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INVESTIGATION OF THE DISEASES PRODUCED BY VINYL CHLORIDE

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The rapid development of the polyvinyl chloride industry in our country has raised for us a problem in industrial hygiene, toxicology and occupational pathology.

In the aim of investigating this problem, a group of hygienists and clinicians have examined the conditions of work and the diseases affecting the workers of two plants manufacturing polyvinyl chloride.

The clinical manifestations encountered raise the problem of interpretation of the etiopathogenesis, of theoretical as well as practical importance, and of defining the clinical picture as well as of the necessary preventive and therapeutic measures.

Our study was necessary in view of the fact that the existing scientific facts at our disposal were few and lacking in detail, especially as regards the observed clinical manifestations.

Danilevskii (1) had demonstrated that the monomers, the starting products, exert an aggressive action from the biologic point of view. They have the property of producing destruction of the skin and of the mucosa. Some of them are allergens. They act on the parenchymatous organs by producing degenerative changes and on the hematopoietic system, leading to an anemia of hemolytic type.

Hervieux and Tessier (11) found, among 145 workers of a polyvinyl plastics factory, 17 cases of chemical dermatitis.** Pletsitzer, Bondar and Smirnova (cited by Danilevskii), in studying the chronic effects of the vapors of vinyl chloride, observed in man the development of toxic angioneurosis.

* Dr. Lefevre gives the reference as Medicina interna 6, No. 8:963-77, 1962; in Index Medicus (5:N-1277, 1964) the above reference is given. The original is being ordered.

** In fact, in their account, the authors speak of 17 cases of "intolerance" or only 10 cases of pruritus, without eruption, of the forearms and of the face appearing in the summer, as seeming to be due possibly to vinyl chloride.

These few clinical studies have not permitted, at the present time, the characterization of a clinical picture.

Concerning experimental work, Mastromatteo, Fischer, Christie and Danziger (7) in studying the toxic action of vinyl chloride on a group of 5 rats, 5 mice and 5 guinea pigs, demonstrated the appearance of congestion of the liver and lungs after repeated exposure to narcotic doses of 10, 20 to 30%. In the animals that were sacrificed or that died during exposure, a congestion of the liver and kidney, and in some cases, even a fatty degeneration of the liver were observed.

Among the toxic substances, Lazareev includes vinyl chloride among the mild narcotics.

In pursuing the study of the clinical symptomatology of workers exposed to the monomer vinyl chloride, and by means of laboratory tests, we concluded that our findings permit the definition of a clinical picture which may aid the practicing physician in the recognition of the first symptoms of acute or chronic intoxication by vinyl chloride and of recommending measures for prevention and treatment.

Laboratory studies have added some data concerning the mechanism of the pathogenesis of these intoxications.

These circumstances have convinced us to publish our findings.

Material and Method of Investigation

In the course of 4 years, we have had under observation 163 workers engaged in the manufacture of polyvinyl chloride (PVC) in two factories: 54 workers in plant "A" and 114 in plant "B".

For the most part, the subjects were young, below 30 years of age and have never worked in any other industry.

Pre-employment medical and detailed laboratory examinations were carried out in order to prevent the hiring of those who would present some contraindications. Records were maintained in the personnel file for each employee of the results obtained in the course of routine medical examinations and on the occasion of the thorough examination, clinical as well as laboratory, done annually.

In addition to the medical examination, the following laboratory analyses were done:

- Dysproteinemia test
- Electrophoresis of serum proteins
- BSP hepatic "clearance"
- Cold pressor tests
- Digital plethysmography in certain cases.

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The cases that exhibited clinical nervous, digestive, cutaneous and angioneurotic manifestations, were routinely hospitalized in the clinic for occupational diseases in order to carry out the complex laboratory tests and to establish therefrom, if possible, the cause of the intoxication.

Thereafter, it was necessary to examine the clinical manifestations and the results of the tests in order to characterize the clinical picture and to formulate preventive measures.

