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Review

ISCHEMIC HEART DISEASE AS DEFICIENCY DISEASE

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Abstract - Four classes of agents capable of producing human illness have been identified: toxicity, heredity, infection and deficiency. The leading paradigm for the etiology and pathophysiology of ischemic heart disease in the 20th century was that of intoxication by too much of the wrong kind of dietary fat. This overemphasis on lipid metabolism persists because important data are neglected and because of inattention to details. For example, heart disease risk does not correlate with fat intake within nations in contrast to between nations. Also development of ischemic heart disease involves *inter alia* arterial spasm, cardiac rhythm, metabolism of connective tissue, glucose and homocysteine, plus paraoxonase activity and thrombus formation which generally are unaffected by dietary fat. Homocysteine thiolactone accumulates when homocysteine is high. This lactone specifically inhibits lysyl oxidase which depends on copper to catalyze cross linking of collagen and elastin in arteries and bone. The lactone is hydrolyzed by paraoxonase, activity of which can be decreased by copper deficiency. Just as cholesterol was an important focus for heart disease as intoxication, homocysteine can become an excellent focus for a paradigm shift to heart disease as deficiency because supplementation with several nutrients can alter homocysteine metabolism and decrease its plasma concentration. These supplements include betaine, copper, folate, pyridoxine and vitamin B-12. Opportunities for research on ischemic heart disease as deficiency disease are plentiful.

Key words: Cholesterol, copper, homocysteine, intoxication, lipids, lysyl oxidase, paraoxonase, vitamin

INTRODUCTION

History

The epidemic of ischemic heart disease (IHD) is a phenomenon of the 20th century. The disease probably is not new, however. With a description of calcified coronary arteries, Leibowitz (59) traced its history to 21st dynasty Egypt (c. 1000 BC). John Hunter, who died in 1793, suffered from angina pectoris for 20 years and realized that the pain put his life in jeopardy. (59). His contemporary, Edward Jenner, associated angina with calcified coronary arteries (59). Osler (79) noted a close connection between angina pectoris and lesions of the coronary arteries: narrow orifices, fresh thrombus or obliterative endoarteritis. Herrick (25,26) realized that it was possible to survive sudden obstruction of the coronary arteries. Vital statistics have improved and disease definitions have changed since 1900 (42). In the United States deaths from diseases of the heart did not exceed tuberculosis until 1910 (42).

Classification of illnesses

In 1977 (38) all diseases were divided into two classes based on whether or not their etiologies were comprehensible or incomprehensible. Analysis of comprehensible illnesses such as intoxication with arsenic, Huntington chorea, staphylococcal food poisoning and pellagra led to the suggestion that human illnesses are caused by four classes of etiologic agents: toxicity, heredity, infection and deficiency (43). This exercise provides mental clarification to assist in understanding the etiology of ischemic heart disease.

Imagination probably conceived these concepts before they were recorded by Aristotle (toxicity), the Talmud (heredity), Boccaccio (infection) and Lind (deficiency) (38,43). Although these ideas are familiar now, initially they were bold.

Diversity of agents within these classes is immense. No one knows how many agents can cause illness, but millions of chemical compounds have been identified. At a minimum there are a few thousand genetic diseases and infectious agents. Probably the number of essential nutrients is not much greater than fifty if one counts the amino acids, the minerals, the vitamins and water (43).

Cancers and ischemic heart disease are considered to be incomprehensible because origins are obscure and mechanisms are complex. There are plenty of other prevalent diseases of unknown etiology. It has been suggested that physicians spend most of their time treating patients whose diseases are of obscure origin (41,47).

Many believe that ischemic heart disease is of

multifactorial origin. The introduction of the word multifactorial into medical thought on the origin of disease seems to be recent. White, who mentioned the plausibility of the combination of several etiologic factors, did not use the term in 1944 (100). The term was used in Friedberg's text (19) in 1966. Its use is convenient; it seems to explain the many apparently dissimilar observations on factors that seem to influence risk.

