Manuscript #286

1. Title:
Homocyst(e)ine and expression of tissue factor as measured by Factor VIIa

2. Writing Group:
(lead) P. Schreiner            K. Wu                M.R. Malinow             V. Stinson
        J. Nieto                    A. Folsom              L. Chambless             H. Ghaddar

3. Timeline:
Data on homocyst(e)ine exist for 679 of the ultrasound cases and controls; of these, 325 participants in the PPL ancillary study (192 controls, 133 cases) have measures of Factor VIIa, Factor VII:c, and Factor VII:Ag in addition to homocyst(e)ine. If approval is granted for this proposal, analyses can proceed as soon as the PPL data are available to this writing group.

4. Rationale:
We have previously shown (Circulation, Feb. 1994, AHA Council on Epidemiology and Prevention abstract) that, within the predominantly normal levels of homocyst(e)ine (H(e)) found in the ARIC Study cases and controls, increasing levels of H(e) are positively and statistically significantly associated with several procoagulant hemostatic factors (platelet count, Factor VII:c, Beta-thromboglobulin, and tissue plasminogen activator), after adjustment for age, race (White vs. African-American), gender, cigarette smoking (current vs. former/never), and case/control status. In addition, when measures of hemostatic activity/potential are placed in a multivariable model as independent variables with H(e) level as a continuous dependent variable, Factor VII:c remains a significant predictor of H(e) (partial beta=0.0122, p=0.0193, after adjustment for the covariates of age, race, gender, cigarette smoking and case/control status). However, because Factor VII:c is a measure of circulating Factor VII zymogen (inactive) as well as actual activity (the amount of Factor VII converted to Factor VIIa in the presence of thrombin), we propose to look at the association of H(e) with Factor VIIa as an indirect assessment of tissue factor, the cell surface receptor and cofactor for Factor VIIa. Direct measurement of Factor VIIa has recently been described by Morrissey and coworkers at the Oklahoma Medical Research Foundation in Oklahoma City—these investigators have demonstrated that the amount of Factor VII converted to Factor VIIa depends on tissue factor, which is currently considered the major physiologic trigger of the coagulation cascade. In vitro work suggests that one of the roles of H(e) in altering hemostasis is in directly increasing expression of tissue factor. Factor VII:Ag will be used as a stable measure of Factor VII. Other considerations that potentially belong in this proposal: Is the association between H(e) and Factor VIIa affected by the postprandial (3.5 hours postload) state? Does Factor VII:c vary by fasting and nonfasting status?

5. Research Hypothesis:
In a nonrandom subsample of the population-based ARIC visit 1 cohort, homocyst(e)ine levels within the normal range (~10 µmol/L) are directly associated with Factor VIIa, as a measure of tissue factor.

6. Data analysis:
We propose to conduct our own analyses on the extant H(e) data and the Factor VII data when it becomes available. Conventional cardiovascular risk factors such as age, race, gender, smoking, obesity and lipids will be examined as potential covariates, as well as B-vitamin supplement use as an affecter H(e) levels (only as a covariate--diet and supplement B-vitamin intake is being addressed by Tomoko Shimakawa in another ARIC
writing group). Because of the potential differences in the effect of triglycerides on Factor VII:c levels in fasting and nonfasting individuals, triglycerides will be adjusted for in the multivariable model. Further, given that this is a nonrandom sample, tests of case/control status as both an effect modifier and a confounder to the association between H(e) and Factor VIIa will be assessed. Sampling weights generated by the CSCC for the case/control sample may potentially be used in these analyses, particularly if case status appears to be an effect modifier.