Regression of Atherosclerosis
The Journey From the Liver to the Plaque and Back

Edward A. Fisher

Abstract—Cardinal events in atherogenesis are the retention of apolipoprotein B–containing lipoproteins in the arterial wall and the reaction of macrophages to these particles. My laboratory has been interested in both the cell biological events producing apolipoprotein B–containing lipoproteins, as well as in the reversal of the damage they cause in the plaques formed in the arterial wall. In the 2013 George Lyman Duff Memorial Lecture, as summarized in this review, I covered 3 areas of my past, present, and future interests, namely, the regulation of hepatic very low density lipoprotein production by the degradation of apolipoprotein B100, the dynamic changes in macrophages in the regression of atherosclerosis, and the application of nanoparticles to both image and treat atherosclerotic plaques. (Arterioscler Thromb Vasc Biol. 2016;36:226-235. DOI: 10.1161/ATVBAHA.115.301926.)

Key Words: apolipoproteins B ■ autophagy ■ atherosclerosis ■ macrophages ■ nanoparticle

It was a great honor to have been selected by my peers in the ATVB Council to deliver the 2013 George Lyman Duff Memorial Lecture at the Scientific Sessions of the American Heart Association in Dallas. Because this award is meant not only to commemorate the many important contributions of Dr Duff to the field of atherosclerosis but also to recognize the career achievements of the recipient, I arranged the lecture to cover 3 main themes that have been important long-term foci of my research program, namely the secretory regulation of apolipoprotein B (apoB; particularly of the apoB100 form) and its associated hepatic lipoprotein very low density lipoprotein (VLDL), the regression of atherosclerosis, and theranostics—the imaging and treatment of atherosclerosis by nanoparticles. Because these 3 themes include studies on the production of other hepatic lipoproteins and on the regression of atherosclerosis through increases in reverse cholesterol transport, the Lecture (and article) title has tried to capture this spectrum.

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The published work in each area served as an introduction to the sections, with the emphasis in the presentation being on our most recent studies. This was to avoid giving the impression that a qualification for the Duff Lecture Award was to already have become a duffer! In some cases, then, extensive presentation of the primary data will not be possible in this article in order not to interfere with subsequent publication of research reports.

Secretory Regulation of ApoB and VLDL

VLDL is assembled in the liver and serves many important roles in lipid and lipoprotein metabolism, one of which is the transport from the liver to the circulation of triglycerides and cholesterol. The triglyceride is used in peripheral tissues either for energy or for energy storage. After VLDL particles are depleted of triglycerides, they are remodeled to cholesterol-enriched remnants, some of which are removed from the circulation (mainly by the liver, but also by peripheral cells, including macrophages in atherosclerotic plaques), with the others becoming LDL particles. Although lipid transport to peripheral tissues is an essential metabolic function of VLDL, that it is the precursor of LDL, the strongest risk factor for coronary artery disease, has also provided an impetus to better understand VLDL assembly and secretion.

Although VLDL has several apolipoprotein species on its surface (eg, apoE, apoCI, CII, and CIII), there is a specific requirement for apoB for the assembly and secretion of VLDL. Besides being an important structural component, the apoB100 form has regulatory functions by its being a ligand for the LDL receptor. In humans, the form of apoB made in the liver is apoB100, whereas in the intestine, it is apoB48. ApoB48 arises from the translation of an apoB100 mRNA that has been edited to alter a codon for glutamine to be a translational stop codon, resulting in a protein 48% of the size of apoB100.

Rodents have relatively high levels of the editing complex in their livers, so they produce a VLDL particle with either 1 apoB100 or 1 apoB48 associated with it. Given the goal to understand human VLDL metabolism through the window of animal and in vitro models, we have typically focused on the apoB100 species produced by rodent hepatic cells. An obvious question is: why not use as a model system HepG2 or Huh7 cells, given that they produce exclusively apoB100 and they...
are of human origin? Unfortunately, these cells are not competent to secrete appreciable quantities of VLDL, instead assembling the apoB100 into lipoproteins of considerably greater density. Thus, rodent hepatic cells (including primary rat and mouse hepatocytes and the rat hepatoma line, McA-RH7777 [McA]), which secrete most of their apoB100 on VLDL particles with characteristics similar to those of humans, have long served investigators interested in VLDL assembly and secretion. The use of these models will continue, but with iPS technologies, the production of human and humanized hepatocytes for study and manipulation is rapidly developing to provide additional model systems in vitro.

