Atherogenic and anti-atherogenic factors in the human diet

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Abstract

New atherosclerosis causative factors and preventive modalities have been identified. Atherogenic factors include lipid oxidation products, such as cholesterol oxidation products, malonaldehyde and other aldehydes; trans-fatty acids; some saturated fatty acids (lauric, myristic and possibly palmitic acids); and myristic acid plus cholesterol. Lipid oxidation products are well suited to induce arterial damage, based on their known cytotoxic effects; evidence also indicates the possibility of plaque promotion and stimulation of thrombogenesis. Anti-atherogenic factors include antioxidants, fish oils and other polyunsaturates (if protected from oxidation), fibre and trace minerals such as copper, manganese, selenium and zinc. Iron is unique, being considered as both a potential promoter of atherosclerosis (component of ferritin, conceivably inducing lipid oxidation) and a possible anti-atherogenic component (of antioxidant enzyme catalase). It is apparent that an entire new series of research challenges has been uncovered.

Introduction

Coronary heart disease (CHD) and cancer continue to be the greatest causes of morbidity and mortality among developed nations. CHD has always been a controversial disease with respect to its multifactorial etiology and, in view of the latest recommendations to the public on what dietary factors are causative or preventive of CHD, great sums of money have been gained or lost. For this discussion, we have grouped those dietary factors which promote the forerunner to CHD, namely atherosclerosis, as being atherogenic; these are contrasted with
those factors believed to be anti-atherogenic, i.e. those which reduce the prevalence or slow the progression of CHD. The fact that many of the factors listed in either grouping are unfamiliar to the reader may reflect the fact that significant new findings are being discovered at a rapid pace and that the original, very popular lipid hypothesis, i.e. the basic idea of how dietary factors (saturated fat and cholesterol) affected CHD, has been undergoing modification for several years. Two examples will be given: (1) saturated fat has long been considered to be cholesterolaemic (and therefore atherogenic) but based on research in the area of low-density lipoprotein (LDL) peroxidation it can be argued that consumption of a polyunsaturated-rich diet could be deleterious because LDL is more susceptible to peroxidation when polyunsaturates are a prominent part of the dietary fat; and (2) hydrogenated vegetable oil shortenings have long been recommended as replacements for animal fats such as butter, lard and tallow; nevertheless, the wisdom of this recommendation is now being questioned in view of several studies linking the consumption of vegetable shortenings to hypercholesterolaemia and CHD. The active principles in the hydrogenated shortenings include the saturated fats along with trans isomers formed in the hydrogenation process. These and other equally surprising new findings will be discussed.

In choosing the terms ‘atherogenic’ and ‘anti-atherogenic’ we have attempted to simplify the conceptual framework of this review. Therefore, dietary factors that are hypercholesterolaemic are grouped with truly atherogenic (cytotoxic) factors in spite of the fact that hypercholesterolaemia is not exactly the same as atherogenicity. To illustrate, most cases of CHD occur among persons with normal serum cholesterol levels, and many people with hypercholesterolaemia do not exhibit symptoms of CHD. Nevertheless, the risk of CHD rises as serum cholesterol, and more specifically, as serum LDL rises. The exceptions to the latter relationship provide much stimulation for antioxidant/lipid oxidation products (LOPS)/cholesterol oxidation products (COPS) research, because it is possible that elevated serum lipids are less damaging if LOPS/COPS are kept low by a high antioxidant intake.

**Atherogenic factors in the human diet**

CHD is a multifactorial disease in which diet is only one of many factors involved. Nevertheless, that diet is somewhat easily altered and has enormous economic ramifications, and since Western societies tend to rapidly identify ‘scapegoats’, large sums of money for research on the lipid hypothesis have been available and there has been, until recently, a tendency to exclude alternative hypotheses regarding diet and CHD. Fortunately, some changes are occurring and many newer areas of CHD research have developed rapidly in the past decade. Based on this newly available data we cite the following as atherogenic factors in the human diet: COPS, LOPS, trans-fatty acids and saturated fats (limited to myristic, lauric and possibly palmitic acids), and possibly dietary cholesterol, in combination with high levels of the cholesterolaemic saturated fatty acids. These are summarized in Table 1. Finally, some recent work has identified stored iron (serum ferritin) and therefore dietary iron as a CHD risk factor, but many studies
Table I. Atherogenic factors in the human diet.