Results and Discussion

We have observed that at first contact with the poison, most frequently at the time of changing the charges, during emptying or leakages due to various causes, particularly the nervous manifestations appeared. After 3 months to 1 year of employment, digestive disturbances were added to the nervous disorders. In certain cases, the nervous manifestations changed into angioneurotic manifestations (Raynaud syndrome); finally, in other cases there was scleroderma or chemical dermatitis. At times, all these disturbances appeared at the same time (see clinical observations).

In order to characterize this clinical picture more clearly, we are presenting the objective symptomatology observed in its increasing order of disturbances, so that the physician may recognize this intoxication from its first symptoms. We are describing them with the frequency found for the various clinical manifestations so that their significance may be appreciated.

In the order of appearance of the symptomatology produced by vinyl chloride, we shall arrange them into the following groups of manifestations: nervous, digestive, angioneurotic, and cutaneous.

Nervous Disorders

Certain workers stated that at the first exposure to the monomer, or vinyl chloride, the first inspirations have an agreeable taste which they could not define exactly. This is compatible with the opinion of Sebit (cited by Danishevskii) who stated that the monomer, or vinyl chloride, has a pleasant ethereal taste, and with the opinion of Lazarev (4) who holds that this substance cannot be tasted except at narcotic doses of 7 to 10%.

After several inspirations, a euphoric state sets in; 11% of the subjects sing, whistle or laugh. (The euphoric state and the pleasant taste persist for only a short time). Most often, during exposure to the poison, the subjects experience a heavy feeling in the legs, are no longer able to coordinate movements and become dizzy (47%). According to them, this state is similar to alcohol intoxication.

These disturbances occurred most frequently in the course of the manufacturing process, at the end of the charge, during the discharge of latex, as at other times when the monomer is released in concentrations as high as, according to Petre (9), 5.5 mg/m^3 which is greatly in excess of the maximum permissible limit of 0.03 mg/m^3 .

* Translator's note: (applicable to Romania). In the USA, the TL is 300 mg/m^3 , or 500 ppm.

Subsequently, in 45% of the cases, a somnolence sets in, which diminishes alertness and can occasion work accidents.

After a stay in the open air, the symptoms diminish progressively, then disappear.

In the case of 6 workers who were engaged in the repair of certain defective parts, complete narcosis appeared, which disappeared after they were removed into the open air.

After a period of several months of working in this environment, a state of somnolence persists after working hours. At home, the subjects exhibit a hypersomnia, sleeping between 9 and 14 hours a day. One person slept, with a brief interval, continually for two days. The sleep is deep, without dreams.

From this point of view, particular attention must be paid to night work, because the workers could easily fall asleep at the work site.

When there is an abundance of vinyl chloride vapors, there are complaints of formication of the lower extremities followed by a sensation of heat over the entire body.

Since the monomer vinyl chloride is lighter than air, it could be that it acts directly on the integument; this would agree with the opinion of Danizewski (1).

Anorexia, attributed to the toxin in 23% of the cases, sets in rapidly.

In 12% of the cases loss in weight of 4 to 17 kg. occurred.

After repeated exposure, headaches are reported (36% of the cases), nervousness (9%), faulty memory (3%), insomnia (3%) and a general asthenia (7%).

These symptoms indicate the establishment of a neurologic asthenia subsequent to more prolonged exposure to the poison.

We wish to point out that in most of the cases, we have observed these clinical symptoms without considering the significance of the resistance of the organism.

In general, after the first symptoms, protective measures for the workers were instituted so as to prevent the appearance of acute intoxication.

According to existing knowledge, it seems that the poison has a momentary narcotic action, even after repeated exposure.

In certain cases, a neurologic asthenia sets in.

Digestive Manifestations

After a variable period of time, in the course of which the neurologic manifestations predominate, digestive symptoms appear.

The first symptom which presents itself is anorexia (23% of the cases). This indicates a general intoxication. Subsequently, vertigo appears (in 18% of the cases) and, more rarely, edema.

Later, pains in the epigastric region follow (16% of the cases), a feeling of discomfort, of heaviness, of pressure in the right hypochondrium (7% of the cases) or of the left hypochondrium (5% of the cases).

The patients present pains, of the boring type, which however do not assume the nature of pancreatic attacks. All express a distaste for fats.

