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VCM - VINATEX

We have come across the attached article on studies of Vinatex workers. This encapsulates much of what we have reported to you already on Milford Ward's work and views on immunological changes. On p206 it introduces the finding of reduced lung transfer factors which needs much more careful examination. The article came from a book entitled "Induced Disease: Drug, Irradiation, Occupation" published this year by Grune & Stratton and edited by L Prege with ISBN number 0-8089-1225-9.

J Stafford

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11 Vinyl Chloride Monomer-Induced Disease: Clinical, Radiological and Immunological Aspects

Ronald G. Grainger
Anne E. Walker
A. Milford Ward*

The story of vinyl chloride induced disease has been described as a watershed in the history of occupational medicine.[1] The understanding of this disease has precipitated new attitudes toward occupational hazards and has made obligatory an immediate response to the first evidence of damage due to industrial processes.

Within the last decade, the complicated multi-system symptomatology, the signs, and the radiological and pathological features have been defined. The toxic chemical, vinyl chloride monomer (VCM), and the specific industrial processes with which it is associated have been identified. The pathogenesis of vinyl chloride disease (VCD) has been intensively studied and there is now strong evidence that immunological processes are involved. Since 1974, the levels of permissible exposure to VCM have been lowered substantially by industrial legislation; there is a good possibility that current exposure levels will not be high enough to induce disease in the future.

Our own involvement with vinyl chloride came about when workers at a local polyvinyl chloride (PVC) manufacturing plant developed symptoms of the disease. We present here our clinical, radiological, and immunological studies of workers from this factory.

MANUFACTURE OF POLYVINYL CHLORIDE

The process of converting vinyl chloride monomer (VCM) to polyvinyl chloride (PVC) by polymerization was discovered in Germany

* The authors wish to thank Mrs V. Morris for her assistance in preparing the manuscript.

in the mid 1930s. Production is now world-wide, resulting in an annual output of approximately eight million tons. The uses of PVC are many and varied as it is used extensively both in the home and in industry.

PVC is manufactured by the polymerization of VCM; 500 to 1,500 molecules of the monomer produce one molecule of PVC, depending on particle size.[2] VCM (monochloro ethylene, or C_2H_3Cl) is a liquid gas at normal temperature and pressure. It has a pleasant odor, which can be detected at a concentration of 400 parts per million.

The polymerization process takes place in a large reactor or autoclave approximately 6 ft. 6 in. in diameter and 11 ft. 3 in. high with a capacity of approximately 290 cu. ft. (Fig. 11-1). Liquid VCM is dispersed in water with a suspending agent and a catalyst. During polymerization, the mixture is constantly agitated by a central paddle, and carefully controlled pressure is applied within the reactor. As the process is exothermic, the autoclave is continuously water-cooled. Polymerization takes approximately eight hours, and at the end of this time, 92–95 percent of the monomer has been converted to polymer. Excess monomer is then drawn off and the thick slurry of PVC in water is run out of the bottom of the reactor, centrifuged, dried, bagged, and sent for processing. The PVC slurry contains a considerable quantity of VCM: up to 500 parts per million.

Despite constant stirring during polymerization, some of the thick slurry of PVC settles on the inner lining of the autoclave and on the central paddle. To ensure the purity of the next batch of PVC, this residual scale has to be removed before the vessel is recharged. Descaling used to be performed manually; an operator would climb into the autoclave

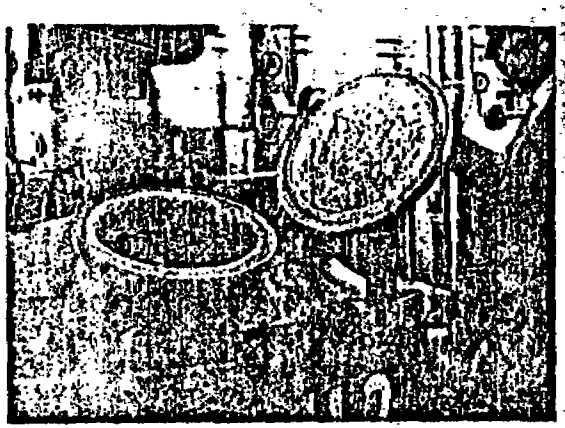

Fig. 11-1. reactor or autoclave is a cylinder with a domed top and bottom. The illustration shows a worker opening the upper hatch door through which the cleaners climbed to descale the inner walls. The total height of the reactor is 11'3"

through the hatch in the dome (Fig. 11-1) and mechanically descale the vessel wall with hammer and chisel.

The health hazards of PVC manufacture appear to be entirely related to exposure to VCM. VCM gas is readily absorbed by the lungs. Workmen have most often been exposed to VCM when the reactors are first opened after polymerization, during manual descaling of the reactor, and during maintenance work on pipes carrying the liquid VCM. However, the drying of the PVC slurry and bagging of the final PVC powder are not without hazard.

The PVC slurry contains approximately 500 parts per million of VCM, whereas the dry powder contains less than five parts per million. Microscopic examination reveals that PVC particles have a markedly pitted surface in which unpolymerized VCM may be retained. The smallest particles of PVC (0.5 μm in diameter) are easily inhaled and may carry unpolymerized VCM into the lungs.

CLINICAL EFFECTS OF EXPOSURE TO VINYL CHLORIDE MONOMER

Acute

Exposure to high concentrations of VCM gives rise to temporary narcosis, dizziness, weakness of the legs, impaired coordination, and sudden loss of consciousness. (At one time, VCM was considered for use as an anesthetic; it is chemically related to chloroform.) Only in the last four years have environmental levels of VCM been adequately and accurately monitored in PVC manufacturing plants. Current levels are probably as low as five parts per million, but it is possible that twenty years ago, levels were as high as 1,000 parts per million, and in 1973 around 500 parts per million. VCM has a pleasant smell and an agreeable taste. The initial symptoms of narcosis are not unpleasant, and it is probable that some workers have deliberately "sniffed" the VCM.

Chronic Exposure

In 1966,[3] acro-osteolysis (AOL), and in 1973 angiosarcoma of the liver were identified as complications of chronic exposure to VCM (Chapter 15). Suciu[4] described Raynaud's phenomenon, sclerodermatous skin changes, and liver dysfunction in PVC production workers. Experiments with rats exposed to high levels of VCM indicated a high incidence of liver, bone, and ceruminous gland tumors. An American epidemiological study of PVC production workers revealed an association between angiosarcoma of the liver and prolonged exposure to VCM.

