Acquired Atherosclerosis: Theories of Causation, Novel Therapies

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Two clinicians independently developed a safe vitamin-based therapy to prevent heart attacks and strokes in thousands over periods of decades and, in one doctor's practice, reversed the disease. Other supplements and practices further those ends.

Eight theories try to explain atherosclerosis: the (a) cholesterol; (b) homocysteine (McCully, 1969); (c) antioxidant (Taylor, 1979); (d) viral-damage (Minick, 1979); (e) free-radical (Halliwell & Gutteridge, 1986); (f) LDL-modification (Steinberg, 1987) theories, and the (g) clonal (Benditt & Benditt, 1973) and (h) micronutrient (de Villiers & Serfontein, 1989) hypotheses. Each yields important truths, yet none takes account of the two clinicians' results or assembles the pieces of the puzzle.

Using a large body of solid, yet largely ignored research together with evidence from 15 years' study of vitamins, I propose a working hypothesis. It apparently explains the disease, the two doctors' results, the success of others at reducing cardiovascular risk using other supplements, and leaves few anomalies. This review explores implications for prevention and treatment, long-term elimination of the epidemic, and offers suggestions for research.

1 University of California pathologists Rinehart and Greenberg fed year-old, herbivorous rhesus monkeys diets deficient in single vitamins (1949). With these diets, about as high in animal protein (casein) as typical Western human diets, they tried to induce cirrhosis of the liver (M.M. Suzman personal communication 1970 to K.S. McCully). That failed; but after 6 months to 4 years, all those fed food somewhat low in vitamin B_6 (Pyridoxine) had atherosclerosis. Those adequately supplied with B_6, even if deficient in another tested vitamin or high in cholesterol, developed no artery lesions. A vitamin-C-deficient diet, too, should have induced artery damage (see 7.1).

Moses M. Suzman, an internist with a 23-year-old practice in Johannesburg, South Africa was a personal friend, former working associate of, and in close contact with Rinehart. Suzman theorized that environmentally acquired atherosclerosis (as distinguished from familial hypercholesterolemia, or FH) is a vitamin-deficiency disease. He suspected multiple vitamin and mineral deficiencies in those on Western diets and had earlier conceived what he called a pandemic B_6-deficiency.

This would explain why coronary-artery disease appears in people anywhere who adopt Western diets. Abundance of dietary B_6 would explain lack of the disease, e.g. among the Chinese (Addendum 4); and in blacks — despite low serum B_6, very high blood pressure, and heavy smoking (Serfontein & Ubbink, 1985) — as contrasted to whites in South Africa. (The few black patients Dr. Suzman has treated had spent many years as live-in workers in, say, a hospital and consumed Western food.) He reasoned that sensible diet, exercise, not smoking might help only insofar as they relieve B_6 deficiency. And since few in Third World countries outside of South Asia eating traditional diets develop the disease, it isn't a necessary aspect of aging.

1.1 Research has confirmed a widespread subclinical B_6-deficiency in cells of human tissues (Azuma, 1976; Folkers, 1977; Serfontein, 1984). Heart patients typically have serum B_6 concentrations 1/5 to 1/4 of those in the healthy (McCully, 1983). Before a heart attack, this deficiency shows also in plasma and erythrocytes (Serfontein & Ubbink, 1988; Kok, 1989). Kok found no evidence to support the contention that heart attacks lower B_6.

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The level of B_6 in tissue and red blood cells is probably more important than that in serum: enzymes that metabolize the pro-oxidant four-carbon sulfhydryl amino acid homocysteine (abbreviated Hcy) (see 3.1) are in cells (K.S. McCully pers. comm., 1990). Cellular B_6, difficult to measure by present techniques, is not always evidenced by that in serum (Gruberg & Raymond, 1981; Shultz & Leklem, 1987). "The greater part of the body's B_6 is in muscle, associated with glycogen phosphorylase" (Bender, 1989); some is in albumin and hemoglobin (Ubbink, 1987).

Why a B_6-deficiency? (a) High fat consumption is harmful in relation to atherosclerosis not so much because fats are fats but because they contain no B_6: B-vitamins are soluble in water, not fat; (b) People in Western societies eat refined "garbage foods" from which almost all micronutrients have been discarded to prevent spoilage; and in the case of B_6, destroyed in some of its vitamins more than others by heat and light, by radiation, oxidation; (c) In the remaining 1/3 of diet much is lost in transportation, storage, preservation, cooking; (d) People are exposed to B_6-antimetabolites: from chemicals in food, air, water; in and on prescription drugs (Isoniazid, Penicillamine, Cycloserine, Hydralazine (Berkow, 1977), contraceptive pills), dyes etc. (Gaby, 1985). Some B_6-antimetabolites increase requirement for the vitamin; deoxypyridoxine injected into animals damages arteries (Mushett & Emerson, 1956).

1.2 Dr. Suzman, a former Rockefeller Foundation Scholar published statistical studies showing superiority of long- over short-term anticoagulant/antithrombotic therapy for heart patients (1965,1971). He had pioneered long-term use of the procedure since 1946, and combined it with beta-blockers. In 1969, learning of developments in theory (3.2), he shifted his emphasis to B_6. Now 87, he treats mostly stress, hypertension, and cardiovascular patients.

Dr. Suzman wrote of his vitamin-based therapy with a group of heart patients in one published abstract (1973). Later submissions were rejected by peer-review, which "rewards conformity and excludes criticism" (Mann, 1977), and which Suzman decries as a giant obstacle to medical progress (pers. comm., 1990).

