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Brief Summary

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#156. CLINICO-PATHOGENIC CONSIDERATIONS OF RAYNAUD'S PHENOMENON IN WORKERS OF THE POLYVINYL CHLORIDE INDUSTRY

Study Conducted at the Unified Hospital of the City of Gheorghiu-Dej

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Translation of: "Consideratii clinico-patogenice asupra fenomenului Raynaud la muncitorii din industria policlorurii de vinil," Medicina Interna, Volume 21, No. 4, 1969, Bucharest, pp. 473-482

The intensive development of the polyvinyl chloride industry throughout the world raises the question of the influence exerted by these macromolecular compounds on the organism, that is, the aspects of toxicology and vocational pathology generated by the process of production of these plastics. The specialized medical literature affords a fairly small body of data; studies relating to the pathogenic mechanism, the intermediate metabolism, and the toxicology of the substances produced is still in a state of observation, and the experimental data obtained with animals are not fully in keeping with clinical findings.

Polyvinyl chloride as a polymerization product appears to be inert from the physiological standpoint [13, 15, 17]. The occupational hazards associated with its production are generated by the monomer by intermediate or derivative chemical substances arising in the course of the manufacturing process [6, 12, 15]. Cases of dermatitis, irritation of the eyes, and pulmonary changes in workers handling the finished product have nevertheless been observed [13, 19].

Studies conducted by Smirnova, Filatova, and Danishevskiy (cited by Suciu [17]) have shown that in the process of manufacture of polyvinyl chloride the monomer, vinyl chloride, is the element that exerts an aggressive effect on the organism, especially on the central nervous system and the higher vegetative centers. Patty [13] states that in high concentrations vinyl chloride leads to depression of the central nervous system reaching the point of narcosis, while in small concentrations it produces a state of euphoria and hepatic and renal lesions, and in direct contact is an irritant to the skin.

Peripheral vascular changes have been observed in workers in the polyvinyl chloride industry and have been analyzed by Suciu [17], who observed Raynaud's phenomenon in 6% of the workers examined, while Gabor and Raucher [7] observe it in 13.4% of the workers exposed to this agent. Filatova [6] describes acrocyanosis, capillary vascular spasms, and dermographia. Rex Wilson [18] finds phenomena of acroosteolysis in 31 of 3,000 workers examined at a polyvinyl chloride enterprise, 22 of whom exhibited Raynaud's phenomenon in one or both hands.

The pathogenesis of these peripheral vascular manifestations has been interpreted by Suciu [17] and Gabor [7] as a disordering of the vasomotor centers of

the hypothalamus, accompanied by inhibition of their reactivity, and by Filatova [6] as a general vegetative dysfunction, with a predominance of vascular disorders, while Rex Wilson believes that the manifestations of acroosteolysis associated with Raynaud's phenomenon are generated by local chemical and physical action associated with an idiosyncratic factor. Mention is to be made of the fact that the authors cited above find changes of the scleroderma type at the level of the hands of workers exposed to the hazard. In the studies referred to in the foregoing [7, 17, 18] the fact is emphasized that manifestations of the angioneurotic type have not been found in workers handling the finished product, polyvinyl chloride, or in those who convert the polymer to plastic.

Despite all the studies conducted on the angioneurotic manifestations observed in workers in the polyvinyl chloride industry, the pathogenic aspect is still far from being clarified. In addition, no other affection of the peripheral circulation has been the subject of greater controversy than the intermittent spasm of the digital arterioles associated with changes in color of the skin of the fingers, the so-called Raynaud phenomenon. From the hypothesis advanced by Raynaud who explains the pathogenesis of the disease as hypertonia of the vasomotor tonus of central origin, to that advanced by Lewis (cited by Allen [1]) who asserts that the primary factor is a local vascular defect of the digital arteries, to the current theories additionally involving enzyme disorders in the production and destruction of catecholamines at the vascular level, experimental clinical research has not produced sufficient evidence to confirm or invalidate any of the hypotheses.

The purpose of the present study is to analyze the clinical-pathogenic aspects of Raynaud's phenomenon observed by us in a certain number of workers at a chemical plant producing polyvinyl chloride, a plant at which all stages of manufacture are concentrated, from production of acetylene, through synthesis of the monomer, vinyl chloride, to the finished product, polyvinyl chloride. The production process utilizes acetylene, which, by reacting with hydrochloric acid, forms vinyl chloride polymerized by two processes: emulsion and suspension. The resulting latex is removed from the residue of non-polymerized vinyl chloride and is then centrifuged in order to eliminate the vehicular solution, after which the polyvinyl chloride is dried and packed in sacks in the form of a powder.