In the mid 1980s, Roger Davis, Sven Olofsson, and their colleagues showed that the number of apoB-associated lipoprotein particles secreted by hepatic cells was regulated by the degradation of apoB. This major finding was in stark contrast to what was known about the bulk of hepatic proteins, namely that their secretion was driven primarily by the level of synthesis. Their work turned the attention of many investigators to the nature of this degradation process. I started my own laboratory around the time of these discoveries and joined the hunt shortly after I was introduced to VLDL metabolism by Julian Marsh.

Not surprisingly, the regulation of apoB degradation has turned out to be complex with different proteolytic processes depending on the metabolic state of the hepatic cell. The current summary is depicted in Figure 1. There are 3 main pathways of apoB100 degradation, one at each end of VLDL assembly and secretion, and the third somewhere in between. My laboratory and our collaborators have made primary discoveries in all 3 pathways, which have been integrated into the fabric of the field woven by a host of investigators. Limited space precludes an in depth survey of apoB/VLDL research, even restricting the focus to Figure 1, so only the contributions of my laboratory to the early and middle pathways of apoB100 degradation will be discussed, as in the Lecture.

The early pathway is proteasomal-endoplasmic reticulum-associated degradation (ERAD), particularly relevant whenever lipidation of apoB100 polypeptides being translocated into the ER lumen is insufficient because of low levels of either triglyceride synthesis or of microsomal triglyceride transfer protein activity. This results in the failure to stabilize the conformation of apoB100 polypeptides by cotranslational lipidation, and the aberrantly folded molecules become engaged by the quality control machinery of the ER and targeted by ERAD to the proteasome (shown in collaboration with Henry Ginsberg and Jeffrey Brodsky). Although this pathway is particularly active in HepG2 and Huh7 cells, likely because they synthesize subnormal amounts of triglycerides, in rat hepatoma and primary rat and mouse hepatocytes, ERAD is less active, yet substantial degradation of apoB100 can occur. A particular

![Figure 1](http://atvb.ahajournals.org/)

**Figure 1.** Apolipoprotein B (apoB) degradation and the pathway to very low density lipoprotein (VLDL). The nascent apoB100 polypeptide becomes associated with lipids transferred by microsomal triglyceride transfer protein (MTP) during its translocation across the endoplasmic reticulum (ER) membrane. When there is an insufficient level of either lipid synthesis or MTP activity, much of apoB100 gets shunted to the proteasomal-ER–associated degradation (ERAD)/proteasome pathway. The immature VLDL particles (pre-VLDL) are transported in vesicles to the Golgi, where they either (1) complete their maturation to fully lipidated VLDL particles or (2) VLDL particles that fail to normally mature (because of metabolic circumstances, such as treatment with fish oils or insulin) get shunted from the Golgi to autophagosomes, which eventually fuse with lysosomes as part of autophagy. There is yet another opportunity to intercept VLDL particles before they enter the systemic circulation, namely at the cell surface through interactions with either LDL receptors or HSPGs, in a re-uptake process. PDI indicates protein disulfide isomerase; PERPP, post-ER, pre-secretory proteolysis; and TG, triglyceride.
example of this is the reduction of VLDL-triglyceride and apoB100 secretion by diets rich in fish oils, which are used clinically in patients with hypertriglyceridemia. We showed that the active fatty acids in fish oil (DHA and EPA) stimulated apoB100 degradation in primary rat and mouse hepatocytes as well as in McA cells, but this did not involve ERAD. Rather, engaged was a pathway that Kevin J. Williams and I dubbed post-ER, presecretory proteolysis.5 As shown in Figure 1, post-ER proteolysis turned out to be autophagy.6

