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The Vinyl Chloride Disease.

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P.L. Viola

Summer (1970)

The vinyl chloride disease.

A new occupational disease, characterized by lesions of the bones and integuments, by angioneurotic disturbances, nervous and digestive disturbances, has been observed during the last few years among the personnel who work in the synthesis of polyvinyl chloride (PVC). Diagnosed as "acroosteolysis" after the specific osseous modification which characterizes it, the disease has been studied more from the radiological and clinical point of view than from the etiological and pathogenetic one. An investigation of the polymerization processes and of the substances used in various industries demonstrated that vinyl chloride (VC) is the only compound common to the various technological cycles. Keeping in mind that the disease was caused by monomer, an experimental study was undertaken to investigate the toxic effect of the compound. As published in other places (1),(2), it became apparent that in rats, it caused modifications of the bones, of the connective tissue and of the small arteries, similar to those observed in human beings affected by acroosteolysis. In the present paper, a synthesis of the present knowledge on the subject is made, mentioning briefly the results of experimental investigations, combined with some considerations on the etiology and the pathogenesis of the syndrome and on the industriel hygiene measures to be adopted.

Vinyl chloride is a monohalogenated derivative of ethylene of formula CH_2-CHCl, whose synonims are: chloroethylene, chloroethane, ethylene chloride. It is producei industrially by means of synthesis of acetylene and chlorhydric acid or by pyrolisis of symmetric dichloroethane and less frequently by saponification of 1,2 dichloroethane with casustic soda. At normal temperature and pressure, it is a colorless gas with a sweetish odor, 2.23 times heavier than air;

Table 1.

1,2 dichloroethane
1,2 dichloropropane
Tetrachloroethylene
1,1,2 - trichloroethane
1,2 dichloroethylene
Acetaldehyde
1,2 dichloroethylene-trans
Chloroprene
Methylene chloride
1,1 dichloroethane
Carbon tetrachloride
1,1,1 trichloroethane
1,2 dichloroethylene-cis
Chloroform
Trichloroethylene
Benzene
Water
Ethane
Ethylene
Propane
Isobutane
Carbon anhydride
Propylene
n-Butane
Acetylene
Cyclopropane
1-Butene
Isobutene
2-Butene-trans
Allene
2-Butene-cis
1,2 Butadiene
Methylacetylene
Methyl chloride
Ethylacetylene
2-Chloropropene
Ethyl chloride
1-Chloro-1-propene-trans
1-Chloro-1-propene-cis
N-propide chloride
Vinyledene chloride
Isopropyl chloride
Vinyl bromide
Normalpenthane
Isopenthane
Methane
Mercury

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The principal physical characteristics are:

Molecular weight	62.50
Specific weight of liquid	0.99 (-25 C°/4 C°)
Boiling point	-13.37 C°
Freezing point	-160 C°
Steam pressure	mm Hg 10 100 692 2660 C° -87.5 -55.8 -15.8 425.0
At 25 C° and 760 mm Hg	density - 2.55 gr/liter 1 ppm - 0.00256 mg/liter 1 mg/liter - 391 ppm
Flash point	-78 C°
Autocombustion temperature	472 C°
Explosive limit	between 4 and 21.7% in air volume
Specific volume	at 70°F 1 atm. 6.2 CUFT/LB
Gas density	15 C° (air - 1) 2.15
Critical temperature	158.4 C°
Critical pressure	52.7 atm.
Latent boiling heat (boiling point)	5.5 K cal/mol
Latent fusion heat (fusion point)	1,181 K cal/mol
Specific heat, liquid at 20 C°	0.27 cal/g (C°)
Specific heat, gas C p. 25 C° 1 atm.	0.205 cal/g (C°)
Liquid viscosity -20 C°	0.281 centipoise

Easily flammable, easily polymerizable, it is normally inhibited by addition of phenol (from 50 to 500 ppm). It decomposes easily, producing chlorhydric acid, phosgene and carbon monoxide. The MAC of vinyl is 500 ppm.
Slightly soluble in water, soluble in alcohol, very soluble in ethe nd carbon tetrachloride.

The commercial vinyl chloride used in the polymerization process contains a high number of impurities which collectively represent 0.1 to 1% of its volume (Table. 1). This can vary both qualitatively and quantitatively, according to the method by which the monomer has been synthesized. In the vinyl chloride obtained by synthesis of chlorhydric acid and acetylene calcium carbide, the most outstanding chloride impurities are: 1,1 dichloroethane; 1,2 dichloroethylene; 1,2 trans-dichloroethylene, together with minor quantities of 1,2 dichloroethylene-cis; 1,1,2-trichloroethane; carbon tetrachloride; 1,2 dichloroethane; 1,1-dichloroethylene and traces of chloroform; 2-chloroprene; 1-chloro-trichloroethylene; 1-propene-trans; acetic aldehyde; methylene chloride and inorganic mercury. In the vinyl chloride obtained by cracking of 1,2-dichloroethan the highly boiling chloride impurities in greater quantity are: 1'1,2-dichloroethane; 1,1-dichloroethane; 1,1-dichloroethylene; chloroprene; 1,2-dichloroethylene-trans; 1,2-dichloroethylene-cis; chloroform;

1,1,2-trichloroethane and traces of benzene. Not to be forgotten are saturated and unsaturated hydrocarbides like: ethylene, propane, isobutane, propylene, 1-butene, acetylene, 2-butene-trans, 2-butene-cis, methyl chloride, 1,1-dichloroethylene (4).

The polymerization process of vinyl chloride (CH_2-CHl) consists of the subjection of an aqueous mixture of the monomer to particular conditions of temperature and pressure in the presence of a catalyst to bind among themselves the single molecules for the purpose of creating a macromolecule of polyvinyl chloride (PVC). The reaction occurs in suitable autoclaves of metal of a volume varying between 3 and 25m^3, fitted with a large agitator with blades. The polymer is synthetized in suspension (slurry) and lattice (latex) form, and in this case it is discharged at the end of each synthesis process, over special metal filters. The autoclave remains empty, but on the internal walls polymer crusts remain, which must be removed. This cleaning can be done automatically by means of violent jets of water or with solvents, or manually by means of metal spatulas. In this case the autoclave, emptied of the polymer, is subjected to degassing either by blowing in of air or filling repeatedly with water and thus maintaining continuous aspiration to remove the residual gases. Those who are employed in the cleaning process enter through a manhole into the interior of the receptacle and scratch the polymer from the walls with a metal spatula. They remain in the interior of the autoclave for periods varying between 15 and 45 minutes according to the size of the receptacle and the work systems used. In the automated plants where the crusts are removed by means of water jets under pressure, the personnel enters the autoclaves only irregularly and for brief periods of time..

