ARIC Manuscript Proposal # 721

PC Reviewed: 03/07/00  Status: Deferred  Priority: _____
SC Reviewed: _________  Status: _____  Priority: _____

1.a. Full Title: Adhesion molecule expression differences between Caucasians and African-Americans as a risk factor for premature cardiovascular events

b. Abbreviated title: Adhesion Molecules in African-Americans

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3. Timeline:
   Proposal prepared 3/1/00
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   Distribution of manuscript 2/1/01
   Official Analysis/Data Verification 4/1/01
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   Submission to Journal 7/1/01
4. Rationale:

Racial differences in cardiovascular events (stroke and myocardial infarction) are known to exist, with African Americans having a higher morbidity, mortality, and incidence of stroke and myocardial infarction compared to Caucasians. Young blacks (<65 years of age) lose more years of life compared to whites due to cardiovascular disease among hypertensives. While higher frequencies of hypertension, diabetes, elevated lipoprotein levels, and low socioeconomic class have been identified as risk factors, other potentially treatable factors have not been fully elucidated.

It is known that blacks have higher immunoglobulin concentrations, higher incidences of autoimmune diseases (e.g. SLE, scleroderma, and dermatomyositis), and an increased frequency of autoantibodies compared to whites. These findings suggest that blacks have a more active immune system than whites. Recent evidence has suggested that adhesion molecules such as ICAM-1, VCAM-1, L selectin, and P-selectin contribute to atherogenesis. Animal studies have suggested that interruption of adhesion molecule expression prevents accelerated atherogenesis or reduces ischemic insult. Few, if any, studies have directly investigated the hypothesis that the increased incidence, morbidity, or mortality of cardiovascular events in blacks is due to differences in expression of these adhesion molecules. Initial regression analysis of ARIC data by Folsom et al. have shown that some hemostatic parameters (vWF, FVIIIc, white blood cell count, fibrinogen) correlated with ischemic stroke, supporting the concept that abnormalities of hemostatic and inflammatory markers are associated with increased risk of stroke. A comparison of adhesion molecule expression between African-Americans and Caucasians may identify important risk factors as well as potential therapeutic targets for cardiovascular disease. Intervention in patients with abnormal adhesion molecule expression as a risk factor for cardiovascular disease may reduce the excessive cardiovascular morbidity and mortality in African-Americans. Therefore, we propose to examine adhesion molecule expression differences between African-Americans and Caucasians to determine if these differences contribute to accelerated atherogenesis and cardiovascular mortality in African-Americans.

5. Main Objectives:

African-Americans with premature (<60 years of age) stroke, myocardial infarction (MI), or coronary heart disease have increased adhesion molecule expression compared to age- and sex-matched Caucasians prior to the incident event.

6. Data (variables, time window, source, inclusions/exclusions):

In a case-control manner the following variables would be compared:

Variables – Controlled – age, sex, hypertension, diabetes, hyperlipidemia, smoking, obesity, stroke, myocardial infarction, coronary heart disease

Variables – Measured – CRP, E-selectin, L-selectin, P-selectin, ICAM-1, VCAM

Time window – ARIC study timeline using the baseline visit (visit 1) as the measured immune parameter source with prospective case ascertainment of stroke, myocardial infarction, and coronary heart disease cases.
Methods – Comparison of adhesion molecule expression between African-American and Caucasian cardiovascular cases will be made as well as comparison between race/sex/age matched controls.

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<td>Control adhesion molecule expression</td>
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As a second level of analysis, a comparison of associations between adhesion molecule expression and cardiovascular events will be made across racial groups (i.e. stratify on race and compare quartiles of adhesion molecule expression). Ultimately odds ratios (as estimates of relative risk) for cardiovascular events could be made by comparing the upper quartile of measured adhesion molecule expression with the lower quartile.

Source – ARIC nested case cohort design and available measurements or available serum for additional testing, if necessary, through an ancillary proposal

Expected results - We would expect that if our hypothesis were true, African-Americans with stroke, MI, or coronary heart disease would have increased adhesion molecule expression prior to the incident event, as evidenced by higher E, L, or P-selectin, ICAM-1, or VCAM expression compared to Caucasians, and, perhaps, to control cases. It is also possible that race-based adhesion molecule expression differences would be identified in controls. This finding may have implications for other inflammatory disease states.