

PART I. TOXOCOLOGICAL INVESTIGATIONS OF VINYL CHLORIDE-
POLYVINYL CHLORIDE

A. Clinical Studies

CLINICAL MANIFESTATIONS AND COURSE
OF VINYL CHLORIDE DISEASE

G. Veltman, C.-E. Lange, S. Jühe, G. Stein, and U. Bachner

*Department of Dermatology
Institute for Experimental Hematology and Blood Transfusion
University of Bonn, Federal Republic of Germany*

In April 1972, on the occasion of an international symposium of physicians employed by the chemical industry, we reported for the first time in the Federal Republic of Germany on two patients whose clinical symptoms were in accordance with the syndrome of "occupational acroosteolysis," as it was known at the time, in workers in polyvinyl chloride (PVC) production.¹ The symptoms occurring in these cases, Raynaud's phenomenon, hardening of the skin, lesion of bones, reminded the dermatologist of the long-known clinical picture of systemic sclerosis, which presents corresponding histological changes in the internal organs.²⁻⁴ Therefore, thorough further examinations were carried out on these patients, and also on all further patients, who were sent to us by physicians in the environment of the plant or came to us of their own free will. In the process, we paid particular attention to the vascular system, the hematogenic system, the liver, the spleen, the lungs, the nervous system, and the digestive system; finally we made sure that the possibility of auto-aggressive disease was eliminated. As a result, in initially 13 workers employed in PVC production we observed numerous grave, not previously described, symptoms in various systems of organs, namely circulatory disturbances, thrombocytopenia, splenomegaly, and changes of the liver. These were the basis of the detailed study we published,⁵ which led us to the conclusion that long-term exposure to vinyl chloride can trigger a complex syndrome. As this syndrome is comprised of changes of the skin, the bones, and the vessels and pathological findings in the most various systems of organs, it can no longer be adequately defined by "occupational acroosteolysis," the term used so far. It was for this reason that we suggested the term "so-called vinyl chloride disease."

Today we have at our disposal the test results of 70 patients out of about 128 workers in a PVC-producing plant; a number of these have been examined further in cooperation with the Department of Medicine and the Institute of Pathology. The findings gave added further proof to our previous results.^{6,7}

Our findings have encouraged us—as have the latest publications of international literature on the subject—to dispense with adding "so-called" in designating the syndrome. We now use the term "vinyl chloride disease" for the comprehensive syndrome. In the following paragraphs, our findings will be discussed in detail, and in the process we intend to deal (as far as that can be done today, that is, after 1 or 2 years of observation) with the further course of clinical changes after the job was given up, for such information is of interest for a prognosis.

TABLE 1
SURVEY OF INITIAL SYMPTOMS OBSERVED IN 70 PATIENTS FROM A PVC FACTORY

Symptoms	No. of Patients	%
Upper abdominal complaints	42	60.0
Tiredness	27	38.6
Frequent dizziness	26	37.1
Paresthesia (numbness and tingling) in fingers and/or toes	22	31.4
Increased perspiration	19	27.1
Sensation of cold in individual fingers or hands	18	25.7
Arthralgia	17	24.3
Potency troubles	13	18.6
Pain in the head	9	12.9
Pain in the calves	9	12.9

These 70 patients had been occupied 7.7 years on the average (from 6 months to 21¼ years individually) with cleaning autoclaves, but also with centrifuges, drying and sifting processes, and wrapping PVC as a dry end product.

The initial symptoms they complained of are shown in TABLE 1.

The survey in TABLE 2 shows the frequency of clinical, scintigraphic, and radiological findings, and also the pathological results of laboratory tests. The symptoms that were most frequent were: thrombocytopenia (81 percent); increased BSP retention (67.2 percent); splenomegaly (57.4 percent); and reticulocytosis (41 percent). These findings may be regarded, therefore, as outstanding principal signs.