Upon objective examination, in 30.2% of the cases, a hepatomegaly without icterus has been established. The liver exceeds by the costal border 2 to 3-finger widths without a lowering of the upper limit of the liver. Upon repeated examinations we have found that the border of the liver has an elastic consistency, then becomes harder and acquires the consistency of epidemic hepatitis.

We have found that 6% of the hepatomegalies became later complicated by splenomegaly. After removal from exposure, without other treatment, the hepatomegaly regressed and in the majority of the cases, the overall condition became normal.

Our observations show that in many cases hepatomegaly develops without any association with the digestive symptoms.

We have observed the fact that in 6.8% of the cases who had formerly experienced epidemic hepatitis, the hepatomegaly had appeared more rapidly, although at the time of their employment in the factory, the liver was within normal limits.

The enlargement of the liver pointed out to us the difficulty of an etiopathogenic interpretation.

The question arose of the diagnosis of toxic hepatomegaly or of that due to anicteric virus infection. This is why most of the patients afflicted with hepatomegaly were hospitalized in the department of occupational diseases.

Granted that:

the hepatomegaly appears after repeated exposure to the poison;

the border of the liver is of soft and uneven consistency;

the hepatomegaly disappeared after change in work without other treatment;

it appeared in a group of people who were subjected to treatment by injection among whom there were cases of epidemic hepatitis;

in spite of the absence of these manifestations in the other sections of the industry, it had not been supposed, at first, that the enlargement was of toxic nature.

The hypothesis of an occupational origin is favored also by the fact that in patients subjected to chronic intoxication by lead or mercury, before the

establishment of attacks of developing illness (lead colics) we can observe a similar hepatomegaly which disappears after treatment with EDTA (10).

Laboratory tests carried out by us were:

electrophoresis of serum proteins

thymol reaction

zinc sulfate test

bromsulphalein (BSP) test, and

liver biopsy.

Electrophoresis of serum proteins (see Table I in Appendix) shows among the 36 cases with hepatomegaly:

a diminution of albumin, below 53%: 11 times;

an increase of more than

5% of α_1 -globulins: 10 times

9% of α_2 -globulins: 20 times

13% of β -globulins: 9 times

21% of γ -globulins: 10 times.

This shows that the electrophoretic pattern is identical with that of viral hepatitis - in which principally the α_2 -globulin is increased.

We noted that the thymol reaction, the zinc sulfate, and the Greenstedt tests were positive only in 6 cases which shows us that in the determination of the disturbances, the electrophoresis of serum proteins is of particular value.

Two cases of 11 showed a pathologic change in response to the BSP test, indicating that the liver lesions are not localized in the parenchyma.

Since we have found hepatomegaly without protein changes and with a normal BSP, one might be led to believe that the poison produces a transient congestion of the liver, identical with that demonstrated experimentally; this in turn shows that the hepatomegalies which we have observed are of toxic nature.

As a result of repeated intoxication, the congestion can change into a toxic acute hepatitis, accompanied by electrophoretic changes similar to those of viral hepatitis, and finally, these lesions can become chronic. In 2 cases in which hepatomegaly persisted for more than a year and in which the border of the liver was of firm consistency, a liver biopsy revealed the picture of chronic hepatitis.

Among 20 patients with hepatomegaly, the serum aldolase was found to be increased between 0.75 mg. P and 1.200 mg. P in 17 cases (Manta, Muresan and Sirbu) (6), which demonstrates that the aldolase level is the most sensitive test.

A fact to be kept in mind is that we have also found a modification of the protein metabolism among workers exposed to the toxin who were not afflicted with hepatomegaly (see Table II).

Of the 26 cases examined, we found:

an albumin level lower than 53%: 14 times,

an increase of more than 5% of α_1 -globulins: 6 times

9% of α_2 -globulins: 16 times

13% of β -globulins: 8 times

25% of γ -globulins: 3 times.

This shows us that disturbances of the protein metabolism can precede hepatomegaly in certain cases, and that the poison sufficiently influences this metabolism.

