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CHRONIC TOXIC LIVER DAMAGE IN THE CASE OF
WORKERS IN PVC PRODUCTION

by

H. J. Marsteller, W. K. Leibach, R. Müller, S. Jühe,

C. E. Lange, H. G. Rohner and G. Veltman

Medical Clinic (Director: Prof. H. J. Dengler)

Pathological Institute (Director: Prof. P. Gedigk)

and Skin Clinic (Director: Prof. A. Leinbrock),

at the University of Bonn.

For more than 30 years, polyvinylchloride (PVC) has been valued in many branches of industry as a versatile, useful plastic, and consequently it has been produced on a large scale industrially, worldwide.³ The fact that until 1966 no observations concerning chronic intoxication had been published in the Western Literature explains the widespread conception that only relatively inert substances appear in the PVC production.

The re-publication elsewhere 4 years later¹⁹ of a Roumanian paper appearing for the first time in 1963¹⁸ concerning illnesses caused by vinyl chloride, in which Raynaud syndrome, dermatitis, "sclerodermia", thyroid insufficiency and hepatomegalies were reported, was followed by publications from France,^{2,4} England⁷, the USA^{3,5,6,13,14,22} and Germany^{8,9,10,17}. On the basis of 55 descriptions of cases, altogether, these made known the picture

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of illness, narrowed to "occupational acroosteolysis". An extensive symptomatic picture with the suspicion of liver function disturbances was present in only 8 of the 55 workers 7,8,9,10.

With the designation of occupation acroosteolysis, the view of the liver damage observed for the first time in 1949 in the USSR within the framework of PVC production²¹ was obscured; these have been described as more or less pronounced "hepatitis" (in the case of 15 out of 48 workers). The cited Roumanian observation of toxic limited hepatomegalies (in about 50 to 168 people investigated)^{18,19} and Russian communications¹⁵ concerning partially subclinical "chronic epithelial hepatitis" (in 15% of the workers investigated) also thus have remained unnoticed.

Results.

Detectable esophagus varices and splenomegalies in some workers in a plant producing PVC, together with uncharacteristic changes in the liver parenchyme, as well as the literature references which were difficult to classify, concerning "sub-clinical" liver damages, gave us the incentive to investigate the morphological substrate of the liver changes by detailed laboratory diagnostic X-rays and scintigraphic investigations by means of laparoscopy and directed liver biopsy. Thus, up to the present time we have correspondingly investigated up to 20 out of 45 mole autoclave workers in a PVC production installation

(30 to 56 years old, duration of exposure 1-1/2 to 21 years), with the suspicion of liver damage*. In this case, we obtained the results shown in Tables 1 and 2.

In addition to this, the following parameters have been tested (repeatedly, for the most part), and had proven to be entirely unsuspecting or normal: hypostasis reaction, blood picture, blood sugar, urine status, lues reaction, LDH, cholinesterase, acid phosphatase, iron and copper in the serum, thymol test, serum protein and electrophoretically separated subfractions, cholesterol, β -lipoproteids, triglycerides, as well as plasma coagulation factors. Of the immunological parameters, the rheuma factors, antineuclear factors, LE cells, immune globulin fractions G, A, and M, the complement fraction β_1 A and the cold antibody have at first been tested because of the delineation from the

* Out of a total of about 120 PVC workers in the plant, 45 have thus far been examined in the University Skin Clinic at Bonn, a smaller portion because of manifest skin phenomena, but also for reasons of prophylaxis. In the case of most of these 45 workers, there was clinically and (or) biochemically a suspicion of an etiological unclear liver damage. Up until May 1973, it was possible for 20 of them to be laproscoped, primarily those in which this suspicion appeared to be well-founded. Naturally, we could not make any statements concerning the frequency of such liver damage on the basis of these numbers).

Table 1. Anamnestic data, clinical and clinic-chemical findings in the case of 20 PVC workers. For bilirubin, transaminases and alkaline phosphatase, maximum values are given from 3-6 determinations, and for the bromsulfalein sample the maximum values from 2 determinations.