He spoke of those methods and his results to 30 medical audiences worldwide. They listened "in stony silence" and "without any attempt at rebuttal!" (pers. comm., 1984; emphasis is his). Research pathologist/biochemist Kilmer S. McCully (1969) and neurophysiologists Edward R. Gruberg and Stephen A. Raymond (1981) were receptive. This review includes details from correspondence with Dr. Suzman, otherwise unavailable documents he sent me, 39 telephone conversations, and his editing of a draft.

1.3 Two therapeutic classes of patients.

1.3.1 Non-heart patients. A high proportion of adults who have always eaten Western diets and feel healthy, test normal on electrocardiograms, etc., have advanced atherosclerosis (Enos, 1953). Intimal thickening was found in 97% of 176 consecutive babies, dead of any cause in their first month. In some, artery occlusion was deemed the possible cause of death (Jaffe, 1971). Let skeptica contrast her photo micrographs to the finding in an Eastern culture (Vlodaver, 1969).

Dr. Suzman decided that most subjectively healthy adults of average body size who have always eaten Western diets need 100 mg of B_6 a day. They could eat 133 bananas, 833 three-inch oranges, or 18.6 pounds of raw calf liver every day (Gruberg & Raymond, 1981), or take B_6 tablets.

Thousands of present and former patients are in Johannesburg. In their enclaves surrounded by a sea of restive, often violent blacks, they enjoy an unusual camaraderie. If more than a few had a cardiac problem or a stroke, he would learn of it through the grapevine. To his knowledge, among those sent to him since 1950, almost none who took 100 mg of B_6 daily had a heart attack or other cardiac problem, and none had a stroke.

1.3.2 Heart patients. Many hundreds have been referred to Dr. Suzman. Those of average body size take each day in divided "doses" 200 mg of B_6, half in a B-complex that includes choline, 5 mg of folate, and 100-600 IU of vitamin E. He instructs them also to reduce animal protein to 1/4-1/2 their customary level and to derive most protein and calories from

plant foods (1973). Diabetics take a third 100 mg B_6. More recently he has added K, especially for patients with arrythmias and/or taking diuretics; Zn to strengthen the immune system; Mg to reduce sensitivity to spasm and arrhythmia and improve intracellular uptake of K; 100 mcg of Se; and Cu for the Cu-deficient.

Patients start this regimen right away, with conventional medications. As with his other patients, he doesn't urge changes in health-related habits (other than diet). In a 17-month clinical study, all on this regimen gained in exercise tolerance and feeling of well-being. Angina diminished or disappeared, electrocardiographic signs reverted to or approached normal (1973). The patients "served as their own controls": those who abandoned the regimen would suffer heart problems, return of angina. Although some continued visits for years, most stopped their medicines within two years and continued supplements/diet without periodic office visits. He kept in touch with scores by mail for as long as 10 years. Many report they have enjoyed improved quality of life for decades.

In his latest abstract (1978), to the VIII World Congress of Cardiology in Tokyo, copies of which were given to those present, of 62 typical heart patients followed for an average of 52 months, there were four reinfarcts (6.5%), of which two (3.2%) were fatal. He doesn't know of any heart patient who has had a stroke — even among stressed hypertensives.

1.4 Reversal of acquired atherosclerosis. Kuzuya induced the disease in rhesus monkeys with a B_6-deficient diet and reversed it by supplementing B_6 (1977). Opening the coronary and other arteries, he confirmed atherosclerosis and its amelioration brought about by the supplement (1977), See 7.1 on reversal of the disease in guinea pigs and humans with vitamin C.

Some heart patients had presented with peripheral atherosclerotic disease, revealed by lack of pulse in the legs, unusual delay in refilling of venous blood after the elevated leg was lowered, etc. (He gave up coronary arteriography, obtaining the same information from clinical observation.) In every such patient re-examined after a few years, blood flow in the legs had been restored. Physiology textbooks state that arteries throughout the body are constructed alike. So Suzman inferred, what happened in those leg arteries happens also in coronary, carotid, and other critical blood vessels in both cardiac and non-cardiac patients (Dr. Ellis (1.4) reached this same conclusion after he observed that B_6 supplements soften and rejuvenate arteries in the arms and hands), and that this explains patients' subjective and objective improvement. Such clinical observations need to be confirmed, perhaps using the new digital ultrasound *(Wall St. J.* 4/17/91).

1.5 Our second clinician is John Marion Ellis, Medical Director of Clinical Research, Titus County Hospital District, Mt. Pleasant, Texas. For 29 years Dr. Ellis pioneered treatment of painful hands, including cases resulting from repetitive motion — usually avoiding surgery at the carpal tunnel (Ellis & Folkers, 1990) —and tenosynovitis. Patients take 50 mg of B_6/day. These thousands, like Dr. Suzman's non-heart patients, continue a Wes tern diet; they don't take other supplements or substantially change habits regarding exercise, body weight, smoking (Ellis, 1985). Those with carpal tunnel syndrome (CTS) or adult-onset diabetes, or both, take B_6 100-200 mg for about 3 months, less after that. Pregnant patients start with 50; if they develop edema, begin to drop glassware, or an arm becomes paralyzed during sleep, 200 (Ellis & Folkers, 1990).

Few of his hand pain and arthritis patients had heart attacks or bypass surgery (1985). Nearly all of those had presented with "symptoms of severe B_6-deficiency" that respond to B_6 supplements — such as advanced atherosclerosis and/or diabetes, angina, CTS, numbness, tingling, and edema in arms, hands, and fingers.

1.6 Dr. Suzman's and Dr. Ellis' records, the only known prospective clinical evidence supporting our hypothesis, can be criticized as anecdotal. Yet the results are not equivocal, and the utility of their therapeutic regimen can hardly be doubted.

