



Heart disease: the greatest 'risk' factor of them all

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Summary By the turn of the last century, flying in the face of over a hundred years of research and clinical observation to the contrary, medicine abandoned the link between infection and atherogenesis; not because it was ever proven wrong, but because it did not fit in with the trends of a medical establishment convinced that chronic disease such as heart disease must be multifactorial, degenerative and non-infectious.

Yet it was the very inability of 'established' risk factors such as hypercholesterolemia, hypertension and smoking to completely explain the incidence and trends in cardiovascular disease that resulted in historically repeated calls to search out an infectious cause, a search that began more than a century ago.

Today, half of US heart attack victims have acceptable cholesterol levels and 25% or more have none of the "risk factors" associated with heart disease, including smoking, high blood pressure or obesity, most of which are not inconsistent with being caused by infection [7,56].

Even the case of the traditionalist's latest 2003 JAMA assault to 'debunk' what they call the "50% risk factor myth" [20] falls woefully short under scrutiny. In one group 30% died of heart disease with a cholesterol of at least 240 mg/dl, a condition which also existed in 21% who did not die during the same period. And the overlap was obvious throughout the so-called risk categories. Under such scrutiny, lead author Greenland conceded that if obesity, inactivity and elevated cholesterol in the elderly are included, just about everyone has a risk factor and he likened the dilemma of people who do or do not wind up with heart disease akin to the susceptibility of people who are exposed to tuberculosis but do not get the disease.

In Infections and Atherosclerosis: New Clues from an old Hypothesis? Nieto stressed the need to extend the possible role of infectious agents beyond the three infections which have in recent years been the focus of research: Cytomegalovirus (CMV) *Chlamydia pneumoniae* and *Helicobacter pylori* [39].

Mycobacterial disease shares interesting connections to heart disease. Not only is tuberculosis the only microorganism to depend on cholesterol for its pathogenesis but CDC maps for cardiovascular disease bear a striking similarity to those of State and regional TB case rates.

Ellis, Hektoen, Osler, McCallum, Swartz, Livingston and Alexander-Jackson all saw clinical and laboratory evidence of a causative relationship between the mycobacteria and heart disease. And Xu showed that proteins of mycobacterial origin actually led to experimental atherosclerosis in laboratory animals [61,62].

Furthermore present day markers suggested as indicators for heart disease susceptibility such as C-Reactive Protein (CRP), interleukin-6 and homocysteine are all similarly elevated in tuberculosis.

It therefore behooves us to explore the link between heart disease and typical and atypical tuberculosis.

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Introduction

The American Heart Association (AHA), the first organization leading towards field specialization, was an offshoot of The National Tuberculosis

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Association, without whose money and help it would not have survived. In one of its first Bulletins, the AHA came up with a long list of the similarities between tuberculosis and cardiac disease [2], a view supported by Ellis in *The New England Journal* half a century later [15]. In a 'name that disease' Ellis fleshed-out a malady whose mortality rate was 200 to 300 per 100,000, was widespread, and by whom many in their prime were struck down. Treatment was only partially effective. Doctors recommended diet and exercise. Special hospitals were built for it. Ellis's readers only recognized the disease as TB when he said it struck 75 years ago, the white plague of the 20th century, for the mortality rate for ischemic heart disease (IHD) at the time of Ellis's writing was also 200 to 300 persons per 100,000.

Yet it was not until after WWII that the subject was pursued in earnest. Sometime in 1965, Rutgers's investigators Virginia Livingston, M.D. and Eleanor Alexander-Jackson PhD, fueled by Fleet and Kerr Grants, working with sterile heart and coronary artery specimens from recent catastrophic attacks, established low grade mycobacterial infection, staining 'acid-fast', and not decolorizing with acid-alcohol in all ischemic heart disease specimens [32]. Even in stained slides of the heart muscle itself, Livingston saw that the individual nuclei of heart muscle fibers were infected by small acid-fast globoidal bodies and appeared to enter into a gradual state of digestion (Ibid).

In 1896 Hektoen, studying how tuberculosis attacked blood vessels of the cardiovascular system by implantation thru the blood, saw the disease eventually penetrate all layers of the arterial wall, including its muscular coat, leading in many cases to degeneration of a whole arterial segment [23]. Furthermore, he saw the attack as initially involving either the intima or adventitia of the vascular wall.

By 1908, William Osler, arguably the greatest physician since Hippocrates, and to this day an icon for accurate clinical judgment, made clear that arteriosclerosis was frequently associated with tuberculosis [42].

