

TECHNICAL PROPOSAL C

**TISSUE AND URINARY GLYCOSAMINOGLYCAN CHANGES
RELATED TO VINYL CHLORIDE INJURY: USE AND EARLY
DETECTION AND DIAGNOSIS**

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During the second year of this proposal, work will continue to complete studies undertaken during the first year. These will include a completion of our evaluation of the effects of vinyl chloride exposure with and without liver injury on the urinary glycosaminoglycan excretion patterns. We have begun and, hopefully, will complete during the middle of the second year the evaluation of 24-hour urine sample collections from workers who fall into high, medium, and low exposure categories (exposure data coming from the Vinyl Chloride Medical Surveillance Data Bank). In addition, individuals already demonstrated to have liver injury, with both high vinyl chloride exposures as well as low, will also be studied.

There will be two control groups involved in this study. One will be those derived from individuals with other fibrogenic liver diseases, such as cirrhosis, hepatitis, and alcoholic liver injury. Since the preliminary data suggests the possibility that the urinary excretion patterns for vinyl chloride injury are distinctly different from these other frequently found non-occupational illnesses, this work will involve determination of the specific GAG excretion fractions and their complete biochemical characterization. This is needed in order to determine the usefulness of specific GAGs in the assessment of vinyl chloride injury as well as other chemical liver injury. Such data will have great value in future assessments of the effects of many types of hepatic toxic chemicals and exposure to them in the work place. These studies are expected to result in the development of specific tests for early liver damage and would, hopefully, become part of the routine medical screening of workers with potential exposure to hepatic toxic chemicals. Methods to determine the chemical characterization and identification of these specific GAGs are cited in the original grant application.

Animal studies to be conducted during the second year will be the experiments, described in the original application, designed to determine the direct effects of vinyl chloride exposure on the experimental animals on the GAG changes in tissue and urine. These studies will involve both animals exposed to relatively high (10 to 20 thousand parts per million) and relatively low (25 to 50 parts per million) levels of vinyl chloride. These studies will enable us to identify the specific testing parameters that would lend themselves best to routine screening

in the working population, as well as to assess the specific role of the GAG in fibrogenesis both in their reversible and irreversible stages. Depending on these observations, those specific GAG changes in the urine that appear to be valuable as indicators of liver injury will be further developed into a "final" procedural modification for the determination of these urinary GAG fractions by quick simply methodology--spot tests, perhaps--that can be used as a routine medical screening.

In the third year, studies will be made with other animal models; and we will conclude our evaluation of the human population. The animal model studies will include:

- (1) A study of the effects of partial hepatectomy on urinary and liver GAG levels - These studies will be done to assess the effect of cell division and cell regeneration on the liver and urinary GAG levels. This is of vital importance since many individuals working in the industrial environment also have non-occupationally related liver injury--such as viral hepatitis and alcoholic injury--which stimulate liver cell division and liver regeneration.
- (2) Studies of the role of GAG in fibrogenesis, generally - One set of studies will involve the effect on urinary and tissue GAG after stopping chemical liver injury (carbon tetrachloride) before and after the stage of irreversibility.
- (3) Studies of the incorporation of radio sulfur labeled GAG subunits into liver tissue during fibrogenesis induced by both carbon tetrachloride and vinyl chloride exposure.
- (4) Studies of prolonged exposure to determine the specific effects of the presence of developing cancer on the GAG levels - This will be conducted both in the animals with vinyl chloride-induced angiosarcoma and/or primary hapatoma, as well as in experimental animals carrying transplantable hepatomas (Novikoff).

SUMMARY

Preliminary results, both in the human material and in the preliminary animal experiment studies, indicate that the GAG changes in both urine and tissue may well be in the earliest demonstrable change to occur with liver injury. Work in the second and third years will help confirm the usefulness of these parameters in early detection, identify the significant leads for the design of future studies of the role of GAGs and, hopefully, give further information that may permit interference

with and/or modification of GAG metabolism's leading to fibroses of the liver. Finally, these studies will help produce the data concerning the relative specific effects of cancer development and how this may differ from non-occupational hepatocellular injury, such as that due to viruses or alcohol.