<table>
<thead>
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<th>Lipid oxidation products</th>
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<tr>
<td>Cholesterol oxidation products</td>
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<tr>
<td>Hydroperoxydienes (as precursors to) (n)-alkanals, trans-alkenals, (trans, trans)- and (cis, trans)-alka-2,4-dienals, 4-hydroxy-(trans)-2-alkenals</td>
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<tr>
<td>(trans)-Fatty acids</td>
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<tr>
<td>Some saturated fatty acids</td>
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<tr>
<td>Cholesterol + myristic acid</td>
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<td>Iron (ferrous)?</td>
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have disputed this finding and there are scientific grounds on which to argue the reverse hypothesis. Therefore, iron will be discussed under both the atherogenic and anti-atherogenic categories.

COPS have been intensively studied for the past two decades and research in this area has received extensive review [1–3]. A synopsis of the research on COPS indicates clearly that cytotoxicity is a common characteristic of a wide variety of COPS. It is also well established that loss of endothelial cells is one of the earliest stages of atherosclerosis, as revealed by studies of monkeys fed high-saturated-fat high-cholesterol diets [4]. Interestingly, powdered eggs were the major source of cholesterol in this study and is a foodstuff known to contain high levels of COPS [5,6]. Several previous studies, involving simultaneous comparisons of purified (by methanolic extraction) cholesterol with the more polar COPS, have consistently demonstrated COPS to be cytotoxic, cholesterol to be free of cytotoxicity, and COPS exhibiting several properties consistent with angiotoxicity [7–9]. These data are summarized in Table 2.

Angiotoxicity is related to the first step of the process leading to clinical CHD — namely, endothelial cell death and endothelial damage. Atherosclerotic lesions of plaque, representing the second step, are found in the intimal layer of cells, causing thickening and eventual occlusion, or at least conditions favouring myocardial infarction. The final stage of CHD is myocardial infarction, frequently the result of thrombosis or arterial spasm. Evidence available suggests a role for COPS in all three stages [1,2].

Some epidemiological data have implicated COPS in CHD. Two populations of immigrants moving from India to London and the West Indies displayed high morbidity and mortality from atherosclerosis without common major risk factors (i.e. high serum LDL, low plasma high-density-lipoprotein (HDL), hypertension, diabetes, or smoking [10,11]). An important component of Indian cooking is ghee, a clarified butter product. Ghee contains significant levels of COPS (12% of sterols) and could explain the high prevalence of CHD among these populations, especially in the absence of cholesterolaemia [12].

There is also some evidence suggesting that dietary COPS may be atherogenic via their effects on lipoprotein metabolism. Rabbits fed cholesterol containing 5% (w/w) COPS displayed a 5-fold increase in plasma total cholesterol concentration when compared with rabbits fed purified cholesterol [13], data suggesting that the
increased plasma cholesterol concentration was attributable to increased very-low-density lipoprotein (VLDL) by the liver. Other studies using HepG2 cells [14] and primary hepatocytes [15] have shown that COPS can stimulate cellular cholesteryl ester synthesis and secretion in lipoproteins. Another potential mechanism by which COPS can increase the atherogenicity of plasma lipoproteins is by increasing LDL cholesteryl ester content, i.e. increasing the cholesteryl ester/apolipoprotein B (apoB) ratio of LDL particles. Carr and co-workers [16] have shown that cholesteryl ester enrichment of plasma LDL is strongly correlated with atherosclerosis development in primates, and that production of cholesteryl ester-enriched LDL is regulated largely by the secretion of apoB-containing lipoproteins by the liver [17]. Recent research in our laboratory has demonstrated that the addition of dietary COPS to HepG2 cells results in the secretion of apoB-containing lipoproteins enriched with cholesteryl esters [18]. These findings could have serious clinical implications, and further research is required to determine the precise role of COPS in the assembly and secretion of hepatic lipoproteins.

The case implicating COPS would be strengthened by linking them to the final step in CHD, thrombosis. Prostacyclin produced by endothelial cells slows the adhesion of platelets to the vessel wall, thereby reducing the risk of loss of integrity, a factor which if left unchecked could result in thrombosis. COPS have been shown to be far more inhibitory of endothelial prostacyclin production than cholesterol [19]. Because platelets secrete platelet-derived growth factor, which in turn stimulates hyperplasia of such cells destined to become foam cells, stage two of CHD can also be accelerated by COPS. A summary of the detrimental properties of COPS is presented in Table 2.

