Chapman University

Chapman University Digital Commons

7-30-2014

Why Did Ancient People Have Atherosclerosis?: From Autopsies to Computed Tomography to Potential Causes

Gregory S. Thomas
Long Beach Memorial

L. Samuel Wann
Columbia St. Mary's Healthcare, Milwaukee

Adel H. Allam
Al-Azhar University, Egypt

Randall C. Thompson
University of Missouri - Kansas City

David E. Michalik
University of California, Irvine

See next page for additional authors

Follow this and additional works at: https://digitalcommons.chapman.edu/esi_pubs

Part of the Biological and Physical Anthropology Commons, Economic Theory Commons, Ethnic Studies Commons, Latin American Studies Commons, Other Anthropology Commons, Other Economics Commons, and the Social and Cultural Anthropology Commons

Recommended Citation

Authors

Gregory S. Thomas, L. Samuel Wann, Adel H. Allam, Randall C. Thompson, David E. Michalik, M. Linda Sutherland, James D. Sutherland, Guido P. Lombardi, Lucia Watson, Samantha L. Cox, Clide M. Valladolid, Gomaa Abd el-Maksoud, Muhammad Al-Tohamy Soliman, Ibrahem Badr, Abd el-Halim Nur el-din, Emily M. Clarke, Ian G. Thomas, Michael I. Miyamoto, Hillard Kaplan, Bruno Frohlich, Jagat Narula, Alexandre F. R. Stewart, Albert Zink, and Caleb E. Finch

Why Did Ancient People Have Atherosclerosis?☆

From Autopsies to Computed Tomography to Potential Causes

Gregory S. Thomas*,†, L. Samuel Wann‡, Adel H. Allam§, Randall C. Thompson‖, David E. Michalik¶,
M. Linda Sutherland#, James D. Sutherland**, Guido P. Lombardi††, Lucia Watson‡‡, Samantha L. Cox§§,‖‖,
Clide M. Valladolid¶¶, Gomaa Abd el-Maksoud##, Muhammad Al-Tohamy Soliman***, Ibrahem Badr†††,
Abd el-Halim Nur el-din‡‡‡, Emily M. Clarke§§§, Ian G. Thomas‖‖‖, Michael I. Miyamoto¶¶¶,
Hillard S. Kaplan###, Bruno Frohlich****, Jagat Narula††††, Alexandre F. R. Stewart‡‡‡‡, Albert Zink§§§§,
Caleb E. Finch‖‖‖‖‖

*Long Beach, CA, USA; Irvine, CA, USA; Milwaukee, WI, USA; Cairo, Egypt; Kansas City, MO, USA; Newport
Beach, CA, USA; Laguna Hills, CA, USA; Lima, Peru; Mexico City, Mexico; Cambridge, United Kingdom;
Philadelphia, PA, USA; Giza, Egypt; Alexandria, Egypt; 6th of October City, Egypt; Los Angeles, CA, USA;
Middlebury, VT, USA; Mission Viejo, CA, USA; Albuquerque, NM, USA; Washington, DC, USA; New York, NY,
USA; Ottawa, Ontario, Canada; and Bolzano/Bozen, Italy*

ABSTRACT

Computed tomographic findings of atherosclerosis in the ancient cultures of Egypt, Peru, the American
Southwest and the Aleutian Islands challenge our understanding of the fundamental causes of atherosclerosis.
Could these findings be true? Is so, what traditional risk factors might be present in these cultures that could
explain this apparent paradox? The recent computed tomographic findings are consistent with multiple
autopsy studies dating as far back as 1852 that demonstrate calcific atherosclerosis in ancient Egyptians and
Peruvians. A nontraditional cause of atherosclerosis that could explain this burden of atherosclerosis is the
microbial and parasitic inflammatory burden likely to be present in ancient cultures inherently lacking
modern hygiene and antimicrobials. Patients with chronic systemic inflammatory diseases of today, including
systemic lupus erythematosus, rheumatoid arthritis, and human immunodeficiency virus infection,
experience premature atherosclerosis and coronary events. Might the chronic inflammatory load of ancient
times secondary to infection have resulted in atherosclerosis? Smoke inhalation from the use of open fires for
daily cooking and illumination represents another potential cause. Undiscovered risk factors could also have
been present, potential causes that technologically cannot currently be measured in our serum or other tissue.
A synthesis of these findings suggests that a gene-environmental interplay is causal for atherosclerosis. That is,
humans have an inherent genetic susceptibility to atherosclerosis, whereas the speed and severity of its
development are secondary to known and potentially unknown environmental factors.

Steeped in the importance of modern lifestyles as causal in the development of atherosclerosis, most physicians are surprised when confronted with studies demonstrating that ancient people also had atherosclerosis. This new information does not easily fit into our understanding of its pathogenesis. When reading a new manuscript in a journal, we want to determine if the new information changes our ideas about a disease. Shall we behave or think differently? This is more easily accomplished if the new information builds on our current understanding of disease pathophysiology, diagnosis, or treatment. However, if it challenges the foundation of our understanding of the disease, the new information is much more challenging to process.

Such is case when physicians are faced with studies demonstrating atherosclerosis in ancient Egyptians, Peruvians, and Native Americans [1–4]. How do physicians and scientists square this with their understanding of atherosclerosis' causes? We reach for traditional risk factors: the diets of these ancient people must have been rich; they were inactive; they must have had a harmful lifestyle in some way. But what if none of these were the case?

The Horus Team's discoveries challenge our current understanding of the causes of atherosclerosis. A review of past studies, however, demonstrates that while we have extended previous work, we have indeed built on the foundations of past investigators. Following this initial review, we will examine how we can integrate this new information and explore potential causes of atherosclerosis in ancient peoples.

AUTOPSY STUDIES

In one of the earliest published autopsies in which a light microscope was used, physiologist Johann Nepomuk Czermak (Fig. 1A) described the autopsy findings of 2 ancient Egyptian mummies curated by the Physiologic Institute of

§§§University of California—Los Angeles, Los Angeles, CA, USA; ||||||Middlebury College, Middlebury, VT, USA; ¶¶¶Mission Heritage Medical Group, St. Joseph Heritage Health, Mission Viejo, CA, USA; ###Department of Anthropology, University of New Mexico, Albuquerque, NM, USA; ****National Museum of Natural History, Smithsonian Institution, Washington, DC, USA; ††††Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; ‡‡‡‡John and Jennifer Ruddy Canadian Cardiovascular Genetics Centre, University of Ottawa Heart Institute, Ottawa, Ontario, Canada; §§§§Institute for Mummies and the Iceman, European Academy of Bolzano/Bozen (EURAC), Bolzano/Bozen, Italy; and the ||||||||Davis School of Gerontology, University of Southern California, Los Angeles, CA, USA. Correspondence: G. S. Thomas (gthomas1@memorialcare.org).

