Almost all our detailed knowledge about the endothelium is proximate knowledge about its structure, development, and functioning, and how its dysfunctions lead to disease. The other, evolutionary half of endothelial biology has been neglected. Some researchers are unfamiliar with the fundamental distinction between proximate and evolutionary questions, and methods for formulating and testing evolutionary hypotheses about the endothelium remain underappreciated. This chapter offers a brief overview of the distinction between evolutionary and proximate explanations, followed by an introduction to evolutionary medicine and its applications to the endothelium.

Evolutionary, or Darwinian, medicine simply brings the power of evolutionary biology to bear on the problems of medicine. Some areas, such as pathogen evolution and population genetics, are well developed. Another aspect, emphasized in Darwinian medicine, is the enterprise of formulating and testing hypotheses about why natural selection has not shaped bodies that are more resistant to disease. The six key reasons for traits that leave bodies vulnerable to disease are reviewed below. Each is illustrated with examples from general medicine, and then with examples from a major disease of the endothelium, atherosclerosis.

TWO SEPARATE BIOLOGICAL QUESTIONS

Ernst Mayr passed away early in 2005 at age 100, shortly after publishing his twentieth book and the last of his 700+ scientific articles. One of his enduring contributions was his dogged emphasis on the importance of distinguishing proximate from evolutionary (sometimes called ultimate) biological explanations. His treatise, The Growth of Biological Thought, traces these two only-occasionally intersecting threads in biology: one that studies how things work (proximate), the other that studies why organisms are the way they are (evolutionary) (1). His final book, What Makes Biology Unique, continues and updates the theme (2). Over and over again, he makes the point that every biological trait needs both a proximate explanation of its structure and operation, and an evolutionary explanation of why it is the way it is. For example, an explanation of the structure of chlorophyll and how it captures photons and traps their energy in chemical bonds is essential. Equally important, however, is an evolutionary explanation of the biological history of chlorophyll and how its particular form gives a selective advantage. As many will know, the story is intriguing, with the machinery for photosynthesis evolving in one-celled organisms about 3.5 billion years ago, probably in the precursors to cyanobacteria. It has been only about 1 billion years, however, since those organisms were incorporated into the eukaryotic cell as chloroplasts. A complete biological explanation of chlorophyll needs both a proximate description of how chloroplasts work, and an evolutionary explanation of the selection forces and phylogenetic pathways that gave them their current characteristics, instead of others.

The distinction between "how" and "why" questions was developed further by Tinbergen, in a seminal article describing his famous "Four Questions" (3). Here, he divides proximate questions into two subtypes: those about the structure of a trait and those about its ontogeny. He also divides evolutionary questions into those about how a trait gives a selective advantage and those about the phylogeny of a trait. Implicit in this classification is the need to address four separate questions when offering a full biological explanation for any trait. All too often, the four questions are inadequately distinguished or incorrectly taken to be alternatives. Sometimes the evolutionary questions are not taken seriously or are ignored completely.

Much of this situation is understandable because education about these aspects of evolutionary biology often is
limited, even for some biologists. It remains lamentable nonetheless. Biology would progress faster if evolutionary questions about every trait were addressed systematically. In medicine, this is of particular importance. Many physicians have naïve notions about the body, such as the belief that a normal genome exists, or that the body is designed like a machine, or that its flaws result mainly from the limited powers of natural selection. Asking evolutionary questions reveals that the body is a bundle of trade-offs, with no trait perfect, and substantial vulnerabilities persisting not just because selection is too weak, but also for several other reasons.

**DARWINIAN MEDICINE**

In the past decade, rapid progress has been made in using evolutionary principles to understand why bodies are so vulnerable to disease (4–8). The obvious explanation, the limits of natural selection in the face of mutation and drift, is certainly important. However, five additional reasons must be considered in any assessment of why a trait appears suboptimal. Each of these reasons deserves separate consideration for medical conditions in general, and for aspects of the endothelium in particular.

