VITAMIN B6: THE OVERLOOKED KEY TO PREVENTING HEART ATTACKS

Joseph G. Hattersley

ABSTRACT: Vitamin B6 (pyridoxine) opens the door to eliminating the 20th century's epidemic of heart attacks, cardiac arrests and strokes. Although shunned by the researchers who receive the bulk of heart disease research funding, it is creating excitement among a growing number of investigators. In this article relevant bits of B6's history are presented to show how it can prevent heart attacks with almost no side effects from moderate amounts. This article will also integrate the effects of vitamin B6 deficiency with Mathias Rath and Linus Pauling's theory (blaming heart attacks on deficient vitamin C and excess Lp(a) and Bruce Lipton's *histamine* theory into a general theory of atherogenesis.

ABBREVIATIONS: MSOI = Multi-Source Oxysterol Injury; HC = homocysteine; CBS = cystathionine beta synthase; B6 = vitamin B6; Lp(a) = lipoprotein(a).

PART I

In 1949, James F. Rinehart and Louis D. Greenberg, pathologists in San Francisco fed young, mostly herbivorous rhesus monkeys high-protein Western-style diets deficient in single vitamins. They were trying to induce rheumatic heart disease, but failed. However, after six months to four years—to their surprise—each monkey given a diet lacking in vitamin B6 had arterial plaques similar to those seen in most human autopsies (1). The finding, although confirmed by others (2, 3), was generally ignored in the growing, ill-founded frenzy over cholesterol.

But, Moses M. Suzman, an internist/neurologist in Johannesburg, South Africa, already suspected a "pandemic" deficiency of B6 in Western cultures as a prime cause of heart attacks. So beginning in 1950, pre-cardiac patients referred to him—whatever their ailment—took 100 mg of B6 a day. For more than 20 years *he urged no other change in their lives.*

Joseph G. Hattersley
7031 Glen Terra Court, S.E.
Olympia, WA 98503-7119
(360) 491-1164
Fax: (360) 493-1360

Why *pre*-cardiac? Seventy-seven percent of 300 American soldiers killed in Korea—average age 22 years—had "gross evidence of arteriosclerosis in the coronary arteries;" in several, one or more heart arteries were partly or completely occluded (4). It was much the same in American college students who died in auto accidents.

And as we age, hardening and clogging worsens. So Dr. Suzman's patients would be expected to have increasing risk of cardiovascular events with age, as their friends and neighbors experienced. But, over 44 years, his tens of thousands of patients had "far fewer cardiac problems than would have been expected." Dr. Suzman could not recall a patient of his who had a coronary spasm or cardiac arrest, or even a stroke among stressed hypertensives. He also believes that he ,would have heard of a heart problem, so it would not be a case of lost contact. Unlike most allopathic physicians, Suzman and John Ellis (see below), permanently relieved thousands from the discomfort and insecurity of certain degenerative diseases—so long as they took the vitamin. Patient loyalty enabled unusually accurate tracking. Also, special factors in Johannesburg

where thousands of Suzman's former patients lived, created an unscientific yet genuine "grapevine" through which he would learn of such misfortunes if there were any (6).

What about heart patients? After World War II, Dr. Suzman pioneered long-term use of antithrombotic/anticoagulant therapy (7, 8). In 1969 he switched heart patients to 200 mg of B6 (half in B-complex), 5 mg of folic acid, and 100-600 international units of vitamin E. In 1972 he added vitamin C, selenium, magnesium, and other nutrients. Heart patients were recommended a semi-vegetarian diet. They took conventional heart medicines such as Inderal, usually for a year or less (9, 6). Many of his "hundreds and hundreds" of "former" heart patients enjoyed improved health for decades.

Meanwhile, in Mt. Pleasant, Texas, the distinguished clinician/researcher John Marion Ellis repeated Rinehart and Greenberg's discovery. In 1962 he began to treat carpal tunnel syndrome (CTS) and tenosynovitis using 50 - 200 mg of B6 daily (10, 11). He noted that relatively few of his patients taking the vitamin had heart attacks or underwent bypass surgery.

Those few also had symptoms of advanced B6 deficiency: CTS, numbness, tingling and edema in arms, hands and fingers, diabetes, etc.—the often ignored "handwriting on the wall" warning of increased risk of heart disease. Similar observations are reported by Jonathan Wright of Kent, WA (13).

Why does vitamin B6 prevent heart attacks? The *homocysteine theory of arteriosclerosis* was proposed in 1969 by research pathologist Kilmer S. McCully (14, 15) at Harvard Medical School and Massachusetts General Hospital. E. R. Gruberg and S. A. Raymond put the theory in understandable language in *Atlantic Monthly* for May 1979 (16) and in their excellent book *Beyond Cholesterol* in 1981 (17).

