ATHEROSCLEROSIS:

EARLY DIAGNOSIS IS THE MISSING ELEMENT

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As we anticipate modification of the current guidelines for managing risk factors, one might contemplate our current approaches to arteriosclerosis. The major resources devoted to this disease are still spent after the clinical presentation of severely affected patients. Expensive techniques to diagnose and treat specific lesions in the coronary, peripheral and cerebral arteries consume a huge outlay of funds in industrially developed countries. As affluence grows in developing countries, we are seeing the same approach. Evaluating chest pain with relatively insensitive techniques such as resting electrocardiograms, exercise tests and radio-nucleotide scans often leads to angiography or expensive multi-slice computed tomography. Even when lesions are demonstrated, the direct link to the clinical symptoms is not made with certainty. Only during an acute event does the direct attack on a lesion seem to make a difference. We now have excellent studies in stable patients demonstrating little additional benefit from procedures such as angioplasty and coronary by-pass surgery when systemic treatment of arteriosclerosis by risk factor reduction is used instead[1-6]. This treatment using aggressive life style change and drugs that produce lipid lowering and blood pressure control are still needed after such procedures. Why are we spending our precious resources on poorly documented and expensive therapies that seem justified by practice patterns rather than logical interpretation of scientific evidence?.

We have seen tremendous progress in the identification of causative risk factors for cardiovascular disease. The past 20 years has seen success in programs that have addressed these on a community wide basis and in the clinic. Development of guidelines for clinicians in the management of these risk factors such as elevated LDL or the sum of LDL and VLDL (non-HDL) cholesterol as well as for blood pressure control have had a significant impact on clinical events in many countries. Physicians can now approach the asymptomatic individual with a therapeutic regimen supported by strong clinical trial data. In the United States, almost 50% of persons who are over 50 years of age are on statins or other drugs if the LDL cholesterol values were above guidelines[7]. Unfortunately, our recent survey data suggest that those persons below forty

with similar lipoprotein values are far less likely to be treated with drug therapy. This may derive from the current model using a ten year time frame for assessing risk[8]. If one is only interested in the hazard produced by risk factors over the next decade, very few individuals in the younger age groups will be judged as having significant risk. However, risk of a major vascular event may remain very high within the next 20 or 30 years since the clinical presentation of this disease tends to accelerate during the sixth decade of life. The fact that a modest majority of people will die of some other cause, and that individuals with significant risk factors may live to their 9th or 10th decade is often used to question benefit of treatment in asymptomatic individuals.

Our current partial success in treatment and prevention has provided a certain level of satisfaction that has lead to a loss of urgency in attempting to cure this disease. The rise of the clinical manifestations of arteriosclerosis with affluence in rapidly developing countries seems to confirm that this process we call arteriosclerosis is intrinsic to the "good life". At a time when so much attention is being given to the burden of modern healthcare on national budgets, there is too little attention given to the value of treating arteriosclerosis as a slowly developing, insidious, systemic disease. We know that the disease already exists in some children and in many individuals in their young adult years, below age 35. This has been well illustrated in very careful autopsy studies from the Korean and Vietnam Wars and more recently from the Bogalusa Heart Study and the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study among others[9-11]. The extent of lesions have been related to pre-existing risk factors in these studies[12-14]. What if we diagnosed these complex lesions with certainty in the second, third and fourth decades of life (before 40 years of age)? Would we leave these individuals untreated even though they are unlikely to have myocardial infarctions, stroke or sudden death in the next decade?.

In the public health and medical approaches to management, it is easy to recognize parallels between arteriosclerosis in 2011 and tuberculosis (TB) in 1921. TB was the major cause of death in 1921 in the USA. In the 1923 revised edition of the "Principles and Practice of Medicine" by William Osler and Thomas McCrae[15], the history of tuberculosis, its histopathology and clinical presentations were well described. The decline of this disease was noted in England and this was attributed to recognizing the risk factors of poor nutrition, over-crowding, alcoholism, spitting on the streets, working in mines and cutting stone, etc. The English were addressing these issues on a community level. Studies in the laboratory were underway; examination of differing antibodies had been made in the belief that immune susceptibility might be an important factor in some individuals. Vaccination studies in animals and humans were noted to be promising. In Osler's time, early work with a skin test to diagnose TB was reported and of interest to specialists. Climatic treatment was recommended - "The requirements of a suitable climate are a pure atmosphere, an equable temperature not subject to rapid variations, and a maximum amount of sunshine". High cost treatment approaches were also in vogue. Physicians and other healthcare workers built careers devoted totally to treatment of TB. Large institutions called "sanitaria" were built to provide "the advantages of rigidly enforced rest, good food and physical exercise". Drug treatment of the time consisted of creosote, cod-liver oil and arsenic. A variety of surgical procedures were performed in many patients such as induction of pneumothorax, draining pleural exudates and resection of destroyed segments of the lung.