Lange[5] introduced the name vinyl chloride-induced [illegible]ase for the systemic disorder that included dysfunction of the liver and lungs, [illegible] osteolysis, sclerodermatous skin changes and throm-

bocytopenia in PVC production workers. Specifically, the disorder was characterized by the following.

LIVER

Angiosarcoma of the liver. In 1974, the B. F. Goodrich PVC production plant in Louisville, Kentucky, voluntarily and admirably revealed that six of its employees who had been exposed to VCM had recently died of angiosarcoma of the liver (ASL).[30] All six employees had worked as reactor cleaners and had been exposed to high concentrations of VCM. Confirmatory experimental evidence that VCM could induce ASL in animals was soon produced.[31]

ASL is a rare histological variety of malignant liver tumor and is variously described as Kupffer cell sarcoma, hemangio-endothelioma, and hemangioblastoma. The essential histological feature is that the liver vascular sinusoids are lined by proliferating tumor cells of endothelial or Kupffer cell origin. There is a dense intra-sinusoidal network of reticulin fibers.

ASL is almost always the result of exposure to toxic substances such as thorium dioxide (after angiography and other radiodiagnostic procedures), prolonged arsenic intoxication (therapeutic, vineyard workers) as well as vinyl chloride monomer (VCM reactor cleaners).

Within months of the initial Goodrich announcement, several other patients with VCM-induced ASL were reported in the United States, the United Kingdom, Sweden and Germany. By 1976, as many as 47 cases of ASL secondary to VCM exposure had been reported; two of these patients were from United Kingdom.[32] Almost all of these patients had worked as reactor cleaners in PVC production plants and had therefore been exposed to the high concentrations of VCM which were prevalent before the danger was appreciated. It is calculated that the mean period from initial exposure to VCM to the development of ASL is about 17 years.

Clinically, the patients present with features of abdominal tumor, liver failure, ascites, and hemorrhage. Radiology reveals a large liver, often with splenomegaly and ascites. Angiography demonstrates stretching of the intrahepatic arteries around tumor masses, abnormal tortuous distorted arteries with rapid filling of hepatic veins (Fig. 11.11). Ultrasound and isotope studies provide confirmatory evidence of multiple intrahepatic masses.

The diagnosis of ASL is made by histological examination on tissue, preferably obtained by laparotomy rather than percutaneous needle biopsy, which may cause severe hemorrhage. The outcome is inevitable fatal.

In VCM-induced ASL there is often a diffuse fibrosis of the portal, perivascular and periductal tracts, of a type rather different to the much

Fig. 11-2. Selective coeliac arteriogram showing stretching of intrahepatic arteries by masses, some of which are hypovascular and others which are hypervascular. Abnormal tumor vessels with premature filling of intrahepatic veins (arrow). This angiosarcoma is not the result of vinyl chloride exposure but is due to an injection of thorotrast for venography twenty years earlier.

may reveal evidence of this with a distorted liver pattern, an enlarged portal vein and splenomegaly.[33]

It is surprising that as far as is known, no person who has developed ASL has also had skin or bone changes of the type described above as being caused by VCM exposure. It seems that two different mechanisms are involved in VCM-induced liver tumor and in the cutaneous and acroosteolytic manifestations.

BONES

Acro-osteolysis (AOL) due to exposure to VCM was first described by Cordier[4] in 1966. Industrial AOL has a triad of signs—lytic bone changes, Raynaud's phenomenon and sclerodermatous skin change. The incidence in PVC production workers was approximately 3 percent, and was almost exclusively confined to men who had worked as manual cleaners of autoclaves or reactors.[3,7]

SKIN CHANGES

Sclerodermatous skin changes affect mainly the hands, and vary from

to complete tethering of the skin of both hands, thereby interfering with manual dexterity. In severe cases with AOL, the fingers are clubbed and the nails become shortened and curved into a typical watch-glass appearance (Fig. 11-3). In one severely affected man, the skin changes involved the hands, arms, face, trunk and proximal thighs. Histologically, the skin changes differ from idiopathic scleroderma only in that the skin appendages are preserved in the VCM-induced disorder. Direct microscopy of the nail folds shows capillary abnormalities similar to those observed in patients with idiopathic scleroderma.[11] Blood flow studies confirm that both capillary and finger blood flow are impaired. Sympathectomy has proved helpful in relieving the Raynaud's phenomenon in some patients.[7,10]

LUNG FUNCTION

Dyspnea is a common symptom in PVC production workers. Miller[8] reported that 80 percent of PVC production workers had restrictive airways disease after 20 years of exposure. Reduction in lung volume and vital capacity have also been reported. Chest radiographs usually show little abnormality, but reticular and nodular opacities have been reported, and will be further discussed below. Marked defects in lung perfusion were found in production workers at the local factory examined in our study.[9] In one case, histology of the lung revealed focal thickening of the alveolar wall, and macrophages in the alveolar spaces. The affected individual had worked on the production of a particularly fine PVC powder with a particle size of 0.5 μm. One other case of PVC-induced pneumoconiosis has been described.

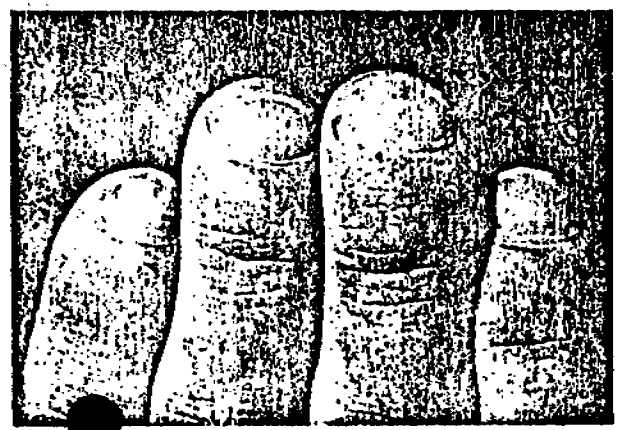

Fig. 11-3. Fingers of reactor cleaner with vinyl chloride disease. Note short terminal segments of fingers and marked [illegible] to produce clubbing of the

Table 11-1
Symptoms in 37 PVC Production Workers—British Study by Present Authors (A.E.W.)

