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March 11, 1974

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Building 1, Room 520
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ATLANTA, GA 30333

Special Delivery

SUBJECT: Review and Recommendations
concerning Hepatic Angiosarcoma
apparently related to vinyl chloride
exposure (Conference of 3/2/1974)

Dear Dr. Heath:

At the conference at the NIH on March 2, 1974, data was presented concerning 6 proven cases of angiosarcoma of the liver (possibly a seventh case) occurring at the B.F. Goodrich plant at Louisville, Ky. On the basis of the exposure there to vinyl chloride, the cases presented by Dr. Popper from Germany and the animal studies mentioned, it seems essentially inescapable that the lesions occur incident to the exposure to vinyl chloride. There were a number of similarities among these cases. The tumor pathology was identical and the tumor behavior seemed to be one of local extension rather than widely metastatic. Case #1 might be tumor of multicentric origin.

The liver lesion in the non-tumor portions of the liver was of great interest. Material from four cases without known tumor was reviewed, presenting similar pathology. Primarily, there was widening and fibrosis of the portal areas, some collagen in the sinusoid near the periphery of the lobule and peculiar sinusoidal lining cells, presumably the precursors of the angiosarcoma cells. It would appear that the portal fibrosis, or, maybe, more

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importantly, the sinusoidal fibrosis leads to fairly early portal hypertension, hemodynamically similar to idiopathic portal hypertension (Banti's disease). Esophageal varices and marked splenomegaly were present in some of the cases.

Unfortunately, neither the tumor nor the liver lesion preceding it provoke very marked alterations in the hepatic tests. The most consistent appears to be small to moderate increases in the SGOT, some increase in serum alkaline phosphatase and sometimes small rises in the serum total bilirubin. Other tests seemed to be variably abnormal (LDH, serum globulin). Coupled with the mild test abnormalities was increased spleen size in a number of the cases.

The central problem is that of how to monitor exposed workers for early evidence of hepatic toxicity. It would appear that the hepatic lesion precedes tumor formation, as a rule, by some years. Also that there is some relationship to a long duration of exposure for both lesions. It is recognized that rather large numbers of workers are involved for screening purposes. My suggestions are as follows:

1. Biochemical screening at the time of new employment (base line) and for all workers, then once per year. I would suggest this be increased to every six months after the 10th year of exposure.
2. Preferably the biochemical tests should be those able to be done by the SMA (or other automated means).
3. It might be of use - experience would tell - to program the SMA for the SGPT (as well as SGOT) and possibly for the GGTP. This type of liver lesion appears to produce little hepatocyte injury and thus transaminase-type tests are going to be of limited value, but there may be nothing currently better.
4. More intensive investigation could then be done on the cases that drop out with test abnormalities. I would suggest repeat tests in one month, possibly again in another month. Hopefully the abnormalities will be modest in number and therefore practically could be investigated more thoroughly.

The hepatitis B antigen probably should be done when the enzyme tests are elevated to help clear the picture of unrelated viral hepatitis. If abnormalities persist one month, I would advise then a physical examination, history taking (alcohol, medications, recent transfusion or hepatitis contacts, etc.)

#5. If the cause of the hepatic test abnormalities is not clear, i.e. now possibly vinyl chloride-related liver disease, a liver scan with technetium would seem indicated and useful. As discussed at the conference, at this point practicably it is likely the patients would be referred to private physicians or clinics for further work-up.

#6. There are a number of other considerations. The proline hydroxylase test might be of interest and utility in screening. The BSP test seems not to be (not surprising, in light of the Banti-like disorder). It remains uncertain if the hepatic lesion might still advance to tumor with withdrawal from vinyl chloride exposure. I doubt this tumor will be associated with alpha-fetoprotein, but this should be determined, especially by radioimmunoassay.

#7. I doubt that unusual biochemical tests will turn out to be of much value over customary hepatic tests, since the hepatic tests are usually based on reduction of functional mass, hepatocyte injury or bile duct obstruction, none being prominent here. Nonetheless some rather intensive investigation of a tumor case and a few of the "liver disease" cases might provide useful information applicable to screening.

#8. Liver scan features showing some degree of splenomegaly or "spotty" hepatic uptake probably should be arbitrarily interpreted in this setting as vinyl chloride toxicity.

#9. Liver biopsy, when indicated as considered by physicians caring for these patients, can be very helpful, it appears, and should be encouraged. However, if the scan suggests tumor type of defects, needle biopsy might be somewhat hazardous with this vascular type of tumor.

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- # 10. The idea of monitoring a "control" population, was raised and is attractive if feasible.
- # 11. An effort should be made to follow up former exposed employees to see what has occurred after leaving exposure areas.
- # 12. For workers in high exposure work (autoclaves), some of the techniques used in the lead industry (air currents, gas masks, showers, etc.) might be of value in reducing the degree of exposure.
- # 13. There seems to be urgent need for data re the biology of vinyl chloride (metabolism, excretion, tissue levels, etc.)

Very truly yours,

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