Case number	Age (years)	Workplace	Exposure (years)	Special anamnes's	Alcohol consumption per day	Hepatosplenomegaly (cm)	Bilirubin >1.0 mg/100 ml	Bromsulfalein sample >5% after 45 minutes	SGOT > 12 (21) mU/ml***	SGPT > 12 (33) mU/ml***	Alkaline phosphatase > 48 mU/ml	Thrombocytes (x 10 ³ /mm ³) (norm: 150-300) (x 10 ³ /mm ³)	Acroosteolysis
1	33	A	3 1/2	a) leer	-	3	-	6,8	23	17		74/99/119/133 149/163/173	+
2	32	A+	3 3/4	a) leer	g) Glas Wein	5	3	12,5	19	16		62/63/68/70/94 133	+
3	35	A	9	a) leer	1 Flasche h) Bier	-	3	1,1	15,1	19	17	37/64/73/74/75 76/81/81	+
4	41	A+	3 1/2	a) leer	1 Flasche h) Bier	1,5	-	1,1	8,6	19	15	99/111/114/210 283	-
5	34	A	5	a) leer	1 Flasche h) Bier	-	1,5	21,5	21	23 (40)		116/119/137 140/163/175	+
6	47	A+	18	b) 1972 Billroth II Ca? Aszites	-	3	5	15,6		19	81	80/90/90/100	-
7	51	A+	16 1/2	a) leer	1) 3-4 Flaschen Bier	3	3	9,1	19	17		40/45/52	-
8	45	A	8 1/2	a) leer	1 Flasche h) Bier	-	-	8,8	13			17/25/30/37/38	-
9	42	A	6 3/4	a) leer	1 Glas j) Bier	1,5	-	13,8	25	23 (63)		128/176/214 230/235	-
10	31	A	4	a) leer	-	-	3	1,7	7,1 (28)			92/122/122	-
11	47	A	12	c) seit 1967 Hyperlipidämie, Leberschaden	k) bis 2 Flaschen Bier	-	1,5	6,2	15	15		51/87/99/133	-
12	56	A+	18	d) Druckschmerz im rechten Oberbauch	2 Flaschen l) Bier	1,5	-	6,1				70/122/125/141	-
13	36	A	4 1/4	a) leer	1 Flasche h) Bier	-	-	7,6				99/144/171	-
14	35	A	4 3/4	a) leer	1 Flasche h) Bier	1,5	-	8,5	32 (27)	30		112/114/132 156	-
15	36	A	1 1/2	a) leer	1 Glas j) Bier	3	-	6,3	17	17	56	113/134/211	-
16	50	A+	21	e) 1955 Ikterus, 1968 chronischer Leberschaden	-	1,5	-	8,7	15	15		124/174/176 187/193	-
17	44	A	13 1/2	a) leer	1 Glas j) Bier	1,5	-		15			136/140/152 251	-
18	41	+	1 1/2	f) Druckschmerz im rechten Oberbauch	k) bis 2 Flaschen Bier	-	-	6,1	19	17 (47)		143/160/189 189/224	-
19	30	A+	2 1/2	a) leer	-	1,5	-	8,4	17			111/157/202	-
20	30	A+	4	a) leer	bis 2 Flaschen k) Bier	3	-	7,5	15	15		94/128/157 248	-

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Table 1. (continued)

- Key:
- a) None
 - b) 1972 Billroth II Ca? Ascites
 - c) Since 1967, Hyperlipidemia' "liver damage"
 - d) Pressure pain in the upper abdomen
 - e) 1955 icterus, 1968 chronic liver damage
 - f) Pressure pain in upper right abdomen
 - g) 1 glass of wine
 - h) 1 glass of beer
 - i) 3-4 bottles of beer
 - j) 1 glass of beer
 - k) up to 2 bottles of beer

*A = autoclave cleaner, A+ = autoclave cleaning and other work in the production process.

**Numbers in parentheses = values in the substrate optimization method.

sclerodermia; however, because of the generally uncharacteristic findings, control measurements of these were no longer made later, with increasing clarification. The Australia (SH) antigen was always negative. A cholelithiasis was found only in 1 patient (case 15): a solitary concretion, shifting positions, without hindering excretion.

Table 2. X-ray and laparoscopic-histological findings in the case of 20 PVC workers (autoclave cleaners).