Skin changes consist first (FIGURE 1) of the well-known clubbing-like swellings and shortenings of the terminal phalanges of one or several fingers, accompanied by watch glass-like nails and shortening of the respective nail plates. These symptoms correlated with the radiological findings to be described later. Secondly, there are scleroderma-like skin changes, seen as very coarse (FIGURE 2), comparatively sharply delimited whitish to ivory-colored infiltrates, mostly raised above the skin level, and ranging in size from grains to small nodules, or, plaque-like (FIGURE 3). These are found above the metacarpo-phalangeal joints,

TABLE 2
FREQUENCY OF CLINICAL, SCINTIGRAPHIC, RADIOLOGICAL AND PATHOLOGICAL
LABORATORY FINDINGS IN 70 WORKERS FROM A PVC FACTORY

No. of Patients Examined	Finding	No. of Patients	%
70	Thrombocytopenia (17,000–143,000/ μ l)	57	81.0
67	Increased BSP retention (5.1–25.6 after 45 min)	45	67.2
68	Splenomegaly (scintigraphy)	39	57.4
58	Reticulocytosis (16–37%)	24	41.0
70	Increased serum enzymes (SGOT, SGPT, AP, SP)	10	14.3
70	Scleroderma-like skin changes	8	11.4
70	Varices in esophagus and/or fundus of stomach	8	11.4
70	Acroosteolysis	6	8.6
70	Raynaud's phenomenon	6	8.6
70	Leukopenia	5	7.1

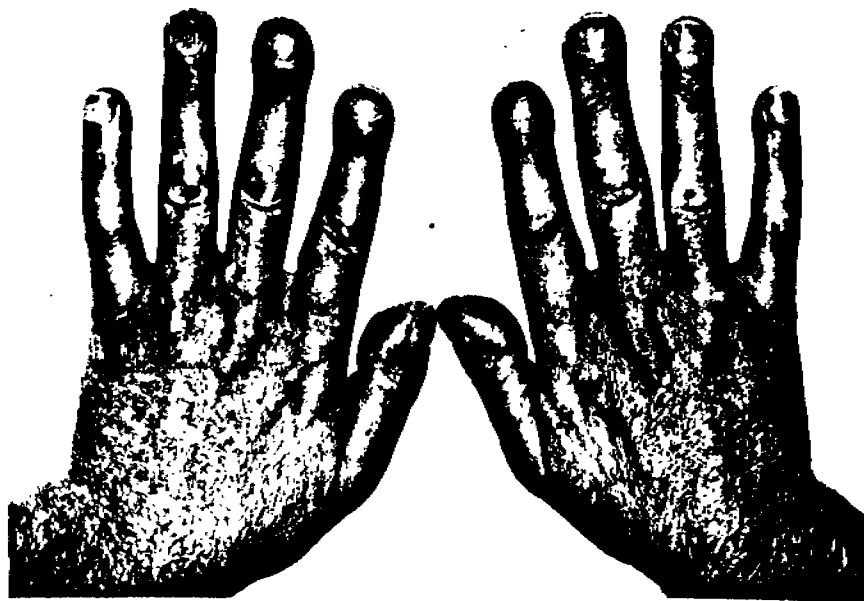


FIGURE 1.