2 Our next task is to understand how these two doctors' therapies work. The pivotal issue is the causal mechanism of artery wall damage. Preventing this would

preclude all the consequences and complications of atherosclerosis (B_6, 1979).

Contrary to "... all roads lead to atheroma" (Steinberg, 1989) — which seems to accept all theories as correct — a single mechanism is proposed: the "Two-Source Oxysterol Injury (TSOI) Hypothesis". Oxidized cholesterol particles damage arteries. Cholesterol particles can be oxidized before they are ingested and can also become oxidized in the body through metabolic conversion of methionine. Either route alone can damage arteries; the two in tandem as in Western diets are doubly deadly. Suzman's/Ellis' therapies interdict oxidation by both routes.

Both are linked almost exclusively to the low density lipoprotein fractions, explaining why LDL and VLDL and, I propose, lipoprotein (a) are "bad". Oxidation transforms a benign substance necessary for life into a killer. 2.1

We consider, in four steps, the first route. Schultze and Winterstein found that cholesterol in foods oxidizes when exposed to air, particularly with light (1904). Taylor called the oxidized particles oxycholesterols, or oxysterols. Many food products common in Western diets contain powdered egg yolk, also used in restaurants. In powdering, cholesterol particles are exposed not only to air but also to heat and/or radiation, which speed oxidation.

The same is true of powdered milk, including powdered baby formula, and products made with it such as custard preparations, cake mixes, and dried soups (Taylor, 1979). Oxysterols are present in stored lard reused in fast food restaurants for deep frying (Peng & Taylor, 1984). Many chemi cals used in food-processing are oxidizers (de Villiers & Serfontein, 1989).

Oxysterols are also present in air-dried but not powdered egg yolk (Taylor, 1979) used in certain animal feeding tests (Fag-giotto, 1984). Fresh USP-grade cholesterol, used in other feeding tests, contains up to 5% of 32 auto-oxidation products; five-year-old, 40% (Taylor, 1979).2.2 Oxidized cholesterol particles, given intravenously or in diet, damage arteries proportionately to their concentration. Serum cholesterol does not rise. The damage closely resembles that inflicted mechanically (Taylor, 1979). "If only *0.25 percent* of serum cholesterol is oxidation contaminants, the aortic smooth muscle cells could be injured within 24 hours (emphasis added)" (Peng & Taylor, 1984). The discovery has been confirmed (Morin & Peng, 1989); Hill explored mechanisms (1984). Already disrupted tissues oxidize more quickly than healthy ones (Halliwell 8c Gutteridge, 1986). (Reperfusion damage by oxysterols, when blood flow is restored after blockage, is only a side issue.)

Only a single cell need be damaged to launch the atherosclerotic process (Benditt & Benditt, 1973). Oxysterols promote arterial spasm (Galle, 1990), and Hey generates oxysterols (3). Oxidized cholesterol also damages vitamin D, affecting the metabolism of Ca and leading to abnormal calcification (Jonathan Collin lecture to Well Mind Association, Seattle, 1990) and artery hardening. In a test in White Carneau pigeons using concentrations of oxysterols estimated to be typical in Western diets, serum Ca accumulation was 42 percent higher in test than in control birds (Jacobson, 1985).

As has long been known, biological oxidations involve free-radical reactions, which mediate artery wall damage. These chemically unstable molecules, together with other reactive molecules such as hydrogen peroxide and singlet oxygen, combine readily with structural proteins, enzymes, and other substances. They injure essential components of cells in many parts of the body. The relation of free radicals to artery damage has been explored in several books and more than 250 journal articles, yet their precise mode of operation is not known.

Free radicals, many of them associated with B_6 antagonists, form in the body in reaction not only to diet but also to alcohol, tobacco smoke, air pollutants, solvents, pesticides, medicines, anesthetics, radiation, formaldehyde. Oxygen is necessary for formation of free radicals from all these substances.

2.3 Oxysterols exist in the milk of mothers consuming Western diets, their babies' umbilical cord blood (Eberlein, 1965), serum and brain cells (Peng & Taylor, 1984), etc. At autopsy, atherosclerosis correlates with the accumulation of lipid peroxides and hydroperoxides in

serum and atheromas (Gey, 1986).

Levels of ingested oxysterols in high risk groups should be tested: (a) in the laboratory (Koopman, 1987); (b) simple hydrocarbon alkanes, ethane and pentane, from unsaturated fatty acids, are exhaled proportionately to the concentration of radicals in the body (Van Gossum & Decuyper, 1989).

2.4 Endogenously synthesized cholesterol and dibrominated exogenous cholesterol, included LDLs, do not damage intimal linings *in vivo* or cells *in vitro* (dibromination highly purifies cholesterol). Thus *only oxidized cholesterol particles damage arteries* (Taylor, 1979; Luc 8c Fruchart, 1991). Lp(a) attaches to an extra glycoprotein, apoprotein (a). How it damages arteries is not known (Utermann, 1989; Rath & Pauling, 1990A). Lp(a) may not damage arteries by a different mechanism than other LDLs.

Endogenous cholesterol is protected from oxidation by antioxidants in serum (Gey, 1986). Ingested oxysterols move almost exclusively to LDL/VLDL (Peng & Taylor, 1984) (and to Lp(a)?). LDLs appear to deliver oxysterols/free radicals (and Hcy (3.1) (Olszewski & McCully, in press) to artery walls and other peripheral tissues. The minimal oxysterols found in HDL (high density lipoprotein) cholesterol must be those it is carrying (with Hcy) away from artery walls to the liver. The cholesterol in egg yolk, red meat, and other fresh foods of animal origin then is non-athero-genic unless oxidized in storage or preparation. We shall see that Suzman's and Ellis' B_6 only regimen for healthy people eliminates ingested oxysterols.