A turning point in the battle with TB occurred with the development of isoniazid and multiple other agents that provided effective treatment. However, the real advance came when it was recognized that many young people had tuberculosis in a sub-clinical indolent stage and that it could be diagnosed in such persons. The injection of a tiny amount of "purified protein derivative" of tuberculin bacteria (PPD) provided a highly specific and sensitive skin test giving a definitive diagnosis of previous TB exposure and the likely presence of indolent disease. The test was low cost and easily administered by personnel with little training. By 1960, it was in common use in students in colleges and graduate schools and continues to be systematically applied today. We now monitor those with risk factors for tuberculosis such as HIV infection and environmental exposure. The discovery of a positive skin test results in treatment even though the person may appear asymptomatic and fully healthy. The result has been a marked reduction in the prevalence of this terrible disease. Managing risk and monitoring those with major risk factors for TB remains part of the management paradigm.

Using the TB analogy, we appear to be in the Oslerian period of arteriosclerosis. We know the major causal risk factors, we have effective therapy for these and we have begun many good community programs. Physicians are aware of guidelines and are attempting to treat high risk individuals. We have improved our diagnostic tests for those with gross symptomatic lesions but we are still in the phase of using highly expensive technical approaches to attack individual lesions with only some emphasis on curative treatment for the generalized disease. Too many people present with the disease by dying. How do we make progress from our current partially successful efforts?.

Individuals with complex lesions, in their twenties and thirties, defined at autopsy in the PDAY study, should have been detected while alive and diagnosed as having arteriosclerosis. The causative risk factors in such patients may be operative at a much lower level than in others with less susceptibility. In these patients, it may be very useful to treat lipoprotein concentrations considered to be relatively innocuous in the general population. Smoking may be particularly toxic in such patients. There may be new and important risk factors in these very young people. A focus of research on these individuals might lead to discovery of other causal factors. An additional decade or two of treatment in such patients may have a very significant impact on sudden death and acute coronary and cerebrovascular syndromes. The issue is to diagnose the disease and use risk factors as venues for treatment rather than diagnosing risk factors and hope that we will be treating those who would have the disease.

So how do we produce a cost effective means of detecting early arteriosclerosis, without significant risk, in every person over 20 years of age in the population? Our research on the cellular, chemical and physiologic characteristics of the diseased artery wall, even in the very early phases of the disease is providing exciting information that should be useful in this effort. A diseased artery, before development of complex lesions, is sending signals that could distinguish it from a healthy artery. Much of the research is already done documenting that measuring some of these signals is feasible. Detecting a pattern of chemical signals or a characteristic physiologic response should be possible with sophisticated equipment at low cost in every primary care clinic. Practicing physicians and their staff use computers and complex machines for multiple tasks in the modern office. Providing a procedure to diagnose early arteriosclerosis need not be more complicated. The missing element is a concerted well funded effort to refine the technology, define the data analytic tools and fully test several approaches to this goal of early diagnosis. Clinical lipidologists as a group should challenge the scientific and engineering talent in this world to meet this most pressing need. It is easy to justify the organizational and financial efforts required for success. The missing element is the strong belief that it can be done. This disease is too prevalent, too personally devastating and too costly for the medical community to be apathetic and overly patient in bringing this dream to fruition.

References

1. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2)trial. Lancet 1997;350:461-8.

2. Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. N Engl J Med 1999;341:70-6.

3. Hueb W, Soares PR, Gersh BJ, et al. The Medicine, Angioplasty, or Surgery Study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: one-year results. J Am Coll Cardiol. 2004;43:1743-51.

4. Henderson RA, Pocock SJ, Clayton TC, et al. Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy. J Am Coll Cardiol 2003;42:1161-70.

5. Katritsis DG, Ioannidis JP. Percutaneous coronary intervention versus conservative therapy in nonacute coronary artery disease: a meta-analysis. Circulation 2005;111:2906-12.

6. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal medical therapy with or without PCI for stable coronary disease: the COURAGE trial. N Engl J Med2007;356:1503-16.

7. Mann D, Reynolds K, Smith D, Muntner P. Trends in statin use and low-density lipoprotein cholesterol levels among US adults: Impact of the 2001 National Cholesterol Education Program Guidelines. Ann Pharmacother. 2008;42:1208–1215.

8. National Cholesterol Education Panel. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. Circulation. 2002;106:3143–3421.

9. Berenson GS, Wattigney WA, Tracy RE, et al. Atherosclerosis of the aorta and coronary arteries and cardiovascular risk factors in persons aged 6 to 30 years and studied at necropsy (the Bogalusa Heart Study). Am J Cardiol 1992;70:851-858.

10. Henry C. McGill, Jr, C. Alex McMahan, and Samuel S. Gidding Preventing Heart Disease in the 21st Century: Implications of the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study Circulation, Mar 2008; 117: 1216 - 1227.

11. Tuzcu EM, Kapadia SR, Tutar E, et al. High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults: evidence from intravascular ultrasound. Circulation. 2001: 103; 2705–2710.

12. Mahoney LT, Burns TL, Stanford W, et al. Coronary risk factors measured in childhood and young adult life are associated with coronary artery calcification in young adults: the Muscatine Study. J Am Coll Cardiol. 1996: 27; 277–284.

13. Berenson GS, Srinivasan SR, Bao W, et al. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults: the Bogalusa Heart Study. N Engl J Med. 1998: 338; 1650–1656.

14. McGill HC Jr, McMahan CA, Zieske AW, et al. Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth: the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Arterioscler Thromb Vasc Biol. 2000: 20; 1998–2004.

15. OslerW and MCCrae T. The Principles and Practice of Medicine (Ninth Edition). D. Appleton and Company publishers. New York and London.

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