MacCallum's survey [34], established that of all infectious etiologies traced, only one specifically, tuberculosis, caused arteriosclerosis. At autopsy, he cited 101 cases of advanced tuberculosis. Of these, there were 49 cases in children in the first decade of life, none of which showed arterial changes. Even in the second, third and fourth decades there were only 11 autopsies who died of TB with moderate cardiovascular sclerosis while 13 showed nothing. But by the fifth, sixth, seventh and

eight decades, true to current coronary timetables, there were only 2 autopsies with normal arteries and 26 with TB arteriosclerosis (Ibid).

By 1972, Schwartz, aware that the 'lardaceous', waxy degeneration misnamed by Virchow as starch-like "amyloid" (starch was called amyllum), showed that not only did amyloid degeneration of elderly cardiovascular systems occur more frequently than hardening and atheromatous lesions of their arteries, but that patients with amyloid degeneration, upon necroscopy, usually revealed signs of lingering pulmonary and lymphonodular tuberculosis [59].

Classic thought said that atherosclerosis began with the appearance of cholesterol and fat-laden macrophages called "foam cells". The fact that some of these macrophages died, just added to the debris.

Macrophages died, tradition dictated, because they could not eliminate cholesterol the way they got rid of bacteria. They simply stuffed themselves with more and more cholesterol converting into the large 'foam cells' that filled the plaques of advanced atherosclerosis. Macrophages, then, literally ate themselves to death.

But there were obvious flaws in classic thought. First, unlike with other microbes, human macrophages were not that good at eliminating germs like tuberculosis, which in turn killed many of them. Second cholesterol by itself, normally the most abundant steroid in man, was on the rise in Japanese blood during the very decade (1980–1989) when the incidence of coronary heart disease was on its way down [40]. In the meantime, in the US, half the people who had a heart attack had acceptable cholesterol levels, including its HDL and LDL fractions.

Although cholesterol thus seemed an imperfect criterion for determining coronary heart disease, its intimate interaction with TB and the mycobacteria presented extremely interesting coincidental findings. Not only were virulent mycobacteria the only pathogens that relied upon cholesterol to enter the body's white blood cells or macrophages [17], but, it was the Mycobacteria that in addition were able to produce [31], esterify [29], take up, modify, accumulate [4], and promote the deposition of and release [26] of cholesterol.

Orthodox thought went on to say that smooth muscle cells of the cardiovascular system somehow responded to fat proliferation under the influence of certain platelet factors, which functioned in clotting to eventually cause inflammation. But what was always vague was just why such inflammation should occur from fat proliferation. Livingston and Alexander-Jackson

clarified this, finding in all specimens, an infectious agent behind that inflammation and fat propagation [32].

Others noticed

A 1973 watershed study by Benditt and Benditt reported that cells found in atherogenic plaque had a monoclonal origin, derived from a single cell population [6]. Confirmatory studies [43,44] prompted the revival and legitimization of a search for an infectious cause.

But by concluding that such monoclonal origins were caused by "Chemical mutagens or viruses or both" Benditt and Benditt ignored a third major possibility, tuberculosis and the mycobacteria, each fully capable of churning out its own monoclonal enzymes once systemic [13,45].

Nevertheless, in no small part as a result of this study, much of the world's scientific and medical community focused on an extremely limited role for tuberculosis and the mycobacteria in heart disease, and at the same time ignored studies that kept seeping into the Index Medicus. In the same year Livingston pursued her heart work at Rutgers, the Russians began proving the link between tuberculosis, atherosclerosis and heart disease [8,25,27,28].

Which infection?

Since a 1988 report of raised antibodies against *Chlamydia pneumoniae* in patients with heart disease appeared, it was hoped that the microbe might be behind atherosclerosis [21,41,50]. Hurting this hypothesis was the low incidence of atherosclerosis in the tropics despite chlamydia's high frequency there [52].

Loehe and Bittman concluded that although *C. pneumoniae* on occasions might be present, it was not a causative factor [33] because there was no correlation between the severity or extent of atherosclerosis and the involvement of chlamydial infection at the same site. This report was in concert with Thomas [57] and Gibbs [19]. Combined, they seemed to ask: What if *C. pneumoniae* was just a passenger bacteria, a friendly bystander?

When in 1995 MC Sutter's editorial *Lessons For Atherosclerotic Research From Tuberculosis And Peptic Ulcer*, warned we might be overlooking the role of a microorganism in atherosclerosis, he did not have chlamydia specifically in mind [53].

Nevertheless, statistics showed that people who used a lot of antibiotics had less heart attacks, and so by 2000 the CDC found that 14% of the cardiologists in Alaska and West Virginia treated heart patients with antibiotics for angina, heart attacks, angioplasty or after by-pass surgery.

And certain antibiotics seemed to work, but the question was their efficacy based upon their anti-Chlamydial activity? Azithromycin, for example has well known activity against certain mycobacteria as well.

