## CHAPTER 46

## How the Unified Model Helps to Explain, or Is Consistent with, Established Observations

Part 1. Observation: Lipid-Lowering Reduces Acute IHD Events
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Box 1. Illustrative Relationship between the Unified Model and Benefit of Lipid-Lowering.

### • Part 1. Observation: Lipid-Lowering Reduces Acute IHD Events

Lipid-lowering regimes achieve marked reduction in acute IHD events, while causing only minimal reduction of stenosis in the angiographically measured plaques (Chapter 44, Parts 6d and 7a). Attempts to reconcile these two facts have elicited various conjectures.

#### 1a. Reduced Inflammatory Response and/or Better Function of Endothelium

It has been proposed (for instance, by Brown 1993, p.1788, p.1789, + Libby 1995, p.2848, Figure 3) that reducing the influx-rate of lipoproteins into the intima stabilizes plaques against rupture because the reduced influx-rate decreases all aspects of the inflammatory response, including the number of lesional T cells and macrophages which may release matrix-degrading enzymes inappropriately.

We might add that reduced influx of lipoprotein into the intima should also lessen the clinical CONSEQUENCES of a plaque rupture, because reduced accumulation of lipids should reduce the frequency of foam cells --- which produce thrombogenic tissue factor (Chapter 44, Part 7b).

Some other analysts postulate a role for the endothelium, in the reduced frequency of acute IHD events after lipid-lowering. For example, Thomas A. Pearson (citing Flavahan 1992) writes that "LDL cholesterol reduction" may restore the ability of endothelial cells to produce EDRF --- endothelium-derived relaxing factor --- and such restoration "may be an important mechanism" to explain the rapidly resulting decline in acute IHD events (Pearson 1993, p.1073). Referring to the reduced rate of cardiac events, John Bittl (1996, p.1300) writes that "The mechanism for this benefit has been attributed to minor regression of fixed stenoses, generalized improvement in endothelial function, and a decreased risk of plaque rupture during lipid-lowering therapy (Treasure 1995; Anderson 1995)." William Parmley offers a similar summary, when he says there are two hypotheses for the benefit (Parmley 1997, p.12):

"The first is that normalization of endothelial function is highly protective against clinical events. The second is that removal of the lipid pool plaques and lipid laden macrophages, particularly at the margins of plaques, may stabilize them so that they are less likely to break down. Perhaps both of these mechanisms are playing an important role in the dramatic reduction in clinical events which occurs from lipid lowering."

We agree that several mechanisms may contribute to the observed clinical benefit from reduced serum levels of atherogenic lipoproteins --- and we certainly do not dismiss a role for the endothelium.

#### 1b. How Our Unified Model Helps to Explain the Observations

Acquired mutations (which are permanent) are a fundamental part of our Unified Model, and lipid-lowering does not reverse such mutations (by definition). But since the Unified Model proposes that the COMBINATION of certain lipoproteins and acquired mutations is necessary for atherosclerosis, the model predicts effects from changing the frequency of either partner.

(A) HOLDING RADIATION DOSE CONSTANT. At equal accumulated radiation dose (a potent mutagen), individuals with the higher plasma levels of atherogenic lipoproteins will fare worse. With greater influx of atherogenic lipoproteins into the intima per unit time, the urgency is greater for smooth muscle cells (SMCs) to do all their jobs well (Chapter 45, Part 4a). While a higher lipid-load does not increase the absolute number and type of radiation-induced dysfunctional SMC clones, the higher lipid-load means that a growing FRACTION of the clones are severely inadequate to cope with the elevated demand on their performance. Thus, the atherosclerotic process PROGRESSES at a larger fraction of the mini-tumors, and a growing fraction of fibrous caps become inadequate to contain their thrombogenic lipid-pools, and more plaques rupture per unit time. Part 1c and Box 1 explain this fraction-concept in much more detail.