McCormick (69) considers multifactorial aetiology of heart disease to be a dangerous delusion. It has been suggested that beri-beri (45), pellagra (39) and scurvy (42) might have been considered multifactorial illnesses when their origins were as incomprehensible early in the 20th century as ischemic heart disease has been later in that century. The multifactorial concept may distract us from the possibility that ischemic heart disease may not be as complicated as it appears.

The four classes of etiologic agents that encompass the comprehensible illnesses (above) can cooperate in several ways to increase the likelihood of illness (43). Hereditary enzyme deficiencies can increase the toxicity of environmental agents as can certain infections. There are several examples in which deficiency, heredity and toxicity cooperate to produce illness (loc. cit.). Similarly, unusually high requirements for nutrients can be inherited. Thus when ischemic heart disease is transferred, eventually, into the comprehensible class of illnesses, several factors may be found to be important.

Often it is assumed that ischemic heart disease is an hereditary illness because some families have several affected members and some families have none. That is, host factors predominate. It seems unlikely that most ischemic heart disease is primarily hereditary for two reasons. First, in the wealthier nations, ischemic heart disease is far too common. For example, in the United States, approximately one-fourth of all deaths are from IHD (3). Cleave and Campbell (13) provide an excellent discussion of the prevalence of hereditary illness and conclude that each hereditary illness is found usually in less than five per 1,000 live births. Next, people who emigrate from nations where risk is low to nations where risk is high experience an increase in risk (45). The best evidence on this point is Japanese (45,34,74).

It will be argued here that the homocysteine field has been neglected by many investigators mainly because of overemphasis on lipids, neglect of important data and inattention to details. Kilmer S. McCully is prominent among a few scholars who have taken a broader view and who provide alternatives to the lipid hypothesis (70,71,72). Some common aspects of these alternatives will be illustrated near the end of this essay.

OVEREMPHASIS ON LIPIDS

The lipid hypothesis probably is the most widely accepted and the most intensively studied hypothesis on the origin of ischemic heart disease. Proponents of this hypothesis advocate the view that habitual ingestion of large amounts of dietary fat is hazardous: that is, large amounts of dietary fat are toxic. Based on the concepts above, ischemic heart disease is fat intoxication. Unfortunately, the lipid hypotheses often is referred to as the diet-heart hypothesis as if lipid is the only characteristic of diet that can affect risk (67). Research on lipid metabolism has dominated both concepts and investigations of atherosclerosis and ischemic heart disease for several reasons.

Early in the last century cholesterol fed to rabbits produced histological changes in aortas that resembled atherosclerosis in humans (1,98). A decade later it was found that the hyperlipidemia induced by this method could be increased by adding a bile acid to the diet (84). These dietary additives have become so imbedded in experimental atherosclerosis that authors sometimes neglect to mention them. Still later Keys *et al*. (34) found a tight, linear increase in the concentration of cholesterol in serum of people with the amount of fat in their diet in a large international survey.

The concentration of cholesterol in blood plasma can be increased or decreased easily by changing the characteristics of the fat fed when people are evaluated under tightly controlled conditions (24,33).

Although this work was done over many decades, it set the course of research on atherosclerosis and ischemic heart disease for much of the 20th century.

Thomas Kuhn introduced the concept of "paradigms" to both scientists and historians of science. He took paradigms "to be universally recognized scientific achievements that for a time provide model problems and solutions to a community of practitioners". The paradigm provides scientists "not only with a map but also with some of the directions essential for map-making" (58). Dietary fat and lipid metabolism became the defining paradigm (54).

NEGLECT OF IMPORTANT DATA

When epidemiologic studies are done on an international basis; i.e. when death rates in different nations are compared, there is an association between risk and percentage of the diet that is composed of fat (32). This association is found only occasionally when studies are done in single nations where there are large cultural differences among the subgroups of the population studied (45).

Ravnskov (83) reviewed ecological, dynamic population, cross-sectional, cohort, case-control studies, and randomized trials and concluded *inter alia* that "there is little evidence that saturated fats.... are harmful or that polyunsaturated fatty acids.... are beneficial". Some have suggested that lack of evidence for this relationship should not dissuade us from believing in the relationship (27,62).