Bibliographical Notes

The first investigations on the toxicity of vinyl chloride were made in 1930. Patty et al (5) observed that guinea pigs exposed to concentrations of 5,000 to 1,000 ppm did not present any appreciable disturbances; at concentrations of 25,000 to 50,000 ppm there were alterations of equilibrium, motor ataxia and narcosis; from 100,000 to 250,000 ppm increase of the respiratory frequency, narcosis and convulsions; at concentrations of 400,000 ppm, the animals demonstrated rapid narcosis, accompanied by bronchial spasms, convulsive manifestations of the joints and death. The guinea pigs exposed to the high concentrations showed signs of congestion and edema of the lungs, hyperemia of the kidneys and the liver. Keeping in mind that the toxicity of vinyl chloride is lower than that of chloroform we thought of a possible use of this substance as an anesthetic in surgical practice. Lehmann and Flury (6) also came to similar conclusions having observed that vinyl chloride is rapidly eliminated from the organism and that the animals subjected to repeated narcosis did not show appreciable organic lesions. Peoples and Leake (7) confirmed the low toxicity of vinyl chloride. Shaumann (8) observed that the vinyl chloride administered by respiratory route distributes in the blood to 15% in the plasma and to 85% in the red blood corpuscles and that 10 minutes after the suspension of administration, the concentration in the blood is already reduced by about 80%. He also observed that the toxicity of this substance for the cardiac muscle is about six times lower than that of ether. These investigations were subsequently criticized by Von Oettingen (9) and Oster et al (10) who discouraged the use of vinyl chloride as an anesthetic, having observed grave disturbances of the cardiac rythm in dogs exposed to concentrations of 100,000 ppm. In these animals, electrocardiographical examination demonstrated: alternated tachycardia and bradycardia, inversion of the R wave, modification of the QRS complex.

sinus arrythmia, transitory axial deviation, atrioventricular block, multifocal ventricular extrasystoles, inversion of the T wave with superelevation of the ST segment in 2nd deviation. This research was also confirmed by Carr et al (11).

Abandoning any thought of using vinyl chloride as an anesthetic, this substance was subsequently studied in terms of the work risk which the latter presented. Mastromatteo et. al. (1961) (12) studied its toxicity in mice, rats and guinea pigs after exposure to concentrations varying between 100,000 and 400,000 p.p.m. Exposure was extended for a maximum of 30 minutes. The guinea pigs turned out to be the most resistent, inasmuch as they were able to survive even after having been exposed to the maximum concentrations, while the mice and rats died already at concentrations of 200,000 - 300,000 p.p.m. All animals fell into profound narcosis at the 100,000 p.p.m. concentration. The dead animals showed signs of pulmonary congestion, often associated with edema and hemorrhagic manifestations, epithelial lesions of the trachea, congestion of the liver and the kidneys. In one guinea pig a fatty infiltration of the liver was observed. These animals often showed modifications of the blood coagulation. Lester et.al. (1963) (13) observed in rats, which had been exposed for 19 days to vinyl choloride concentrations of 50,000 p.p.m and for 92 days to concentrations of 20,000 p.p.m., a constant increase of the size of the liver without however any histological lesions either in this organ, or in the kidneys, the spleen, the lungs, nor modifications of the body weight, the hematocrit, the hemoglobulin, the prothrombyn rate. Torkelson et.al. (1961) (14) exposed rats, rabbits, guinea pigs and dogs to vinyl chloride vapors for 4 - 6 months at concentrations varying from 500 to 50 p.p.m. controlling the behavior of the hematic crasias, of the ureic nitrogen, of the

nausea, difficult digestion, hepato-splenomegalia and the serological signs of toxic hepatitis, with decrease of the albumin, increase of alfa, beta and gamma globulins and of the aldolase. Some workers subsequently also presented peripheral-circulatory disturbances similar to those of the Raynaud syndrome. In some cases appeared cutaneous lesions, initially limited to prurigenous manifestations and contact dermatitis, upon which followed, in due time, pimples, blisters and crusts. Some presented restricted edema of the hands with the clinical characteristics of scleroderma. Dermo-muscular biopsy confirmed the existence of a highly chronic dermatomyoma. The investigation of the iodine demonstrated in some cases the involvement of hyperthyroidism.

Cordier et. al. (1966) (24) observed in two workers employed in the cleaning of autoclaves used for the polymerization of vinyl chloride the appearance of acroosteolytic lesions on the distal phalanges of the hands which radiologically presented a transverse zone of lysis with disappearance of the bony tissue. In one case existed osteolytic manifestations of the first toe of the feet as well. The bony lesions were accompanied by painful manifestations of the toes which were aggravated by cold, acroparesthesia, general disturbances of the nervous system with asthenia, somnolence during the day, nocturnal insomnia. The toes seemed slightly swollen, the fingernails were streaked, the skin presented blistery whitish lesions, especially at the level of the forearms and the anatomist's snuffbox. Histological examination of the skin gave evidence of modifications of a degenerative type of the connective tissue which appeared separated in large collagenous strips with loss of the staining affinity. The elastic reticule was confused and strongly reduced. No pathological modification was detectable with regard to the other organs and systems. Removed from the work, after two years the two patients showed disappearance of the cutaneous modifi-

Schalit (1951)(15) holds, as does Lazareew (1954)(16) that the toxicity of vinyl chloride for man, even though limited, is however still lower than that of gasoline fumes and that of chloroform, while Danisewski et.al.(1961)(17) call attention to the injurious effect of monomer on the integuments, the mucous membranes and the parenchymal organs. Harris (1953)(18) described necrotic lesions of the mucosa and on the skin by liquid vinyl chloride. Angio-neurotic manifestations were pointed out in subjects exposed to monomer vapors, by Filatova et al (1958)(19) and by Plesitzer et al (1961)(20). Danzinger et al (1960)(21) reported that two workers died after prolonged exposure to strong concentrations of vinyl chloride, probably due to cardio-circulatory disturbances. Grigorescu and Toba (1966)(22) isolated in the urine of 43 subjects, out of 53 who had been exposed to vinyl chloride vapors, traces of monochloracetic acid, and in the blood serum signs of disprotidemia with increase of the alfa and decrease of the gamma globulins, studying the metabolism of monomer in the human organism, thinking that this, at the hepatic cell level, in the presence of water, transforms into ethylene monochlorhydrate and subsequently into chloralio and monochloroacetic acid which passes into the urine as such or combined with glycocol. More recently Sucio et al (1967)(23) have described a toxic syndrome characterized by nervous, digestive, circulatory, cutaneous modifications in workers exposed to vinyl chloride, These authors observed that when the concentration of monomer in the air is so high as to be perceptible by the sense of smell, the men presented a state of euphoria which could be followed by asthenia, feeling of heaviness in the legs, dizziness, somnolence and even paresthesia of the lower joints, sense of heat, headaches, hyper-excitability, insomnia, neuroses. In the subjects exposed to the monomer for a longer time, with the nervous symptomatology were associated disturbances of the digestive apparatus with anorex

alkaline phosphatase, the glutamic-pyruvic and ossalacetic transaminases; the urine and the histiopathological alterations of the various organs after the death of the animals. The hematological and enzymatic constants did not present significant modifications in spite of degenerative lesions of the liver and tubular and interstitial modifications of the kidneys being observed in rats exposed to concentrations of 500 ppm for four and a half months, in the liver of rabbits and rats exposed for six months to concentrations of 200 ppm and an increase of liver size in rats exposed to concentrations of 100 ppm for 6 months. The animals exposed to concentrations of 50 ppm for 7 hours a day for a duration of six months did not present any organic lesions. On the basis of these results the authors advised to lower the MAC of vinyl chloride from 500 to 50 ppm.