3 But first we integrate into our hypothesis the Hcy theory.

3.1 A peroxidation process modifies LDLs, attacking their unsaturated bonds and releasing free radical reactions. Thiols, possibly involved in the process, are reducing, or deoxidizing substances that are easily oxidized to free radicals in the presence of transition metal ions. Thiolation is the introduction of thiol groups (monovalent radical -SH attached to carbon) by reaction of Hcy thiolactone (Hcy-T) with free amino groups (K.S. McCully, pers. comm., 1991). Modification accelerates uptake and degradation by tissue macrophages, particularly those derived from foam cells in the artery walls, and requires trace "redox" metals, typically copper and iron (Parthasarathy, 1987). Modification produces oxysterols and oxidizes polyunsaturated fatty acids (PUFAs) (Steinberg, 1987; Heinecke, 1987; Carew & Parthasarathy, 1988). The Hcy theory integrates the following evidence:

Artery damage correlated ($r = .965$, $p < 0.001$) with the concentration of Hcy-T infused into chaired baboons at levels typical of untreated homocystinurics (Harker, 1976). (Harker reported use of oxidized *homocystine;* but in a letter (Reddy & Wilcken, 1982) he said he had used Hcy-T, a direct product of methionine metabolism *in vivo* (3.2) (Spindel & McCully, 1974; Olszewski & Szostak, 1989). It is highly soluble and inexpensive; but after storage, breakdown products Hcy diketopiperazine or HC1 may act directly on artery walls (Harker, 1976; Dudman & Wilcken, 1982). In recent tests Hcy-T was prepared fresh daily.

In other baboons on the same infusions, B_6 supplements prevented artery damage (Harker, 1974). Concentrations 2-5 times higher produced occlusion in a week. The correlation of lesion scores and cholesterol readings was 0 (Harker, 1976). The same result was found in rabbits (McCully 8c Ragsdale, 1970; Spindel & McCully, 1974; McCully, 1990B). And intimal cells were killed by Hcy *in vitro* proportionately to concentration (McCully, 1983).

Modification of LDLs was initiated *in vitro* only by 4 thiol-containing substances including Hcy (Parthasarathy, 1987). But: (a) cysteine is normally present in the body only in its oxidized form, and excess cystine does not injure arteries; (b) Reduced glutathione is much more abundant in cells than in serum; it protects cells against free radical damage. Excess glutathione may play a role in LDL metabolism but is not known to injure arteries; and (c) 2-mercaptoethanol is not found in significant quantity *in vivo* (K.S. McCully, pers. comm., 1990).

Thus only Hcy is known to modify LDLs to their oxidized, free radical form *in vivo.* Hcy promotes oxidation, growth (McCully, 1983), and is cocarcinogenic

(McCully & Vezeridis, 1988).

In hypercholesterolemic patients, the cholesterol atherosclerotic index (LDL/ HDL) was 2.2 times that in controls. The Hcy atherosclerotic index was 3.5 times higher (Olszewski & McCully, *Atherosclerosis,* in press).

3.2 Hcy is generated through normal metabolism of methione from animal protein — abundant in red meat, cows' milk, and milk products — and in much smaller amounts in vegetable proteins. Methionine remains relatively stable in food-processing, etc.

The atherogenicity of (unpowdered) milk is controversial. Among 2,403 middle-aged British men, in 10 years 2 (1.2%) of 164 who drank >1 pint of pasteurized milk daily and 16 (9.9%) of 162 non-milk drinkers had heart attacks. "The relationship with IHD (ischemic heart disease) is strong and adjustment in a regression model for a number of co-variates reduces the trend only marginally, even when 'prevalent IHD' at base-line is added" (Elwood, 1991). Milk proteins reduce serum uric acid (Garrel, 1991), high in some atherosclerotic patients (Levine, 1989), which may serve as an antioxidant (Ames, 1991). The heat of pasteurizing destroys 86 percent of the B_6 in milk (Gruberg & Raymond, 1981).

Total Hcy — including the predominant protein-bound form not detected in early tests — is significantly elevated in heart patients (Kang, 1984; Swift & Shultz, 1986; Brattstrom, 1988; Olszewski, 1988), and in people with other cardiovascular diseases (McCully, 1983). Members of high risk families appear to have inherited an impaired capacity to metabolize methionine (Brattstrom, 1984). Others get elevated Hcy by other routes: smokers, men, women after menopause (either surgical or natural), old people, diabetics, alcoholics unless with serious liver disease, people deficient in thyroid activity or with chronic renal failure (McCully, 1983; Swift & Shultz, 1986).

Conversely, a group of Down-syndrome patients, whose risk is low (Murdoch, 1977), had less Hcy ($p < 0.01$) than matched patients with other types of mental retardation (Chadefaux, 1988). Down-syndrome patients are trisomic for chromosome 21, which carries the gene for cystathionine beta-synthase (4.2; K.S. McCully, pers. comra., 1991).

4 Three cent B_6 tablets are the sole consistent difference between the Suzman/ Ellis regimen for non-heart patients and that of the vulnerable millions around them — both groups on uncontrolled Western diets. That fact and Hendrix's study (1991) throw doubt on the viral injury hypothesis. Are herpes viruses, etc. less common in areas such as China where acquired atherosclerosis is rare?

4.1 B_6 destroys ingested oxysterols in those diets. It probably functions through an effect on cystathionine beta synthase (K.S. McCully, pers. comm., 1991), not as an antioxidant.

