CLINICAL MANIFESTATIONS IN VINYL CHLORIDE POISONING

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As civilization developed, man passed through the Stone Age, the Iron Age, and the Bronze Age. Now we are living in the Plastics Age.

As supplies of iron, copper, lead, and other metals decrease, they are replaced mostly by plastics. The conquest of space and Mount Everest, the rapid development of industry, and the higher standard of hygiene and clothing would not have been possible without the development of the plastics industry.

Plastics are obtained from salt, petroleum, wood, methane, gas, quartz, etc. Because our country possessed these raw materials, the plastics industry was developed and large plants were built.

Simultaneously with the development of the plastics industry, studies for observing the health status of workers exposed to the new chemicals were initiated. There has been a rapid increase in the number of chemicals used, and we do not yet know all the adverse effects of these new chemicals. Some substances cause diseases in man which cannot be reproduced in animals, such as, arterial hypertension, Raynaud's phenomenon, scleroderma, and gastric-duodenal ulcer, and unfortunately, when animals are exposed to toxic substances, they cannot describe the onset and evolution of the disease.

Plastics, as finished articles, are considered generally harmless. The problem is, to what extent do the monomers or substances used in the chemical industry determine acute or chronic effects in the human organism.

In 1961, the study of clinical and biological manifestations in workers of two plants manufacturing vinyl chloride from acetylene and hydrochloric acid was begun. The workers were examined before the opening of the plant and then periodical examinations were performed. Some of them were admitted to the Clinic of Professional Diseases for ascertainment of the diagnosis.

In the medical literature we consulted, we found few data on clinical and experimental effects of vinyl chloride. Mastromatteo *et al.*[30-32] have shown that in a concentration of 10–30% vinyl chloride caused pulmonary, hepatic, and renal congestion in 5 rats, 5 mice, and 5 guinea pigs. Plesitzer *et al.*[33] have shown that chronic exposure to vinyl chloride vapors causes toxic angioneurosis in man. Danishevsky and Egorov[4] showed that the monomers react aggressively, causing destructive changes in the tegument and mucosa, some of which are allergenic. Tessier and Harvieux[35] described 17 cases of chemical dermatitis in 145 workers employed in the plastics industry.

We wanted to follow up the workers exposed to vinyl chloride and other toxic substances in order to obtain a more complex clinical picture and to detect the bio-toxicologic effects of vinyl chloride. In addition to clinical and biochemical investigations, Prodan *et al.*[37,38] from our department studied experimentally the acute and chronic effects on various animals.

Materials and Methods

In 1962, 114 workers from the "A" factory and 54 workers from the "B" factory, who were exposed to vinyl chloride, were examined. Most workers were

young and had not worked in other industries. These 168 workers had repeated clinical examinations and blood pressure readings. The laboratory examinations consisted of serum protein studies, Takata-Ara, thymol, and Grienstedt reactions and electrophoresis of serum proteins. The plethysmographic test (at low temperature) was also performed. In the subjects admitted to the Clinic of Professional Diseases these examinations were repeated and supplemented with a hepatic clearance test using bromosulfonphthalein (BSP).

The 114 workers of the A factory had repeated examinations by the same staff in 1963, 1966, and 1969. In a group of the cases, Suciu *et al.*[36] determined the pulmonary artery pressure. Repeated plethysmography was carried out by Raucher, Suciu, and Pislaru (Institute of Hygiene of Cluj).

Since 1962, to the present, 72 patients (51 men between 20 and 53 years of age and 21 women between 19 and 39 years of age) were admitted repeatedly to the Clinic of Professional Diseases of Cluj. The cases with nervous, digestive, skin, and angioneurotic manifestations were admitted preferentially.

Results and Discussion

The dynamic study of the clinical and laboratory examinations in correlation with the vinyl chloride concentration in the air showed that during the periods of high concentrations between the years 1963 and 1964, acute and subacute poisonings occurred. During the subsequent years, when the concentrations decreased 22 times, the acute and subacute poisonings completely disappeared and chronic manifestations occurred (Table 1).

Nervous Manifestations

After the first breaths in an environment with a high concentration of vinyl chloride, the workers have the feeling of a pleasant taste in the mouth, and then a euphoric condition (11 percent) occurs. This euphoria is marked by singing, whistling, and sardonic, careless laughter. Movements become slow, giddiness appears (47 percent), and a condition resembling inebriety sets in. If work is continued somnolence occurs (45 percent) and in 6 percent of the cases complete narcosis was found. On the night shift, the workers readily fall asleep. The somnolence also continues after leaving the factory. At home these workers

Table 1
Vinyl Chloride Concentrations Correlated to Occupational Disease

Year	Vinyl Chloride Concentration (mg/m³)	Cases of Occupational Disease
1962	2298	17
1963	675	17
1964	286	8
1965	126	2
1966	98	2
1967	100	—
1968	108	1
1969	111	5
1970	111	—
1971	119	—
1972	146	—

sleep, deeply and dreamlessly, for 9–14 h. A worker, in the absence of his wife, slept for 3 days intermittently, being waked by his neighbors.

The workers detect the presence of the toxic substance in the room by the occurrence of a sensation of formication and of warmth in the lower limbs, which confirms the opinion of Danishevsky and Egorov[8] that vinyl chloride would act on the tegument. In fact, vinyl chloride is heavier than the air and persists as a compact layer which may catch fire and cause explosions. This happened in the A factory, where 15 persons suffered slight burns following an explosion.