Therefore, the hepatomegalies that we have found are principally of toxic nature. At first, they are in effect congestive, and later they assume the forms of acute hepatitis, identical with anicteric viral hepatitis; certain ones of them can become of chronic nature.

We wish to emphasize the fact that the disturbances of the protein metabolism can appear in certain cases before the onset of hepatomegaly.

Our investigations show that electrophoresis of serum proteins and determination of aldolase activity are of greatest importance in the biochemical diagnosis.

At the last examination, in 9% of the cases, a dyspeptic syndrome of ulcerating type was demonstrated, although we were unable to discover any radiologic changes to this effect.

In the knowledge of the predominantly narcotic action of the poison, it is more probable that the derangement of the cortical dynamics after repeated exposure leads to a disturbance of the diencephalic centers which comes into play in the pathology of these manifestations.

We continue our observations.

Angioneurotic Manifestations

These were demonstrable in 6% of the cases in the form of the Raynaud syndrome. (Distribution as to sex: 3/4 of the cases were men.)

We might mention the fact that in 3.6% of the cases with Raynaud's syndrome, there was also scleroderma and hepatomegaly.

In order to illustrate the clinical picture more clearly, we wish to cite the following observation:

Case 1: VV., male, aged 26 years, has been engaged for 2 years in the process of polymerization. Family and personal history, normal. Smokes 10 to 20 cigarettes daily.

At the beginning, the patient observed that during the release of toxic vapors, there was first a euphoric state and then a state similar to inebriation. At home, he slept between 9 and 14 hours daily.

At work, his hands immersed in the latex, he felt formication, numbness, and then a sensation of heat. When the solution was white, he observed a coloration of the skin. In contact with cold water, it was observed that the fingers became pale, then red and cyanotic. Concomitantly, the same phenomenon appeared on the great toes. This occurred also upon exposure to cold air.

At the same time, he was affected by persistent edema of eyelids, of the face, the neck and chest; the skin became glossy, the nails "uneven" and the face assumed the appearance of a full moon.

From the clinical point of view, a Raynaud's syndrome was evidenced, hepatomegaly with scleroderma of the face, neck and thorax, even of the lower and upper extremities, but particularly of the fingers (dermatologic examination made by Dr. Capusan). Musculocutaneous biopsy showed typical changes of dermatomyositis (Dr. V. V. Papilian).

The plethysmogram showed significant inhibition of the vasomotor centers.

In addition, the urinary 17-ketosteroids were increased to 8.5 mg. in 24 hours.

The lunar facies made us think of a thyroid insufficiency. The iodine uptake confirmed this belief.

The dysproteinemia tests, electrophoresis of serum proteins and the BSP test gave normal results.

By its narcotic action, the poison produces first cortical inhibition; then appear the disturbances of the diencephalic centers, principally the vasomotor and metabolic disorders. The symmetrical nature of the vascular disturbances, the plethysmographic changes and even the tissular disturbances and the scleroderma vouch in favor of this fact.

The thyroid insufficiency, evidenced by the iodine uptake, shows that the poison has either a direct influence on the thyroid or an indirect one via the "hypothalamus-hypophysis," which produces inhibition of thyroid function.

After removal from exposure, the scleroderma and the vasomotor disturbances greatly diminished.

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In half of the cases, plethysmography showed an inhibition of the vasomotor centers. As to the remaining cases, the relationships were normal. Especially in the cases where the plethysmogram was normal, the disturbances disappeared completely after removal from the toxic exposure, but in the rest of the cases, they greatly diminished, which would indicate their connection with the toxic environment.

By means of the cold pressor test and by tension oscillography, Raucher, Suciu and Pislaru have found paradoxical reactions and an absence of reactivity in 66% of the cases in plant "A" and in 55% of the cases in plant "B," which pointed out to us that vinyl chloride determines the vasomotor disturbances in a great number of the cases. Only 6% of the cases had clinical manifestations (Raynaud's syndrome).

As concerns the changes in arterial tension, we found that the maxima as well as the minima were more than 10 to 15 mm below normal values.

Cutaneous Manifestations

Pruritus, which was found in 4.8% of the cases, without being accompanied by skin changes, was the earliest symptom.