Symptoms	Number Affected	Percentage
1. Excessive fatigue, weariness	22	59.4
2. Coldness of hands	20	54.0
3. Aches in bones or joints	20	54.0
4. Tingling or discomfort of feet	17	45.9
5. Dyspnoea	17	45.9
6. Tingling or discomfort of hands	16	43.2
7. Coldness of feet	16	43.2
8. Muscles aches or pains in limbs	15	40.5
9. Impaired power of hand-grip	15	40.5
10. Loss of libido	13	35.1
11. Pain behind the eyes	3	8.1

THROMBOCYTOPENIA

This is a well-documented finding in VCD. Veitman[12] found that 80 percent of VCD patients had platelet counts between 17,000 × 10^6 and 14,300 × 10^6 per liter, and Wegman[12] states that 35 percent of PVC workers had abnormal platelet counts. Bone marrow studies reveal no abnormality.

ENDOCRINE ABNORMALITIES

Hypothyroidism has been reported in VCM-exposed workers. Suciu[4] found six cases in 168 workers. Sexual impotence is a common complaint in VCM-exposed workers. Low levels of 17 ketosteroids have been reported.[4,12]

MISCELLANEOUS SYMPTOMS

Although direct symptomatic enquiries may be suspected of maximizing symptoms, exposed workers continue to suffer many unexplained and persistent symptoms. These are well documented and it is interesting to compare the presenting symptoms in 37 British workers seen personally in 1974 (Table 11-1) with those from a German study published in 1975 (Table 11-2).[12]

RADIOLOGICAL ASPECTS

Acro-osteolysis induced by VCM is associated with radiological changes which are fascinating, unexpected, probably uni[illegible] and pathognomonic. AOL consists of localized zones of bone necr[illegible] and absorption in the hands (and feet), associated with marked coldness and ischaemia of the fingers, which is induced by exposure to cold (Raynaud's

Table 11-2
Initial Symptoms in 70 Patients from PVC Factory—German Study[12]

Symptoms	Number of Patients	Percentage
1. Upper abdominal complaints	42	60.0
2. Tiredness	27	38.6
3. Frequent dizziness	26	37.1
4. Paraesthesiae (numbness and tingling) in fingers and/or toes	22	31.4
5. Increased perspiration	19	27.1
6. Sensation of cold in individual fingers or hands	18	25.7
7. Arthralgia	17	24.3
8. Sexual potency difficulties	13	18.6
9. Pain in the head	9	12.9
10. Pain in the calves	9	12.9

in several different countries in the 1960s.[13] Presumably earlier cases had occurred, but were not at the time recognized as being related to VCM or PVC.

The bone absorption is always remarkably well defined, often consisting of multiple, clear-cut, deep erosions, as though a bit of bone had been removed by a bone punch. The erosions usually are not outlined by compact bone, but a thin white margin may be seen (Fig. 11-9). The erosions always involve bone surfaces—usually bony prominences, but occasionally articular surfaces. Fragments of bone may be detached, particularly at the tufts of the terminal phalanges, and these detached fragments may undergo further fragmentation and absorption. There is now firm evidence that the healing of bone lesions by new bone formation may occur in the months or years after exposure to VCM has been terminated (Fig. 11-5).

There is no periosteal reaction, nor do any localized changes in the overlying skin and subcutaneous tissues appear. The fingers may be clubbed and the nails shortened when the terminal phalanx is affected (Fig. 11-3). The bone lesions are not usually tender or painful.

The distribution of the bone lesions is a highly characteristic feature. The extremities, especially the hands and fingers, are most severely involved (hence the name acro-osteolysis). The tufts of the terminal phalanges of the fingers are the most severely affected bone areas. The VCM-induced bone changes of AOL tend to show a remarkable right–left symmetry (Figs. 11-4 through 11-9).

Articular bone erosions occur most frequently in the interphalangeal and metacarpo-phalangeal joints of the fingers (and toes), but other joints, especially those of the sacroiliac, may also be affected by these character-

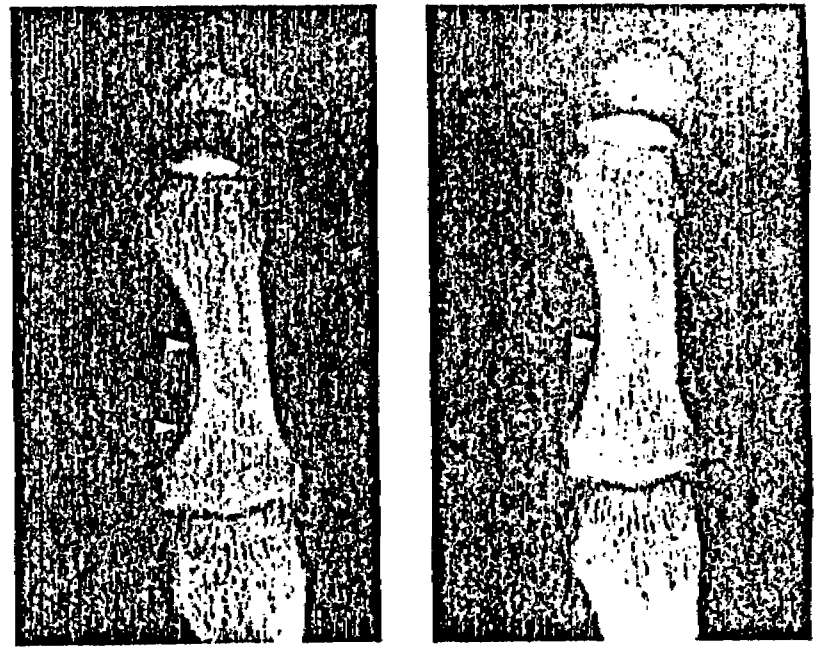

Fig. 11-4. Above left: A.D., 20/11/74. Left middle finger showing transverse band of bone absorption across the mid shaft of the terminal phalanx. Some fragmentation at the base of the separated tuft. Marked shortening of the terminal phalanx with clubbing of the soft tissues. Note periosteal cortical absorption on the radial side of middle phalanx (arrow). Erosions at the corner of this bone. Above right: A.D., 11/7/77. Left middle finger showing considerable healing. The separated distal fragment has consolidated and now has a triangular proximal end approaching the base of the phalanx. The terminal phalanx remains very short. Note healing of the previously eroded cortex on radial side of the middle phalanx (arrow). Cortication and healing of the previous erosions at the corners of this bone.

THE PHALANGES

It is probable that Raynaud's ischemic skin changes always precede radiological evidence of bone lesions in the fingers.