COPS have also been shown to occur in the lipoproteins of fasted humans [20] and to be absorbed post-prandially by chylomicrons and other mechanisms.
after a meal rich in fat and COPS [21]. The level of COPS peaked about 3 h post-prandial and was, in those subjects that exhibited a sharp increase in plasma COPS, quickly cleared from the circulation in a manner that appeared to represent classic detoxification. In research on the hamster, dietary COPS predominantly appear in the liver [22]. Moreover, lymphatic absorption of COPS in rats has been recently demonstrated [23].

The significance of plasma levels, lipoprotein distribution and absorption of COPS is unknown, but should provide the focus of intense study in the immediate future. This is especially true given new research on the potential role of antioxidants in the prevention of CHD by retarding the peroxidative changes in LDL. We have made informal observations that humans consuming high levels of fruit, vegetables and whole grain cereals tend to experience low levels of circulating plasma COPS. How does the level of COPS caused by in vivo lipid oxidation compare with those caused by post-prandial absorption of a meal rich in COPS? This is a crucial question with regard to elucidating the potential role of in vivo oxidation and/or dietary COPS in CHD.

COPS are not the LOPS of importance to CHD. Biological oxidations of LDL are now believed to be a necessary step in foam-cell formation [24,25], and involve extensive loss of polyunsaturated fatty acids and the appearance of a number of aldehydic breakdown products [24]; the cytotoxicity of these species is well-established [25]. Therefore, the situation for LOPS and COPS is much the same, as many aspects of CHD are adversely affected by both types of degradation products. The occurrence of LOPS in rancid foods has long been recognized as a quality problem in foodstuffs and the potential for adverse health effects has been previously hypothesized [1,2]. As was the case for COPS, research into these intriguing questions has been stymied by methodology. The traditional methods for measuring rancidity in foods, peroxide value and thiobarbituric acid reagent, were good for assessing potential organoleptic problems but did nothing to monitor the accumulation of individual fatty acid degradation products. Recently, an important advance in this area has been reported [26]. High-field ¹H nuclear magnetic resonance spectroscopy has been used to identify numerous aldehydes, many known to be cytotoxic, from heated culinary oils. Logically, the more polyunsaturated oils exhibited the greatest accumulation of detrimental fatty acid breakdown products; saturates were more resistant [26]. Methods now exist for the determination of individual COPS and LOPS in foods, plasma, plasma lipoproteins, and tissues. It is therefore possible for the first time to answer some critical questions regarding the relative importance of both dietary and biologically generated COPS and LOPS and the importance of antioxidants.

The other atherogenic lipids in the human diet include saturated fats, cholesterol and trans-fatty acids. Of these, the relationship between dietary saturated fatty acids and plasma cholesterol levels has received the most attention. Early human studies demonstrated that fatty acid chain length and degree of unsaturation were important determinants of cholesterolaemic response [27,28]. Additional studies served as a basis for the development of regression equations [29,30] that have been useful in prediction for groups of subjects' cholesterolaemic responses to short-term modifications in dietary fatty acid consumption. Generally, these equations predict that saturated fatty acids are approximately twice as potent in
raising plasma cholesterol levels as are polyunsaturated fatty acids in lowering them. ‘Potency’ is often expressed as the cholesterolaemic response (in mg/dl) induced per unit of total dietary energy consumed in the form of a given fatty acid. Both Keys and Hegsted documented the negligible influence of stearic acid \((C_{18:0})\) and acknowledged [29,30] the earlier work of Hashim et al. [31] and Grande [32] demonstrating that saturated fatty acids less than 12 carbon atoms in length did not significantly influence plasma total cholesterol concentrations. Therefore, as early as 1965, it was generally agreed that almost all of the hypercholesterolaemic effects attributed to dietary saturated fatty acids were accounted for by three individual fatty acids: lauric \((C_{12:0})\), myristic \((C_{14:0})\) and palmitic \((C_{16:0})\) acids.