There is agreement by the various researchers on the evidence of the anesthetic effect of vinyl chloride which seems to be dangerous only when its concentration in the air exceeds 120,000 ppm (8). The parameter on which are evaluated the toxicity for man of the various concentrations were derived from the experimental observation remembering that the rats exposed for 2 hours to 70,000 ppm presented equilibrium disturbances, at 100,000 ppm modifications of the corneal reflexes, at 150,000 ppm respiratory disturbances (13) and at 300,000 ppm death occurred after 30 minutes (12).

More detailed information on the toxicity of vinyl chloride was furnished by observation on man. These demonstrated that exposure to 4,000 ppm for 5 minutes does not cause any disturbance while at 12,000 ppm dizziness may occur (13), at 16,000 ppm after only 5 minutes, apart from the loss of equilibrium, modifications of hearing and vision occur at 25,000 ppm man loses space and dimensional evaluation of objects and sometimes also the sense of warmth in the feet (5), at 70,000-100,000 complete anesthesia occurs, above 120,000 ppm human life is in danger (

cations, radiological recovery of the osteolytic process, improvement of the nervous disturbances with persistence of the paresthesia, the asthenia and the vasomotor disturbances.

After this first observation, other cases were observed in Europe and the United States of America. In France, Chatelain and Motillon (1967)(25) described five cases of acroosteolysis in workers employed in the cleaning of autoclaves. The bony lesions were mostly localized in the fingers. In some cases, the distal extremity of the nail phalange was sharpened (tapered), assuming an aspect which the authors called "sucked beet sugar"; in other cases the osteolytic process involved the central part of the phalange with loss of the substance in transverse strips, with the radiographical aspect of a pseudo-fracture; finally, in other cases the bony lesion manifested itself in the form of small roundish zones of diminution or densification of the bony tissue. The fingers seemed deformed, stumpy, with dystrophied nails. Bioptic examination of the skin of the fingers evidenced the signs of an endo-arteritis and chronic endoarteriolitis, alteration of the nerve bundles, fibroses of the superficial skin. These same patients were subsequently also studied by Marin et al (26) who pointed out that in each case there had been a symptom period, characterized by paresthesia and pain in the fingers of the upper and lower limbs and that subsequently appeared the vasomotor disturbances of a Raynaud syndrome. The hands appeared cold, livid, edematous, often with a "drumstick" aspect, with nails deformed like "watch glass". The skin appeared infiltrated, thickened, inelastic with the characteristics of sclerodactyly. The osseous lesions began with the signs of an osteoporosis of the distal part of the phalanges upon which followed a partial absorption of the peripheral part of the bone or a lysis in horizontal band. The arteriopal peripheric circle

appeared slowed down, with the signs of a distal vasoconstriction. The study of the vasal circulation showed an increase of the arterio-capillary resistences by vascular modifications which diminished the character and the elasticity of the small vessels at the level of the arterio-capillary pole. In three patients the clinical examination was completed by the biopsy of the skin of the fingers and in one of these also by the histological examination of a bony fragment of the third phalange of the middle finger. This investigation demonstrated the existence of vascular, nervous lesions of the connective tissue and of the bony tissue. In the more superficial layers of the skin, at the level of the papillae, the capillaries were dilated with swelling of the endothelium and edema of the perithelial zone. In the deep layers, the capillaries presented an intense perithelial hyperplasia with formation of a tube of fusiform cells which developed in onion bulb form. This perithelial proliferation presented in some points a fibro-blastic transformation and subsequent sclero-hyaline degeneration of the entire vascular wall with atrophy of the endothelium and stenosis of the thin vessel up to its complete obliteration. The arterioles also presented very similar alterations which went from a perithelial proliferation to the total sclero-parietal hyalinosis with obstruction of the vessel lumen. The nerves presented sclero-hyaline thickening of the perinerve with fibrous invasion of the nerve, atrophy and degeneration of the nerve fibrils. The Wagner-Meissner tactile corpuscles and the Pacini corpuscles did not seem altered. The connective tissue, poor in cells, affected by an extensive degenerative process, appeared separated in large collagenous strips separated among themselves by empty spaces. The elastic, atrophic reticule was composed of few irregular fibers, separated among themselves. The perspiratory glands often appeared atrophic, while the epidermis presented zones of hyper-

plasia with hyperkeratosis. The cortical of the bone was slightly thinner with a continuous osteoblastic edge; the bony marrow indicated in some zones an initial fibrosis. The periosteum presented a pronounced sclero-hyaline thickening with chondroid metaplasia of the deeper layers. The small blood vessels presented the signs of a capillary and a constipating arteriolitis as in the skin.

Harris and Adams (1967)(27) submitted to radiographic examination 588 workers employed in the polymerisation of vinyl chloride. Among the 150 employed in the cleaning of the autoclaves, two presented osteolytic lesions of the fingers, the toes and the kneecap, combined with parestesia, vasomotor disturbances and cutaneous modifications of the hands and forearms. The fingers were stumpy, swollen, with thickened skin, strewn with micronodular formations. Histological examination of a skin segment of the finger showed thickening of the derma, subversion of the cottocutaneous connective tissue in which were visible partially hyalinized acellular collagenous nodules. The walls of the small arteries of the skin appeared thickened by a pronounced hypertrophy of the average and the interval.

An investigation conducted in the United States of America on 3,000 persons exposed to vinylchloride, permitted Wilson et.al.(1967) (28) to evidence in thirty-one cases clear signs of osteolysis of the hands. The lesions were accompanied by vasomotor disturbances, parestesia and sclerodermic-type modifications of the skin. The lesions began with a diminution of the thickness of the cortical zone of the distal phalanges to which were sometimes associated small losses of osseous tissue in half-moon shape. Progressively the lysis became more evident with thinning of the phalanges and with zonal losses of tissue. In due time could be observed a not-always-complete recovery of the osseous lesion. The majority of the patients were employed in the

cleaning of autoclaves and the lesion for the most part manifested itself after about a year of work.