(B) HOLDING ATHEROGENIC LIPOPROTEINS CONSTANT. At equal plasma levels of atherogenic lipoproteins, individuals with the higher accumulated radiation dose will fare worse. On the average, they will have more mini-tumors of dysfunctional SMCs, and therefore, more plaques. The mini-tumors will produce plaques with various degrees of dysfunction and of vulnerability to rupture, because no two radiation-induced mini-tumors have the SAME mutated genome (Chapter 45, Part 5a). A higher frequency of radiation-induced mini-tumors raises the frequency of both mildly dysfunctional and severely dysfunctional varieties.

## 1c. Box 1: Effect of a DECREASE in Lipid-Load

Scenario "A" in Part 1b means that if two individuals have the same number of radiation-induced dysfunctional SMC mini-tumors, the individual with the LOWER plasma levels of atherogenic lipoproteins will fare BETTER, all other things being equal. Likewise, if ONE person lowers his/her lipid-load, the individual earns a lower risk of fatal Ischemic Heart Disease. Box 1 provides an illustration of how this happens.

Because mini-tumors of dysfunctional smooth muscle cells will have various DEGREES of dysfunction, we can rank them in Box 1 (Column A) on a scale of competence. In our hypothetical illustration, dysfunctional SMCs of Class-A clones are the most nearly competent. SMCs of Class-K clones are the least competent.

To quantify their variation in competence, we say that Class A can handle a lipid-load of 90 arbitrary units every month without progression of prior atherosclerosis (Box 1, Column D). By contrast, Class K can handle only 2 arbitrary units/month. Rates matter (Chapter 45, Part 5a). In the text and in Box 1, "lipid-load" refers only to the lipoproteins which are atherogenic (not to all lipoproteins).

We make the reasonable approximation that Class A mini-tumors are the most nearly competent BECAUSE they have accumulated the fewest mutations for dysfunction (Chapter 45, Part 5a), whereas, at equal radiation dose, we approximate that Class K mini-tumors are the least competent because they have acquired the MOST mutations for dysfunction. Accumulation of MANY mutations for dysfunction in the same cell-nucleus is less likely to occur than accumulation of a few such mutations, from equal accumulated radiation doses. So it follows that Class K mini-tumors occur less frequently than Class A mini-tumors, at equal radiation doses. We arbitrarily establish a factor of about 2-fold disparity in frequency, in our illustration (Box 1, Columns B and C).

Box 1 uses our illustrative input to show how a reduction in lipid-load (from 60 arbitrary units per month to 40 arbitrary units per month) reduces the fraction of sites where the atherosclerotic process progresses. Because of the reduced lipid-load, a higher fraction of the 773 dysfunctional clones becomes able to stop progression, and thus fewer sites ever develop large thrombogenic lipid-pools with incompetent containment --- the proximate cause of so many acute IHD events.

## 1d. Distinction between Comments in Part 1a and the Unified Model

The comments above closely resemble some of the comments in Part 1a about the inflammatory response. Indeed they should. The distinction, between such comments and our Unified Model, is the model's addition of the mutational component, which proposes how certain acquired mutations and atherogenic lipoproteins operate together.

When levels of atherogenic lipoproteins are reduced, a SMALLER fraction of dysfunctional SMC clones (dysfunctional due to acquired mutations) will be severely inadequate at their tasks of handling the lipid-load, per unit time, and a larger fraction will be ABLE to cope with the lesser load per unit time. In the lesions which are already advanced when the lipid-load is reduced, coping means especially producing, repairing, and maintaining an adequate fibrous cap. At a reduced plasma level of atherogenic lipoproteins, the rate of influx into the intima per unit time is lower, and the rate of efflux may be adequate to STABILIZE various lipid-pools at sizes with which more of the mini-tumors can cope. Although the mutation-induced dysfunctions persist, the frequency of fatal consequences can be reduced by lowering plasma levels of the atherogenic lipoproteins.

Box 1 illustrates how lipid-lowering can halt PROGRESSION of the atherosclerotic process at an increased fraction of sites. This halt will involve not only the stenotic sites, but also the many pre-stenotic sites (Chapter 43, Parts 3e and 4). Progression of atherosclerotic lesions predicts subsequent cardiac events (Blankenhorn 1994, pp.183-184, for instance). Less progression --- as in our Box 1 --- means fewer acute IHD events.

