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26 November 1984

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Dear Dr.Bennett:

You may find the attached paper by Tamburro, Makk and Popper of interest (Hepatology 4(3):413-418 (1984)). I'm sure Maurey Johnson can fill you in on details.

I'm proceeding on the assumption that Sir Richard Doll will be asked to review the epidemiology literature on vinyl chloride. I passed the information to Dr. Johnson since he is Chairman of the CMA and the SPI vinyl committees concerned with health and toxicology. Maurey indicated strong interest and support. I will do all I can to expedite the formalities, but I cannot imagine anything less than wholehearted support by U.S. industry. The timing is appropriate since we should have the Environmental Health Associates' update of the old Tabershaw-Cooper study fairly well along by then. The Doll review will supplement the EHA report and may even indicate areas that need special analysis. It is essential that the review be published. I will be glad to do all I can do to aid him in getting papers and reports.

Thank you for the information on your conversations with Sir Richard. I hope your joint review of the angiosarcoma registry is proceeding well.

Sincerely yours,

Theodore R. Torkelson

Theodore R. Torkelson, ScD.
Health and Environmental Sciences

Enc.

cc: M. N. Johnson, M.D. - B. F. Goodrich Co.
Carol Stack, PhD. - CMA

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Early Hepatic Histologic Alterations Among Chemical (Vinyl Monomer) Workers

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Focal hepatocellular hyperplasia and focal mixed (hepatocytes and sinusoidal cells) hyperplasia are early histological alterations indicative of vinyl monomer exposure. To evaluate their uses in screening chemical workers, 93 liver biopsy specimens from 78 persons were examined in double-blind duplicative fashion. Forty-eight specimens were from exposed chemical workers, 35 of them having liver biopsy(ies) for hepatic test abnormalities and 13 for nonliver-related reasons. A comparison group consisted of 30 nonchemical workers who had undergone liver biopsy for nonliver related reasons. Twenty-three of the exposed workers (48%) had hepatic lesions consistent with exposure: 17 (35%) of these had focal hepatocytic hyperplasia, while 6 (13%) had focal mixed hyperplasia or more advanced lesions. Only five of the comparison group had like findings: four (13%) had focal hepatocytic hyperplasia; one had focal mixed hyperplasia and sinusoidal dilatation. This individual had persistent hepatic test abnormalities with the focal mixed hyperplasia and a sinusoidal dilatation, and on subsequent biopsy, angiosarcoma (and a history of using hair spray containing vinyl chloride propellant). Ten individuals had 25 multiple biopsies also read double-blindly; 10 had two or more readings of the same biopsy. Duplicate 21 of 23 (91%) and multiple 27 of 28 (96%) biopsy interpretations in the same individual were identical. Only 6% of either duplicate and/or multiple readings disagreed. Both focal hepatocellular and mixed hyperplasia were always associated with abnormalities in hepatic test results of which indocyanine green clearance was the most sensitive and γ-glutamyl transpeptidase the least specific. Focal hepatocellular hyperplasia is a more common finding and occurs earlier than the focal mixed hyperplasia among vinyl monomer exposed workers. Follow-up for 5 to 7 years yielded no biochemical or histological evidence of spontaneous progression of this lesion in a work environment where vinyl chloride levels were 10 ppm with time-weighted averages of 1 to 2 ppm. Focal mixed hyperplasia is, as noted, a later and less frequent finding among vinyl monomer-exposed workers. Some individuals with this lesion develop hepatic angiosarcoma independent of subsequent vinyl monomer exposure. In screening for chemical liver injury, indocyanine green clearance supplementary to routine tests is recommended with confirmation by liver biopsy.

Industrial exposure to vinyl chloride, other vinyl monomers, and related chemicals is associated with various histological lesions in the liver, notably subcapsular, portal, and perisinusoidal fibrosis, and hyperplasia of hepatocytes and sinusoidal cells (1–4). Focal hepatocytic and focal mixed hyperplasia (hyperplasia of hepatocytes and sinusoidal cells) are early histological alterations (5, 6). To determine their applicability for screening exposed workers, liver biopsies from 78 individuals were studied in duplicate blind fashion to determine whether these lesions were: (i) associated with vinyl chloride exposure, and (ii) occurred in nonexposed populations without hepatic disease.