Case No.	X-ray for esophagus (O) or fundus (F) varices	Laparoscopy	Histology
1.	-	indicated capsule fibrosis, splenomegaly.	centrolobular collagenization of sinusoid walls, localized stellate cell activation, localized fatty degeneration.
2.	-	clear capsular fibrosis, beginning disorganization, considerable splenomegaly.	centrolobular collapse fields, slight enlargement of collagen fibrilles in the portal fields.
3.	+ (O)	clear capsular fibrosis, beginning disorganization, localized spotty reddening and vessel drawing, splenomegaly.	-----

Table 1. (continued)

Case No.	X-ray for esophagus (O) or fundus (F) varices.	Laparoscopy	Histology
4.	-	network capsular fibrosis, hepatomegaly.	collagenization of sinusoid walls, slight cellular fatty degeneration, stellate cell fibrosis.
5.	-	-----	slight portal fibrosis localized fatty degeneration (moderately large drop size), slight stellate cell activation, hydropic swelling.
6.	+ (O and F)	beginning to complete disorganization, portal hypertonus, ascites, clear splenomegaly.	Septal and central fibrosis.
7.	+ (O and F)	network to surface-like capsular fibrosis, beginning disorganization, beginning portal hypertonus, clear splenomegaly.	irregular to septal fibrosis, localized round cell infiltration of portal field, leucocyte delineated cell necroses, localized stellate cell activation.

Table 2. (continued)

Case No.	X-ray for esophagus (O) or fundus (F) varices	Laparoscopy	Histology
8.	-	spotty capsular fibrosis.	indicated fibrosis of the portal fields, isolated large-drop, fatty degeneration.
9.	-	slight capsular fibrosis, splenomegaly.	indicated septal fibrosis of the portal field, centrolobular collagenization of the sinusoid walls, localized large-drop fatty degeneration, stellate cell activation.
10.	-	clear capsular fibrosis, beginning disorganization, clear splenomegaly.	fine septal fibrosis, localized collagenization of sinusoid walls.
11.	-	indicated capsular fibrosis, questionably beginning disorganization.	moderate fibrosis of the portal fields, fine septal intralobular fibrosization without inflammatory activity, slight disseminated large-drop fatty degeneration.
12.	-	irregular capsular fibrosis, hepalmegaly.	septal fibrosis of the portal fields, narrow intralobular

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Table 2. (continued)

Case No.	X-ray for esophagus (O) or fundus (F) varices	Laparoscopy	Histology
12. (cont)			septa, slight cholestasis, slight dissemination, fatty degeneration.
13.	-	slight capsular fibrosis.	slight fibrosis of the portal fields, slight cholestasis, localized large-drop fatty degeneration, individual cell necrosis , glycogen nuclei.
14.	-	slight capsular fibrosis.	intralobular fibrosization regions, moderate disseminated large-drop fatty degeneration.
15.	-	clear capsular fibrosis, hepatomegaly.	indicated septal fibrosis of the portal fields, large-drop fatty degeneration, localized stellate cell activation.
16.	-	slight capsular fibrosis.	slight fibrosis of the portal fields, moderate disseminated fine large-drop fatty degeneration, stellate cell activation, numerous glycogen nuclei.

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Table 2. (continued)

Case No.	X-ray for esophagus (O) or fundus (F) varices	Laparoscopy	Histology
17.	-	clear capsular fibrosis.	septal cirrhotic disorganization, localized knotty cell regeneration.
18.	-	fine-moderately coarse knotty disorganization.	septal fibrosis, localized collagenization of sinusoid walls, moderate disseminated fatty degeneration, stellate cell siderosis.
19.	-	no definite pathological findings.	indicated septal fibrosis of the portal fields, slight localized large-drop fatty degeneration, slight stellate cell activation.
20.	-	hepatomegaly, questionable beginning disorganization, fatty degeneration of the liver.	indicated septal fibrosis of the portal fields, moderate disseminated large-drop fatty degeneration, individual cell necrosis, stellate cell activation.

From Tables 1 and 2, it may be seen that in most patients neither the biochemical parameters for the evaluation of liver function alone, nor the laparoscopic and histological findings alone could have stimulated special attention. The deviations from the standard which were detected in each individual investigation were in any case not very pronounced, not constant, and ambiguous. Only the frequency of a similar liver surface picture and identical histological evaluations with the background of identical occupational exposure with otherwise not striking anamnesis led to special weighting. Setting up the noteworthy findings according to their frequency (Table 3) shows that in the group presented here the acroosteolyses named previously had not been the leading symptoms of the occupationally caused damage within the framework of the PVC production^{2-8, 13, 14, 22}, but instead there were thrombocytopenias and more or less strongly pronounced chronic-toxic liver damage with splenomegaly and signs of portal hypertension in individual cases.