## • Part 2. Observation: Lipid-Lowering Benefit Occurs with Little Change in Stenosis

An analogy, between an atherosclerotic plaque and an office building, may help to elucidate the observation that lipid-lowering regimes achieve marked reduction in acute IHD events, while causing only minimal reduction of stenosis in the angiographically measured plaques (Chapter 44, Parts 6d and 7a).

The plaque's "office building" consists of the extracellular matrix (the structural proteins and proteoglycans), and in more advanced plaques, the microvasculature, crystallized cholesterol, and sometimes deposited calcium. The plaque's "population" consists of the extracellular lipids, and the smooth muscle cells, macrophages, foam cells, T cells, platelets, and other relatively mobile constituents of a plaque. Their interactions constitute a complex "hive of activity" (Chapter 45, Part 2c) --- the inflammatory response.

If a plaque's population is growing, the structure must expand too. A new "wing" is added ... with more floors. Normal smooth muscle cells, adjacent to the dysfunctional patch, also may grow into the plaque --- especially if the dysfunctional SMC clones are becoming senescent.

And what happens when the inflammatory response becomes less intense, so that the plaque's population is gradually DECLINING?

Just as a population can evacuate an office building while leaving the edifice intact, so could a plaque's inhabitants vacate some of the offices while leaving the edifice intact. As the plasma levels of atherogenic lipoproteins decline, the population in the plaque can also decline ... and do so, without tearing down the building. So it does not surprise us that a large clinical benefit occurs in lipid-lowering trials, while hardly any change (angiographically measurable "regression") occurs in the size of the edifice. It is often not the EDIFICE, but rather, contact between the thrombogenic lipid pool and the bloodstream, which causes the acute IHD events (Chapter 44, Part 7b). Reducing the frequency of thrombogenic lipid-pools can produce clinical benefits, even though the plaque's edifice remains.

## • Part 3. Observation: "Culprit Plaques" Are Often the Less Stenotic Ones

The plaques which trigger acute IHD events (unstable angina, myocardial infarction, sudden death) are often the less stenotic plaques (Chapter 44, Parts 6d and 7a).

### 3a. What Is Meant by "Often?

What is meant by "often"? In 1986, Brown and co-workers reported some data on frequencies, summarized in Brown 1993, p.1786-1787:

"Acute ischemic syndromes are most commonly precipitated when mild or moderate coronary lesions [which they define as <70% stenosis] become disruptively transformed into severely obstructive culprit lesions. Such disruption usually involves fissuring of the fibrous cap of the atheroma, often

with intramural hemorrhage and mural or occlusive thrombus ... Among patients undergoing thrombolytic therapy for acute myocardial infarction, the severity of the atherosclerotic stenosis underlying the thrombotic occlusion was measured at <50% diameter stenosis in one third of cases and between 50% and 60% stenosis in another third (Brown 1986)."

It is worth noting that, in the remaining third of those patients with acute myocardial infarction, the culprit lesions must have been those with >60% stenosis. So very stenotic lesions also cause acute troubles. Do they cause more than their share, or less? The answer is not at hand. We would need to know the ratio of (culprit mild-moderate lesions over total mild-moderate lesions), to compare with the ratio of (culprit severe lesions over total severe lesions).

In 1988, Little and co-workers reported frequencies from their study of 29 patients with myocardial infarction who each had had a coronary angiogram beforehand --- at an average of 706 days beforehand (Little 1988, p.1159, Table 1). Little and co-workers found that in 66% of the 29 patients, the most severe pre-infarction stenosis existing in the infarct-related artery was less than 50% luminal diameter narrowing. In 97% of the 29 patients, the most severe pre-infarction lesion in the relevant artery was less than 70% diameter stenosis (Little 1988, p.1159). These are important data.

Nonetheless, such data are not informative about how those culprit lesions might have evolved during the nearly two years, on the average, between pre-infarction measurement and the infarction. Major progression at a particular plaque-site can occur very rapidly --- for instance, due to silent rupture ("subclinical episodes," Chapter 44, Part 7 at its outset and Part 7a).