Prague [5]. He described 1 mummy as a poorly preserved youth with few organs available for study. The second mummy, however, was a better preserved adult woman. Though her heart and lungs had been removed, her entire aortic arch was present and could be evaluated. Microscopic evaluation demonstrated that the anterior wall of the descending thoracic aorta contained "multiple considerably large and calcified plaques." Czermak was not only a pioneer in the then un-named field of paleopathology, he and neurologist Ludwig Tuerck later spearheaded the introduction of the laryngoscope into medicine [6,7].

With permission from Gaston Maspero, director of the Egyptian Museum and Antiquities Service, Cairo University, anatomy professor Grafton Elliot Smith (Fig. 1B) "unrolled" the mummy of the Pharaoh Menephtah on July 8, 1907, in the Cairo Museum [8]. Menephtah, the 13th son and successor of Ramses II (Ramses the Great) ruled Egypt from 1213 to 1203 BCE. "Unrolling" of the linen wrappings of a mummy by this time had become a euphemism for unwrapping a mummy and performing a gross autopsy. Wrapped in fine linen, the well-preserved Menephtah was bald, and what little hair he had was white [8]. Upon gross examination of the aorta, Smith described it as "affected with severe atheromatous disease, large calcified patches being distinctly visible" [9]. In another rendition, he commented, "the aorta was in an extreme stage of calcareous degeneration, large bone-like patches standing out prominently from the walls of the vessel" [8].

Smith sent 3 cm of the mummified aorta for further examination to Samuel George Shattock, curator of the Pathologic Section of the Royal College of Surgeons' Museum in London. Publishing in the *Proceedings of the Royal Society of Medicine*, Shattock confirmed the microscopic presence of calcific atherosclerosis, which was up to 6 mm in length [9].

The mummified remains of Pharaoh Menephtah are curated in the Royal Mummy Room of the Cairo Museum, now called the Egyptian National Museum of Antiquities. His nameplate declares that he had suffered from arteriosclerosis. This provocative description stimulated the development of a team in February 2008, eventually named Horus, which sought to determine if the nameplate was indeed correct [10]. Not being aware of Smith's [8] and Shattock's [9] work from a century ago, we were skeptical.

While Smith was performing gross autopsies of often royal mummies housed at the Cairo Museum, Marc Armand Ruffer (Fig. 1C) was supplied mummy parts and a few intact mummies from the archeological expeditions of Smith, Flinders Petrie, Douglas Deary, Henry Keatinge, and Gaston Maspero [11]. The dam at Aswan was soon to be elevated and the anticipated upstream flooding provided the impetus for the expeditions to recover specimens that would be covered in water [12]. As the bulk of the specimens provided were limbs and thus not of use as museum pieces, Ruffer described no hesitation in dissecting them. Presenting his initial work in July 1908 at meetings of the British Medical Association in Sheffield, England, and the Cairo Scientific Society in December 1908 [13], Ruffer published his results in 1910 and 1911 [11,13]. He described atherosclerosis to be as common in ancient Egypt as it was in his time. Using visual and microscopic evaluation of approximately 2 dozen specimens, he commented, "When we consider that few of the arteries examined were quite healthy, it would appear that such lesions were as frequent three thousand years ago as they are today." Commenting further, regarding the "nature of the lesions. There can be no doubt respecting the calcification of the arteries, and that it is of exactly of the same nature as we see at the present day, namely,

FIGURE 1. Johann Czermak, Grafton Elliot Smith, and Mark Armand Ruffer. (A) Portrait of Johann Czermak (public domain), via Wikimedia Commons. (B) Portrait of Grafton Elliot Smith by John Cooke in 1915 (public domain), via Wikimedia Commons. (C) Portrait of Mark Armand Ruffer during service as an Egyptian official. Courtesy Timothy Weakley.

calcification following on atheroma." He described atherosclerosis in the carotid, subclavian, aorta, iliac, femoral, profunda, perineal, posterior tibial, and brachial and ulnar arteries. While Ruffer was aware of the findings of Shattock's limited autopsy, he was not aware of those of Czermak [14,15].

On the basis of his findings of atherosclerosis and other ancient Egyptian diseases including schistosomiasis, smallpox, pyorrhea (severe periodontitis), tuberculosis, abscesses, and urinary calculi, Ruffer is regarded as the father of paleopathology [14]. Among Ruffer's legacies is the chemical solution that now bears his name. Needing to soften the hard and brittle mummified tissue to enable sectioning for microscopic analysis, Ruffer showed that soaking specimens in a solution of alcohol, 100 parts, and 5% carbonate of soda solution, 60 parts, caused a gradual softening of the tissues over a period of days to weeks [15]. This also required a daily adjustment of the alcohol percentage.

In 1927, University of Buffalo pathologist Hubert U. Williams reported the results of a gross and microscopic autopsy of a mummy from the Lima area of Peru, circa 700 CE provided by the Field Museum of Natural History of Chicago. Calcific arteriosclerosis with thrombus formation was present in the right posterior tibial artery [16].

The first description of atherosclerosis of the coronary arteries of any ancient mummy was in 1931 by another University of Buffalo pathologist Allen R. Long with the autopsy of Lady Teye, an ancient Egyptian woman of approximately 50 years of age supplied by the Metropolitan Museum of Art, New York [17]. Atherosclerosis was also present in her aorta and renal arteries.

In 1955, Andrew Tawse Sandison performed histologic evaluations of available tissue of multiple Egyptian mummies using the increasing sophisticated staining and microscopic techniques of his time. To do so, he developed an often-used modification of Ruffer solution. Sandison confirmed these early reports with his documentation of the not infrequent presence of atherosclerosis in a number of ancient Egyptian mummies [18].