Homocysteine (HC) results from normal metabolism of methionine, abundant in red meat, milk and milk products. Evidence published since 1964 (18) shows even slightly elevated HC is an independent risk factor for heart disease and stroke. If elevated, it puts one at risk without indolence, age, diabetes, smoking or any other conventional risk factor.

Although HC's concentration is only about one thousandth that of cholesterol, it promotes the tiny clots that initiate arterial damage (19), as well as catastrophic clotting that precipitates most heart attacks and strokes (20), arterial spasms, aneurysms (21), growth and obesity (22), cancer (23 - 25) and much more.

Some of the evidence in brief:

(a) Baboons infused with HC for five to 30 days developed arterial damage proportionate to its concentration: $r = .965$, $p < .001$. Other baboons given stronger doses had atherosclerosis and thrombosis in a week (26, 27) (see also Part II). The correlation of cholesterol to lesion scores was zero; similar results were found in rabbits (28).

(b) Men with high HC levels had over 3 times more heart attacks than those with low HC levels (29, 30).

(c) Men with three clogged coronary arteries had higher HC than men with one (31).

(d) The anti-atherogenic, anticlotting benefit of fish oil (32, 33) probably results in large part from lowering HC (34).

More evidence may come from a Framingham-type study in Wales, where HC was measured in 5,000 men; they are being followed for some years to see if those with high levels have more heart attacks (35).

Here's how B6 enters the picture. It is required for the metabolism of all amino acids and serves a multitude of other functions. Specifically, it is a co-factor in the conversion of HC into useful and generally nontoxic cystathionine (15, 36). Folic acid, riboflavin (vitamin B2) and cobalamin (B12) likewise participate in the re-methylation of most HC back into methionine (36), which is not dangerous when B6 is adequate.

But like most other vitamins and most minerals, all these (except methionine) are wanting in the tissue, muscle and red blood cells of most people eating Western diets and living in toxic, stressed environments. Pregnant women (10) (see also Part II) and older people (even those on RDA strength multivitamin supplements) are particularly lacking in B6 (37 - 39). This is a "functional deficiency" in which there is insufficient B6 to prevent the tiny clots that start arterial damage, much less the more serious clotting and arterial spasms.

This fits neatly into the belatedly accepted understanding that cholesterol, even supposedly "bad" low density lipoprotein cholesterol, is benign. Except in fewer than one percent of most Western populations who inherited a tendency to ultra-high levels (familial hypercholesterolemia), cholesterol doesn't damage arteries until oxidized (40, 41).

Cholesterol molecules combine with oxygen molecules forming **oxysterols**, or oxyradicals. These are carried by the low density lipoproteins (LDLs) (42), which are then only accomplices to arterial damage through oxidative modifications of arterial walls. Damage is proportional to oxysterols' concentration (43), and at autopsy atherosclerosis correlates with the accumulation of lipid peroxides and hydroperoxides in serum and atheromas (44). Oxysterols are not free radicals; how they relate to free radicals needs to be determined at the molecular level.

HC generates oxysterols (45). Other than certain polyunsaturated fatty acids, HC is the only dietary substance that is known to create oxysterols in the body (47).

PART II

But there had to be more pieces to the puzzle than homocysteine. Like all of us eating Western diets, Suzman's and Ellis's pre-cardiac patients put *already formed* oxysterols into their mouths in foods that had been exposed to oxygen with high heat in processing: products containing powdered egg yolk, powdered milk, gelatin, foods fried in melted lard, *etc.* (40). HC and these sources of oxysterols are linked in the *Multi-Source Oxysterol Injury* hypothesis (6). Some oxysterols circulate normally, serving a protective function as does cholesterol itself; but after we eat processed foods, their concentration may reach 1,000 times normal (48).

Their non-cardiac patients also ate margarine and other partially hydrogenated oils. These contain dangerous **trans** fatty acids (49, 50) which also appear to make oxysterols in the body (51). Yet vitamin B6 safeguarded nearly all these patients.

This protection is utterly mysterious unless B6 is an *antioxidant*. And sure enough, A. L. Witting (52), M. Nabu (53), Fumio Kuzuya (who worked with Rinehart and Greenberg after 1949) (54, 55) and two researchers in China (56) found that B6 does act as an antioxidant, at least in high enough concentration. It may also perform a similar function by modifying the activity of cystathionine beta-synthase (CBS) (46), the enzyme that promotes conversion of HC into cystathionine using B6 as a coenzyme (15).

So vitamin B6 joins beta-carotene, vitamins C and E, bioflavonoids, coenzyme Q10 and others in the family of antioxidants. But do not eat a processed-food diet as some of Suzman's and Ellis's pre-cardiac patients chose to do, and depend on B6 for protection, even with other supplements. You might be unusually susceptible like the "few." Further, supplements do not supply all the nutrients we need, and processing destroys many of important and presently under appreciated food components required for health. Environments, like dietary habits, have worsened since the 1950s - 60s.