Materials and Method

Three hundred workers and technicians are employed at the plant at which we conducted the present study, in the process of production of the monomer and synthesis of the polymer. The purpose of our study was to detect those clearly exhibiting Raynaud's phenomenon and to analyze the clinical aspects and the changes in vascular reactivity in these persons as a function of the working conditions and the hazards existing in the respective departments. We did not include in the study those exhibiting debatable cutaneous vasomotor symptoms which depend more on the endocrine habit or constitutional state; observation of these persons over a period of time and subsequent research will enable us to make an evaluation of the occupational makeup.

We observed manifest Raynaud's phenomenon in 8 workers, that is, in 2.7% of the total number of personnel. Of these 8 workers 3 are men and 5 women,

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their ages ranging from 20 to 40 (Table 1) and the average age being 26.1 year. The time elapsing between commencement of work in the respective departments and appearance of the first symptom range from 15 months to 41 months, and averaged 23 months. Mention should be made of the fact that in the monomer production department (vinyl chloride), which is in the open air, we encountered the affection in only 2 workers: a female worker (who takes samples for analysis of the monomer) and a mechanic (who is employed in repairing and maintaining the machinery). The other 6 workers were employed in the polymer-suspension department, 2 in centrifuging the latex and 4 in drying it, these being work stations at which the machinery is situated in closed buildings provided with a mechanical ventilation system and at which the monomer remaining unpolymerized is removed in appreciable amounts.

TABLE 1.

1	2	3	4	5	6	7		
S.I.	40	M.	Monomer 8	Medical mechanic 12	41	—	—	—
D.V.	27	F.	Monomer 8	Laborant 13	30	111	215	333
G.L.	20	F.	Polimer 9	Operator chimist 14	25	175	121	554
T.V.	22	F.	Idem 10	Operator chimist 14	15	175	121	554
P.E.	25	F.	Idem 10	Operator chimist 14	21	175	121	554
D.E.	25	F.	Idem 10	Operator chimist 14	27	175	121	554
I.N.	22	M.	Polimer 11 centrifugi	Operator chimist 14	25	112	120	354
C.D.	28	M.	Idem 10	Operator chimist 14	31	112	120	354

Key: 1, Name of patient; 2, age (years); 3, sex; 4, work station; 5, occupation; 6, time till appearance of symptoms (months); 7, concentration of monomer at work stations, mg/m^3; 8, monomer; 9, polymer drying; 10, same; 11, polymer centriguge; 12, mechanic; 13, laborer; 14, chemical worker.
Commas indicate decimal points.

The production process divides the group of workers exhibiting Raynaud's phenomenon into 2 categories: those who were exposed only to the action of a monomer, vinyl chloride, and those who were exposed to the monomer and the polymer. It is to be seen from Table 1 that analysis of the air at the work stations to determine the amount of vinyl chloride yielded values exceeding the admissible concentration of 30 mg/m^3; the values range from 112 to 554 mg/m^3. The survey conducted at the work stations also reveals that all these workers, because of the specific nature of the work stations, had the skin of their hands subjected to contact with the monomer or the polymer still containing a certain percentage of vinyl chloride. The 6 workers in the polymerization-suspension department cleaned the drums of the driers or latex separation centrifuges manually, without using the gloves specified in the labor safety standards.

The clinical manifestations were characterized by the occurrence of intermittent attacks of pallor accompanied by paresthesia and followed by cyanosis at the level of the skin of the hands, and in 3 of the patients also at the level of the toes and heel (Table 2). In the case of the hands the phenomenon

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is manifested on all fingers, including the thumb (Figure 1). Anamnesis established that with all the patients the crises began during the cold season of the year, being initiated by cold or contact with cold water. In the case of one of the patients the crises occurred spontaneously during occupational activities, without the ambient temperature being low and without the patient coming into contact with cold objects. Emotional conditions were not found to be implicated as the initiating factor, as is found to be the case in the basic Raynaud's disease.

TABLE 2.

1	2	3	4	5	6	7
8	3	5	3	3	2	6

Key: 1, Raynaud's phenomenon in both hands; 2, Raynaud's phenomenon in hands and feet; 3, sclerodermia in hands; 4, cutaneous micronodules; 5, hyperhydrosis; 6, fragmentation of phalanges; 7, cortical finning of phalanges.