In Yugoslavia, Kovac et.al. (1969)(29) studied this new disease syndrome in a group of seventy workers. Among those employed in the cleaning of the autoclaves were detected eight cases of acroosteolysis of the hands and in some cases also of the feet, in fourteen subjects existed only alterations of the skin, the skin sensitivity and of the peripheric circle. The acroosteolytic lesions were accompanied by an abnormal flexibility of the distal extremity of the phalanges. The skin of the forearms and the hands presented zones of thickening of the skin near the zone of leukoplasia. Bioptic examinations showed degenerative modifications of the connective tissue, of the small arteries and the bone. No pathological alteration was observed among the personnel employed in the handling and processing of finished PVC.

At the XVI International Congress of Occupation Medicine in Tokyo, Dinman et.al. (1969)(30) reported notes and results of an investigation made in PVC plants in the United States of America. Five thousand and eleven workers out of a total of 22,000 men/years employed in thirty-two plants were observed. Twenty-five workers employed in the cleaning of autoclaves presented acroosteolytic lesions of the hands. The average was one patient out of 116 workers exposed, or more precisely, one per 525 men/years. Sixteen workers presented restricted osseous lesions of the hands of unclear interpretation and therefore were not included in the statistics. The osseous lesions were uniformly preceded by vasomotor and sensitivity disturbances and presented a clinical and radiological symtomatology similar to that already described by the various authors. Biochemical or immunological alterations were not detected. The illness manifested itself primarily in those who were employed in the cleaning of autoclaves while no pathological altera-

tion was observed among the personnel employed in the processing and handling of the finished product.

Pointing out the constant association of a Raynaud syndrome with the accroosteolytic lesions, the authors advanced the hypothesis of an enzymatic alteration with an inhibition of the monoamine oxydasis and a prolonged local action of the catecholamines, not excluding a particular individual biological predisposition.

PERSONAL INVESTIGATIONS

Experimental and clinical investigations have been made to study the toxicological properties of vinyl chloride, the work atmosphere and the clinical and radiological characteristics of the disease. The diffusion of vinyl chloride has been studied in the animal organism and the organic alterations induced by monomer in rats after an exposure of twelve months. The personnel of an establishment for the polymerization of PVC was periodically controlled (observed) with medical, radiographical and laborator tests.

Materials and Methods - The analytical examinations of vinyl chloride were done by means of the gas-chromatography method. A C. Erba - Biochemical G. apparatus was used with flame ionization indicator and Speedomax registrator model G. 2.5 mV f.s., copper column of 2.5 m.; filled with diethyl sylsebacate at 25% with 60-80 mesh celite. Nitrogen transport gas at 0.8 atm. - 1 ml/4.5 sec.; auxilliary H_2 gas 0.45 atm, air 1.2 atm. C.° temperature detector 180°, evaporator 150°, column chamber (tube) 60°.

The dosing of vinyl chloride in the work atmosphere was carried out with an infrared apparatus (UNOR). The determinations were executed

in the various phases of the work process in all the zones where the personnel were located for work purposes and above all at the points where the concentrations are presumed to be the highest.

The distribution of vinyl chloride was studied in the respiratory air, the blood, brain, liver, kidneys, and urine of rats which had breathed for one hour air containing monomer at a concentration of 10,000 ppm. Ninety rats of the Wistar strain were used, of a medium weight of 300 gr., divided into five groups of sixteen animals. Ten rats were used to study the concentration of monomer in the exhaled air. After the end of the treatment the animals were kept in separate glass cages which were perfectly air tight and of known volume, from which every fifteen minutes an air sample was taken for gas-chromatographic examination, then the air in the receptacle was renewed. The tracing of vinyl chloride in the organs was made by sacrificing at intervals of fifteen minutes an animal of each group, and collecting in separate glass receptacles the brain, the liver, the kidneys which were rapidly homogenized. For the blood and the urine the appropriate apparatus was used built by C. Erba for the gas free in the blood.

An experimental investigation was made to study the toxic effect of vinyl chloride on the animal organism, as already stated before (2). Twenty-five male rats, of an average weight of 150 gr. were exposed for four hours a day for five days a week over a period of twelve months to vapors of said substance. During the procedure the animals were kept in a plastic case in which circulated an air current containing vinyl chloride in a percentage of 3% by weight equal to 30,000 ppm. At the end of the twelve months the surviving animals were sacrificed at intervals of twenty days. The paws, the brain, liver, kidneys, thyroid were submitted to histological examination before

fixation, inclusion, and staining with hematozyline-eosine, Van Gieson, PAS, Weighrt, --illegible-- Gomori. Twenty-five rats of the same strain were kept as controls.

The personnel of a plant for the polymerization of vinyl chloride of a total of 120 persons was was submitted for five years to medical control with periodic radiographic examination of the hands and chest and a complete check-up comprising: hemochromocytometric examination, platelet count, test of the hepatic and renal functions, azotemia, glycemia, uricoemia, cholesterinemia, aldolasis, electroforctic examination of the serum, alkaline and acid phosphatase, Waaler-Rose reaction, Latex test, LE cell count, phosphoremia, calcemia, calcuria and phosphaturia, iodine protidemia, mercury search in the urine, E.C.G.

RESULTS

Hygienic working conditions - The hygienic working conditions were studied at length, related to the concentration of vinyl chlorid to which the men were exposed. The major quantity of monomer was found in the filters and in the autoclaves. At the beginning of our inquiry it was noted that on the filters at the moment of the polymer discharge the vinyl chloride concentration was of the order of 2,000 ppm. and in the autoclaves lacking an efficient means of degassing, the monomer concentration remained high above the maximum tolerable values (MAC). On the gangway and in the other work locations between 10 and 150 ppm. were recorded. Comparing the results of our exam with those made in five other establishments, it turned out that in four plants were cases of acroosteolysis were found, at the moment at which entered those employed in the cleaning, the monomer concentration in the autoclaves was of the order of 2,000 ppm, while in another two

establishments where no illness was observed at all in the workers, the vinyl chloride did not exceed 150 ppm. When applying aspiration lids on the filters and an efficient air exchange at the interior of the autoclaves during the cleaning process, a clear drop was noted in the vinyl chloride concentrations in the work environment and in the appearance of any organic disturbances among the personnel.

Experimental Investigations - An investigation was made to study the distribution of monomer in the animal organism. At the end of the process there was the maximum concentration of vinyl chloride in all the organs and particularly in the blood, with a varied distribution among corpuscles and plasma. The red cells contained more monomer than th serum in a very divergent ratio according to the concentration to wh[illegible] the animals were exposed. Vinyl chloride is present in the urine as soon as emitted, but the major quantity is found in the expired air which represents the main channel of elimination of the compound. The monomer concentration in the expired air, the blood, urine and the various organs falls rapidly during the first hour, to disappear completely after three - four hours. It seems that vinyl chloride has very unstable connections with organic components in that it tends to free itself spontaneously from the urine, the blood and the organ homogenates.