Keys and Hegsted disagreed in their interpretation of the relative cholesterolaemic effects of lauric, myristic and palmitic acids [29,30]. Keys interpreted these three saturated fatty acids to be essentially equivalent on a percent energy basis; Hegsted believed myristic acid to be the most potent saturated fatty acid. In both cases the authors were inferring independent fatty acid effects from multiple regression equations fitted to data compiled from a large number of dietary trials. Limitations of such inferences were duly noted by both authors, in part because of the inter-dependence of these individual dietary fatty acids within the experimental diets used. Characterization of cholesterolaemic effects for specific fatty acids is further complicated by the fact that commonly consumed dietary triacylglycerols are comprised of fatty acids that may also vary in their degree of unsaturation, isomeric orientation of double bonds and position within the triacylglycerol molecule.

In 1970, McGandy attempted to address the independent cholesterolaemic effects of lauric, myristic, palmitic and stearic acids while minimizing some of the limitations posed above [33]. Subjects were fed a semi-synthetic diet in which specific saturated fatty acids were varied independently of one another in a diet containing 300 mg of cholesterol/day and ranging widely in linoleic acid abundance. Results showed a less potent effect for myristic acid and a more potent effect for lauric and stearic acids when expressed relative to the natural fats fed in the earlier study [29]. It was concluded that myristic and palmitic acids were approximately equivalent in hypercholesterolaemic properties and that positional specificity of stearic acid within the triacylglycerol molecule may influence its cholesterolaemic response.

Subsequent to the McGandy study, almost 20 years elapsed before the public policy of heart disease prevention began to drive renewed interest in this area for the purpose of changing the composition of the food supply [34,35]. Bonanome and Grundy [36] fed subjects liquid-formula diets and confirmed earlier findings [27,29,30] that stearic acid was hypocholesterolaemic relative to palmitic acid. Additional work found that lauric acid was also hypocholesterolaemic relative to palmitic acid [37]. However, Hayes and co-workers provided evidence that, under certain conditions, palmitic acid can be approximately equivalent in cholesterolaemic response to oleic acid \((C_{18:1o})\), long regarded as neutral [38–40]). These conclusions include the absence or near absence of dietary cholesterol and a low LDL concentration in human subjects or animals. In addition, Hayes provided data in monkeys and gerbils suggesting that, under the conditions
described above, myristic and linoleic acids are the only dietary fatty acids with consequential (and opposing) cholesterolaemic effects [41,42]. Dietschy and co-workers demonstrated hypercholesterolaemic responses for lauric, myristic and palmitic acids, relative to all others tested [43,44]. No significant differential effects among these three fatty acids were detected.

Recently, Katan and co-workers [45] attempted an approach similar to McGandy's [33]. Subjects were fed semi-synthetic margarines enriched in either myristic, palmitic or oleic acid such that each fatty acid accounted for at least 10% of total energy. Myristic acid was found to be the most hypercholesterolaemic, followed by palmitic and then oleic. It is interesting and perhaps significant that HDL cholesterol also increased for both men and women on the myristic acid diet.

The trans-fatty acid issue is yet another controversial one in CHD research. For decades, the 'authorities' in the U.S. have recommended that the public use vegetable oils and shortenings in place of animal fats such as lard and tallow. However, a recent study of 85000 nurses has suggested a strong relationship between consumption of the trans isomer and CHD, either non-fatal myocardial infarction or sudden death from CHD [46]. An 8 year follow-up revealed 431 cases of CHD and a relative risk ratio of 1.5 ($P<0.001$). That the major rise in CHD in this century coincides with increased intake of trans isomers and the more recent decline in CHD appears to coincide with the use of more lightly hydrogenated oils was reviewed [46]. In an interesting hypothesis paper, Simopoulos [47] has reviewed literature related to the potential role of trans-fatty acids in insulin resistance, a risk factor for CHD. Increasing consumption of trans isomers, saturated fat and linoleic acid (provided by the significant increases in vegetable oil consumption and hydrogenated vegetable shortenings) and decreases in linolenic acid consumption could lead to insulin resistance [47]. Other factors involved in insulin resistance include increases in body weight, alcohol intake, and decreases in physical activity and decreases in the consumption of arachidonic, eicosapentaenoic and docosahexaenoic acids. The ability of trans isomers to inhibit enzymes involved in elongation and desaturation of fatty acids may exacerbate the situation [48]. Other evidence concerning deleterious trans isomer effects include modest elevations of Lp[a] [49], some variants of which are highly atherogenic.