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Clinical examination of the skin revealed the skin of the hands of 5 of the patients to be slightly infiltrated and rough, presenting the aspect of sclerodermia, and the phenomenon of hyperhydrosis, and in 3 of the patients micronodules on the dorsal surface of the hands and toes, nodules of the size of a pea situated in the thickness of the skin (Figure 2) (such nodules have also been described by Rex Wilson [18]) in one of the patients studied. We must emphasize that we encountered no sclerodermal changes at the level of the skin of the feet, even if Raynaud's phenomenon was also present in the feet.

Figure 1.

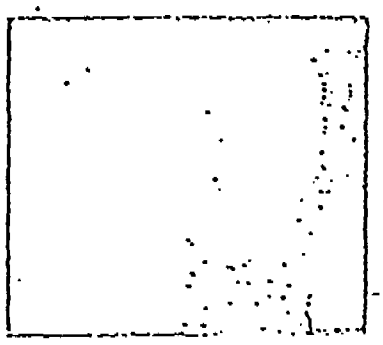

Figure 2.

Radiological examination reveals phenomena of acroosteolysis: in 2 of the patients fragmentation of the last phalanx (Figure 3: fragmentation of the last phalanx of the middle finger of both hands is observed, as well as cortical finning of the phalanges), and finning of the cortex of the phalanges in the remaining patients.

Anamnesis established that none of the patients exhibited manifestations of the angioneurotic type in his collateral ancestry, and the symptomatology in question occurred only after these patients started work in these jobs.

Of the 8 patients only one was a smoker.

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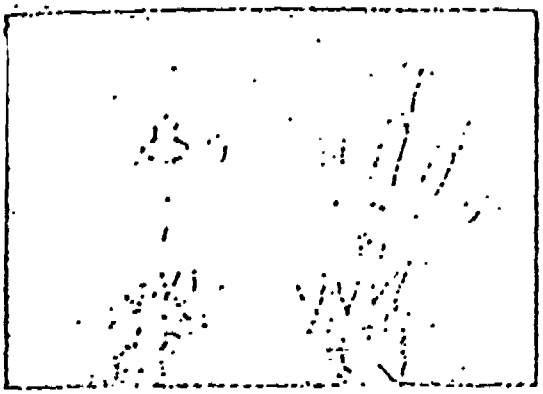

Figure 3.

The endocrine constitutional picture of the patient was normal, the basal metabolism ranging from +2% to +10%, and the menstrual cycles of the women were normal. The pregnancy occurring in one of the patients in no way modified the nature of the angiospastic attacks.

Clinical examination of the cardiovascular apparatus reveals nothing unusual, aside from arterial hypertension in 3 of the patients (37%), the tension figures being 100/60 mm Hg, both in clinostatism and in orthostatism. ECG examination revealed a normal picture: in 3 of the patients there were minor flow disturbances in the right branch which fall within the physiological limits. Clinical examination of the peripheral circulation shows the arteries to be supple and the pulsation to be normal, as is also the oscillometry. Photoelectric plethysmography detected at the level of the distal phalanx of the fingers reveals a curve of normal morphology except for the attacks (Figure 4 A). During Raynaud's phenomenon the radial, cubital, tibial, and pedal arteries were palpated, but the photoplethysmogram showed a linear trace. Eyeground examination reveals arteriolar spasms in 4 of the patients (50%), although 2 of them were hypertensive. From the neurologic standpoint the patients exhibit headaches and dizziness, and 3 of them also phenomena of hypersomnia.

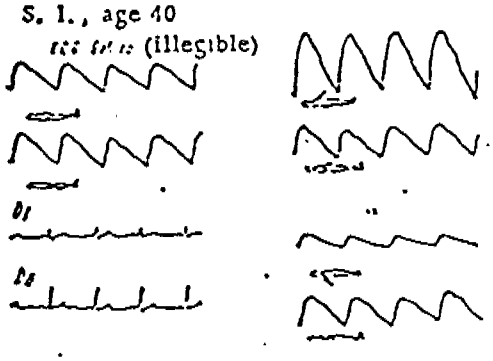

Figure 4.

Clinical and biological tests relating to the hepatic function, the renal function, and the matabolism in general yielded normal results; the serum lability tests were negative; the GPtransaminases ranged from 6 to 22 u.K.; the total proteins ranged from 7 to 8.4 g%; electrophoresis with serines from 56 to 70%, and the γ-globulins from 10 to 16%; the Sia test was negative, and the cold agglutinin test also negative. The results of the Kunkel and Burnstein dyslipidemia tests fell within normal limits, and the serum cholesterol between 171 and 200 mg%. The other biological tests — hemogram, V.S.i.L., glycemia, urea, creatinin, and urine test were normal. Pulmonary radiological examination of the thoracic duct and of the esophagus yielded normal results.