Although changes in dietary fat can produce changes in

plasma cholesterol under controlled conditions, evidence for a similar phenomenon among free-living people is practically non-existent. By 1983, I had found approximately 30 research articles in which authors failed to find evidence for a relationship between dietary fat intake and risk of heart disease or concentration of cholesterol (40). The first of these articles was published in 1959 (101). The collection now has reached approximately 50 negative articles (40,45,49).

These studies were done within single nations in contrast to the data collected on an international basis (32). Some weak correlations have been found) (40). No association between dietary fat and serum cholesterol was found in Framingham (21) or NHANES (23). Some of the enthusiasm for dietary fat-heart disease relationship, at least in regard to cholesterol lowering, arises from over-citation of favorable work and under-citation of unfavorable work (49,82).

Some authors collected appropriate data but either did not examine it completely or upon examination found nothing (40). Considering the great deal of interest in the putative relationship between dietary fat and heart disease, it seems unlikely that data were not examined. In my experience, scientists do not withhold statistically significant correlations.

There have been myriad recommendations that people should eat less fat. Some of these suggestions are made with juxtaposition of apparently increasing dietary fat in the United States with increasing risk of coronary heart disease in the first half of the last century (49). The increase in dietary fat probably is artifactual (9); the increase in disease was real (42).

If an increase in dietary fat occurred, the amount of the increase was too small to account for the increase in heart disease risk (30,99). It has been suggested that if nearly everyone in United States eats too much of the wrong kind of fat, dietary fat is no longer of epidemiologic interest because only a minority of people in the U.S. die of ischemic heart disease (36,45). In the United States, for example, only one fourth of the deaths are due to ischemic heart disease (3). Although the lipid hypothesis has been helpful in understanding ischemic heart disease, we should consider the possibility that this concept has outlived its usefulness (49).

INATTENTION TO DETAILS

Atherosclerosis is the most frequent cause of acute myocardial infarction; many other causes have been described (11). It may seem surprising that ischemic heart disease can occur in the absence of risk factors (4). Conversely, 69 percent of the men in the highest cholesterol quintile (256-514 mg/dl) were free of heart disease for 20 years (31). Stehbens (89,90) presents detailed, lengthy and persuasive arguments on why coronary heart disease should not be considered an inevitable consequence of atherosclerosis.

Adherence to the idea that industrialization has led everyone to eat too much of the wrong kind of fat presents some difficulties. For example, in the United States less than half of the deaths of people over 80 years of age are from ischemic heart disease (42). People dying over the age of 90 have more atherosclerosis than people who die before 70 and are less likely to die of ischemic heart disease (29). Similarly atherosclerosis was the cause of death found at post-mortem examination in less than one-fourth of 200 people older than 85 years (56). Under these circumstances dietary fat is of neither epidemiologic nor pathophysiological interest.

Epidemiology has not revealed that women eat less or better fat than men. Nor is there an experiment showing that women (or female animals) tolerate fat better than men (or male animals). That men with heart disease are more likely to die suddenly and women are more likely to die with thrombosis also cannot be explained by differences in dietary fat (60,88).

Table 1 summarizes some factors related to atherosclerosis and ischemic heart disease; lipid metabolism is only one of them. It seems unlikely that ischemic heart disease will disappear from among the leading causes of death in industrialized nations unless its etiology, pathogenesis, and pathophysiology become comprehensible as a whole (49). To understand heart disease, we must be aware of, and understand some aspects of the phenomena of Table 1.

Table 1 Ischemic heart disease phenomenology (45)

Arterial endothelial damage	Macrophages
Arterial spasm	Matrix carbohydrates
Connective tissue metabolism	Monocytes
Endocrinology	Paraoxonase
Endothelial and vascular permeability	Physiology
	Pinocytosis
Foam cells	Platelets
Growth factors	Smooth muscle cells
Homocysteine	Thrombus formation
Lipid metabolism	Uric acid metabolism
Lysosomes	Vasoactive amines

These factors probably are considered to be details best ignored by enthusiasts for dietary fat. Their broad consideration may result in lack of attention to some of the minutiae associated with any one of them. Some of these are unexplainable by this lipid hypothesis.

