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"The So-called Vinyl Chloride Disease - An Occupational Systematic Sclerosis?"*

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Summary: included in original copy (in English).

" VINYL CHLORIDE DISEASE"

I. Introduction

In the past year, we could observe for the first time a disease in Germany which occurred in autoclave workers in the polyvinyl chloride (PVC) manufacturing industry. We have designated this disease system as the "so-called vinyl chloride disease." This disease has become known as "occupational acroosteolyses syndrome" and "occupational acroosteolyses" from foreign publications.

In 1963, the frequent appearance of the following symptoms in PVC-employees was described: narcotic syndrome, neurasthenical complaints, hepatomegaly, Raynaud's syndrome, dermatitis, and scleroderma-like skin changes as well as transformed functions of the thyroid gland (33). Before that, in 1958, the appearance of "chronical angioneurosis" had been determined in employees of a PVC-manufacturing plant (12).

In 1966 in Belgium, two workers were observed to have Raynaud's syndrome, neurasthenia, scleroderma-like skin changes and in addition, band-like osteolyses of the fingertip phalanges was observed for the first time. A year later, two such cases became known in England (16).

Likewise, in 1967 a report entitled "Acroosteolyses Syndrome of an Occupational Origin" was published in France of similar clinical and x-ray alterations found in five autoclave employees (5). Three thousand employees in the PVC-manufacturing industry were examined in 1967 in North America (36). In this examination, 31 employees were found with acroosteolyses, with and without Raynaud's syndrome. In addition, drumstick-like thickened finger tip phalanges and knotty skin alterations were present in eight employees.

These symptoms became known as "occupational acroost - olyses." This designation was kept in later occupational Anglo-American research. In the results of later epidemologic examinations, the terms Raynaud's syndrome and

acroosteolyses were promoted for the diagnosis "occupational acroosteolyses" (9).

The main symptoms - Raynaud's syndrome, skin indurations, and bone lesions, even if only seldom occurring in the form of band-like osteolyses, are also found in progressive scleroderma. At this point, a search for further organ manifestations of the "so-called vinyl chloride disease." was considered opportune. Therefore, we have given careful internal examinations to all patients. The following organ systems were considered: skin, circulatory system, bone system, blodd building system, liver, spleen, lung, nervous system, digestive tract. Furthermore, the examinations were carried out to the final determination of an autoagressive disease.

II. Our Examinations

Since Feb., 1972, we have examined ten patients, ages ranging from 29 to 46 years. All were employed as autoclave employees in a PVC-manufacturing plant. Their jobs included, in addition to cleaning the autoclaves, also working at times on the separator, the dryer and the screening installations and in packaging the finished dry PVC.

The employment period was between 1 3/4 and 12 years (average: 5 years). The first disease alterations occurred in 7 patients in one and one-half to two years,

and in thr e patients, two to three and one-half years after initial employment. The average latent period was about two years.

Seven patients listed increased cold sensation in the area of the fingers or hand as the first disease symptom, and this was coupled with deafness and "Kribbel" paresthesia. In one case, the first symptom appeared as an increased painful pressure of the finger tips and paresthesia, in a second loosening of the nails, and in a third, the first symptoms were a club-like expansion of the individual finger joints. In addition, the following generalized complaints were ascertained: 7 patients complained about increased perspiration, 5 about frequent dizziness, 3 about occasional nausea at work, 3 about reduction of vision, 3 about poor hearing, and 2 about headaches.

1. Skin

Clinically, we determined a participation of the skin in the symptoms of 8 patients. We observed knotty infiltrate, a shortening and drum-like expansion of the fingertip phalanges, and a transformation of the nails to "watch glass" nails. This is in addition to the almost regular, partly constantly present, partly recurring, and mostly cyanotic swelling of the finger or the entire hand, which lead to a feeling of tension and in some cases to a clear loss of motion. Likewise, as a result of outer circulation disturbances in the skin, an increased sensitivity to the

cold occurred in the hands and usually in the feet of 7 patients. In 4 of these patients, repeated Raynaud phenomena could even be provoked by cold exposure experiments.

Drumstick-like club expansion of the finger-tip phalanges of one or almost all fingers were visible by sight in 7 patients. This correlates well with the x-ray alterations, presented later in this article, mainly on the right hand. The nails of the affected fingers were "watch-glass" shaped, with the exception of one patient, in which case a koilonychia had formed. In contrast to "true" drumstick fingers, we found not only an expansion but also a distinct shortening of the end phalanges and the fingernails (Fig. 1). This is certainly connected with the delayed fingernail growth reported by 3 patients.

The presence of scleroderma-like skin changes was very characteristic in 8 cases. These changes were relatively sharply defined but very rough, white to ivory in color, and usually an infiltrate projecting somewhat above the surface skin. Size and shape varied from the size of grain to small knots, or even more flatly shaped. These type of indurations were observed mainly on the finger joints and in direct proximity to the Proc. styloideus, on the ulna side of the hand and the distal third of the under elbow (Fig. 2), with a distinct lessening

Fig. 1. Scleroderma-like knotty skin infiltrate on the outstretched fingers and into the hand joints. Drumstick like club expansion and distinct shortening of the end phalanges. Also, watchglass curvature of the nail plates.

Fig. 1.

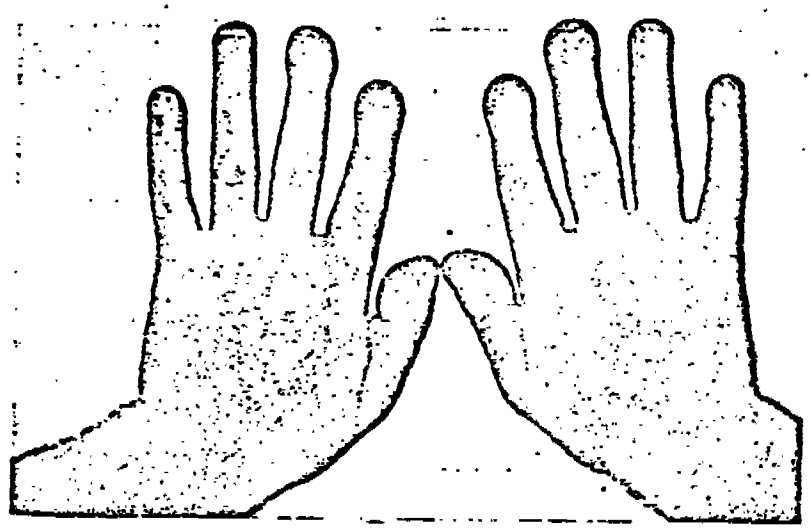
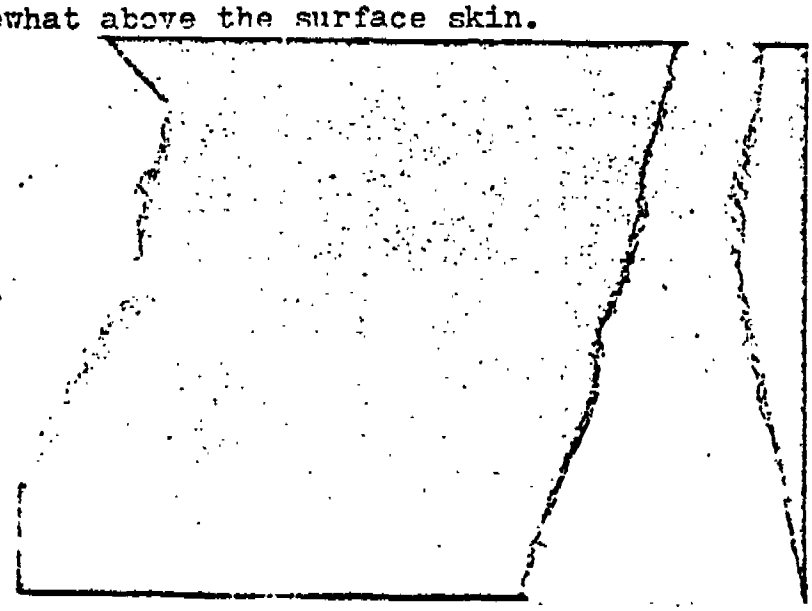


Fig. 2. Projecting infiltrate on the distal third of the bent side of the right underarm: sheetlike, coarse and relatively sharply defined, yellowish, and projecting somewhat above the surface skin.

Fig. 2.



towards the proximal side. Less often observ d were morphologically similar changes on the sides of the outstretched fingers, distal of the olecranon, and in the face (cheek and cheekbone region).

A noteable fact is that the first symptom reported by 6 patients concerned fingers 1-3 on the right hand. only in three of the patients did the first complaints arise from the second or respectively second and third fingers of the left hand. A breakdown of the respective skin changes of the individual patients is found in Table I.

Table I. Summarized Representation of skin changes in 10 patients with so-called Vinyl Chloride Disease.