### 3b. Why Are Less Stenotic Lesions "Much More Numerous"?

From these studies and others, it seems established that the majority of acute IHD events are precipitated by atherosclerotic lesions which were, fairly recently, only mildly to moderately stenotic. Brown and colleagues propose a sensible explanation for why this is so: The mild to moderate lesions are "much more numerous." Here is the context (Brown 1993, p.1787):

"Although a given severe (>=70%) lesion is more likely to progress or totally occlude than a given mild or moderate lesion, clinical events are more frequently precipitated by lesions initially of the less severe type because these are much more numerous in the patient's anatomy (Brown 1989) and also because the majority of occlusions of severe stenoses occur without an event (Webster 1990)."

As far as it goes, we like the Brown 1993 explanation. Our Unified Model takes another step and also explains WHY less severely stenotic lesions are "much more numerous" and WHY some of the most severe stenoses continue growing "without an event."

The Unified Model interprets greater stenosis as usually signaling a greater degree of dysfunction in the SMC mini-tumor at that site. (The extra incompetence of the site's smooth muscle cells, at doing all of their jobs right, causes extra inflammation and an extra large "edifice" at that site.) The most severely incompetent mini-tumors generally evolve from cells which have accumulated multiple mutations. Since the frequency of cells with many mutations is lower than the frequency of cells with fewer mutations, the frequency of severely stenotic sites is relatively low.

The fact that SOME plaques can occlude a lumen without having "an event" (a known rupture) is consistent with the model, too. The model says that SMC mini-tumors differ in their mutations, and therefore they differ in their types and degree of dysfunction (Chapter 45, Part 5). It follows that some mini-tumors which are severely dysfunctional --- and produce very large plaques --- may nonetheless be adequate with respect to producing strong fibrous caps. They are the ones whose plaques can continue to grow, without having a rupture which kills the host.

### 3c. Observation: Progression of Lesions Is Not Uniform

The statement directly above relates to the observation by Valentin Fuster and others that all plaques do not inexorably follow the same path of behavior. For instance, Fuster presents text and a diagram showing a common path for the least severe lesions (types I, II, III), after which the path of a particular lesion is unpredictable. Fuster 1994 (p.2127):

"The type IV lesion has a predominance of extracellular lipid, mainly diffuse, and the type Va lesion has a high lipid content, mainly localized, and a very thin capsule. Types IV and Va lesions can evolve at an intermediate rate (months to a few years) into the more stenotic and fibrotic types Vb and Vc lesions. However, it appears that more often and acutely, these lesions rupture, and then a change in their geometry and subsequent thrombus formation may lead to the type VI complicated lesions ..." Also he notes that when stenosis evolves GRADUALLY instead of abruptly, the process all the way to occlusive stenosis can be silent (asymptomatic), because the resulting ischemia stimulates the growth of protective collateral circulation.

Such variation in the evolution of atherosclerotic plaques is exactly what our Unified Model predicts --- because the SMC mini-tumors have different mutations, and therefore they differ in types and degree of dysfunction (Chapter 45, Part 5).

## • Part 4: Observations: Atherosclerotic Plaques Are Localized; Distribution Varies

Munro and Cotran (Munro 1988, p.251) comment that a comprehensive theory of atherogenesis should include an explanation for "the focal nature of the lesions and their general distribution."

### The Focal Nature

In our model, the focal nature of the lesions, adjacent to plaque-free tissue, results from mutation-induced mini-tumors of dysfunctional SMC clones.

Quite obviously, routine processing of lipoproteins in the arterial wall does NOT result in atherosclerotic plaques everywhere. Why do we find atheromatous lesions highly localized, with apparently normal arterial tissue adjacent in the same artery? Because induction of dysfunctional clones (mini-tumors) of smooth muscle cells is a random and rare occurrence. Despite exposure to ionizing radiation (or other mutagens), the overwhelming share of arterial smooth muscle cells do not acquire the combination of mutations required to become both clonal and incompetent (Chapter 45, Part 4b).