Vitamin E, Se, and Zn that Dr. Suzman's heart patients take are antioxidants and free-radical quenchers. The onset of lipid peroxidation was suppressed *in vitro* until substantially all the lipophilic vitamin E had been consumed (Gey, 1987; Machlin & Bendich, 1987; Jessup, 1988). Hydrophilic ascorbate also delayed oxidation of LDL *in vitro* in dose-related degree (Tappel, 1980; Jessup, 1988). When both E and C are used, oxidation is delayed synergisti-cally (Gey, 1986; Niki, 1987). Thiamin, the carotenes, and patothenic acid in B-complex are also antioxidants and free radical scavengers.

Vitamins E and C sharply reduced heart attacks (Shute, 1969). (Compare research such as that by Riemersma (1991).) Although Shute's therapy blocked both routes of oxidation, the results weren't as good as Suzman's. The drugs Suzman uses at the start may have made the difference. "Attempts" to verify Shute's results used smaller quantities and shorter times (Hoffer, interview 1989).

The most effective form of E is unesteri-fied mixed tocopherols concentrated. Synthetic and esterified forms do not function as antioxidants. The vitamin is most effective with fat-soluble ascorbyl palmitate and 1 g/day of citrus bioflavonoids *(Alt: News.,* March 1991).

And Se, in proportion to its quantity, enables the metalloenzyme glutathione peroxidase, generated by the liver, to inactivate peroxide free radicals (Halliwell &

Gutteridge, 1986). Dr. Suzman now suggests Se and Zn to noncardiac patients as well as heart patients, to protect both groups against diseases of aging in which free radicals are or may be involved, including Alzheimer's, arthritis, cancer, cataracts, etc. (Harman, 1990).

4.2 Sufficient B_6 prevents modification of LDLs by cofactoring the immediate conversion of Hcy (methionine reacts with serine, mediated by the enzyme cystathionine beta-synthase) into the antioxidant cystathionine, and that into cysteine. This catabolism, or demethylation, traverses the *transsulfuration pathway* (McCully, 1983; Ueland fe Refsum, 1989; Wilcken & Dudman, 1989). Because much of the water-soluble vitamin is lost in urine, a generous daily intake is required to maintain a sufficient concentration to perform this coenzyme function and to dispose of ingested oxysterols. Mg and K are also required as cofactors. If not enough B_6 and other micronutrients are ingested, as in people on un- or minimally-supplemented Western diets Hcy and, presumably, ingested oxysterols accumulate.

4.3 B_6 also inhibits blood-platelet aggregation that can lead to thrombosis (McCully, 1983). Hcy-T free base causes platelet aggregation *in vivo* (McCully & Carvalho, 1987). Side effects from the quantities of B_6 discussed (6) are innocent compared to those of long term aspirin *(Wall St. J.* 11/17/89; Kingham, 1989).

5 Summary. Environmentally acquired atherosclerosis is, as Suzman theorized, a vitamin deficiency disease: B_6 deprivation or injection of a B_6 antagonist induces atherosclerosis in monkeys; B_6 supplementation reverses the disease in monkeys, and prevents it in people on Western diets regardless of diet and health practices. It does all this in two ways: (a) it eliminates ingested oxysterols; (b) it prevents accumulation of Hcy that would modify LDLs generating new oxysterols and oxidized PUFAs; also, it enables the body to dispose of artery plaques.

Corollaries, (a) The antiatherogenic effect of probucol derives from its antioxidant action (Gey, 1986; Regnstrom, 1990), and Dr. Suzman suspects that beta-blockers are antioxidants (Oliver et al, 1963). Drugs that increased heart attacks (Hoffer, 1989) must have promoted LDL-oxidation. The blunderbuss, lowering LDLs or their ratio to HDL and/or to total cholesterol can reduce risk to the minor extent it lowers the quantity of oxysterols reaching LDLs by the two routes (see Olszewski, 1989).

(b) Traditional risk factors are atherogenic to the extent they increase ingestion of oxysterols and/or accumulation of Hcy. Hypertension is rampant in much of the Third World, yet heart attacks and strokes are rare. Dr. Suzman doesn't know, if his heart patients quit the diet, whether more would have heart attacks. Several risk factors can be further interpreted.

In acquired atherosclerosis serum cholesterol is usually low or normal (Serfontein, 1985; McCully, 1990A). Accumulation of oxidation products in LDLs enhances lipid accumulation and foam cell formation (Pyridoxine Deficiency, 1986; Morin & Peng, 1989; Olszewski, 1989). High serum cholesterol and lipid deposits are thus symptoms rather than causes; they are a part of the body's defensive response to oxysterol-caused injury.

Fitness correlates negatively with cardiovascular risk among healthy American adults from middle and upper socio-economic levels (Blair, 1989). But in healthy adults on the same kinds of diets — fit or not — 50-100 mg of daily B_6 reduces heart attacks to a greater degree. I suggested to Blair that in his questionnaires (*Wall St. J.* 11/3/89) he ask about participants' daily supplemental B_6 and C. No reply has been received.

Exercise prevents heart attacks among the Masai of Africa but not among Americans in America. Masai develop atherosclerosis from meat, milk, and blood, rich in methionine. Walking 10 to 20 miles each day with their cattle enlarges their arteries so much that blood flow is not hindered (Mann, 1972). But Jim Fixx and other American runners eating Western diets died of heart attacks: ingested oxysterols appear to tip the balance.

Serum concentrations of B_6 were 13 ng per ml in infancy, 7 in the 4th decade, and 3 in the 7th decade of life (Hamfelt, 1964). Many elderly people taking RDA (recommended dietary allowance)-strength vitamins are B_6 deficient, even in serum, and more deficient in B_6 than in

other vitamins (Vir & Love, 1977).

