CHAPTER 45
Unified Model: Intersection of Lipoproteins and Dysfunctional Clones of Smooth Muscle Cells

• Part 1. Introduction: Who Needs Another Model?

In this chapter, we present a Unified Model of Atherogenesis and of Acute IHD Death which seems to us to account for several otherwise unexplained and important aspects of Ischemic Heart Disease. For brevity, we will refer to it as our "Unified Model." We think the model is consistent with the observations reported by others, as well as with the new observations contributed by this book.

Who needs another model?

In the July 1, 1992 issue of the Journal of the American Medical Association, David H. Thom et al write (Thom 1992, p.68): "Established risk factors for coronary heart disease (CHD) such as serum lipids, smoking, hypertension, diabetes, age, gender, and family history, are usually estimated to account for less than half the variation in CHD."

Five years later, in the November 6, 1997 issue of the New England Journal of Medicine, in the Shattuck Lecture ("Special Article"), Eugene Braunwald states (p.1364): "Although much has been learned about the causes of coronary heart disease, the gaps in knowledge are noteworthy; for example, fully half of all patients with this condition do not have any of the established coronary risk factors (hypertension, hypercholesterolemia, cigarette smoking, diabetes mellitus, marked obesity, and physical inactivity)."

If it is true that so many cases lack any explanation, then "another model" should be welcome.

1a. Invitation in the New England Journal, 1997

A comprehensive theory should include the ACUTE events as well as the preceding atherogenesis, and so a model must deal also with Peter Libby's astute question (Libby 1995, p.2845): "What is it about certain plaques that renders them particularly susceptible to disruption and the ensuing acute manifestations such as myocardial infarction or unstable angina?"

In a recent editorial in the New England Journal of Medicine, Attilio Maseri issues an invitation for innovative research and new hypotheses (Maseri 1997, p.1014): "The weak relation between [acute] ischemic events and flow-limiting stenoses in the coronary and carotid arteries leaves room for innovative research (Maseri 1995). However, it is easier to study the details of accepted paradigms than it is to develop new hypotheses ..."

The search today for another PREVENTABLE cause of the acute ischemic events is emphasized by Valentin Fuster (Fuster 1994 p.2129): "Identification of vulnerable or unstable lesions prone to rupture, and measures for reversal of this pathological process, currently are subjects of worldwide investigation."

1b. A New "Smoking Gun": Stimulus for a Unified Model

This book has uncovered a new "smoking gun" with respect to causation of mortality from Ischemic Heart Disease. The irrefutable, strong, and positive dose-response uncovered here between PhysPop and IHD mortality demands an explanation. The dose-response is a clue of "smoking gun" magnitude, if ever there was one --- and it suggests a Unified Model of Atherogenesis and Acute

IHD Death. Our model offers an answer to Libby's question in Part 1a, and to several other questions. In addition, it points to a ready path to more PREVENTION of IHD deaths.

It should be self-evident that our Unified Model owes a lot to the work of others, already described in Chapter 44.

• Part 2. Lifelong "Foreign-Body Wars" in the Arteries: Role of Smooth Muscle Cells (SMCs)

As we see it, all our arterial beds (coronary, cerebral, and other) are in a lifelong process of clearing plasma lipoproteins out of the intimal layer after their influx (Chapter 44, Part 5). In that location, they are "foreign bodies," since normal metabolism would not use them in that place. We think that massive quantities of lipoproteins are processed in a lifetime in innumerable arterial walls. And obviously, most of this is handled successfully, since we rarely (if ever) see massive atherosclerosis all over the body.

2a. Diffuse Intimal Thickening

What we do observe, beginning in childhood, is gradual THICKENING of the intimal layer, and the arrival of smooth muscle cells (SMCs) --- capable of synthesizing connective tissue as needed (Chapter 44, Part 1a). McGill, citing earlier work (Geer 1968), concludes "as most others have" that the thickening of coronary intimas "represents normal arterial development, and is not a pathologic response to injury" (McGill 1984, p.447). Munro and Cotran also describe the thickening phenomenon as normal (Munro 1988, pp.250-251):

"In infancy, the endothelium of large and medium-sized arteries is generally directly apposed to [next to] the underlying media, but as the individual grows, these two structures become separated by accumulating extracellular matrix [connective tissue] and cells. The matrix contains collagen, elastin, proteoglycans, and fibronectins. Smooth muscle cells, macrophages, and T lymphocytes are present within the matrix, presumably having arrived from the media and arterial lumen. The smooth muscle cells can then be regarded as an intrinsic intimal population, and are often designated myointimal cells. After a few years of life the intima, now being composed of endothelium and underlying cells and matrix, continues to increase in height and is said to show diffuse intimal thickening. In general, this thickening can be taken as normal, presumably the result of hemodynamic or other stresses to the artery wall over time."