**Novel Environments**

Much, even most, of modern chronic disease arises because we live in environments far different from those our bodies were selected for (see Chapter 16). Paradoxically, our greatest threats now come from our grand success at providing ourselves with all manner of tasty food available with little effort at any time. A third of adults are overweight in many developed countries, and rates of obesity are rising quickly everywhere food is plentiful, giving rise to Syndrome X and all its complications (9). The preferences that shaped our current food supply shape our personal dietary habits. On the African savannah, tendencies to eat fat, sugar, and salt and minimize exercise were generally useful; today, they are fatal (10).

**Infection and Vulnerabilities from “Arms Races”**

A second major reason why natural selection cannot make bodies that defend themselves better from disease is because natural selection is simultaneously making other organisms better able to penetrate defenses (11). Worse yet, the rate of evolution in bacteria and viruses is orders of magnitude faster than is the rate for slowly reproducing organisms such as humans.

**Limits on What Selection Can Do**

This brings us to what selection can and cannot do. Some scientists attribute flaws in the organism mainly to the inevitability of mutations and the slow rate at which selection can purge them from the gene pool. Such mutations and the limited speed of selection are indeed significant factors explaining the body’s imperfections. However, they are by no means the only or the most important factors. Furthermore, their importance often is overrated by those who hold fundamentally mistaken views, such as that the body is a well-designed machine, or that there exists a single normal genotype/phenotype. The body does work like a machine, but its origins were far different from any design shaped with the forethought of an engineer. It is cluttered with remnants of previous features that limit optimality. Consider the path of the recurrent laryngeal nerve, from the brainstem all the way down to just above the lung, where it wraps around the subclavian artery before ascending again to pass behind the thyroid gland on the way to the larynx. The vas deferens makes an equally circuitous path (12). Such “design flaws” exist because the body is profoundly path-dependent: Just like the arrangement of keys on a typewriter keyboard, once structures are in a particular conformation, changing them can be very expensive or impossible. An automobile designer can move the gasoline tank if it proves vulnerable to rupture, but natural selection can never alter the awkward and dangerous path of childbirth through the narrow ring of the pelvis.

**Trade-Offs**

Trade-offs are another source of traits that seem less than perfect. Here the problem is the same as that faced by any human designer. No trait can ever be completely perfect because at some point making one trait better will make others worse. Bones could be thicker, but they would then be heavier and less mobile. Joints could be more flexible, but that would risk damage to muscles. The immune system could be more aggressive but only at the cost of constant tissue damage.

**Selection Maximizes Reproduction, Not Health**

It is a common mistake to think that the body is designed for health, and all disease arises from design flaws. Actually, bodies are products of evolution, not design. They are merely phenotypes that maximize the transmission of genes (13,14). If a gene increases reproductive success, it will spread, even if it causes disease or shortens life. Aging itself may result, in part, from pleiotropic genes that cause aging but that are nonetheless selected for because they give a benefit in youth when selection is strong (15,16). Likewise, much of the increased mortality in males compared to females comes from the reproductive benefits of increased allocation of effort to competition at the expense of tissue repair (17). Increased reproduction at the expense of health does not seem to be an obvious major factor in shaping the endothelium, but men develop atherosclerotic disease more rapidly than do females, almost certainly because sexual selection has resulted in systems that allocate more effort to competition and less to tissue protection and repair in males as compared with females (17,18). In particular, traits that benefit a fetus may be selected for, even if they damage the mother.
Defenses Are Useful Despite Their Costs