Decades later, Michael Zimmerman demonstrated the presence of atherosclerosis in 2 mummified Aleutian Islanders [19,20] and an Inuit woman [20]. Each also suffered from pulmonary anthracosis, consistent with significant smoke exposure during their lifetimes [19–21].

RADIOGRAPHIC STUDIES

Examining x-rays of Egyptian and Peruvian mummies at the Field Museum of Natural History, in Chicago, Roy Moodie [22] was the first to report x-ray evidence of atherosclerosis in 1931. Atherosclerosis was apparent in the arteries overlaying the scapula and ribs and in the forearm of a pre-dynastic Egyptian woman, dating prior to 3100 BCE. Moodie [22] described the artery in the forearm as resembling a piece of badly kinked heavy wire.

The development of computed tomography (CT) scanning by Godfrey Hounsfield in 1971 substantially improved the ability to evaluate arteries radiographically. William Murphy [23], Paul Gostner et al. [24], for example, demonstrated calcific atherosclerosis in both carotids, the distal aorta and right iliac artery in Ötzi the Iceman, a European mummy dating back to 3300 BCE. Their discovery represents the earliest documentation of atherosclerosis in humans.

Similarly, Wybren Taconis, George Maat, and Maarten Raven [25] described the results of the CT examinations of ancient Egyptian mummies housed at the National Museum of Antiquities in Leiden. Arterial calcifications were found in 3 mummies: the upper and lower extremities of a woman approximately 40 to 52 years of age, and in the lower extremities of 2 men approximately 40 to 47 and 45 to 55 years of age, respectively.

HORUS TEAM FINDINGS

Given this pioneering work, in retrospect, it should not be surprising that the Horus Team found CT evidence of atherosclerosis in 29 of 76 ancient Egyptian mummies (38%). That atherosclerosis was present in 23 of 61 mummies (37%) from Peru, the American Southwest, and the remote Aleutian Islands was not anticipated [25]. The Peruvians and Native Americans of the American Southwest were prehistoric people and the Aleutians were hunter-gatherers [1].

WHY?

We suggest that a gene-environment interplay [26] is the most likely explanation for the presence of atherosclerosis in these 4 disparate cultures. That is, the genes that make us human render us susceptible or vulnerable to atherosclerosis. Studies by Wang et al. [27] suggest that arterial degeneration begins early in postnatal life and is progressive in all human populations in which post-mortem studies have been performed. In 2 U.S.-based studies, for example, Stary [28] found 45% of infants to have aortic foam cells, whereas aortic lesions were observed in 100% of the aortas of 48 fetuses by D'Armiento et al. [29]. The environment of our life, the discovered and potentially undiscovered risk factors we are exposed to, determine the speed and extent that we develop atherosclerosis.

Genetically determined lifelong lipid levels are illustrative of the gene-environment interplay. Individuals with 2 defective low-density lipoprotein (LDL) receptor genes, homozygotes for familial hypercholesterolemia, are subject to a lifelong LDL in the range of >500 mg/dl. Left untreated, death from atherosclerosis typically occurs during childhood. The parents of a homozygote, obligate heterozygotes, will typically have an LDL roughly one-half that of their child, often dying of atherosclerosis in their 40s and 50s. Persons with favorable mutations, such as PSCK9^{142x} and PCSK9^{579x}, have genetically determined low PCSK9 levels and thus lifelong low LDL cholesterol levels, and have been shown to experience >80% fewer cardiac events than do those with more common alleles [30].

Although close examination of these 4 disparate cultures might yield traditional risk factors accounting for atherosclerosis, an equally plausible explanation is that risk factors for atherosclerosis exist that have not yet be to be discovered. It was not until 60 years ago that we became aware of any causative risk factors for atherosclerosis, so why would we necessarily have discovered all of them by the present time? Just as it is difficult to reckon with the prevalence of atherosclerosis in these ancient cultures, clinicians are not infrequently baffled when presented with a young person with newly diagnosed coronary artery disease with a dramatic dearth of traditional risk factors.

WHAT RISK FACTORS MIGHT HAVE EXISTED AMONG THESE ANCIENT PEOPLES?

Inflammation

Without antimicrobials, infectious micro-organisms could not be effectively treated in ancient civilizations. Each of the 4 cultures studied by the Horus Team were located adjacent to a fresh water source such as the Nile or tributaries of the Colorado River. With insufficient knowledge of hygiene, water was likely contaminated with human waste and that of their livestock, if present. Such environments, together with crowded living conditions, would have fostered rampant acute microbial infections and enduring infestations with skin and gut parasites.

In 1974, an interdisciplinary team performed what may have been the most comprehensive multidisciplinary autopsy of a mummy [31–33]. The subject was Nakht, a teenage boy who worked as a weaver circa 1200 BCE in Thebes (modern-day Luxor). Histologic and antigen immunoassay testing demonstrated that he harbored 4 different parasites: *Schistosoma* [34], *Taenia* species (tapeworm) [34], *Trichinella spiralis* [35], and *Plasmodium falciparum* (malaria) [31]. If Nakht is representative of the ancient Nile residents, these populations must have endured enormous, lifelong inflammatory burdens.

Though not found in the examination of Nakht, *Mycobacterium tuberculosis* was also common in ancient Thebes [36]. *Mycobacterium tuberculosis* was also detected in 2 of 12 Andean mummies circa 140 to 1200 CE [37]. Seven of the 12 carried other *Mycobacterium sp.* Salo et al. [38] reported the presence of *Mycobacterium tuberculosis* in a Peruvian mummy circa 1050 BCE, and Corthals et al. [39], reported the presence of *Mycobacterium sp.* in an Inca mummy from Northwest Argentina circa 1600 BCE.

The infectious burden of the current day Tsimane, an indigenous forager-horticulturalist culture living in the lowland forests and savannas east of the Andes in Bolivia, may be analogous to that experienced in ancient cultures given the Tsimane's subsistence lifestyle and infrequent access to modern medical care. Using 40- to 49-year-old men and women evaluated during an annual physical examination as an example, Gurven et al. [40] found that ≈70% and ≈20% were suffering from gastrointestinal or respiratory symptoms suggestive of an infectious cause, respectively.