We would add: ... presumably the result of the continuous "Foreign-Body Wars" in the arterial intima --- the residue from mild inflammatory responses invoked when needed to help clear out the lipoproteins (and other foreign bodies). Of course, the intima's endothelial cells have roles in this inflammatory response, too.

2b. Development of Fatty Streaks

Also observed is widespread development, within the intimal layer, of fatty streaks --- in which smooth muscle cells have roles again. Fatty streaks are present "in most people under the age of 30 years regardless of their country of origin" (Fuster 1994, p.2126). Fatty streaks are found "in the coronary arteries of half of the autopsy specimens from children aged 10 to 14," according to Ross (Ross 1993, p.801). For a very long time, the relationship of fatty streaks and atherosclerotic plaques was hotly debated.

Under current classifications (mentioned in Chapter 43, Part 2c), Type I intimal lesions are those with isolated "foam cells" (macrophages containing lipid droplets); Type II lesions (flat fatty streaks) have foam cells of both the macrophage and SMC type; Type III lesions (raised fatty streaks) have "multiple but small extracellular lipid cores as well as lipid droplets in foam cells and an increasing number of smooth muscle cells" (Fuster 1994, p.2127). Writing about fatty streaks somewhat earlier, Munro and Cotran hold the view that (Munro 1988, p.250):

"On balance, it appears that fatty streaks are of universal occurrence and distribution, and most --- especially those in the aorta --- either disappear or remain harmless. In certain locations, (e.g., in coronary arteries) and especially in the predisposed individual, these streaks may conceivably evolve into fibrous plaques."

2c. Atherosclerotic Plaque: A Complex "Hive of Activity"

An atherosclerotic plaque can be a complex biochemical entity, humming with activity.

For instance, there is the continuing ingress and egress --- balanced or not --- of native and denatured lipoproteins. There is activity by monocytes, macrophages, T-cells, and platelets, all of which can secrete other molecules of great consequence (see, for instance, Munro 1988 or Libby 1995). In a large plaque, a micro-vasculature is growing to supply it with blood. Monocytes are transforming themselves into macrophages, which are trying to engulf the lipids. Such foam-cells produce large amounts of "tissue factor," a powerful stimulus of blood clotting. A highly thrombogenic lipid-pool can accumulate (Chapter 44, Part 7b).

Within this hive of activity, the smooth muscle cells need to provide high-quality collagen, elastin, and proteoglycans --- in the right quantity and at the correct speed. In advanced plaques, the products from SMCs are crucial to create, repair, and maintain a strong fibrous cap over the deadly lipid pool (Chapter 44, Part 7c).

• Part 3. Start of a "Whole New Ballgame": Dysfunctional Clones of Smooth Muscle Cells

When a failure occurs in the lifelong "Foreign-Body Wars," it is localized. Lipids start serious accumulation at a particular site in the intima --- not everywhere. Only particular patches become atherosclerotic plaques, surrounded by grossly normal tissue. Why does a plaque develop where it does? Is this totally random? We do not think so.

How do we visualize the change from routine processing of lipoproteins throughout the arteries, to the growth of a life-threatening and localized atherosclerotic plaque?

We envision it by paying attention to the new epidemiologic finding of this book with respect to mortality rates from Ischemic Heart Disease. We have uncovered a strong, positive dose-response between medical radiation and IHD death, in a huge prospective study (study-population of 150,000,000 people) --- a study based on neutral, objective data sources (Chapters 40 and 41). And we ask:

What can ionizing radiation do which could CAUSE a dose-dependent increase in death from Ischemic Heart Disease?

