

## Dietary Prevention of Coronary Heart Disease The Lyon Diet Heart Study

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This issue of *Circulation* contains an article<sup>1</sup> that I believe deserves special attention from cardiologists and physicians. It reports the 46-month mean follow-up findings on the original report of the study on “Mediterranean  $\alpha$ -linolenic acid-rich diet in secondary prevention of coronary heart disease,” the so-called Lyon Diet Heart Study. This study was undertaken because of the interest of the investigators in explaining the very much lower mortality from cardiovascular disease, mainly coronary heart disease, in the countries bordering the Mediterranean compared with that in northern Europe. The initial report<sup>2</sup> was published in *Lancet* in 1994 after the study was terminated by its Scientific and Ethics Committee at 27 months mean follow-up time of what had been planned as a 5-year study, because the benefits in the experimental group at that time were so favorable. Despite the striking findings in the first report of a 70% reduction in all-cause mortality due to a reduction in coronary heart disease (CHD) mortality and comparable large reductions in nonfatal sequelae, I have encountered few cardiologists here who are aware of that study.

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It is much to the credit of Dr de Lorgeril and associates that they persisted in following the original enrollees despite the official termination of the study and publication of the initial findings so that they are now able to report their more extended observations. With the mean follow-up time of 46 months per patient, the initial remarkably beneficial effects of the experimental dietary program persisted compared with the control group consuming the “prudent Western-type diet.”

Let me list the several important messages I believe are inherent in the results that are clearly and modestly presented in this article.

1. At a time when health professionals, the pharmaceutical industries, and the research funding and regulatory agencies are almost totally focused on lowering plasma cholesterol levels by drugs, it is heartening to see a well-conducted study finding that relatively simple dietary changes achieved

greater reductions in risk of all-cause and coronary heart disease mortality in a secondary prevention trial than any of the cholesterol-lowering studies to date. This is emphasized by the finding that the unprecedented reduction in risk of CHD was not associated with differences in total cholesterol levels between the control and experimental groups and that the survival curves showed a very early separation quite unlike what has been reported in the cholesterol reduction studies.<sup>3</sup> This study does not contradict the importance of plasma cholesterol in the genesis of CHD—the authors measured and acknowledge its contribution to the outcomes in their study—but it indicates that there are other powerful risk factors within the realm of diet that must be considered if we are to achieve maximal dietary benefits in reducing this number 1 cause of mortality in the world today.

2. The continued high adherence of the experimental group to the program over the full 46 months of mean follow-up per patient is quite remarkable, considering that the Science and Ethics Committee had officially terminated the study when the mean follow-up time was 27 months. This occurred even though all patients in the study were informed of the outcome and despite the publicity from the initial publication of the striking benefits of the trial, which seems to have influenced some in the control group to modify their diets toward that of the experimental group. The continued good adherence to the experimental diet indicates that it was readily tolerated. The unprecedented magnitude of the benefits achieved is especially notable because the study was undertaken in a very-low-risk population. Of the 36 selected countries listed, the American Heart Association’s 1998 Heart and Stroke Statistical Update<sup>4</sup> ranks France second to the lowest in cardiovascular mortality in men, with only Japan ranked lower, and France ranked the lowest in female cardiovascular mortality.

3. This study points to the inadequacy of the “Phase One” or “Step One” dietary management of CHD (10-10-10, as the percentages of energy from saturated, monounsaturated, and polyunsaturated fatty acids<sup>5</sup>) promoted by both the National Cholesterol Educational Program of our National Heart, Lung, and Blood Institute and the American Heart Association, which is quite similar, with regard to the total fat intake of 30% of energy, to that of the experimental diet for the present study. The Step One diet, however, has too high an intake of saturated fats. Furthermore, although the Step One diet indicates an adequate intake of polyunsaturated fatty acids (PUFAs), it makes no additional recommendation for the need to lower intake of the n-6 ( $\omega$ 6) class of the essential PUFA, linoleic acid, which is high in most vegetable oils, and to increase the intake of the other essential n-3 ( $\omega$ 3) class,  $\alpha$ -linolenic acid, which is present in only a few vegetable oils, notably canola oil (low-erucic-acid rapeseed oil,  $\approx$ 10% to

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11%  $\alpha$ -linolenic acid) as recommended to the experimental group, soybean oil ( $\approx 7\%$ ), and flaxseed oil (50%  $\alpha$ -linolenic acid). The even more highly unsaturated fatty acids in fish oils are also of the n-3 class of essential fatty acids. The authors make the telling point that clinical dietary trials that lowered saturated fatty acids and raised PUFA intake in an effort to lower cholesterol failed to improve the overall clinical prognosis of their experimental groups; only the trials that also lowered intake of n-6 PUFAs and increased n-3 fatty acids successfully lowered cardiovascular and all-cause mortality in the experimental cohort.

