Atherosclerosis☆

A *Longue Durée* Approach

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Fernand Braudel popularized the *longue durée* approach to scholarly investigation in the mid-20th century. The *longue durée* approach can be loosely translated to mean "look for the big picture, synthesize data collected using all available methodology over the long periods of time to identify fundamental principles, rather than becoming preoccupied with isolated observations." Braudel, a historian and economist, emphasized observation of enduring historical structures and analysis of long-term, panoramic economic trends rather than concentrating on detailed descriptions of particular events or individuals. He also urged the use of insight gained from many scholarly disciplines to identify the essential underpinnings of social change [1].

Braudel's *longue durée* approach may also be useful in the study atherosclerosis, which is among the most important diseases affecting mankind. Cardiologists' immediate attention is understandably focused on dealing with individual patients and the current epidemic of atherosclerotic heart disease, concentrating on applying the latest scientific advances in diagnosis and treatment. A broader "big picture" view of atherosclerosis includes observations made throughout the lifetime of an individual, as the disease evolves from a subclinical state to acute manifestations such as chest pain, myocardial infarction, stroke, and sudden death. Insight may also be gained by studying atherosclerosis in populations as well as in individuals, and over the entire span of human existence, not just in contemporary society, looking at the effects of widely varying environmental, cultural, and societal conditions and evolving genomes. We can also learn from studying atherosclerosis in creatures other than *Homo sapiens*.

Like Braudel, physicians and biologists benefit from observations made using analytic methods of many disparate disciplines other than their own, including anthropology, archeology, and the physical as well as biologic sciences. A broad view is needed to better understand many of the key features of atherosclerosis that may not be apparent looking only at the patient immediately in front of us. Indeed, if we are to counter the current global epidemic of atherosclerosis, we need not only a knowledge of medicine—an understanding of the genomic, pathophysiologic, pharmacologic, and nutritional aspects of atherosclerosis—but also knowledge of the sociologic, economic, and cultural underpinning of the rapid changes now occurring in developing countries of the world, where communicable diseases are being replaced by heart disease and cancer as leading causes of death and disability.

PATHOLOGIC OBSERVATIONS OF ATHEROSCLEROSIS

The protean pathophysiologic manifestations and extent of atherosclerosis increase with advancing age [2—9]; they begin early in life, and complications and clinical manifestations occur later. Lobstein introduced the term "arteriosclerosis" in the early 19th century on the basis of autopsy observation of gross pathologic anatomy. His observations were expanded by the renowned pathologists Virchow and von Rokitansky, who used similar detailed microscopic analysis of postmortem specimens to come to diametrically opposing views of the genesis of atherosclerosis. Virchow held that cellular inflammatory changes observed in the atherosclerotic vessel walls was of primary importance, whereas von Rokitansky considered them secondary to humoral disease.

Using 21st century histologic techniques, Mayerl et al. [10] found immunohistochemical and immunofluorescent evidence of inflammation on several of von Rokitansky's original pathologic specimens, supporting Virchow's belief that inflammatory processes underlie the formation of atherosclerosis, demonstrating that different conclusions may be drawn by re-examining old data using new techniques, again demonstrating the value of a *longue durée* approach. In another analogy to historical methodology, Leopold von Ranke fostered the concept of source-based history *(wie es eigentlich gewesen ist)*, re-examining and reinterpreting original historical documents rather than accepting the translations of others [11]. These expanded histologic observations of inflammation in historic pathologic specimens are further supported by the use of newer measures of inflammation, C-reactive protein, interleukin-6, tumor necrosis factor, and other circulating markers [12].