Something more conclusive

As the millennium approached, something much more irrefutable was happening. It had previously been found that injecting normocholesterolemic rabbits with either the mycobacterial elements of heat shock protein 65 (HSP-65) or with heat-killed *Mycobacterial tuberculosis* resulted in atherosclerotic changes [61]. Heat-killed *M. tuberculosis* was always rich in HSP-65.

Heat-shock proteins of mycobacterial origin like HSP-65 were specific proteins whose synthesis inside the microbe was increased immediately after a sudden increase in temperature. They were one of a number of survival strategies that the mycobacteria used, in this case to diminish the harmful effects of high temperature. Now these mycobacterial elements were not only being implicated in the origin of the atherosclerosis of cardiovascular blood vessels and fatty streak formation [18], but an increase in antibodies against them after angioplasty was being associated with re-stenosis or future closure of coronary vessels [37].

In addition, it became obvious that mice injected with higher doses of heat-killed TB developed significantly larger areas of atherosclerosis despite the fact that their diet was devoid of high-fat content [1]. Xu, also using tubercular HSP-65, proved the same thing in New Zealand white rabbits [62]. In rabbits with normal serum cholesterol, injecting the TB preparation led to the formation of all the classic features of arteriosclerosis in humans- the inflammatory cell accumulation and the smooth cell proliferation (Ibid) that Livingston and Alexander-Jackson had decades ago attributed to the effects of this organism.

The only finding missing from Xu's study with normocholesterolemic animals were foam cells: tissue macrophages in which tuberculosis not only lived but thrived in, capable of ingesting material that dissolved during tissue preparation, especially lipids. However, even then, when Xu's

mycobacterial preparation was given with a cholesterol rich diet, Xu saw all the lesions found in classic human heart disease, including foam cells.

Epidemiologic and pharmacologic considerations

There was also incriminating epidemiologic evidence. The higher incidence of coronary heart disease in young males had a remarkable parallel in bacterial diseases such as TB [52]. And the association between low socioeconomic status and coronary disease found common ground with the incidence of tuberculosis.

The Centers for Disease Control and Prevention (CDC) maps for the total cardiovascular disease and death rates across the country [10] bore a striking similarity to state and regional incidence for CDC maps showing TB case rates in the United States per 100,000 population [9].

In addition, the statins, among the most popular drugs in America (Lipitor, Lescol), though inhibitors of Coenzyme-A compound (HMG-CoA or 3-hydroxy-3-methylglutaryl CoA reductase) and as such lowered serum cholesterol levels, did much more. Specifically, when macrophages were depleted of cholesterol by such pharmacological treatment, mycobacteria such as tuberculosis could not enter the macrophage they usually housed in, thrived and depended upon [17].

Furthermore, this block of macrophage uptake with cholesterol depletion was specific for the mycobacteria and not any other pathogen. In other words, cholesterol played a crucial role in tuberculosis's establishment of intracellular infection for long term survival and the death of 1.9 million people a year.

The recent large British heart protection study took many by surprise when they learned that even lowering "normal" cholesterol levels lowered heart disease risk [12]. This led again to speculation that there must be some other risk factor involved. Lead-author Collins countered that even what we call "normal" cholesterol values are too high, but it is just as easily posited that the lower the blood cholesterol the less likely there is to be chronic mycobacterial infection.

It is hardly a coincidence that studies have shown that statins, which indirectly decrease mycobacterial disease, also lower C-reactive protein (CRP), an age-old, non-specific protein, first identified in 1930, and then found in the serum of various persons with certain inflammatory and degenerative diseases [48]. Recently an elevated CRP

has been touted as an excellent marker for the approximately 25 million US patients that have none of the risk factors associated with heart disease, yet are at risk for a heart attack. However CRP and elevated sedimentation rate have long been excellent markers of active tuberculosis [22], CRP being present at all times when erythrocyte sedimentation rate (ESR) is elevated but returning to normal faster than ESR as tuberculosis, once treated, becomes inactive. Indeed CRP is a sensitive indicator of the activity of tuberculosis [5].

Researchers have even neatly tied in excessive weight and its fat cells to indirectly increasing CRP by dumping interleukin-6 (IL-6) into the blood, which supposedly promotes an inflammatory response, key to signaling the liver, and perhaps the arterial walls themselves, to churn out CRP. But significantly, higher levels of interleukin-6 are consistently found in either the lung secretions [58] or serum [54] where TB resides. Russell noted sustained release of IL-6 repeatedly issued from human macrophages infected with TB [49], a defense strategy the microbe uses to possibly create anergic conditions that prevent macrophages from killing them.

Others look towards elevated serum levels of homocysteine, an amino acid also linked as an index of potential heart disease, as the marker of the future even though a homocysteine marker meta-analysis recently appeared in JAMA, concluding that elevated homocysteine was at most a modest Independent predictor of Ischemic Heart Disease (IHD) in healthy populations [24].