Nr.	Patient	Kälteempfindlichkeit (mit Raynaud-Syndrom = R)	„Trommelschlegelfinger"	Uhrglasnägel	Sklerodermieähnliche Hautveränderungen
1	S. G.	+	+	+	+
2	O. S.	+	+	Koilonychie	+
3	D. Z.	+ (R)	—	—	—
4	J. F.	+ (R)	—	—	—
5	H. D.	—	+	+	+
6	A. W.	—	+	+	+
7	H. A.	+ (R)	+	+	+
8	M. C.	+	+	+	+
9	S. W.	+ (R)	—	—	+
10	K. H.	—	+	+	+
Summe		7	7	6	8

Cold Sensitivity (With Raynaud Syndrome = R)	"Drumstick fingers"	"Watchglass nails"	Scleroderma-like skin changes

Sample excisions were made in the left or right hands of all patients. In all cases - even those, in which patients exhibited clinically "only" Raynaud syndrome without actual proven infiltration - similar changes, for the most part, were shown. The histological changes and their values are shown in Table 2.

It was also determined that the changes in the skin, as an organ system, undoubtedly played an important role in the framework of the "so-called Vinyl Chloride Disease." Eight of the examined patients proved to have distinct clinically visible and protruding rough, scleroderma-like infiltrate. All ten patients exhibited different characteristics, but for the most part had similar histological changes.

The clinical image, with Raynaud syndrome, pale, very rough and usually plate-like infiltration of the skin and the histological results included in that (as previously described) are suggestive of the edematous to infiltrative stage of progressive scleroderma. Also, we found in both disease images a shrinkage of the epidermis with the passing away of the "reteleisten" and simultaneous hyperorthocytosis ("hyperorthokeratose"), an often considerable widening of the cutis by means of an increase of mainly nucleus poor and swollen and/or homogenous collagen bundles by means of a "walling up" of the skin connecting tissue (25), respectively , the raising of

Table I. Histological changes in the skin of 10 patients with so-called vinyl chloride disease.

Nr.	Patient	Epidermis a=Hyperorthocytosis b=Atrophy		Cutis (1. Collagen) a=Increase b=Homogenization		Cutis (2. elastic fibers) a=Decrease b=Fragmentation		Cutis (3. Vessels)	Tissue Condition
1	S. G.	a	b	a	b	a	b	im subepid. Grenzstreifen Cap. mit Endothelschwellg.	Ödem im mittl. Cor., perivasculäre Infiltrate
2	O. S.	—	b	a	b	—	b	normal	sklerotisch
3	D. Z.	a	b	—	—	—	b	normal	kollag. Bindegew. sehr dicht gepackt
4	J. F.	a	—	—	—	a	b	im ob. Corium vereinzelt erweiterte Capillaren	normal
5	H. D.	—	b	a	b	a	b	Gefäßwände im mittleren u. oberen Cor. geschwollen	starkes Coriumödem
6	A. W.	a	b	a	b	a	b	normal	Coriumödem, lockeres, vorwiegend lymphoc. Infiltrat
7	H. A.	a	b	a	—	a	b	normal	spärl. lymphocytäres Infiltrat
8	M. C.	a	b	a	b	a	b	mittl. u. tieferes Corium deutl. Wandverdickung	mäßiges Ödem, lockeres lymphocyt. Infiltrat
9	S. W.	a	—	a	—	—	—	teils Wandverdickung	normal
10	K. H.	a	—	a	b	a	b	oberes Corium: Capill. vermehrt u. erweitert	tieferes Corium sklerotisch

Nr.	Cutis (3. Vessels)	Tissue Condition
1.	Endothel swelling in subepid. borderline capillaries	Edema in middle corium, perivascular infiltration
2.	normal	sclerotic
3.	normal	collag. tissues closely packed
4.	single widened capillaries in upper corium	normal
5.	vessel walls swollen in middle and upper corium	strong corium edema
6.	normal	coriumedema, loose, mainly lymphatic fluid
7.	normal	scanty lymphatic fluid

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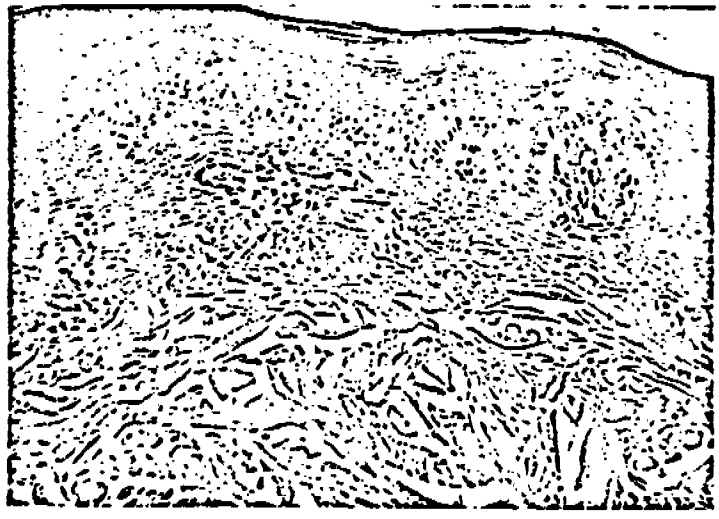
Nr.	Cutis (3. Vessels)	Tissue Condition
8.	distinct wall thickening in middle and deep corium	moderate edema, loose lymphatic fluid
9.	walls partially thickened	normal
10.	upper corium: capillaries increased in number and enlarged in size	sclerotic lower corium

Fig. 3. Hyperorthocytosis and initial decrease of epidermis. In the upper corium, enlarged and increased (in number) capillaries with endothelium swelling and moderately loose mainly lymphatic infiltrate. In the middle corium edema, slight swelling and initial homogenization of the collagen fibers (H.E. Color).



sweat glands (24). Likewise, we observed a mainly moderate intercellular edema and a loose, mainly lymphatic infiltrate between the collagen bundles and around the blood vessels. In the subepidermal border, numerous widened capillaries with endothelium swelling were observed, and the vessels of the middle and deep corium occasionally showed a distinct wall thickening.

In spite of the numerous items in common, there appears to be an important difference to progressive scleroderma with regard to the changes of the elastic fibers. Although in progressive scleroderma, splitting and fragmentation of the elastic fibers occurs, these remain, for the most part (and also in view of the number), relatively protected . Indeed, often one has obtained the impression of an increase of elastic fibers as a result of the increase in skin atrophy. In addition to fragmentation, an indicative to considerable rarefication of the elastic fibers is most noticeable of the histological results in the so-called vinyl-chloride disease (Fig. 3-5).

2. Circulatory System

Seven of the patients complained of an increased sensitivity to the cold in the hands. This was also reported as the first disease symptom. Four of these patients reported recurring whitening of single or all fingers in connection with strong pain and deafness in

Fig. 4. Characteristic swelling and homogenization of the nucleus-poor and widened collagen bundles, separated by a thinned edema in the lower corium.

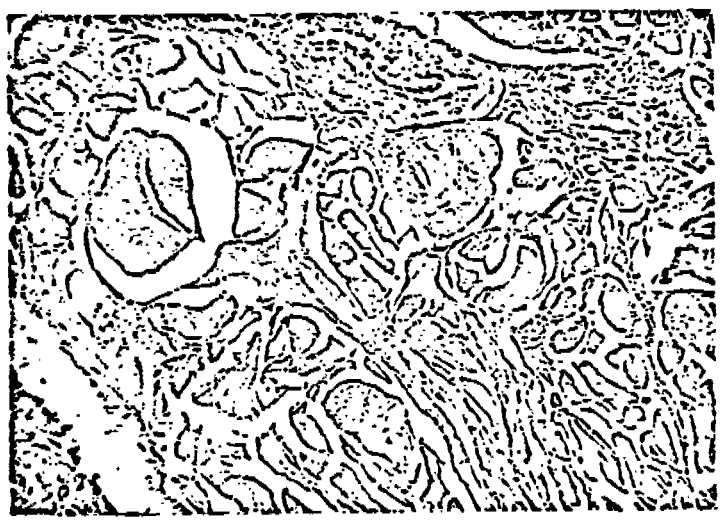
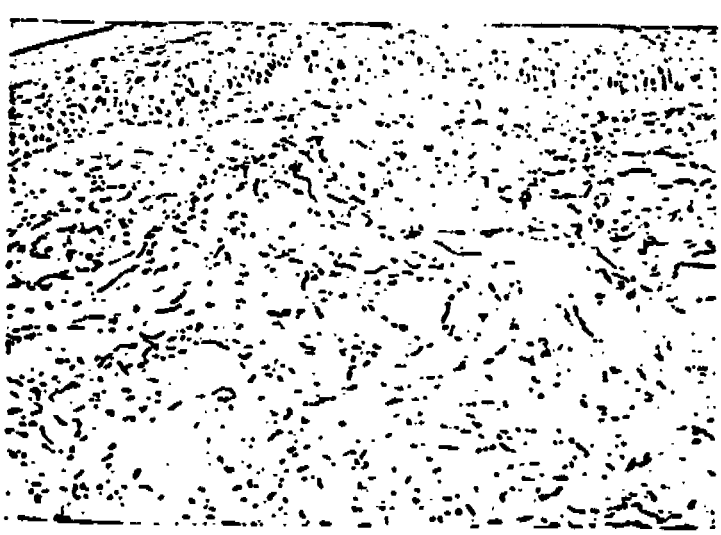


Fig. 5. The elastic fibers show an increase of distinct to complete rarefaction, a splitting and dismembering in the lower corium (Elastica color).



cooler environments. Of these pati nts, two reported this type of symptom in their toes.