The systemic inflammation of chronic infections in these ancient peoples could well have accelerated the development of another inflammatory disease, that of atherosclerosis [41,42]. As long ago as the time of Czermak, Von Rokitanksy and Virchow described the pathophysiology of atherosclerosis as inflammatory (as reviewed in Gotto [43]). The inflammatory burden of chronically infected ancient persons may be analogous to the systemic inflammatory burden carried by contemporary patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), diseases punctuated by premature cardiovascular events. In an analysis of 263 clinic-based patients with established SLE, Esdaile et al. [44] found the risk-adjusted rate of nonfatal myocardial infarction, coronary heart disease death, and stroke over 8.6 years to be 10.1, 17, and 7.9 higher, respectively, than would be expected on the basis of traditional Framingham risk factors. In the Nurses' Health population-based study [45], those who developed SLE over a 28-year follow-up period, and thus would have had a milder form than those who had established SLE in the clinic-based study of Esdaile et al., had a 2- fold increase in the occurrence of cardiovascular events.

In a meta-analysis, Aviña-Zuebiet al. [46] found RA patients to have ≈50% increase in death from cardiovascular disease, even higher among those with more severe RA. In a related study, Stamatelopoulos et al. [47] found the frequency and severity of pre-clinical atherosclerosis to be equivalent between those with RA and those with diabetes. In another chronic inflammatory condition, Farrugia et al. [48] suggested the immune activation and inflammation of human immunodeficiency virus infection is pro-atherogenic and a chief cause for their increased incidence of cardiovascular events.

Distant past maternal stress from infection may also have played a role in the development of atherosclerosis in the offspring of mothers who suffered an infection during the gestation of the offspring. Shortly after Ruffer's tragic loss and before the Great War ended, the world endured a further challenge from the Great Influenza Pandemic, which caused frightening acute mortality, killing 500 million people worldwide (30-fold more deaths than attributed to the war itself). Importantly, the epidemic left a mark on the children exposed during gestation who remarkably had more heart disease 60 years later [49]. Records from the U.S. National Center for Health Statistics showed that the birth cohort of the first quarter of 1919 after the peak mortality experienced 25% excess ischemic heart disease prevalence relative to adjacent calendar quarters. We can thus conclude that transient maternal exposure to infection left a permanent imprint that promotes excess vascular pathology. This impact of a distant insult has been termed "cohort mortality" for the cohort who experienced the distant insult [42].

Finch proposed that inflammation be considered a core cause of human aging, citing its involvement not only

in atherosclerosis but also in the development of Alzheimer's, many types of cancers, and the basic aging process [41,42,50,51].

These findings raise the potential of a unifying hypothesis. Williams's antagonistic pleiotropic hypothesis suggests the potential of natural selection favoring genes that allow species to survive through the age of reproduction but that can be detrimental during post-reproductive life [52]. The need to survive chronic high-intensity exposures to infections during the ≈4,000 generations of human evolution since the advent of *Homo sapiens* and the ≈8,000 generations since the advent of the *Homo* genus could have selected for genes that provide a robust and effective inflammatory response. These same genes could have the opposite effect on survival during later life by promoting the acceleration of atherosclerosis and other diseases of aging [42,53].

Though inflammation per se is not currently regarded as a traditional coronary heart disease (CHD) risk factor, a belief in its importance is suggested by several clinical trials—CANTOS (Cardiovascular Risk Reduction Study [Reduction in Recurrent Major CV Disease Events]) [54] and SOLSTICE (A Study to Evaluate the Safety of 12 Weeks of Dosing With GW856553 and Its Effects on Inflammatory Markers, Infarct Size, and Cardiac Function in Subjects With Myocardial Infarction Without ST-Segment Elevation) [55]—now underway testing the suppression of various aspects of inflammation in the development of CHD.

Looking more broadly, Finch and Crimmins have proposed a general model of the impact of the environment on the aging process. They suggest that 3 groups of past or present factors be considered: 1) damage from infections, direct and indirect; 2) nutritional deficits; and 3) social stress. The pathways connecting each to pathophysiology are as of now incompletely defined but are thought to involve brain-immune-metabolic synergies beginning early in development and continuing throughout life (Fig. 2) [41,50,56].

Smoke inhalation. Indoor (domestic) smoke is a candidate for a pro-atherogenic inflammagen that was likely to have been prevalent in many ancient cultures. The 4 cultures the Horus Team studied all cooked over open fires with Egyptians using wood and coal; the Peruvians using wood or dung; the Ancestral Puebloans using wood; and the Aleutian Islanders using seal oil and wood [1]. A home often filled with smoke would have been especially common among the Aleutian Islanders. They lived in subterranean home structures in which fire was used internally for heating, lighting, and cooking using driftwood and marine mammal oils. The only access for ingress, egress, and ventilation was through 1 of several openings in the roof using a ladder made from a single log into which steps were cut (Fig. 3A) [57–59]. Similarly, the Native American Ancestral Puebloans living along the Colorado River also lived in subterranean homes using the same chimney model of ingress and egress. Their homes too were lit by the light of an indoor fire (Fig. 3B).
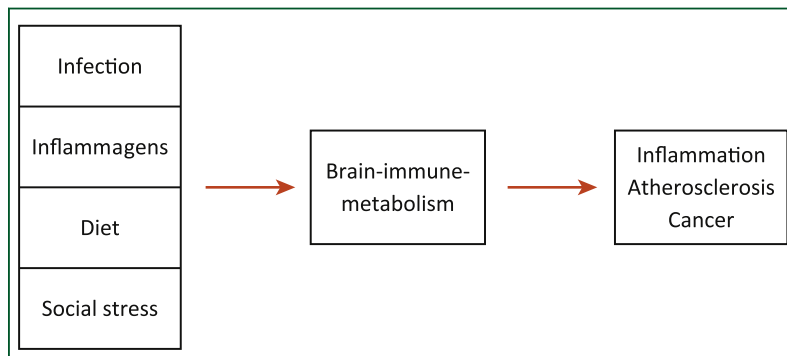

FIGURE 2. **Finch and Crimmins's proposed general model of the environmental impact on the aging (adapted from Finch [42]).** Infections and inflammagen (noninfectious inhaled or ingested particles such as tobacco, fossil fuel, dust, and endotoxins), nutritional deficits, and social stress each result in alterations of the immune system, brain, and metabolism that can result in inflammation, atherosclerosis, and cancer. The process begins early in development and continues throughout life.

The presence of pulmonary anthracosis of soot inhalation discovered by Zimmerman in the autopsy of 2 Aleutian Islanders is consistent with such an exposure [19,20]. Ancient Egyptian mummies have also been found to have anthracosis [13,60,61].