The answer is that ionizing radiation is a proven and potent mutagen (Chapter 2). It is capable --- most likely in concert with other agents --- of converting an individual smooth muscle cell of the artery into a benign mini-tumor consisting of clonal mutated cells which are LESS THAN COMPETENT at performing their crucial functions in the lifelong "Foreign-Body Wars" with intimal lipoproteins (Parts 4 and 5, below). Such mini-tumors would consist of DYSFUNCTIONAL clones. (A clone is a group of genetically identical cells descended from the same progenitor cell.)

• We consider that a "whole new ballgame" begins in a coronary artery wherever ionizing radiation causes this new entity, namely a clone of dysfunctional smooth muscle cells --- which gradually replace a small patch of non-tumorous tissue. We propose that some of these benign tumors have the behavior which leads to the local production of major atheromata.

• In regions adjacent to the mini-tumor, smooth muscle cells continue to perform their functions with competence --- even though they, too, were irradiated --- because exposure to a mutagen transforms only a very small share of cells into dysfunctional clones (the share rising with the dosage). Discussion in Part 4b.

Although we have mentioned only smooth muscle cells, we do not rule out the possibility that ionizing radiation induces some dysfunctional clones also among other types of arterial cells. So far, however, those who have investigated monoclonality in atherosclerotic plaques, implicate arterial smooth muscle cells (Benditt 1988, p.1000. Context in Chapter 44, Part 8).

• Part 4. Some "Wartime Jobs" of SMCs, and the Meaning of Dysfunction

So that the consequences of DYSFUNCTION can be appreciated, we will briefly describe some of the jobs, performed by normal arterial smooth muscle cells (SMCs), in the "Foreign-Body Wars" against lipoproteins in the intima.

4a. Several Functions of Normal Intimal Smooth Muscle Cells

In arterial inflammation, SMCs play the general role which fibroblasts play in other tissues (Chapter 44, Part 1a). In response to biochemical signals, smooth muscle cells synthesize and then secrete ("deposit") collagen, elastic tissue, and proteoglycans, to create interstitial connective tissue (extracellular matrix) as needed for the inflammatory response.

Another function, not mentioned in Chapter 44, is that smooth muscle cells are one of the cell-types which can produce a growth factor having the power to induce both SMC migration and proliferation (Munro 1988, p.255).

And perhaps of real importance, human vascular smooth muscle cells are also one of the cell-types which (A) can either INHIBIT degradation of the needed interstitial connective tissue, or (B) can PROMOTE such degradation when less connective tissue is needed. Peter Libby and co-workers have contributed years of laboratory work which has helped to uncover the multiple sources and complex interactions of the enzymes which control these processes. A very lucid description is presented in Libby 1995 (pp.2846-2847), from which we will extract what smooth muscle cells can contribute:

(A) Smooth muscle cells can express TIMPS --- Tissue INHIBITORS of MetalloProteinases. The metalloproteinases are a family of enzymes (proteins) which specialize in the DEGRADATION of extracellular matrix. This enzyme-family includes interstitial collagenase, gelatinase, and stromelysin. By expressing TIMPS, smooth muscle cells can help protect the extracellular matrix.

(B) Smooth muscle cells can also do the opposite: They can express some matrix-degrading enzymes. In response to biochemical signals, SMCs will express collagenase, gelatinase, and stromelysin.

Another job of normal SMCs, in the "Foreign-Body Wars," is probably to get out of the way when they are no longer needed --- a process which can involve apoptosis (cell suicide).

4b. What Qualifies as a Dysfunctional SMC Mini-Tumor?

Beginning in childhood, arterial smooth muscle cells participate in the mild inflammatory responses associated with successful clearance of most lipoproteins from the intima.

As the years pass, the arterial smooth muscle cells accumulate a rising exposure to mutagens (including ionizing radiation from natural sources and especially from medical radiation) --- and a rising frequency of cells which have acquired one or more mutations. Reminder: A mutation refers to permanent genetic change, and reflects damage which was never perfectly repaired. Of course, not all mutations are consequential. The specific consequences (if any) depend on which segment of the genome is altered.