After repeated exposures the workers complain of headache (36 percent), irritability (9 percent), diminution of memory (13 percent), insomnia (3 percent), general asthenia (7 percent), paresthesia (4.7 percent), tingling (9.4 percent), and loss of weight (28.4%), all symptoms which indicate the onset of asthenovegetative syndrome.

The symptoms become more intense during the cleaning of the autoclaves, when the concentration is higher. After the introduction of measures to remove excess vinyl chloride from the autoclave, the symptoms were reduced.

The incidence of nervous symptoms in 1966 as compared to 1962 is shown in Table 2. The clinical data are in agreement with the experimental data. Thus, Mastromatteo *et al.*[36] reported that at 10 percent vinyl chloride they observed irritability, unrest, loss of coordination of movement, and in some animals narcosis.

In 72 of the admitted cases, the nervous manifestations were: headache (68.6 percent), asthenia (58.8 percent), adynamia (14 percent), dizziness (49 percent), euphoria (11.2 percent), sleeplessness (2.8 percent), loss of memory (35.0 percent), paresthesia of limbs (39.2 percent), loss of weight (46.2 percent), and a decrease of physical force (40.6 percent). It was thus noticed that in some persons the nervous symptoms are of longer duration, for example, the clinical picture of nervous asthenia, with somnolence, disturbances of memory, and loss of weight. One case showed hepatomegaly and polyneuritis and hepatitis.

Prodan *et al.*, in their subsequent experiences with vinyl chloride, have shown that at the beginning of exposure the animals were nervous. Then they became progressively calmer, eventually falling down in a state of narcosis during the

Table 2
Nervous Symptoms in 1966 as Compared with 1962

Symptoms	1962, 168 Cases (%)	1966, 168 Cases (%)	Hospitalized Cases (72) (%)
Euphoria	11.0	1.2	11.2
Dizziness	47.0	10.2	49.0
Somnolence	45.0	16 6	
Sleeplessness	3 0	4.0	2.8
Headache	36.6	6.9	68 6
Nervousness	9.0	0 6	
Loss of memory	13.0	8 0	35.0
General asthenia	7.0	9.0	58.8
Adynamia			14.0
Paresthesia of limbs	4.7		39 2
Loss of weight	28 4		46 2
Complete narcosis	6.0		1.4
Loss of physical force			40.6

first hours of exposure. In this stage a lacrimal and salivary hypersecretion occurred. In the motor stage of narcosis muscular contractions and tonico-clonic convulsions occurred showing an involvement of the motor areas in the central nervous system. The surviving animals returned to normal. The LD_{100} in rats rises to 525.5 mg/liter and in guinea pigs and rabbits it is over 700 mg/liter.

We observed that if after slight exposures the workers went out in the air, the nervous symptoms disappeared after a short time. We suggest the installation of oxygen therapy at the working places. After inhaling oxygen for 2–3 min, the return to a normal condition is very rapid.

It can be seen in TABLE 2 that the nervous symptoms are reduced by two-thirds as the concentration of vinyl chloride in the working place is reduced. The lowering of the toxic concentration also has an influence on the digestive symptomatology.

Cardiovascular Manifestations

Arterial Hypertension

In 1962 when the plant was opened, in the 227 workers examined, the arterial blood pressure was 10–20 mm Hg lower, for the maximal and minimal values, than in the control group. The decrease of the normal values of the arterial blood pressure (BP) is accounted for by the narcotic effects. The incidence of arterial hypertension is 1 percent.

Simultaneously with the clinical examinations plethysmographic determinations were also made, and it was found that 47 percent of the workers showed vasospastic disturbances.

During the following years the examinations were repeated both in plant A (114 workers) and in plant B (54 workers) by the same staff (Raucher, Suciu, Pislaru) with the same methods. In plant A vasospastic changes were found in 66 percent of the workers and in plant B in 55 percent.

Observing the vasospastic changes in the plethysmography, Frits measured the pressure in the pulmonary arteries in 1965 and then again in 1969 (TABLE 3).

In the same workers from 1965 to 1969 the frequency of the cases with moderately increased pressure (between 32–35 mm Hg) rose from 7 to 11 (from 14 to 18.3 percent, respectively), and the frequency of cases with increases of pressure above 35 mm Hg rose from 3 to 14 (from 3 to 23 percent, respectively); the frequency continued to be 10 percent between the two examinations.

Based on the above data *a continual increase of the number of cases with general and pulmonary constriction was found by the plethysmographic examinations and measurements of pulmonary artery pressure.*

For these reasons we followed up the levels of blood pressure (BP) in 112 workers in 1969 as compared to 1961. Results obtained are shown in TABLES 4

TABLE 3
PULMONARY ARTERIAL TENSIONS

No. of Cases	Year	Values	
		Moderate	High
51	1965	7 (14.0%)	3 (6.0%)
60.	1969	11 (18.3%)	14 (23.3%)
48 (normal cases)		5 (10.4%)	5 (10.4%)

TABLE 4
MEDIUM VALUES OF ARTERIAL TENSIONS (AT) IN 1961

	Age Groups			
	Under 20 yr	20–29 yr	30–39 yr	40 and over
Maximal AT	106.83	111.32	110.92	117.82
Minimal AT	68.75	70.53	72.78	74.70
No. of cases	24	131	50	23

TABLE 5
MEDIUM VALUES OF ARTERIAL TENSIONS (AT) IN 1969 ARE INCREASED COMPARED WITH 1961

	Age Groups			
	Under 20 yr	20–29 yr	30–39 yr	40 and over
Maximal AT	125.00	132.16	130.54	138.08
Increased	18.17	21.84	19.62	20.18
Minimal AT	72.50	74.32	77.70	83.00
Increase	3.75	3.79	4.92	8.30
No. of cases	2	37	45	28

and 5. Therefore, a slight increase in the values of the systolic blood pressure by 5 mm Hg (average) was noticed in 1969 as compared to 1961. Normal values of the BP were considered to be 15/9 up to the age of 60, and 16/10 over 60 years of age. The frequency of the arterial hypertension in 1969 reached 18.75 percent and the prehypertensive conditions 17.85 percent, the normal values being 63.39 percent. In 8 cases admitted to the hospital, arterial hypertension was discovered (11.1 percent) and in 7 cases arterial hypotension was found (10.1 percent). It was observed clearly that long exposure to vinyl chloride seems to cause vasoconstriction and the arterial hypertension.