Pathologists [13,14] have created a robust literature describing various anatomic features ascribed to atherosclerosis, including the use of terms such as: intimal

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sclerosis; atheroma; Monckeberg medial sclerosis; focal atherosclerosis; atherothrombosis; lipid-laden; fibrotic and ruptured plaques; and plaques that appear to be vulnerable to future rupture, platelet aggregations, and acute thrombosis. Considerable evidence has accumulated to support Virchow's assertion that inflammation plays a key role in the development of atherosclerosis [12]. Pathology was among the earliest medical sciences and continues to provide key insights, but a precise definition of atherosclerosis and clarification of its fundamental and proximate causes and ultimate consequences for the whole, living individual must include physiologic, biochemical, subcellular, and genomic tools [14].

BEYOND GROSS ANATOMY AND HISTOLOGY

Spectacular advances [15–17] in medical imaging over the past 3 decades provide considerable insight into the pathophysiology of atherosclerosis, acute coronary syndromes, and other clinical consequences of atherosclerosis. Catheter-based intravascular ultrasound and optical coherence tomography and noninvasive approaches using magnetic resonance imaging, computed x-ray tomography, and nuclear imaging are all proving useful not only in defining basic biologic processes, but also aiding in the development of new and more-effective treatments.

Evolving definitions of atherosclerosis should remind us that methodological advances and increasing knowledge of basic pathophysiologic mechanisms have long fostered confusion and controversy over a precise definition of many diseases, including atherosclerosis. A *longue durée* approach to understanding atherosclerosis accounts for changes in technology, perspective, and even the language and culture of investigators and observers, which naturally vary over time, as well as changes in the subjects and the disease process itself. The *longue durée* approach teaches us that our observations of a phenomenon may change as our power of observation changes, and we must be careful not to confuse these different descriptions with real changes in the phenomenon being observed.

ATHEROSCLEROSIS OCCURS EARLY IN LIFE AND EARLY IN HUMAN HISTORY

Atherosclerosis not only starts early in life [2,3], even during the prenatal period [18], but it has also been part of the human condition for many thousands of years [4–6,19–23]. Fatty atherosclerotic streaks have been observed during post-mortem examinations of young children [2,3], and in far more-advanced forms in young adults dying of trauma. Atherosclerosis was present in 77% of soldiers dying from trauma in the Korean War [7], 45% in the Vietnam War [8], and 8.5% in the Iraq War [9]. This decline tempts us to give credit to our modern public health campaigns for reducing disease burden by encouraging healthy behavioral changes in smoking, dietary, and exercise habits.

But a careful analysis of the different methods used in these studies, conducted during a period of rapid change in medical technology, suggests that the definition of atherosclerosis was not the same in these 3 groups of young military personnel dying of war-related causes, and a raw comparison of the incidence of atherosclerosis in the 3 groups is misleading. For instance, the Vietnam study employed angiography of perfusion-fixed coronary arteries to diagnose atherosclerosis, whereas the Korean and Iraq studies relied on direct visualization of atherosclerotic plaques in the coronary arteries. The Korean study also defined microscopic evidence of arterial fibrous thickening as well as fatty streaking as evidence of atherosclerosis. In this context, it is not surprising that few young, active combat soldiers had angiographically apparent stenosis of their coronary arteries, while they may well have had early atherosclerotic lesions that did not impinge on the lumen of the coronary artery. Both Braudel and von Ranke remind us to look at our data critically over time.

With our focus on these and other scientific breakthroughs, superimposed on our current frightening epidemic of obesity and diabetes, we often think of atherosclerosis as a modern disease, caused by dietary excess, physical inactivity, and tobacco smoking. However, in 1852, pathologist Johann Czermak [19] found evidence of calcific aortic atherosclerosis during the autopsy of the mummified ancient remains of an Egyptian woman. In 1909, Samuel Shattock [20] found atherosclerosis in the aorta of the Pharaoh Menephtah, believed to have been the pharaoh referred to in Exodus, and in 1911, Sir Marc Armond Ruffer [21] published histologic evidence of atherosclerosis in multiple 3,000-year-old Egyptian mummies. A. T. Sandison [24] subsequently demonstrated the presence of atherosclerosis in arteries throughout the body in Egyptian mummies. More recently, Michael Zimmerman [22] demonstrated atherosclerosis in naturally frozen mummies found in Alaska. Zimmerman's findings are particularly notable, as the cultures in which these ancient humans lived did not practice agriculture, but were hunter-gatherer-fisher people. Because of the destructive nature of the process, relatively few autopsies have been performed on ancient mummies.