One group of rats was exposed for a year to vinyl chloride vapors at a concentration of 3%. During the exposure the animals presented a state of slight drowsiness, yet at the beginning of the treatment they did not present modifications of the body growth, behavior, nor macroscopically or radiologically traceable organic modifications. After the

tenth month some animals had started to present decrease of the body weight, of aggressivity, reaction to external stimuli and some equilibrium disturbances. Thirteen animals died through complications of the cardio-respiratory apparatus, accompanied by bronco-pulmonary manifestations, sometimes hemmorrhagic, and extensive pleuro-cardiac reactions. Two animals died due to hemoperitonea. Signs of suffering of the brain, the liver, and the kidneys existed in the majority of the animals. Six rats also presented modifications of the skeleton and the soft tissues of the paws.

The small metatarsal bones presented an extensive periostal proliferation of elements of the cartilagineous type, which seemed to originate directly from the tissue by metaplasia of same. At the periphery of the newly formed cartilage, the cellular elements were compacted and tangientially arranged to the cartilage so as to constitute a perichondral layer. The isogenous groups of the cartilage were irregularly arranged and the nuclei contained in these appeared of non-uniform size and often two or more nuclei were present in one cell. The edges of the cartileges appeared irregular through the presence of digitiform formations, an expression of a diverse growth potential. Manifestations of chondroid metaplasia were also present in zones of mature, compact bone in which the cartilagenous elements were arranged at -illegible- around a central osseous nucleus as observed in the osteo-chondromatous processes. In the small bones the chondroid metaplasia process was sometimes very extensive and the bones appeared as if soaked with a mucoid substance which altered the characteristic arrangement of the osteomes with disappearance of the cement lines. The skin of the paws presented zones of hyperkeratosis, superficial thickening of the epidermis, vacuolization and degeneration of the basal layer, disappearance of the cutaneous connections,

slight accentuation of the papillary layer of the skin. Almost constant was an edematous state of the epidermic zone. The connectiv tissue appeared changed due to separation of the collagenous bundles. Diminution and fragmentation of the elastic reticule was present. The small arterial vessels presented signs of sub-endothelial fibrosis with thickening and separation of the elastic covering, often associated with a partial hyalinization and homogeneization of the walls and with a proliferation of the endothelium. Some vessels seemed completely occluded with proliferation of the connective tissue in "onion skin" form. The small nerve bundles often appeared englobed and infiltrated by fibrotic processes. The microscopic examination of the brain demonstrated diffuse degenerative lesions of the grey and of the white matter. The external granular layer often appeared reduced and in some areas a reduction of the middle cells and gigantic cells existed. The hypercolored, atrophied neurons were numerous with di appearance of the nucleoli and sometimes even the nucleus. At the level of the white substance were zones of intense reactive gliosis, constitute in large part of protoplasmatic and fibrillar astrocytes, some of which were arranged in tubes around the blood vessels. These presented manifestations of neuronophagia with satellitosis by arrangement of oligodendroglia elements around the altered nervous cells. Slight proliferation of microglial elements especially in the zones of most intense gliosis. Zones of intense spongiosis were present with accumulation of astrocytary elements with abundant basofilous cytoplasm, of the gemistocyte type and of microglial elements whose aspect reminded one of the "scavenger cells". In the cerebellum, signs of atroph of the granular layer, often represented only by a few isolated nuclei. The layer of Purkinye cells was in some zones profoundly altered in

that the cells appeared affected by an intense degenerative process and one could observe all the diverse aspects of this alteration of the healthy cell to the most affected one, from which had disappeared any characteristic morphology and remained only small homogeneous bodies with indistinct boundaries. The molecular layer appeared, with the exception of restricted zones, rather undisturbed.

The liver, often increased in volume, sometimes had an unexpected color with a smooth surface and was often more friable than normal. Histological examination demonstrated in the majority of the cases the signs of a diffuse interstitial hepatitis with numerous hepatic cells affected by regressive processes which went from a turbid degeneration of the cytoplasm to necrosis with distinct protoplasmatic and nuclear polymorphism. Some hepatocytes presented gigantic nuclei and double nuclei. In the hotbeds of the cellular necroses always existed a corpusculate exudation composed of round-cellular elements of lymphocyte and plasma-cellular type. The often hypertrophic Kupfer cells presented an abnormal proliferation. The triangular spaces appeared increased by infiltration of round and polynucleatic cells and of eosinophiles with marked cellular polymorphism. The congestion of the portal capillaries and of the centrolobular veins and of the sinusoids with numerous hotbeds of parcellar necrosis in the middle zone was not infrequent. A diffuse adipose degeneration with small drops with restricted zones of acidophile necrosis and formation of bodies similar to the round, acidophile ones in viral hepatitis and to those of "Councilman" in yellow fever was often present. In some cases the signs of an intense fibrosclerotic reaction were traced beside the degenerative processes. The kidneys never seemed excessively altered by the prolonged exposure to vinyl chloride, even though the signs of a tubulo-nephrosis sometimes associated with a chronic

interstitial nephritis were always present. Modifications of a modest nature took place in the thyroid where an increase of the para-follicular cells and sometimes the signs of a colloidal goiter were observed. The control animals never presented the histopathological modifications of the skeleton and of the various organs.

Medical investigation - The personnel of an establishment for the polymerization of polyvinyl chloride were submitted from 1966 to this date to repeated medical observations. During the course of the first investigation, one case of acroosteolysis was identified among the personnel employed in the manufacture.

A young man of 35 years, employed for three years in the cleaning of autoclaves, presented acroosteolytic lesions of the third distal phalange of the first, second, third, and fifth finger of the right hand and the first, second, third of the left hand (fig. 1). The fingers were slightly swollen, pasty, on the back skin of the hands and the face of the palm of the forearms [sic.] small white pimples were noted, the nails of the first and of the second fingers of both hands were enlarged and rounded in "watch-glass" fashion. During the winter months the cold caused pain in the hands which became pale and often presented chilblains. The disturbances became more pronounced recently. The patient did not report pain in the hands either during work or when touching the fingers. For about two years he had digestion difficulties and a certain aversion towards fats. His body weight was reduced and he often reported asthenia and headaches. The liver exceeded by two fingers the costal arch, it was of normal consistency, moderately painful to the touch. The arterial pressure was 140/100. Normal ECG. The laboratory exams gave the following results: MacLagan, 4 u.t.; Wunderly 5.5 u.t.; Kunkel test 6 u.; Hanger test

neg.; aldolasis 6.4 u/cc., total proteinemia gr. 7.7/100 cc., albumin globulin ratio 0.50; albumin 34%, globulin 66%; alfa globulin[1] : 1%; alfa[2]: 6%; beta globulin 21%; gamma globulin 38%; iodine protidemia 3.85 gamma%; mercury of urine 20 y/liter. The hemochromocytometric exam, azotemia, glycemia, uricoemia, cholesterolemia, alkaline and acid phosphatase, Wealer-Rose reaction and the Latex test were within the physiological limits; the LE cell search was negative, the phosphoremia, calcemia, calciuria and phosphaturia were normal.

