

K-1711- (100)

Handwritten notes and stamps: "N", "PV", "4/27/5", and a circular stamp with "10".

TRANSLATION

An excerpt from clinical research

Authors: Prof. Dr. W. Creutzfeldt
Goett.
Prof..
London

German Medical Journal - 98 (1973)
Pages 2311 - 2314
Georg Thieme Publishers, Stuttgart,
West Germany

Chronic-toxic liver damage in
PVC production workers

H.J. Marsteller, W.K. Leibach, R. Mueller, S. Juehe, C.E. Lange, H.G. Rohner
and G. Veltman

Medical Clinic (Director: Prof. Dr. H.J. Dengler)
Institute of Pathology (Director: Prof. Dr. P. Gedigk) and
Clinic for Skin Diseases (Director: Prof. Dr. A. Leinbrock) of the
Bonn University.

Polyvinyl chloride (PVC) has been a popular plastic for 30 years.
now because of its diverse application possibilities. It is there-
fore produced in large industrial volumes worldwide, (3). That un-
til 1966 no observations were made public in the western world con-
cerning its chronic toxicity may be attributed to the widely accept-
ed belief that the production of PVC involves merely relatively in-
ert substances.

The re-publication of a Rumanian study, first disclosed in 1963(18),
four years later(19) deals with affliction caused by prolonged con-
tact with PVC. The study, citing such afflictions as e.g. the Raynaud
Syndrome, dermatitis, (scleroderma), thyroid insufficiencies and hepa-
tomegaly pioneered other such studies originating from France (2,4),
Britain (7), United States (3,5,6,13,14,22) and Germany (8,9,10,17).
However these reports summarized the affliction on the basis of 55
patients examined as being "occupational acroosteolysis". More in-
depth symptomatology pointing to liver function disturbances was on-
ly verified in 8 out of these 55 patients (7,8,9,10).

The diagnosis "occupational acroosteolysis" overrules findings made
in 1949 in the USSR which related verified liver damages to PVC manu-
facture and which were diagnosed as more or less pronounced hepatitides,
in 15 out of 48 patients. Also ignored were the cited Rumanian find-
ings dealing with toxicity related hepatomegalies (in * 50 out of
168 patients) (18 and 19) and Russian reports citing partially sub-
clinical "chronic-epithelial-hepatitides in 15% of workers examined.

Vertical handwritten notes on the left margin: "Please find out what effect A.D.H. inhibition has on the thyroid function - liver reference".

Vertical stamp: "R&S 131149"

Results

The in several PVC plant workers substantiative esophageal varices and splenomegaly together with uncharacteristic liverparenchyma changes and the vague literary reference to "sub-clinical" liver damages motivated us to further pursue the morphological substrate of liver changes by means of laboratory analyses, radiology and scintigraphic examinations, laparotomy and target liver punctures. According to this procedure 20 out of 45 autoclave workers in a PVC manufacturing plant between the ages of 30 to 56 and whose exposure to the chemical varies from 1-1/2 to 21 years, have been examined to date in order to determine the presence of liver irregularities. Tables 1 and 2 present corresponding findings. In addition the following parameters were re-examined, in most instances more than once, and found to be near normal or normal:

Sedimentation tests, hemograms, sugar tolerance tests, urine analyses, Lues reaction tests, "LDH", cholinesterase tests, acid phosphatases, serum iron and copper, thymol, albumin tests and electrophoretically divided sub-fractioning; cholesterol, β -lipoprotein, triglyceride and plasmatic coagulation factor testing. To define scleroderma the following immunology parameters were analyzed: Rheumatic factors, anti-nuclear factors, LE cells, immunoglobulin fractions G A and M, complement fraction β_1 A and cold antibodies. These analyses were however later abandoned as it became increasingly clear that findings lacked relevance. Australia (SH) antigens were consistently negative. Only one patient examined showed signs of cholelithiasis (case 15); a changeable solitary concretion whose discharge was not obstructed.

According to test results indicated in Tables 1 and 2, it may be deduced that in most patients' cases neither the biochemical parameters followed to determine liver function nor laparoscopic and histological findings warrant special attention. The in, isolated cases found deviations from the normal were all very slight, inconsistent and ambiguous. Only a combined study of liver profiles and related histological evaluations acquired any significance when appraised on the basis of job-related exposure to a given product(s), otherwise such findings might be regarded as rather insignificant anamnesis. The outline of attention-worthy findings according to frequency of occurrence (Table 3) shows, that, in the grouping presented, the designated acroosteolysis was not the main symptom of occupational diseases within the PVC manufacturing field (2-8, 13, 14, 22) but thrombocytopenia and more or less pronounced chronic-toxic liver damages (12) with splenomegaly and signs of portal hypertension in some cases.

