UNIVERSITY OF LOUISVILLE
LOUISVILLE, KENTUCKY 40202

SCHOOL OF MEDICINE
DEPARTMENT OF MEDICINE
DIGESTIVE DISEASES AND NUTRITION SECTION

HEALTH SCIENCE CENTER
WALNUT & PRESTON STREETS

November 30, 1976

The second meeting of the "Ad Hoc Committee on Videotaping" was held at St. Anthony Hospital. The committee worked for 1½ hours on the objective of developing videotape materials that will focus upon informing BFG clients during their annual physical. Each medical screening is performed at St. Anthony's during a 2-hour segment of time. Usually 8 clients are scheduled each day Monday through Friday. Ms. Walker and Young will ascertain the number of testing locations and approximate amount of time spent in each. They will report at the next meeting of this committee (Thursday, December 2). Topics for programs were "brainstormed":

1. What is involved in medical screening?
2. What do these tests try to determine?
3. The history and rationale of medical screening.
4. BFG and other medical surveillance programs.
5. Client interview re reaction to medical screening.
6. Bio-statistics and BFG workers.
7. The "whys" of preventive medicine.
8. The roles of the various professionals working on VC Project.
9. An overview of the VC Project.
10. Medical findings at BFG.
11. Entertainment intermission.

These topics and other suggestions for programs will be discussed at the next meetings on December 2 and December 7 so let's "put on our thinking caps". The meeting will be held at the Carmichael School Room 113. Call if you can't make it. 588-5801.

MD:mm

cc - R. M. Abell
J. G. Whelan, M.D.
L. Makk, M.D.
C. H. Tamburro, M.D.
J. L. Creech, M.D.
M. M. Dechman
J. W. Duvall
M. Walker, R.N.
S. Young, R.N.
B. Gray, R.N.
Doc Hamilton
L. Madras

The American Association for the Study of Liver Diseases

Abstract #35--Initial Features of Vinyl Chloride Hepatic Injury.

Fenton Schaffner, Hans Popper and Irving J. Selikoff
Mt. Sinai School of Medicine

Mr. Chairman, Members and Guests --

Prolonged exposure to vinyl chloride monomer has resulted in a development of angiosarcoma in the liver. May I have the first slide, please?

The early lesions produced in the liver were studied in mice repeatedly exposed so that the precursor lesions of angiosarcoma could be ascertained in modes of clinical screening suggested. The mice were placed in special chambers containing 2500 or 6,000 ppm gaseous vinyl chloride for 5 hours a day, 5 days a week, for 1,3, and 6 months. The livers were examined electron microscopically.

NEXT SLIDE. The normal mouse liver sinusoid is lined by thin endothelial lining cells.

NEXT SLIDE. The earliest changes are large vacuole formation in the hepatocyte cytoplasm near the sinusoidal plasma membrane. The sinusoidal microvilli are more irregular than the normal with shedding of pieces of cytoplasm into the Disse space. Many, but not all of the sinusoidal lining cells are thickened and their cytoplasm contains sparse organelles. The lipocytes are normal.

NEXT SLIDE. After 6 months, many sinusoids in each lobule are filled with several types of mesenchymcal cells. Macrophages containing large phagosomes are most abundant. Lipocytes are larger than normal and their fat droplets are bigger. Several cells are seen in each cluster with large nuclei and relatively empty cytoplasm. These cells are usually in a literal position, lining the sinusoids.

NEXT SLIDE. Small clusters, or foci of hepatocytes show both rough and smooth hypertrophic endoplasmic reticulum, and only occasional hepatocytes contain autophagic vacuoles--the only sign of hepatocellular injury noted. The macrophages, containing large phagosomes, often have needle-like crystals, reminiscent of uric acid and lysosomes in the sinovial membrane in the macrophages in gout.

NEXT SLIDE. Focally, sinusoids are dilated; some packed with erythrocytes and some clusters of platelets, usually aggregated where the sinusoidal lining is missing. There's one here and another over here. When the animals are allowed to recover for a month, after 6 months of exposure to vinyl chloride, hepatocytes appear normal. But several sinusoids are completely filled in many places in each lobule with lining cells, some of which now have more organelles than normal, particularly endoplasmic reticulum.

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NEXT SLIDE. These cells form small clusters with increased nuclear cytoplasmic ratio and abnormality of nuclei, (NEXT SLIDE) suggesting early angiosarcoma found in 3 of 23 animals examined after 6 months' exposure.

NEXT SLIDE. Our studies indicated that the changes in the liver produced by vinyl chloride are: 1) foci of hepatocytes with hypertrophied endoplasmic reticulum; 2) alteration and proliferation of sinusoidal lining cells accompanied by the accumulation of macrophages and hypertrophy of lipocytes. This focal proliferation of endothelial lining cells fills the sinusoids and leads to dilated sinusoids nearby. Fibrosis is not a feature of the early lesions in the mouse liver. The sinusoidal damage provokes an inflammatory response, contributes to the peliosis, the peliotic focal sinusoidal dilatation and leads to the transformation to angiosarcoma from sinusoidal endothelial lining cells.