In order to make the above complaints in all the patients objective, the skin temperature of the arm was measured, the arm and leg measured with an oscilloscope, and the arm examined with a plethysmograph (at rest), and exposure of the arm to cold was made after previous adaption to room temperature. In this last experiment, the underarm was held in flowing water for 15 minutes, and subsequently the time required for rewarming was determined. In five patients with acroosteolyses and scleroderma-like skin changes, a two sided arm-hand arteriograph was made in the transfemoral pathway (Priv. Doz. Dr. Beltz, Radiologic Clinic, Director, Prof. Dr. P. Thurn). In two other patients, arteriographs were carried out in an outlying hospital (once through direct puncture of the A. brachialis, the other time through a transfemoral entry) due to the existing Raynaud syndrome (By Prof. Dr. Schüssel, Prof. Dr. Schober, Siegburg City Hospital).

A capillary microscopic examination of the fingernail grooves was made in four patients, in which the fourth finger, left, was used.

An examination of the eye background of all patients was made because of suspicion of general angiopathy. An opthalmodynamometric measurement was made (University Eye

Clinic, Bonn, Prof. Dr. W. Straub).

Finally, the blood pressure of all patients was made with the patients lying down.

The skin temperature was considerably lower in the hands of 6 patients (up to 10°C below normal). In the cold exposure test, the rewarming period was lengthened in 9 cases (up to 60 minutes longer) and in four of the patients, Raynaud syndrome allowed recovery in single or all fingers of both hands.

No indication of inferior circulation of the extremities was observed oscillographically and plethysmographically.

All arteriographed patients exhibited pathological vessel build up. Five of the patients examined in the Radiological Clinic showed an arterial decrease in circulation in the fingers and in certain cases even in the hands.

Minor changes were evident in the finger arteries by a slight narrowing of the vessel opening of the Aa. digit. vol. propr. and the Aa. digit. vol. communes. Segmentary localized stenosis was also found. In more advanced stages, a delayed filling of the finger arteries was determined. These showed an almost total diffuse and relatively uniform stenosis. High degree stenosis to subtotal closure were found in the area of the base and middle phalanges, foremost on the fingers with acroosteolyses, while the rest showed a clear dense vessel net.

The tissue in the end finger phalanges appeared noticeably thickened in that area. A shortening of the end finger phalanges results from this substance defect. This may be related to an effect which is caused by a compression of the arteries localized there. In patients with characteristic changes, the filling time of the finger arteries was clearly retarded. The circulation of the finger arteries was greatly limited - the opening plugged partly to the periphery, and collateral was not evident. In theses cases, segmentary closings of the finger arteries or even a deficiency in the filling of the arteries in the entire finger were apparent next to the high degree stenosis. Both wrists likewise exhibited narrowed openings and side branches were absent to differentiated degrees. The circulatory changes described didn't allow a certain correlation to be made as to the number and size of the acroosteolyses. In fingers without acroosteolyses, the circulatory changes were, as a whole, less marked.

In two cases concerning patients with Raynaud syndrome without acroosteolyses, outer arm arteriographs proved the existence of a two-sided narrow calibered Aa. radiales et ulnares. The finger arteries were to some extent greatly restricted, segmented or even completely closed off, so that the middle and end phalanges were only incompletely maintained. This finding was more evident on the right than on the left. In the arteriographs of the

left hands of the other patients (transfemoral entry) showed a closure of the A. interossea, 3 transverse fingers proximal to the hand. The hand arteries were considerably constricted, and the Aa. radiales et ulnares proved to have a conspicuously narrow caliber. A complete representation of the angiographic results are in the preliminaries.

In the microscopic capillary examinations, nail grooves of the examined four patients exhibited an ampulla-like widening of the capillary loops, as have been described for the Raynaud syndrome (20). This result was brought about by patients, who although clinically exhibited circulation disturbances, proved to have no Raynaud syndrome.

In the eye background, two patients were observed to have an increased circuitry of the vessels, and in third patient a Fundus hypertonicus (blood pressure 145/85 mm Hg) was found. In a fourth, a distinct constriction of the arteries with cross connections of light congested veins was apparent. In the rest of the six patients, no pathological results were found. The opthalmodynamometric measurements were pathologically examined in two patients. In one patient, in a lying position, this lead to an inclination to an intracranial vessel resistance.

The blood pressures of 9 patients were in the nor-

mal range (systolistic between 100 and 140 mm Hg, diastolic between 60 and 85 mm Hg). One patient proved to have a low hypertonic value between 130/95 and 140/105 mm Hg.

Circulation disturbances in the hands represented a main symptom of the examined patients. These symptoms would be most strongly represented by the Raynaud syndrome. Four patients, who exhibited no Raynaud symptoms clinically proved to have capillary microscopic results as described for Raynaud syndrome. The objectivity of these complaints was achieved through a determination of the rewarming time required after exposure to the cold and by measurement of the skin temperature after adaption to room temperature.

The oscillograph and plethysmograph results, normal in all cases, leads to the suspicion that the origin of the given complaints is not in the area of the large arm arteries. Indeed, the arteriographic results show changes especially in the area of the finger and hand arteries. This corresponds to the changes which occur in the Raynaud syndrome of different types (19), but are even less distinct than that of progressive scleroderma. As far as is yet possible to judge from the small number of patients examined, a relationship exists between the amount of exposure and the extent of the angiographic results. Thus, the most complex changes were seen in a patient who was exposed for

over eleven years.

The eye backgrounds of six patients were insignificant, and those of the other four patients could not be uniformly intrepreted.

The opthalmodynamometric results, indicating intracranial spasms or respectively vessel resistance, in two of the four patients examined could represent the fact that similar vessel changes as described for the extremities are also present in the brain.

3. X-Ray Examinations

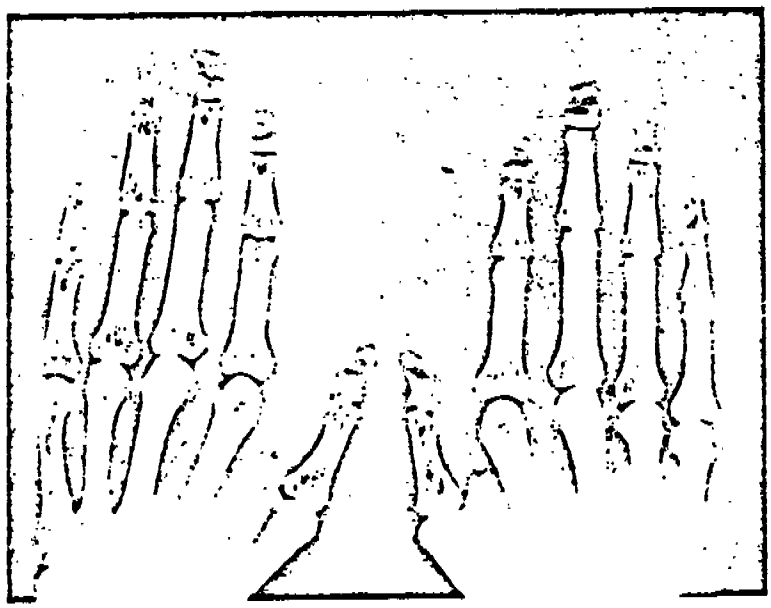
X-rays were made of the skulls, thoraxes, and upper and lower extremities as well as of the shoulder and peovis. The pathological results are reproduced in Table 3.

The most noticeable alterations - which until now have been determined to be the main symptom of the "occupational disease acroosteolyses" - were present in the hands: Six patients exhibited typically striped or band-like osteolyses in the end phalanges. In some cases the Proc. unguicularis, separated by osteolyses, proved to have additional fragmentation (Fig. 6). In these cases, fingers 1-3 of both hands were primarily affected. Six patients proved to have bone defects on the edges of the proc. unguiculares and five had a diffuse bone atrophy of the hand skeleton. One patient had acroosteolyses in addition to clear fungus-like widening of the Proc. unguicularis, widening of the shaft and shortening of the end phalanx of the finger. Furthermore, thickened

Table 3. Bone changes in ten patients afflict d with the so-called vinyl chloride disease.