The earliest human evidence of domestic smoke inhalation comes from the sooty deposits suggestive of anthracosis on the inner surface of ribs in burials from the city of Catalhöyük 8,500 years ago in southern Turkey [41,62,63]. Also relevant to Peruvians is the recent suggestion of the use of tobacco in the region, as determined by the presence of nicotine in the hair of mummies from northern Chile [64]. By abundant evidence, cigarette smoke is atherogenic, and even secondhand (passive smoke exposure) increases the risk of arterial calcification [65,66]. Passive cigarette smoke exposure may serve as a model for domestic smoke exposure. Anthracosis due to household smoke (domestically acquired particulate lung disease, also called "hut lung disease") is well documented in case reports [67,68]. Rodent models show responses to wood smoke that are pro-atherogenic, such as gelatinase and methane mono-oxygenase activity in aortas after hardwood smoke exposure [69,70].

Yet-to-be discovered risk factors. We are limited in our assessment of other potential causes of atherosclerosis by what we can measure and thus subject to testing. After serum cholesterol could be measured, Carl Muller [71] could correlate cholesterol levels with CHD in a group of heterozygous familial hypercholesterolemia patients in the 1930s. A decade later, the work of Cohn et al. [72], Gofman et al. [73], and others [43] paved the way for low- and high-density lipoprotein cholesterol levels to be positively and negatively correlated with CHD, respectively. Three decades later, an assay for high-sensitivity C-reactive protein was developed, following which it could be
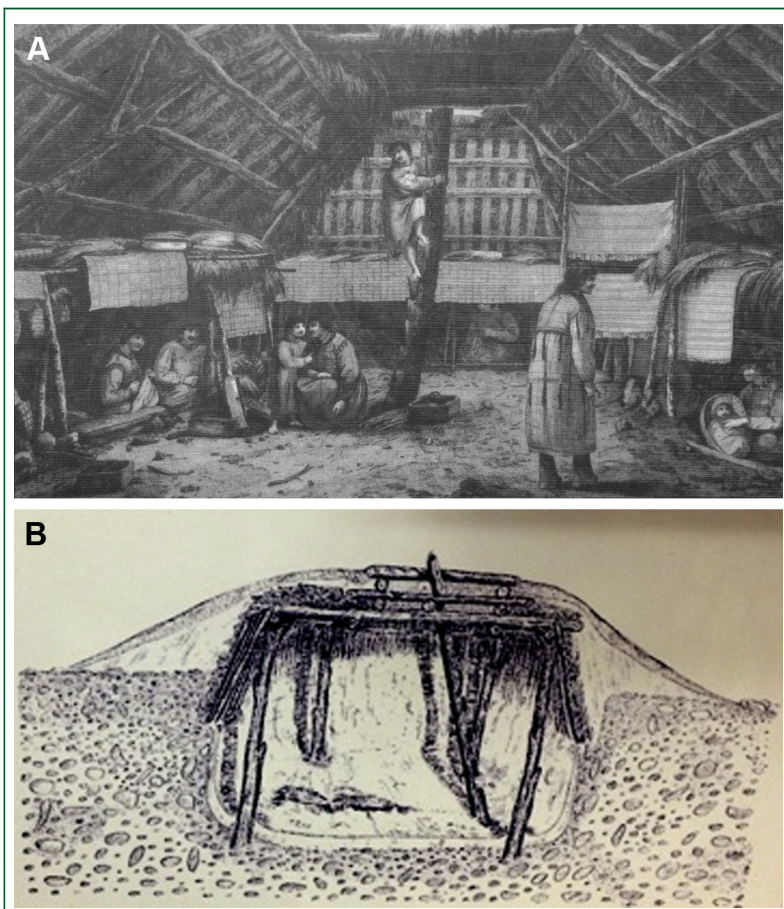
FIGURE 3. Drawings of a barabara and a subterranean pit house. (A) Drawing by John Webber of an Aleutian Island barabara, the typical subterranean dwelling of the Aleutian Islanders. Drawn during Captain James Cook's third around-the-world voyage in 1778 [59]. (B) Drawing of a subterranean pit house, the typical dwelling of the Ancient Puebloans of the American Southwest. Image from the Lost City Museum, Overton, Nevada.

FIGURE 4. The weighing of the heart ceremony, the judgment day of the ancient Egyptian religion. The heart of the deceased is weighed against the Feather of Ma'at, the goddess of truth and justice [86]. In the Papyrus of Ani circa 1200 BCE (public domain), via Wikimedia Commons.

correlated with atherosclerosis [74]. Multiple potential serum correlates with CHD are currently under active investigation. To believe that other measures will not be discovered and found to be correlative and potentially causal for atherosclerosis would seem to be presumptuous. Likely, there is much to be learned.

GENETIC CONTRIBUTION

Robert Roberts and Alex Stewart [75] suggested that genetic predisposition accounts for 40% to 60% of human susceptibility to coronary artery disease and thus to atherosclerosis. Genomewide association studies have discovered an increasing number of individual single nucleotide polymorphisms (SNP) risk variants that make up this predisposition [76]. The risk associated with each SNP has generally been modest, but the frequency and number of SNP make their contribution substantial [77]. Bos et al. [78] have correlated a number of these SNPs to multivessel bed calcification. In this issue, Zink et al. [79] further explore the current contribution of genetics to atherosclerotic susceptibility and its potential evolutionary changes.

Interestingly, apes and humans share 99% of their genes, yet the lifespan of an ape is one-half that of a modern human (as reviewed in Finch [42]). Among the 1% of differing genes, could many be inflammation-promoting genes favorable to natural selection?

SUMMARY

Autopsy studies performed as long ago as 1852 are consistent with current-day CT scans, demonstrating the surprising result that atherosclerosis was common among 4 diverse ancient cultures. Potential causes include frequent and chronic infections resulting in chronic inflammation, smoke inhalation, or other as yet undiscovered risk factors. A synthesis of these findings is consistent with a gene-environment interplay as causal for atherosclerosis. As humans, our genes result in our susceptibility, our environment and the choices we make within it, determine its speed and severity.