Because of the absence of clinical or biological tests for organic lesion of the vascular apparatus, and also because of the absence of pathological proteins or cold agglutinins, our study was aimed in 2 directions: study of the general and local reactivity of the vascular apparatus on the one hand, and the anatomicopathological aspects provided by cutaneous biopsies taken at the level on the fingers on the other.

Previous studies conducted by Suciu [17], Gabor [7], and Filatova [6] indicated both disturbance of vasomotor activity of the central type and changes

of the vascular vegetative type. Lack of reactivity or paradoxical reaction to the cold pressor test was found by Suciu [17] in 66% of workers exposed to vinyl chloride, arterial hypotension being recorded in the worker's study. In our study of persons exhibiting Raynaud's phenomenon we performed the following tests of vasomotoricity:

1. The cold pressor test, using atomized ethyl chloride for a period of one minute on the inner surface of the forearm, over an area of 30 cm^2.

2. Cutaneous thermometry at the level of the dorsal surface of the hands and feet before and after tests involving the heating of the torso in a light bath at 60° for a period of 30 minutes.

3. Local vasomotor reactivity to various pharmacodynamics.

4. Study, with the aid of the photoplethysmograph, of the local arteriolar reflexes generated by postural endovascular pressure changes (described by Comdorella [3]).

We found the cold pressor to be inverted in only 3 (37%) of the patients, there being observed in these persons a decrease of 10-15 mm Hg in the systolic and diastolic arterial tension (Figure 5). An increase in tension was observed for the remainder of the patients, on the average 15 mm Hg for the systolic and 10 mm Hg for the diastolic. We must note that, although the spraying of ethyl chloride for one minute resulted in virtual freezing of the skin in the respective area of the forearm, Raynaud's phenomenon was not initiated during this test in any of our patients.

The cutaneous thermometry performed under rest conditions at an ambient temperature of 20°, registration being affected with a thermistor, yielded values of 29 to 33° at the level of the dorsal surface of the hand and 29-33° at the level of the feet.

Thermal dyssymmetry, with temperature differences of up to 1°, were observed in 3 of the patients.

One constant clinical element noted in 6 of the patients (75%) was a subfebrile state, the axillary temperature ranging from 37.2 to 37.4°, this not being accounted for by other pathogenic causes.

Thermoregulation changes and subfebrile states were also observed by Filatova

We investigated the peripheral vascular reactivity by the method of indirect heating at a distance, measuring the cutaneous temperature at the level of the extremities. At the same time, we recorded the variations in arterial tension during the test.

For this purpose we made use of a light bath generating a temperature of 60° which we applied to the torsos of the patients; the arms and legs remained uncovered, and the temperature is measured at their level every 2 minutes. The thermal curve recorded indicates a slight reactivity of the thermal regulator and vasomotor center, increases in peripheral temperature of only 1-2° being observed after 30 minutes of heating (Figure 6).

The arterial tension of 4 of the patients (50%) increased by 5-10 mm Hg during the heating test, and remained unchanged in the other patients.

Testing of the cutaneous reactivity to pharmacodynamic agents by Breitman's method (described by N. Gh. Lupu) with adrenalin, dionin, and histamine yielded the results presented in Table 3.

The data in this table show that our patients exhibit local vascular hyperreactivity both to adrenalin and to histamine. The local histamine reaction was intense, the papilla coming to measure 5 to 7 cm in diameter in 50% of the patients and the reaction lasting as long as 3 hours.

The arteriolar reactivity to endovascular postural changes were observed by means of the photoplethysmograph. The phenomena of arteriolar vasoconstriction and vasodilation produced by the posture of a segment explored were found to be normal (Figure 4 B); this demonstrates on the one hand the absence of organic affection at the level of the arteriolar wall, and on the other that the arteriolar reflectivity of the local axonal type is not impaired.

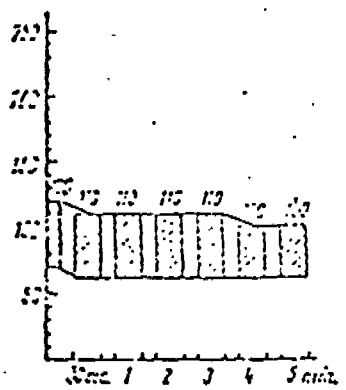

Figure 5.