There is an accumulating list of examples of apoB100 post-ER autophagic degradation induced by diverse metabolic stimuli, which in addition to fish oils, include postprandial levels of insulin.7,8 What seems to be common among these settings is a failure to complete successfully post-ER maturation of VLDL, thought to occur in the Golgi apparatus.9 Thus, although most protein quality control has been studied in the ER, it makes sense that there is a parallel mechanism for complexes that were competent to exit the ER, but judged incompetent to exit the Golgi. Just how fish oils make VLDL Golgi incompetent is the subject of 2 of our papers,6,10 and will not be reviewed here.

In the Duff Lecture, I proposed that the effects of niacin are another example of post-ER autophagic apoB100 degradation regulating VLDL secretion. Like fish oils, niacin has been used to treat patients with hypertriglyceridemia, and its mechanism of action has been largely attributed to events outside of the liver (eg, in the adipocyte) or after VLDL is secreted (eg, hydrolysis of the triglycerides). The studies that have gone into the most detail about possible effects of niacin at the level of the hepatocyte have focused on effects on triglyceride metabolism, particularly their synthesis or transfer to apoB100 by microsomal triglyceride transfer protein.11 There are at least 2 problems, however, in generalizing those results. First, many data are from HepG2 cells, which as noted above, make little true VLDL. Second, if this was the mechanism, lipid insufficiency, as reviewed above and in Figure 1, niacin should have stimulated proteasomal ERAD of apoB100, which in our studies in primary mouse hepatocytes or McA

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**Figure 2.** Macrophage-related events in the arterial wall during atherosclerosis progression and regression. Hyperlipidemia increases the number of circulating GR1+LY6Chi monocytes, which constitute 80% of the monocytes recruited to mouse atherosclerotic plaques in a multistep process involving chemokine–chemokine receptor pairs, endothelial adhesion molecules, including selectins and adhesion molecules. The recruited monocytes differentiate into macrophages or dendritic cells in the intima, where they take up atherogenic lipoproteins via macropinocytosis or scavenger receptor-mediated pathways. The resulting foam cells secrete proinflammatory cytokines and chemokines, as well as retention factors (such as netrin 1, semaphorin 3E, and cadherins) that amplify the inflammatory response and promote macrophage chemotaxis. These accumulating macrophages experience endoplasmic reticulum stress, which, if prolonged, results in apoptosis. This cell death, coupled with defective effector cytokines, results in the formation of the necrotic core that is characteristic of advanced plaques. The mechanisms that promote lipid unloading of the foam cell, including the factors that upregulate ATP-binding cassette subfamily A member 1 (ABCA1) expression on plaque macrophages and cholesterol efflux, reverse the accumulation of these foam cells. In some mouse models, this plaque regression is characterized by an upregulation of CC-chemokine receptor 7 (CCR7) on myeloid-derived cells, a decrease in the expression of retention factors, and reduced monocyte recruitment. The accumulating evidence summarized in our recent review19 supports the idea that the regulation of macrophage the retention/migration factors contributes to macrophage loss from the plaque through reverse transmigration to the lumen or through trafficking to the adventitial lymphatics. Reprinted from Moore et al19 with permission of the publisher. Copyright ©2013, Nature Publishing Group. LDL indicates low-density lipoprotein; LOX1, lectin-like oxidized LDL receptor 1; SR-A1, scavenger receptor A1; and UNC5B, a receptor for netrin 1.
cells does not occur (L. Guo and E. Fisher, unpublished data, 2014). I presented in Dallas data showing that niacin treatment of rodent hepatic cells and of wild-type mice decreased VLDL-triglyceride and apoB100 production, and that these effects were attenuated by genetic or pharmacological deficiency of autophagy. A metabolite of niacin, nicotinic acid adenine dinucleotide phosphate can increase autophagy22 and in our current studies we are focusing on this as the mechanistic basis in the liver for increased apoB100 degradation and reduced VLDL secretion on niacin treatment.

