

Case 4

D W, aged 44 years, had been working at the factory for five years. The skeletal survey did not show acro-osteolysis or any other significant abnormality.

Discussion

These 4 cases show the wide radiological spectrum that may be encountered in men complaining of symptoms which could be related to their work in the polymerization of vinyl chloride. In Cases 3 and 4, no specific changes were encountered; in Case 2 only moderate changes were recorded whilst in Case 1, extensive bony changes were documented. Indeed, in Case 1, most regions of the body were involved and a review of the literature revealed that no previously reported case had such extensive bony changes. It has been suggested that personal idiosyncrasy may be an important factor in the wide variation of the radiological findings (Wilson *et al.* 1967).

The changes in the mandible in Case 1 have not been previously described in occupational acro-osteolysis but it is interesting to note that atrophy of the mandible in idiopathic and familial acro-osteolysis has been recorded by Greenberg & Street (1957), Papavasiliou *et al.* (1960), and Cheney (1965).

Ross (1970) stated that the bone changes regress after the sufferer is removed from the hazard but in our Case 1 the serial films of the hands, feet and pelvis indicated that the acro-osteolysis was extending. Fragmentation of the remaining tufts has been described as part of the healing stage by Wilson *et al.* (1967), but in our Case 1 it was only in the distal phalanx of the left big toe that there was any definite evidence on the 2-year film to indicate bony regeneration.

The stenoses and occlusions of the digital arteries and increased vascularity in the pulps of the fingers recorded on the arteriograms in the first case have also been reported by Lange *et al.* (1974). Narrowing and occlusions of the digital arteries are known to occur in Raynaud's phenomenon (Marshall *et al.* 1966). Certainly, the disability due to the Raynaud's phenomenon in our case seemed out of proportion to abnormalities in the vascular tree. Lange *et al.* (1974) suggested that the dense vascular rete of the terminal pulps of the fingers was due to stasis of contrast in the vessels secondary to the shortening of the phalanges. This may be partly the case but Laws *et al.* (1967) have observed hyperaemia of the pulps of the fingers in a case of clubbing due to bronchial carcinoma and a similar mechanism may apply in our case, as there is a strong clinical resemblance to clubbing.

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DISCUSSION

Dr L Magos said that Dr Preston's Case 1 might be idiopathic acro-osteolysis aggravated by exposure to vinyl chloride. In the two-year follow-up study Dr Preston had found improvement in the fingers, which were usually involved in occupational vinyl chloride acro-osteolysis, and deterioration in the pelvis.

Dr B J Preston replied that idiopathic acro-osteolysis was considered in the differential diagnosis of Case 1 but the distribution of the bony abnormalities other than those in the hands was different from those recorded in idiopathic acro-osteolysis.

Dr K Lloyd Jones added that Dr Preston's Case 1 also had severe involvement of the skin by the scleroderma-like condition seen in vinyl chloride workers together with evidence of other multisystem involvement. It was most unlikely that this combination in a vinyl chloride production worker (autoclave floor worker) would be due to idiopathic acro-osteolysis. It was not considered reasonable to submit this patient to biopsy of the defects in the distal phalanges. Biopsy of the lesion in the mandible had been unrewarding. He was employed as a production worker in a PVC plant and had never been exposed to vibration or the use of power tools.

Dr Anne E Walker
(Royal Hospital,
Chesterfield, Derbyshire)

Clinical Aspects of Vinyl Chloride Disease: Skin

Industrial acro-osteolysis, a triad of Raynaud's phenomenon, sclerodermatous skin change and lytic bone lesions, has been well documented as occurring in workers engaged in the poly-

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merization of vinyl chloride monomer (VCM) to polyvinyl chloride (PVC). Medical surveys of large numbers of employees have shown an incidence of approximately 3% (Wilson *et al.* 1967, Dinman *et al.* 1971). Both these studies also suggested that the disorder was largely confined to reactor cleaners.

In 1974 Lange *et al.* described a more generalized disorder affecting men engaged in the manufacture of PVC. They observed splenomegaly, thrombocytopenia, liver damage and impaired respiratory function, and these changes occurred both in the presence and absence of clinical and radiological evidence of acro-osteolysis.

Clinical Study

In February 1974 I saw one man with severe Raynaud's phenomenon, minimal bone changes in the fingers but no evidence of scleroderma. He was employed as a reactor operator at a local firm which manufactures PVC. Between February 1974 and February 1975, 36 of the men employed at this plant were referred with symptoms thought to be due to exposure to VCM.

The study covers 37 men aged between 26 and 59 years (average 40 years 2 months). Length of employment at the plant ranged from 9 months to 51 years (average 2 years 8 months). Thirty workers had at some time been reactor operators, 4 were maintenance men, 2 worked as 'baggers' and 1 was a warehouseman.

The presenting symptoms are shown in Table 1. The commonest complaint was of excessive fatigue: men claimed to be excessively fatigued after minimal exertion and also reported somnolence. Coldness of the hands was also a frequent complaint.