		Hand Skeleton			Foot Skeleton			Other Skeletal Parts	
		Osteoporosis (Atrophy)	Edge defects (Proc. ung.)	Band-like osteolyses (end phalanges)	Osteoporosis (Atrophy)	Edge defects (Proc. ung.)	Band-like osteolyses (End phalanges)	Arthritis	Bone cysts
		Osteoporose (Atrophie)	Randdefekte (Proc. ung.)	bandförmige Osteolysen (Endphalang.)	Osteoporose (Atrophie)	Randdefekte (Proc. ung.)	bandförmige Osteolysen (Endphalang.)	Arthritis	Knochencysten
1	S.G.	+		+				+	+
2	O.S.	+	+	+	+	(+)			
3	D.Z.								
4	J.F.		+						
5	H.D.			+		+		+	
6	A.W.	+	+	+					
7	H.A.		+	+					
8	M.C.	+				(+)			
9	S.W.								
10	K.H.								
Summe		5	6	6	2	1 (2)	0	4	3

Fig. 6. Band-like osteolyses of the fingertip phalanx 1-3 of both hands and cystic brightening of the end phalanges in the region of the Proc. unguicularis of the fourth finger, left.



areas existed on the transition of the Proc. unguicularis to the shaft. In the foot skeleton, unspecific changes as atrophy and small side defects were apparent in four cases in the Proc. unguicularis. In one case, typical edge separation existed in both big toes of the Proc. unguiculares. The iliosacram joint of four patients exhibited indistinct conture and sclerosis. In five cases, numerous cystic bright spots in the area of the Caput humeri and the Proc. styloideus ulnae were apparent. In addition to this, skeletal x-rays of 72 other PVC employees were evaluated. In these x-rays, three cases of bone atrophy, respectively osteoporosis, were revealed, as well as four cases of small edge defects of single Proc. unguiculares. A complete representation and discussion of the x-ray skeletal alterations were published in another work (32).

Band-like osteolyses found in PVC-employees has been described by countless authors (5,7,9, 10, 16,36). This impressive picture has given this disease its Anglo-American name. Acroosteolyses has, in addition, been described in numerous other disease. These occur in familiar osteolyses, daktylolyses spontanea (Ainhum), Lepra mutilans, syringo myelia, mutilating arthritis psoriatica and acroosteolyses described by von Harnasch. Here, however, they may be neglected, differentially

diagnostically (31, 32). Although band-lik acro-osteolyses has also been described in progressive scleroderma (2), the borderline is clearly possible to determine (31).

There is also data existent for the aforementioned bone edge defects, for osteoporosis, and the scleroderma of the ileosacral joint (10, 16). However, due to the small patient collective, it is not possible to judge if the striking amount of bone cysts found in our patients is characteristic of this disease description. As to the idea of the "Question of Reversibility" of acroosteolyses, this has already been discussed and published as a result of the ten-year course of this disease in a patient (23, 31). According to those results, the osteolytic process in the end phalanx progresses from the distal to the proximal. At the same time, this results partially in a bone build up in the area of the Proc. unguiculares and the sintering into "fractured pieces." The end phalanx remained shortened and did not result in a Restitutio ad integrum.

4. Blood producing and Coagulating System

The following examinations were carried out on all patients: Hb, HbE, erythrocyte count, reticulocyte count, leukocyte count, differential blood picture, thrombocyte count, coagualogramm (Institute for experimental Hematology and Blood Transfusions, Director: Prof. Dr.H.Egli).

Sternal punctures were made in 5 patients (Medical Clinic, Director: Prof. Dr. H.-J. Dengler).

No pathological changes were evident in the red blood picture. Seven patients proved to have a slight reticulocyte between 16 and 26 %. The leukocyte count was under the normal (between 3200 and 3950 leukocytes/µl) in four patients. The differential blood picture was not certainly pathologically changed in any patient. The bone mark examinations offered no indication of damage to the blood building systems. Especially here, the signs of an osteomyelosclerosis, respectively fibrosis, were missing.

All ten patients proved to have a clear thrombocytopenia. The values repeatedly lay between 63,000 and 119,000, with one under the normal of 150,000/µl.

Mainly normal values were found in the determination of the plasma coagulating factors. In one case, Factor VII was slight and Factor X was moderately lessened.

The most noticeable result of these examinations was the decreased thrombocyte count of <u>all</u> patients. The bone mark examinations, with entirely normal results, gave no indication as to the disturbance of thrombocytopoiesis. The thrombocytopenia must therefore at least partially be traced back to the regularly present splenomegaly. Even so, the light reticulocytosis in 7 cases

and the indicated l ukopenia (in 4 cases) may be indicated in the sense of hypersplenism. A substantial disturbance of blood coagulation may not be established due to the nature of the examined factors.

5. Liver and Soleen

Three patients complained of repeated pulling or biting pains in the left upper abdomen, and one patient reported pain in the right abdomen and a "feeling of fullness". Four patients denied totally the use of alcohol, and the rest of the patients reported occasional use of beer and wine. No patient had taken long-term medications.

In the clinical examination of all the patients, no liver was noticeably enlarged. The spleen was distinctly discernable in the right side, in or around the height of the left rib.

The following laboratory tests were carried out as a control of the liver function: BSG, Electrophoresis, Takata reaction, bromsulphalein (BSP.-Test), SGOT, SGPT, alkyl and acidic phosphatase, LDH, cholinesterase, direct and indirect bilirubin, and plasmatic coagulating factor, immunoglobuline, complement fraction beta $_1$A.

A stomach-intestinal passage intigraphy (Radiological Clinic, Directr, Prof. Dr. P. Thurn), and a liver and spleen intigraphy (Dr. Schneider, Institute for Clinical and Experimental Nuclear Medicine, Director: Prof. Dr. C. Winkler) were conducted on all patients.

In two cases, a laparoscope with aimed liver punction (Medical Polyclinic, Bonn, Committee Chairman: Prof. Dr. Kessler) was carried out. With the help of x-rays of the esophagus, stomach and small intestines, esophagus varices were found in one patient. The scintigraphic examination showed a clearly enlarged (7 patients) and slightly enlarged (2 cases) spleen. The spleen was normal sized in only one patient. In no case was the liver enlarged. The activation distribution pattern was loosened in all patients in the area of the liver.

The BSG was normal in numerous controls.

The electrophoresisdiagram was unobtrusive in the normal total albumen of seven patients. In the other three patients, a slight decrease of the beta globulin fraction was observed (5-7 relative %).

The Takata-sample was normal in all ten patients. As a result of the plasma coagulating factors, there was no indication of a decrease in liver synthesis performance in 9 cases. One patient proved to have a slight decrease of Factor VII and a moderate decrease of Factor X. The cholinesterase showed a moderate activity in all cases. The transaminase values of 9 patients were in the upper borderline area, or slightly increased. In one case, they were normal. In two patients the basic and acidic phosphatase was increased, and in one patient

th LDH and direct bilirubin were simultaneously increased. This was noticeable because the slight to clearly increased BSP retention is quite contrary to the relatively low dgree alterations.

In the histological examination of the liver punctures, one patient was found to have a slight periportal fibrosis, and another a slight liver parenchyma damage. No indication of a floride infection or a cirrhotic reconstruction was present. The important results are assembled in Table 4.

With the summarized considerations, complete with respect to the liver functions, we could determine: Almost regularly, the results show the serum-transaminase is slightly increased. This may well be a sign of slight liver parenchyma participation. This is particularly true because no deviations whatsoever from the normal were found in the electrophoresis (with the exception of a decrease of the beta globulin content of some patients), the plasmatic coagulating factor, the enzymes (LDH, alkyl and acidic phosphatase, cholinesterase), and in the bilirubin content of the serum of 8 patients. In two cases, an interim increase of alkyl and acidic phosphatase with one patient and LDH and alkyl phosphatase with a weak positive proof of bilirubin in the other patient could be proven to be a sign of liver parenchyma involvement. However, normal albumin-gammaglobulin

Table 4. Clinical, chemical, serological, and histological results of the liver and spleen of ten patients afflicted with "co-called vinyl chloride disease."

Number	Patient	Splenomegaly (scintigraph.)	Esophagus varices	IgG (mg %)	IgA (mg%)	IgM (mg %)	Beta 1-A Complement fraction (mg %)	SGOT (mU/ml)	SGPT (mU/ml)	BSP Retention % n. 45 min.	Plasma. Coag. Factors, E. phoresis, Bilirubin, alkyl and acidic phosphat., LDH, ChE.	Liver biopsy results
1	S.G.	+	—	3150	60	310	108	33	17	11.8		
2	O.S.	+	—	3200	160	415	117	21	17	7.0		
3	D.Z.	—	—	2100	350	220	120	18	21	4.3		
4	J.F.	+	—	1760	20	135	132	13	8	4.4		
5	H.D.	++	—	4720	300	275	117	10	15	12.9		
6	A.W.	++	+	3320	190	355	117	19	17	16.1		
7	H.A.	+	—	3080	230	140	147	18	21	22.6		7. light periportal fibrosis
8	M.C.	+	—	2720	490	275	141	23	23	25.8		8. light liver parencym damage
9	S.W.	+	—	1420	330	40	150	19	15	8.0	—	—
10	K.H.	++	—	960	370	200	128	21	23	18.4	—	—

relationships with normal eggwhite in the chemical laboratory results are evidence against chronic liver damage, and also against cirrhosis. Because of the totally normal parenchyma structure, at this point there is no histological basis for a fattening or cirrhosis reconstruction of the liver.