Atherosclerosis Regression

Work from my laboratory has focused on regression, and since 2001 we have introduced several models and molecular approaches to study this clinically important goal. Briefly, these include (1) a transplant model, in which plaque-bearing aortic segments are transferred into normolipidemic mice,13 (2) a genetic switch Reversa model, developed with Stephen Young, in which LDL production can be conditionally reduced in Ldlr−/− mice,14 (3) acute treatment models, in which ApoE−/− mice are injected either with apoA1 (in collaboration with Stanley Hazen and Jonathan Smith15), a microsomal triglyceride transfer protein inhibitor,16 or anti–miR-33 (in collaboration with Kathryn Moore17,18).

Figure 2 is taken from our recent review19 and shows some of the events in the arterial wall during atherosclerosis progression and regression based on results from these and other models. Our early results with Gwen Randolph20,21 from the aortic transplant model showed, surprisingly, that part of the regression process could involve changes in macrophage emigration from the plaques. We and others,18,22–24 have also shown regulation of monocyte recruitment and macrophage retention can contribute to the decreased content of macrophages in regressing plaques. It is becoming clear that the quantitative impact of each kinetic arm of monocyte/macrophage trafficking is dependent on the regression model used, as well as on the specific metabolic conditions, and the reasons for the variations are a focus in many laboratories, including our own.

Our first transcriptome profiling (in collaboration with Michael Garabedian and Oscar Puig) of macrophages in progressing and regressing plaques disclosed arginase I, a commonly used murine marker of M2 macrophages,25,26 as the most upregulated gene in regression in the aortic transplant model. We have since established that independent of the models we have used (see the article by Moore et al19 for a review), a general feature of the regressing plaques is enrichment of macrophages with features of the M2 state. In progressing plaques, the predominant phenotype of macrophages is the activated, inflammatory M1 state. In several contexts, M2 macrophages are considered to be anti-inflammatory (eg, they secrete interleukin [IL]-10 and tissue remodeling) but, at the time of our transcriptome report, little was known about their presence or roles in regressing plaques. Logically, the presence of M2 or M2-like macrophages would make sense in that the resolution of inflammation and remodeling of an atherosclerotic plaque to a more normal state is akin to wound healing. Also consistent with M2 macrophages having anti-inflammatory properties are the data that IL-4 and IL-13–based treatments (which polarize macrophages to the M2 state in vitro) retard plaque progression, as assessed by the content of activated macrophages.27,28

figure 3. building theranostic high-density lipoprotein (HDL) particles and their applications. A, shown in cross section is a typical spherical HDL particle. The magnetic resonance imaging (MRI) agent gadolinium (Gd) has been incorporated as a chelate with diethylene triamine penta-acetic acid (DTPA) conjugated to phosphatidylethanolamine. There is also a fluorescent dye (nitro-2,1,3-benzoxadiazol [NBD]), also incorporated as a conjugate with phosphatidylethanolamine. Other imaging agents (such as quantum dots, gold, and iron oxide particles), as well as drugs (statin, liver X receptor agonists) can be placed in the core, where the lipid esters usually are. B, Apolipoprotein E (ApoE)-deficient mice were fed the western diet for 48 weeks, then imaged by MRI without (pre) or 24 hours after injection with HDL reconstituted with Gd. The lower power magnetic resonance images are abdominal cross sections; the higher power inserts show more clearly the aortae. The bright signals in the Gd-HDL injected mouse correlated with plaque macrophage content on subsequent immunohistochemistry. C, ApoE-deficient mice were fed the western diet for 27 weeks, after which they received every other day injections over a week of the indicated materials (rHDL, reconstituted control HDL; low or high [S]-rHDL; HDL reconstituted with simvastatin, but administered at 2 different dose levels). A and B are reprinted from Frias et al19 with permission of the publisher. Copyright ©2004, American Chemical Society, and C is reprinted from Duijvenvoorden et al29 with permission of the publisher. Copyright ©2014, Nature Publishing Group. DMPE indicates di-myristoyl phosphatidylethanolamine.