Later, two different categories of cutaneous manifestations could appear. The first noted was contact dermatitis, then scleroderma could be observed.

1. Contact Dermatitis (4.4%).

On the face and hands (uncovered parts), pruritus followed by urticaria were noted. Papules, microvesicles and large vesicles appeared on the face and hands. There were cases where the microvesicles and the scabs disappeared spontaneously, but in others they were torpid and, after return to work, they reappeared with intensity.

Case 2: K.I., chemical technician, 28 years old. According to his personal history, he had suffered epidemic hepatitis in 1942. Since then, he has had frequent anginal attacks. He has been working for a year and 8 months in the division where sodium mersolate is mixed with different substances. In December 1960, micropapules in plaque-form appeared on the forearms and face, then microvesicles, scabs of which remained. These eruptions were pruriginous. Upon hospitalization in the department of occupational diseases, zones of microvesicles and areas of scabs were noted on the face and forearms, as well as large vesicles at other sites, which after opening, left the skin covered with large scabs.

The vesicles contained a serohemorrhagic secretion.

Sedimentation rate, 2.4 mm/hour.

Leucocytes 6,000 per mm³ of which 76% were polynuclear, 10% lymphocytes, 8% monocytes, 6% eosinophils.

Red cells: 4,600,000 per mm³

Hemoglobin level: 92%.

Plethysmography revealed an inertia of the vasomotor centers.

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The lesions disappeared after treatment with an ointment of delta-cortisone and aureomycin. They reappeared immediately upon his return to work, even upon touching certain objects with his hands. This shows that not only the mersolate but vinyl chloride as well are responsible.*

Change in work brought complete disappearance of the dermatitis.

2. Scleroderma (3.6% of the cases).

In the course of work, certain workers note a pleasant odor, followed at times by emotional and motor disturbances, dizziness and somnolence which, in the case of some, persists after the end of the working day. Others report formication and numbness of the extremities.

Case 3: T.R., age 20 years, has worked for a year and 6 months at the autoclaves. He has worked at no other site. Family and personal history revealed nothing remarkable.

After a year and a half of exposure, diffuse pains developed in the lower and upper extremities, with edema. They were interpreted to be rheumatic pains and treatment brought no relief. An anygdalectomy was performed.

After return to work, a generalized pruritus developed on the face, neck, chest, the abdomen and the extremities.

Dermatologic examination (Dr. Capusan) revealed edema of the eyelids, face, with disappearance of ridges. The skin over the abdomen and the chest could no longer fold.

On the face and chest, grayish spots were seen, that merged together as in the case of chloasma in pregnancy. This clinical picture was interpreted as scleroderma.

The liver was enlarged by 2 finger-widths. The Takata-Ara reaction was faintly positive. The thymol test yielded 14 units.

The proteinogram showed:

total proteins: 6.6 g%

albumin: 48.70%

α_1 -globulins: 4.85%

α_2 -globulins: 10.50%

β -globulins: 14.70%

γ -globulins: 21.20%

Consequently, clinical and laboratory examinations demonstrated the presence of toxic hepatitis.

* The latter statement appears to be insufficiently supported.. (Translator's note)

The ASLO titer showed normal results (250 U of antistreptolysin O). Plethysmography evidenced a marked depression of the vasomotor centers that did not respond to stimulation. Thorn's test showed an inhibition. Dilution and concentration tests gave normal results. The specific dynamic activity of proteins was normal.

The iodine uptake test indicated hypofunctioning of the thyroid.

Arterial tension was 14/7 cm Hg.

Urine was normal.

In this case, as a result of exposure to the poison, disturbances of the vasomotor centers and of the protein metabolism (changes in the proteinogram in the dysproteinemia test) developed. Thyroid insufficiency and chronic hepatitis were found concomitantly.

Mastromatteo states that in polyvinyl chloride intoxication, a thyroid insufficiency exists.

It is interesting to note that in this case, in the period of one year from the time of removal from the toxic environment, the scleroderma, the Raynaud syndrome and hepatomegaly have disappeared. This proves that a toxic source was connected with these phenomena.