A person's population of mutated, arterial smooth muscle cells must include some or all of the following categories:

• The Non-Clonal SMC. For this type of mutated cell, the accumulated mutations do not confer any proliferative advantage, when its neighborhood of smooth muscle cells receives mitotic signals. Thus, any acquired dysfunction is irrelevant because the dysfunction is not magnified by a burgeoning clone (tumor) of descendants.

• The Clonal but Otherwise Competent SMC. The accumulated mutations give this type of cell a proliferative advantage, but its burgeoning clone of descendants is innocuous because the

descendants all are competent at their jobs. Such cells seem to correspond with the Benditts' monoclonal hypothesis (Chapter 44, Part 8).

• The Clonal AND Dysfunctional SMC. The accumulated mutations give such cells a proliferative advantage AND cause them to be incompetent in some degree at performing one or more of their jobs. These are the cells which become qualified as SMC Mini-Tumors consisting of DYSFUNCTIONAL clones --- corresponding with the second part of our Hypothesis-2. And because of their proliferative advantage, such dysfunctional cells gradually REPLACE competent cells, at a localized patch of artery.

• Part 5. Consequences of SMC Dysfunction: Plaques and Plaque Rupture

With respect to the lifelong "Foreign-Body Wars" against lipoproteins in the intima, we propose that plaques develop and that some of them subsequently rupture because mutation-induced mini-tumors (consisting of dysfunctional clones of smooth muscle cells) are unable to do some of their crucial wartime jobs adequately --- jobs required by the early battles and later by the final battles which cause mortality from Ischemic Heart Disease.

5a. Innumerable Genetic Pathways to Dysfunction

Within an arterial smooth muscle cell, there are INNUMERABLE genes involved in completing all the wartime jobs assigned to it. For example, many dozens of enzymes and other proteins are typically required, directly and indirectly, for the synthesis and secretion of a single strand of collagen or elastin or other molecules. Dozens of other enzymes and proteins can also be required to transmit a particular type of signal through the cell's outer membrane all the way to the nucleus of a cell, in order to activate or inactivate various genes. And numerous regulatory genes control the relative dominance of opposing tendencies in a cell.

A disabling mutation, of even ONE of these numerous genes in a clone's progenitor, can cause the clone to perform inadequately.

Ionizing radiation inflicts mutations at RANDOM locations of a cell's genome, and there is no part of the genome which is inaccessible to radiation-induced mutation (Chapter 2, Part 4). Consequently, it is highly improbable that any two dysfunctional clones have identical disabling mutations. For example:

One mini-tumor may evolve from a cell where the xyz-gene is mutated at a segment where damage impairs only slightly the function of the xyz-protein which the gene encodes. In another mini-tumor, the same xyz-gene can be mutated at a segment where the functional consequences are severe. And in yet another mini-tumor, the mutation may remove (delete) the ENTIRE xyz-gene, if the mutation is an unrepaired double-strand chromosome break. Such examples of variation are applicable to every gene required for SMC mini-tumors to do their wartime jobs. On the average, clones having multiple mutations (either in one gene or in several different genes) will be more dysfunctional than clones having a single mutation.

The particular nature of a clone's mutations will determine the changes in its biochemistry and the severity of its resulting dysfunction. The net result of disabling mutations will vary. For example:

• - One dysfunctional clone (patch) of smooth muscle cells might be slow in producing collagen --- producing too little per unit time. RATE MATTERS --- a fact well known to wartime commanders and biochemists alike.

• - Another dysfunctional clone might produce enough collagen, but it might be defective collagen which does not adequately fill its structural function, either in "early" lesions or in full-grown plaques. Quantity fine, but quality inadequate. Other clones might be unable to produce TIMP in the right quantity or quality (Part 4a), or at the NEEDED RATE.

• - Other dysfunctional clones might have their main problem in receiving signals --- with a net result of either under-responses or over-responses. Suppose that the SMCs in an advanced plaque end up over-responding to an apoptosis (suicide) signal. Then SMCs in the fibrous cap will become too scarce, and maintainance of the plaque's fibrous cap will be impaired (Chapter 44, Part 7d). Or

suppose that the SMCs in an advanced plaque end up under-responding to the signal to produce TIMP (Part 4a). The result might well be inappropriate degradation of the collagen structure of the plaque's fibrous cap, and rupture of this weakened cap.