In the Duff Lecture, I extended this finding by presenting unpublished results on the role and source of M2 polarized macrophages in regressing plaques. Perspective on these results has greatly benefitted by my time in David Greaves’ laboratory at Oxford during my Eastman Professorship, and has led to the goal of determining whether the M2 enrichment represents: (1) the conversion of M1 macrophages to a M2-like state when the plaque environment is changed, (2)
the expansion of a pre-existing population of M2-like resident cells in the plaque, or (3) the recruitment of new monocytes that become M2-like. If it is the last possibility, then a related issue is whether the subset of circulating cells belongs to the Ly6Chi or Ly6Clo class. As frequently reviewed, the Ly6Chi monocyte subset is thought to be the precursor of M1 macrophages, and they are therefore sometimes referred to as inflammatory monocytes, whereas the Ly6Clo cells are thought to be precursors of M2 macrophages. Recent studies, however, have shown that in some settings of inflammation, M2 macrophages can be derived from the Ly6Chi subset. To approach this experimentally, we have begun to test the possibility that the M2 macrophages are derived from circulating monocytes, given that we know that even after lipid lowering, monocytes continue to enter the plaque. Experimentally, this has involved doing aortic transplants from Apoe−/− mice with advanced atherosclerosis into normolipidemic mice that were wild-type or with deficiency in CCR2 or CCR5, chemokine receptors used for the recruitment into tissues, including plaques, of Ly6Chi and Ly6Clo monocytes, respectively. As presented in the Lecture, the picture that is forming supports the origin of the M2-like cells from circulating monocytes recruited after lipid lowering, and that the source of the cells is the Ly6Chi pool. Furthermore, in the absence of M2 enrichment, regression was severely impaired, pointing out the parallel between regressing a plaque and healing a wound. Besides rigorously establishing these findings, studies in the near term, in collaboration with Png Loke and Kathryn Moore, will include identifying the type(s) and source(s) of the signals that cause the newly recruited Ly6Chi monocytes to assume M2-like properties.

Atherosclerosis Theranostics

Theranostics is a term that refers to agents that have the dual capability of diagnosing and treating a disease. A little over 10 years ago, my involvement in cardiovascular theranostics began when I envisioned that high-density lipoprotein (HDL) particles could be adapted to deliver gadolinium (Gd) to improve the imaging of atherosclerotic plaques by magnetic resonance. I had been working with Zahi Fayad, who spearheaded the first studies to show that magnetic resonance imaging could detect plaques in atherosclerotic mice, and we wished to increase the sensitivity. As shown in Figure 3A, the form of Gd typically used for imaging is incorporated in the form of a chelate with a phospholipid molecule, and we were able to reconstitute HDL particles containing this form. Their use significantly enhanced the quality of the images (Figure 3B).

This was the diagnostic aspect; HDL infusions in animal models and in humans were shown to regress plaques, suggesting that the administration of the Gd-HDL particles would also be therapeutic. Furthermore, by further adapting HDL to carry both imaging agents and drugs, we envisioned that the therapeutic efficacy could be improved. Indeed, in studies directed by Willem Mulder, whose laboratory incorporated simvastatin into HDL particles, we recently showed that plaque regression resulting from infusion of HDL was dramatically enhanced by the incorporation of statin (Figure 3C). Along with parallel advances in incorporating imaging agents for modalities besides magnetic resonance, the potential for HDL to become a theranostic agent has been amply supported.