Conclusions:

Since it has been impossible to compile any meaningful data relating to work-area concentrations to date and since our knowledge of the PVC production process is only sparse, questions concerning etiological relationship and pathogenicity remain unanswered for the time being.

The morphological picture is however linked to acceptance of chronic-toxic liver impairment as might result from e.g. continuous or repeated contact with chlorinated hydrocarbons. Aside from other as yet unclear subjects is the formal genesis of liver function changes and one question stands out from others namely the question of why portal hypertension occurs in some cases. This point is of special theoretic and practical clinical interest. Classification of these cases in the category of intra-hepatic, pre- or intrasinusoidal block formations and how this relates to the histological picture on the basis of septal fibrosis in the portal canal and system; fibrosis with collagenization of the sinusoidal murals (1,11,16,20) as encountered in these cases has not been conclusively defined because of the fact that portal vein pressures in these patients has not yet been measured.

The relative frequency of slight to pronounced splenomegaly encountered, points to assumption of liver fibrosis.

Corresponding preventive clinical studies in other PVC manufacturing facilities and processing plants appear to warrant action. Periodic and subsequent checking of our patients and extensive animal experiments to gain more in-depth knowledge of cause and prevention are planned.

- 1) From a total of $\pm$ 120 PVC workers from a given plant, to date 45 have been examined in the Clinic of Dermatology of the Bonn University because of skin sensitivity manifestations and also on the basis of prophylaxis. Most of these workers showed signs of etiologically undetermined liver function disturbances according to clinical and/or biochemical tests. By May 1973, 20 workers had been subjected to laparotomy as it was considered that their symptoms warranted such action. Frequency of liver function impairments cannot be made on this basis.

Table 1. -- Anamnesis, clinical and biochemical findings obtained from 20 Autoclave workers. As regards bilirubin, transaminase and alkaline phosphatase, previous values were derived from 2-6 analyses and 2 analyses were made to determine liver functions on the basis of sulfobromophthalein sodium or disodium phenoltetrabromophthalein.

Case Count	Age	Area of occupation	Exposure to product (years)	Special anamnesis	Daily alcohol consumption	Hepatosplenomegaly (expressed in cms)	Bilirubin > 1.0 mg/100 ml	Phenoltetrabromophthalein test 5% in 45 min.	SGOT > 12 (21)mU/ml**	SGPT > 12 (33)mU/ml**	Alkaline phosphatase > 48 mU/ml	Thrombozyt (x10 ³ /mm ³) (Norm: 150-300 x 10 ³ /mm ³)	Acroosteolysis
1	33	A	3 1/2	none		3	-		6.8	23	17	74/99/119/133 149/163/173	+
2	32	A+	3 1/2	"	1 glass of wine	5	3		12.5	19	16	62/63/68/70/94 133	+
3	35	A	9	"	1 bottle beer	1	3	1.1	15.1	12		37/44/73/74/75 76/81/81	+
4	41	A+	3 1/2	"	1 bottle beer	1.5	-	1.1	8.5	19	15	59/111/114/210 233	-
5	34	A	5	"	1 bottle beer	-	1.5		21.5	21	21	116/119/137 140/163/175	+
6	47	A+	18	1972 Bill- roth II Ca? Ascites		3	5		25.6	19	11	80/90.31/100	-
7	51	A+	16 1/2	none	3-4 bottles beer	3	3		9.1	17		60/62	-
8	45	A	8 1/2	none	1 bottle beer	-	-		8.8	15		17/25/30/37/38	-
9	42	A	6 1/2	none	1 glass beer	1.5	-		13.8	25	23 (63)	125/176/214 270/235	-
10	31	A	4	none	---	-	3	1.7	7.1	(26)		52/122/122	-
11	47	A	12	since 1967 hyperlipidamy (liver function disturbance)	up to 2 bottles beer	-	1.5		6.2	15	15	51/57/59/133	-
12	56	A+	18	upper abdomen sensitive to pressure	2 bottles beer	1.5	-		6.1			70/122/125/141	-
13	35	A	4 1/2	none	1 bottle beer	-	-		7.6			89/144/171	-
14	35	A	10 1/2	none	beer	1.5	-		8.5	32 (27)	30	112/114/132 136	-
15	36	A	1 1/2	none	1 glass beer	3	-		6.3	17	17	113/134/211	-
16	50	A+	21	1955 Icterus 1968 chronic l.f.d. (*)	---	1.5	-		8.7	15	15	124/174/176 187/193	-
17	44	A	13 1/2	none		1.5	-			15		136/140/152 251	-
18	41	+	1 1/2	right upper abdomen sensitive to pressure	up to 2 bottles beer	-	-		6.1	19	17 (47)	143/160/189 189/224	-
19	30	A+	2 1/2	none		1.5	-		8.4	17		171/157/202	-
20	30	A+	4	none	up to 2 bottles beer	3	-		7.5	15	15	94/123/157 243	-