### The General Distribution

Munro and Cotran write (Munro 1988, p.250): "The distribution of plaques is important to explain. The most common site is the lower descending aorta, predominantly around the ostia of the major branches, followed by the coronary arteries, usually within the first six centimeters, the arteries of the lower extremities, descending thoracic aorta, the internal carotids, and the Circle of Willis. Some of this localization can be explained by hemodynamic factors, such as shear stress or disturbed flow (Glagov 1972; Ku 1985), but certainly not all of it."

Much of "the rest of it" may be explained by medical radiation, which exposes all of the sites named by Munro 1988. Munro and Cotran continue (Munro 1988, p.250): "Particularly vexing is the problem of determining the reason behind the heterogeneous distribution between and within individual subjects."

Our model predicts that some or most of the answer lies in the differing radiation histories of different cases.

Testing of this prediction will become possible someday, but not yet. The cases occurring today arise from radiation accumulated over a lifetime. For many people over age 50 today, a great deal of irradiation could have occurred during childhood, and some of it, even in-utero. Records are poor, and memories far worse. Unfortunately, even today, medical records seldom report how long a fluoroscopic xray beam is used and which organs are actually in the beam.

## • Part 5: Observations about Endothelium, Homocysteine, Hypertension, Smoking, Diet

We will discuss briefly how our Unified Model relates to many of the established and proposed risk-factors for Ischemic Heart Disease, and to some of the current regimes for primary and secondary prevention.

## 5a. Proposed and Established Risk-Factors for IHD

• - DYSFUNCTIONAL ENDOTHELIUM IS A RISK-FACTOR FOR ATHEROSCLEROSIS. We presented several aspects of this hypothesis in Chapter 44, Part 2. In view of the endothelium's active roles in the passage of lipoproteins into the intimal layer, in the inflammatory response, in thrombogenesis, and in other functions, we have no trouble believing that --- at equal plasma levels of atherogenic lipoproteins and equal accumulated radiation dose --- individuals with an appropriately responding endothelium will fare better on the average than individuals with a dysfunctional endothelium. And this would be true regardless of the specific causes of endothelial dysfunction --- whether the causes are poor nutrition, infections, mutations (either acquired or inherited), or other injurious agents.

• - HIGH BLOOD-PRESSURE IS A RISK-FACTOR FOR ISCHEMIC HEART DISEASE. This is not in doubt. It follows that --- at equal plasma lipoprotein-loads and equal accumulated radiation dose --- individuals without hypertension will fare better on the average than individuals with hypertension. Without hypertension, we expect that the intima will have to handle less lipoprotein per unit time. Great progress has been made since 1940 in controlling hypertension (AHA 1995). Today, specific TYPES of hypertension which confer the most risk are being identified.

• - SMOKING IS A RISK-FACTOR FOR IHD. This seems to be well established. It follows that --- at equal plasma lipoprotein-loads and equal accumulated radiation dose from non-tobacco sources --- individuals who do not smoke will fare better on the average than individuals who smoke. The mechanism which makes smoking a cause of IHD is a separate issue. Benditt, Martell, Trosko, and Chang propose that the mechanism is delivery of mutagens, from smoke, into the coronary arteries (Chapter 44, Parts 8d, 9a, 9b).

• - OBESITY AND PHYSICAL INACTIVITY ARE RISK-FACTORS FOR IHD. In general, these conditions correlate with each other and with elevated plasma levels of atherogenic lipoproteins. (The weight-lipoprotein relationships can complicate prospective research; Appendix I, Parts 3+4). Obesity and inactivity are said to contribute to IHD risk in additional ways. If they do, it follows that --- at equal plasma lipoprotein-loads and equal accumulated radiation dose --- individuals who are slim and active will fare better on the average than individuals who are not.

• - HIGH PLASMA LEVELS OF ENDOGENOUS HOMOCYSTEINE MAY BE A RISK-FACTOR FOR ACUTE IHD EVENTS. We have presented some of the interesting observations on this issue in Chapter 44, Part 10. For cardiovascular diseases, this risk-factor seems potent. With respect specifically to Ischemic Heart Disease, we would have no trouble believing that --- at equal plasma lipoprotein-loads and equal accumulated radiation dose --- individuals who have lower levels of plasma homocysteine would fare better on the average than individuals with higher plasma levels of homocysteine.