These results show that in exposure to toxic substances the plethysmographic examination reveals latent disturbances which elucidate the direction of the evolution of clinical manifestations. Measurement of the blood pressure and the follow-up of the dynamical changes are of real importance in the periodical medical examinations.

The decrease in the BP levels in the first examination showed the narcotic effect of large doses of vinyl chloride. A vasoconstrictor effect was observed after exposure to small amounts.

Examination of the fundus of the eye and the retinal artery blood pressure (RABP) in the admitted cases showed an increased RABP (over 45) with no changes of the fundus of the eye in 2 cases, RABP over 45 and silver reflexes in 2 cases, normal RABP in 12 cases, and RABP below 20 g of water in 13 cases. These last results occurred mainly in the patients with hepatitis. Examination of the RABP shows that in the cases with arterial hypertension and hepatitis low values prevail. Some nervous manifestations could be caused by retinal artery hypotension.

Mârza and co-workers showed experimentally the vasoconstrictor effect of ϵ-aminocaproic acid and of other plastic substances.

Raynaud's syndrome was detected with typical clinical symptoms, by the pressor test at cold temperatures and plethysmography. It must be mentioned

that Raucher, Suciu, and Pislaru during the 1962–1966 period found vasospastic changes in 66 percent of the workers of the A plant and in 55 percent of those in the B plant, without any clinical or objective sign of Raynaud's syndrome.

Clinical Raynaud's syndrome was found in 6 percent of the cases examined during the first 3–4 years. Three-fourths of the cases were young men, and only ¼ were women. In 7 cases Raynaud's syndrome was associated with scleroderma and hepatomegaly.

The symptoms of Raynaud's syndrome disappeared with no therapy after the work place was changed, which shows that its toxic etiology is certain.

In the examinations performed in 1966 by the same staff, it was found that the frequency of Raynaud's syndrome was 2.9 percent as compared to 6 percent in 1962, a decrease of 50 percent, due to a 22-fold reduction of the toxic substance and changing of the working place.

Digestive Manifestations

The clinical picture is predominated by nervous manifestations. They are found particularly in the patients exposed to large doses of vinyl chloride. Concurrently with the nervous manifestations, in some cases digestive manifestations also occur. The first symptom is anorexia (23 percent) which reveals the general intoxication of the organism. Later on, the symptoms included nausea (without vomiting) (28 percent), distension, pyrosis (9.4 percent), epigastric pain (16 percent), sensation of discomfort, pressure in the right hypochondrium (7 percent), and pressure in the left hypochondrium (5 percent). In some cases bar-like pain occurred, but did not reach the intensity of pancreatic drama. Some patients showed elective anorexia toward fats.

It should be pointed out that in 30.2 percent of the cases the clinical examination revealed hepatomegaly without jaundice (TABLE 10). The liver passed beyond the rib margin by 2–3 finger widths, without being pushed down by pulmonary emphysema or other thoracic effect.

At the beginning of exposure the liver had a flaccid or elastic consistency and after repeated exposure to the toxic substance, it became harder, similar to the liver in epidemic hepatitis. In 6 percent of the follow-up cases, hepatomegaly was associated with splenomegaly. The transfer to another working place caused a regression of hepatomegaly, the liver returning to within normal limits in most cases. In most cases hepatomegaly was not accompanied by digestive symptoms, which were only found at the objective examination by palpation.

It should be remembered that in 6.8 percent of the cases, the workers had previous epidemic hepatitis. In these patients hepatomegaly set in more rapidly after they began to work in the toxic environment, although the hepatic tests at their first employment were within normal limits and the liver was not enlarged.

Hepatomegaly raises delicate problems of interpretation. In each case we must first rule out epidemic hepatitis. Most of the patients with hepatomegaly were hospitalized in the Clinic of Professional Diseases where examinations were made in order to rule out anicterigenic hepatitis. It should be mentioned that during the period of our examinations no inoculations were given and no cases of icterigenic epidemic hepatitis were found in this group.

The fact that at first employment no hepatomegaly was found, but after work in a vinyl chloride environment the liver became larger and softer, and the fact that hepatomegaly disappeared with no therapy after a transfer to another working place imply that at the beginning, a toxic congestive hepatomegaly occurs,

similar to that described by us in lead, mercury, and organic solvent poisonings. We also noted that the hepatic congestion precedes saturnine cholic and disappears after EDTA therapy.

In the cases with hepatomegaly we carried out the following procedures: serum protein electrophoresis, thymol, Grienstedt, SO_4Zn, and BSP reactions; in 3 cases with harder livers, hepatic puncture biopsy was done.