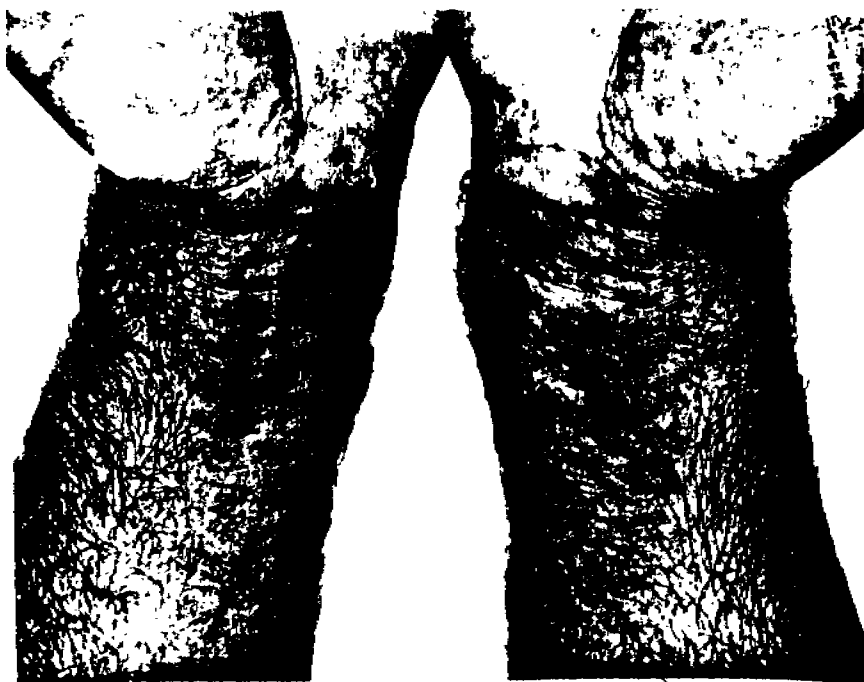


FIGURE 2.

8



FIGURE 3.

on the ulnar side of the dorsum of the hands, in the distal third of the flexor side of the forearms. Less often is there induration in the zygomatic area (FIGURE 4: decrease of infiltrates and only a small erythema 1 year after the job was given up).

These latter comparative photographs show that with some skin changes complete regression may be expected, provided that a certain degree of severity was not exceeded.

The histological findings, on the basis of test excisions taken from the lateral backs of the hands of 36 patients so far (with or without clinical changes) show (FIGURE 5) distinct hyperorthokeratosis and usually a thinning of the epidermis. In the subepidermic boundary layer there are increased and extended capillaries with endothelial swelling and a loose, scant, mostly lymphocytic infiltrate. The cutis (FIGURE 6) shows thickening (sometimes considerable) together with an increase of mostly nucleus-lacking, swollen and/or homogenous collagen bundles; the sweat glands were raised (FIGURE 7), the sebaceous glands and hair follicles showed atrophy due to pressure. The elastic fibers (FIGURE 8), and this is of importance concerning differential diagnosis as compared to the histological findings of systemic sclerosis, show evidence of considerable rarefaction, fissuration, and fragmentation. When these histological findings were subdivided into those taken from clinically changed and those from clinically unchanged skin, it turned out that in clinically changed skin they were always present, but in 6 of 28 cases they were found even in clinically unchanged skin. However, in these latter cases

SL 041509



FIGURE 4.

no direct correlation was found to exist between these findings and the severity of internal findings.

Of the *changes in the bones* we mention the characteristic band-like acrosteolysis of the hands because in this field we have a number of check-ups on the course these took; the results allow us to draw conclusions about the possibilities of regression with this syndrome.

FIGURE 9 shows x-rays of the hands of patient O.S., the upper one being made in 1962. At that time this patient had been working in a PVC-producing plant for about 5 years as an autoclave cleaner. We see band-like osteolysis in the bases of the processus unguiculares of the second, third, and fourth fingers of the left hand, and of the first, second, third, and fifth fingers of the right hand, which in some terminal phalanges extend into the shafts. In the absorbing ligaments



FIGURE 5.