• - LOW LEVELS OF ENDOGENOUS HEPARIN MAY BE AN INDEPENDENT RISK-FACTOR FOR IHD. In a recent review-article, Hyman Engelberg points to numerous lines of evidence for a possible causal role of low endogenous heparin activity in atherosclerosis (Engelberg 1996, p.84, Table 1), and concludes: "Ultimately, experimental observations must be validated by clinical studies in humans." Affirmation of this hypothesis would be fully compatible with our Hypothesis-2, by which we mean that at equal plasma lipoprotein-loads and equal accumulated radiation doses, individuals who have elevated levels of endogenous heparin would fare better on the average than individuals who do not.

• - DIABETES MELLITUS IS A RISK-FACTOR FOR IHD. There is simply no doubt that Ischemic Heart Disease (Coronary Heart Disease), now and for a long time, has been a frequent companion of Diabetes Mellitus --- as noted in Chapter 29, Box 1. Not all the reasons have been identified (discussion in Bierman 1992, for instance). Our Unified Model implies that, at equal dose-levels of medical radiation, diabetics will fare worse than non-diabetics, because diabetics on the average have higher blood-levels of atherogenic lipoproteins.

• - HYPERINSULINEMIA MAY BE AN INDEPENDENT RISK FACTOR FOR IHD. It has not been clear whether the association, between elevated blood-levels of insulin in fasting individuals and subsequent development of Ischemic Heart Disease, means that hyperinsulinemia is a MARKER for several established risk-factors with which hyperinsulinemia correlates (such as unfavorable lipoprotein

levels, hypertension, obesity, etc.), or whether the association means that hyperinsulinemia independently confers a risk above-and-beyond its correlation with such other risk-factors. In April 1996, Jean-Pierre Despres and co-workers discussed the results of several earlier studies and reported the results of their own study (Despres 1996). In their own study, they conclude that hyperinsulinemia makes an independent contribution to the risk (Despres 1996, p.955). Affirmation of their work would be fully compatible with our Hypothesis-2, by which we mean that at equal plasma lipoprotein-loads and equal accumulated radiation doses, individuals who do not have elevated fasting levels of insulin would fare better on the average than individuals who do.

• - PARTICULAR NUTRITIONAL DEFICITS MAY BE RISK-FACTORS FOR IHD. In this group, for instance, one might include below-optimal levels of vitamins B-6, folic acid, and E, or too little absorbable magnesium, or too little consumption of omega-3 fatty acids. Other authors might mention a deficit of various hormone precursors and herbs and roots in the diet. One must expect that ANY substance (dietary or not) which appreciably worsens the problem of atherogenic lipids, or reduces the fraction of gene-injuries which are repaired correctly, or interferes with the body's optimal response to ischemia, thrombus formation, or to myocardial infarction (for instance), should show up as a risk-factor for IHD mortality. For each nutrition-based risk-factor which has been validated, searches for the mechanisms of harm should follow, of course. Appendix-F discusses dietary carbohydrates and fats, especially omega-3 fatty acids and the "Mediterranean Diet."

• - ADVANCING AGE IS A RISK-FACTOR FOR IHD. Accumulated radiation dose to the coronary arteries can only grow as age advances --- from natural, medical, and occupational sources, and from nuclear pollution. Indeed, radiation exposure from medical procedures rises steeply with advancing age, on the average. In addition, serum levels of atherogenic lipids generally start rising in the teen years --- much more for males than females, whose levels catch up when they are in their 50s (Glazier 1954). Some other risk-factors (such as body-weight, on the average, and reduced estrogen levels on the average) also rise with age. Moreover, atherosclerotic lesions take some time (variable) to develop into their life-threatening stages. Our Unified Model predicts that advancing age must be a risk-factor.

