COXI	Other
ajoene	alpha-linolenic-acid
apigenin	chlorogenic-acid
caffeic-acid	ferulic-acid
kaempferol	linalool
oleanolic-acid	myricetin
quercetin	vanillic-acid
salicylic-acid	

Anti-aggregants

s-allyl-l-cysteine-sulfoxide	apigenin
2-vinyl-4h-1,3-dithiin	caffeic-acid
adenosine	cycloalliin
ajoene	ferulic-acid
allicin	kaempferol
alliin	methyl-allyl-trisulfide
allyl-methyl-trisulfide	phytic-acid
allyl-trisulfide	quercetin
alpha-linolenic-acid	salicylates

Antioxidants

allicin	diallyl-heptasulfide	kaempferol	Rutin
alliin	diallyl-hexasulfide	lignin	s-allyl-cysteine-sulfoxide
allixin	diallyl-pentasulfide	myricetin	s-allyl-l-cysteine
allyl-mercaptan	diallyl-sulfide	oleanolic-acid	s-allylmercaptocysteine
apigenin	diallyl-tetrasulfide	p-coumaric acid	salicylic acid
caffeic-acid	diallyl-trisulfide	p-hydroxy-benzoic acid	sinapic-acid
campesterol	ferulic acid	pentadecanoic-acid	Taurine
chlorogenic-acid	glutathione	phytic-acid	vanillic-acid
diallyl-disulfide	ionol	quercetin	

Nutients

Minerals	Vitamins	Amino acids	Fatty acids
Boron	Alpha tocopherol	Alpha amino butyric acid	Alpha linolenic acid
Calcium	Ascorbic acid	Arginine	Arachidonic acid
Chromium	Beta Carotene	Asparagine	Oleic acid
Cobalt	Beta Tocopherol	Aspartatic acid	Palmitic acid
Copper	Biotin	Cysteine	
Germanium	Niacin	Cystine	
Iron	Riboflavin	Glutamic acid	
Magensium	Thiamine	Glutamine	
Molybdenum		Glycine	
Nickel		Isoleucine	
Phosphorus		Leucine	
Potassium		Lysine	
Selenium		Methionine	
Sodium		Ornithine	
Zinc		Phenylalanine	
		Proline	
		Serine	
		Taurine	
		Threonine	
		Tryptophan	
		Tyrosine	
		Valine	

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