In the Duff Lecture, I presented studies in which we showed how a nanoparticle approach could overcome undesirable effects of liver X receptor agonists. Although liver X receptor agonists are thought to have major benefits at the level of the plaque by promoting cholesterol efflux from macrophages and by having anti-inflammatory activities, in mammals, including humans, they also stimulate hepatic lipid synthesis and can cause steatosis and hypertriglyceridemia. As shown in Figure 4, when liver X receptor agonist GW3965 was incorporated into nanoparticles (details about their composition are given in the study by Zhang et al), steatosis was avoided, but beneficial effects on plaques were observed. Currently, we are testing whether reconstituted HDL containing GW3965...
has similar effects. If so, then there will be multiple nanoformulations, based on HDL and other platforms, from which to identify the best candidates to use in human imaging and therapeutic trials.

**Concluding Remarks**

To review the past, describe the present, and speculate on the future in one 30-minute lecture was an interesting experience, especially in Dallas during the week of the 50th anniversary of the assassination of President Kennedy, as well as of my own Bar Mitzvah! As noted earlier, I started my independent career focused on the cell and molecular biological aspects of hepatic lipoprotein metabolism, later adding the area of atherosclerosis, specifically its regression and imaging. Although there are many other exciting topics tempting me to investigate, my inner voice says that it will be ambitious enough to definitively answer some of the important questions raised by the results shared with you in the Duff Lecture and in this review. I look forward to reporting on our progress and hearing about yours as well.

**Acknowledgements**

Needless to say, all of the research in my laboratory has benefitted by the contributions of many mentors, trainees, research technicians, and collaborators. Space limitations do not allow me to list them individually, but their names (and the complete Lecture slide set) can be accessed at https://www.med.nyu.edu/medicine/cardiology/center-prevention-cv-disease/edward-fisher-md-phd-profile. I am particularly indebted to Jan Breslow, who as a young assistant professor are also due to my family and friends.

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**References**


Why did you choose the profession of scientific investigation?

Neither of my parents had anything to do with science. My father worked in a pawnshop, and my mother had a vocational high school diploma in sewing. I think my initial interest in science was pretty much instinctive: isn’t everyone curious as a child? This was reinforced by excellent science teachers in the New York City public school system, especially at my high school, the Bronx High School of Science. My parents worked hard to give my brother and me educational opportunities they never had, and it turns out we both used these to become scientists, he a physical chemist. Why I chose metabolism as a field is based in part from my clinical experiences when I was a pediatrics resident at Duke. We had a chief of metabolism, Jim Sidbury, who was very inspiring. We talked at length about some of the patients with metabolic disorders, and he encouraged me to get the hard science training needed to understand biochemical mechanisms, to make more accurate diagnoses, and to improve treatments. He also pointed me to a joint graduate program at MIT and the Harvard-affiliated hospitals in metabolism, and in one of my first year courses, I attended a lecture by Jan Breslow on lipoproteins, which led to my joining his lab.

Who have been your role model(s) in your scientific and professional life?

I already mentioned two mentors, Jim Sidbury and Jan Breslow, who also became role models as highly successful physician-scientists in the area of metabolic disease. When I became an assistant professor of biochemistry at the Medical College of Pennsylvania, Julian Marsh, another outstanding physician-scientist, was very supportive personally and professionally, and his guidance helped me to establish my lab and to choose among potential independent projects. He also emphasized how important it was to “follow your nose”- to go where the data took you. Jan’s fabulously successful application of the latest concepts and technologies to the questions he was interested in also encouraged me to follow Julian’s advice. It is a good thing, then, that I have a long nose! As a more senior faculty member, I still learn from mentors—for example, by observing Valentin Fuster when I was at Mount Sinai, I was reminded that as hard as you think you are working, you can work harder.

What have been important influences on your professional life?

My parents, despite their lack of sophistication in science, valued knowledge and meritocracy, which became incorporated into my professional DNA. I did, however, disappoint them by not becoming a radiologist. My father tried to encourage this path by one day dragging home a set of golf clubs from the pawnshop because, he told me, radiologists played golf on their afternoons off. As I noted earlier, I had many superb science and math teachers, especially in high school. Many of them had advanced degrees (including PhDs), but came of age during the Depression, could not get research positions, and were more than happy to get teaching jobs. I think by fostering the scientific interests of the likes of me, they were hoping some of us would ultimately take advantage of the opportunities they never had.