• - INHERITED DISORDERS WHICH CAUSE EXCESSIVE BLOOD-LEVELS OF ATHEROGENIC LIPOPROTEINS ARE A RISK-FACTOR FOR IHD. There is simply no doubt that some individuals inherit mutations (de novo or parental) which cause them to experience extremely high blood-levels of various atherogenic lipoproteins. By ages 20 or 30, they sometimes experience angina pectoris and/or xanthomata. Indeed, xanthoma tendinosum has occasionally been observed at birth. Are individuals who have inborn lipid disorders an exception to our Unified Model? Probably not. The fact that such individuals develop atherosclerotic lesions only at a finite number of sites is consistent with a requirement for dysfunctional clones caused by mutations which are acquired AFTER conception. Even mildly dysfunctional clones (Class A, in Box 1's Column A) are probably unable to cope with the enormously high "lipid-load" in the blood-stream of such individuals.

## 5b. Benefits from Pharmaceuticals Other Than Lipid-Lowerers

Valentin Fuster (1994, pp.2137-2140, with lots of references) presents a useful discussion of how (if known) various non-lipid-lowering pharmaceuticals achieve their benefits against mortality from Ischemic Heart Disease.

• - BETA-BLOCKERS. The beta-blockers reduce the rate of acute IHD events by reducing blood pressure and heart rate (Fuster 1994, p.2138).

• - ACE INHIBITORS. Angiotensin-Converting Enzyme Inhibitors reduce the rate of acute IHD events, including myocardial infarction, but "the mechanism of such reduction is uncertain," according to Fuster (p.2138). "Theoretically, it may be due to a decrease in plaque stress caused by lower blood pressure or reduced levels of neurohumoral activation (Francis 1989), thus reducing the possibility of plaque rupture. However, the decrease in blood pressure of these three trials [showing benefit] was relatively too small to suggest this hypothesis." Fuster favors the concept that ACE Inhibitors increase vasodilation of the micro-circulation and thus help to protect the myocardium from infarction during thrombotic episodes. William Parmley (1997. pp.12-13, with many references) mentions that ACE inhibitors not only increase vasodilation, but also may help block the thrombotic activity of Angiotensin II in vessel walls. Parmley reports that several large trials with ACE inhibitors are still underway to explore benefits apparently unrelated to reduced blood pressure.

• - ANTI-THROMBOTIC AGENTS. Such agents include platelet inhibitors and anti-coagulants. Fuster (1994, p.2139, citing many references) reports their effectiveness in preventing acute coronary events. Clot-formation appears to have a role in increasing the size of atherosclerotic plaques (Chapter 44, Part 7 at the outset and Part 7a). Therefore, Fuster reasons that anti-thrombotic agents "may offer some promise in preventing the progression of small coronary atherosclerotic plaques (Chesebro 1992)."

Fuster (1994, p.2139) points out that ASPIRIN is "the best-suited, least toxic, and most widely used antithrombotic agent in acute and chronic coronary artery disease," with benefits demonstrated in both primary and secondary prevention. Since aspirin and other antithrombotic agents each block only one of multiple pathways to thrombus formation, several ongoing trials (listed by Fuster) are trying to establish if use of a combination of agents will produce additional benefits, without unacceptable side-effects.

• - ESTROGEN-REPLACEMENT THERAPY. Such therapy for post-menopausal women appears to produce a large benefit in reduced mortality from cardiovascular disease --- "in part related to reduction in myocardial infarction" (Fuster 1994, p.2139, with references). Fuster reports lines of evidence that estrogens have direct anti-ischemic effects, perhaps acting as coronary artery vasodilators, for instance. Fuster also reports that the benefit comes partly from a resulting 15% decrease in LDL cholesterol, a 15% increase in HDL cholesterol, and inhibited influx of cholesterol through the endothelium into the intima. Citing Rosano 1993, Fuster states that "favorable alterations in lipid metabolism" probably do not explain ALL of the benefit, since the benefit is observed also in women who do not show the measured alterations.

In this context, we remind readers that many "alterations in lipid metabolism" go WITHOUT measurement. For example, the common short-cut of measuring "total triglycerides" --- instead of quantifying their lipoprotein sources, which differ in size and behavior --- may CREATE a number of unexplained results whose explanation is hidden primarily by the short-cut (Chapter 44, Part 4).