POSTSCRIPT

Ruffer's heroic death

Toward what would become the end of the Great World War, Ruffer was dispatched as commissioner of the British Red Cross Society of Egypt to the Greek city of Salonika (called Thessaloniki in Greek) to help with the reorganization of country's sanitary service [80,81]. The mission required a perilous round trip voyage across the Mediterranean Sea during the time of the German submarine blockade. On departing for Salonika in 1916, the same year he received his knighthood, his wife Alice recounted, "When starting in December 1916, on a mission which was evidently attended by dangers … he left with me instructions as to the various unfinished papers at which he and I had

worked together," which included a posthumously published monograph [82,83]. Sadly this premonition proved all too true. On April 15, 1917, the second night of his voyage home on the HM Transport Arcadian, a torpedo from the German submarine UC74 commanded by Wilhelm Marschall sank the ship [81,83,84]. Of the ≈ 1,000 people on board, 279 perished from the explosion or by drowning. Ruffer was among the latter group. Four years later, a former classmate of Ruffer's at Oxford, A. J. Butler, learned that Ruffer had provided the life vest he was wearing following the explosion to a hospital nurse on board who was without one. Ruffer went down with the ship and was not rescued. The nurse ended up caring for a friend of Butler's in Belfast, who recalled the story to Butler for posterity [85]. Ruffer's ultimate act of chivalry was performed 5 years and 2 days following the sinking of the *Titanic*.

Heaven in ancient Egypt: the Field of Reeds

Medicine has been the beneficiary of the decision by ancient people to artificially mummify their dead. Practicing this art for 2 millennia, the Egyptians were particularly adept at the craft. This was not accidental. Mummification was a process associated with their religious belief in an afterlife, called the Field of Reeds, a place of bliss with plentiful food and harvests. In their religious ideology, it was necessary for the Ka (a version of the soul) to periodically return to the body on Earth for sustenance. In order for the Ka to return to and recognize the body, careful preservation was required, hence the 70-day embalming process by the specially trained priests who were expert in the use of dehydrating salts and knew which prayers and rituals were required by each step in the process [86].

A judgment day followed death in this religion dating back to at least 1500 BCE. In the weighing of the heart ceremony, the heart of the deceased was weighed against a feather, the Feather of Ma'at, the goddess of truth and justice (Fig. 4). If the deceased had lived a life of truth and integrity, their heart would be as light as the feather, securing their access to the Field of Dreams. Should the heart of the deceased prove to be heavy with wrongdoing, it would immediately be devoured by Ammut, the monster resting under the balance, and the hope of an afterlife lost forever. Written spells lined the walls of the sarcophagus meant to instruct the heart to provide a story that would ensure a successful rise to the Field of Reeds [86].

REFERENCES

1. Thompson RC, Allam AH, Lombardi GP, et al. Atherosclerosis across 4000 years of human history: the Horus study of four ancient populations. Lancet 2013;381:1211–22.
2. Allam AH, Thompson RC, Wann LS, et al. Atherosclerosis in ancient Egyptian mummies: the Horus study. JACC Cardiovasc Imaging 2011;4:315–27.
3. Allam AH, Thompson RC, Wann LS, Miyamoto MI, Thomas GS. Computed tomographic assessment of atherosclerosis in ancient Egyptian mummies. JAMA 2009;302:2091–4.
4. Thompson RC, Allam AH, Zink AR, et al. Computed tomographic evidence of atherosclerosis in the mummified remains of humans from around the world. Glob Heart 2014;9:187–96.
5. Czermak J. Description and microscopic findings of two Egyptian mummies. Meet Acad Sci 1852;9:27–69.
6. Ingersoll A. The secondary effects of the hypertrophy of the third tonsil. Cleveland Med J 1905;4:301–6.
7. Delavan DB. The centenary of Johann Nepomuk Czermak. Bull N Y Acad Med 1929;5:440–3.
8. Smith GE. 61079: the mummy of Menephtah. In: Smith GE, editor. The Royal Mummies. Cairo, Egypt: Imprimerie de l'Institut Francais d'Archeologic Orientale; 1912. p. 65–70.
9. Shattock SG. A report upon the pathological condition of the aorta of King Meneptah, traditionally regarded as the Pharaoh of the Exodus. Proc R Soc Med 1909;2:122–7.
10. Allam AH, Nureldin A, Adelmaksoub G, et al. Something old, something new—computed tomography studies of the cardiovascular system in ancient Egyptian mummies. Am Heart Hosp J 2010;8:10–3.
11. Ruffer MA. On arterial lesions found in Egyptian mummies (1580 BC—535 AD). J Pathol Bacteriol 1911;16:453–62.
12. Aufderheide AC. The Scientific Study of Mummies. New York, NY: Cambridge University Press; 2003.
13. Ruffer MA. Remarks on the histology and pathological anatomy of Egyptian mummies. Cairo Sci J 1910;4(40).
14. Dutour O. Paleoparasitology and paleopathology: synergies for reconstructing the past of human infectious diseases and their pathocenosis. Int J Paleopathol 2013;3:145–9.
15. Ruffer MA. Preliminary note on the histology of Egyptian Mummies. Br Med J 1909;1:1005.
16. Williams HU. Gross and microscopic anatomy of two Peruvian mummies. Arch Pathol Lab Med 1927;4:26–33.
17. Long AR. Cardiovascular renal disease: a report of a case three thousand years ago. Arch Pathol (Chic) 1931;12:92–4.
18. Brothwell D, Sandison AT. Diseases of Antiquity. Springfield, IL: Charles C, Thomas; 1967.
19. Zimmerman M, Yeatman GW, Sprinz H, Titterington WP. Examination of an Aleutian mummy. Bull N Y Acad Med 1971;47:80–103.
20. Zimmerman MR, Trinkaus E, LeMay M, et al. The paleopathology of an Aleutian mummy. Arch Pathol Lab Med 1981;105:638–41.
21. Zimmerman MR, Jensen AM, Sheehan GW. Agnaiyaaq: the autopsy of a frozen Thule mummy. Arctic Anthropol 2000;37:52–9.
22. Moodie RL. Roentgenologic studies of Egyptian and Peruvian Mummies. In: Laufer B, editor. Volume 3. Chicago, IL: Field Museum of Natural History; 1931.
23. Murphy WA Jr, Nedden Dz Dz, Gostner P, Knapp R, Recheis W, Seidler H. The iceman: discovery and imaging. Radiology 2003;226:614–29.
24. Gostner P, Pernter P, Bonatti G, Graefen A, Zink AR. New radiological insights into the life and death of the Tyrolean Iceman. J Archaeol Sci 2011;38:3425–31.
25. Taconis WK, Maat GJR. Radiologic findings in human mummies and human heads. In: Raven MJ, Taconis WK, editors. Egyptian Mummies: Radiological Atlas of the Collections in the National Museum of Antiquities in Leiden. Papers on Archaeology of the Leiden Museum of Antiquities. Begijnhof, Belgium: Brepols Publishers; 2005. p. 53–78.
26. Chan L, Boerwinkle E. Gene-environment Interactions and gene therapy in atherosclerosis. Cardiol Rev 1994;2:130–7.
27. Wang M, Monticone RE, Lakatta EG. Arterial aging: a journey into subclinical arterial disease. Curr Opin Nephrol Hypertens 2010;19:201–7.
28. Stary HC. Lipid and macrophage accumulations in arteries of children and the development of atherosclerosis. Am J Clin Nutr 2000;72(Suppl 5):1297S–306S.
29. D'Armiento FP, Bianchi A, de Nigris F, et al. Age-related effects on atherogenesis and scavenger enzymes of intracranial and extracranial arteries in men without classic risk factors for atherosclerosis. Stroke 2001;32:2472–9.
30. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med 2006;354:1264–72.