Finally, there exist the body’s many protective responses such as pain, fever, vomiting, cough, and inflammation. Although they cause suffering and often bodily damage, they are useful responses, not defects. Their costs are trade-offs for the benefits they offer. It is all too easy to imagine that defenses are problems. For instance, the fever, pain, fatigue, and cough that accompany a cold do not seem to be obviously useful. This “clinician’s illusion” that they are problems is bolstered because blocking them with drugs seems to cause few complications. However, this is only because the body has so many redundant defense systems, and because the systems that regulate defense expression are shaped to express defenses whenever that is worthwhile. If there is any uncertainty in when to express them, this means a normal system will have many false alarms. Many defenses, such as vomiting or panicked flight, are quite inexpensive compared to the huge cost of not responding to a real danger such as intestinal infection or an approaching tiger. The defense should be expressed whenever the average benefit is greater than the average cost, so many false alarms are normal and to be expected. This has been called “The Smoke Detector Principle,” because we tolerate false alarms from burnt toast to ensure that the alarm sounds every single time even a small fire occurs (19). Disrupting defenses is not, however, completely benign; using drugs to block fever, cough, or diarrhea can lead to serious consequences (6).

EVOLUTIONARY ANALYSIS OF ENDOTHELIAL DYSFUNCTION AND ATHEROSCLEROSIS

The healthy endothelium contributes to several processes of obvious adaptive advantage: control of hemostasis, protection of subendothelial structures from circulating blood, local modulation of hemodynamics, and defense against infection. Endothelial dysfunction, broadly defined, can be lethal, as evidenced by von Willebrand disease and endotoxic shock. Subtler endothelial dysfunction is characteristic of early atherosclerosis, an important disease of the developed world. Although we cannot know for certain, it is unlikely that atherosclerosis caused significant morbidity or mortality in the pre-agricultural era, and indeed modern hunter-gatherers are little affected by atherosclerosis (see Chapter 16). However, atherosclerosis is now epidemic in developed societies worldwide, suggesting a near universal predisposition for the disease, with some of the variation in vulnerability arising from genetic differences. Although some common vulnerability factors, such as low levels of high-density lipoprotein (HDL) cholesterol, may result from the accumulation of multiple rare alleles in a specific population, most probably they result from common allelic variants found in all populations (20). The apolipoprotein E story is particularly germane in this regard (21). Common and widely dispersed genetic patterns are of ancient origin, and thus presumably predispose all humans to disease susceptibility when they interact with modern conditions. Indeed, even in recent historical times, transitions from relatively low to high rates of atherosclerosis have been observed to accompany cultural transitions.

At this early juncture, it is important to acknowledge explicitly that we do not propose that “genes for atherosclerosis” exist. Rather, we believe that those suites of genes, shared by most of us, that now exact a net cost were preserved because they have yielded a net benefit over evolutionary time. This may be because dietary changes interact with these genes to impose costs throughout life, or because the benefits during early life are larger for some genes than are their adverse consequences during adulthood (antagonistic pleiotropy). The massive amount of work constituting the bulk of the current volume provides insights about the proximate mechanisms by which atherosclerosis arises and progresses, and we draw heavily on that mechanistic knowledge. Our task is to suggest reasons why natural selection over the past hundred thousand years conserved an essentially universal vulnerability to such an important disease process.

Although early atherosclerosis usually is characterized as “endothelial dysfunction,” and the progression of atherosclerosis as a “response to injury,” close examination of early events shows the endothelium to be functioning in a largely normal manner, at least as regards one of its primary functions — immunity. For most of hominin history, infections have represented grave threats, whether arising from injury, peripartum infection, or endemic pathogens. The nature, although not the risk, of infectious disease changed as settled communities developed (11). Increased population density permitted human-to-human disease transmission, leading to the rise of epidemic disease, and animal domestication led to the emergence of novel zoonoses, especially evident now as avian influenza threats. Innate and acquired immunological functions that eliminate or suppress infections are highly conserved as powerful and often apparently redundant defenses. The evolution of such systems cannot reasonably be attributed to anything other than incremental beneficial genetic changes that improved the reproductive success of those individuals who had them. The endothelium contributes very importantly to immunity, and one of its functions – the controlled transport of intravascular substances and cells to the subendothelial space – seems to predispose us to atherosclerosis. Although this could be interpreted as a simple defect, it appears much more like an adaptation that has benefits that are equal to or greater than its costs in a classic trade-off.

