ARIC MANUSCRIPT PROPOSAL #682

1.a. Full Title:

TNFa, IL-6 and incident diabetes mellitus.

b. Abbreviated Title (Length 26):

TNFa/IL-6 - Diabetes

2. Writing Group (list individual with lead responsibility first):

Lead: Maria Ines Schmidt
Address: Av. Luiz Manoel Gonzaga, 630/8
Porto Alegre, RS 90470-280
Phone: +55 51 328-7215

Electronic Mail Address: bbduncan@orion.ufrgs.br

Bruce B. Duncan
Christie Ballantyne
L.E. Chambless
Jim Pankow
Aaron Folsom
A. Richey Sharrett

(Please distinguish this proposal, which derives from the “Lab Committee Diabetes Case –Cohort Study”, from the conceptually similar R01 grant, recently submitted by Jim Pankow, which proposes an ancillary study to investigate a broad range of mediators and markers of inflammation with incident diabetes.)

3. Timeline: 9/99 - 12/00

4. Rationale:

Current diagnostic criteria for diabetes permit its diagnosis on the basis of fasting glucose values, feasible in all ARIC visits. Previous criteria were based on a combination of fasting and 2h post-load glucose values, performed in ARIC only at Visit 4.

Type 2 diabetes is a group of hyperglycemic disorders characterized by beta cell dysfunction, in most cases preceded by insulin resistance. The similarity of risk factors between CHD and type 2 diabetes led us to hypothesize that, just as with CHD, the scenario of type 2 diabetes pathogenesis also presents
inflammatory actors. Work by AWGs 539 and 539a provided further support for this hypothesis. Cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), overexpressed in obesity, alter insulin sensitivity and or insulin secretion and are thus likely actors in these associations.

To investigate the inflammation – incident diabetes association more directly, we now propose to investigate the association of TNF-α and IL-6 with incident diabetes in a diabetes case-cohort subset of ARIC.

5. **Main Hypotheses:**

A. The inflammatory cytokines TNF-α, IL-6 are independently associated with incident type 2 diabetes.

B. Associations remain after exclusion of anti-GAD positive cases of diabetes, purportedly of autoimmune origin.

C. Associations will be of similar magnitude for those meeting the current diabetes diagnostic criteria at Visit 4 and not the previous (based on OGTT) and those meeting both diagnostic criteria.

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

   Selection data: CRS or diabetes case indication.

   Exposure data: TNFα and IL-6

   Covariates (Visit 2 unless otherwise stated): Age, gender, center, fasting glucose, smoking, HDL-C, triglycerides, hypertension, sports/leisure/work physical activity (Visit 1), BMI, WHR, fasting insulin (Visit 1)

   Time to event data: v2, v3 and v4 visit dates.

   Baseline and incident diabetes data: component parts to define and characterize diabetes at all visits (fast0802, medication use, physician history, glucos01 and later visit equivalents); plus fasting insulin and 2h glucose (Visit 4), GAD-antibody; anti-diabetes medication use visits 3 and 4.