The potential chemical modifications related to the formation of trans isomers, the oxidation of trans isomers in heated oils and the potential for toxic effects has only begun to be evaluated. In a study of four heated oils, Greek and Italian olive oils, and sunflower and safflower oils, it was noted that a rapid transformation of the cis isomer into trans isomers occurred as they were heated [50]. Oils with about 0.5% (w/w) trans isomer were found after only 7 h of heating at 180 °C to contain as much as 13.5% trans fats, with Greek olive oil exhibiting the greatest resistance to change. Most oils are used for far longer periods in restaurants, although some oil is carried out on the food and is replaced with fresh oil.

Iron is the last potentially atherogenic dietary component to be discussed. Although iron is an essential nutrient, an extensive epidemiological study implicated stored iron (plasma ferritin) in CHD in Eastern Finnish men [51]. Iron is well known to initiate tissue oxidative damage. In a study where the function of
liver storage iron as a potential risk factor for CHD was evaluated independently and in combination with various lipoprotein indices using the CHD data from 11 countries, along with available data on liver iron stores, CHD mortality rates were found to be best correlated with the liver iron-serum cholesterol product in both men \((r = 0.72)\) and, more importantly, in both genders combined \((r = 0.74)\). However, the correlation coefficient \((r)\) for the relationship between liver iron and CHD mortality was only 0.23 in men and 0.49 in women, and \(r\) for that between iron-cholesterol product and mortality was 0.38 in women [52].

A survey in a total of 82 healthy Dutch volunteers revealed a significant negative association (partial regression coefficient \(-0.0010, P \leq 0.05\)) between erythrocyte selenium and serum ferritin levels, possibly connected with the mechanism of decreasing glutathione peroxidase activity in erythrocytes following exposure to iron-mediated oxidative stress [53].

The primary research that ignited a controversy on the possible heart–iron relationship was the study conducted by Salonen and co-workers [51]. This study of 1931 randomly selected Eastern Finnish men over a 5-year (1984–1989) period showed that men possessing 200 µg/l ferritin had a 2.2-fold greater (95% confidence interval, 1.2–4.0; \(P < 0.01\)) risk factor-adjusted risk of acute myocardial infarction when expressed relative to those of men with lower serum ferritin, and the association was stronger in men with serum LDL higher than 5.0 mmol/l (193 mg/dl) than in those with lower LDL levels. The strongest determinants of serum ferritin concentration in the study were the intakes of alcohol and meat. Therefore, the high stored iron level, as assessed by elevated serum ferritin, was suggested as a risk factor in CHD [51]. However, lack of information concerning fruit, vegetable, cereal and antioxidant consumption limits the usefulness of the study.

In a study in West Germany by Oster et al. [54], serum iron levels were found not to be associated with the presence of CHD or its severity. There was a moderately positive correlation between the serum ferritin levels and iron concentrations in heart tissue from patients during bypass surgery, whereas serum concentrations of iron and some other trace elements were not correlated with those in the heart tissue. Aronow [55] reported that serum ferritin is not a CHD risk factor in men and women 62 years of age or older. Serum ferritin levels were determined in 577 elderly people after a 14-h fast. CHD was present in 74 of 171 men and in 172 of 406 women. Increased serum ferritin levels were not seen in men or women with documented heart disease and, in fact, 10% of women without CHD displayed elevated ferritin levels, whereas in only 7% of women with CHD these levels were elevated.

On balance, there would appear to no clear consensus regarding the potential role of iron in CHD.

**Anti-atherogenic factors in the diet**

The studies of anti-atherogenic factors (Table 3) in the human diet are relatively new compared with the traditional studies on atherogenic factors. Nevertheless, the addition or enhancement of anti-atherogenic factors have
potential to reduce CHD to a greater degree than does the restriction of atherogenic factors. It is easier to add than to prohibit dietary components, especially if prohibition involves foods of high culinary value. Such anti-atherogenic factors include antioxidants, fish oils, polyunsaturates, fibre, and the trace minerals iron, copper and selenium. All can be added to the diet without serious sensory problems, assuming the polyunsaturates, including fish oils, are adequately protected against oxidative deterioration.

The antioxidants are very prominent members of the anti-atherogenic agents in the diet and the chronicle of their discovery supplies a fascinating source of reading material. Early work had clearly established the risk associated with elevated serum LDL, but the laboratory evidence was lacking. In an attempt to learn more about how LDL can load cholesterol ester into arterial cells to produce foam cells, Goldstein and Brown [56] incubated LDL with macrophages. This led to the discovery of receptor-mediated endocytosis by which cholesterol enters the cell [56]. However, the native receptor was, of course, down-regulated, indicating that as cholesterol requirements of the cell were met the process slows; this presented difficulties with hypotheses concerning how foam cells could be formed. Subsequent research demonstrated the existence of the scavenger receptor, one that binds to a modified form of LDL, including oxidized LDL, and one that is not down-regulated [57]. These findings provided the explanation for the production of foam cells and stimulated interest in preventing oxidation of the lipidic components of LDL, and antioxidants were the obvious choice of weapon.

A recent review by Jialal [58] summarized the strong evidence supporting the concept that antioxidants are potentially a new modality in the prevention of CHD. It is tempting to speculate that the combined effects of increased antioxidant intake and lowering of plasma LDL may have a synergistic beneficial effect on the risk status of CHD. Numerous antioxidants have been studied, including dietary supplements such as α-tocopherol, β-carotene and ascorbic acid; food additives such as butylated hydroxyanisole; and numerous other naturally occurring antioxidants such as the catechins of red wine [59] and green tea [60].

Epidemiological evidence also strongly supports the contention that dietary antioxidants have a protective effect against the free radical reactions that appear to play a key role in CHD [61]. The evidence for these protective effects is strong in part in view of the variety of epidemiological studies that support this hypothesis, including cross-sectional comparisons between countries, prospective studies and case-control studies of individuals. Prospective studies have supplied data based on both dietary intake and plasma antioxidant levels [61].

<table>
<thead>
<tr>
<th>Table 3. Anti-atherogenic factors in the human diet.</th>
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<tr>
<td><strong>Antioxidants</strong></td>
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<tr>
<td>Fish oils, protected</td>
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<tr>
<td>Polyunsaturates, protected</td>
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<tr>
<td>Trace minerals: Fe, Cu, Mn, Se, Zn</td>
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<td>Fibre</td>
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Another group of anti-atherogenic factors is the various plant fibre components of the human diet which function by lowering plasma cholesterol. This area has been recently reviewed by Ripsin and Keenan [62]. Generally, soluble fibre is thought to be more effective as a hypocholesterolaemic agent than insoluble fibre.

Fish oils and other polyunsaturates have long been associated with a decreased risk of CHD [63]. Most of this effect may be ascribable to their ability to lower platelet activity. It is beyond the scope of this review to summarize the extensive, although sometime inconsistent, data concerning the possible protective effect of highly unsaturated oils. It is, however, possible to postulate that these oils, although possible protective in the native state, can become quite toxic if lipid oxidation has occurred extensively [26]. The many potential interrelationships occurring among dietary COPS, LOPS, antioxidants and polyunsaturates, and in vivo platelet effects, endothelial injury and amplification or diminution of antioxidant effects and lipid oxidation are complex but potentially very important.

Finally, in spite of the hypothesis concerning iron, ferritin and CHD, and in agreement with the significant and mounting evidence against the ‘ferritin hypothesis’, the growing evidence suggests that many trace minerals, including iron, have important antioxidant functions and protect biological tissue against free-radical-induced damage. A recent review by Johnson and Fischer [64] summarized data on copper, zinc and manganese, which are components of superoxide dismutases; selenium, a component of glutathione peroxidase; iron, a component of catalase; and copper, as a component of ceruloplasmin. The latter protein oxidizes iron to the ferric state for binding by ferritin. In this manner, free iron is kept in a bound form and is not able to catalyse free-radical reactions.

Summary

This review has focused on the emerging area of dietary lipid oxidation products, antioxidants and trans-fatty acids as potential factors influencing CHD. An extensive review of the newer data on saturated fats, a sometimes confusing but often oversimplified area, was presented. It is our opinion that the new areas of antioxidants, lipid oxidation products and trans-fatty acids require vigorous research study, since these agents are among the most promising, consistent, logical, and applicable findings that have been reported for many years. It is apparent that an entire new series of research challenges has been uncovered.

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