Serum protein electrophoresis was performed in 36 cases. A decrease in albumin below 53 percent was found in 11 cases, an increase in α-1 globulins over 5 percent in 10 cases, α-2 globulins over 9 percent in 22 cases, and γ-globulins over 21 percent in 10 cases (TABLE 6).

The electrophoretic changes resemble those found in viral acute hepatitis

TABLE 6

ELECTROPHORESIS OF SERUM PROTEINS AND RESULTS OF THYMOL AND SO_4Zn REACTIONS IN A GROUP OF WORKERS WITH HEPATOMEGALY

No.	Name	Albumins	Globulins				Thymol	SO_4Zn
1	C.M.	51	4.3	27.6	13.7	23.7	11	45
2	F.E.	55.1	4.3	10.3	10.1	22 0	6	35
3	T.V.	51.7	4 2	10.3	13.2	20.0	9	50
4	M.V.	55	4.3	11 2	11 0	18 4	6	
5	D.I.						9	40
6	T M.	59.4	5 2	8.4	12 4	14.4	6	30
7	C.S.						10	30
8	J V.	65.6	7.7	8.7	6.5	11.2	6	32
9	S.T.	54.1	2.1	10 3	11 7	21.3	2	45
10	G.T.	61.0	5.5	1.9	11 7	12.2	10	60
11	P.I.						17	48
12	M.D.						10	30
13	F M.	41.4	7.1	12 8	14 2	24 2	10	50
14	T.R.	66.5	1.0	8 5	12.0	12.1		
15	H.S.						10	45
16	C.M.	52.3	4.8	7.1	18 3	17 2	1	45
17	B.P.	58.9	3 1	8 5	12 1	18 2	10	48
18	T.L.	62.7	3.5	8 2	12.7	13 5	16	50
19	K.E.	46.8	5.6	13 8	13.7	19 4	13	53
20	L P.	52.0	3.1	9 7	12.4	22 3	10	54
21	H N.	58.2	4 0	12.2	9.3	16 1	2	
22	A.V.						4	40
23	M.I.	55.5	4.2	9 4	10 4	20 2	11	55
24	C I.	55.6	2.7	10.2	11.0	20.0		
25	P.V.	56.0	3 1	8 5	12 1	19.6	6	32
26	G P.	54.3	4.8	13 2	11 6	19.5	1	
27	F S.	54.3	4.8	12.2	11.6	19 5	1	
28	B G.	51.7	5.0	13.3	13.5	16 7	1	
29	Y.S.	53.1	4.5	8.3	13.1	20 9	1	
30	T.B	51.0	5.2	10.4	12 6	20 7	1	
31	S.C.	56.6	3.6	9.5	14.6	18.2	1	
32	N I.	48.5	5.3	9.5	12.6	24 2		
33	P.I	57.0	3 3	7.8	10 9	20 0	17	
34	K R	42 7	6.1	13 3	16 7	21 8	1	
35	C L.	56 0	4.9	8.3	11.4	20.5	2	
36	T D.	59 2	4.1	7.2	11.7	18 7	41	
37	V V	53 1	3 8	10 1	12 1	20 0		
38	C M.	54.0	3 8	7 4	12 6	19 0		
39	V.A.	57.0	3 8	8 2	12 9	17 6		
40	M M.	55.0	5 1	10 2	12.0	24.0		

in which an increase in α-2 globulins was found. The thymol, SO,Zn, and Grienstedt reactions were positive in 6 cases. In 11 cases BSP was determined; it was pathological in 2 cases.

In 20 cases with hepatomegaly (a group examined clinically by us) increased aldolase between 0.75 and 1.20 g was found in 17 cases.[19]

In 78 workers of the same plant, Gabor and co-workers[19] found a decrease in albumins and an increase in globulins. Serum cholinesterase was increased in all the workers exposed to vinyl chloride except the technicians with low exposure (normal value 0.40–0.60 ml of NaOH N/10). This decrease was significant ($p < 0.01$) in the workers employed in the synthesis and polymerization of the monomer (TABLES 7 and 8).

This shows that during vinyl chloride poisoning, disturbances in protein metabolism may occur which precede the onset of hepatomegaly. For the elucidation of hepatocytolysis we consider serum aldolase, succinodehydrogenase, and transaminases important.

Lester *et al.*[17] found experimentally an increase in the size of the liver with an increase in transaminase and a decrease in prothrombin. They also found spleen enlargement in the animals. Torkelson *et al.*[20] found liver enlargement in rats exposed for 6 months (7 h daily), as well as hepatic and renal degenerative lesions. At a concentration of over 30 percent, Mastromatteo *et al.* found in the dead animals, hepatic, renal, and pulmonary congestion and hepatic degeneration.

Prodan and co-workers[21] showed that with special stains the nuclear DNA is reduced and pulverulent. The cytoplasmic DNA is in a minimal quantity. These changes are centrolobular in animals poisoned with 10 percent vinyl chloride. Hepatic glycogen almost disappeared in the centrolobular cells. In the vitamin-fed animals with interrupted exposure, the changes were less marked. These results show that subcellular lesions exist, which account for the biochemical and enzymatic disturbances.