Atherosclerotic lesions begin as low-density lipoprotein (LDL) particles accumulate in the subintimal space (22). The concentration of LDL in the blood is an important determinant of the rate of accumulation, as is the concentration of HDL available for reverse cholesterol transport out of the tissue. However, the trafficking of lipoproteins across the endothelium is not passive. Rather, LDL and HDL cross endothelial cells (ECs) by means of pinocytosis, which allows the delivery of triglycerides and cholesterol for metabolic support, cell growth, and steroidogenesis.
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The macrophage is another key player in atherosclerosis (22,23). Although macrophages normally resident in the subintima can handle some foreign antigens, the local response to tissue infection triggers an elaborate signaling system marshalling a defense reaction that includes the transendothelial migration of large numbers of monocytes and subsequent differentiation into macrophages to engulf bacteria and expose them to lysosomal enzymes. Macrophage phagocytosis and the intracellular lysosomal degradation of bacteria are efficient, but via coevolution, some organisms have derived strategies to frustrate macrophage capabilities. Thus, although bacteria that can be opsonized are cleared efficiently, many bacteria (e.g., Listeria and tuberculosis) have evolved resistance to the constitutive killing mechanisms used by macrophages such that they can survive, even intracellularly. *Chlamydia pneumoniae* may be of particular importance (24).

The process of the development of bacterial resistance is reminiscent of how LDL particles take up residence in the subendothelium, escape macrophage metabolism, and cause disease. Native LDL particles attach to macrophage LDL receptors and are efficiently engulfed and metabolized, just as bacteria are. As part of this normal process, macrophage LDL receptors are down regulated and, in consequence, individual macrophages do not become overloaded with LDL particles. However, under oxidizing conditions, LDL particles are transformed to oxidized LDL particles that are taken up by macrophages via alternative high-capacity scavenger receptors (CD36 and type A scavenger receptor [SR-A]) normally employed for the ingestion of bacteria. These receptors are not down-regulated by the accumulation of oxidized LDL; macrophages continue to accumulate lipoprotein moieties in a relatively unregulated manner, leading to the cellular congestion evident in foam cells (22). Note, however, that during the early stages, both ECs and macrophages are doing what they are well adapted to do: that is, prevent invasion by microscopic threats. It is probably only in our modern environment that these processes are corrupted by excess lipoprotein levels and oxidative stress that leads to disease.

While macrophage functions are being subverted, the endothelium overlying the early atherosclerotic lesion is intact and functional. Indeed, it appears that the normal vessel is able to heal the early effects of subintimal foam cell accumulation. Fetuses show foam cell lesions, termed “fatty streaks,” during early development, particularly in hyperlipidemic mothers in which the fetal blood cholesterol level correlates closely with that of the mother (25). These early fatty streaks appear to regress later in pregnancy either as fetal cholesterol demand decreases or fetal production increases; fetal cholesterol requirements become less dependent on maternal sources, and fetal blood cholesterol concentration is no longer correlated with that of the mother. The initial accumulation probably reflects an example of fetal–maternal conflict: The rapidly developing fetus requires more cholesterol than it can synthesize and is dependent on transplacental delivery, thus creating a potential conflict with the mother who could use these caloric resources for herself or a subsequent offspring. David Haig has pioneered this line of thought (26), as exemplified in his chapter in this volume on such conflicts and their role in preeclampsia (Chapter 17). The consequences of poor fetal lipoprotein access are profound: Cholesterol deficiencies in the mother can cause severe fetal developmental defects, particularly in the lipid-rich brain. Not all the vascular changes in the fetus may be reversible, however, because postnatal atherogenesis may be accelerated in the offspring of hypercholesterolemic mothers who develop hypercholesterolemia themselves (27).