4. With the high costs of drugs and invasive procedures, which are the mainstay of management of CHD in the United States, promotion of the experimental diet could lead to very considerable savings in the cost of health care.

5. Because there has been considerable morbidity and some mortality from drug and invasive management of CHD, these adverse effects of current treatments could be largely avoided by an effective dietary approach.

6. The authors' plea for a large-scale prevention trial based on the dietary modifications pursued in this trial deserves attention. I would not, however, follow their suggestion that the possible additional benefits from adding drug therapy to their experimental diet be tested, at least not until the full benefits from their experimental program alone are carefully assessed in their own right.

The reason why secondary prevention trials like this one are so useful in testing the efficacy of potentially beneficial programs is that they limit the subjects for study to those already marked for a high incidence of adverse outcomes and eliminate from the study those in the population who are destined to avoid the adverse effects of CHD. Thus, smaller numbers of subjects and much lower costs are required to demonstrate significant benefits than is true when a population-based primary prevention trial is attempted. In the case of CHD risks, however, beneficial results may be extrapolated to the entire population in Western industrialized countries, in which nearly 50% of the population is fated to die of cardiovascular diseases. Because most of us do not know for certain into which 50% of the population we fall, all would be prudent to adopt dietary habits similar to those promulgated in this trial, especially if the striking benefits are confirmed.

Although the authors indicate some deficiencies in their study, it is nevertheless clearly a thorough, serious, and rigorous effort, within the almost unavoidable limitations of dietary studies in free-living populations, and it was conducted very successfully. There were many differences between the control and experimental diets, as the authors indicate, and purists will complain. However, it is necessary to first show a beneficial effect of a diet before embarking on a dissection of the differences to learn which might be providing possible causative roles. Furthermore, anyone seeking a single causative agent for CHD is undoubtedly chasing a will-o'-the-wisp. As a piece of evidence, this study is certainly superior scientifically (and nutritionally) to the soft pap we are constantly being offered from most epidemiological studies.

The many differences between the diets of the control and experimental groups indeed confound any attempts to assign a singular role to the  $\alpha$ -linolenic acid that is highlighted in

this study. However, numerous publications have reported biochemical and physiological effects of the n-3 class of essential fatty acids in humans and animals that would be expected to prevent or ameliorate CHD (for reviews, see References 6 through 8). In addition, studies have reported potent antiarrhythmic effects of long-chain PUFAs, especially of the n-3 class, manifested by prevention of ischemia-induced fatal ventricular arrhythmias in rats, marmosets, and dogs, and there is suggestive evidence that these n-3 fatty acids may prevent sudden cardiac death in humans. This has been the focus of research by my laboratory group, who have found that a concentrate of free fatty acids of fish oils, but also the pure individual n-3 PUFAs eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and  $\alpha$ -linolenic acid (LNA), all prevent fatal ventricular arrhythmias in a reliable dog model of sudden cardiac death with a very high probability.<sup>9-11</sup> We have found the mechanism for this protection to result from the electrophysiological effects of the free, non-esterified, PUFAs when they are simply partitioned into the phospholipids of the sarcolemma without covalently bonding to any constituents in that cell membrane.<sup>12</sup> Once covalently incorporated into the phospholipids of the cell membrane, they are no longer antiarrhythmic until they are liberated again as free fatty acids<sup>13</sup> in the sarcolemma by phospholipases, a lipolytic action that occurs promptly with increased sympathetic activity, as with ischemia, unusual physical effort, or emotional stress. The presence of the free form of the PUFAs partitioned in the hospitable hydrophobic milieu of the acyl chains of phospholipid membranes stabilizes each contractile cardiomyocyte, ventricular and atrial, electrically by requiring a stronger electrical stimulus just to elicit an action potential and markedly prolonging the relative refractory period of the myocytes.<sup>14</sup> These effects in turn result from an action of the PUFAs to modulate ion currents in the myocyte sarcolemma. The currents due to several ions are affected, but so far it seems that the very potent inhibitory effects of the PUFAs on the fast sodium current,  $I_{Na}$ ,<sup>15,16</sup> and the L-type calcium current,  $I_{Ca,L}$ ,<sup>17</sup> are the major contributors to their antiarrhythmic actions in ischemia, whereas the inhibition of the  $I_{Ca,L}$  may be of major importance in preventing triggered arrhythmias caused by excessive cytosolic calcium fluctuations.<sup>17</sup> The effects of the PUFAs are to shift the steady-state inactivation potential to more negative values. Once we knew that the PUFAs were affecting ion currents in the heart, an excitable tissue, we suspected that they must be affecting all excitable tissues, which all use the same electrical communicating system—and they do. We have found very similar effects on  $I_{Na}$  and  $I_{Ca,L}$  in hippocampal neurons<sup>18</sup> and an anticonvulsant effect in an electrical threshold model of epilepsy in rats.<sup>19</sup> Much more remains to be learned about how these fatty acids interact with the ion channel proteins to produce these effects, but the findings increase our appreciation of the potential cardiovascular benefits that these PUFAs may offer.