Many scientists I have interacted with over the years, even over a distance, also have taught me a number of important lessons, both positive and negative. After all, as important as it is to learn what to do, it is equally important to learn what not to do. Actually, it is not just from scientists from which you can glean these lessons—every Sunday I read the interview with a successful business person in the NY Times, and they cover a lot of topics germane to all of us in science, or in most professions, for that matter.

What are your scientific inspirations?

Nature has a richer imagination than we have, and all scientists are both challenged and inspired by this. Figuring anything out is a true accomplishment and a wonderful goal in itself. This is reflected in the guiding principle of the great biologist and thinker Jacques Monod, who said, “Je cherche à comprendre”—“I am trying to understand.” Questions of the trainees in my lab and the students in the courses I teach are frequent reminders of the gaps in my knowledge, and stimulate more thinking/learning. Beyond the intellectual satisfaction, of course, I wouldn’t mind if what we discover has some practical benefit. After all, I was partly inspired to undertake an investigative career after exposure to some of nature’s experiments—the children with metabolic disorders. Now that I am 60+, I also am inspired by those older than me doing first-rate research, of which, I am happy to say, there are many!

How have mentors contributed to your professional development?

I covered a little of this in Answer 2. The contributions include the scientific training obtained under each. What I learned under the tutelage of Jan Breslow, Gary Felsensfeld (post-doctoral advisor), and Gunter Blobel (sabbatical host) provided essential
underpinnings. After all, technical/conceptual proficiency is essential for an independent investigative career, much as mastery of notes, scales, and timing is required for a career in music. Beyond that, are their contributions that are harder to identify explicitly, and are gleaned mainly by observing how these superb scientists supervised trainees, interacted with colleagues, formulated hypotheses, and made decisions, especially when results suggested multiple avenues forward, or worse, failure, which to varying degrees, is a constant companion in science. Not all of my mentors contributing to my professional development, however, were scientists. In particular, my illiterate grandmother, who lived with us, was a font of wisdom about how to deal with life in general, and had the additional skill of making each of her 17 grandchildren feel that he or she was her favorite! My father-in-law, a high school graduate who became a very successful businessman, radiated energizing positivity, and I regretted not knowing him longer.

If you knew then what you know now, would you do anything different?

I would still be a physician-scientist, but given the prolonged periods of funding tightness (in my career, not just the current drought, but also the period before Bill Clinton raised the NIH budget), I might have stayed on at the NIH after my post-doctoral fellowship. Though the NIH intramural program is not without its own problems, it has been largely insulated from the severe funding pressure that the extramural investigators have had to deal with. I might also have chosen different parents, so that they would have had a smarter child, who would grow up to get selected for a Howard Hughes position.

What wisdom do you impart on new investigators?

I do not want to engage in too many platitudes (work hard, have faith in yourself, blah-blah). The reality, as anyone reading this knows, is that the prolonged funding deficiency makes it tough on investigators at all career stages. For the new investigators, at least they have (or should have) start-up packages. With this cash in your pocket, it will be tempting to expand a lab quickly, but this risks having too many projects and people to direct, jeopardizing the timely completion of top-quality research publications, which are crucial to prove to the world (eg, study sections) that you are on your way. Establishing a "track record" as an independent scientist before the time period for early stage investigator NIH "bonuses" expires will make your first R01 application that much more competitive. My hope for all new investigators is that someday they will say, as I do, "If I knew how well I would eventually do, I would not have worried as much when I was an assistant professor."

Another piece of advice is something I heard from Jan Breslow. He said the standard for a successful career is that for whatever problem you work on, the understanding of it changes based on your discoveries. I think this sets a very appropriate and achievable goal, and has more lasting value than some of the "trappings" of science many of us aspire to.

If you were not a scientist, which profession would you pick?