In part, the healing process itself may induce atherosclerosis. Lipoprotein(a) is an LDL-like particle with putative roles in tissue repair and inhibition of fibrinolysis that may also act as a surrogate for vitamin C in animals that have lost the ability to synthesize the vitamin de novo. Lipoprotein(a) is limited to a subgroup of primates (and interestingly appears to have evolved independently in the hedgehog) in which it may have evolved when injuries resulted from trauma and infection. When expressed in a modern milieu, in which endothelial dysfunction is widespread (27), the actions of lipoprotein(a) promote atherosclerosis. In fact, just as for macrophages and the endothelium, lipoprotein(a) is doing what it does best—trying to heal injury.

The aspects of the modern environment predisposing to atherosclerosis in the developed world are well known: dietary excess, sedentary lifestyle, cigarette smoking, air pollution, and diabetes, in addition to the acquired lipoprotein disorders of high LDL and low HDL concentrations. Although it is clear that the nonlipid risk factors can result in endothelial dysfunction, as evidenced by diminution of flow-mediated dilatation or responses to infused acetylcholine, it appears that atherosclerosis develops only in the face of the lipid disorders. The key player is almost certainly LDL — isolated low HDL-cholesterol or high blood pressure in knockout mice without LDL are incapable of causing atherosclerosis; high LDL cholesterol seems to be the *sine qua non* of atherosclerosis. However, native LDL-cholesterol itself does not appear to be sufficient for triggering atherosclerosis; there appears to be a requirement for oxidation. As noted above, LDL oxidation seems to be a key feature of the macrophage’s inability to regulate LDL particle uptake, and oxidation likewise plays an important role in the progression of lesions by stimulating subintimal lipoprotein retention, cytokine elaboration, and the chemoattraction of participating inflammatory cells by macrophages. Oxidized LDL uptake is one of the factors promoting the release of inflammatory mediators. The inflammatory response decreases nitric oxide (NO) production and contributes to “endothelial dysfunction” (by which is meant the vasodilator response to NO-mediated agonists) (28).

Macrophage responses may not be confined to vessels, as recently suggested by observations of macrophage infiltration into adipose tissue, where elaboration of cytokines also occurs. Lerke and Lazar (29) have recently suggested the possibility that fat cells are recognized as invaders by macrophages, triggering responses similar to those causing atherosclerosis. If so, the sequence would add credence to the idea that macrophage
activity and its attendant ill effects on the endothelium are conserved evolutionary responses of broad utility that are rendered harmful by modern environments. Although many aspects of the environment contribute to atherosclerotic, all seem to operate through LDL oxidation which, in a sense, serves to protect LDL particles from intracellular metabolism and, in that way, mimics one of the strategies followed by bacteria.

Returning to the question of why this most useful process has come to cause atherosclerosis, the most obvious factor is the level and kinds of lipids characteristic in contemporary human diets. Hunter-gather and traditional rural societies have serum cholesterol levels far below those of Westernized populations. Indeed, less than 5% of adults in the United States have a total cholesterol of less than 150 mg/dL, the average value in the more biologically “normal” populations (30). Thus, in essence, almost everyone in the United States, and in many other Westernized countries, is hypercholesterolemic, and the situation for triglycerides is similar. Undoubtedly, our societal hyperlipidemias are overwhelmingly due to diet, both its macronutrient composition and its caloric excess, particularly when such a diet is coupled with a sedentary lifestyle. The effect of modern lifestyle is Syndrome X, which in addition to promoting hyperlipidemia also increases oxidative stress, resulting in increased levels of atherogenic oxidized LDL (31).

One way of thinking about atherosclerosis is to view it as the result of an evolved adaptive response that protects against infection but that results in endothelial injury in modern environments. Because the consequences of the injury occur late in life, natural selection preserves those systems promoting atherosclerosis in preference to those suppressing them, a classic case of antagonistic pleiotropy. This is a trade-off, but not quite a classic one. Because the costs were probably minimal until the past century, and because they caused no harm until modern times, the genetic variations that increase vulnerability to atherosclerosis are not really “defects,” but are instead excellent examples of “genetic quirks” that give rise to unward effects only when they interact with factors encountered in modern environments. These speculations about the adaptive roots of atherosclerosis give rise to a specific prediction that individuals who have a genetic predisposition to atherosclerosis may be less vulnerable to infection and more susceptible to other inflammatory diseases. In regards to the question of autoimmune diseases, data demonstrate a strong association between rheumatoid arthritis and accelerated atherosclerosis (32), although the authors of that article suggest that the chronic low-grade inflammation of arthritis activates the atherosclerotic process rather than vice versa. In truth, the relationship may be bidirectional, with each process reinforcing the other.