LAST SLIDE. In conclusion, we feel that screening procedures to detect the early hepatic lesions of vinyl chloride exposure must be directed to the hepatic microcirculation rather than to hepatocytic function as hitherto.

QUESTIONS:

DR. LEEVY: I want to congratulate the Mt. Sinai group. It seems to me that this is a very important contribution in focalizing how one would approach screening for such an industrial toxic. It confirms the suggestion that as one uses a substance whose removal approach V_{max} such as some of the dye (ICT) that this is perhaps going to be the future method for picking up the abnormalities which you can see both in mouse and man. My question is whether or not a single lesion has produced any other kind of noxious agent which you have employed in your mice,since unlike some of these other things, except for arsenic, you do not go out and get angiosarcoma in the other lesions.

There is nothing that I know -- the copper lesions -- Dr. Popper says the copper lesion is the same as this. I don't know.

Dr. LEDFORD: What evidence do you have that the sinusoidal cells are actually the precursors to the tumor? The evidence is really the gradual transition from the focal changes to the abnormal nuclei to cytoplastic ratio to clusters of cells which on thin section are the early angiosarcomas.

DR. PHILLIPS: Yes, I would like to congratulate Dr. Schaffner also on a very interesting paper. There are several points, I think I would like to ask about. One, is that it is interesting that he didn't see fibrosis in the human cases This has been suggested as an early sign of vinyl chloride injury; another one being the splenomegaly. I wonder if -- one question is whether or not you had an evidence of splenomegaly or so-called Banti's syndrome in these animals. And another question I would like to ask is that I note that you use the term sinusoidal cells in this dicussion rather than Ito cells, particularly since Dr. Thomas, Dr. Popper and others suggested that perhaps it might be the Ito cell that is the key cell rather than sinusoidal cells in general and I wonder if you could comment on that.

DR. SCHAFFNER: First, the spleens were large in the animals at 6 months--they were nearly doubled in size and weight. Secondly, the Ito cell is

the lipocyte and this cell is related at least to the fibroblast. Whether it is a fibroblast precursor or not, we are noy sure. At the six month period the lipocytes were large but they did not have large amounts of rough endoplasmic reticulum so if they were going to be making fibres they hadn't started yet. We may have seen the prefibrotic lesion in the mouse. These very large doses of vinyl chloride that we are using I think we got accelerated formation of angiosarcomas, rather than the more gradual development of fibrosis. I think in lower dose levels in more prolonged periods you probably would see it.

DR. TAMBURRO: I would like to add that the similar changes are seen in the human electron microscopy in vinyl chloride exposed people, the exception is that they have increased amounts of collagen. The one point I would like to make, though is that I don't think we should completely eliminate the hepatocyte from the screening procedure. Our own work with Dr. Du in our laboratory indicates that in rats exposed in early stages there is a change in the gluconeogenesis and an increase in pentose phsophate shunt in a manner similar to Weber's correlation concept in primary hepatomas and it concerns us because one doesn't see the cancer developing in the primary liver cell. However, in recent conversation with Dr. Maltoni, he tells me that in exposing young rats to the same levels of vinyl chloride he has now induced primary hepatocellular cancers due to vinyl chloride in about 40-50% of his animals. It may well be that the hepatocyte begins to have biochemical changes early which might be detectable and are characteristic of chemical exposures and that in the case of the younger hepatocyte the detoxifying system may not be adequate and therefore induce the injury to the liver cell whereas an older individual with a more mature hepatocyte it is able to detoxify but the carcinogen then begins to affect other cells that don't have that capacity.

DR. SCHAFFNER: I think that the point is an interesting one and comes down to the semantics of the definition of injury. Undoubtedly the vinyl induces metabolic alterations in the hepatocyte. It is metabolized in that hepatocyte and probably the carcinogen that produces the angiosarcoma is made in the hepatocyte and this undoubtedly leads to metabolic changes, but metabolic changes without other -- at least without the structural criteria of injury and probably without generally interfering with hepatocellular function. In other words the interference with function may be very specific and I think if this is so we are going to have to search for a specific metabolic pathway that is altered rather than for the general--in other words it doesn't pay to do a transaminase in the people exposed.

Thank you very much Dr. Schaffner.

CARDIAC STUDIES

The University of Louisville Vinyl Chloride Project has expanded the medical surveillance program to include cardiac studies. The aim of this program is to examine the effects, if any, that chemical exposure may have had on the heart. Sixty employees were randomly selected by computer to participate in the test. One of the phases of the test includes wearing a tape recorder heart monitor for a 24-hour period.

It should be noted that the monitor is not explosion proof, and employees wearing them will not be permitted to enter Class 1, Group D, areas of the plant. These areas include Buildings 1, 30, 105 and 106 tank farms, 111, 121, 125, 131, 133, Large Poly Area and VCl tank farms. Bldg 115- Cold Room 2nd Floor

The work assignments of affected employees must be modified to accommodate the program.

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