The moderate increase of BSP-retention of 12-26 % found in five patients is unexplainable in connection with the remaining liver function values. This is not explainable solely through the small increase in SGOT and SGPT. According to a differential diagnosis, a fatty or congested liver would be possible. But clinical indications for both diseases are absent, and in addition, a congested liver resulting from right heart insufficiency may be eliminated as a result of x-rays and on the basis of the previously discussed histological examination.

The BSP secretion gave information about the excretory liver cell performance. But, as this is also dependent on liver circulation, the following may well be true: a decrease in circulation originally resulting from a periportal fibrosis leads to an increase in BSP retention in the "so-called vinyl chloride disease."

In addition, splenomegaly (regularly present with only one exception) must be seen closely connected with the changes in the liver, in our opinion. Indications

of a splenomegaly, in the framework of acute infections, are completely missing. A closer representation would be splenomegaly with intrahepatic conditioned portal hypertension, a so-called hepatic block. Due to the above considerations of the histologic results of periportal fibrosis, this may deal with an intrahepatic presinusoidal block. Pressure measurements (blocked liver vein pressure and intraspleen pressure) were not conducted, it is true, but for the most part the scarcely or only slightly diminished liver functions and the regular parenchym construction of the liver as well as the absence of heart insufficiency speak against the presence of a postsinusoidal block. It may be presumed that the pressure in the portal vein in all patients except one is not substantially raised,as a hepatofugal circulation with esophagus varices only came to the forefront in one patient. In spite of this, the changes in the liver could already lead to a presinusoidal block with secondary splenomegaly, as no strict relationship exists between pressure and spleen size. No splenomegaly may be proven when as yet no portal tension is present (4).

A hypersplenism results by means of the splenomegaly, that is, a strengthened blood moulting with a cell decrease in the periphery, which is indicated here by a strengthening of the existing thrombocytopenia, a tendency to-

wards leukopenia, and now and again a slight reticulocytosis. On the basis of the previously considered results, it can not be explained if the splenomegaly causes only a presinusoidal block or if the fibrosation occurrences in the spleen itself are also a result of this.

6. Lungs

A complete anamnesis was made of all patients, with consideration given to the smoking habits. A clinical examination was carried out and x-rays of the thorax completed. In all ten patients a resting spirometry and a plethysmography of the entire body was made, and a blood-gas analysis conducted for nine patients (Prof. S. Schwabe, Medical Clinic, Director: Prof. Dr. H.-J. Dengler).

In the clinical examination we determined a deep percutaneous emphysema in one patient and slight breath delay at the lung borders. In one patient the x-rays of the thorax exhibited a strengthened lung picture on both sides and a thickened Hilus left. The thorax x-rays of the other nine patients were normal.

Indications of primarily restrictive changes in eight patients were found in the examination of the lung functions (spirometry, plethysmography of the entire body).

In five patients, a slight to moderately heavy hypoxemia with a decrease of the P_{O_2} up to 62 mm Hg resulted

from the partial insufficiency.

The presence of a partial insufficiency in connection with the spirographic results indicating primarily restrictive changes speaks for the presence of a diffusion disturbance, as is found in beginning diffuse lung fibrosis. This then raises the question that similar changes may occur in the lung tissue as are shown in the collagen and elastic fibers of the skin tissue.

7. Immunology Results

The serogical examinations were carried out on all patients: determination of immunglobulin IgG, IgA, and IgM as well as the complement fraction beta $_1$A, with the help of radial immune diffusion; examination of antinuclear factors (Medical Clinic, Director, Prof. Dr. H. J. Dengler) and LE-cells; examination for the presence of CRP, streptococcus antibodies (ASL-Titer), rheumafactors (Latex and Waaler-Rose test), and cold agglutinin. Furthermore, the direct and indirect Coombs test and Lues seroreactions (Wa.-R.: KBR with cardiolipin, KBR with beef heart extract; flocculation reactions: VDRL test, MKR II) were carried out. As is shown in Table 4, all patients were found to have deviations in the immunglobulin fraction: in one patient, the IgG was increased; the IgG and IgM in three patients; the IgG, IgA, and IgM in two patients; in a further

patient only the IgA was increas d. One patient had a slight IgA increase with a simultaneous slight decrease of IgM, and in one case the IgA was decreased. In three cases, the complement fraction Beta $_1$A was on the lower normal borderline, and in one case was slightly decreased. Antinuclear factors and LE-cell phenomona could not be proven in any case. All other examinations had normal results.

As antinuclear factors, LE-cells or positive rheumaserology were not found in any patient, and in addition, BSG, electrophoresis and Crp gave no indication of acute infection, one can consequently eliminate the possibility of an autoimmunity disease.

The deviations in the immunglobulin fraction could best be connected with existing liver parenchym damage. Moreover, the IgA and IgM values attained were as those from patients with an uninfectious fat liver or respectively inactive alcoholic liver cirrhosis (13, 14). In contrast to these disease descriptions, the IgG is clearly increased and achieves values which could also be attained with active alcoholic liver cirrhosis. Accordingly, the changes of the immunglobulin fractions were indicated in connection with the chapter "Liver/Spleen" as an expression of a <u>chronic-toxic damage to the liver</u> with a gradual differentiating infectious participation of the mesenchym. The low values of the complement

fraction Beta $_1$A found in four patients are particularly worth noting. From these values, and on the basis of the other results, a complement fixation process can not be considered. A closer approximation would be that this globulin is formed in decreasing amounts because of the respective liver parenchym damage.

8. Further Results

In addition to the previously mentioned examinations, the sober blood sugars, Rest-N, creatinin, uric acid, sodium, potassium, calcium, and chloride were determined in all patients and the urine tested for protein, sugar, bile color and pH-values as well as urine sedimentation. Only normal results were obtained.

The results of the thorough neurological examination of the patients will be reported at a later date.

9. The so-called vinyl chloride disease without acroosteolyses and clinical skin changes.

The internal results of the ten previously examined patients helped us become aware of three other patients whose symptoms, although exhibiting no clinical skin changes and no acroosteolyses, indicated obvious concurrence with the previously determined internal results found in this disease. The most important results will be placed in a short casuistic.

F.S., 52 years old, employed since 1957 in the autoclave

room of a PVC manufacturing plant. Sinc the beginning of the 60's, has experienced increased dizziness and numbness, and in the last year strong pressure in the upper abdomen. Dislike for fatty foods. -About two years ago, distinct sensitivity to cold in the fingers, slightly less in the feet. -May 16, 1972, esophageal varices bleeding, May 18, 1972 received in Surgical University Clinic, Bonn. The laboratory results obtained there: thrombocytes 73,000/µl, electrophoresis o.B., slight decrease of plasma coagulating Factors V, VII, and X. X-ray results: MDP and esophagus: esophageal varices in middle and lower third esophagus. Stomach fundus varices. Percutaneus splenoportography: intrahepatic block, collateralcirculation over the vena coronaria ventriculi. -June 8, 1972 - splenectomy with establishment of a splenoral anastomosis. Intraoperativ raised liver and spleen diagnosis: spleen clearly enlarged, the liver surface slightly uneven, but not representative of a typical cirrhosis. No distinct signs of high pressure in the portal vein. Only slight degree raised pressure in arteries, veins, liver, spleen. Macroscopic and microscopic diagnosis of liver and spleen (Pathological Institute, Director, Prof. Dr. P. Gedigk): Liver - a slight fibrosis of the portal fields, next to an insignificant flock-like fat increase. Any statement concerning the

tiology of th fibrosis is no longer possible. No clues were present indicating a chronic hepatitis or cirrhotic alteration. Spleen: a 300 g heavy, 15x 7 cm large spleen. Histologically, this deals with a chronic blood congestion in the spleen (so-called fibroadenia of the spleen). In section cuts of the spleen hilus, there are recent obstructive thrombus within the spleen veins. Postoperatively, the thrombocyte count rose to 504,000/ l.*

We have carried out control experiments since Oct. 5, 1972. Thrombocyte: 97,000/ l, total protein electrophoresis o.B., transaminasis in upper normal range (SGOT 17 and 19 mU/ml, SGPT 15 mU/ml), acidic and alkali phosphatase 79 and 83 mU/ml). BSP test, 16.7 % retention after 45 min. Serological Examination: CRP slightly positive, IgG 2960 mg %, IgA 820 mg %, IgM 220 mg %, complement fraction Beta $_1$A 99 mg%. Lung function and blood analysis: indicates a moderately restrictive ventilation obstruction, slight lung emphysema, partial insufficiency. Temperature measurements (arms): on both sides, distal of the hand joint, a temperature deficit, which was 4-7° C on the end phalanges Histological results of a sample excision of the right hand: Narrowing of the epidermis and basophile degeneration

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* We thank the Surgical Clinic, Director: Prof. Dr. A. GÜtemann, for their willing relinquishment of the case histories.

of the collagen fibers in the upper corium, a sign of senile degeneration. In the middle and lower corium, no far reaching alterations of the collagen and elastic tissues were evident.