Radiological changes are always more marked and frequent in the distal parts of the terminal phalanges of the fingers. The earliest changes are small, angular, marginal defects in the terminal phalangeal tufts; these lesions may be simulated by congenital variations in ossification and by previous trauma. There may be small detached fragments of bone related to the defects; these fragments may later be absorbed. As the tuft changes are very liable to observer error, they are not to be relied on unless the sign is unequivocal and there is no history of trauma.

Transverse defects in the terminal phalanges are due to circumferen-

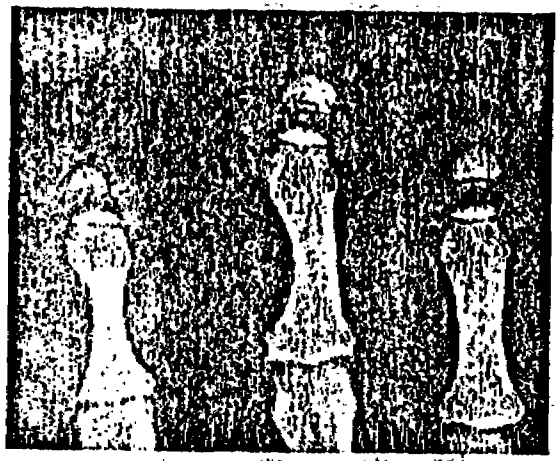

Fig. 11-5A. A.D., 20/11/74. Left index, middle and ring fingers showing identical changes with absorption of the middle third of each of the terminal phalanges. (The right fingers showed identical changes.)

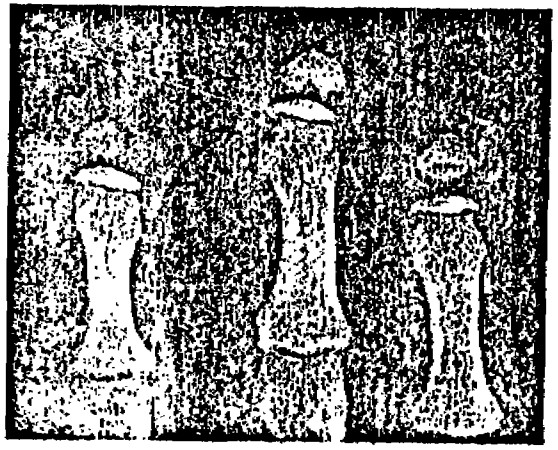

Fig. 11-5B. A.D., 20/9/76. Same fingers showing considerable he[illegible] with the proximal surface of the detached tuft becomin[illegible]onsolidated and growing towards the bases. (The right fingers showed identical healing changes.)

Fig. 11-6. A.D., 20/11/74. Left elbow showing erosion of the cortex of the olecranon process (arrow). (A similar lesion affected the right olecranon.)

so, detach the phalanx's distal portion, which may fragment and/or undergo sclerosis (Figs. 11-4 and 5). These transverse defects were seen by Dinman et al.[14] in 1.2 percent of 5,011 PVC workers (Table 11-3).

The loss of a substantial portion of the mid-shaft of the terminal phalanx results in approximation of the detached distal fragment to the base, thereby shortening the distal segment of the finger (Figs. 11-4 and 5) and accentuating the finger clubbing, which is often a prominent feature (Fig. 11-3).

The combined effect of tuft marginal erosions and transverse defects across the shaft may result in complete absorption of the distal portion of the terminal phalanx; this was found in 0.18 percent of Dinman's series (Table 11-3).

Table 11-3
*Prevalence of Radiological Changes in Terminal Phalanges**

Characteristic	Controls 2,407 (percent)	PVC workers 5,011 (percent)
Marginal defects	2.04	7.11
Transverse defects	0.25	1.22
Total resorption of distal portion phalanx	0.08	0.18
Shortening	0.46	1.26
Clubbing	0.08	[illegible]0

* From Dinman et al. 1971.[14]

Fig. 11-7. A.D., 20/11/74. Multiple bone erosions of the left ischial tuberosity. All of these lesions involve cortical bone and the bone surface. (Similar lesions affected the right ischium.)

The changes of AOL are much less marked in the middle and proximal phalanges. The subperiosteal compact cortical bone along the shaft may be absorbed, exposing the underlying trabeculae (Fig. 11-4). This change is more marked on the radial aspect of the intermediate phalanges, producing an appearance similar to the subperiosteal bone resorption of hyperparathyroidism, but the delicate, lace-like trabeculation seen in that disease has not been observed in AOL.

The fingers are always more severely affected than the toes with regard to both Raynaud ischemic skin changes and bone-destructive lesions.

Following cessation of exposure to VCM, the bone defects may begin to heal.[15] Small detached fragments become incorporated into larger fragments (Figs. 11-4 and 5); the detached end of the terminal phalanx grows toward its base, often with an arrowhead front (Fig. 11-5) until contact is made. The two ends of the bone may then completely fuse, so reconstructing a "new" terminal phalanx. The contours of the new structure are, however, quite different from those of the original phalanx. The new structure is shorter, broader, and stumpier, resulting in a permanently short terminal segment of the finger (with an excess of pulp and soft tissue) and accentuating the finger clubbing (Figs. 11-3 through 11-5).

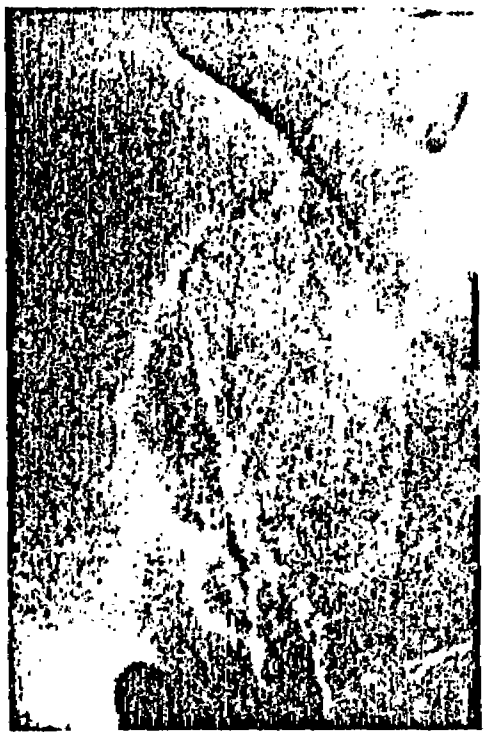

Fig. 11-8. A.D., 20/11/74. Right sacroiliac joint showing deep erosions into the iliac bone. (Similar lesions were present in the left sacro-iliac joint.)