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Table 3. Frequency of pathological findings in the case of
20 PVC workers.

Symptoms	Number of cases
Increased bromsulphalein retention	19
Thrombocytopenia	16
Liver-spleen changes found by laparoscopy*	14
Splenomegaly in selective spleen scintigrams (in liver scintigram in 2 other patients)	7
Splenomegaly, clinical	7
Hepatomegaly, clinical	6
Acroosteolyses	4
Esophagus varcises (simultaneous fundus varcies in 2 patients)	3

*Histologically, small to moderately severe hepatic alterations
in all 19 cases.

Discussion.

Since no measurements of workplace concentrations have thus far been possible, and we have only knowledge full of gaps concerning details of the course of production, the questions of the etiological relationships and pathogenesis remain open, for the time being. The morphological picture is completely compatible

with the assumption of a chronic-toxic liver damage, such as can appear, for example, in the continuous or repeated administration of chlorinated hydrocarbons. In addition to various other unexplained points, in the formal genesis of the liver changes, the question of how we arrive at portal hypertension in some cases is also unsolved, above all, and is of a special theoretical interest as well as practical-clinical interest. The classification of these cases into the group of intrahepatic, presinusoidal or intrasinusoidal block forms, as is obvious from the histological picture on the basis of the septal fibrosization of the portal fields and the wire-mesh fibrosis with collagenization of the sinusoid walls^{1,11,16,20}, is still not guaranteed because of the lack of measurements of the liver vein occlusion pressure and the portal vein pressure in these patients. The relative frequency of moderate to pronounced splenomegalies permits us, to be sure, to presume the pressure-mechanical significance of the liver fibroses.

Corresponding preventive investigations in other plants manufacturing or processing PVC appear to be indicated according to our findings. Continuing investigations in our patients and detailed animal experimental studies for the explanation of the picture of the illness are planned.

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Dr. H. J. Marsteller, Dr. H. G. Rohner, Dr. W. K. Lebach
University Medical Clinic

University Lecturer Dr. R. Müller

Pathological Institute of the University

Dr. Susanne Jühe, Dr. C. E. Lange, Prof. Dr. G. Veltman

University Skin Clinic

53 Bonn 1, Venusberg

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ELISA	0/12	1/12	17	14	Severe HISTOLOGY	2/8	25%
	39%	40%	14	25%	MINOR HISTOLOGY	11/32	35%
	<4 yrs	4-10	10-19	>20 yrs.			

ICG:				LOW DOSE ONLY	
NUMBER:	4	4	2	3	
BIOCHEM TEST	N	A	N	A → N	
ICG	A	A	N	N	
BIOPSY	A	A	N	A → ?	

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FORM FOR ABSTRACTS TO BE PUBLISHED IN GASTROENTEROLOGY

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HEPATOTOXICITY AMONG POLYVINYL CHLORIDE (PVC) PRODUCTION WORKERS DURING FIRST YEAR OF SURVEILLANCE PROGRAM. J.L. Creech, L. Mark, J.G. Whelan, Jr. and C.H. Tamburro. Department of Medicine, Division of Digestive Diseases, University of Louisville School of Medicine and St. Anthony Hospital, Louisville, Kentucky.

Vinyl chloride and polyvinyl chloride (PVC) have been causally linked with hepatic fibrosis and angiosarcoma. All 1,183 employees of a PVC production plant were screened for hepatic lesions; 309 worked in PVC production areas, 411 in non-PVC production areas, and 463 in maintenance and administrative areas. Surveillance included history and physical examination with emphasis on toxic, chemical, drug and viral exposure, and biochemical liver function tests including alpha feto proteins, carcino-embryonic antigen (CEA) and hepatitis B antigen. Heavy ethanol consumption occurred in 23% of employees. Abnormal liver function tests were present in 27% (315), and were persistently abnormal in 7% (75). Initially, abnormal liver functions were found equally among PVC (25%) and non-PVC (27%) workers, however, persistent abnormalities were almost three times as frequent among PVC (11% vs 4.5%) workers. Of the 182 patients screened by isotope scans, 19 (11%) liver scans and 23 (13%) spleen scans were abnormal. Thirty-two biochemically abnormal but asymptomatic employees were biopsied; 14 had varying degrees of fibrosis; 8 had marked portal fibrosis, dilated sinusoids, atypical sinusoidal lining cells and diffuse subcapsular fibrosis, 2 angiosarcoma, 1 fatty liver and 1 sarcoidosis. Angiographic studies were performed on 30, one half of whom had evidence of portal hypertension. Angiosarcoma tumors show a characteristic tumor blush which may differentiate it from other lesions.