Endocrinology includes metabolism related to diabetes mellitus, hypertension, menopause and thyroid hormone, etc. Homocysteine and paraoxonase are recent additions to this list. These factors will be discussed below.

NEWER CONCEPTS

If dietary fat is only loosely related to heart disease risk and thus heart disease is not a disease of fat intoxication, one must consider other etiologic explanations. Four other alternatives have been proposed which may answer the question "What determines who lives long and who dies early of ischemic heart disease"? when people consume the Western diet for a lifetime (49).

These concepts may be new to some readers although they have been in development for several decades. Consequently, only brief outlines of the ideas will be summarized. References cited can be of assistance in obtaining detailed information.

Theories attempting to explain important natural phenomena have been found wanting historically if they explained only limited characteristics of the phenomena (6,49,77). Both individually and collectively, these concepts explain phenomena of ischemic heart disease that elude those who advocate the importance of fat intoxication.

Elevated plasma homocysteine is an independent risk factor for premature coronary atherosclerosis in men (20). Only specific aspects of homocysteine metabolism and heart disease risk related to dietary deficiency are mentioned here.

Jerome L. Sullivan provides evidence that ischemic heart disease is a disease of iron intoxication. In brief, male-female differences in risk, and the increase in risk of women that occurs after menopause, may be explained by greater male stores of iron early in life and increasing accumulation of iron by women later in life (91,92). Collectively, the other three explanations strongly indicate that ischemic heart disease is caused by dietary deficiency.

The fetal programming hypothesis has been summarized by David J.P. Barker in two editions of his book (7). In brief, being small at birth and not catching up by the first birthday (or then being too fat), predisposes to diabetes mellitus or hypertension in middle age. Undernutrition *in utero* is important in this phenomenon that leads to ischemic heart disease.

The copper deficiency theory on the origin and development of ischemic heart disease is based on experiments with animals and human volunteers, epidemiological observations, iatrogenic maneuvers and experiments of nature. In brief, the Western diet often is low in copper. Copper deficiency is the only nutritional insult that elevates cholesterol, blood pressure, homocysteine and uric acid, has adverse effects on electrocardiograms and arteries, impairs glucose tolerance, promotes thrombosis and oxidative damage, and to which males respond differently than females. More than 80 anatomical, chemical and physiological similarities between animals deficient in copper and people with ischemic heart disease have been identified (49,51). Iron overload can induce copper deficiency (50).

No long-term copper supplementation has been done in patients with cardiac arrhythmia, dyslipidemia, glucose intolerance, hypercholesterolemia or hypertension. However, dietary regimens found to alleviate some of these conditions may have included an increase in copper intake as a hidden variable: for example, the Lifestyle Trial (46), the protective effect of legumes on cholesterol, blood pressure and diabetes (52), and the benefit of whole grain foods on coronary heart disease (48) and the benefit of chocolate to lipoprotein oxidation (53). Spencer (87) described two men and a woman whose premature ventricular beats, which had persisted for years, were thought to be due to coronary heart disease. These premature beats disappeared after they ingested 4 mg of copper (as copper gluconate) per day.

AN EXPERIMENT

Introduction and methods

Durrington and the Macknesses are largely responsible for calling attention to the enzyme paraoxonase, which is one of the newer, important phenomena related to ischemic heart disease. In brief, low paraoxonase activity is found in conditions associated with increased risk of ischemic heart disease such as familial hypercholesterolemia, insulin-dependent diabetes mellitus (64,66) and the metabolic syndrome (85). Among diabetics paraoxonase activity is inversely proportional to blood glucose (57). Low activity also predicts both fatal and not-fatal myocardial infarction (63). Paraoxonase concentration is lower in Belfast, where heart disease risk is higher, than in Toulouse where risk is lower (65). The desirability (16) of a quest for dietary and pharmacological means of modifying serum paraoxonase has been suggested.