DIFFERENTIAL DIAGNOSIS OF THE BONE CHANGES IN THE FINGERS

Scleroderma, whose radiological appearance is most similar to that of VCM-induced disease, is more common in women. Its skin changes differ from those of VCM disease in that ulceration of the tips of the fingers, loss of appendages and soft tissue calcification frequently occur. Esophageal and bowel involvement, with characteristic radiological appearances, are seen in idiopathic scleroderma but have not been reported in the industrially induced disorder.

Hyperparathyroidism may cause radiological phalangeal changes

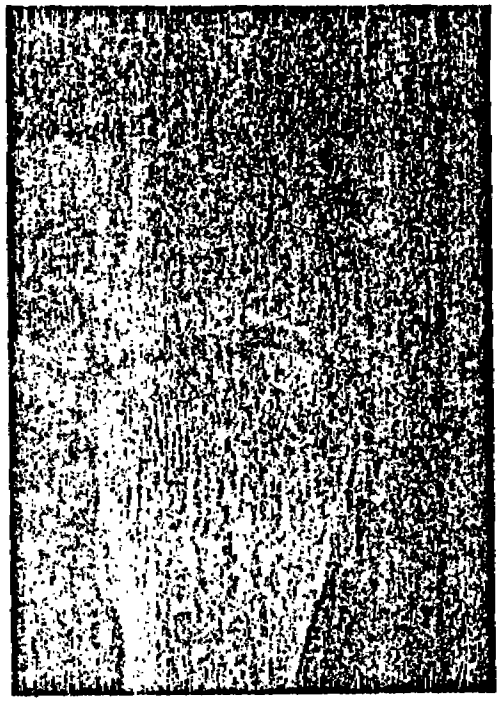

Fig. 11-9. A.D., 20/11/74. Deep erosion of central portion of articular surface of the head of the first left metatarsal. (The head of the first right metatarsal had a similar but smaller articular erosion.)

very similar to those caused by VCD, but the large osteoclastoma lesions, vascular calcifications and biochemical changes that occur in hyperparathyroidism are absent in VCD.

Ischemic atrophy of the phalanges as seen in diabetes, frost-bite, and ergotism may closely simulate VCM-induced changes; the history and clinical features are decisive.

Neuropathic lesions caused by syringomyelia, tabes (usually toes), leprosy, and congenital insensitivity to pain may resemble VCM-induced changes; furthermore, peripheral nerve lesions may produce similar erosive and destructive changes in the extremities. But the associated clinical features and the history will decide.

Rare conditions such as familial acro-osteolysis[16] (sometimes associated with osteo-sclerosis of the Albers-Schonberg type) and idiopathic acro-osteolysis may produce changes in the phalanges very similar to those of VCM-induced AOL; however, there may be a family history, whereas there is no history of VCM exposure in the other condi-

Severe psoriatic arthropathy and sarcoidosis may produce bone lesions having a slight resemblance to AOL, but the clinical features are quite different.

It cannot be too strongly emphasized that exposure to VCM is the key factor in confirming a diagnosis of VCD. Almost every patient diagnosed to have AOL due to VCM exposure has worked as a reactor or autoclave cleaner; it is the manual scraping and cleaning of the reactor's inner walls that subjects the workers to levels of exposure sufficient to induce bone necrosis.

OTHER BONE LESIONS

Phalangeal lesions have been emphasized here because of their invariable predominance, but bone lesions may occur in other locations. They are always present on corticated bone surfaces—either articular or nonarticular—and appear as punched-out, clear-cut, small areas of bone destruction, sometimes bordered by a thin white margin. The lesions occur predominantly on bony prominences or pressure points, such as the olecranon process (Fig. 11-6), os-calcis ischial tuberosities (Fig. 11-7), or the angle of the mandible. Neither periosteal reactions nor overlying local skin changes (other than the scleroderma of VCD) are present, and the lesions are painless, requiring a skeletal radiological survey for their detection and enumeration. The bone erosions have a very strong predilection to be symmetrical both in site and in size on the two sides of the body (Figs. 11-4 through 11-9).

One of our own patients[17] was a 35-year-old male who had worked in PVC production (including reactor cleaning) for five-and-a-half years. He continued cleaning and scraping reactors for several months after AOL symptoms had developed. He appears to have the most severe and extensive bone and skin changes ever recorded in AOL due to VCD, with severe destructive changes in the phalanges (Figs. 11-4 and 11-5), ulnar styloids, olecranon processes (Fig. 11-6), medial and lateral humeral epicondyles, outer ends of the clavicles, upper ends of the humeri, halluces, cuneiforms, malleoli, os calces, lower poles of the patellae, greater trochanters, ischial tuberosities (Fig. 11-7), sacroiliac joints (Fig. 11-8),[7] and angles and vertical rami of the mandibles. Most of the radiographs in this chapter are of this patient. It should be added that considerable healing of the phalangeal lesions occurred a few years after exposure to VCM was terminated (Figs. 11-4 and 5).

ARTICULAR LESIONS

The sacroiliac joints appear to be particularly prone to the bone changes of VCD. Dodson et al.[18] reported four sacroiliac cases; several

others have also been recorded. The lesions are the usual clean-cut erosions, sometimes corticated, usually multiple, extending deeply from the articular surface into the adjacent bone, particularly of the ilium, but also of the sacrum (Fig. 11-8). The appearances are quite different from those of ankylosing spondylitis in which the erosive changes are much less well defined, shallower, and accompanied by changes in the surrounding bone; ankylosing spondylitis eventually heals with bone ankylosis. It will be interesting to follow up patients with VCD changes in the sacroiliac joints in order to determine the end stage.

Articular erosions may also occur in several other joints, particularly those of the hands, arms, feet and legs (Fig. 11-9). The bone lesions consist of well-defined articular erosions; there is no surrounding osteoporosis, no joint effusion and no para-articular swelling (Fig. 11-9).

VASCULAR CHANGES IN THE HAND

Four of our more severely affected VCD patients had retrograde radial arterial catheterization and hand arteriography (RGG). Each showed occlusion of some of the digital arteries (Figs. 11-10 and 11); the occluded segments were both long and short.

Digital arterial occlusions were by no means invariable in fingers severely affected by Raynaud's phenomenon or AOL. There was an increase in the number of small vessels in the vascular tufts of the pulps at the fingertips. The cause of this change is not known; while it could represent an attempt to produce collateral circulation, it may alternatively result from stasis of blood flow in the fingertips—an effect of shortening and bone destruction. Similar hyperemia of the terminal pulp's vascular rete has been reported in hypertrophic pulmonary osteoarthropathy.[19] (Clubbing of the fingers is a feature of both AOL due to VCM and hypertrophic pulmonary osteo-arthropathy.)