Many people's livers cannot easily convert pyridoxine hydrocholoride, the form of B6 found in most supplements, to pyridoxal phosphate (PLP), the form that is active in the body (57). For some this may be only inconvenient (see Part III) but unconverted pyridoxine can cause severe neurological damage (58) to a prematurely born baby and predispose it to atherosclerosis in later life (59).

Recent findings by biochemical pathologist Willem J. Serfontein fully support the reliance Suzman and Ellis placed on B6. In double blind tests, 10 mg daily in a highly absorbable slow release formulation lowered HC in 10 days to a defined "safe" level (31) in *15 percent* of a large group of men who had moderately elevated HC. Microgram quantities of slow release cobalamin did it in 15% of this group, microgram quantities of folate in 60%, and a patented combination of the three, in 90%. A placebo didn't lower HC (60).

Why doesn't the 15-percent finding nullify claims for efficacy of B6? Some of Harker's HC-infused baboons were given B6; their blood platelets, like those of homocystinuric patients whose blood is high in HC because of an inherited enzyme defect, were protected while taking B6 (26). Pyridoxine protected them, as well as most of Suzman's/Ellis's pre-cardiac patients.

How? Since B6 lowered HC minimally in most of the tested men, the remainder still circulated in their blood, and presumably in that of baboons, whose cardiovascular systems and metabolism are similar to ours. If B6 couldn't quench the oxysterols HC generates (45), arterial damage would not be prevented. And if HC itself damaged arteries, they would still be injured.

It is theorized that (1) *homocysteine damages arteries only through creating oxysterols.* And (2) *antioxidant B6 in ample quantity quenches both (a) the oxysterols generated inside the body by HC and (b) the ones people put in their mouths.* Tests of the hypothesis are planned.

Clearly, antioxidants can prevent formation of oxysterols; but can they do what biochemists consider unlikely, which is to convert oxysterols back into cholesterol? B6 might, through an action on CBS (61), or through a yet unknown, enzyme system (62).

The *histamine* theory of cellular biologist Bruce H. Lipton (63) implies a further protective mechanism for B6. Provoked by *erratic* stress, mast cells on the surfaces of blood vessels emit histamine, a potent mitogen, or stimulator of cell division. The enzyme histidine decarboxylase, produced by *transdifferentiated* microscopic endothelial cells, converts histidine into histamine. When it accumulates (64), histamine leads to plaque formation and inflammation (63).

Ascorbate possesses some antihistaminic properties (65). Treatment of human diabetics with either antihistamines (66) or vitamin B6 (12) lessened vascular leakage and stemmed retinal degeneration, suggesting that B6 also functions as an antihistamine. Conceivably, it may lessen retinopathy by some effect on highly reactive HC thiolactone—the form of HC found in the circulation as a complex of lipoproteins (67)—which is also inflammatory (61).

To cap the story: U. S. imports of pyridoxine hydrochloride grew 6,530 percent from the mid-1960s when heart attacks peaked, to 1991; before that, such imports varied little (15). Production by Hoffman-La Roche, the sole domestic producer, is not known since 1963. Nearly all of the vitamin is used in supplements. Any explanation of this dramatic decline in heart attacks should take this into account (15).

The surge in B6 imports is coincident with improvement in cardiac health, as would be expected given B6's anti-clotting action. Although consumption of other supplements has grown similarly, McCully proposed that this enormous increase in B6 intake is the principal cause of the improvement, which continues as he predicted (15). And this giant unplanned test may explain why cardiac rates aren't falling in some countries (6).

So pyridoxine deserves a prominent place in our cardioprotective supplements program. Although some may need 40 times more of it than some others (68), a good starting daily amount for asymptomatic adults of average body size would be 50 mg (but see Part III). Take it in divided amounts for most nearly constant concentration.

PART III

How then does all this integrate with Matthias Rath's theory blaming heart attacks on deficient vitamin C and too much of the kind of LDL cholesterol known as Lp(a) (69, 70)?

Dr. Rath agrees that oxysterols can damage arteries in most animals, which generate their own ascorbate and do not have Lp(a). However, in primates (including humans) and in guinea pigs, which do not generate vitamin C and do have Lp(a), he argues that oxysterols cannot damage arteries without Lp(a)'s "overshooting" of its normal repair function (70). Rath's therapy does lower cardiac risk (71).

But the relation of that risk to Lp(a) has been thrown into doubt (72), and the theory does not fully explain, the success of his therapy. Western diets are deficient in many nutrients besides vitamin C, including B6, folate and minerals such as magnesium, all contributing to elevation of homocysteine.