If a correlation is made in the cases of poisoning with vinyl chloride between the angioneurotic changes associated in some cases with hypothyroidism with corticoadrenal insufficiency with arterial hypertension, it might be supposed that

TABLE 7
CHOLINESTERASE VALUES IN WORKERS FROM DIFFERENT WORKING PLACES (GABOR *ET AL.*[19])

Working Place	$X \pm$ S.E.	Significance Test	Probability
A. Monomer synthesis	0.30 ± 0.11	Between A and B: 5	$p < 0.01$
AB. Polymerization	0.30 ± 0.09	Between AB and B: 5.5	$p < 0.01$
B. Maintenance	0.40 ± 0.10		

TABLE 8
CHOLINESTERASE IN WORKERS GROUPED AFTER WORKING YEARS (GABOR *ET AL.*[19])

Years of Work	$X \pm$ S.E.	Significance Test	Probability
0–3	0.30 ± 0.03	0.87	$p > 0.10$
3–6	0.35 ± 0.08		

TABLE 9
DIGESTIVE SYMPTOMS IN 1962 AND 1966

Symptoms	1962 (%)	1966 (%)
Anorexia	23.0	10.3
Epigastric pains	16.0	9.0
Pains in right hypochondrium	7.0	23.0
Pains in left hypochondrium	5.0	5.7
Hepatomegaly	30.2	11.4

vinyl chloride probably affects the vasomotor and metabolic centers. Vinyl chloride monomer also causes an irritation of the reticuloendothelial system, resulting in hepatosplenomegaly. Prodan and co-workers[21] have found experimentally a reduction in the red pulp and an increase in the white pulp in the spleen.

An argument for the toxic nature of the digestive manifestations could be the decrease of the symptoms simultaneously with the reduction of the concentration or the removal of the patient from the toxic environment.

TABLE 9 shows the results of the clinical examinations carried out in 1962 and 1966. From the table a decrease in hepatomegaly of almost 3 times can be seen. The increase of the pain in the right hypochondrium is due to biliary dyskinesia which was detected on admission to the hospital. This pain subsides after administration of antispastic drugs. In some cases hepatomegaly subsides after duodenal tubage, which indicates congestive hepatomegaly.

No particular changes were found in relation to the working years.

Hepatomegaly without positive hepatic tests and pathological electrophoretic changes were due to a toxic hepatic congestion (Prodan *et al.*[21,22]). Mastromatteo *et al.*[20] found hepatic congestion experimentally. Hepatomegaly with positive hepatic tests may turn to chronic hepatitis in time. In two cases with positive tests and hard liver the biopsy (Papilian) showed signs of chronic hepatitis. The patients had not suffered from epidemic hepatitis previously.

The electrophoretic changes were followed up in 24 workers exposed to vinyl chloride without hepatomegaly. In these cases no diseases were found which evolved with electrophoretic changes.

In 14 patients out of 24 (TABLE 10), the albumins were below 53 percent, in 6 cases the α-1 globulins were higher than 5 percent, in 16 cases the α-2 globulins were over 9 percent, in 1 case the β-globulins were over 13 percent, and in 16 cases the γ-globulins were more than 25 percent.

We followed up 72 cases admitted to the hospital, who showed obvious manifestations. We found a lack of appetite in 29 cases, nausea in 42, vomiting in 20, distension in 43, pain in the right hypochondrium in 57, epigastric pain in 25, constipation in 3, and pain in the left hypochondrium in 4. Hepatomegaly between 1½ and 5 cm was found in 54 cases. In 27 cases hepatomegaly was associated with positive hepatic tests. In 36 cases with hepatomegaly in which a GPT test was performed, values over the normal were found in 18 cases. The values found were between 45 and 493 I.U., showing that a toxic hepatocytolysis exists. This was also shown experimentally by Prodan and co-workers.[21]

A BSP test was done in 26 cases and in 22 cases it had pathological values (over 5 percent retention). The thymol test was performed in 51 cases, and it had values over 6 units in 45 cases; Grienstedt over 1.5 ml was found in 29 out of the 56 examined cases; SO,Zn was more than 40 in 40 of the 49 reactions performed. In 24 cases with hepatomegaly the proteinogram examination showed

TABLE 10
SERUM PROTEIN ELECTROPHORESIS AND RESULTS OF THYMOL AND SO_4Zn REACTIONS IN A GROUP OF WORKERS WITHOUT HEPATOMEGALY

No.	Name	Albumins	Globulins				Thymol	SO_4Zn
1	V.V						2	55
2	B.S.	47.0	5.8	10.8	14.1	26.6		
3	M.C.	47.2	6.7	10.7	11.2	24.0		
4	H.E.	55.9	4.9	10.4	11.9	17.1		
5	G.N.	50.0	5.5	11.5	9.7	22.9		
6	K.E.	40.8	5.9	11.5	11.2	22.6		
7	M.O.	60.9	2.7	8.9	10.1	19.0		
8	J.I.	50.0	3.7	12.3	12.0	22.5		32
9	M.V.	50.0	5.4	7.9	14.7	21.7	10	35
10	M.S.	52.5	4.1	5.0	11.2	21.7		
11	O.A.	52.0	3.4	10.0	12.2	22.0	1	33
12	T.P.	53.0	5.0	7.3	13.8	21.0	10	40
13	V.V.	49.0	4.1	8.0	15.2	26.6	10	25
14	M.M.	58.0	3.7	6.4	14.0	17.2	10	45
15	P.	61.7	4.1	9.7	8.8	17.9	13	40
16	N.M.	51.0	4.7	11.3	12.1	21.0	13	35
17	B.L.	52.4	3.8	10.3	13.2	20.1	14	55
18	L.S.	57.2	3.1	6.7	6.0	27.3	7	35
19	R.I.	47.7	5.3	9.6	14.4	22.8	2	38
20	G.P.	49.0	5.3	11.2	13.1	21.0	13	35
21	E.F.	59.0	3.8	7.1	12.1	17.9	8	35
22	P.O.	54.4	4.0	6.7	12.8	22.4	10	58
23	M.V.	50.1	5.1	9.6	11.0	23.9	2	
24	P.G.	56.0	2.2	8.8	11.2	11.9	10	30

increased α-2 globulins in 23 cases and γ-globulins in 24 cases. The changes in the proteinogram are of acute, subacute type. Increased sideremia (over 120 percent) was found in 4 out of 11 cases. Direct bilirubinemia was over 1 g in 4 cases and over 1.5 mg in 4 cases. Jaundice was present in 2 cases. Serum cholinesterase was determined in 9 cases; in 4 it was below 150 μmol/ml/h.