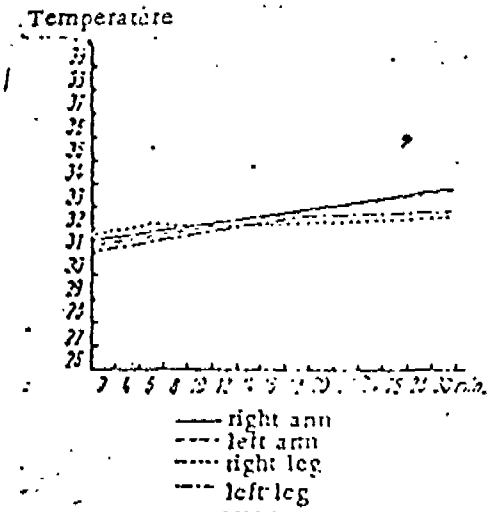

Figure 6.

As regards the anatomical pathological changes, thickening of the horny layer, zones of swelling of the conjunctive tissue of the derma accentuated at the level of the nodules, were observed in skin perforations taken at the level of the fingers and of the previously described nodules. The presence of clear zones of customary coloration, which proved to be due to an accumulation of acid mucopolysaccharides, was observed at the level of the papillae corii. Lymphopolyblaseic infiltrates sometimes arranged in trains are observed in the thickness of the derma.

TABLE 3.

1	2	3	4	5	6	7	8	9
10	102	60	250	6 750	3 600	10 800
11	150	120	360	4 020	3 600	7 200
12	—	—	—	7 200	0 000	10 800

Key: 1, Substance; 2, latency period (seconds); 3, average latency; 4, minimum latency; 5, maximum latency; 6, duration (seconds); 7, average duration; 8, minimum duration; 9, maximum duration; 10, adrenalin; 11, dionin; 12, histamine.

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The zones with the cutaneous nodules described by us did not differ from the surrounding tissue: the nodules merely represented regions in which the modifications referred to above were intensified. The arterioles exhibited no anatomical pathological changes for increase in the amount of mucopolysaccharides in the vascular wall.

The patients were observed for a period of 1-1/2 years, and at the end of this time disappearance of the cutaneous micronodules were observed in 2 of them (2 months after change of job), and in 3 of the patients complete disappearance of Raynaud's phenomenon. In the other patients the vasospastic attacks persisted, but with much lower intensity; obvious improvement was achieved with adrenal--blocking medication of the guanetidine sulfate type, in doses of 10 mg daily.

Findings

The study conducted permits us to advance the opinion that Raynaud's phenomenor occurs in persons working in the production of polyvinyl chloride, the phenomenon being generated by the monomer, vinyl chloride, which exerts a general effect by inhalation and by local action. We believe the vasospastic attacks to be generated by exaggerated peripheral vascular reactivity to adrenergic chemical mediators, a hyperreactivity caused by disruption of the central vasomotoricity coordination mechanisms. The local hyperreactivity to adrenalin and the efficiency of adrenal-blocking medication strengthens this assumption. The local allergy phenomena generated by the monomers could also play a part in the functional vasomotor changes going to make up the factors referred to in the foregoing. The local hyperreactivity to histamine, as well as the fact that one of the workers exhibited attacks at his job when in contact with the noxious medium at normal ambient temperature, induces us to assign the allergic factor also a role in the pathogenic mechanism.

The appearance of the anatomical pathological changes at the level of the skin of the hands, the scleroderma, the cutaneous nodules, and the osseous changes revealed by radiology we interpret on the one hand as local irrigation disturbances generated by vasospasm, and on the other by the local direct, toxic or allergic, action of vinyl chloride. The possibility is not to be excluded that the toxic action is exerted locally, on the enzyme apparatus, which degrades the adrenergic substances at the level of the arterial.

The persistence of Raynaud's phenomenon in some of the workers after change of jobs is probably of the same pathogenic type as Raynaud's phenomenon appearing in persons working with tools producing vibrations, in which the phenomenon appears or persists even after the workers have been removed from the noxious medium. There is probably an occurrence of irreversible functional changes in the central or peripheral vasomotoricity, as well as changes in the sensitivity of the adrenergic vascular receptor.

The normal aspect of arteriolar reflexes of the axonal type generated by postural pressure changes, as revealed by photoplethysmography, and the data supplied by cutaneous biopsy, enable us to reject the hypothesis of organic lesions of the arterioles.

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