The adaptive significance of the systems that leave us vulnerable to atherosclerosis is only one half of a full evolutionary explanation. We also need to know the phylogeny of those systems, and particularly if path dependence has constrained them so that natural selection cannot shape a less vulnerable mechanism. Although it would conceivably be possible to develop alternative ways of preserving the functions of lipoproteins necessary for blood-borne triglyceride and cholesterol delivery while preventing excessive pinocytic delivery to subendothelial spaces, such an adaptation would probably seriously compromise cholesterol-dependent cellular and immune processes. Because immune function has such obvious selective value – whereas atherosclerotic disease, primarily manifest late in life, presumably is not a major selection force – there would seem to be little tendency to shape such an adaptation. However, too much of a good thing is dangerous, as illustrated by chronic inflammatory diseases such as rheumatoid arthritis accelerating atherosclerosis. Conversely, in situations in which innate immunity is compromised (e.g., by inactivating mutations of the Toll-like receptor 4 (TLR4) receptor, a pattern recognition receptor involved in lipopolysaccharide clearance), atherosclerosis is decreased (33). Thus, in the trade-off of immune function versus atherosclerosis, the benefits of immunity provide greater advantages early in life when selection is stronger, thus leaving us with a strong predisposition to atherosclerosis. A signal detection analysis of the costs and benefits of various regulatory settings could further illuminate the situation (19).

Are other evolutionary factors at work? A direct infectious hypothesis has been championed by Ewald, who contends that atherosclerosis is triggered by infections that have coevolved with humans (24). Of particular interest has been the relationship of Chlamydia pneumoniae, an organism capable of living inside inflammatory cells in blood vessel walls. Ewald suggests that the bacterial infection, rather than being a bystander colonizing a disrupted vascular wall, is pathogenic. He further notes that in the case of inflammatory arthritis, a higher incidence of joint-fluid C. pneumoniae infections are associated with a higher prevalence of the apolipoprotein e4 genotype. Because this is a risk factor for coronary disease, it is possible the mechanism mediating risk is an increased susceptibility to C. pneumoniae infection and vascular inflammation. Clearly, if true, the early lesions could attract macrophages, increase local oxidative activity and, in the presence of LDL particles, trigger atherosclerosis. An attempt at testing this hypothesis by treating patients with established atherosclerosis with antibiotics was negative (34), but it is still plausible to assume that the role of the bacterium is prominent in the early disease but not after atherosclerosis has progressed.

C. pneumoniae is not the only infection thought to accelerate atherosclerosis: Many chronic subclinical infections, including periodontitis, sinusitis, bronchitis, and diverticulitis – in fact any source of chronic endotoxemia – may provoke an inflammatory response and increase the risk of atherosclerosis (35). The other major player in the atherosclerotic picture, HDL, may be a defense against atherosclerosis-promoting infectious agents by acting as a scavenger of lipopolysaccharide (36).