Obviously these subjective symptoms were difficult to evaluate or measure. However, one feature was noteworthy: 36 of the 37 stated that on at least one occasion they had felt overcome by the vinyl chloride fumes, describing themselves variously as 'unsteady', 'slightly drunk' and

'rubbery-legged', and this suggested that the men had been intermittently exposed to very high levels of VCM, which in experimental studies produces anaesthesia. These symptoms were most frequently experienced when men were hosing down the reactors during emptying, but also by men when inside cleaning the empty reactor, and by maintenance men when unblocking pipes carrying VCM.

None of the 37 men had evidence of sclerodermatous skin change. One man previously employed at the plant had extensive sclerodermatous skin change affecting the hands, forearms, face, trunk, thighs and dorsum of the feet; additionally he had extensive lytic lesions of the bones, phalanges, feet, pelvis and jaw (K Lloyd-Jones, personal communication). In 5 men there was clinical evidence of Raynaud's phenomenon; in 2 it was a marked feature, with rapidly occurring colour changes from blue black to blanched white to a flushed pink. Individual fingers on the same hand might show a different colour change at any one time; on one occasion I observed a harlequin effect: the index finger was blanched white on the radial side and blue black on the ulnar side. Eight other men described symptoms of Raynaud's phenomenon but at examination only had rather cold hands. Coldness of the feet was a common complaint, but difficult to evaluate clinically.

During the last year 4 men have shown some thickening of the skin with limitation of extension of the fingers and mild 'clawing' of the hands. These changes become more marked when the hands are cold.

Of the 37, 4 developed a curious swelling of the face, largely periorbital and tending to improve in warmer conditions; the swelling was firm, and suggestive of sclerodema rather than scleroderma.

Skin biopsies were obtained from the dorsum of the hand in 15 men. The epidermis and adnexal structures showed no abnormality. In the dermis there was some destruction of elastic tissue, but it was probably a normal age change. In one man with severe Raynaud's phenomenon the dermal arteries showed some medial thickening.

Arteriography of the brachial arteries was carried out on 4 men. In the one man with severe sclerodermatous skin change the digital vessels in all the fingers were almost totally occluded. In the other 3 men there was patchy occlusion of the digital vessels, mainly in the ring and little fingers.

Table 1

Presenting symptoms in 37 men

Symptom	No. of cases
Cold hands	20
Paraesthesia	16
Impaired grip power	15
Cold feet	16
Aches in bones	20
Aches in muscles	15
Dyspnoea	17
Excessive fatigue	22
Loss of libido	13

Blood flow measurements assessing total finger blood flow and capillary flow were performed on a small number of men. In 5 men capillary flow fell abnormally on cooling and was slower in returning to normal on rewarming. In 3 men total finger blood flow was also abnormally reduced on cooling and slower to return to normal.

Immunological studies have shown a high level of cryoprecipitate in the symptomatically affected men (A. Milford Ward).

Discussion

In the survey of 37 men, of whom at least 36 appeared to have been exposed to high levels of vinyl chloride monomer on at least one occasion, sclerodermatous skin change was not observed. However, 5 had severe Raynaud's phenomenon and at least 5 others had abnormally cold hands which interfered with their normal dexterity. These circulatory changes are only a part of a generalized disorder which may result in dyspnoea, cramp-like pains in the limbs, paraesthesia, excessive fatigue and, in some cases, impaired liver function. The symptoms may be severe enough to limit normal activity and may occur without changes in the hands.

The relative sparsity of clinical change in the skin or evidence of pathology on biopsy contrasts with the marked sclerodermatous and plaque-like changes described by others (Cordier *et al.* 1966, Harris & Adams 1967, Wilson *et al.* 1967). Perhaps the early recognition and removal from exposure prevented more severe skin change in the men under observation. Most of the above authors observed improvement in the sclerodermatous skin change on preventing further exposure. However, in one case described by Harris the skin change appeared to resolve spontaneously whilst the man continued working.

In my series there has been little improvement in the vascular signs during the period of observation, and this is in accord with the findings of others (Adams 1974, personal communication and M. N. Johnson 1975, personal communication). However, Suciu describes the disappearance of Raynaud's phenomenon within one year (Suciu *et al.* 1963). In two instances cervical sympathectomy is recorded as producing clinical improvement (Takouchi & Mabuchi 1973, Markowitz *et al.* 1972).

At the present time it is not known whether the peripheral vascular disorder is directly related to the presence of circulating immune complexes or to some other alteration in the sensitivity of the vessels to exposure to cold.

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DISCUSSION

Dr Leo Djerassi (*Department of Occupational Medicine, Haifa, Israel*) said that in one patient in his series the presenting syndrome of vinyl chloride disease was a pale moonlike face. This particular type of sclerodema (not scleroderma) had already persisted for five years after exposure had ceased.

In one case of scleroderma-like syndrome a skin biopsy showed no change in elastic or fibrous tissue but several areas of perivascular infiltration, small round nuclear cells, mostly lymphocytes and larger mononuclear elements.