MATERIALS AND METHODS

Liver biopsy specimens from 48 vinyl monomer chemical workers and 30 nonchemical workers with and without hepatic biochemical abnormalities were studied. Hepatic tests were performed annually or semiannually on all 48 chemical workers; these included determination of activities of SGOT, SGPT, alkaline phosphatase (AP), and γ-glutamyl transpeptidase (GGT), as well as total bilirubin, prothrombin time, total serum protein, albumin and indocyanine green clearance (ICG). In addition, a history and physical examination, radioisotopic liver-

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spleen scan and abdominal plain film were done annually. Thirteen of the chemical workers had liver biopsies performed for nonliver-related reasons, and 35 had biopsies done because of abnormalities in screening tests and/or the liver-spleen scan.

A comparison population consisted of 29 individuals who were not chemical workers but who had undergone an abdominal operation and gave informed consent for a liver biopsy, done during the same 3-year period at the same hospital, by the same medical-surgical team. The same hepatic tests, except for GGT and ICG clearance, were done on this group. None had a history of exposure to halogenated hydrocarbons. During this time, one additi nal individual underwent liver biopsy because of persistent hepatic test abnormalities. She had a history of contact with vinyl chloride used as a propellant in hair spray.

PATHOLOGICAL EXAMINATION

Observations on humans (7–13, Tamburro, C. H. et al., *Gastroenterology* 1979; 77:A43, Abstract) and animals [14–20, Boorman, G. A. et al., *Fed. Proc.* 1980; 39(Part 1):546, Abstract] obtained after prolonged vinyl chloride exposure have identified lesions in the nontumorous parenchyma. (i) Foci of enlarged hepatocytes with increased cytoplasm, and large hyperchromatic nuclei were seen; the hepatocytes varied in size and more often had several nuclei. The foci were multiple, poorly circumscribed and differed from the surrounding parenchyma where there were twin hepatic plates with nuclei adjacent to the sinusoidal border (Figure 1). In these areas, sinusoids often were slightly dilated and the reticulin framework was focally increased as shown by silver impregnation (Figure 2, A and B). (ii) Sinusoidal cells were increased in number, particularly in areas of sinusoidal widening, and were associated with nuclear and cytoplasmic enlargement (Figure 3A). They consisted of: (a) ellipsoid endothelial cells which usually were flat or had nuclei, diffusely periodic acid-Schiff-positive cytoplasm and projected "pillow-like" into the often dilated sinusoids (Figure 3B); (b) Kupffer cells (macrophages) with periodic acid-Schiff-positive granules; (c) fat storing (Ito) cells with fine vacuoles; (d) occasional fibroblasts with elongated, almost rectangular nuclei with loose vesicular chromatin patterns and associated with perisinusoidal fibrosis best recognized by silver and trichrome stain (Figures 3C and 4), and (e) few lymphocytes and occasional plasma cells or segmented leukocytes.

FIG. 1. *Focal hepatocytic hyperplasia (early stage).* Ill-defined focal area of enlarged hepatocytes with increased cytoplasm (*curved arrows*). H & E, 100×.

Pure hepatic changes were referred to as focal hepatocytic hyperplasia (FHH). Sinusoidal cell hyperplasia associated with the hepatocytic changes were referred to as focal mixed hyperplasia (FMH). The liver biopsies were coded and then interpreted blindly by two of the authors (H. P. and L. M.). The cases with disease were subdivided into those characteristic of nonchemical injury without steatosis, with steatosis alone or steatosis with fibrosis, and into those with evidence of chemical injury. Chemical injury was identified by: (a) FHH with or without focal increased reticulin framework; (b) FHH with increased reticulin deposition with or without sinusoidal dilatation; (c) portal fibrosis with sinusoidal cell dysplasia, and (d) hepatic angiosarcoma. Focal hepatic hyperplasia, with or without focal increases in reticulin in the absence of other evidences of hepatocellular dis-