PULMONARY RADIOLOGICAL CHANGES

Dyspnea was a frequent presenting symptom in our series (Table 11-1). Radiology of the chest was normal in this group, but Selikoff et al.[20, 21] reported that the chest radiographs of 13.3 percent of 985 PVC polymerization workers showed linear, nodular or reticular changes. Ventilation and perfusion isotope scans have shown occasional lung perfusion defects in our group.[9] Lung function tests have been difficult to interpret partly because of the high incidence of tobacco smoking, but six of our patients showed impaired carbon monoxide diffusion defects.

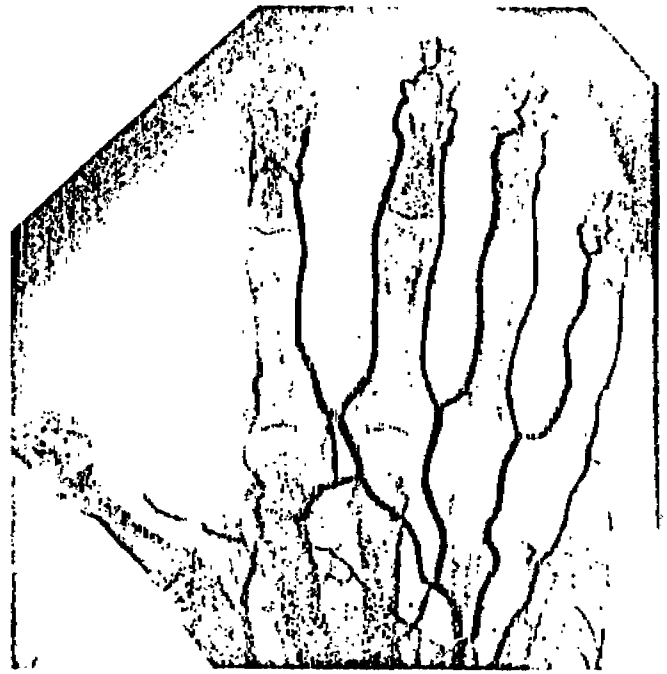

Fig. 11-10. A.D., 1975. Arteriography of left hand showing occlusion of the ulnar digital artery of the thumb, and the radial digital artery of the index finger.

THE PATHOGENESIS AND IMMUNOLOGY OF VINYL CHLORIDE DISEASE

The multisystem clinical features of VCD strongly suggest that a circulatory factor is involved in its pathogenesis. The histological finding of perivascular inflammatory infiltrate and the end-stage narrowing of dermal vessels with subintimal fibrosis are also suggestive of a circulating, complex disorder.[22] The accumulated clinical, histological and immunological evidence suggest that VCD is a complex-mediated disease, with thrombocytopenia and splenomegaly being secondary features that follow complement activation and a persisting immune response.

Evidence is presented here to suggest that a metabolite of VCM (probably chlorethylene epoxide) binds to IgG, promoting aggregation of IgG molecules. Exposure to cold precipitates these complexes; the complexes in turn stimulate complement activation, causing platelet aggregation and fibrinogen conversion to fibrin. Both of these processes occlude capillaries and other small vessels. Raynaud's phenomenon, as well as the

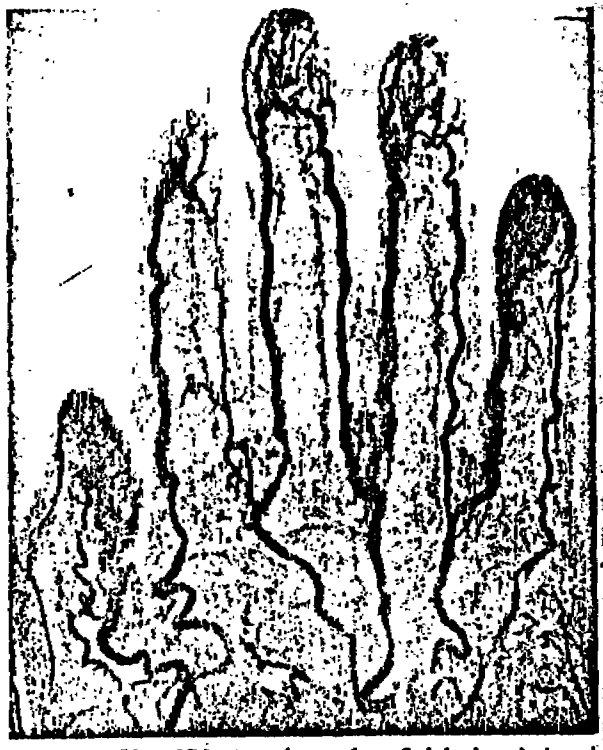

Fig. 11-11. V., 1975. Arteriography of right hand showing patchy occlusion of the ulnar digital artery of the index finger. Note dense arterial rete in the pulp of the terminal segments of all the fingers except the index.

dermal osseous and other clinical manifestations, are explainable with this small vessel occlusion hypothesis.

Metabolism of Vinyl Chloride Monomer

Animal studies in the metabolism and excretion of VCM have shown that VCM may be eliminated in three principal ways: (1) expiration by the lungs of unchanged VCM, (2) expiration of CO_2 derived as a metabolite of VCM, and (3) urinary excretion of the metabolites of VCM.

The major urinary metabolites are thio-diglycolic acid, S (2-chlorethyl) cysteine, N-acetyl S (2-chlorethyl) cysteine, and urea. Intermediate or alternative metabolites of VCM include monochloracetic acid, 2-chloroethanol, 2-chloroacetaldehyde, and chlorethylene epoxide.[23]

It appears that the proportion of VCM that is metabolized is greater when the animal is exposed to a small dose. Saturation of the major or primary metabolic pathway results in redirection through alternative and

potentially toxic metabolic pathways.[24] The cyclic chlorethylene epoxide is a highly unstable alkylating agent with a very short biological half-life but a high potential biological activity. It has a marked affinity for free sulphydril pool in rats. This affinity for sulphydril radicals allows the chlorethylene epoxide to cross-link between and to aggregate molecules of IgG and other plasma proteins in vivo. The metabolite IgG complexes and aggregates are readily precipitated on cooling.