Removed from the department after two years, his general condition inproved, the asthemia and the headaches disappeared. The radiographic exam of the hands demonstrated that the acroosteolytic lesions were replaced by a process of osseous recovery. The periferic circulatory disturbances persisted; so did the deformation of the nails.

No other cases of acroosteolysis were observed among the personnel employed in the polymerization process. Five workers presented circulatory disturbances with Raynaud phenomenon. Fifteen presented hepatomegalia and signs of small hepatic insufficiency, but their condition was greatly improved after modifying their diet which was excessively rich in animal fats. The iodine protidemia was, on the average, maladjusted toward the low values of the /illegible/, the quantity of mercury found in the urine was below /illegible/ ..

Similar investigations were made in other establishments occupied in the process of polymerization of vinyl chloride, employing a total of 500 workers, among which thirteen cases of acroosteolysis were diagnosed. Hence the opportunity existed to compare the results of our investigation and to extend over a larger number of cases our observations on which basis it was possible to trace a picture of the symtomatology and the course of the disease.

DISCUSSION

The prolonged exposure to vinyl chloride vapors in concentrations sufficient to produce a state of poisoning, induces in man a disease which can have an acute or a chronic progress. The acute form is caused by exposure to very high concentrations of monomer. It is characterized by general malaise, headaches, dizziness, asthenia and sometimes nausea, vomiting and chills. If exposure to monomer is prolonged and above all if its concentration in the ambiant air is higher than 100,000 ppm. unconsciousness, narcosis, cardiac and respiratory disturbances also appear, which could even cause the death of the patient. The effect of the monomer in these cases is primarily on the nervous centers besides that on the myocardium, and death occurs due to cardio-respiratory disturbances.

Chronic poisoning arises instead through exposure to lower concentrations of vinyl chloride and is characterized by alterations of the nervous system, of the circulatary and digestive system, the bones and the skeleton. The nervous disturbances are the first to manifest themselves each time the vinyl chloride concentration is sufficiently high to be perceived by smell. / illegible _/ may be a state of euphoria upon which follow / illegible _/ astenia, heaviness of the legs, vertigo and after prolonged exposure also a sensation of tingling in the inferior joints, of heat all over the body and somnolence which may persist even after discontinuing the work. These disturbances disappear after a day or two of rest, but if exposure to very high concentrations continues, a state of neurosis can appear together with headaches, states of excitation, reduction of memory, general asthenia, nocturnal insomnia often accompanied by

digestive disturbances with a sense of heaviness in the epigastrium and in the right hypochondrium /sic./, difficult digestion, bloating, anorexia especially with regard to fats and hepatosplenomegaly. Under these conditions food intake is reduced and body weight tends to decrease. The liver is increased in volume and can present signs, almost always slight, of modification of the hepatocyte function. Often the spleen is also increased in volume.

Besides these nervous and digestive disturbances, there is specific evidence of poisoning, in a certain number of cases a Raynaud syndrome may establish itself which manifests itself by pain and crises of asphyxia of the fingers and sometimes of the toes after exposure to cold. In these cases the patients complain about cold hands, pain at the pressure of objects, paresthesia; the fingers are pale, rarely livid, cold, deformed by a hard edema with inelastic, thickened and atrophic skin which does not glide on the underlying tissues and is therefore difficult to lift off in folds. The skin of the back of the hands and of the distal part of the forearm presented whitish papullae with zones of hyperkeratosis. Sphygmography does not reveal modifications of the arteriolo-capillary circulation, but arteriography shows an intense distal vasoconstriction of the arteries at the level of the fingers.

The most characteristic sign of the disease is represented however by the osseous lesions of the hands. Exterior signs of the lesion, but which are not necessarily present, are: pain to touch of the distal part of the fingers, abnormal flexibility of the nail phalanges, paresthesia, deformation of the nails which are often streaked and which tend to be enlarged. The osseous modifications manifest themselves for the most part at the level of the nail phalange of the fingers of the hand, more rarely in the toes and in the kneecap. Thickening of the

marginal part of the pelvis, increase of the sacro-iliac space, images of pseudo-fracture of the cubital styloid, were observed. The inter-phalangeal joints can be involved in the disease process by which the articular ends are deformed and maladjusted one on top of the other. It is a particular characteristic of the lesion that it is symmetrical in both hands and that it affects almost always more than one finger. (Fig.1). The pathological process may initially be extremely limited and in these cases during the radiographic examination they present themselves with a diminution of the thickness of the cortical part of the phalange or with small half-moon shaped incisions, perpendicular to the edge of this, or with limited round zones of osseous diminution. In a subsequent stage the illness presented more characteristic radiographical images. The end phalanges can be extremely tapered so as to have the aspect which French authors call "sucked beet sugar", since is diminished in thickness, deprived of the cortical part and has a pointed distal extreme. (Fig.2). In other cases, the phalange presented in its distal third a loss of substance along a transverse zone in all its thickness, with a picture which recalled that of a fracture (Fig.3). The distal part is sometimes limited to a very small fragment which may in due time disappear, for the bone seems as if amputated (Fig.4). After these patients are removed from their specific work, one observes a process of recovery of the lesion and the zones of diminution are slowly replaced by an intense osseous proliferation, rich in osteophytes, in which is no longer recognizeable the characteristic trabecular pattern. In this stage of the illness, the formation of small round zones of osseous increase is frequent. After discontinuation of exposure to the toxic action of vinyl cloride, the general conditions of nutrition improve rapidly.

as do those of the digestive functions. The nervous disturbances are slower to disappear but the angioneurotic ones persist. The fingers often remain shorter, in the shape of drumsticks, with the nails having a watchglass shape.

In our investigation we did not find significant modifications of the thyroid, the kidneys, the cardio-circulatory apparatus, nor functional modifications of other organs nor a major incidence of neoplastic forms.