This data indicates that seemingly mild but persistent biochemical abnormalities are often the only indication of far advanced or severe hepatic injury in PVC workers. Early histological and angiographic studies appear to be required for complete evaluation.

MAILING ADDRESS OF PRINCIPAL AUTHOR

Date

Carlo H. Tamburro, M.D.

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Dr. Schanker, Dr. Senior, members and guests:

The development of angiosarcoma among vinyl chloride workers initiated a surveillance program, one of whose purpose is to determine the effectiveness of liver function studies in the detection of vinyl chloride liver injury. 315 or 27% of the 1,183 employees of a polyvinyl chloride production plant were initially found to have abnormal liver function tests. Persisting abnormalities were found in 75 or 7% and occurred three times more frequently among the vinyl chloride workers. 45 of the 75 persistently abnormal employees have been etiologically investigated.

May I have the FIRST SLIDE PLEASE?

Only three biochemical liver function tests, serum glutamic pyruvic transaminase, gamma glutamic transpeptidase, and alkaline phosphatase correctly indicated liver dysfunction in 80 or more percent of the cases. As shown here in RED, in 75% of the individuals, however, the Gamma GGT was abnormal in the absence of any other biochemical, radiological or histological findings. All other liver function studies were either less effective, as shown here, or have not as yet been found useful. ICG and bile acid clearances are presently under study.

NEXT SLIDE PLEASE

447 employees have received radioisotopic liver and spleen scans, 40 of whom were biochemically and histologically studied. As shown on the left in YELLOW, 50% had abnormal liver scans and biochemical and histological abnormalities. However, as shown in RED, 11% had abnormal liver scans, but were biochemically and histologically normal. In contrast, as shown on the right in YELLOW, 35% had normal liver scans, but were found to be biochemically and histologically abnormal.

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33 of these individuals had angiographic and hemodynamic studies. As shown in the NEXT SLIDE, on the left in YELLOW, 33% of these individuals had radioisotopically enlarged spleens and an elevated wedged hepatic vein pressure of greater than 17 mmHg. 11%, however, as shown in RED, had enlarged spleen scans, but normal wedged hepatic vein pressures. Moreover, as shown on the right in YELLOW, 11% had normal spleen size, but had elevated wedged hepatic pressures.

As seen in the NEXT SLIDE, angiographic studies of angiosarcoma, demonstrated a characteristic tumor blush as shown here at 8 seconds. Most liver tumor's blush occur in the arthrially phase 7 to 9 seconds after injection and are completed by the portal venus phase at the most 20 seconds after injection. As shown in the NEXT SLIDE, angiosarcoma's tumor blush remain visible far beyond the venus phase as seen here, 38 seconds after injection.

May I have the LAST SLIDE PLEASE?

Liver histology in these 40 individuals demonstrated various histological lesions including portal fibrosis, atypical sinusoidal lining cells, subcapsular fibrosis, fatty infiltration, increased vaculated nuclei and angiosarcoma. As shown here in the first column on the left in RED, only one of the 17 individuals with less than four year's exposure to vinyl chloride had significant pathological findings. In contrast, similar histology was found in one of the 12 individuals with four to ten year's exposure, in three of seven with 10 to 19 year's exposure, two of whom had angiosarcoma and in 3 of 4 with 20 year's exposure, one of whom also had angiosarcoma.

May I have the LIGHTS PLEASE?

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In summary; No singular biochemical or radiological test is sufficiently sensitive to include all possible hepatocellular injury due to vinyl chloride exposure, and when used singularly, may lead to false indications of liver cell injury. Secondly, angiosarcoma of the

liver produces a very late venous phase tumor blush, which can assist in its differential diagnosis. Thirdly, liver injury, characterized by biochemical, histological, and hemodynamic abnormalities appears to occur more frequently with increasing exposure to vinyl chloride and/or its associated products.

Finally, angiosarcoma appears to develop after prolonged exposure and with the development of excessive fibrosis and hepatocellular injury. Thank you.

This speech was presented at the 25th Anniversary Meeting of the American Association for the Study of Liver Disease on October 29, 1974 at the Ambassador Hotels in Chicago, Illinois, by Dr. Carlo H. Tamburro.

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