Advances in medical imaging technology now allow us to perform noninvasive, nondestructive "autopsies" in living humans as well as long-dead mummies. X-ray computed tomography (CT), which is exquisitely sensitive in detecting calcified deposits within atherosclerotic plaque [7], is particularly well suited to providing epidemiologic insight into both current and ancient populations. The presence and degree of calcification of the coronary arteries as measured by CT has been shown in large contemporary, multiethnic population studies to be closely correlated with future coronary events [25]. We, and others [4–6,23,24] have used CT technology to detect evidence of atherosclerosis in ancient human mummies from Egypt, Peru, the Americas, the Aleutian Islands, and Europe.

Although it is clear that atherosclerosis has been in human populations for thousands of years, progressing

slowly from infancy to adulthood, this evidence is largely related to observations of subclinical, asymptomatic disease. It was not until the 20th century that James Herrick [26] recognized the relationship between obstruction of the epicardial coronary arteries and acute myocardial infarction. Pre-dating Herrick's insightful observations, many clinical descriptions have been made of what were surely symptoms of angina pectoris and acute myocardial infarction, dating at least to 1555 BCE, when a scribe entered the following vignette on what eventually came to be known as the Ebers' medical papyri [27]: "If thou examist a man for illness in his cardia, and he has pains in his arms, in his breasts and on one side of his cardia … it is death threatening him."

These observations in a relatively large number of ancient humans alive over 4,000 years of human history and living in a variety of cultures, including pre-agricultural hunter-forager societies, raise serious questions about conventional attribution of the risk of developing atherosclerosis to diet and environment. Albert Zink and his colleagues [23,28] made additional advances in our understanding of human atherosclerosis by not only demonstrating CT evidence of calcific atherosclerosis in the mummified remains of the 5,300-year-old "Iceman," but also showing that he had several single nucleotide polymorphisms known to predispose to atherosclerosis in contemporary humans. From the *longue durée* perspective, our current epidemic of atherosclerosis may be but a blip on the evolutionary calendar. The relationship between basic evolutionary biology and medicine deserves more attention [29].

MODERN DAY HUNTER-GATHERERS

Studies of the few remaining contemporary hunter-gatherer populations may provide valuable insight into how our prehistoric human ancestors lived and the kinds of diseases including atherosclerosis that they may have developed under far different environmental influences than are present today. Contemporary residents of the remote island of Kitava in Papua New Guinea [30] and the Tsimane [31] people living in the Bolivian Amazon basin have been carefully studied. Their diet is thought to be similar to what Stone Age men ate 500,000 years ago, consisting largely of nuts, berries, vegetables, eggs, insects, fish, and wild meat, but no sugar, dairy, or refined fat [32]. These people are remarkably free of clinical cardiovascular disease, as defined by clinical history of heart attack or stroke, abnormal blood pressure, reduced peripheral arterial pulses, abnormal electrocardiogram or elevated cholesterol [30,31]. More sophisticated modern imaging methods have not been employed to detect subclinical atherosclerosis in these very remote communities.

It is tempting to extrapolate observations in these hunter-gatherer societies, which may emulate Paleolithic conditions to contemporary society, to help us combat the epidemic of obesity, diabetes, hyperlipidemia, hypertension, and atherosclerosis, but many confounding variables must be accounted for. For instance, many lines of evidence suggest that inflammation and the presence of an increased inflammatory burden or heightened inflammatory response can predispose to the development of atherosclerosis [33—35]. Despite the infrequency of heart attack and stroke, hunter-gatherer people have an extremely high inflammatory burden. Infection, trauma, childbirth, and starvation often lead to death in hunter-gatherer populations in the first decades of life. Even though survivors may have lived into old age, long enough to develop clinical manifestations of atherosclerosis, we need further studies to better understand the relation between diet, exercise, inflammation, and heredity on the development of atherosclerosis.