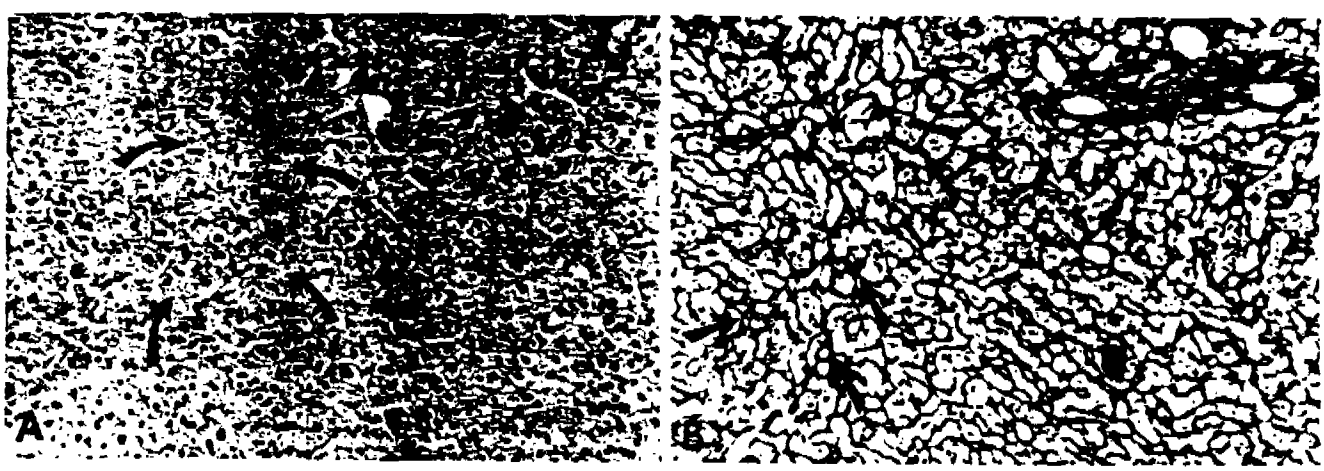

FIG. 2. *Focal hepatocytic hyperplasia (later stage).* (A) Focal hyperplasia of the hepatocytes (*curved arrows*) with variation in cell size as well as cell nuclei which are frequently double, polychromatophilic or can be vacuolated. H & E, 100×. (B) Slight focal increases of reticulin framework (*arrows*). Silver impregnation, 100×.

FIG. 3. *Focal mixed hyperplasia.* (A) Hyperplasia of sinusoidal cells (*curved arrows*) and hepatocytes (*straight arrows*) with sinusoidal dilatation. H & E, 250×. (B) Sinusoidal cell dysplasia with conspicuous proliferation of polymorph sinusoidal cells (*straight arrows*) some of which show bizarre nuclei, e.g., helmet shaped (*curved arrows*). H & E, 400×. (C) Same area showing focal increases in reticulin framework (*arrows*) with early sinusoidal dilatation. Silver impregnation, 250×.

ease or steatosis, was considered the minimum presumptive evidence of chemical exposure. FMH with increased reticulin and dilatation of sinusoids was considered a more advanced stage. Portal fibrosis with FMH and sinusoidal dilatation was taken as being even more advanced. Sinusoidal cell dysplasia and/or evidence of malignant transformation, was looked upon as terminal stages of chronic vinyl chloride injury.

FIG. 4. *Perisinusoidal fibrosis.* Perisinusoidal fibrosis in space of Disse surrounding hepatocytes (*arrows*) with numerous fat-storing sinusoidal cells. Trichrome, oil.

Histories of work with and exposure to 22 potentially hepatotoxic chemicals were available for all chemical workers. An estimate of total and average exposure to each of the 22 chemicals was made by using a rank order system of estimating exposure based on each worker's occupational history (21, 22). Exposure to each chemical was ranked on a scale of 1 (lowest) to 6 (highest). These rankings were done *a priori* for each job for each year of the plant's operation based on best estimates from available information and industrial expertise. Each worker's cumulative exposure was based on the various job classifications held during employment. Thus, separate, average, and cumulative exposure indices were developed for each employee.