Thus, our Unified Model helps to answer a fundamental question: WHY do plaques of a single person differ from each other, for instance in the amount and form of accumulated lipid, the density of smooth muscle cells, the amount of fibrotic material, and the severity of the inflammatory response and its various other constituents? Plaques differ from each other because dysfunctional clones, of arterial smooth muscle cells, suffer from different sets of mutations.

5b. Libby's Question: Why Are CERTAIN Plaques Prone to Rupture?

We return to Libby's question (Libby 1995, p.2845): "What is it about certain plaques that renders them particularly susceptible to disruption and the ensuing acute manifestations such as myocardial infarction or unstable angina?"

Our Unified Model proposes an answer:

At different sites, the consequences of dysfunction accumulate in various degrees, because no two plaques share all the same mutations. Some dysfunctional clones will produce fibrous caps which are inherently more vulnerable than other caps to rupture. Moreover, an inferior cap which would suffice at a relatively quiet site may readily rupture, if it is located where the coronary arteries experience much greater twisting and mechanical stress (blood pressure, turbulence) than at other locations. Our model predicts that the plaques which DO rupture are determined jointly by the degree of their gene-based weakness and the degree of their external stress.

At sites of equal mechanical stress, plaques differ in their degree of vulnerability to "disruption" because they arise from mini-tumors of smooth muscle cells, and those mini-tumors suffer from DIFFERENT degrees of gene-based dysfunction. Particular mixtures of mutations result in fibrous caps which are more vulnerable to rupturing than the caps which result from other mixtures of mutations.

And Hypothesis-2 proposes that the main cause of these arterial mini-tumors is medical radiation. Were it not for these radiation-induced tumors, the normal inflammatory response, operating in its full majesty, would usually triumph in the lifelong "Foreign-Body Wars" of the arteries.

5c. What about Cases of IHD with No History of Medical Radiation?

We are well aware that Ischemic Heart Disease develops in some people who really have no history at all of medical irradiation. Such cases are consistent with our model.

To be clear: Our model does NOT "predict" that there was no Ischemic Heart Disease in humans before the introduction of xray machines. There are two crucial reminders. The first reminder is that every human being everywhere receives lifelong exposure to ionizing radiation from natural sources. The second reminder is that the coronary arteries are exposed to some OTHER mutagens besides ionizing radiation.

Our Unified Model of Atherogenesis and Acute IHD Death readily embraces a role for non-radiation mutagens also. Any mutagen qualifies if it can convert an arterial smooth muscle cell into the progenitor of a dysfunctional clone of smooth muscle cells. Whatever the source of acquired mutations (acquired at any interval after conception), the key issue is repairability --- because perfectly repaired gene-damage has no consequences.

It is worth noting that infants can acquire mutations during their gestation. With respect to xray-induced mutations, pelvimetry by xray examination was introduced soon after the 1896 discovery of the xray. How commonly was pelvimetry used? We can offer an estimate only for the 1947-1970 period. During those years, approximately 7.5% of mothers in the USA had such pre-delivery xray examinations --- so about 1 infant in every 13.5 experienced pre-birth medical radiation (Chapter 2, Part 2d).

In future research, on the role of acquired mutations in Ischemic Heart Disease, are there good reasons to focus on medical radiation, instead of on mutagens in general? Yes.

- The first reason: Medical radiation is a proven mutagen which has an irrefutable and positive dose-response with IHD mortality. That dose-response is staring at us from Chapters 40 and 41 --- and demanding "Explain me!"

- The second reason: Medical radiation is a mutagen to which vast numbers of people actually receive exposure during a lifetime.

- The third reason: Ionizing radiation has some unique and undisputed properties which give it access to every gene in every type of cell, and which enable it to cause complex double-strand chromosomal injuries --- some of which are never correctly repaired (Chapter 2, Part 4, and Appendices-B+C). The doubling-dose for xray-induced structural chromosomal mutations is very low (Chapter 2, Part 4b). Indeed, the xray doses accumulated from some common, current, nontherapeutic medical procedures are equivalent to such doubling-doses (Chapter 2, Part 7e). Medical radiation may well be the single most menacing mutagen to which people are routinely exposed.

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