31. Millet N, Hart G, Reyman T, Zimmerman M, Lewin P, ROM I. Mummification for the common people. In: Cockburn A, Cockburn E, Reyman T, editors. Mummies, Diseases and Ancient Cultures. 2nd edition. Cambridge, UK: Cambridge University Press; 1998. p. 91–105.

32. David R, Archbold R. Conversations With Mummies. New York, NY: William Morrow; 2000.

33. Clarke EM, Thompson RC, Allam AH, et al. Is atherosclerosis fundamental to human aging? Lessons from ancient mummies. J Cardiol 2014 Feb 27 [E-pub ahead of print].

34. Reyman TA, Zimmerman MR, Lewin PK. Autopsy of an Egyptian mummy: 5. Histopathologic investigation. Can Med Assoc J 1977;177: 470–2.

35. de Boni U, Lenczner M, Scott JW. Autopsy of an Egyptian mummy: 6. Trichinella spiralis cyst. Can Med Assoc J 1977;177:472.

36. Zink AR, Sola C, Reischl U, et al. Characterization of Mycobacterium tuberculosis complex DNAs from Egyptian mummies by spoligotyping. J Clin Microbiol 2003;41:359–67.

37. Konomi N, Lbwohl E, Mowbray K, Tattersall I, Zhang D. Detection of mycobacterial DNA in Andean mummies. J Clin Microbiol 2002;40: 4738–40.

38. Salo WL, Aufderheide AC, Buikstra J, Holcomb TA. Identification of Mycobacterium tuberculosis DNA in a pre-Columbian Peruvian mummy. Proc Natl Acad Sci U S A 1994;91:2091–4.

39. Corthals A, Koller A, Martin DW, et al. Detecting the immune system response of a 500 year-old Inca mummy. PloS One 2012;7:e41244.

40. Gurven M, Stieglitz J, Hooper PL, Gomes C, Kaplan H. From the womb to the tomb: the role of transfers in shaping the evolved human life history. Exp Gerontol 2012;47:807–13.

41. Finch CE. The Biology of Human Longevity: Inflammation, Nutrition, and Aging in the Evolution of Lifespans. Amsterdam, Netherlands: Academic Press; 2007.

42. Finch CE. Evolution of the human lifespan, past, present, and future: phases in the evolution of human life expectancy in relation to the inflammatory load. Proc Am Philos Soc 2012;156:9–44.

43. Gotto AM Jr. Jeremiah Metzger lecture: cholesterol, inflammation and atherosclerotic cardiovascular disease: Is it all LDL? Trans Am Clin Climatol Assoc 2011;122:256–89.

44. Esdaile JM, Abrahamowicz M, Grodzicky T, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. Arthritis Rheum 2001;44:2331–7.

45. Hak AE, Karlson EW, Feskanich D, Stampfer MJ, Costenbader KH. Systemic lupus erythematosus and the risk of cardiovascular disease: results from the Nurses' Health Study. Arthritis Rheum 2009;61: 1396–402.

46. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum 2008;59:1690–7.

47. Stamatelopoulos KS, Kitas GD, Papamichael CM, et al. Atherosclerosis in rheumatoid arthritis versus diabetes: a comparative study. Arterioscler Thromb Vasc Biol 2009;29:1702–8.

48. Farrugia PM, Lucariello R, Coppola JT. Human immunodeficiency virus and atherosclerosis. Cardiol Rev 2009;17:211–5.

49. Mazumder B, Almond D, Park K, Crimmins EM, Finch CE. Lingering prenatal effects of the 1918 influenza pandemic on cardiovascular disease. J Dev Orig Health Dis 2010;1:26–34.

50. Finch CE, Crimmins EM. Inflammatory exposure and historical changes in human life-spans. Science 2004;305:1736–9.

51. Finch CE. Inflammation in aging processes: an integrative and ecological perspective. In: Masoro EJ, Austad SN, editors. Handbook of the Biology of Aging. 7th edition. Salt Lake City, UT: Academic Press; 2010.

52. Williams GC. Pleiotropy, natural selection, and the evolution of senescence. Evolution 1957;11:398–411.

53. Ding K, Kullo IJ. Evolutionary genetics of coronary heart disease. Circulation 2009;119:459–67.

54. Cardiovascular Risk Reduction Study (Reduction in Recurrent Major CV Disease Events) (CANTOS). [Online study record]. February 2014.

Available at: http://www.clinicaltrials.gov/ct2/show/NCT01327846? titles=CANTOS&spons_ex=Y&rank=1. Accessed February 17, 2014.

55. A Study to Evaluate the Safety of 12 Weeks of Dosing With GW856553 and Its Effects on Inflammatory Markers, Infarct Size, and Cardiac Function in Subjects With Myocardial Infarction Without ST-segment Elevation. [Online study record.] July 2013. Available from: http:// www.clinicaltrials.gov/ct2/show/NCT00910962?term=SOLSTICE& rank=1. Accessed February 17, 2014.