Nevertheless homocysteine, it is claimed by some, although not deposited in blood vessel walls like cholesterol, can damage the inside lining of these vessels and make platelets more likely to clot, the scenario which leads to stroke or heart attacks.

Homocysteine is formed from another amino acid in our diets, methionine. But methionine is also the protein that *M. tuberculosis* brings systemically into its host to initiate its own protein synthesis [11].

Homocysteine can, in addition, be turned back into methionine and its level lowered in the blood but this requires two essential cofactors: vitamin B12 and "folate" or folic acid, both of which can be lowered in tubercular infection, leading to elevated homocysteine levels [35,46].

Nieto's extensive review concludes that the introduction of antibiotic therapies in the 1940s and 1950s could have contributed to the decline of heart disease and heart attacks in the last few decades [39]. Although the tetracyclines appeared in the 1950s it was only after the introduction of

the macrolides, in particular erythromycin in the 1960s that the cardiovascular disease mortality curve began to sink. Though it was hypothesized that such decline was the effect of tetracycline and the macrolides against *Chlamydia pneumoniae*, many of the atypical mycobacteria were also sensitive to erythromycin and the tetracycline doxycycline [36]. Also, the antibiotic time-curve Nieto cites excludes the actual introduction of anti-tubercular antibiotics.

Although erythromycin is very effective against *P. pneumoniae*, the microorganism may persist in the respiratory tract despite adequate blood levels of the antibiotic [51].

There can be no doubt that the availability of antibiotics lowered the morbidity and mortality of cardiovascular disease. Netter mentions that tuberculosis, once often associated with cor pulmonale was less so linked in recent years, probably because of the widespread use of antibiotics and antimicrobial agents [38].

Conclusion

When Nieto stressed the need to extend the possible role of infectious agents beyond the 3 infections which have in recent years been the focus of research: Cytomegalovirus (CMV) *C. pneumoniae* and *Helicobacter pylori* [39], was he picking Sir William Osler's brain regarding that arteriosclerosis was frequently associated with tuberculosis? [42].

Still many ridicule the possibility that microbes might be the agents of arteriosclerosis, the same minds that in another far gone era would have jeered the possibility that syphilis in its late stages had a special predilection for the arteries and could cause devastation of major cardiovascular vessels until these minds were proven wrong. But the lessons of syphilis are far-gone, or are they?

When by 1982, keynote speaker and then Harvard infectious disease guru Louis Weinstein addressed the annual session of the American College of Physicians he mentioned: "We thought initially that the disease (tuberculosis) was disappearing, but we are now seeing up to 27 different syndromes and extapulmonary forms etc. It is today's great mimic, a greater mimic than syphilis ever was" [60].

In *Atherosclerosis and Tuberculosis: Are They Both Chronic Diseases?* after going over the many similarities between tuberculosis and *C. pneumoniae*, Anestad focuses on Norwegian 20th century statistics in which two things become obvious. First, that until 1945 tuberculosis was easily the

leading cause of infectious death in Norway, surpassing cardiovascular death at the time. Second that as the diagnosed cases of tuberculosis fell from his statistics, cardiovascular disease increased dramatically until 1975, when they somewhat tapered [3]. At first glance, these statistics seem unrelated even though they are on the same bar graph. But are they? Or are we just looking at another example of Weinstein's reference to occult TB finding an expanded niche in the cardiovascular system in one of its quests to become "a greater mimic than syphilis ever was"?

In *Tuberculosis In Disguise*, Rab and Rahman document cases of congestive heart failure and IHD with chest pain, raised erythrocyte sedimentation rate, leukocytosis and inverted T-waves across the chest leads otherwise indistinguishable from the real thing, which turned out to be miliary tuberculosis [47]. Rab and Rahman again warned "confusion may occur because tuberculosis can mimic so many other conditions".

Certainly with tuberculosis and the mycobacteria we have a human population affected that dwarfs syphilis in its prime. At least a staggering 1.7 million around the globe die of tuberculosis each year, while another 1.9 billion are infected with *M. tuberculosis* and are at risk for active disease [14]. It would take such a disease to adequately explain the scope of cardiovascular disease, which affects about 61 million people, or almost one-fourth of the population in the US alone.

Almost 6 million US hospitalizations each year are due to cardiovascular disease. (www.cdc.gov/nccdphp/aag/aag_cvd.htm)

The linkage of tuberculosis to acute myocardial infarction is nothing new [16,30,55]; yet serious clinical trials have never been undertaken. And one is left wondering whether the present flurry of trials designed to simply label the markers in the blood that TB and the mycobacteria throw our way is ever really going to quell the near epidemic cardiovascular disease that is presently in our midst.

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