We noted that in the cases with hepatomegaly, the hepatic tests were altered in a different manner showing the possibility of an evolution toward chronic hepatitis. The correlation between the toxic substance and hepatitis may also be seen by the association of hepatomegaly with other ailments (TABLE 11).

One case of a necrotic papilliferous hepatic carcinoma with pulmonary metastases should be mentioned. This patient was followed up for 10 years; he worked first in a section where vinyl chloride was obtained from acetylene and then for 6 months in a section where vinyl chloride was obtained from dichloromethane.

TABLE 11
HEPATOMEGALY ASSOCIATED WITH OTHER AILMENTS

	No. of Cases
Hepatomegaly, Raynaud's syndrome	6
Hepatomegaly, Raynaud's syndrome, dermatitis	1
Hepatomegaly, arterial hypertension	4
Hepatomegaly, splenomegaly	10
Hepatomegaly, polyneuritis	1
Hepatomegaly, anemia	1

Prodan and co-workers[17] showed experimentally that animals intermittently exposed to vinyl chloride recover, and even may gain, body weight more rapidly than those exposed continuously. In the group intermittently exposed and with a surplus of vitamin C, hepatocellular lesions were less marked.

In the animals exposed to vinyl chloride the hepatocellular lesions are severe, involving the whole lobule and being more marked in the center of the lobule. The cell contours are blotted, the nuclei are hypochromic and pyknotic, and the cytoplasm is basophilic with cytoplasmic vacuolizations and granular and granulovacuolar intumescence reaching the stage of hepatocellular necrosis. A fibroblastic and Kupfferian proliferation can be observed, starting from the portal space and advancing toward the center of the lobule, displacing Remak's cords.

From the clinical laboratory examinations it is shown that in acute poisoning transient hepatic congestions, acute and chronic toxic hepatitis may be encountered. Other toxic substances used in the plastics industry may also have a role in causing these changes, but the prevailing role is played by vinyl chloride. The condition eventually became chronic as was shown by liver biopsy and experimentally.

Respiratory Manifestations

The workers exposed to vinyl chloride show coughing and sneezing, and in some cases bronchial rales appear, which are difficult to distinguish from the bronchial rales occurring in bronchitis of smokers. In most of the cases admitted to the hospital in the last few years, pulmonary emphysema was found.

The respiratory tests performed in 157 workers exposed to vinyl chloride in 1969 gave the results shown in TABLE 12. From the table we can see a decrease in the respiratory volume and in the vital capacity. The maximal expiratory volume per second (MEVS) shows the most marked decreases depending upon age; the velocity index showed similar decreases. The decreases in the MEVS and in the velocity index denote respiratory insufficiency. In the cases admitted to the hospital during the last 10 years, pulmonary fibrosis of linear type was found.

Anastasatu and co-workers described radiologic pulmonary changes of pneumoconiosis after exposure to styrene.

Prodan and co-workers[17] have found experimentally at the anatomopathological examination, after chronic exposure to vinyl chloride, lesions of pulmonary fibrosis. The fibrosis is accompanied by interstitial infiltration with a chronic character. With special stains (periodic acid-Schiff-Hotkiss-McManus) the neutral mucopolysaccharides rise in the alveolar walls in all the animals exposed to vinyl chloride.

In acute poisoning with vinyl chloride an acceleration of the respiratory movements of the animals is found, and then bradypnea with irregular frequency,

TABLE 12
RESPIRATORY VALUES ACCORDING TO AGE GROUPS

Respiratory Tests	Age Groups				
	Under 20 yr	20-30 yr	30-40 yr	40-50 yr	50 and over
Vital capacity	99.0	99.7	98.1	98.1	96.4
Respiratory volume	94.1	90.0	87.7	78.0	89.1
MEVS	68.1	67.9	64.2	63.2	68.4
Velocity index	0.92	0.86	0.83	0.79	0.88

cyanosis, apnea, and death. A congestion of the conjuctiva was found, and anatomopathologically pulmonary congestion could be seen.

Therefore, the pulmonary effects are not as intense as other effects, and they may be caused by other factors, too, such as dust, acids, or bases.

Cutaneous Manifestations

During the period of exposure to large amounts of vinyl chloride, the clinical picture shows two aspects: subacute and acute intoxication. It should be stressed that 80 percent of the workers reported that they suffered from transient dermatitis but clinically nothing was found. Possibly, small doses at varying time intervals have the role of desensitization and prevent the occurrence of allergic dermatitis.

The earliest symptom is pruritus which was found in 4.8 percent of the cases without being associated with skin changes. Later on distinct skin changes of contact dermatitis appeared (4.4 percent).[5] On the bare parts of hands and face, papules appeared, which first broke and then became madescent and formed intense crust. The lesions disappeared when work was discontinued and suddenly reappeared when work was resumed. In 11 out of the 72 cases admitted, dermatitis associated with other manifestations was detected. The sclerodermic aspect was seen in 3.6 percent of the cases.