Moreover, measures of B_6 deficiency, like RDAs, were developed without consideration of the vitamin's relation to atherosclerosis. A *functional* deficiency of B_6 (Gruberg & Raymond, 1981) is a lack of enough of the vitamin to provide the discussed benefits. How much B_6 is "enough" depends on (1) body weight and (2) the amount of methionine and oxysterols in the diet, but much more on (3) the degree of arterial plaque accumulation. Getting rid of that is a more onerous task than simply keeping already clear arteries plaque free; and the larger the accumulation, the more onerous. Plaque accumulation depends partly on biochemical individuality: a few may require 40 times more B_6 than a few others (Williams, 1956). For most, it must hinge principally on their dietary history.

Many can't conceive of atherosclerosis' having a simple cause, much less a simple preventive. But libraries were filled with tomes about "risk factors" for malaria. After Ronald Ross (cf Gruberg & Raymond, 1981), the prevailing data could be interpreted usefully whereas it had been wiuiout clinical use. The wisdom about pellagra met the same fate (Hoffer, 1988). The pellagrologists' efforts were a little more futile than those of today's heart specialists — another passing phenomenon? — managing another vitamin-deficiency disease after it starts with, again, palliative, now very high technology methods.

Suppose the diet deficient vitamins were supplied in sufficient quantity to destroy ingested oxysterols, enable the rapid and complete metabolism of Hcy, dispose of pre-existing artery plaques, and prevent formation of new ones. Then why should poor diet, other bad health practices, or risk factors ("risk markers") (McCormick & Skrabanek, 1988) increase risk of the disease any more than bad diet and health practices cause pellagra or beriberi if enough niacin and thiamin is ingested?

6 Medical journals have documented and the media have publicized anecdotal B_6 side effects. Widely used drugs, radiation, surgery have often deadly side effects. Yet reports of side effects exclude supplemental Bg's use for a successful life saving purpose (Frank Press, pers. comra., 1991)! In most such reports (e.g. Dalton & Dalton, 1987) the vitamin was (a) taken in larger quantity than here discussed (500 mg/day can produce neuropathies); and (b) used as a drug rather than as a nutrient to be blended with other nutrients. Some in the Daltons' study also took Mg and other supplements that might, in sufficient quantity, have stopped the symptoms (see below). But the article did not present the amounts.

From the late 1960s through the early 1980s, "well over a hundred thousand" patients of Orthomolecular physicians took megavitamins, most of them with antipsychotic drugs, many for 20 years and more. The average quantity of B_6 was 600 (six hundred) mg/day. Other vitamins taken daily included, on average, 3 g of C, 3 g of niacin, and 600 IU of E (Hawkins, 1986). "None of us in the Orthomolecular psychiatric service ever noted B_6 toxicity" (D. Hawkins, pers. comm., 1988). Abram Hoffer, using 100-150 mg a day, "never had to take anyone off Pyridoxine unless they were allergic to something (other than the Pyridoxine) in the tablets" (pers. comm., 1988). (Has any physician followed a large number of former patients taking megadose B_6/C/E?)

Any symptoms that Suzman's and Ellis' patients had, they didn't recognize as B_6 side effects or considered trivial versus the perceived benefit of avoiding heart attacks and at least ameliorating other B_6 deficiency related diseases (Gaby, 1984, 1985). Any early side effects from B_6 in quantities here discussed begin gradually and are innocent and reversible. The therapy's protective benefits justify an effort to eliminate symptoms should they start: reduce the quantity and use cofactors and substitutes (7), but continue the therapy.

A few persons, even among those lacking a pre-existing neurological problem and not taking prescription B_6 antagonists, gradually develop side effects from as little as 50 mg of B_6 daily (Dalton & Dalton, 1987). Some symptoms also characterize B_6 deficiency (Gruberg & Raymond, 1981); too much may in some cases lower bio-availability (W. F. Cathcart III, pers. comm., 1990; Rudman & Williams, 1983).

Some 30-40% (L. Bolles, pers. comm., 1991) cannot convert ingested supplemental Pyridoxine hydrochloride into pyri-doxal-5-phosphate (PLP), the coenzyme vitamin of B_6. They might avoid nausea by substituting PLP for the hydrochloride supplement or adding a potent B-complex (7.2).

Rimland wrote (1974) that nervousness, insomnia, and a feeling of being "wired" that a few get from 50-200 mg a day can usually be prevented by taking a Mg supplement (take with an absorbable form of Ca, preferably at night). Other measures include reducing B_6; taking Zn, 25-30 mg a day (Pfeiffer n.d.); for optimum absorption, Zn should be taken before breakfast (T.L. Nghiem, unpubl. 1988).

Should side effects persist, I suggest a substitute regimen — beneficial also for persons who do not have B_6 side-effects — including nutrients mentioned in 7. Although one could probably eliminate cardiovascular risk without supplemental B_6, not all of its many other services are likely to be rendered by other supplements. So a minimum of 10 mg a day is suggested.

7 The TSOI hypothesis also explains relevant functions of the other suggested supplements.

7.1 Vitamin C. Willis — decades ahead! — found the appropriate degree of deficiency in guinea pigs and rapidly induced intimal lesions "indistinguishable from (those) in early human atherosclerosis" (1957). This he did with a scorbutic diet or infection — which induces a condition of subclinical scurvy (Ramirez & Flowers, 1980; Cathcart, 1981), possibly because of increased degradation and excretion due to greatly enhanced oxidation of ascorbate in inflammation by activated neutrophils (Roberts et al, 1984). Willis rapidly reversed the plaques with supplemental ascorbate. Also, serial arteriography confirmed plaque shrinkage from vitamin C supplementation in six of 10 heart patients; in control patients, plaques grew or didn't change (1954).