Immunological Abnormalities

The major immunological abnormalities in VCD include hyperimmunoglobulinemia with a polyclonal increase in IgG, cryoglobulinemia, cryofibrinogenemia, and in vivo activation of complement via the classic activation pathway.[22] There is also evidence to suggest mild T-cell depression with a reduction in the circulating T-cell population and a reactive increase in the circulating B-cell population. Immunofluorescent examinations of skin and lung biopsies have demonstrated the deposition of IgG with associated complements C3 and fibrin in relation to the histological lesions described in small blood vessels.

Hypothetical Mechanisms in the Immunological Pathogenesis of Vinyl Chloride Disease

The association of known immunological abnormalities and metabolic data relating to VCD permits the formulation of a hypothetical model for the pathogenesis that will explain the diverse features of this multi-system illness.

An alternative metabolite of VCM—probably chlorethylene epoxide—binds to IgG, producing a structural conformational change that promotes aggregation of the IgG molecule. (The aggregated molecules or structurally anomalous monomers may also become antigenic, but this is probably of minor significance.) The IgG aggregates remain soluble, but they are cryoprecipitable and may initiate complement activation. Precipitation of the IgG aggregate by cold causes complement activation that results in platelet aggregation (with consequent apparent thrombocytopenia), and conversion of fibrinogen to fibrin with polymerization. Occlusion of small vessels results from both of these mechanisms. Occlusions of the skin capillaries may cause the anomalies observed by Maricq;[25] the resulting ischemia will stimulate new collagen biosynthesis.[26] Occlusion of small "end" vessels in cortical bone may result in the characteristic lytic lesions, while occlusion of dermal vessels may result in sclerodermatous changes.

The final phase in this hypothetical mechanism is sustained perpetuating,

which explains why the disease appears to progress for many months after removal from VCM exposure.

EXPERIMENTAL EVIDENCE

Eighty-eight workers from a local VCM polymerization plant were studied by one of us (A.E.W.). They were divided into three groups on clinical evaluation (Table 11-4): 9 patients with definite VCD, 44 patients with possible VCD, and 35 asymptomatic patients.

Immunochemical and immunological investigations showed a gradation of abnormalities throughout the three groups: polyclonal increases in IgG, cryoglobulinemia, in vivo complement conversion, and a cell-mediated immune defect (Table 11-4).

The cryoglobulin was a mixed cryoglobulin comprising IgG, C_3, and fibrinogen.

The rheumatoid factor as assessed by latex agglutination was universally negative, but hemagglutination showed low titer positive results in eight of the nine persons in Group I, and ten of the 44 in Group II, indicating the presence of aggregated IgG in the serum of the more severely affected individuals.

Direct immunofluorescent examination of skin and muscle biopsies from Group I individuals showed close correlation between the presence of cryoglobulin and that of IgG, C_3, and fibrin both within the lumen of small vessels and adherent to the vascular endothelium.

Ultracentrifugal analysis. IgG preparations from Group I patients appeared visually less stable than those from Group III and from healthy volunteers. Sedimentation velocity analysis indicates the presence of high molecular complexes exceeding 19S, but these complexes are produced in vitro due to the instability of IgG prepared from VCD patients (Group I). Some preparations give lower than normal values for IgG; for these, the normal S°20W concentration dependence of the sedimentation coefficient

Table 11-4
Immunological Abnormalities in Vinyl Chloride-Induced Disease (VCD) and VCM-Exposed Workers

Clinical Group	Number	Cryoglobulin	In vivo C_3 conversion	PACIA assay positive (MAG or RF)
I VCD	9	8 (90%)	6 (66%)	5 (55%)
II possible VCD	44	15 (33%)	19 (44%)	12 (27%)
III VCM exposed	35	0	0	0

is reversed. The molecular disintegration after initial dimerization[27] and the reversed concentration dependence of the S value constitute further evidence of the structural anomaly within the IgG molecule.

Interaction with Protein A indicates a chemically induced IgG structural anomaly. Addition of Protein A to purified IgG from VCD patients resulted in immediate precipitation of a heavy complex. This feature was not observed with normal IgG or IgG from asymptomatic VCM-exposed workers (Group III). In a gel-phase technique, stable Protein A:IgG complexes have only been seen in either (definite or possible) VCD patients, or in rheumatoid arthritis. The structural anomaly of IgG in rheumatoid patients is well documented[28] and the finding of similar results in VCD patients is further evidence of a chemically induced IgG structural anomaly.

The PACIA assay for circulating complexes[29] depends on the presence of immune complexes or immunoglobulin aggregates in the test sample that inhibit agglutination of IgG-coated latex particles by an agglutinator substance. The agglutinators currently employed are murine agglutinator (MAG) and rheumatoid factor (RF). The presence of significant quantities of circulating complexes in 50 percent of Group I and Group II workers with MAG suggests that the majority of complexes in VCD are greater than 20–22 S, although positive results with the RF agglutinator show that 11–55 S complexes are also present.

Conclusions of Experimental Evidence

Ultracentrifugal analysis and PACIA assay give direct evidence of the presence of circulating complexes in VCD. This confirms the indirect evidence obtained from cryoprecipitation and in vivo complement activation. Further direct evidence is provided by immunofluorescent microscopy. Evidence for the molecular anomaly in IgG is provided by the Protein A interaction and by sedimentation velocity analysis. It has not yet been proven that the metabolite:IgG complex is antigenic, but the presence of aggregated IgG is sufficient to activate complement by the classic activation pathway, thereby triggering the final recycling stage in the pathogenesis of vinyl chloride-induced disease.

Summary of Immunological Studies

It is postulated by us that the pathogenesis of vinyl chloride-induced disease is the occlusion of small blood vessels in skin, bone and other tissues by aggregation of platelets, and the conversion of fibrinogen to

fibrin (which encourages thrombosis). It is suggested that these vessel-occluding processes are initiated by the precipitation (particularly by cold) of immunoglobin (IgG) aggregates that have resulted from structural changes induced in the IgG molecule by a metabolite of vinyl chloride monomer. This metabolite may well be chlorethylene epoxide.

ETIOLOGY OF VINYL CHLORIDE-INDUCED DISEASE

At the present time, it is not known how VCM produces such a wide range of abnormalities in so many body systems—both in humans and in animals. One possibility is that of a direct toxic effect on the tissues by VCM or one of its metabolites. Another possibility is that the tissue damage is secondary to vascular and/or immunological change. Most probably a combination of these (and possibly other unknown) factors is responsible for the many and varied pathological changes.

