An Introduction to the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study

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In the mid-1980s, three pioneers of atherosclerosis pathologic research, Robert Wissler MD, Jack Strong MD, and Henry McGill MD initiated the PDAY study. The founding idea was that atherosclerosis developed over the life span of an individual and if the process could be arrested or delayed early in life, the epidemic of acquired cardiovascular disease could be prevented. Essentially, they wanted to build on the observation that atherosclerosis had been identified in the young casualties of the Korean and Viet Nam conflicts by demonstrating the relationship of early atherosclerosis to established risk factors which included elevated serum lipid levels, hypertension, diabetes, smoking, and obesity. The principals all had experience with primate models where all of these risk factors were confirmed to cause atherosclerosis

To accomplish this goal, the investigators established a network of pathology laboratories across the country. These centers, utilizing a standard protocol, harvested, precise regions of the left and right coronary arteries and the abdominal aorta, sites of known atherosclerosis accumulation and origin of abdominal aortic aneurysms, in 15-34 year old casualties of accidental or unexpected death. Demographic factors including age, gender, and ethnicity were obtained from the deceased and atherosclerosis lesions were mapped and graded according to the American Heart Association Grading criteria. Risk factors were measured from post mortem blood specimens restricted to those individuals whose resuscitation minimized the potential for contamination by fluid shifts (smoke exposure, lipids, glycemic status). Hypertension was assessed as a categorical variable and based upon renal arterial thickness and correlated with presence of an ante-mortem blood pressure of > 140/90 mmHg. Later analyses added measurements such as apolipoproteins and c-reactive protein. Genetic information was obtained. Overall, more than 2000 individuals were enrolled in the study across the country, with complete data obtained on more than 50% of the cohort.

A bibliography of PDAY publications is provided in this section of the IAS website. These papers provide the methodology, main findings, and several review articles summarizing the implications of the PDAY results.

The most important finding of the PDAY study was establishing a clearly defined relationship between the known risk factors for atherosclerotic heart disease and the direct measurement of atherosclerotic lesions. This extended across all American Heart Association grades in decedents ranging from 15-34 years old with no known clinical heart disease. By mapping the location of atherosclerotic lesions by age and grade, a clear age-related progression to more advanced lesions was demonstrated. By the fourth decade of life, a substantial percentage of the cohort, had lesions considered by AHA criteria as vulnerable plaque. These findings supported population-based recommendations to promote heart healthy lifestyles including avoidance of tobacco products, proper nutrition (lower consumption of saturated fat and salt in particular), and avoidance of obesity. PDAY findings were consistent with similar findings from the Bogalusa Heart Study in individuals who suffered premature deaths and had risk factors measured ante-mortem.

PDAY also demonstrated gender differences in the progression of atherosclerosis (women slower), the accelerative effect of the presence of multiple risk factors, the presence of a graded relationship of serum cholesterol levels to atherosclerosis, differences in risk factor relationship to arterial locus (tobacco much greater in the aorta than coronaries), and the presence of atherosclerotic risk in individuals with normal cholesterol but other risk factors. Finally, PDAY published perhaps the first demonstration of genetic influence on atherosclerosis development by showing an independent effect of Apo E genotype.

While the original aim of PDAY was to support population-based interventions to lower cardiovascular risk, it became clear that a high risk subgroup within the PDAY cohort with more advanced disease could be identified. This led to development and validation of a risk score to predict advanced American Heart Association atherosclerotic lesions using subclinical imaging modalities. These studies suggested that measurement of the PDAY risk score as early as 25 years prior to atherosclerosis imaging was highly predictive

of the atherosclerosis outcome measure, further supporting the importance of early recognition of risk factors. Ongoing research uses existing PDAY specimens and also new specimens from victims of accidental death, managed according to the PDAY protocol, for genetic and –omic approaches to understanding cardiovascular risk.

There are a number of important limitations to the PDAY study. Ultimately, given the single assessment point, PDAY was cross-sectional. Post-mortem data collection led to attenuated relationships of serum/plasma measures to endpoints. Potentially important family and medical history data was unavailable. A graded relationship of blood pressure to endpoints could not be established. Carotid artery specimens were unavailable because of the need to preserve bodies for burial.

The founders of PDAY fervently wanted their research material distributed as widely as possible. Thus, we have included on the IAS website this introduction, a PDAY bibliography, and slides showing the main findings of the PDAY study including the complete Kritchevsky lecture delivered by Henry McGill at the American Heart Association Spring Epi/Lifestyle Scientific Sessions.

Given the powerful impact of the PDAY study, particularly on those interested in the prevention of atherosclerosis, and understanding the limitations presented above, it is important to determine how the PDAY study fits into current evidence paradigms. Can PDAY be assigned a role stronger than "high quality observational data"? If one believes that atherosclerosis is a disease, and waiting for an atherosclerosis-related event is too late, then the PDAY study directly measures, in the most accurate way possible, a clinical end point. Though not longitudinal, PDAY provides strong evidence demonstrating that chronic exposure to identifiable risk factors precedes by decades preventable life shortening cardiovascular events. This data should provide the foundation to attack atherosclerosis much earlier in the life course, through modification of risk development by public health measures and by trials in high risk individuals.

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