1. Full Title: The Association of Paraoxonase Genotypes with Incident Coronary Heart Disease, Carotid and Peripheral Artery Atherosclerosis, and Lipoprotein Phenotypes; the ARIC Study
   Abbreviated title: Paraoxonase and CHD

2. Writing group:
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3. Timeline:
   Paraoxonase genotypes have been determined. Data analyses can begin as soon as data arrives at Chapel Hill. First draft of the manuscript should be ready by summer 1998.

4. Rationale:
   Paraoxonase is an HDL associated enzyme, which has been named according to its ability to hydrolyze insecticide paraoxon. Its physiologic task and substrate(s) are not known, but it is assumed to protect LDL particles from oxidation by hydrolyzing lipid peroxides.
   A common AIG polymorphism has been described in the coding region of the paraoxonase gene. The A allele codes for glutamine (A isoform) and the G allele codes for arginine (B isoform) at codon 192 of the enzyme. The allele frequencies of A and G alleles in Caucasian populations have been around 0.75 and 0.25, respectively. B-isoform of the enzyme has higher paraoxonase activity than the A-isoform (1-2), but it is not known whether the activities differ in terms of protection from oxidation or other putative physiologic tasks.
   A second polymorphism of the paraoxonase gene has been described affecting position 54 and involving a methionine to leucine change (2). It is in linkage disequilibrium with the polymorphism at position 192.
At the moment there are at least four cross-sectional case-control studies, which have found an association between the G allele (B-isoform) of the paraoxonase enzyme and increased CHD risk (3-6). Three of these studies have been carried out on Caucasians. In the fourth study, the association was race-specific existing in Asian Indians, but not in Chinese individuals (5). Furthermore, one study has reported that the allele coding for leucine at position 54 is associated with the increased CHD risk (2). On the other hand, there are at least two negative studies on the relationship of A/G polymorphism with CHD (7,8). No prospective studies have been published and no study has included black individuals. Two of the four positive studies have been carried out on patients with NIDDM suggesting that the effect may be strongest in persons with increased oxidative stress. Interestingly, it was recently reported that cigarette smoke extract inhibited paraoxonase in a dose- and time-dependent manner and this was suggested to be one of the mechanisms for increased atherosclerosis among smokers (9).

The relationship of paraoxonase polymorphism to lipid and lipoprotein phenotypes has been controversial. A theoretical background for these genotype-phenotype studies is that paraoxon is a very effective irreversible inhibitor of two key enzymes of lipid metabolism, lipoprotein lipase and hepatic lipase. Hegele RA and coworkers have reported significant associations between the variation in paraoxonase genotype and variation in quantitative lipid and lipoprotein traits from two different populations in Canada (10,11), whereas most other studies have found no association (1,5,7,8).

The large sample size and prospective nature of the ARIC study provides unique possibilities to solve some of the discrepancies mentioned above. Furthermore, repeated examinations of the ARIC study provide good possibilities to analyze genotype-phenotype relationships. The association of the variation in paraoxonase genotype with variation in quantitative lipid and lipoprotein traits can be analyzed both cross-sectionally using between-individual variation and longitudinally using within-individual variation over time.

5. Main hypothesis:
The G allele of the paraoxonase gene, coding for arginine at position 192, is positively associated with the risk of incident CHD, carotid atherosclerosis, and peripheral artery disease independently of lipid phenotype and blood pressure. The increase in risk is particularly prominent in persons with increased oxidative stress, e.g. in smokers and in diabetic persons.

Secondary hypothesis:
Paraoxonase A/G polymorphism is not associated with variation in quantitative lipid and lipoprotein traits. Of particular interest here are HDL-cholesterol, apolipoprotein AI and other variables related to HDL metabolism.

6. Data (variables, time window, source, inclusions/exclusions):
Paraoxonase genotypes have been determined on cohort random sample, cases with incident CHD, carotid atherosclerosis cases, and cases with peripheral artery disease. They will be analyzed using the case-cohort design. Persons with prevalent CHD or
history of stroke or TIA at baseline will be excluded. Other variables needed include age, gender, race, field center, "standard" CHD risk factors, esp. smoking, diabetes, HDL cholesterol, apo AI.

REFERENCES: