

Clinical Aspects of Vinyl Chloride Disease

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Acro-osteolysis

The word acro-osteolysis means dissolution of the extremity of a bone and it is applied to the distal phalanges of the hands and feet. There are many causes, e.g. scleroderma, psoriasis, hyperparathyroidism, sarcoidosis, ergotism, diabetes, tabes, syringomyelia, familial and idiopathic acro-osteolysis. A similar appearance may occur as a result of trauma. Recently, acro-osteolysis of the hands of workmen associated with vinyl chloride polymerization processes has been recorded by Cordier *et al.* (1966), Wilson *et al.* (1967), Harris & Adams (1967), Dinman *et al.* (1971), and Lange *et al.* (1974).

We would like to present the radiological findings in four patients who had been involved in the production of polyvinyl chloride.

Methods

All patients had the following regions examined by plain film radiography: hands, feet, shoulders, elbows, knees, ankles, pelvis, chest, skull, mandible and spine. Case 1 (AD) also underwent a barium swallow, meal and follow-through, angiography of the hands and serial films of the hands at 6 months and 2 years after presentation, and a film of the pelvis at 2 years.

Case Reports

Case 1

A D presented at the age of 35 years with symptoms of severe Raynaud's phenomenon, pain in many joints, trismus, and thickening and tightness of the skin. He had been engaged in the polymerization processes of vinyl chloride for 5½ years. A radiograph of the hands (Fig 1) showed dissolution of the central parts of all the terminal phalanges except for the little fingers, erosion of all the terminal tufts, thinning of the central parts of all the middle phalanges but particularly those of the little fingers where there is extension into the base, thinning of the middle and distal parts of the proximal phalanges of the ring and little fingers and erosions with a well-defined sclerotic margin at the base of the right first metacarpal and at the tips of both ulnar styloid processes. In addition, soft tissue thickening was present over the wrist and the whole of the hand. A film of the feet showed acro-osteolysis of the terminal phalanges of both big toes, a large erosion in the head of the left first metatarsal bone and small erosions in the head of the right first metatarsal bone and the right medial and intermediate cuneiform bones. The radiograph of the pelvis

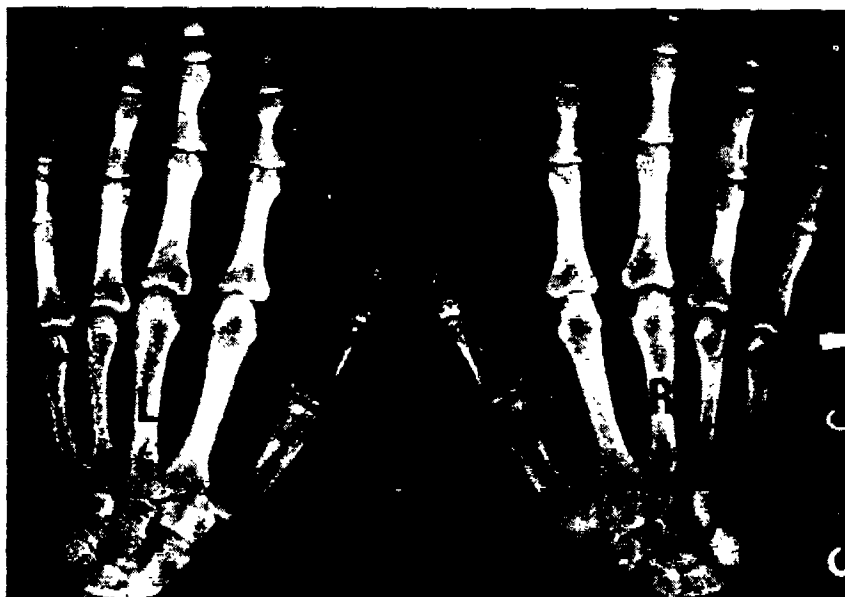


Fig 1 Case 1 Hands (1.5.73), showing transverse defects in distal phalanges, osteolysis, erosions and soft tissue thickening



Fig 2 Case 1 Mandible, ascending ramus

revealed large erosions at the tips of the ischial tuberosities, peripheral joints of the left clavicle, lateral epicondyles of the humeri, inferior femoral condyles, both medial and lateral calcanei.