The bioptic examination of the papulae which often appear on the skin of the hands and forearms of those exposed to vinyl chloride vapors always revealed diffuse degenerative manifestations. The epidermis and its annexes appeared normal but the dermic connective tissue separated in collagenous bundles, poor in cells. This has lost its staining affinity for anilin blue and bright green, while staining well with saffron and trichromic color, PAS and muci-carmine. The elastic reticule stained well with orceine, with PAS and muci-carmine, presenting slight metachromasia with Toluidine blue; it was atrophic and reduced to few fragmented and scattered fibers. The nerve ends appeared atrophic and degenerative in the sclerotic process. The Wagner-Meissner and Pacini corpuscles were not altered. The capillaries and the arterioles of the deep layer of the skin are constantly altered by a state of capillaritis and constipating arteriolitis. These vessels seemed surrounded by a tube of perithelial elements with one or several layers; the wall is affected by a process of fibro-hyalinosis with diminution, up to the complete obliteration of the vessel lumen (26). Sometimes the small arteries of the skin have walls extremely thickened with hypertrophy of the middle, and fibrotic thickening of the internal part (27). The capillaries of the skin appeared on the contrary dilated, with swollen endothelium and often with a peripheric halo of

edema. Biopsy of an osseous fragment of the phalange of a man affected by acroosteolisis demonstrated that the periosteum presented a very pronounced sclero-hyaline thickening with chondroid metaplasia in large bands in the deeper layers (26).

More than sixty cases of acroosteolysis were described, for the most part among the personnel employed in the cleaning of autoclaves. Their incidence varied from 1.5% according to Harris, to 3% according to Wilson, 4.5% according to Chatelain, 12.8% according to Kova. The average age was between twenty-five and forty years.

The etiology of the disease suggested by technical considerations and the study of the working conditions, has confirmed that of the experimental research. It is impossible not to think of vinyl chloride as the principal etiological agent since it is present in all the work atmospheres and its toxic effect on the human organism is known. It is true that in the polymerization process many other substances are used, but for the most part of those no traces of gas remain in the autoclaves as opposed to monomer which always remains in considerable quantity. Furthermore, these additives are not always equal, since when a check of the manufacturing methods and the substances used was made in six companies, it was found that the only compound which was always used and by all in the last ten years, was vinyl chloride. The relation between monomer and the nervous and digestive disturbances is too evident to permit doubt as to this aspect of the problem. There is resemblance between the alterations of the connective tissue, the elastic reticulum of the nerve endings and the vessels of those animals, to those presented by men affected with acroosteolisis. The connective tissue is separated in cell-poor collagenous bundles, the elastic reticule is notably diminished and in part fragmented; the small nerve

bundles are inglobated and infiltrated by fibrotic processes; the small arterial vessels present a diminution of their lumen up to the complete obliteration by modification of the vessel walls. Marin referred to the results of a biopsy performed at the level of the acroosteolytic lesions of the phalanges of a man, and defines the fundamental histopathological alterations of the lesions: a thickening of the periosteum with chondroid metaplasia of the deeper layers. It is the same as observed in the paws of rats exposed for one year to vinyl chloride vapors. The small metatarsal bones present an abundant periostal proliferation of elements which are initially of the cartilaginous type and which seem to originate from the underlying osseous tissue. Subsequently this proliferation gives way to an often perichondral layer. In the deeper layers ample zones of mature, compacted tissue are replaced by cartilageneous tissue, rich in basic substance. From all these references it seems sufficiently demonstrated that the functional and organic modifications observed in the men occupied in the polymerization process are caused by vinyl chloride. It must, however, be pointed out that the compound studied by us is not chemically pure, but is a commercial compound which, as already described, contains numerous impurities, some of which present a definite toxicity for the animal organism. The total / illegible / of these contaminated compounds varies between 0.1 and 1% but the quantity of each substance which actually penetrates into the organism during the inhalation of vinyl chloride is extremely reduced. This is not a sufficient argument to exclude a priori their participation in the lesions encountered in man and in the animal, because some of these, like carbon tetrachloride, can produce a toxic effect even at very low concentrations, but of course their effect cannot be determined. One impurity which has particularly claimed our attention is mercury which

can be present in the monomer obtained by synthesis of acetylene and of chlorhydric acid. It can be seen in the literature (35, 36, 37, 38, 39, 40) that in the process of synthesis, at the level of active carbon, an intermediate organic compound also called Biginelli compound forms, which is chloro - 2 - chlorvinyl - mercuryl or mercurylchloride-β-chlorvinyl ($C_2H_2H_3Cl_2$), which when reacting with chlorhydric acid forms vinyl chloride ($CH_2 = CHCl$). An as-yet-unpublished investigation was made to study whether organic mercury compounds exist in commercial monomer. This possibility could be excluded because the compounds which form at the level of active carbon impregnated with mercuric chloride are split from the chlorhydric acid, which in the phase subsequent to synthesis comes in contact with the monomer in the so-called "felling towers". Furthermore, the mercury, exclusively in the inorganic form, is found in extremely small quantities in the monomer which arrives at polymerization and its concentration varies between 10 and 60 y/kg. A check made on the personnel employed in the autoclaves demonstrated that the quantity of mercury in the urine does not, on the average, reach 30 /illegible/, that contained in the hair is negligible. The possibility, even though remote, of a participation of the contaminating compounds in the organic modification induced by vinyl chloride cannot be excluded. Neither can the hypothesis of a toxic effect on the human organism by the residual gases which remain in the autoclaves after the polymerization process. As in fact other authors (24, 26) have stated, in the bubbles which form in the residual crusts (deposits) always remains monomer with traces (lower than 0.1%) of: 1,1 - dichloroethane; 1,2 - dichloroethane; perchloroethylene; acetaldehyde; carbon tetrachloride; vinyl bromide; 1 - chlorpropane; vinylidene chloride; 1,2 - dichloroethylene; trichloroethylene; benzene;

methyl chloride; methylene chloride; chloroform; 1,1,1 – trichloroethane.

The pathogenesis of this disease syndrome is complex. Vinyl chloride penetrates the respiratory tree and with the blood spreads throughout the whole organism, it does not seem to contract bonds with the organic components, it crosses the cellular barriers easily and is eliminated from the organism through the expired air and in minor quantity through the urine. Its effect at the level of the nervous system is rapid and intense. The hepatocyte feels the toxic effect of monomer as do the peripheral arterioles and the connective tissue, where the collagenous structures to a major extent are affected. It might be interesting in this respect, through a possible work hypothesis, to determine the affinities which exist between the modifications induced by vinyl chloride and those found in the experimental lathyrism (31, 32). The Raynaud syndrome cannot be separated from the arterio-capillary lesions which are caused in part by the toxic effect of vinyl chloride, as was experimentally demonstrated, and in part by a traumatic effect which is related to the specific autoclave cleaning work. In fact, to remove the polymer crusts, the workers use metal spatulas with short wooden handles which are used alternatively with one hand or the other, pushing with the palm of the hand. The vascular modifications in particularly predisposed subjects can be caused in part by these microtraumas with the mechanism of the instruments vibrating, and probably with the involvement of neurological components.