Not only do guinea pigs, like primates including people, not generate their own C, they also share with humans the presence of Lp(a). Thus the guinea pig may well be a good model for study of human atherosclerosis. 40 mg/day of C per kg of body weight prevented artery damage (Rath & Pauling, 1990B).

Amply supplemented C lowers heart attack risk in two principal ways: (a) Its powerful antioxidant action helps other antioxidants and B_6 to eliminate ingested oxysterols before they can reach artery walls by the direct route; (b) It cofactors metabolism of methionine through an alternative pathway for sulfate-ester synthesis so that no Hcy is generated (McCully, 1983). C also assists B_6 and Cu in maintaining strength and integrity of arteries and capillaries, thus minimizing infiltration of oxidized LDLs, and performs related functions.

7.2 Other, (a) Riboflavin, cobalamin, and folate (i) enable the phosphorylation of ingested B_6 into PLP; (ii) they and choline cofactor remethylation of Hcy into methionine, which is not atherogenic unless B_6 is deficient. Because about half of Hcy generated is remethylated, these nutrients may be as important in avoiding Hcy accumulation as B_6.

5 mg of oral folate (Brattstrom, 1988; Wilcken, 1988) or 1 ml of intramuscular hydroxycobalamin (Lindebaum, 1988) reduced serum Hcy in non-heart patients not found deficient in the respective vitamins by conventional tests. Among those with initially very high concentrations Hcy dropped more than 50% on 2 weeks of folate and 80% after one injection. 1-2 mg of folate daily is recommended; the injections can be self-administered.

Although those three B vitamins and choline exert an antioxidant effect indirectly by lessening accumulation of Hcy — oral folate and intramuscular cobalamin lower Hcy more sharply than B_6 — they are not themselves antioxidants. They therefore cannot reduce ingested oxysterols. They then need, if B_6 supplementation is very small, to be augmented with E (100-200 IU) and/or C (2-4 g) and/or Se (100

(b) Co-enzyme Q10 is a powerful antioxidant and offers many other important health benefits without known side effects at any dose level (K. Folkers, pers. comm., 1991). This vitamin-like substance is required for survival; the body's ability to extract it from food and to generate its own supply diminishes with age (Folkers,

1986; Bliznakov, 1988). For the healthy, then, 10 mg/day is suggested for young adults, increasing to 30 by retirement age. Co-QlO does not interrupt the indirect Hcy route, so might not by itself eliminate heart attacks in people on Western diets.

(c) Mg is a cofactor in several of B_6's actions and serves many other functons. In a N-E province of Finland, famous for the highest heart attack rate in the world, available Mg in soil — and thus in drinking water — is about 1/3 that in the S-W part of the country (Med. *World News* 2/1/74).

(d) Essential fatty acids are suggested, particularly n-3 (Kromhout, 1955; Leaf & Weber, 1988) in moderation (Tapel, 1980; Esterbauer, 1987; Garrido, 1989) and n-6 (Braverman & Weissberg, 1988); unpatentable garlic (Barrie, 1987) and onions *(Alt. News.* April 1991) provide anticlotting/ fibrinolytic benefits without side effects.

(e) 100 mg/day of niacin (not timed-release) or niacinamide should help healthy people avoid cardiovascular disease and cancer; heart patients benefit by larger quantities (Hoffer, 1989). B_3 forms Hcy thiolactonyl nicotinamide, so elevates free fatty acids and promotes lipolysis of adipose tissue (Maccari, 1982). Consult a nutritionally-oriented physician for help handling the flush from taking niacin.

(f) A high-fiber, sugar-free diet rich in complex polysaccharides such as vegetables and whole grains (Hoffer, 1989) may provide esential nutrients not yet recognized as essential, so possibly not available in supplements.

(g) Every stress increases the body's need for B_6 and so worsens its deficiency, promoting accumulation of ingested oxysterols and oxysterol-generating Hcy. Moderate exercise and relaxation techniques such as relaxation response (Benson, 1975) minimize stress, among other benefits.

8 Exceptions: (a) Patients on L-dopa for Parkinson's disease who take supplemental B_6 must also take a decarboxylate inhibitor such as Madopar (Gruberg & Raymond, 1981; Berkow, 1987); (b) Patients with G-6-PD deficiency or sickle-cell anemia must avoid supplemental C (Goodman, 1985); (c) Homocystinurics who do not respond to B_6 alone have been successfully treated with betaine, B_6, and folate (Wilcken & Dudman, 1983); (d) persons with liver disease should take Mg only under a physician's guidance; (e) any who get gastritis from acidic ascorbates can use ascorbyl palmitate.

9 For the future, consider pellagra. People consuming a varied, nutritious diet never got it. To protect those who might from junk food diets, parts of the lost niacin and of some of the other sloughed-off micronutrients are restored in Western industrial countries to manufactured "foods".

But because of accumulated arterial plaques, a varied, nutritious Western diet and even a semivegetarian diet adopted in mid-life *(Add.* 2) doesn't eliminate cardiovascular events. Yet suppose sufficient vitamins were ingested throughout life to preclude oxidation of LDLs by either route. Then formation and growth of artery plaques could be forestalled using only modest fortification of processed foods. Materially increasing and meeting RDAs of C by fortification would help. But Suzman's and Ellis' experience with non-cardiac patients suggests that fortifying B_6 alone should suffice.

How much? To protect those who cling to high methionine/high Oxysterol diets, smoke, live indolent, stressful lives — 25 mg daily throughout adult life (Gyorgi, 1971') and smaller quantities in earlier years might protect fully. That would exceed the original B_6 content of the original foods, making up for deficits and losses elsewhere, and might be more than some will need. Fortifying riboflavin/folate/choline sufficiently should enable all to convert ingested B_6 into PLP and maintain balance among the ingested B vitamins.