The initial report of the Mediterranean  $\alpha$ -linolenic acid diet recorded a complete prevention of cardiac sudden death in the 302 subjects in the experimental group but 8 deaths in the 303 subjects on the control diet.<sup>1</sup> This effect of the diet was perhaps supported by the finding of an increased concentra-

tion of n-3 PUFAs in the plasma lipids of the experimental compared with the control groups. Although prevention of sudden cardiac death may be contributing to the striking reduction in mortality in the present report, the numbers are small, as the authors note, and this effect seems not to account for the total benefit, for 2 reasons. First, the overall reduction of mortality of 70% reported exceeds the percentage of deaths, 50% to 60%, reported to occur within 1 hour of acute myocardial infarction,<sup>4</sup> and the total cardiovascular deaths in this study were not limited to sudden cardiac deaths after acute myocardial infarctions. Second, the study reports markedly beneficial effects on nonfatal cardiovascular morbidity, which must be attributed to other effects of the diet (antiatheromatous?) rather than its antiarrhythmic effects.

In conclusion, we should anticipate that as research increases our understanding of the pathogenesis of coronary atherosclerosis, it will reveal to open and alert minds many possibilities for preventing this now ubiquitous malady of CHD. Many factors in this polygenetically based disease are interacting with other internal and exogenous factors to cause expression of the manifest disease state. Dietary factors must be very important, and this study shows that they extend beyond cholesterol. As stated, the role of n-3 PUFAs was important in the strikingly beneficial outcomes in the experimental group. In a study included in a published talk,<sup>20</sup> Professor P.C. Weber and I attempted to use the method of environmental medicine to examine the diets of our forebears during the 2 to 4 million years that our genes were being adapted to the environment. During all but the last 10 000 to 15 000 years (too short a period to permit genetic adaptations), our forebears subsisted as hunter-gatherers. During that long period of adaptation, our estimates suggest total dietary fat to be  $\approx 20\%$  of energy, with saturated fat perhaps 7% to 8%, and the n-6 and n-3 classes of PUFAs slightly lower, with a ratio of n-6 to n-3 PUFAs of perhaps 4 to 3. With the onset of the Industrial Revolution, saturated fatty acids rose dramatically with the increased availability of red meat and hydrogenation of PUFAs, largely for margarine. The plant-based n-6 fatty acids also have increased as the public has been repeatedly admonished to increase intake of PUFAs. Meanwhile, the n-3 fatty acids have been largely disappearing from our diets in Western industrialized countries, so that the ratio of n-6 to n-3 PUFAs is now estimated to be  $\geq 15$  to 1. Today, we are not surprised to recognize that nature has adapted the n-6 PUFAs to important cell regulatory functions via the arachidonic acid cascade, whereas we seem to be surprised, to the level of disbelief, by the possibility that the n-3 class of essential fatty acids has also been adapted over the same long time period to other essential regulatory functions, which in several important ways balance or block the excesses of too much n-6 PUFAs, eg, the effects of arachidonic acid cyclooxygenase metabolites on platelet aggregation and arteriolar vasoconstriction, the effects of lipoxigenase metabolites of arachidonic acid on the proinflammatory leukotrienes, and the proarrhythmic effects of the cyclooxygenase metabolites of arachidonic acids (except prostacyclin) but not of the cyclooxygenase metabolites of eicosapentaenoic acid.<sup>20</sup> I suspect that we are just beginning to scratch the surface of the potential biolog-

ical importance to health and disease of the n-3 class of essential PUFAs.

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