Films of the mandible showed erosion of both the ascending and descending rami, thinning of the body towards the symphysis.

Films of the spine showed no abnormalities.

Monitoring films of the hands at six months and two years showed interesting defects in the distal phalanges, proximal phalanx of the ring finger, and right distal part of the thumb. At 2 years there was resorption of the distal phalanges, and the findings thus suggesting a progressive process.

Serial films of the pelvis showed osteolysis of the iliac crest (Fig 3) but no



Fig 2 Case 1 Mandible, revealing marked erosion of ascending ramus

revealed large erosions around both sacroiliac joints, at the tips of the greater trochanters and along both ischial tuberosities. The radiographic survey of the peripheral joints recorded erosions at the lateral end of the left clavicle, left upper humerus, medial and lateral epicondyles of the right humerus, medial condyles of the left humerus, both olecranon processes, inferior parts of the patella, both lateral femoral condyles and anterior aspects of the tibia, both medial malleoli and posterior aspect of the left calcaneum.

Films of the mandible (Fig 2) revealed considerable erosion of both ascending rami, causing marked thinning of the bone; on the left side this extended upwards to involve the condyle.

Films of the skull and spine and barium swallow, meal and follow-through examination showed no abnormalities.

Monitoring films of the hands and feet were taken at six months and 2 years after presentation and these showed interesting changes. At 6 months, the films of the hands recorded the following changes: (a) central defects in the distal phalanges of the little finger; (b) further osteolysis, particularly of the bases of the distal phalanges; (c) periosteal reaction along the proximal phalanges of the left thumb and index finger, and right ring finger; (d) shortening of the distal part of the finger. Radiographs of the hands taken 2 years after presentation showed even further resorption of the bony fragments of the distal phalanges, and the proximal fragments appeared dense thus suggesting avascular necrosis.

Serial films of the feet showed extension of the acro-osteolysis of the big toes in the first 6-month period (Fig 3) but on the 2-year film there appeared to be

some healing as there was new bone formation at the tip of the distal phalanx of the left big toe. However, the erosion at the head of the right first metatarsal bone had progressed in size over the 2-year period. The film of the pelvis two years after presentation showed a slight increase in the size of the erosions of the ischial tuberosities.

In view of the patient's persistent and increasing symptoms and signs in the hands, arteriography of the hands was performed and it was done under general anaesthesia. The large vessels were patent but in the left hand there were occlusions in the digital artery on the ulnar side of the thumb and radial artery of the index finger, and narrowing of the digital artery on the ulnar side of the little finger. In the right hand, slight narrowing and tortuosity of the radial artery of the index finger and medial digital artery of the little finger was shown. In both hands, hypervascularity of the terminal tufts was recorded.

Case 2

F P, aged 38 years, had been engaged for two years in the manufacture of polyvinyl chloride. Acro-osteolysis was recorded in both index fingers and the right thumb. Erosions with a well-corticated margin were visualized at the base of the right first metacarpal bone, medial epicondyle of the left humerus and inferior poles of the left patella. Some increase in the soft tissues was noted and this is best assessed by observing the region over the radial and ulnar styloid processes.

Case 3

D D, aged 28 years, had been involved for 2 years in the processes of polymerization of vinyl chloride. The skeletal survey revealed no evidence of acro-osteolysis or any other significant abnormality.



Fig 3 Case 1 Feet, six months after presentation

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 I. 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-

merization of vinyl chloride. Large numbers of cases of acro-osteolysis have been reported since 1967, Dinman *et al.* suggested that this was due to reactor cleaner

In 1974 Lange reported a disorder affecting the fingers of PVC thrombocytopenic purpura, both in the pre-radiological evidence

Clinical Study
In February 1974 Raynaud's phenomenon was observed in the fingers of a worker employed in a firm which manufactures PVC. The worker had been employed since 1974 and February 1975 at this plant was due to exposure to

The study covered 59 years (average employment at 5½ years) of 4 workers had at 4 were maintained and 1 was a wa-

The present study was common fatigue: most after minimal exertion. Coldness was a complaint.