RESULTS

Hepatic lesions consistent with chemical exposure were found in 37% of the exposed workers with hepatic test abnormalities. Among the exposed workers without test abnormalities, 23.5% (3/13) had hepatic lesions consistent with exposure. In the nonchemical worker comparison group, none with normal test results (0/11) and only one (6%, 1/18) with abnormal liver screening tests had hepatic lesions consistent with chemical exposure. This latter individual had no history of chemical exposure and/or alcohol consumption, but had undergone surgery for biliary stones. The person biopsied because of persistent abnormalities in hepatic tests had FMH and marked sinusoidal dilatation. This individual was later found to have hepatic angiosarcoma possibly caused by continued use of hair spray which contained vinyl chloride as a propellant. Table 1 lists the type and frequency of hepatic lesions in those individuals with and without liver test abnormalities.

REPRODUCIBILITY

Reproducibility of the biopsy readings was evaluated in 17 individuals with 32 biopsies. Seven individuals had only one biopsy (2 needle, 5 wedge); 10 individuals had multiple biopsies (25 total). Biopsies were examined at least twice in a double-blind manner with 3 to 9 months between readings. Biopsy findings from each reading were recorded directly on a semiquantitative computer-

TABLE 1. CORRELATION OF HEPATIC BIOCHEMICAL AND HISTOLOGIC ABNORMALITIES IN CHEMICAL WORKERS AND NONOCCUPATIONALLY EXPOSED PERSONS

Hepatic test results*	Biopsy diagnosis	Chemically exposed workers (no.)	Nonworker comparison group (no.)
Normal (24)	Normal	(13)	(11)
	Steatosis (≥5%)	1	0
	Sinusoidal dilatation	1	0
	Hepatocellular variations	0	3
	Portal fibrosis	0	2
	Portal inflammation	0	3
	FHH	0	0
	FMH	0	0
Abnormal (54)	Nonchemical liver injury	(22)	(17)
	Steatosis (≥5%)	11	4
	Hepatitis	2	1
	Granulomas	3	3
	Alcoholic injury	2	1
	Other lesions	4	0
	FHH	7	2
	FMH	2	0
	Chemical liver injury	(13)	(2)
	Focal peliosis	1	1
	Angiosarcoma	0	1
	FHH	13	2
	FMH	0	1

* SGOT, SGPT, AP, total bilirubin and prothrombin time.

TABLE 2. COMPARISON OF BIOPSY READINGS

Identification no. (17)	Needle biopsies* (15)			Wedge biopsies* (17)	
	1st	2nd	3rd	1st	2nd
3				A, A	
10				A, A, A	
14				A, A	
20				A, A, D	
33				A, D	
26				A	A
35	A			A	A
36	A			A	
24	A			A	
17				A	
22	A, A			A	
24	A, A			A	
6	A	A	A	A	
23	A	A		A	
27	A, A	A	A	D	
8	A, A				
30	A, A, A				

* A, agreement; D, disagreement.

ized questionnaire which included the 24 histological features under study. The consistent reproducibility of the biopsy readings is shown in Table 2.

The consistency in the readings between multiple biopsies in the same individual was very high. In only one case was one of the four biopsies read differently: the wedge was read differently from the needle biopsy. The reproducibility of biopsy readings from multiple needle versus multiple wedge biopsies from a single individual in all readings was consistent. Multiple biopsy readings at different times from the same biopsies showed that all needle-biopsy duplicate readings, and 12 of the 14 wedge-biopsy duplicate interpretations were identical. Ninety-six per cent (43/45) of all biopsy readings, whether duplicate or from multiple biopsies, yielded reproducible, consistent interpretations.

Technical artifacts (excessive thickness, torn or fragmented specimens) greatly impede correct identification. Similarly, fatty infiltration and/or chronic disease (hepatitis, granuloma) may obscure the characteristic lesions. We determined, however, the presence or absence of these lesions in six individuals who had a concomitant granulomatous process (four individuals with granuloma were repeatedly read as negative, and two individuals with granuloma were repeatedly read as positive for chemical liver injury).

CORRELATION OF HISTOLOGICAL LESIONS WITH EXPOSURE

From the histological observations, the biopsies of the chemical workers fell into three categories: (i) no histological evidence of liver disease (N); (ii) liver disorders inconsistent with chemical injury, (iii) chemical liver injury inferred from histological criteria specified. Individual exposure ratings were not disclosed until after all final histological determinations and categorizations were completed.