The immunological changes described above strongly favor the hypothesis that an immunological chain of reactions may be the cause of small vessel damage and occlusion, ultimately resulting in ischemic tissue changes.

VCM enters the body by direct inhalation of gas and when small particles of PVC (carrying VCM) are inhaled. Inhaled particles of PVC may, themselves, exert a toxic reaction.

It is very interesting that no PVC polymerization worker has been reported to be suffering from both AOL and angiosarcoma of liver. This suggests that VCM may initiate more than one type of toxic reaction, or that there is considerable individual variation in organ susceptibility to toxic levels of VCM. As angiosarcoma of the liver usually develops after a long latent period (15–20 years), some workers with AOL due to VCM may subsequently develop liver tumors.

CONCLUSION

Since 1974, the levels of exposure to VCM in PVC production plants have been reduced to five parts per million. No further cases of VCM-induced disease should appear if these new standards are maintained. It is, however, quite possible that highly exposed workers employed in the industry before 1974 will develop angiosarcoma of the liver at a later date.

The safety of workers handling finely particulate PVC polymer is not yet established; this aspect requires further study and careful monitoring of both the industrial processes and the exposed workers.

REFERENCES

1. Gauvain S: Vinyl chloride. introduction to the problem. Proc Roy Soc Med 69:275–277, 1976
2. Barnes AW: Vinyl chloride & the production of PVC. Proc Roy Soc Med 69:277–280, 1976
3. Lilis R, Anderson H, Nicholson WJ, et al: Prevalence of disease among vinyl chloride & polyvinyl chloride workers. Ann NY Acad Sci 246:22–41, 1975
4. Suciu I, Drejman I, Valaski M: Investigation of diseases due to vinyl chloride. Medicina Interna (Bucharest) 15:967–978, 1963
5. Lange CE, Jühe S, Stein G, et al: Vinyl chloride disease—an occupational systemic sclerosis. Int Arch Occ Health 32:1–32, 1974
6. Cordier, JM, Fievez C, Lefevre MJ, et al: Acro-osteolysis combined with skin lesions in 2 workers exposed in cleaning autoclaves. Cahiers Med Travail 4:14–19, 1966
7. Wilson RH, McCormick, WE, Tatum CF, et al: Occupational acro osteolysis. Report of 31 cases. JAMA 201:577–581, 1967
8. Miller A, Teirstein AS, Warshaw R, et al: Changes in pulmonary function in workers exposed to vinyl chloride and polyvinyl chloride. Ann NY Acad Sci 246:42–51, 1975
9. Darke CS: Vinyl chloride & the production of PVC. Proc Roy Soc Med 69:277–281, 1976
10. Takouchi Y, Mabuchi C: A case of occupational acro-osteolysis presumably caused by vinyl chloride. Japan J Industrial Health 15:385–394, 1973
11. Maricq HR, Johnson MN, Whetstone CL, et al: Capillary abnormalities in polyvinyl chloride production workers. JAMA 236:1368–1371, 1976
12. Veltman G, Lange CE, Jühe S, et al: Clinical manifestations & course of vinyl chloride disease. Ann NY Acad Sci 246:6–17, 1975
13. Harris DK, Adams WGF: Acro-osteolysis occurring in men engaged in the polymerisation of vinyl chloride. Brit Med J 3:712–714, 1967
14. Dinman BD, Cook WA, Whitehouse WM, et al: Occupational acro-osteolysis. 1. An epidemiological study. Arch Environ Health 22:61–73, 1971
15. Williams DMJ, McLachlan MSF: Healing of phalangeal defects in acro-osteolysis. J Soc Occ Med 26:98–99, 1976
16. Cheney WD: Acro-osteolysis. Am J Roentgenology 94:595–617, 1965
17. Preston BJ, Lloyd Jones K, Grainger RG: Clinical aspects of vinyl chloride disease. Proc Roy Soc Med 69:284–286, 1976
18. Dodson VN, Dinman BD, Whitehouse WM, et al: Occupational acro-osteolysis III. A clinical study. Arch Environ Health 22:83–91, 1971
19. Laws JW, El Sallab RA, Scott JT: An arteriographic & histological study of digital arteries. Brit J Radiology 40:740–747, 1967
20. Lilis R, Anderson H, Miller A, et al: Pulmonary changes among vinyl chloride polymerisation workers. Chest (Supplement) 69:299–303, Feb 1976
21. Selikoff IJ: Discussion. Proc Roy Soc Med 22:281, 1976
22. Ward AM, Udnoon S, Watkins J, et al: Immunological mechanisms in the pathogenesis of vinyl chloride disease. Brit Med J 1:936–938, 1976
23. Green T, Hathway DE: The biological fate in rats of vinyl chloride in relation to its oncogenicity. Chem Biol Interac II: 545–562, 1975
24. Williamson KS: Review of animal studies. Proc Roy Soc Med 69:281–283, 1976
25. Maricq HR, Darke CS, Archibald R McL, et al: In vivo observations of skin capillaries in workers exposed to vinyl chloride. An English-American comparison. Brit J Ind Med 35:1–7, 1978

26. Jayson MIV, Bailey AJ, Black C, et al: Collagen studies in acro-osteolysis. Proc Roy Soc Med 69:295–297, 1976
27. James K, Henney CS, Stanworth DR, Structural changes occurring in 7S globulins. Nature: 202, 563–566, 1964
28. Johnson PM, Watkins J, Scopes PM, et al: Differences in serum IgG structure in health and rheumatoid disease. Circular dichroism studies. Ann Rheumatic Diseases 33:366–370, 1974
29. Cambiaso CL, Riccomi H, Masson PL, Automated determination of immune complexes by their inhibitory effect on the agglutination of IgG coated latex particles by rheumatoid factor or Clq. Ann Rheumatic Diseases, Supplement 1:36, 40–44, 1977
30. Block JB: Angiosarcoma of the liver following vinyl chloride exposure. JAMA 229:53–54, 1974
31. Maltoni C, Le Femine G: Carcinogenicity bio-assays of vinyl chloride: Current results. Ann NY Acad Sci 246:195–218, 1975
32. Lee FI, Harry DS: Angiosarcoma of the liver in a vinyl chloride worker. Lancet 1:1316–1318, 1974
33. Taylor KJW, Barrett JJ, Williams DMJ et al: Preliminary results of Grey scale ultrasonography in the detection of vinyl chloride related liver and spleen disease. Proc Roy Soc Med 69:292–295, 1976