L.M., 51 years old, employed for 11 years in all rooms of the PVC manufacturing plant, has cleaned autoclaves only seldom. -1962, period of medical tretament due to heart pains and lumbago. At that time, no pathological liver and spleen diagnosis was clinically obtained. Since 1968, increasing pain in left upper abdomen and since this time, spleen enlargement is evident.

In 1969, diagnosis in the Medical Polyclinic and Surgical Clinic. Medical Polyclinic: splenomegaly, liver function disturbance with BSP retention of 10 % after minutes, but otherwise with unobtrusive liver chemical values. Thrombocytopenia of 44,000 thrombocytes/ l and slightly extended bleeding period. Of the other laboratory values, only the electrophoresis showed a deviation from normal values with a moderate increase of Beta-globulin to 15.4 rel. %. Sternal punctures unobtrusive, x-ray examination of the extremities: no indication for osteomyelosclerosis. The origin of the splenomegaly could not be explained. Surgical University Clinic: intrahepatic block,

probably with liver parenchyma damage and initial development of esophageal and stomach fornix varices (splenoportography, liver and spleen scintigram).

In 1970, the examinations in the Medical Polyclinic resumed: spleen enlarged, as compared to x-rays of 1969. Thrombocytopenia between 46,000 and 81,000 thrombocytes/µl, BSP test: 5.3% retention after 45 minutes. Other laboratory values, including the liver chemistry, had results in the normal range. Laparoscopy: Distinct splenomegaly. As a whole, the liver was not enlarged and exhibited a brown-red color. A fine - wavy surface relief was impressed, which resulted in a somewhat colorful picture due to capsule fibrosis as well as a clearly increased blood and lymph vessel picture. No certain signs of parenchyma structural alteration were present. Liver histology: moderately strong periportal fibrosis. A statement concerning the genesis is not possible.

Esophagoscope: beginning esophageal varices. Sternal puncture: o.B.

In October, 1972, examinations in the above named clinic: Anamnesis: further pain in left upper abdomen, especially with bending and at mealtimes. Dizziness and feeling of unsteadiness which emerged daily and lasted up to one-half an hour. Hearing loss, strong inner unrest. Clinical Results: spleen extended palpatori-

cally almost to the left pelvic ridge. Oth rwis no clinical deviations from the norm. Laboratory Results: normal red blood picture, a reticulocytosis of 16°/oo, leukopenia of 2350 leukocytes/µl, normal differential blood picture, thrombocytopenia of 30,000 thrombocytes/µl. Liver Chemistry: total protein, electrophoresis, Takata-Ara reaction, SGOT, SGPT, alkali and acidic phosphatase, direct and indirect bilirubin in the normal range. BSP test, 13 % retention after 45 minutes. Coagulating factors: .slightly extended thrombin period, prothrombin, Factors VII and X moderately decreased. Serological Examination: IgA 600 mg %, IgG 1600 mg %, IgM 200 mg %, complement fraction Beta $_1$A, 84 mg%. No proof of LE-cells, anti-nuclear factors or cold agglutinen. CRP, ASL, latex fixation, Waaler-Rose test, and the classical Lues-Seroreaction o.B. Lung function examination (spirogram, entire body plethysmogram, blood-gas analysis): indicates a restrictive ventilation obstruction with slight partial insufficiency. MDP: indicates a low-degree esophagus varices, esophagastric hiatus hernia, deformation of the Bulbus duodeni, large spleen, no proof of a ulcer or tumors in the stomach or duodenum. Histologic results of a sample excision of the right hand: thickened collagen fibers here and there in the lower corium and strong rarefication of the elastic fibers. Otherwise, no noticeable results.

B.K., 47 years old, employed since 1954 in a PVC manufacturing plant. In 1954-56, employed as autoclave clean r for one and one-half years, and again in 1968 again for three months. Otherwise mainly employed at the screening installations. Experienced cold sensitivity and much shaking in the hand for 1 to 2 years. Experienced syncopal-like dizziness and numbness for 2 to 3 years. Noticeable tiredness, slowing down, and forgetfulness, slackening of libido for 4 to 5 years. In 1969, bleeding duodenal ulcer with "tar" stools. Nonsmoker. In April, 1970 and Oct., 1972, renewed "tar" stools. Due to numerous bleedings during the stationary treatment on Oct. 31, 1972, a two-thirds resection of the stomach according to Billroth II was carried out; sufficient emptying of ascites. Liver: macroscopic: cirrhosis-like changes; microscopic (Pathological Institute, Director: Prof. Dr. P. Gedigk): slight increase of the tissue and a thin round-cell infiltration of the portal field. No proof of chronic hepatitis or cirrhotic structural alteration.

From Dec. 11 to 21, 1972, stationary at the Skin Clinic. Clinical Examination: spleen clearly palbable underneath the left rib joint, otherwise no important pathological findings. Laboratory Examinations: Light hypochiomic anemia with a normal differential blood

pictur thrombopenia with 90,000/µl with slightly lengthened thrombin period and a decrease of Factor X in the blood diagnosis. Liver Chemistry: BSP test, 15.6% retention after 45 minutes; electrophoresis, transaminase, LDH, alkali and acidic phosphatase, bilirubin, iron, and copper in the serum, all in normal range. Other Examinations: Electrolytic, Rest-N, classical Lues-Seroreaction, all normal. X-Ray Examination (MDP and Esophagus): esophagus and stomach fundus varices. Liver and spleen scintigraphy: strong atypical configured liver with enlarged left lobe. Spleen significantly enlarged with strongly increased colloidal storage. Lung function and blood analysis: small lung emphysema, partial insufficiency. Temperature measurement: Temperature deficit distal of the hand joint on both sides, on the end finger joint of both sides, deficit of 10° C. Histological Results: from a sample excision of left back hand: orthohypercytosis, constricted epidermis. The entire collagen fibers in the middle and lower corium showed a significant insufficiency of nucleus and homogenization, which increases in the deeper corium. In contrast to that, the elastica coloring shows an unobtrusive structure of the elastic fibers.

All three patients had worked between 11 and 18 years-that is, long-term-at the same PVC manufacturing plant in various capacities. Their main subjective complaints

during the past years included numbness, dizziness, pressure or pain in the upper abdomen, and increased sensitivity to the cold in the hands.

Some of these complaints were also reported by the other ten patients. In the recorded internal results, a great deal of concurrence was seen between the group of ten patients and the above three patients. On the basis of skin temperature measurements, two patients proved to have a lessened circulation in the hands. All three exhibited a decreased arterial O_2 saturation as the expression of a partial insufficiency in the lungs, which gave an indication for the existance of a restrictive ventilation disturbance and lung emphysema found in the lung function examinations.

The clear thrombocytopenia (and in one patient, a simultaneous leukopenia resulted), liver damage, and the characteristic spleen enlargement were particularly impressive. The liver damages were also evident in the laboratory examination of all three patients by means of a clearly raised BSP retention, in which only one patient had a simultaneous increase of transaminasis and the alkali phosphatase. The deviations in the coagulating factors and the immunglobulin fractions, as well as the decrease of the complement fraction Beta $_1$A, likewise correspond to the results found in the other ten patients.

Pathologically-anatomically, the liver of the three patients proved to have a fine-waved surface relief macroscopically, and in one patient, there was capsule fibrosis and increased blood and lymph vessel view. Histologically, a more or less strongly characteristic fibrosis of the periportal fields was found in all cases which had lead to an intrahepatic block(proven in one patient with a splenoportography) and with that, the formation of esophagus and stomach fundus varices.

These characteristic liver alterations, in connection with the characteristic splenomegaly and thrombocytopenia as well as the lung function disturbances lead to the conclusion that this likewise deals with the so-called vinyl chloride disease, and shows, in contrast to the other characteristics, the serious prognosis of this disease in the advanced stages. In two patients, this resulted in esophagus, respectively stomach, fundus varices, for which a splenoral anastomosis was performed after a splenectomy in one case and in another case a two-thirds resection of the stomach was undertaken. The disease progression was clearly evident in the third patient, for in that case it has not yet resulted in esophagus varices bleeding. During the past two years, the patient has experienced further enlargement of the spleen, the thrombocytopenia has become more distinct,

and in addition, leukopenia has set in.