• - THYROID-HORMONE THERAPY. For hypo-thyroid individuals, adjustment of thyroid-hormone levels to more favorable values generally results in more favorable (less atherogenic) lipoprotein patterns.

• - Verified benefits from pharmaceutical agents are certainly compatible with our Unified Model, even when such agents achieve the benefit via co-actors in this disease OTHER THAN atherogenic lipoproteins and medical radiation. Obviously we expect that, at equal initial levels of atherogenic lipoproteins and equal accumulated radiation dose, individuals who take favorable pharmaceuticals should fare better on the average, with respect to IHD, than individuals who do not receive such help.

## • Part 6: Some Wise Words from Earl P. Benditt

This chapter has explored how our Unified Model either helps to explain, or is consistent with, a great variety of observations about Ischemic Heart Disease. There is much, much more to be learned about the specific roles of acquired mutations in this disease. We would like to associate ourselves with the wise words of Earl P. Benditt, who wrote in 1988 (Benditt 1988, pp.1000-1001):

"Progress in science depends on consideration of various hypotheses as we search for the best explanations of natural phenomena. Recent progress with genetic analysis of cell function and disease aberrations clearly indicates the vast complexity yet to be uncovered."

The findings in Chapters 40 and 41 very strongly suggest that mutations, acquired in coronary arteries from medical radiation, are an important cause of mortality from Ischemic Heart Disease. Our Unified Model proposes HOW acquired mutations could cause such mortality. Much remains "yet to be uncovered."

Meanwhile, it deserves emphasis again that the powerful, positive dose-response uncovered in Chapters 40 and 41 between PhysPop and IHD MortRates, for both males and female, is a fact --- not an hypothesis.

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*Box 1 of Chap. 46*

***Illustrative Relationship between the Unified Model and Benefit of Lipid-Lowering***

Please see text in Chapter 46, Part 1c. All entries below are arbitrary, for illustration only. "Lipid-load" is in arbitrary units, and of course refers only to the lipoproteins which are atherogenic.

| (A) Mini-Tumor Class: Most Nearly Competent = A. Least = K. | (B) Frequency in a Universe of 773 Mini-Tumors. | (C) Percent of Universe. | (D) Lipid-Load/Month at Which Atherosclerosis Is Stabilized. |
|---|---|---|---|
| Class A | 95 | 12.29% | 90* |
| Class B | 90 | 11.64% | 80* |
| Class C | 87 | 11.25% | 70* |
| Class D | 80 | 10.35% | 60 |
| Class E | 76 | 9.83% | 50 |
| Class F | 70 | 9.06% | 40 |
| Class G | 65 | 8.41% | 30 |
| Class H | 60 | 7.76% | 20 |
| Class I | 55 | 7.12% | 10 |
| Class J | 50 | 6.47% | 5 |
| Class K | 45 | 5.82% | 2 |
| Sum | 773 | 100.00% | |

| At a lipid-load (Col.D) of 60 units/month: | Reduce lipid-load to 40 units/month: |
|---|---|
| (95+90+87+80), or 352 mini-tumors (Col.B) are coping well enough to mean that the atherosclerotic process is not progressing at their plaque-sites. 352/773 = 0.46 | (95+90+87+80+76+70), or 498 mini-tumors are coping well enough to mean that the atherosclerotic process is not progressing at their plaque-sites. 498/773 = 0.64 |
| (76+70+65+60+55+50+45), or 421 mini-tumors (Col.B) are NOT coping well enough to prevent progression of the atherosclerotic process at their plaque-sites. 421/773 = 0.54 | (65+60+55+50+45), or 275 mini-tumors are NOT coping well enough to prevent progression of the atherosclerotic process at their plaque-sites. 275/773 = 0.36 |

* Mini-tumors capable of coping with loads > 60 can also cope with 60 units, of course.

SUMMARY: Progression of the atherosclerotic process predicts cardiac events. Box 1 illustrates how a reduction in the serum levels of atherogenic lipoproteins halts progression at Class E and Class F sites. They become "stabilized." One could "play" with the arbitrary numbers in this box, but the point would remain.

Related text = Part 1c.

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