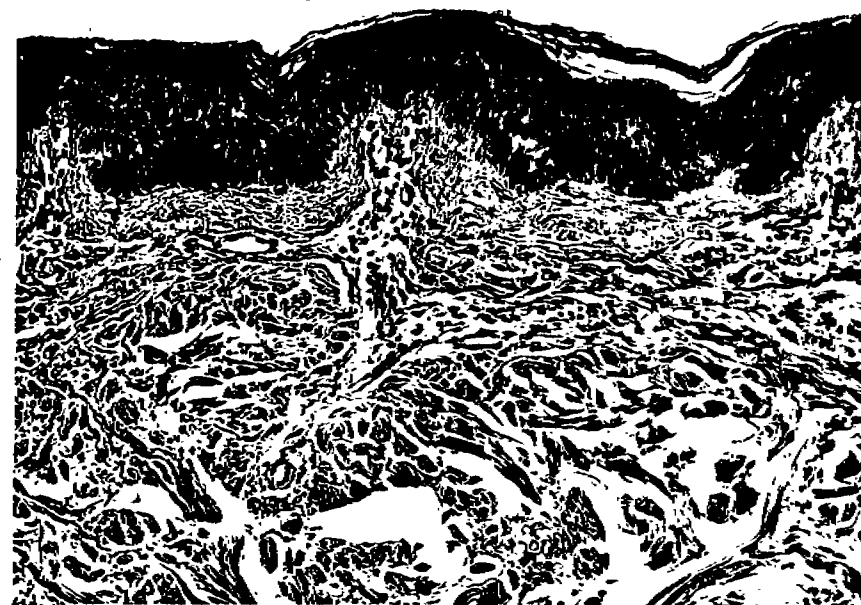


FIGURE 6.

SL 041510

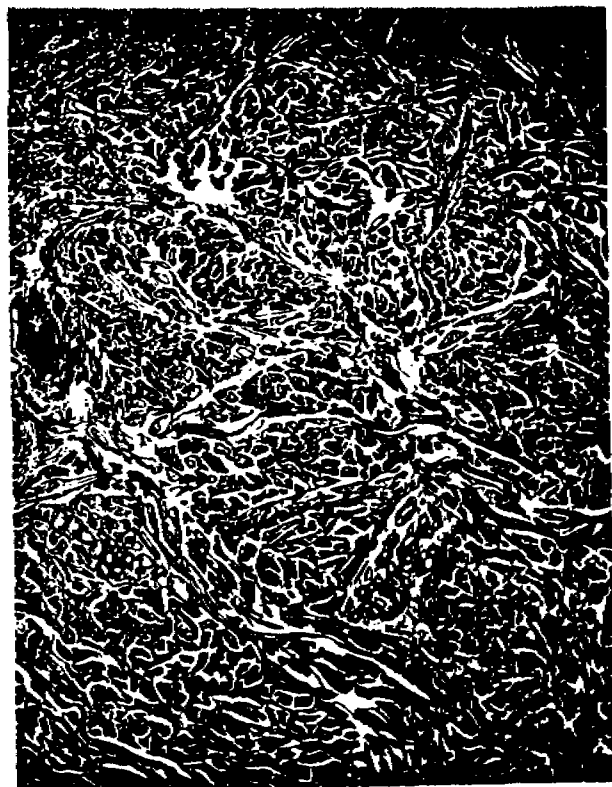


FIGURE 7.

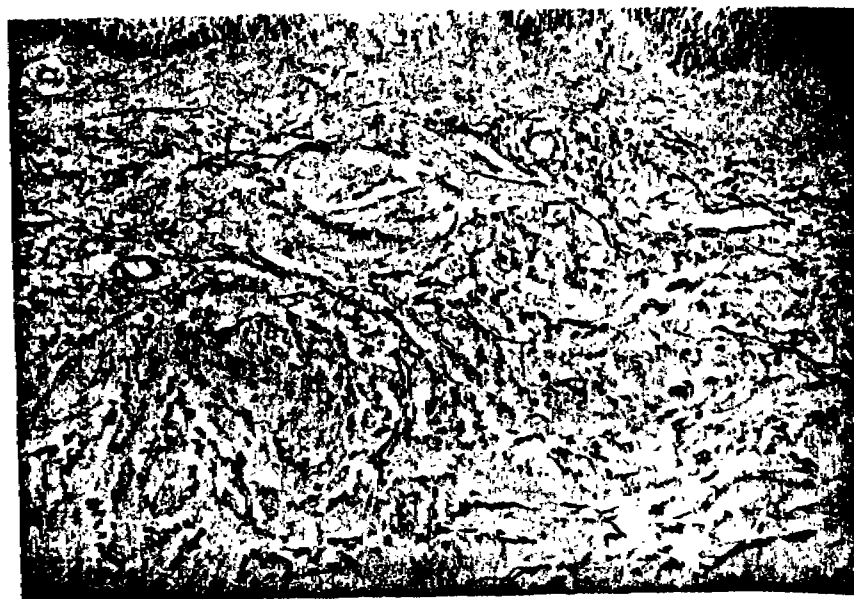


FIGURE 8.