Obviously it was difficult to evaluate the feature was not on at least one by the vinyl chloride itself various

Table 1
Presenting symptoms

Symptom
Cold hands
Paraesthesia
Impaired grip power
Cold feet
Aches in bones
Aches in muscles
Dyspnoea
Excessive fatigue
Loss of libido

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 5½ 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
Paresthesia	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 on an initial training period. He felt nauseated whilst working weeks he had worked four years. The other men had never been in a reactor.

Dr Premysl V Pelna
blood flow measurer

Dr Anne Walker said that the measurements were made on 10 men in an ambient temperature room which was cooled to the room temperature.

During the three hours the finger was measured and capillary flow impedance. Additional measurements were taken back of the hand with

Dr A Milford Ward
(*Department of Industrial Hygiene, Hospital Medical*)

Evidence of an Inflammation in Vinyl Chloride
The occurrence of loss of bone density, thickening of the acro-osteolysis (vinyl chloride in the overall frequency low and no series immunological indicated that the to the skin and system one with tissues.

Immunological studies of 58 workers revealed evidence of a disorder in 21 of the immunological clinical features. The duals show the disease process. The features are immune complex of 10 individuals clinically; in 7 symptomatic of active employment duals who were immune complex

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, Hallamshire 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 (8 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-

cal, and at present speculative, initiating sequence of reactions in this disease process also raises the question whether other unsaturated halogenated hydrocarbons may also be involved in a similar chain of events.

Further studies are in progress in an attempt to clarify the initiating reaction sequence and to define the precise relationship between vinyl chloride and the observed immunological anomalies.

DISCUSSION

Dr Leo Djerassi said that fatty liver might be the early histological change in liver caused by vinyl chloride. In one of his cases which began with splenomegaly, liver biopsy showed a fatty liver. The patient did not consume alcohol habitually. The finding was not surprising, as chlorinated hydrocarbons were known to cause fatty liver. The clinical development of this case brings us to the evidence of immunological phenomena in those exposed to vinyl chloride, and to the possibility of another target organ - the spleen. Splenomegaly was the first deviation in this case, and increased progressively. Hypersplenism followed. Splenectomy and splenorenal shunt were indicated because of oesophageal bleeding. The patient's condition improved sufficiently to enable him to work full time on a nonstrenuous job.

Professor Margaret Turner-Warwick (Cardiothoracic Institute, Brompton Hospital, London SW3) asked what was the cause of the T cell depression mentioned, and whether the spontaneous sheep rosette T cell counts were confirmed by other *in vitro* tests such as PHA transformation.

Was there evidence whether C3 conversion was triggered by the classical or by the alternative pathway?

Was evidence found of immune complex deposition in capillaries of the skin and lung as well as in the larger vessels mentioned?

Dr A Milford Ward replied that the cause of the T cell depression was not clear, but it was a feature often seen in circulating immune complex disorders and in autoimmune states. The low rosette counts were partially confirmed by a mild depression of the PHA reactivity of the peripheral blood lymphocytes.

Complement activation in vinyl chloride disease was by the classic pathway with conversion of C4 as well as C3, as would be expected with IgG class antibody directed against the antigenic groupings.

Immune complex deposition was found in capillaries and small vessels in skin, muscle and lung.

Dr L Magos said he would like to see the patients classified by grade, since it was always frustrating to read of 'severely affected' people without knowing what 'severely affected' meant. The grading could be based on degree of splenomegaly, acro-osteolysis, scleroderma &c.

Dr A Milford Ward replied that the classification used in this study was a clinical one, based on history, physical examination, and an assessment of the patient's ability to continue his employment. It therefore included such aspects as splenomegaly, acro-osteolysis, and scleroderma.

Dr E Vigliani (Milan, Italy) asked whether the presence of B and T in the tissues could be detected by immunofluorescence.