Present knowledge is insufficient to explain the pathogenesis of the osseous lesion. This modification was termed acroosteolysis due to a certain radiological similarity with the illness described by Guy-Laroche and Hochfeld (33) in 1948 and by Harnsch (34) in 1950. This illness is characterized by the progressive absorption of the bone of the extreme distal of the joints and by peripheral circulatory

disturbances of which an idiopathic form and a familiar form are described. The acroosteolysis of Guy-Laroche and Hochfeld is often associated with a generalized osteoporotic process and can affect not only the joints but also the bones of the elbow, the collarbone, the jaw, the nose bone and the sella turcica. The illness has been related to neurotrophic disturbances (35) and by some authors (36) to an osseous reabsorption progress determined by an excessive growth of the capillaries of the bone.

The osseous modifications of the vinyl chloride disease cannot be confused with the "acroosteolysis" of Guy-Laroche, nor with the "massive osteolysis" of Gorham and Stout which consists of angiomatosis of the blood and lymph, nor with the illness of Pierre-Marie and Léri which is basically a chronic, evolutive polyarthritis in which there is a resorption of the extremity of the bone, nor with the Raynaud disease, nor with psoryasic rheumatism in which acroosteolytic manifestations e added to the cutaneous disease, nor with the osseous modifications of syringomyelia, scleroderma and sclerodactylia and even less with the illness of Ainhum or with the osteolysis of leprosy or tabes.

The acroosteolysis of vinyl chloride is a disease manifestation with its own known etiology, symptomatology and clinical progress, with well-defined histopathological and radiological modifications, for which can be used the term "acroosteolysis" but only with reference to the radiographic outline of these lesions.

The functional and organic disturbances caused by vinyl chloride only manifest themselves when the concentration of monomer in the air is sufficiently high, and it is of basic importance to know the maximum tolerable limit below which the monomer is not harmful for the human organism. Concentrations below 150 ppm. are certainly not dangerous

because it was possible to determine that in two polymerization plants where the vinyl chloride in the air never exceeded this value in about twenty years of activity neither functional disturbances nor organic lesions were ever observed among the personnel. From 150 to 500 ppm. there exists a reasonable margin of safety because the nervous system disturbances such as asthenia, myalgia, headache, general malaise, as nausea and the disturbances of the digestive tract become evident, as confirmed by the majority of the authors (23), when vinyl chloride is well perceptible by smell. The olfactive threshold of monomer varies between 8000 and 10000 ppm., but we hold that among those which present modifications of the bones, liver, and blood vessels, which always follow upon nervous and digestive disturbances, must necessarily have spent a long time in surroundings where the vinyl chloride concentration greatly exceeded the limits set by MAC. The data furnished by the literature and by our investigations seem to agree in showing that the vinyl chloride illness would not have occurred if the monomer concentrations had always remained within the limits set by the MAC. Let us say that the disease, at least in its more severe manifestations, is bound to disappear if the necessary industrial hygiene measures are universally adopted.

PREVENTION

The prevention of the vinyl chloride disease has essentially the goal of eliminating the monomer as much as possible from the work environment. The two principal sources of contamination are the autoclaves and the latex filters. For the autoclaves the best solution is that of automatic cleaning by hydraulic means, but if this measure is not feasible, one can also obtain good results with an accurate and

rational degassing method. At the end of the synthesis process, as soon as the porthole of the autoclave is open, an aspiration sleeve must be connected to it to remove the residual gases, the elimination being facilitated by total filling of the autoclave with water. After the wash water has been discharged, the aspiration sleeve is lowered to the bottom of the autoclave where it remains until the end of the cleaning process, being careful to close the discharge hole situated at the bottom of the autoclave to avoid the possibility of monomer vapors leaking through. After the air at the interior of the autoclave has been completely renewed and ascertaining with the proper, portable apparatus (MSA) that the monomer concentration is sufficiently low, the personnel is allowed to enter the interior of the autoclave.

The latex filters are another source of contamination because each time the polymer is discharged a great quantity of vinyl chloride pours into the atmosphere. It would therefore be suitable that said filter be isolated in a different environment, provided with efficient ventilation, or that good aspiration caps be applied on them to convey the monomer to the exterior. It is necessary to always remember that in no point must vinyl chloride be smellable because when it is perceived with the sense of smell its concentration in the air is higher than the maximum tolerable limit. An ideal polymerization plant from the point of view of industrial hygiene would be constructed almost "outdoors", putting the autoclaves--in which must be installed an automatic cleaning system--under an ample protection roof with sliding lateral walls thus permitting the most complete air circulation. The filters would have to be lodged in a separate environment furnished with an efficient aspiration system. Under these conditions the risk of exposure to vinyl chloride would be practically reduced to zero and the vinyl

chloride disease would remain only a memory.

In combination with these technical measures it is necessary to provide a medical control service for the personnel. It is in fact necessary to exclude from the autoclave cleaning work the subjects affected with cardio-respiratory disturbances and those which present angioneurotic manifestations of the extremities. The personnel must be submitted to periodic medical visits and examination of the hepatic function and to radiographic examinations of the hands. Those which present excitability of the nervous system, insomnia, somnolence during the day, or digestive disturbances with hepatosplenomegaly and signs of hepatic involvement, decrease of body weight, disturbances of the cardiac rythm, signs of myocardiac involvement, Raynaud syndrome or osseous lesions of the osteolytic type, must be removed from the work environment.

CONCLUSIONS

In these last few years years, a new occupational disease characterized by disturbances of the nervous system and the digestive system, by angioneurotic manifestations and osseous lesions, has manifested itself among those occupied in the cleaning of the autoclaves used for the polymerization of vinyl chloride. In man the disease is accompanied by degenerative manifestations of the connective tissue, the elastic reticule, the peripheric arterioles and osseous lesions characterized by thickening of the periosteum, chondroid metaplasia of the deeper layers and radiologically by acroosteolysis. In animal experiments, vinyl chloride causes histopathological modifications of the connective tissue, of the arterioles and the bones, similar to

those observed in man, apart from degenerative lesions of the liver and the brain. The vinyl chloride disease appears in man through prolonged exposure to monomer concentrations notably above the limit values set by MAC. In fact the nervous disturbances which are the first to manifest themselves are most evident when the characteristic sweetish odor of monomer is perceptible in the air, i.e., when its concentration exceeds 8000 ppm. Systematic controls in some factories have confirmed that the disease has always manifested itself where the vinyl chloride concentration in the air was very high. Men exposed for twenty years to concentrations below 150 ppm. never presented either organic disturbances or lesions. It should be remembered however that even though the 500 ppm. limit set by MAC gives a reasonable safety margin, even a reduction of that would be favorable.

Industrial hygiene measures are advised to eliminate the risk of the vinyl chloride disease in the polymerization plants.

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