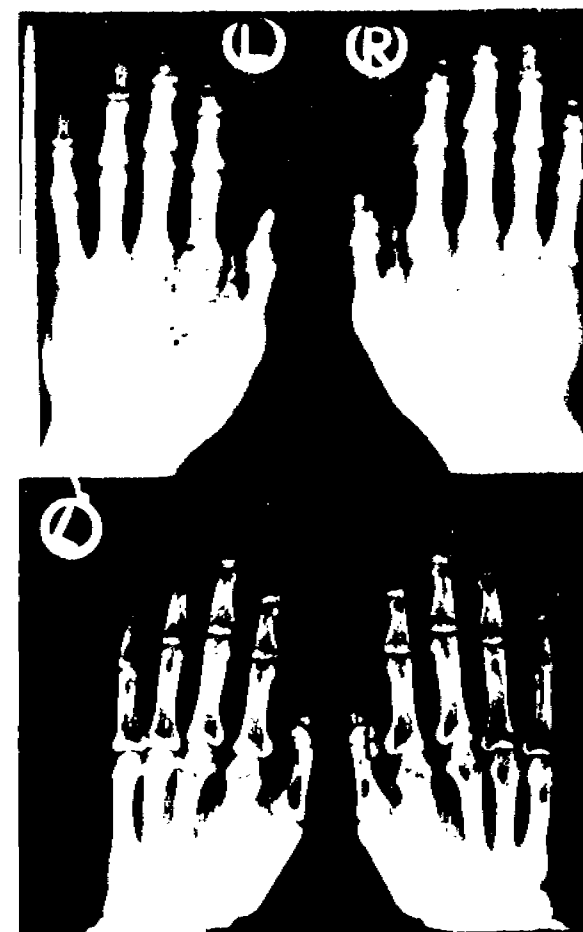


FIGURE 9.

small fragments of bones or sequestra can be seen. A fracture line extended through the processus unguicularis of the fourth right-hand finger. In 1969 the patient was pensioned off as an invalid because systemic sclerosis together with heart and circulatory troubles was suspected. The lower x-ray was made in 1974, that is, $5\frac{1}{2}$ years after retirement. Part of the processus unguiculares have been reformed, but osteolysis has advanced in the proximal direction along the shaft. There are clearly visible fissures in the processus on the stumps of the terminal phalanges. The fracture line which ran through the processus unguicularis of the fourth right-hand finger can no longer be detected. The terminal phalanx of the fifth right-hand finger presents itself as structurally intact, but shortened. Return to normal has not occurred to date. However, in the following x-rays (FIGURE 10) improvement or even complete restitution can be seen, which has also been the case with other patients. The findings date from the years 1972 and 1974.