In one case of Raynaud-like phenomenon which started about eight months after initial exposure, the manifestations usually appeared two or three hours after work began, and the full-blown phenomenon could be observed on the shop floor. This same patient left the factory because of loss of libido, and Dr Djerassi wondered whether this was an immediate transient complaint due to the narcotic effect of vinyl chloride monomer, or a prolonged disturbance connected with the vinyl chloride disease as stated by Dr Anne Walker.

Dr Anne Walker, in reply, said that the sclerodema-like change observed in 4 of the men varied considerably from day to day but in two men had persisted for at least eighteen months after the last exposure.

In 15 biopsies from 13 patients an excess of inflammatory cells in a perivascular distribution were present in 4 of the specimens. The cells were largely lymphocytes.

Loss of libido was the presenting complaint in one patient and had persisted since the man left the firm approximately three years ago. In 3 of the workers complaining of impotence, urinary excretion of androsterone and dihydroepiandrosterone were very low. These measurements were made approximately twelve months after the last exposure to vinyl chloride.

Dr Marcus M. Key (*University of Texas School of Public Health, Houston, Texas*) asked if baggers and warehousemen had previously worked as reactor cleaners.

Dr Anne Walker replied that they had not. Usually men started as baggers and later became reactor operatives and cleaners. The one warehouseman had

never been in a reactor. One of the baggers had spent an initial training period as a reactor cleaner but had felt nauseated whilst in the reactor. After the first two weeks he had worked entirely in the dry building for four years. The other bagger was an epileptic and had never been in a reactor.

Dr Premysl V Pelnar (*Montreal, Canada*) asked what blood flow measurements were done?

Dr Anne Walker said that blood flow measurements were made on 10 men. The subjects were kept in an ambient temperature of 27°C for one hour, then the room was cooled to 10°C for the next hour and finally the room temperature was raised to 27°C for the final hour.

During the three hours total finger flow in the index finger was measured by means of a plethysmograph and capillary flow in the middle finger by electrical impedance. Additionally, the skin temperature on the back of the hand was measured.

Dr A Milford Ward

(*Department of Immunology, Hullamshire Hospital Medical School, Sheffield, S10 2RX*)

Evidence of an Immune Complex Disorder in Vinyl Chloride Workers

The occurrence of Raynaud's phenomenon and loss of bone density in association with dermal thickening which constitutes the syndrome of acro-osteolysis (AOL) has been recognized in the vinyl chloride industry since the mid 1950s, but the overall frequency of the syndrome has been low and no series have been subjected to thorough immunological investigation. Recent studies have indicated that the disease process is not confined to the skin and skeletal tissues, but is a multi-system one with involvement of many organs and tissues.

Immunological and immunochemical investigation of 58 workers from a single factory has revealed evidence of a chronic soluble complex disorder in 21 individuals. The extent and severity of the immunological abnormalities parallels the clinical features to a large extent, but some individuals show laboratory evidence of an active disease process at a stage when the clinical features are minimal or absent. Circulating immune complexes were demonstrated in 9 out of 10 individuals who were severely affected clinically; in 7 out of 15 individuals who were symptomatic to a degree that they were incapable of active employment; and in 5 out of 28 individuals who were symptomatic but able to work. Immune complexes were not detected in 5

individuals from the factory who were completely asymptomatic.

The major features of the disorder include hyperimmunoglobulinemia, cryoglobulinemia and cryofibrinogenemia, and *in vivo* complement activation via the classic pathway with C4 and C3 conversion. There is, in addition, evidence for a reduced T cell population, with low spontaneous sheep cell rosette counts, and an increased B-cell population, as evidenced by an absolute increase in lymphocytes showing membrane bound immunoglobulins. The total lymphocyte counts are usually normal or slightly increased. Some patients show non-organ-specific antitissue antibodies of low titre but rheumatoid factor is universally negative.

Immunofluorescent examination of biopsy material from skin (3 patients), muscle (1 patient) and lung (1 patient) has shown the presence of circulating immune complexes, with deposition on vascular endothelium and occlusion of small vessels. In those vessels which show subintimal proliferation and luminal occlusion, immunoglobulin, complement and fibrinogen are present in the subintimal regions of the vessel wall.

Experimental evidence on the metabolism of vinyl chloride suggests that at least part may be taken up by the liver and become incorporated into amino acid synthesis. The incorporation of the chloride radical into protein synthesis could result in a structurally abnormal protein which would react as antigenically 'foreign' material.

The association of these experimental data with the observed immunological profile allows the construction of a theoretical model of the disease process. The initiating sequence is at present speculative and remains to be proven by further study, but the later sequence of events can be adequately explained by the immunological abnormalities. Structurally abnormal or antigenically 'foreign' protein escapes tolerance and incites an immune response with B-cell proliferation and hyperimmunoglobulinemia. The immune complex formed by interaction of the antigen and antibody is cryoprecipitable and will activate the complement sequence. The cryoprecipitate and the reactions secondary to complement activation will produce vascular occlusion and fibrinogen/fibrin conversion and polymerization.

The frequency with which abnormalities have been detected in this series, especially in that group in whom there were no overt clinical signs, suggests that the disease process may be more common than generally supposed. The theoretic-

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R. N. Wheeler, Jr.

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