Comparisons of average and cumulative exposure ratings of each worker for vinyl chloride showed that chemical workers with histological evidence of chemical liver injury had the most persons with highest exposure ratings to vinyl chloride. Earlier studies showed that all chemical workers who developed hepatic angiosarcoma had an average vinyl chloride exposure rating of 3.5 or greater (23). Of the chemical liver injury group, 55% had an average vinyl chloride exposure rating of 3.5 or greater. Only 22% of chemical workers with liver disease and 32% of exposed workers without evidence of liver disease had ratings of ≥3.5 (Figure 5).

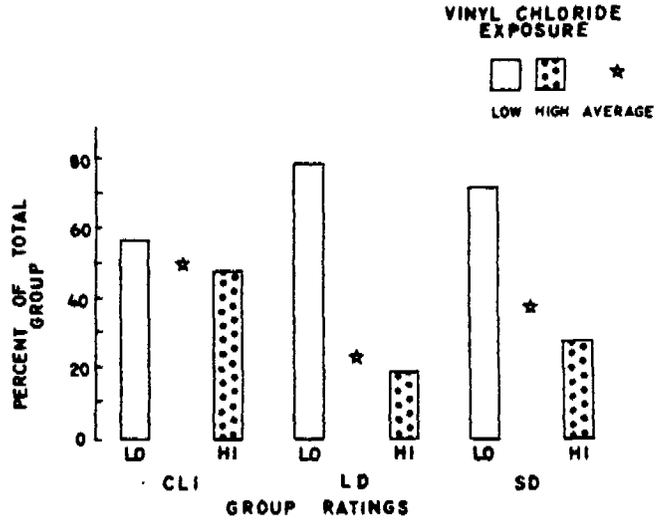

FIG. 5. *The high (Hi, ≥3.5), low (Lo, <3.5) and average (*) vinyl chloride exposure ratings among the different histological groups.* CLI, group with histological evidence of chemical liver injury; LD, group with histological evidence of liver disease (with or without steatosis) without evidence of chemical injury; SD, standard or "normal" group—no histological evidence of liver injury.

Correlation of Biochemical Studies and Histological Findings

Both FHH and FMH were never encountered when hepatic test results were normal. As in previous studies, ICG clearance, at 0.5 mg per kg dose and GGT were the most sensitive of the laboratory screening tests in the detection of all types of liver disease, followed by SGOT, SGPT, and AP (Figure 6). The laboratory tests most sensitive in detecting chemical liver injury and having the highest specificity were ICG and AP, while GGT and SGOT were more sensitive in detecting nonchemical liver disease (Figure 6A). Specificity was associated particularly with abnormalities in AP activity and ICG clearance (Figure 6B). GGT was the least specific and most sensitive with a false-positive rate of 20%. The pattern is the same for the frequency with which the abnormalities occurred in these workers. In evaluating nonchemical injury in both exposed and nonexposed persons, significant steatosis as well as hepatitis and granulomas was found to be regularly associated with abnormalities in hepatic test results.

DISCUSSION

The histologic findings extend the original observations made in vinyl chloride-associated hepatic angiosarcoma and hepatic injury (1, 5, Tamburro, C. H. et al., *Gastroenterology* 1979; 77:A43, Abstract). Focal hepatocytic megalocytosis in the absence of other evidence of acute or chronic lesions seems the earliest detectable change after vinyl monomer exposure. Later, hyperplasia and hypertrophy of sinusoids accompanies the similar focal hepatocytic process which now assumes a poorly defined shape and is associated with perisinusoidal fibrosis and proliferation of fibroblasts and/or their precursor (Ito) cells. The sinusoidal cell activation involves macrophagic and endothelial-lining cells as well as focal sinusoidal enlargement. Eventually the mixed hyperplasia (hepatic and sinusoidal cells) is followed by sinusoidal cell dysplasia, palisading of sinusoidal-lining cells and, finally, by malignancy as seen in both man and experimental animals (6, 7, 8, 18).