That is a deceptively tough question. During those inevitable nadirs that occur during a career in which the odds are stacked against you, I have asked myself this, and could think of nothing else! So, I would get back up, dust myself off, and try harder. I am also a physician, but early on realized that a predominately investigative career was a better fit, though I enjoy patient contact and still do a limited amount of clinical work in preventive cardiology.

Which direction do you envisage your science taking?

To motivate myself, I always imagine that my best work is still ahead of me. Of course, the trivial possibility is that this is because what I have done so far is rubbish, but I prefer the more positive view—though some of the studies have been terrific and have answered a number of questions, they raise even more important and interesting ones, tantalizing in reach with new insights and technologies. I mentioned some of these questions in each section of the Duff Lecture—the cell biology of VLDL assembly and secretion, the regression of atherosclerosis, and “theranostic” nanoparticles—and I expect they will keep me busy for the foreseeable future.

What are your nonscientific activities?

I am married and have 4 children, 3 of whom are human, the other being a dog. As corny as it sounds, I love being with them—and with the kids grown up—occasions when we get together, like the recent Thanksgiving, are that much more special. The upside of the kids being grown up is that my wife and I get to take more trips together and we really enjoy traveling. In fact, she tells our friends that the reason she married me was that I was a good traveling companion! Other activities—there is the music mania (see below), and whiskies/wine (especially in the company of friends), and walks with a pipe and our dog.

What sports do you follow?

As a Bronx native, I HAD to root for the Yankees when I was growing up. I was not totally faithful, however, and went to the opening day of the first season of the NY Mets, skipping school with my buddies. I was also a rabid Knicks fan as a kid, but it has been a long time since they have been a team to get excited about. Maybe this year (I say this every fall).

Having lived in NY, Boston, Philly, and DC, I adapted by rooting for the local teams in all the major sports, and now I do not get caught up in how any of them are doing during most of the season, but like to watch the playoffs/championships, and if one of them makes it, I root for them. If multiple ones do, then I have a problem.

What are your favorite books, movies, music (pick one or all)?

My dear friend and fellow former editor-in-chief of ATVB, Mark Taubman, and I are music fanatics. We share hard drives with over 8,000 albums on them—consisting of music of every genre, and I mean every. We have influenced each other over the years. For example, Mark had little awareness of jazz and I only knew the "hit" operas, like La Boheme and Traviata. Now he knows...
as much about the jazz greats as I do, and I am a big fan of some of the more obscure operas. Movies: I embarrass my brother-in-law all of the time with my ignorance—he is a Hollywood mogul, and when he introduces me to actors and actresses, I rarely know who they are. But I did love Annie Hall, which is probably a Baby Boomer thing. To this day, if I find it on TV while surfing channels, I always stop to watch. Books: Over the past few years, I have tried to fill-in the classics I never read. My high school teachers would be proud—I have really enjoyed Austen, Flaubert, Balzac, and others. I also read short stories—Raymond Carver, Flannery O’Connor, Alice Munro are a few authors that come to mind. Oh yeah, Agatha Christie, especially the Poirot stories, which were first encountered in the TV versions to which my wife and I became addicted after we lived in England.

What are your favorite foods and are they heart healthy?

I used to believe in knowing your enemy, and just loved eating all sorts of heart unhealthy foods—especially good hot dogs, which were legion in the NY area. When I was asked in 1995 to join the AHA Nutrition Committee, one of their most publically influential ones, given that the dietary guidelines are written by its members, my wife thought this was very funny. In fact, she found a cartoon showing a hot dog vendor in NY with a disclosure sign next to his cart that said, “The fact that you want one of these means you really couldn’t care less about nutrition” and had it framed next to my invitation letter to join the committee. When I decided to get serious about my creeping weight gain a few years ago, I made a number of heart healthy diet modifications. More salads, more fish, rice cakes instead of bread, etc. Even the occasional hot dog I have is 97% fat free. Not only did I pleasantly surprise myself that I had the discipline to make and maintain these changes, other people were impressed—the local AHA affiliate gave me a “Lifestyle Change Award”!
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