In most people, HC may be required as "the match to light the fuse" before Lp(a) can do damage. At a concentration of *16 micromoles per liter*, HC is safe in primitive Venda tribespeople of northeast South Africa (31), but a level near zero may be risky in people on micronutrient-depleted Western diets in toxic environments. Peter C. Harpel found that at half that concentration—a physiological level—*HC activates Lp(a)*. It "induces a more than *80-fold* increase in the affinity between Lp(a) and plasmin-treated fibrin, and a four-fold increase with unmodified fibrin" (73). Oxysterols, which HC generates (45), must likewise activate Lp(a). Further, HC thiolactone partially reduces, *i.e.* "deoxidizes," Lp(a). It can react with the sulfhydryl group of the kringle domain of Apolipoprotein(a), *oxidizing* its disulfide bonds to *generate* Lp(a) (46).

So both Lp(a) and oxysterols probably must participate to damage arteries. They are like *connected-body Siamese twins*; but instead of helping each other to survive, they cooperate to do damage. Johan Ubbink confirms the finding and proposes it may explain atherogenicity of both HC and Lp(a). If this interdependency can be confirmed *in vivo*, people with high, difficult to lower Lp(a) will benefit by easily lowering HC (74).

Rath's theory, further, is hard put to explain certain observations: (a) a vitamin C-deficient diet did *not* induce arterial damage in Rinehart and Greenberg's monkeys (75); (b) the close correlation of cardiac risk (29 - 30) and damage (31) to concentration of HC; (c) Harker's prevention of blood platelet damage in HC-infused baboons and in some homocystinuric patients using B6 (26), and (d) Suzman's/Ellis's prevention of most heart attacks in pre-cardiac patients without any vitamin C (Part I). For most people, vitamin B6 appears to draw the sting of Lp(a) by quenching oxysterols from all sources; it thus severs that other "Siamese twin."

Dr. Rath's theory fails to take into account one of nature's major redundancies. Taking what biochemists call the alternative pathway, enough *ascorbate* diminishes the ability of HC to generate and activate Lp(a) (76). How important this mechanism is, compared to the mechanism Rath emphasizes, is not known. Including it, and vitamin C's antihistaminic action, helps explain the success of his therapy and integrates his theory further into MSOI.

What about side effects?

None of Suzman's/Ellis's/Wright's patients has complained of B6 side effects. When a pyridoxine hydrocholoride tablet is swallowed, if folate, B2 and B12 are adequate, most people's livers quickly absorb 35 - 40 mg of B6 and convert it into PLP (77). A heart patient's liver may absorb much more.

The remaining pyridoxine, behaving in the body as a drug, appears to have been the agent responsible for neurological side effects (62) in a few who took far more than any therapeutic need, usually for a long time and alone like a drug (78). Paradoxically, an excess can in some cases lower bio-availability (79), and the tablet filler may also cause side effects. B6 in large

amounts is also contraindicated for patients taking certain medications for Parkinson's disease.

So, from a 50-mg tablet, only 10 - 15 mg of pyridoxine remains. After a peak at 20 minutes, its half-life is 12 minutes. Thus, after 24 minutes three-quarters is gone and in an hour less than 1 mg remains. If a 25 mg dose is taken every 10 - 12 hours, virtually all might be absorbed by the liver, leaving none to produce any damage. If side effects still develop, they can usually be reversed by switching to pyridoxal 5-phosphate and adding magnesium. B6 functions best as one of the lead players, if not the maestro of a "biochemical symphony" involving a sensible diet, aerobic exercise, and an individually tailored program of safe food supplements.

How much B6 would people need to ingest throughout life to **prevent** atherosclerosis? Paul Gyorgi, its discoverer, suggested 25 mg/day for adults (81). Ellis suggests each 6 ounces of pasteurized cows' milk, every half pound of bread, every pound of processed high protein food should be fortified with 3 mg of "available" vitamin B6 (pyridoxine is the more heat resistant form of the vitamin) (17). After tests with slow-release B6, Serfontein predicts that 5 - 6 mg per day would suffice (except for heart patients), and that adults could obtain this amount from fortified foods.

Expanded food fortification should include folate, cobalamin and at least magnesium and zinc. Vitamin C intakes should be raised to tenfold the RDA, and an equivalent amount of bioflavonoids (which may double the efficacy of ascorbic acid) should be added (83). These nutrients, ingested from inception, might end the 20th century's epidemic of heart attacks, strokes and cardiac arrests in about two generations (10).

Because all degenerative diseases have "on the membrane level [and] on the genetic level, very much a common denominator" (84), this program should also lower the incidence of such diseases as diabetes (12) and cancer (23, 24, 25).

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