* l.f.d. = liver function disturbance

* A = Autoclave maintenance workers plus other functions in the manufacturing process

** Figures in parenthesis = values via substraoptimized method.

Table 1. - Radiological and laparoscopic-histological findings obtained from 20 PVC workers (autoclave maintenance workers).

R&S 131153

Case no.	X-rays esophagus (E) or fundus (F) varices	Laparotomy	Histology
1	-	Signs of capsular fibrosis, splenomegaly	centro-lobular collagenization of sinusoid murals, grouped fatty degeneration
2	-	Obvious capsular fibrosis, initial reconstruction, considerable splenomegaly	centro-lobular collapse, slight increase collagenic fibrils in portal system
3	+ (E)	Obvious capsular fibrosis, initial reconstruction, *red spots and reticulation, splenomegaly	-----
4	-	Reticular capsular fibrosis, hepatomegaly *regeneration	Collagenization of sinusoid murals, slight fatty deg. of cells, slight starcell siderosis
5	-		Slight portal fibrosis, fatty deg. slight starcell activation, hydropic swelling
6	+ (E&F)	Initial to complete reconstruction, portal hypertension, ascites, obvious splenomegaly	Septal and central fibrosis
7	+ (E&F)	Reticular to surface covering capsular fibrosis, initial regeneration, initial portal hypertension, obvious splenomegaly	Irregular to septal fibrosis, roundcell infiltration into portal system, white blood cell necrosis, starcell activation
8	-	Spotty capsular fibrosis	Indication of portal system fibrosis, isolated fatty degeneration
9	-	Slight capsular fibrosis, slight splenomegaly	Indication of septal/portal fibrosis, centrolobular collagenization of sinusoid mural fatty deg., slight starcell activation
10	-	Obvious capsular fibrosis initial reconstruction, splenomegaly	Slight septal fibrosis, massive collagenization of sinusoid murals
11	-	Indicated capsular fibrosis, and possible initial reconstruction	Massive fibrosis of the porta canals, septal intralobular fibrosis, regenerative activity not in evidence, slight dissemination of fatty deg.

12	-	Irregular capsular fibrosis, hepatomegaly	Septal fibrosis in portal can- narrow intralobular septa, slight cholesterosis, light disseminated fatty deg.
13	-	Slight capsular fibrosis	Slight fibrosis in portal ca- nal, slight cholesterosis, fatty deg. single cell necro- sis, glycogen deposits
14	-	" " "	Isolated intralobular fibrosis massively disseminated fatty deg.
15	-	Obvious capsular fibrosis	Indicated septal fibrosis in portal canals, massive fatty deg., starcell activation (grouped)
16	-	Slight capsular fibrosis	Slight portal canal fibrosis, massively disseminated (small droplet) fatty deg., slight starcell activation, massive glycogen deposits
17	-	Obvious capsular fibrosis	Cirrhotic/septal/reconstructio lumpy cell regenerates
18	-	Fine to medium granular re- construction	Septal fibrosis, massive cell genization of sinusoid mural widely disseminated fatty de slight starcell siderosis.
19	-	Uncertain pathological finding	Indicated septal fibrosis, slight (large droplet) fatty deg., slight starcell activa- tion
20	-	Hepatomegaly, questionable re- construction, fatty deg. in the liver	Indicated septal fibrosis/ portal canals, massively dis- seminated (large droplet) fa- ty deg., single cell necrosis. starcell activation

Table 3.- Frequency of pathological findings in 20 PVC workers

Symptoms	Count
Increased phenol-tetrabromophthalein retention	19
Thrombozytopenia	16
Liver-spleen changes determined via laparorrhaphic tests *	14
Splenomegaly in selective spleen-scintigrams (present in 2 patients' liver-scintigram as well)	7
Clinical splenomegaly	7
Clinical splenomegaly	6
Acroosteolysis	4
Esophageal varices (2 patients also showed signs of fundus varices)	3

* All 19 cases showed signs of slight to massive hepatic changes, according to histological findings.

R&S 131155