EARLY HOMINIDS AND BEYOND, TO THE ORIGINS OF LIFE

Homo sapiens are thought to have emerged as a new species about 200,000 years ago, but preservation of sufficient soft tissue in mummified human remains is unlikely to extend much beyond the age of the Iceman, who was frozen into an Alpine glacier approximately 5,300 years ago [23,28]. However, deoxyribonucleic acid (DNA) from fossilized Neanderthals, whose species diverged from humans approximately 500,000 years ago, has been sequenced [36]. Spontaneous atherosclerosis occurs in many species besides humans, including wild animals such as buffalo, hippopotamus, cows, and non-human primates, both vegetarians and meat eaters [37,38]. Fuster et al. [39] made seminal observations in pigs regarding the critical interaction between platelets and the arterial wall in the development of atherosclerosis, noting that pigs with inherited von Willebrand disease had less intimal proliferation and much smaller atherosclerotic plaques than did pigs with normal platelets. These observations underlie much of our modern understanding of the pathophysiology of acute coronary syndromes, including myocardial infarction, the end stage of an atherosclerotic process that may have been underway in a given individual for decades prior. Even nonmammals such as birds [40], which are phylogenetically related to dinosaurs, can develop atherosclerosis, perhaps dating the earliest genetic origins of atherosclerosis to the Mesozoic era, 252 to 66 million years ago. It is humbling to be reminded that we humans are wedged developmentally together with nonhumans, closer to pigs than chickens perhaps, in the *longue durée* picture of the evolution of atherosclerosis.

Humans may always have had the genetic propensity to develop atherosclerosis, with environmental influences determining final phenotypic expression. The recently acquired ability to sequence the entire human genome is having profound influence on our investigations of human diseases, including atherosclerosis. Unlike many of the hereditary cardiomyopathies and dysrhythmias, which are single-gene disorders, genetic predisposition to atherosclerosis is due to multiple common genes, widely distributed in the entire population, each genetic

polymorphism having limited effect on the final phenotype [41,42]. Genome-wide association studies have identified more than 40 genetic risk variants associated with coronary artery disease, but 10 of these variants occur in more than 75% of the population, and the risk effect of each variant is relatively small, averaging an increased incidence of disease of about 18% [43]. The nature of how these common genetic polymorphisms interact with the environment to produce atherosclerosis and clinical coronary artery disease remains unexplained, but is the subject of intense investigation. Most of the known genetic risk factors for atherosclerosis are linked by network analysis to lipid metabolism and inflammation. The role of bacterial or viral infections, particularly in the pre-antibiotic era, are uncertain.

Part of the answer may lie beyond the cell nucleus and nuclear DNA. Mitochondrial DNA, located in the cytoplasm, consists of only approximately 16,000 base pairs and encodes only a few proteins, but it does control adenosine triphosphate and reactive oxygen species (ROS) production, thus having a strong impact on cell proliferation. The mitochondrial adenosine triphosphatase inhibitory factor 1 triggers a ROS-mediated retrograde prosurvival and proliferative response [44] and innate immunity [29] affecting atherosclerosis. Mitochondrial DNA, which is transmitted through female oocytes, has a much higher mutation rate than nuclear DNA does and may provide a more plausible explanation for the relatively rapid changes apparent in the genetic regulation of atherosclerotic processes [45]. Mitochondria regulate the essential flow of energy through the cell, generating adenosine triphosphate and acetyl-coenzyme A, which together with histone phosphorylation and acetylation, modulate nuclear gene expression.