The reason these patients with such deep-lying damages of the parenchymatous organs have passed over the clinical and histological skin changes typical for the so-called vinyl chloride disease (no acroosteolyses was proven), may possibly be explained by the type of employment in the PVC polymerization process. This shall be discussed in more detail in the following.

III. Job Conditions

What is then the suspected origin for the above-described disease? This question can only be answered through an analysis of the manufacturing process of vinyl chloride to polyvinyl chloride, and the materials used there as well as the by-and intermediate-products and the compounds resulting from these.

The end product, vinyl chloride (VC), was first synthesized in 1833 and is a colorless gas at room temperature (b.p. -13.9° C, freezing pt., -154° C). It is heavier than air and has an aromatic odor. In the gaseous state, it is easily inflammable. The narcotic effect was proven early (29). Vinyl chloride may not, however, be used as a narcotic because it leads to a disturbance of the heart rhythym in the concentrations necessary for such an effect (28).

A 30-minute exposur of a 30 vol% VC giv n to rats and guinea pigs lead from a narcotic stage to death. (26) Congested lungs, lung edema, blood congestion in the liver and kidney and a decreased blood coagulation was viewed autoptically. In long-term experiments conducted at low concentrations (200 ppm daily for 7 hours over 6 months) given to rabbits, centrolobular degeneration and necrosis with foamy vacuolization was present in the liver. Furthermore, periportal cell infiltration was also present (34). Recently, it was reported that in long-term (12 month) exposure of rats to VC, tumors of the skin, lung, and bone resulted. (35)

Acute intoxication in industry due to VC has seldom been observed. Reports of a reversible dizziness, slight disorientation, and burning in the feet have been made by two workers who received 2-5 % VC for three minutes (11).

Three cases of poisoning have become known from Canada, in which VC-gas was determined to be the origin in two separate cases (8). Intense stupor and decreased blood coagulation were found to be symptoms. One of the two died. A third died while cleaning a tank for ten minutes. The exact details of death could not be exactly determined in this case. Vinyl chloride leads to a toxic alteration of the skin similar to that of a second degree burn (15).

On the basis of the previously described animal experimental results, the maximum on-the-job concentration (MAK-value) was set at 100 ppm in 1970 (18).

Different methods of production are known for the polymerization of VC to PVC, and in each of these methods there are again countless modifications (6). The most widely used method is the suspension process. In this process, deionized water is added to the reaction container (autoclave or reactor), followed by numerous additives. These additives include suspension materials as polyvinyl alcohol, methyl cellulose, and gelatine; emulsifiers (sulfonated oil); surface reactive materials (sorbitmonolaureate); and buffer solutions (as sodium bicarbonate, for example). Furthermore, trichloroethylene may be added to give the polymer a lower molecular weight. Catalysts are used to initiate polymerization (usually organic peroxide).

After the reactor is closed and evacuated, liquid VC is pumped in under pressure. This reaction mixture is kept in motion by means of a rotating propellor and by the warming of the reactor walls to 50 - 55°C. As the polymerization depends upon the addition, it must later be cooled. Depending on the degree of polymerization and the desired molecular weight of the end product, the process is interrupted and the excess VC is

pumped to a gasometer for reuse.

From the initial steps in the production of PVC up until this stage, the process takes place in a closed system, from which no gas escapes under normal circumstances. In the further production processes of the reaction mixture and in the cleaning of the reactors, VC and other gas-forming substances may escape, which the workers then inhale.

The reaction mixture is pumped into a mixture container after the VC is suction-pumped from the autoclaves. There, the excess VC is again removed by means of a vacuum pump. Afterwards, the mixture is carried to a supply bin, from where it is sent to the centrifuge. The polymer is separated here from its aqueous phase. Finally, the polymer is dried in kettles, and separation according to particle size takes place in the screening installation. The finished powder-like polymer is then packed in paper containers or transported in tank cars.

After the reaction mixture has been removed, the autoclave is opened and sprayed with water with the use of a high pressure handle. If it is not clean after such treatment, the autoclave is again filled with water. After the water is let out, one or two employees enter the autoclave and remove the numerous, very solid coating from the wall with trowels, or sometimes with hammer and chisel. These so-called autoclave employees are thus

not solely employed in the autoclaves but also work on the centrifuges, the dryers, and the screening equipment, as well as the packaging of the polymer.

In addition to the industrial use of the here-by described suspension process, the emulsion process is also used in plants where some of the examined patients worked. This process serves not only to produce the homopolymer PVC but also the mixed polymer polyvinyl acetate. The polymerization is likewise carried out in autoclaves, but in contrast to the suspension process, other additives (emulsifiers) are added. The reaction mixture is not conducted to the centrifuge and drying equipment after the gas is extracted but sprayed in a nozzle over storage tanks, in which hot air is present. The polymer contained in the sprayed emulsion droplets are thereby directly dried and are precipitated on the filters. The gases contained and the steam formed from the heat are blown free. Screening and packaging of the polymer follows as in the suspension process.

In the course of the processes which lead to the polymerization of VC to PVC, VC and other gaseous compounds enter the air of the work rooms. With each autoclave cleaning conducted with a water pistol, residual gas escapes into the working area. Although no measurements of work level concentrations of the gaseous

compounds are available, it may be assume that thes would be present in significant amounts. At times, concentrations are obtained which produced a pre-narcotic syndrome in the autoclave employees. This syndrome consists of stupor, dizziness and nausea.

However, a moderate amount of odor-perceptible gas also emerges from the centrifuge, the storage and mixing tanks, and the spraying towers as well as the connections carrying to and from and the drying and screening equipment. Also, the cleaning of the inner autoclave walls with trowels and chisels present opportunities for the workers to be exposed to gases diffusing from wall precipitates or those found as underground polymer precipitates. After ventilation of the reactors, 50 to 100 ppm were measured (6). The air analysis in the region of the inner reactor walls, that is, in the region in which the employees' hands and face are exposed, reached concentrations of 500 to 1000 ppm.

However, the largest amount of gas is released by leakage (for example, in the ventilation) from the exposed autoclaves. This can only be eliminated after the reaction process is completed and by insufficient VC recovery after cessation of polymerization. Presently, there have been only single examinations concerning the degree of cleanliness of the utilized VC and the quali-

tative and quantitave composition of the gases present after completion of polymerization in the autoclaves. There is, however, no doubt that the dominant portion consists of vinyl chloride. The chemical analysis of the residual gas from the autoclaves gave the following composition (the method applied was not reported): 90 % VC, 8.5 % CO_2, small amounts of vinyl acetate, trichloroethylene and nitrogen, traces of argon (8).

IV. Discussion

In the previous sections, the examination results of 13 employees of PVC manufacturing industries were reported. Countless serious diagnoses of the different organ systems, described for the first time, were brought up. (Table 5) From these results, it could be determined that the characterized disease symptoms can no longer be sufficiently described by the previously used term "occupational acroosteolyses."

A slight to severe thrombocytopenia was found in all of the examined patients. Twelve of them were found to have a slight to defined splenomegaly. On the basis of laboratory-technical examinations, restricted liver functions were proven in 11 cases which histologically corresponds to a periportal fibrosis. Esophageal varices had formed in four patients, caused by the periportal fibrosis and the resulting portal hypertonia.

Table 5. Compilation of the important diagnos s of all examined patients with the so-called vinyl chloride disease.

Number	1	2	3	4	5	6	7	8	9	10	11	12	13
Patient	M.G.	O.N.	D.Z.	J.F.	H.D.	A.W.	H.A.	M.C.	K.W.	K.H.	L.M.	F.N.	H.K.
Skin changes a. Clinical	+	+	-	-	-	-	+	-	-	-	-		
b. Histolog.	+	+	+	+	+	+	+	+	+	+	+		-
Circulation Disturbances	+ (II)	+ (II)	+ (II)	+	+	+	+ (II)	+	+ (II)	+	+	+	+
Bone Alterations	+	+	+	-	+	+	+	+	+	+	+		
Thrombocytopenia	+	+	+	+	+	+	+	+	+	+	+	+	+
Splenomegaly	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver Changes	+ Oesophag. Var.		+ Oesophag. Var.	+	+ Oesophag. Var. portale Fibr.	+	+ Oesophag. Var. portale Fibr.	+	+ Oesophag. Var. portale Fibr.	+ Oesophag. Var. portale Fibr.	+ Oesophag. Var. portale Fibr.	+ Oesophag. Var. portale Fibr.	
Ventilation and/or diffusion obstructions	+	+	+	+	+	+	+	+	+	+	+	+	

a - = leukocytes < 6000/µl; + = leukocytes > 6000/µl; +++ = < 60000/µl.

b + = enlargement to rib, ++ = enlargement over ribs, +++ = enlargement over navel.