Problem: Those who eat little processed food or cola drinks might still not get "enough" B_6. No campaign of public education will bring some to use appropriate supplements throughout life, and especially not in all the permutations and combinations brought out in 6 and 7. So without B_6 fortification, thousands might needlessly die or be disabled every year. A to-be-determined (or guessed-at) quantity must reach the intestines, allowing for loss by heat of cooking, etc.

Babies will still be born with defective hearts or FH, rheumatic fever may still damage hearts, and nonatherosclerotic cardiovascular events, though fewer, will still occur. Otherwise, heart attacks and strokes should become unusual.

10 Confirmation. Clinical and experimental evidence and theoretical work supporting TSOI are accumulating worldwide at an accelerating pace, including now at the Framingham project. Three sets of potentially confirming data may already exist, (a) See the third paragraph of 6. (b) Permanente Medical Group, Oakland, California, keeps decades-long computerized clinical records of tens of thousands of patients. Those records do not include supplemental B_6 (A. Klatsky, pers. comm., 1991). So I asked whether they show ascorbate supplements > 2 g/day.

(c) Walter Willett (1984) is tracking incidence of heart attacks among members of a sample population consuming various amounts of B_6 in diet and supplements. No conclusions appeared by 1989 (pers. comm.). The continuing test might need to cross-allow for large ingestion of C. If one category includes only those ingesting 50 mg B_6 or more daily, that epidemiological survey might answer our question, how much B_6 supplementation will be required to eliminate acquired atherosclerosis, but not the question of how much fortification will be required *(Add.* 2). It will not be as convincing as a randomized prospective double-blind test using 50 mg a day.

Addenda: (1) Conventional explanations of the large drop in heart attacks/ strokes since 1965 principally in the U.S. (McCormick & Skrabanek, 1988) fail (McCully, 1983). Average annual U.S. imports of synthetic Pyridoxine HC1 were 11 tons in the mid-1960s, 605 tons in 1983-85 (U.S. Dept. of Commerce). Production by Hoffman-La Roche, Inc., the sole domestic producer, is not known since 1963. Nearly all of the product is consumed by humans. Consumption of other supplements has experienced similar growth. The vitamin fad hasn't spread: this giant "controlled" test explains other nations not having fewer heart attacks.

I propose that (i) people anywhere on Western diets who ingest <2 mg of B_6 and 60 mg of C a day are not having fewer heart attacks (a long-term study of MDs' deaths might confirm this); (ii) secular increases in incidence and severity of B_6 deficiency related diseases (Gaby, 1984, 1985) are striking those who ingest about 2 mg of B_6 daily.

(2) The Pritikin program of strict semi-vegetarian diet and superb lifestyle, without any supplements, reduces heart attacks among American adults primarily because the diet is relatively low in methionine and rich in B_6 (McCully, 1983) and C. But it doesn't eliminate them (Barnard, 1983): (a) study of Pritikin brochures suggests the diet includes oxysterol-laden prepared foods; (b) because of toxics and stress, more protective nutrients may be required than can be ingested in food; (c) evidence cited earlier suggests that when patients start the residence program after decades of consuming Western diets their arteries are loaded with plaques; these, we see, cannot be dependably eliminated without supplements. Similar programs include numerous supplements in generous quantity (Whitaker, 1985). A follow-up study of Whitaker's program, comparable to Barnard's study is needed.

(3) The traditional Japanese diet included little red meat, milk, milk products, or processed food, and many fresh vegetables. Principal sources of protein were fish and tofu (Masse Mackey interview, 1986). Thus, people ingested relatively little methionine, few oxysterols, and presumably ample B_6 and other micronutrients. The effect of diet in preventing atherosclerotic heart attacks and strokes overwhelmed that of Japan's B_6 depleting high-stress society at increasing them.

Heart attacks and atherosclerotic strokes are increasing rapidly, as Kilmer McCully predicted 15 years ago (pers. comm., 1990). Sudden heart attack death *(Economist* 10/24/87) strikes managers and others as young as 40-50 years of age. Estimates of the annual death toll range up to 100,000 *(Seattle Post-Intelligencer* 8/6/90, 3/24/91). (Shinya Nishimaru of the private Food and Ecology Study Institute writes of "the 41 years of living theory".)

Why? (a) "Government studies show that today's family spends about 65 percent

of its home food budget on pre-packaged processed foods, up from 30 percent in 1959, and that children eat half their meals at fast-food outlets" *(Seattle Post-Intelligencer* 11/11/90); (b) Consumption of beef is increasing as import-quota restrictions are relaxed (*Wall St. J.* 11/16/89), lowering its still high price. These trends (i) increase dietary methionine and oxysterols, (ii) decrease Bs, C, and other micronutrients. (4) Diets are mostly vegetarian in Eastern China and South Asia, yet the heart attack rate is low in China, very high in India and Pakistan (Fackelmann, 1989). Two simple yet plausible reasons: (a) Per-capita consumption of 5.5 oz/day of cows' milk *(Economist* 1/7/88), part of it in paste form, in India; bacteria in the paste may generate added B_6 (M.M. Suzman, pers. comm., 1991), and see 3.2 on varying interpretations of milk's atherogenicity; (b) Consumption in India, at least, of ghee (Wysham, 1970), a prized clarified form of butter containing 12.3 percent oxysterols (fresh butter, none). Ingestion of 1 g is probably enough to oxidize 0.3% of dietary cholesterol by weight and thus to damage arteries (Jacobson, 1987). The relative importance of milk and ghee should be studied.

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