Cases of cholagenesis after using substances with an action on the nervous system, such as hydrazinophthalazine are reported in the medical literature.

Among the 170 workers exposed to vinyl chloride,[6] we found 3 cases of papuliferous mucinosis, myxedematous lichen in two women (ages 17 and 21) and a man (age 35). All 3 subjects had Raynaud's syndrome of the upper arms, but no other disease in their history. All of them also showed signs of general poisoning. In the women a hard, unpainful tumefaction of the type of clero-myxedema, involving the subcutaneous tissue of the face, eyelids and giving the aspect of a mongoloid face with rigidity of expression, appeared at the same time.

The papulous, lichenoid, symmetrical eruption showed more significant variations. In 1 patient it occurred on the backs of the hands having a miliary aspect, the necklace-like elements reminding one of annulare granuloma. In the other women the lesions were micropapulous, of the size of a pin head, and were situated on the flexor surface of the forearms, being confluent in placards and giving the appearance of orange peel.

In a man, the placards were not well delimited, being situated on the flexor surfaces of the forearms and on the pectoral region and formed of lenticular papules. All of the papules were pearl-like, white, and translucent.

Thyroid iodine uptake was normal in the first woman patient and oscillating in the second. At the beginning the uptake was greater but after 5 and 24 h it was lower than the lower limit of the normal values. In the man, the uptake was at the lower limit of the normal values.

Histological examination with hematoxylin and eosin staining showed connective bundles, dissociated by a weak fibrillary material, with basophils and a myxedematous aspect, representing the predominant substance. The mucoid substance has no affinity toward Van Gieson's fuchsin, but becomes deeply stained with Alcian and Hallé blue. A metachromasia occurs on toluidine blue staining, which causes us to consider the substance of mucopolysaccharide origin.

Because it was assumed that sodium mersolate did not cause dermatitis, investigations were made by Căpuşan and co-workers[7] and they found that sodium mersolate may cause dermatitis. However, it should be mentioned that dermatitis may occur even in places where no work with sodium mersolate is done.

In repeated dermatological examinations Căpuşan and Suciu have found a rise of dermatitis from 4.4 percent in 1962 to 7.4 percent in 1966. No scleroderma was found. An ointment therapy based on cortisone was applied with very good results.

In 3 cases, after recovery from the lesions, pearl-like scars occurred on the forearms and on the neck.

In all the workers who had generalized dermatitis, after the working place was changed, all the manifestations disappeared. In one case in which the skin lesions disappeared, when the worker passed again through his former working area, without touching anything, the eruption appeared immediately, demonstrating the allergic sensitization mechanism on the skin and in respiratory pathways.

Endocrine Alterations

In some cases with scleroderma, the clinical aspect was thyroid insufficiency. In these cases a decrease in ioderma was found, and at iodine uptake the typical aspect of thyroid insufficiency was noticed.

Having a narcotic action, the toxic substance at the beginning produced a cortical inhibition, then disturbances of the diencephalic centers appeared, particularly of the vasomotor and metabolic ones. This fact is supported by the symmetrical character of the vascular disturbance, the plethysmographic alterations, and the metabolic disturbances by the scleroderma.

Thyroid insufficiency detected by iodine uptake shows that the toxic substance has an influence on both the thyroid (directly) and the hypothalamus hypophysis (indirectly) causing a thyroid inhibition.

After removal from the toxic environment, the scleroderma and the vasomotor alterations greatly diminished.

The question arises why did sclerodermic changes appear only in 3.6 percent of the cases? Possibly in these cases a latent functional thyroid insufficiency existed, which was evidenced by the action of the toxic substance

In 17 cases admitted to the clinic, low values of the 17-ketosteroids were found (between 2.5 and 11 mg %) denoting transient cortical adrenal insufficiency which would account for asthenia and the allergic type skin reactions.

In 15 cases admitted to the clinic, the iodine uptake test was performed. In 8 cases normal results were obtained, in 1 case thyroid hyperfunction was found, and in 6 cases, thyroid hypofunction. In 24.1 percent of the cases, sexual impotence was clinically evidenced. It should be mentioned that no laboratory examinations were performed. The reduction of sexual desire indicates the narcotic action of vinyl chloride on the nervous system, particularly because hypersomnia of 10–14 h appears after the work is finished. Sexual desire returns after work interruption or during holidays, showing that is a functional nervous impotence.

In their experimental investigations, Prodan and co-workers showed a decrease in vitamin C content in the cortex of the adrenal gland in all the animals with acute poisoning. Increased values were found in the animals given C vitamin. Vitamin C plays a role in reducing mild adrenocortical insufficiency.

Hematologic Changes

In plant B in 11 cases, all males, the red blood cell count was 3,500,000–4,000,000 and in 2 cases below 3,500,000. In all the cases the hemoglobin level was below 80 percent. The leukocyte count was between 4,000 and 5,000 in 14 cases; it was below 4,000 in 3 cases (who had subacute poisoning). In the cases with chronic poisoning and in those which evolved with neoplasm of the biliary ducts, the leukocyte count was 3,500. A tendency to anemia and leukopenia was noticed.

In the cases admitted to the hospital paleness was seen in 27. In 5 cases the red blood cell count was between 3,000,000–3,500,000, in 22 cases between 3,500,000–4,000,000, in 39 cases between 4,000,000–5,000,000 and 1 case over 5,000,000. In 7 cases hemoglobin was below 11.5 percent.

The leukocyte count was between 3,000–3,500 in 4 cases, between 3,500–4,000 in 4 cases, and over 4,000 in 6 cases.