In the cases of scleroderma, the majority of the subjects presented a thyroid insufficiency and an inhibition of the vasomotor centers.

In 3 cases a dermomuscular biopsy was performed, which revealed chronic dermatomyositis. In one case only did the manifestations of scleroderma fail to regress after removal from the working environment. In the other cases, these symptoms disappeared, which substantiates for us the idea that these changes are operative in a reversible period.

The manifestations of the scleroderma, accompanied by disturbances of the vasomotor centers appear as a result of exposure to vinyl chloride and disappear after cessation of work in this environment, proving that this is the poison that in this case has produced the vasomotor disturbances and the metabolic of the hypothalamus. The participation of the thyroid in their production reduces the problem of this thyroid insufficiency to 2 eventualities: direct action of the poison on the gland, or consequence of thyroid inhibition of central origin.

The manifestations of collagenosis, verified histologically, which occur in cases of intoxication by narcotic substances, reveal to us that in the pathogenesis of collagenosis there occurs at first, in these cases, a disturbance of protein metabolism due to the activity of the central nervous system and followed by the appearance of an endocrine disorder (thyroid insufficiency).

The reversibility of the disturbances indicates in our opinion that there is a possibility of recovery if intervention takes place in the initial phase.

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Cases of collagenosis after administration of hydrazinophthalazine or other substances whose action is predominantly on the central nervous system are described in the literature. This would confirm our observations.

As a result of investigations into the environmental conditions performed by hygienists and physicians, recommendations were formulated for the protection of the workers and for leakproofing the equipment. In spite of these measures, some cases of the disease have occurred during the past year.

Thanks to treatment instituted according to the indications of repeated clinical examinations, and removal from the working environment, we have succeeded in controlling the oldest cases, given that they were undertaken during a period of reversible disorders.

The recognition by certain physicians of the manifestations that we have just described has permitted the detection of intoxications from the start, and the institution of adequate measures of prevention and treatment.

CONCLUSIONS

1. Vinyl chloride and the vinyl monomers possess a narcotic action and produce, depending upon concentration, in addition to characteristic neurologic manifestations, a state of euphoria (12%), followed by a state of inebriation similar to that of alcohol intoxication. In certain cases narcosis can appear.

After leaving the working environment, a state of somnolence (45%) persists, with hypersomnia.

Vinyl chloride acts on the skin and produces a sensation of formication and of heat.

2. After repeated exposure, a neurologic asthenia sets in in which somnolence predominates.

3. After a variable period of time, dyspeptic disturbances are added to the neurologic manifestations; these are at first not characteristic; they are in the form of epigastric pains (16%), swelling, discomfort, feeling of heaviness in the right hypochondrium (7%) or the left (5%) with anorexia, particularly for fats.

In 30.2% of the cases, congestive hepatomegaly appears, which may mimic toxic hepatitis without jaundice; some cases may become chronic.

In 6% of the cases, the hepatomegaly is accompanied by splenomegaly. The proteinogram and the aldolases are the most sensitive tests and show changes similar to those of acute hepatitis: increase in α -globulins and of the β - and

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γ -globulins; the thymol test, Greco's reaction and the zinc sulfate test are positive only in few of the cases.

4. After 3 years of exposure in 9% of the cases a syndrome typical of ulcer without radiologic changes becomes manifest.

5. In 6% of the cases the Raynaud syndrome has appeared, particularly among the young men. Plethysmography shows in half of the cases an inhibition of the vasomotor centers.

6. In addition, allergic dermatitis in 4.4% of the cases, and scleroderma in 3.6%, has been observed.

7. The clinical and laboratory findings are of great importance in occupational pathology because in numerous cases diseases appear in man that cannot be reproduced in the animal (Raynaud's syndrome and scleroderma).

The sudden and frequent appearance of these manifestations in the PVC division of several plants, and in certain divisions in normal individuals who are still relatively young, and their disappearance in the majority of the cases after the institution of protective measures and change of work, have shown us decisively that vinyl chloride and the vinyl monomers have played a part in the production of these manifestations.

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