The changes in the respiratory tract were conspicuously numerous. The majority of the patients (eleven) proved to have functional disturbances in the sense of partial insufficiencies and gave indications of mainly restrictive alterations.

Circulation disturbances of the hands and feet up to the Raynaud syndrome were given as the first symptom by almost all patients and could be objectively judged in eleven cases. The scleroderma-like alterations of the skin in the arm region, typical for this disease, could be observed in 8 cases. No strict relationship existed between the amount of circulation disturbance and the distinctness of the skin changes.

Acroosteolyses has given this disease its name, especially in American literature, and we saw this in 6 patients. Up until this point, acroosteolyses and Raynaud syndrome had been given the central position in the disease diagnosis. Other authors placed the disease occurrence at 3-5 % of the employees. We could confirm this statement, in regard to the Raynaud syndrome and acroosteolyses symptoms. Yet, with respect to the internal results of our examinations, it may be assumed that the death rate is significantly higher. In our examined patients, this would lie at 10 % of the employees employed at the plant, although

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Acroosteolyses has given this disease its name, especially in American literature, and we saw this in 6 patients. Up until this point, acroosteolyses and Raynaud syndrome had been given the central position in the disease diagnosis. Other authors placed the disease occurrence at 3-5 % of the employees. We could confirm this statement, in regard to the Raynaud syndrome and acroosteolyses symptoms. Yet, with respect to the internal results of our examinations, it may be assumed that the death rate is significantly higher. In our examined patients, this would lie at 10 % of the employees employed at the plant, although

no previous serial examination has been undertaken. With this aspect in mind, the suspicion voiced by some authors that constitutional factors play an important role in the origination of this disease may be placed in the background. The toxic occurrences should be placed foremost. The high mortality rate of mainly young men indicates on the one hand an entirely special occupational sector, and on the other, the complex nature of the disease. In spite of the differing effects of this disease, in which skin and bone alterations or conversely internal changes are seen as the main symptoms, a common trait may be found. In all the organ systems we examined, changes in the tissues or respectively the vessel tissues were always found.

The tissue alterations of the liver were particularly impressive. As a result of an increase of collagen fibers, a fibrosis of the portal fields with the remaining normal parenchyma structure occurs. In comparison with this result, the small toxic changes of the liver parenchyma becomes insignificant. It can not be presently decided if the observed spleen enlargement should be viewed as the single result of hyperportal tension or if it is also primarily due to a fibrosation in this organ. The four patients with the most definite splenomegaly exhibited esophageal and partial stomach fundus

varices.

The origin of the thrombocytopenia remains unclear. It is certainly not solely due to the splenomegaly and the liver changes, as this has been determined to be a uniform symptom in one patient with a splenectomy as well as in a patient without liver and spleen changes. According to our results, we would assume the lowered thrombocyte count is the first objective symptom. This is all the more important because the thrombocyte count is a value that is easily determined and therby offers a possibility of inner-industrial procedural control.

The indicated restrictive ventilation disturbances combined with hypoxemia indicate that fibrosation also occurs in the lung tissue. The skin gives evidence of a histological increase and a thickening of the collagen fibers with simultaneous destruction of the elastic fiber network. The corium vessels exhibited only discret changes in the form of edematosis swelling. In comparison, the caliber constriction and segmentary osteolyses, particularly in the region of the hand and fingertip phalanges, may be proven angiographically. Possibly, the osteolysis of the fingertip phalanges may be an indication of a trophic disturbance. Circulation disturbances in the sense of a Raynaud syndrome - which existed in 4 of the patients examined here - were found in addition to numerous internal diseases as well as

progressive scleroderma and results of toxic influences (17). The Raynaud syndrome and the clinical and histological changes of the skin are suggestive of this systematic disease. In progressive scleroderma, the vessels and the tissues also become important. Although on one side, the paralells between progressive scleroderma and the "so-called vinyl chloride disease" are very clear, the two diseases are quite well separated, on the other side (23). Above all, however, there exists no doubt that the disease described by us is occupationally dependent and has a toxic origin. As it has already been described, the patients have been constantly exposed to gases because of their occupation. These gases emerge from the PVC synthesis, and these gases contain a mixture of numerous volatile substances. The main fraction consists, however, of vinyl chloride (8). Other substances, as vinyl acetate and trichloroethylene, are only present in trace amounts. The narcotic effects of VC are familiar. The employees examined by us anamnetically revealed that VC periodically escapes in significant amounts in different phases of the production process, and that this produced tiredness, dizziness, and nausea.

From animal experimentation, it is known that VC has toxic liver effects in significant. This has, among other things, lead to a new determination of the MAK value (18).

Furthermore, the em rg nce of Raynaud syndrome has be n observed in plants which produce only the monomer, and not PVC (1, 27). In the most recent period, long-term vinyl chloride exposure in animal experiments produced damages in the bone construction.

Various authors have determined the employment in autoclaves to be the deciding factor in the origin of acroosteolyses, Raynaud syndrome and skin changes. At this time there is no known patient afflicted with occupational acroosteolyses who was not at least periodically employed as an autoclave cleaner. It was assumed that the origin of this disease was a result of the coinciding of a perinhalation or percutanous toxic substance, the physical alteration of the hands during the cleaning of the autoclaves, and a disposition factor. We suspect, in contrast to that, that it is not so much the constant microtraumatization of the hands in manual autoclave cleaning which is the main factor for the formation of the osteolysis but the close contact with the polymerization precipitate. This contains large amounts of the diffused VC such that the inner reactor walls (even after previous spraying of the autoclave with water) contain 600 - 1000 ppm vinyl chloride. A further indication of the percutanous penetration of VC is indicated by tha fact that we found scleroderma-

like skin changes only in the region of unclothed skin areas.

On the basis of the expounded results and considerations, we believe that the penetrating suspicion exists that ong-term VC exposure is capable of producing a complex disease. This is expressed in the fibrosation of the parenchyma organs examined by us: the lungs, liver, and spleen as well as the circulatory system. With this, the disease obtains the character of a systematic disease in which the prognosis becomes serious in advanced stages. The disease thus is far wider reaching than the previously described disease, "occupational acro-osteolyses". We would therefore like to eliminate this symptomatic designation and propose the name "vinyl chloride disease."

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Die sogenannte Vinylchlorid-Krankheit — eine berufsbedingte Systemsklerose?*

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Vinyl Chloride Disease

Summary. The health status of 13 workers employed for 1.75—18 years in a polyvinyl chloride factory was studied. Eight of them had scleroderma-like skin changes (Fig. 2) characterized histologically by thickening and homogenization of the collagen bundles (Figs. 3 and 4) and fragmentation and rarefaction of the elastic fibers (Fig. 5). In 7 patients, thickening of terminal finger phalanges resembling clubbing was noted (Fig. 1); 11 patients had circulatory disturbances of the extremities (4 of them had Raynaud's syndrome) and 6 patients band-like osteolyses of terminal finger phalanges (Fig. 6, Tables 1—3).

In addition to these disturbances, thrombocytopenia was observed in all patients, in 12 patients splenomegaly and in 11 patients malfunction of the liver (increased BSP retention). Histological examination of liver biopsies taken from 5 patients who underwent laparoscopy revealed marked fibrosis of the portal areas. 4 patients had esophageal varices (Tables 4 and 5) and 8 patients showed partial pulmonary insufficiency with signs of predominantly restrictive changes of the lungs.

These pathologic changes in a series of different organs are far more extensive than the syndrome of occupational acroosteolysis already known. Long-term exposure to vapors of vinyl chloride is strongly suspected of causeing this complex disease. Therefore it is proposed that this systemic disease be designated vinyl chloride disease.

Key words: Occupational disease — Polyvinyl chloride production — Vinyl chloride — Scleroderma-like skin changes — Raynaud's syndrome — Vascular changes — Acroosteolyses — Thrombocytopenia — Splenomegaly — Esophageal varices — Liver fibrosis — Pulmonary ventilation disturbances.

Zusammenfassung. Es wurden 13 Arbeiter untersucht, die zwischen 1¾ und 18 Jahren in einem PVC-herstellenden Betrieb beschäftigt waren. 8 von ihnen wiesen sklerodermieartige Hautveränderungen (Abb. 2) auf, die histologisch charakterisiert sind durch Verbreiterung und Homogenisierung der kollagenen Faserbündel (Abb. 3 u. 4) sowie Fragmentation und Rarefizierung der elastischen Fasern (Abb. 5). Bei 7 Patienten bestanden trommelschlegelartige Auftreibungen einzelner Fingerendphalangen (Abb. 1). 11 Patienten zeigten Durchblutungsstörungen der Extremitäten (4 von diesen ein Raynaud-Syndrom) und 6 Patienten Acroosteolysen einzelner Fingerendphalangen (Abb. 6, Tabellen 1—3).

* Die Arbeit wurde mit dem Franz Koelsch-Preis 1973 ausgezeichnet.