The blood picture shows a tendency toward lymphocytosis with a decrease in granulocytes. Toxic purpura was found in 1 case and polyglobulia in another case.

The results of the blood picture are given in TABLE 13.

The sedimentation rate was increased in 40 cases to 60–105 at 1 h. The medullogram revealed a hyperplasia of compensatory type.

Blood catalase (Gabor and co-workers[12]) is increased in the exposed workers, which would be accounted for by the increase of antitoxic function in the liver.

We want to emphasize particularly leukopenia, splenomegaly and the increase in the white pulp of the spleen detected experimentally by Prodan and co-workers.

Prophylactic and Therapeutic Measures

In the first months measures were taken to reduce the toxicity by hermetization (elimination of the remaining vinyl chloride from receptacles is performed by cleaning with warm vapors under pressure); utilization of gloves for protection of the skin of the hands; reduction of the working hours to 6; periodical medical examination at 6 months; transfer to another working place if poisoning is suspected; improvement of ventilation; interdiction of smoking; and administration of vitamin C for 10 days a month, vitamin B complex, and iron specimens. In the cases with chronic hepatitis vitamin B_{12} and iron specimens should be administered. For the prevention of skin lesions ointments with cortisone are indicated.

The complex measures applied by us resulted in the disappearance of the acute and subacute intoxications.

TABLE 13
RESULTS OF THE BLOOD PICTURE

Elements	I*	II	III	IV	V	VI	VII	VIII
Polynuclear leukocytes	44	58	60	38	60	54	35	58
Lymphocytes	51	32	32	58	26	32	29	40
Eosinophils	3	1	4	2	4	2	3	0
Mononuclear leukocytes	2	9	4	2	10	12	13	2
Basophils	0	0	0	0	0	0	0	0

* Cases.

We are still continuing our observations in order to determine the long-term chronic effects of vinyl chloride.

SUMMARY

In 1962 when a new polyvinyl chloride plant went into operation, 227 workers engaged were examined; arterial hypertension was found only in 1 percent, and the rest were normal.

In 1962, 114 workers in plant A, and 54 in plant B (a total of 168), underwent repeated medical and laboratory examinations. We found mainly nervous manifestations: euphoria in 11 percent; dizziness in 47 percent; somnolence in 45 percent; complete narcosis in 6 percent (these workers slept for 9–14 h); headache 36 percent; nervousness 9 percent; loss of memory 13 percent; general asthenia 7 percent; paresthesia 4.7 percent; formication 9.4 percent; and loss of weight 28.4 percent. In 72 cases admitted to the clinic we found: headache in 68.8 percent; asthenia 58.8 percent; adynamia 14 percent; dizziness 49 percent; euphoria 11.2 percent; sleeplessness 2.8 percent; memory disturbances 35 percent; paresthesia of limbs 39.2 percent; and physical weakness 40.6 percent. In 1966 the nervous manifestations were reduced to one-third, due to a 22-fold reduction of vinyl chloride in the working atmosphere.

We also found cardiovascular manifestations. By plethysmography we found in A plant 66 percent with vasospastic manifestations and in B plant 55 percent. The pulmonary arterial pressure over 35 mm Hg increased from 6–23 percent. The average systolic pressure in 1969 compared to 1961 increased by 20 mm Hg and the diastolic pressure by 5 mm Hg.

Raynaud's syndrome fell from 6 percent in 1962, to 2.9 percent in 1966 due to reduction of vinyl chloride.

Digestive symptoms included: anorexia 23 percent; vomiting 23 percent; pyrosis 9.4 percent; epigastric pains 16 percent; pressure in right hypochondrium 7 percent; hepatomegaly 30.2 percent; and splenomegaly 6 percent. The proteinograms show an increase of α-2 globulins in 21 percent. Bromsulfalein was pathological in 2 cases out of 11. Aldolase was increased in 17 cases out of 20, and serum cholinesterase was lowered in all workers exposed (Gabor *et al.*). Thymol, Grienstedt and SO_4Zn reactions were positive in 6 cases.

In the 72 cases admitted to the Clinic there were 27 positive hepatic tests, with GOT and GPT over normal in 18 cases. BSP in 22 from 26 cases had a retention over 5 percent. The proteinogram modifications were of the acute and subacute type. Hepatic biopsy showed chronic hepatitis in 3 cases.

After reduction of vinyl chloride in the working atmosphere the hepatomegaly was lowered to one-third. We observed a single case of hepatic papillar carcinoma with metastasis. One of our cases died of acute pancreatitis.

Pulmonary changes included a lowering in respiratory volume and vital capacity. Maximum expiratory volumes showed the greatest decrease. Lung fibrosis of the linear type and emphysema appear at radiography.

The dermatological changes reached 80 percent in the first month. Scleroderma was observed in 36 percent, and 3 cases of papulomucinosis were found. Contact dermatosis has increased from 4.8 percent in 1962 to 7.4 percent in 1969.

In 15 cases the iodine uptake test was performed: there were 6 cases of thyroid hypofunction, 8 normal cases, and 1 case of thyroid hyperfunction.

In 17 hospitalized cases there was a reduction of 17-ketosteroids between 5 and 11 mg %. In 24.1 percent of cases sexual impotence was present.

Hematologically there were anemias of the hypochromic type and leukopenia, also monolymphocytosis was observed.

Measures, such as hermetization, reduction of working hours to 6, vitamin therapy, changing of working place, and reduction of toxic substances from the air (22-fold) reduced all symptoms by two-thirds.

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