CONCLUSION

The implications of an evolutionary view of the endothelium are several. First and most obviously, in the absence of
profound changes in the environment or human nature, it is unlikely that atherosclerosis can be prevented in the general population through the public health measures known to be effective – diet and exercise – although they can be effective for those individuals capable of modifying their behavior (37). The burgeoning epidemic of obesity suggests that the lifestyle causing hyperlipidemia is triumphing to the extent that reducing cholesterol values to those of hunter-gatherers by lifestyle interventions is simply unrealistic. As a society, we seem to be much more willing, even eager, to embrace antiatherosclerotic strategies that depend on the administration of costly drugs to already-ill individuals nearing the end of the natural history of atherosclerotic diseases. Given current costs, inequalities in health care delivery, and the poor public health infrastructure, such treatments, unfortunately, cannot reasonably be provided for population-wide treatment and, in any case, they are not that effective. More promising preventive approaches include modifications like statins and antioxidants, although one line of argument developed above suggests the need to be on guard for the possibility that antioxidants may increase other vulnerabilities. Epidemiological evidence supporting the benefits of dietary antioxidants is encouraging, although the effectiveness of antioxidants in intervention trials has been disappointing (23). Trials in established atherosclerosis may, however, be a case of too little, too late, as atherogenesis is already well advanced, perhaps beyond the period in which antioxidants could be effective. What is clear is that only with the development of effective preventive approaches that can be widely applied will any progress be made in preventing the complications of atherosclerosis.

One potentially beneficial feature of modern society is found in Barker’s hypothesis, which implies that improved maternal nutrition may decrease the development of features described as the “thrifty phenotype” – a set of metabolic adjustments programmed to promote calorie retention but which increase the risk of late-life atherosclerosis (38,39). Unfortunately, to realize the benefits of improved maternal nutrition, the environment of the offspring throughout life would have to promote avoidance of calories and fat excess, which again seems impracticable.

Genetic engineering has been held out as a possible cure for atherosclerosis. We believe the evidence is overwhelmingly that only a small min the focus on “gene hunting” for atherosclerosis should therefore be on finding common allelic variants or haplotypes controlling “normal” homeostatic functions. This is not to say that elucidation of monogenic diseases will not lead to a better understanding of the vulnerabilities of atherosclerotic disease progression, just as a molecular understanding of the LDL receptor in familial hypercholesterolemia contributed so importantly to the development of drugs useful in preventing further progression of atherosclerosis. The identification of the Milano Apo A1 mutation (40), which exerts a powerful protective effect against atherosclerosis by markedly enhancing reverse cholesterol transport and presumably acting to heal the early atherosclerotic lesions before the sequence of reinforcing mechanisms is recruited, may be another example of how a monogenic disease can inform the development of prevention strategies.

Just as genetic determinants are likely to be “normal” alleles, normal immune processes predispose to atherogenesis. Could atherosclerosis be prevented by the selective modulation of immune function, specifically the physiological functions of macrophages involved in atherogenesis? Similarly, perhaps endothelial transport of LDL molecules can be targeted. The endothelium has its own protective mechanisms against the transport of larger lipoproteins such as very-low-density lipoprotein (VLDL). Perhaps a “vaccination” that slowed LDL-cholesterol transport could have promise for slowing atherosclerosis. Ceruloplasmin is a potential source of oxidized LDL (41); perhaps the copper-depleting drug developed for the treatment of Wilson’s disease of the liver, trientine, could possibly have an antiatherosclerotic effect. Such speculations demonstrate the heuristic value of an evolutionary perspective on the endothelium. We anticipate that readers of this volume will bring a mass of sophisticated knowledge about the proximate mechanism involved in endothelial diseases. We hope that this chapter will encourage some of them to ask new evolutionary questions about why the endothelium is the way it is, and why it leaves us so vulnerable to such common and devastating diseases. If they do, progress in endothelial biomedicine will occur even faster.

KEY POINTS

- Posing and testing evolutionary hypotheses about characteristics of the endothelium will speed scientific progress.
- Every aspect of the endothelium needs both a proximate and an evolutionary explanation.
- The same design features that lead to vulnerability to atherosclerosis offer other substantial benefits.
- Few genes that predispose to endothelial disease are defects; most are quirks that pose risks only in the modern environment.

Future Goals

- To describe every aspect of the endothelium in relation to an evolutionary explanation
- To describe every disease of the endothelium in relation to an evolutionary explanation that encompasses the six reasons for vulnerability

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