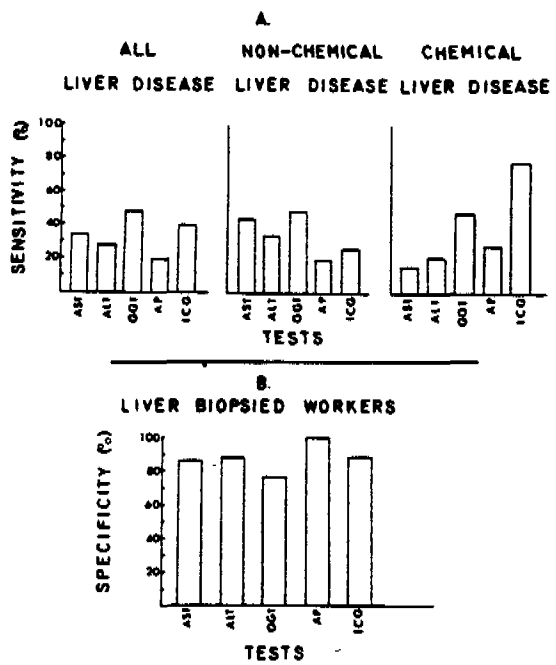

FIG. 6. *The occurrence of biochemical screening test abnormalities in various histological groups with liver injury.* (A) Sensitivity (percentage of biopsied workers correctly identified as having liver disease) of laboratory screening tests in all types of liver disease, chemical and nonchemical liver injury. (B) Specificity (percentage of biopsied workers correctly identified as not having liver disease) of laboratory screening tests in liver biopsied workers. AST, SGOT; ALT, SGPT

Our data, supplemented by individual exposure history, demonstrates then that FHH is the earliest consistently identifiable histological lesion in workers exposed to vinyl monomer chemicals. It is relatively rare in nonchemical workers without liver disease but resembles focal regenerative hyperplasia (24) sometimes accompanied by portal hypertension. By contrast FMH, being a more advanced lesion, was only found in chemically exposed workers and in a person with a history of exposure (hair spray). This supports the concept that these lesions are related to prolonged or repeated chemical exposure.

Whether the early lesions (FHH) may be precursors in the development of angiosarcoma or only evidence of cellular adaptation without progression requires follow-up. However, the consistency of the results of the hepatic screening tests over a 7-year follow-up period and the absence of changes in the histological finding on serial biopsy of these workers suggest that FHH is not progressive when the worker is removed from exposure or exposure is very low (25). By contrast, FMH, especially sinusoidal cell dysplasia, may be associated with development of angiosarcoma as illustrated in one of our cases; quite likely, it is a nonreversible lesion.

Diagnosis of these histological lesions in both needle and wedge liver biopsy is highly reproducible. Inconsistency appeared more often among the duplicate readings of wedge biopsy specimens and between wedge and needle biopsy specimens from the same individual. This did not occur between duplicate readings of needle biopsies nor in reading of multiple needle or multiple wedge biopsies. Silver impregnation for assessment of the reticulin framework is useful in verifying FMH. The finding of early histologic lesions only in those individuals with hepatic test abnormalities gives objective support to the usefulness of hepatic tests to indicate liver injury. However, as in previous studies (26–28) GGT has proven to be excessively sensitive as a screening test for liver injury. Abnormalities of AP activity provide especially good correlation with the presence of subclinical chemical liver disease but lack the sensitivity needed for a primary screening test. ICG clearance provides both the sensitivity and specificity needed for primary screening and/or confirmatory study for those workers with elevated activities of the commonly used hepatic enzymes. This, along with AP activity provide sufficient specificity for identifying those workers at high probability of chemical liver injury calling for confirmation by liver biopsy to reveal the specific lesion(s). The type of histological lesions may account for these biochemical findings in that the cellular hyperplasia and sinusoidal dilatation and perisinusoidal fibrosis interfere particularly with

hepatic microcirculation (29–31). This impairment is reflected in diminished ICG and less so by elevated serum activities of the intracellular enzymes, such as the aminotransferases whose release better mirrors hepatocellular dysfunction. These correlations strongly suggest a need to change the presently required federal screening for chemical exposure workers.

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