In response to this suggestion, some male, weanling rats of the Sprague-Dawley strain were made deficient in copper with a purified diet based on sucrose (62%), egg white protein (20%) and corn oil (10%) containing all nutrients known to be essential for rats but deficient in copper and zinc unless supplemented. This diet has been the use for decades (35) with minimal modification (44). All animals received sufficient zinc; half of them received adequate copper. Thirty four days later blood was collected from the vena cava under anesthesia and organs were collected following death by pneumothorax. Copper was measured in diet and organs by atomic absorption spectrometry following destruction of organic matter with nitric and sulfuric acids and hydrogen peroxide (2). Lipids were measured by colorimetry using commercial kits (Roche Diagnostics, Mannheim Germany). Paraoxonase was measured according to Eckerson *et al*. (17). Results were compared by the *t*-test for unequal variances (80).

RESULTS AND DISCUSSION

Results are summarized in Table 2. Deficiency was verified by increased cholesterol and decreased liver copper. Hypercholesterolemia from copper deficiency has been found in at least 22 independent laboratories world wide (49). Paraoxonase activity was decreased as concentration and, to a greater degree, per mole of high-density lipoprotein (HDL).

Paraoxonase is located almost exclusively on HDL and experimental evidence that the enzyme protects low-density lipoprotein (LDL) against lipid peroxides has been cited (16). They also suggest that protection by paraoxonase is likely to last longer than that afforded by fat-soluble vitamins. The decrease of paraoxonase activity per unit of HDL from copper deficiency indicates that not all HDL molecules are necessarily equally protective.

Decreased activity of paraoxonase from copper deficiency relates to several aspects of homocysteine metabolism. Homocysteine and heart disease risk may be associated because homocysteine thiolactone increases with homocysteine levels (28). Homocysteine thiolactone hydrolase and paraoxonase are identical (28) by several criteria including amino acid sequence, serial purification and substrate specificity. Thus low paraoxonase activity produces accumulation of homocysteine thiolactone from impaired hydrolysis. This accumulation (70) modifies low density lipoprotein to cause intimal injury (76) and inhibits lysyl oxidase (61) which depends on copper to catalyze the cross-linking of collagen and elastin (78). Insufficient lysyl oxidase leads directly to vascular disease (78).

Homocysteine is increased in plasma of rats deficient in copper (93) and can be decreased in men by copper supplementation (94). Homocysteine fed to rats interferes with copper utilization (8). Thus copper deficiency can increase homocysteine in plasma and copper physiology can be affected adversely by high homocysteine. Interference with copper physiology by homosysteine includes decreased cardiac and hepatic copper, decreased superoxide dismutase and increased oxidative damage (8). Superoxide dismutase can contribute to the primary defense against metabolically generated free radicals (78) and can be impaired by copper deficiency (78). Some of the damage to arteries in the atherosclerotic process and to hearts after infarction may be caused by free radicals (68,86).

Decreased paraoxonase activity accompanied by high homocysteine and high homocysteine thiolactone may contribute to some of the numerous anatomical similarities (49) between animals deficient in copper and people with ischemic heart disease. Of these, arterial elastic degeneration, foam cells, and necrosis along with coronary artery aneurysms, elastic fragmentation and necrosis plus decreased myocyte-myocyte struts in the cardiac wall are most likely to result from impaired lysyl oxidase and thiolation of LDL. The accompanying decreased oxidative defense may help to increase thiobarbituric acid reactive substances (49).

High homocysteine concentrations predict hip fracture risk in elderly men and women in Holland (96) and in Framingham (73). The resulting accumulation of homocysteine thiolactone (above) specifically inhibits lysyl oxidase (61) in bone, as well as in arteries. Inferior bone matrix containing defective collagen synthesized under these circumstances may lead to fragile bones and osteoporotic fracture. There can be no medical doubt that people deficient in copper have osteoporosis (55) because of numerous reports of increased transparency of bones on X-ray in deficiency. Whether or not people with osteoporosis are deficient in copper is undecided.

GENERAL DISCUSSION AND CONCLUSIONS

In the middle of the 20th century heart disease often was considered an inevitable concomitant of advancing age. Research prompted by the observations that cholesterol could be found in both plasma and plaques gradually changed this idea. Established scientists doing lipid research were busy, no doubt; excitement generated by their findings left little time for consideration of findings unrelated to lipids.