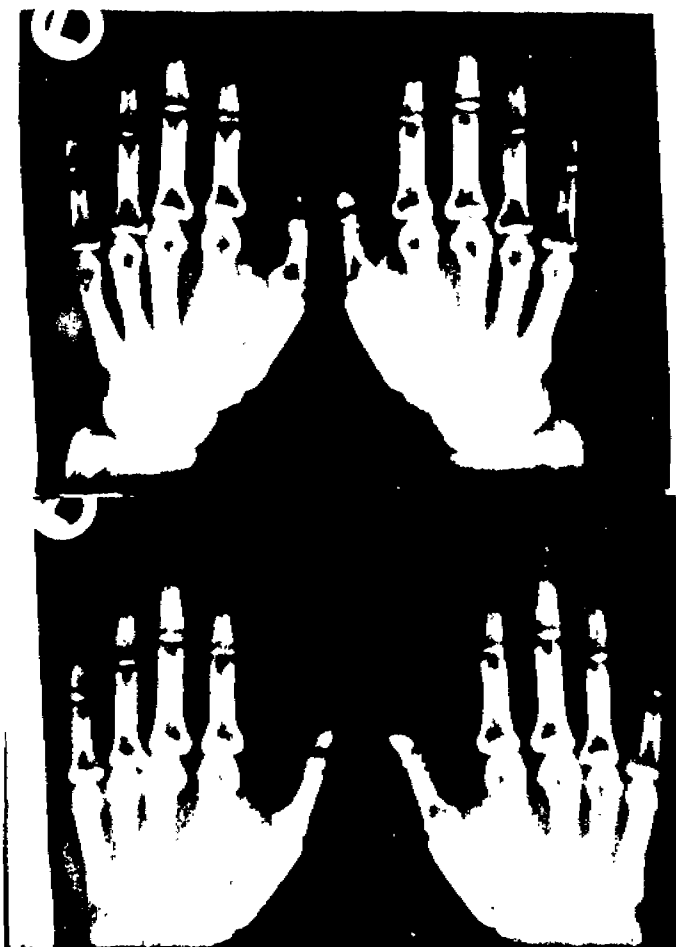


FIGURE 10.

In close connection with the above findings are the evident *vascular changes*, which we revealed by means of *arteriography* in 7 patients. They range from slight narrowing of the vascular lumina in the digital arteries to demonstrable retardation of the filling process, strong stenosis, and subtotal occlusions in the proximal and central phalanges, which, especially in the fingers affected by acroosteolysis, went as far as complete segmental occlusion or even complete absence of filling of the arteries along the whole length of the finger. Whereas (FIGURE 11) the patient who had been exposed for 11 years and whose bone changes do not show any restitution shows the most severe vascular changes (strong narrowing of all vessels in the palmar arch, occlusions, and vascular ruptures from the second to the fifth fingers), the vascular changes of that patient whose lesions of the bones have healed in the meantime (FIGURE 12) are



FIGURE 11.

considerably smaller in comparison: there is only a moderate narrowing of the vessels.

Our investigations revealed for the first time the occurrence as well as the frequency of *thrombocytopenia*. This result is the first objective finding at all in most cases; consequently, the platelet count should be an obligatory test in PVC production workers.

In 81 percent of all persons examined slight to severe thrombocytopenia was found, with values ranging from 17,000–143,000/ μ l, whereas the lower norm is 150,000/ μ l. However (TABLE 3), a clear-cut correlation between platelet count and period of exposure is not demonstrable with our findings. A causal relation between the extent of splenomegaly and the degree of thrombocytopenia is also missing. In all patients with strong splenomegaly there was thrombocytopenia;