Perhaps a billion and a half years ago, mitochondria evolved from aerobic bacteria, which colonized primordial eukaryotic cells, enabling them to use oxygen to produce energy more efficiently than with anaerobic glycolysis. The influence of mitochondrial DNA occurs early in the atherosclerotic process, leading to impaired bioenergetics, promoting atherosclerosis and hypercholesterolemia through changes in cell proliferation and apoptosis [46], leading ultimately to unstable atherosclerotic plaques that are perhaps vulnerable to rapid progression to occlude the vessel lumen. These epigenetic processes are also under intense investigation. Atherosclerosis is a complex disease. The evolving fields of transcriptomics, proteomics, and metabolomics will enable us to unravel features of the human genome and better understand its pathogenesis of atherosclerosis and perhaps identify new targets for treatment [47].

AN EXPLOSION OF DATA

Relating the vast quantities of genomic data being generated using next-generation sequencing to daily clinical practice presents enormous challenges in medical informatics. Here again, medical scientists may benefit from the experience of colleagues in social science who use the tool of prosopography to investigate common characteristics of a historical group, even members of pre-modern societies without written records, to create a collective biography by analyzing statistically relevant archeological and anthropological data [48]. At some level, this process seems remarkably similar to the sophisticated bioinformatics processes being used to decipher the human genome. If we can recreate a vision of man before writing was invented, perhaps we can decipher the 5 billion gigabytes of information now being created in modern society every 10 min to reduce the impact of atherosclerosis on humans today [42].

Contemplating the enormity of the information and knowledge about the stuff of life that has accumulated in the last 10 years, following the billion years since the first bacteria entered a eukaryotic cell, it is difficult not to agree with Francis Collins [49], a pioneer of the Human Genome Project and director of the National Institutes of Health, who said: "Scientists aren't generally prone to effusiveness. We are privately excited about our work, but in public we often, and rightly, emphasize skepticism and caution. But there are exceptional moments where skepticism is set aside, electricity fills the room, and a scientist with palpable passion and flashing eyes describes unabashedly a change in the landscape that will have lasting significance. Just a few months into the new millennium, I had that experience."

PERSPECTIVE—THE *LONGUE DURÉE* APPROACH

Braudel might suggest that we reserve judgment on the impact of the genomic and bioinformatics revolution on the management of our patients with atherosclerosis until we have had time to digest the flood of new information. Randomized controlled trials, registries, guidelines, and appropriate use criteria [50], all late 20th century inventions, are essential pieces of the increasingly complex puzzle of atherosclerosis. A tremendous amount of work remains to be done to extract actionable components and translate them for human use before we head into the examining room to treat individual patients. Sequencing the entire human genome surely will go down as a landmark of the 21st century, as did Watson and Crick's demonstration of the structure of DNA in the 20th century and Darwin's and Mendel's observations of genetics in the 19th century, but, in the big picture, the impact of these advances on mankind is just beginning [51]. It is an exciting beginning.

Atherosclerosis is not a recent phenomenon in human history, nor is it exclusive to *Homo sapiens*. Indeed, the genetic and biologic capacity for developing atherosclerosis may involve processes that date to the very origins of life. In the course of 250,000 years of human existence, our changing relationship with our environment has led us to evolve, both our genotypes and our phenotypes. Change was relatively slow during the Paleolithic and early Agrarian eras, but has progressed exponentially in the Modern era. It is estimated that there were fewer than 250 million humans on Earth 1,000 years ago. We now number more than 6 billion.

As we have progressed from living in subsistence communities of hunter-forager-farmers to living as consumer

societies in cities with many millions of inhabitants, fewer of us are dying from starvation, from infections or trauma, or during childbirth. "Prosperity" is spreading rapidly from the developed to the developing world, bringing with it an aging population afflicted with obesity, diabetes, hyperlipidemia, hypertension, and nicotine addiction—all precursors or accelerators of atherosclerosis. We humans will need to use all our combined creative genius to contend with our new environment, some of which we created ourselves, if we are to survive as a species for another 250,000 years.

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