Apparently dissimilar observations that either did not fit the lipid intoxication paradigm or contradicted it took decades to accumulate and become validated. Aspiring scientists apprenticed to those doing lipid research probably spent nearly all of their effort in learning about lipid chemistry, concepts and methods, etc. and did not read widely enough to notice other things. Thus the overemphasis on lipids, the ignoring of important data and the inattention to details of epidemiology, metabolism and

Table 2 Clinical data, mean (SE)

Diet	Cholesterol mg/dl	Liver Cu mg/kg	Paraoxonase U/ml	Paraoxonase/HDL U/mmole
Adequate	113 (4.7)	10.6 (0.41)	146 (4.2)	208 (10.5)
Deficient	131 (5.5)	1.48 (0.12)	114 (4.1)	137 (5.4)
p	<0.020	0.00001	0.0001	<0.000021

pathology may have been almost accidental.

Acceptance of the homocysteine theory of arteriosclerosis was delayed by a defining paradigm that said atherosclerosis and ischemic heart disease are the result of intoxication by a diet high in fat. This paradigm distracted researchers from other possibilities.

The possibility that ischemic heart disease is the result of dietary deficiency is not new, but it has not received much attention. Gresham and Howard (22) referred to "relative or absolute lack of some trace substance". Morris *et al*. (75) mention "risk of some deficiency". The Chipperfields (12) suggest "deficiency of mineral salts"and that copper deficiency may be important. Relative or absolute deficiency of copper has been suggested as being important in heart disease etiology (37,38). Prior *et al*. (81) raise the question of an "unmeasured" dietary variable. Even Keys *et al*. (33) mention the possibility of "some mysterious substance in cocoa butter". Most of these authors seem to be echoing Chamberlin who advocated "multiple working hypotheses" (10) to avoid neglecting important data when attempting to explain important natural phenomena.

Others have suggested that the increasingly refined Western diet may induce multiple mild deficiencies that increase risk (71,72,95). Dietary deficiency can increase homocysteine. Betaine (14) and copper (94) supplements can lower homocysteine as can supplementation with vitamins B-6, B-12 and folic acid (5,72).

Serious consideration should be given to more trials to determine whether or not dietary supplementation can decrease heart disease risk. These trials can range in size from very large trials similar to those prompted by the lipid hypothesis to smaller trials to determine if people already ill can benefit. For example, animal experiments have shown that the cardiovascular damage induced by copper deficiency is reversible in relation to cardiac enlargement and cytochrome oxidase activity (15), abnormal electrocardiograms (97) and heart failure (18). Only limited evidence for similar effects is available on people so far (87). Nutritional diseases should have nutritional solutions.

Research related to the origin and pathophysiology of ischemic heart disease should emphasize dietary deficiency more than intoxication with fat. Intakes of vitamins and trace elements should be measured during pregnancy and data compared with the usual measurements of infant and placental size because fetal programming may be the result of deficiency. Agricultural research should be shifted from changing the lipid composition of foods to improving concentrations of vitamins and minerals. Nutritional counseling should emphasize increasing intakes of vitamins and trace elements instead of fat avoidance.

Experiments with animals should seek common characteristics between some of the four newer concepts outlined above: the homocysteine theory of arteriosclerosis, the copper deficiency theory of ischemic heart disease, iron intoxication and fetal programming. These experiments can resemble the one reported here or that cited showing iron overload can induce copper deficiency. Currently links between the metabolism of homocysteine and copper are strongest; contributions of specific deficiencies to fetal programming are almost unexplored.

SUMMARY

The concept that ischemic heart disease is a disease of intoxication is tenable no longer. Too much negative data have accumulated, only some of which are mentioned here. Also excessive amounts of the wrong type of fat cannot explain newer facts about heart disease risk such as fetal programming or the effect of low paraoxonase. Just as cholesterol was an important focus for heart disease as intoxication, homocysteine can become an excellent focus for a paradigm shift to heart disease as deficiency because supplementation with several nutrients can alter homocysteine metabolism, decrease its plasma concentration and, presumably, decrease risk.

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