SL 041512

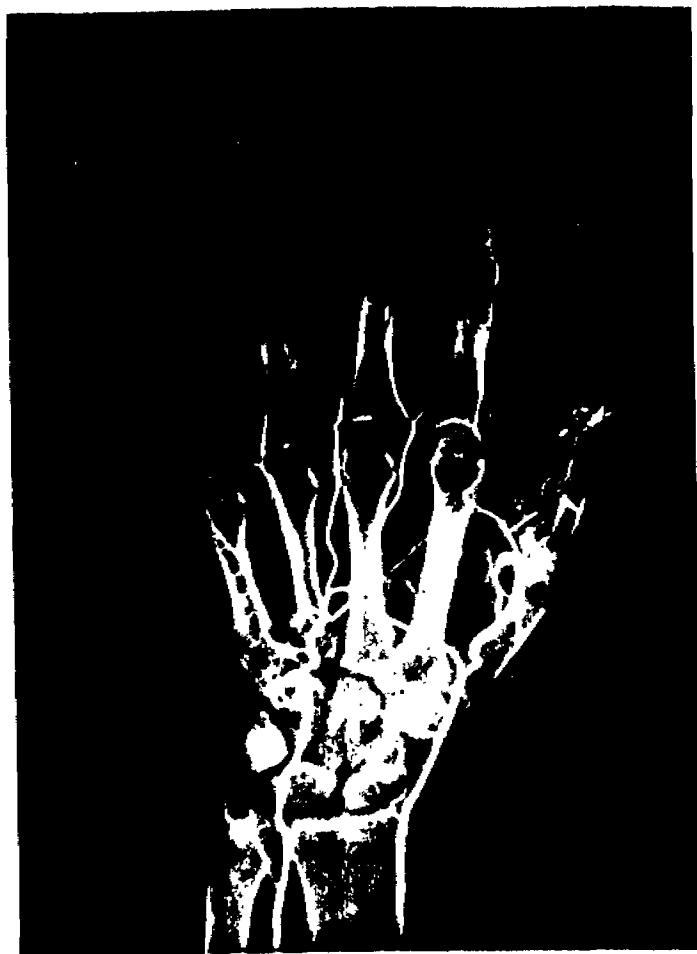


FIGURE 12.

TABLE 3
CORRELATION BETWEEN THROMBOCYTE COUNT AND PERIOD OF EXPOSURE

Thrombocyte Count	No. of Patients	Years of Exposure
More than 150,000	13	10.4
150,000-100,000	25	6.9
99,000-60,000	25	6.7
Less than 60,000	7	8.8

TABLE 4
DEVELOPMENT OF THE THROMBOCYTE COUNT AFTER WORKERS
HAD QUIT THEIR JOBS

Thrombocyte Count	No. of Patients	Improved	Deteriorated	No Change
150,000-100,000	12	3	8	1
99,000-60,000	13	3	9	1
Less than 60,000	4		3	1

such thrombocytopenia existed also in patients who did *not* suffer from splenomegaly. In view of the normal findings concerning bone marrow, which have been described before, and the determination of platelet functions, thrombocytopenia probably results in increased platelet destruction, in other sites and not in the spleen alone.

In only 6 out of 29 patients (TABLE 4) has an improvement of platelet count been observed 1 to 1½ years after they quit their jobs. There is a contrast between this finding and the fact that in the case of bone and skin changes restitution tendencies were proved to be more frequent.

REFERENCES

1. JÜHE, S. & G. VELTMAN. 1972. Zur Klinik der sog. Vinylchlorid-Krankheit (sklerodermieähnliche Veränderungen bei Arbeitern der PVC-herstellenden Industrie). I. Internationales Symposium der Wersärzte der chemischen Industrie 27.4.1972, Tagungsbericht, S. 267-276.
2. JÜHE, S. & C.-E. LANGE. 1972. Sklerodermieartige Hautveränderungen, Raynaud-Syndrom und Akro-osteolysen bei Arbeitern der PVC-herstellenden Industrie. Deut. Med. Wochschr. 97: 1922-1923.
3. STEIN, G., JÜHE, S., C.-E. LANGE & G. VELTMAN. 1973. Skelettveränderungen bei der sog. Vinylchlorid-Krankheit. Röntgenblätter 26: 350.
4. LANGE, C.-E., S. JÜHE, G. STEIN & G. VELTMAN. 1974. Die sog. Vinylchlorid-Krankheit—eine berufsbedingte Systemklerose. Intern. Arch. Arbeitsmed. 32: 1-32 (dort ausführliche weitere Literaturangaben).
5. JÜHE, S., C.-E. LANGE, G. STEIN & G. VELTMAN. 1974. Ueber die sog. Vinylchlorid-Krankheit (eine neue Berufskrankheit). Berufsdermatosen 22: 4-22.
6. LANGE, C.-E., S. JÜHE, H. J. MARSTELLER, R. MÜLLER & G. VELTMAN. 1973. Leberschäden im Rahmen der sog. Vinylchlorid-Krankheit. Verhandlungen der Deutschen Gesellschaft für Arbeitsmedizin. 13. Jahrestagung in München 17-19.5. 1973. A. W. Gentner Verlag. Stuttgart, Germany.

SL 041513