56. Crimmins EM, Finch CE. Infection, inflammation, height, and longevity. Proc Natl Acad Sci U S A 2006;103:498–503.

57. Veniaminov I. Notes on the Islands of the Unalashka District. Reprint. Kingston, Ontario, Canada: Limestone Press; 1984.

58. Cook JA. A voyage to the Pacific Ocean undertaken by the command of His Majesty for making discoveries in the northern hemisphere to determine the position and extent of the west side of North America, its distance from Asia and the practicability of a northern passage to Europe in the years 1776–1780. (Cook's Third Voyage). London, England: G. Nicol, Bookseller to His Majesty, in the Strand, and T. Cadell in the Strand, 1784:512–4.

59. McCartney AP, Veltre DW. Longhouses of the Eastern Aleutian Islands, Alaska. In: Frohlich B, Harper AB, Gilberg R, editors. To the Aleutians and Beyond: The Anthropology of William S. Lauglin. Publications of The National Museum of Ethnographical Series 20. Copenhagen, Denmark: Department of Ethnography, The National Museum of Denmark; 2002. p. 249–65.

60. Shaw AFB. A histological study of the mummy Har-mose, the singer of the eighteenth dynasty (circa 1490 B.C.). J Pathol Bacteriol 1938; 47:115–23.

61. Walker R, Parsche F, Bierbrier M, McKerrow JH. Tissue identification as histologic study of six lung specimens from Egyptian mummies. Am J Phys Anthropol 1987;72:43–8.

62. Hodder I. Women and men at Çatalhöyük. Sci Am 2004;290:76–83.

63. Andrews P, Molleson T, Boz B. The human burials at Çatalhöyük. In: Hodder I, editor. Inhabiting Çatalhöyük: Reports from the 1995–99 Seasons by Members of the Çatalhöyük Teams. McDonald Institute Monographs. Cambridge, and London, UK: McDonald Institute for Archaeological Research and British Institute of Archaeology at Ankara; 2005. p. 261–78.

64. Echeveria J, Niemeyer HN. Nicotine in the hair of mummies from San Pedro de Atacama (Northern Chile). J Archaeol Sci 2013;40: 3561–8.

65. Peinemann F, Moebus S, Dragano N, et al. Secondhand smoke exposure and coronary artery calcification among nonsmoking participants of a population-based cohort. Environ Health Perspect 2011;119:1556–61.

66. Xu L, Jiang CQ, Lam TH, Thomas GN, Zhang WS, Cheng KK. Passive smoking and aortic arch calcification in older Chinese never smokers: the Guangzhou Biobank Cohort Study. Int J Cardiol 2011; 148:189–93.

67. Moran-Mendoza O, Pérez-Padilla JR, Salazar-Flores M, Vazquez-Alfaro F. Wood smoke-associated lung disease: a clinical, functional, radiological and pathological description. Int J Tuberc Lung Dis 2008; 12:1092–8.

68. Gold JA, Jagirdar J, Hay JG, Addrizzo-Harris DJ, Naidich DP, Rom WN. Hut lung: a domestically acquired particulate lung disease. Medicine (Baltimore) 2000;79:310–7.

69. Campen MJ, Lund AK, Doyle-Eisele ML, et al. A comparison of vascular effects from complex and individual air pollutants indicates a role for monoxide gases and volatile hydrocarbons. Environ Health Perspect 2010;118:921–7.

70. Seilkop SK, Campen MJ, Lund AK, McDonald JD, Mauderly JL. Identification of chemical components of combustion emissions that affect pro-atherosclerotic vascular responses in mice. Inhal Toxicol 2012;24:270–87.

71. Muller C. Angina pectoris in hereditary xanthomatosis. Arch Intern Med 1939;64:675–700.

72. Cohn EJ, Strong LE, Hughes WL, et al. Preparation and properties of serum and plasma proteins; a system for the separation into fractions

of the protein and lipoprotein components of biological tissues and fluids. J Am Chem Soc 1946;68:459–75.

73. Gofman JW, Hanig M, Jones HB. Evaluation of serum lipoprotein and cholesterol measurements as predictors of clinical complications of atherosclerosis; report of a cooperative study of lipoproteins and atherosclerosis. Circulation 1956;14:691–742.

74. Ridker PM. Hyperlipidemia as an instigator of inflammation: inaugurating new approaches to vascular prevention. J Am Heart Assoc 2012;1:3–5.

75. Roberts R, Stewart AF. Genes and coronary artery disease: where are we? J Am Coll Cardiol 2012;60:1715–21.

76. Roberts R, Marian AJ, Dandona S, Stewart AF. Genomics in cardiovascular disease. J Am Coll Cardiol 2013;61:2029–37.

77. Deloukas P, Kanoni S, Willenborg C, et al, for the CARDIoGRAMplusC4D Consortium. Large-scale association analysis identifies new risk loci for coronary artery disease. Nat Genet 2013; 45:25–33.

78. Bos D, Ikram MA, Isaacs A, et al. Genetic loci for coronary calcification and serum lipids relate to aortic and carotid calcification. Circ Cardiovasc Genet 2013;6:47–53.

79. Zink A, Wann LS, Thompson RC, et al. Genomic correlates of atherosclerosis in ancient humans. Glob Heart 2014;9:203–9.

80. Sandison AT. Sir Marc Armand Ruffer (1859—1917): pioneer of paleopathology. Med Hist 1967;11:150–6.

81. Finch CE. Atherosclerosis is an old disease: summary of the Ruffer Centenary Symposium, The Paleocardiology of Ancient Egypt, a meeting report of the Horus Study team. Exp Gerontol 2011;46:843–6.

82. Ruffer MA. Diseases of the ancient Egyptians. In: Moodie RL, editor. Studies in the Paleopathology of Egypt. Chicago, IL: University of Chicago Press; 1923.

83. Torpedoed in the Aegean Sea. [Online memoir]. August 22, 2009. Available at: http://www.firstworldwar.com/diaries/torpedoed.htm. Accessed February 20, 2014.

84. WWI U-boat Commanders: Wilhelm Marschall. Available at: http://uboat.net/wwi/men/commanders/195.html. Accessed February 20, 2011.

85. Butler AJ. The Brazen Nose. Oxford: Brasenose College, Oxford University; May 1933. p. 278.

86. Budge EAW. The Book of the Dead. Reprint. New York, NY: Gramercy Books; 1999.