Dr A Milford Ward replied that lymphoreticular tissue was not examined histologically or immunologically so the presence of T and B cells could not be assessed in tissues. T and B cell counts were performed on peripheral blood.

Dr Ruth Lilis (Mount Sinai School of Medicine, New York) asked whether immune complexes were found in the kidney. There were in the literature a number of cases of Goodpasture's syndrome in persons exposed to chlorinated hydrocarbons.

Dr A Milford Ward said that renal tissue was not examined. None of the patients showed clinical evidence of renal disease, and it was not considered ethically justified to biopsy the kidney in the absence of proteinuria or haematuria. Antibodies to renal glomerular basement membrane were not detected.

Dr I F H Purchase, Mr C Richardson and Dr D Anderson (ICI Central Toxicology Laboratory, Alderley Park, near Macclesfield, Cheshire)

Chromosomal Effects in Peripheral Lymphocytes

Vinyl chloride produces liver tumours in animals exposed by inhalation (Maltoni & Lefemine 1974) or dosed by the oral route (Maltoni *et al.* 1975, Purchase 1975, unpublished). Epidemiological studies demonstrated that workmen exposed to vinyl chloride had an increased risk of developing certain tumours, particularly hepatic angiosarcomas (Creech & Johnson 1974). In common with other carcinogenic chemicals, such as benzene, recent studies have demonstrated that workmen exposed to vinyl chloride have an increase in the percentage of lymphocytes with chromosomal abnormalities (Funes-Cravioto *et al.* 1975, Ducatman *et al.* 1975, Purchase *et al.* 1975). Studies of this type carried out on lymphocytes recovered from peripheral blood provide an easy clinically applicable method of assessing damage to living cells caused by carcinogenic chemicals. If there is a quantitative relationship between the percentage of chromosome abnormalities and the amount of exposure to the chemical, the estimation of chromosome abnormalities

may provide a measure of exposure with effect.

We have studied including exposure from the same control subject exposed population based on the time are autoclave of workers who have plant; Group 1: vinyl chloride (PVC) claves; Group 2: same area as C define exposure VCM apart workers have and 4 the low as an autoclave subsequently as it has been included.

Blood samples were (Difco Labo Lymphocytes All slides were unbiased and individual were where 200 cells of each had been treatment were

The results given in Table 1 have normal had a 46, XY chromosome between 48- have been present.

When the groups is compared had higher control group results control group results compared

Table 1

Results from 100 employed in P1 according to B

Group 1
Group 2
Group 3
Group 4
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malities

may provide a useful tool for determining levels of exposure which do not produce this mutagenic effect.

We have studied a population of 80 workers including exposed workers, nonexposed workers from the same industrial site, and nonexposed control subjects from another environment. The exposed population has been divided into groups based on the type of work carried out: Group 1 are autoclave operators; Group 2 are maintenance workers who have worked in the polymerization plant; Group 3 are those who work in polyvinyl chloride (PVC) production but not with autoclaves; Group 4 are maintenance workers in the same area as Group 3. It is virtually impossible to define exposure of these groups of workers to VCM apart from saying that the autoclave workers have the highest exposure and Groups 3 and 4 the lowest. One worker, who was employed as an autoclave worker for 11 years and subsequently as a maintenance worker for 14 years, has been included in Group 1.

Blood samples were taken and lymphocyte cultures were prepared using standard Difco kits (Difco Laboratories, Detroit, Michigan, USA). Lymphocytes were cultured for 48 or 72 hours. All slides were coded before scoring, to ensure unbiased analysis. One hundred cells per individual were analysed (except for one individual where 200 cells were analysed), using the classification of Buckton & Pike (1964). Workers who had been exposed to X-rays or prolonged drug treatment were excluded from the study.

The results of the chromosome analysis are given in Table 1. All individuals were found to have normal male karyotype, except for one who had a 46, XY karyotype with inversion of No. 3 chromosome. There was no significant difference between 48- and 72-hour cultures so these data have been pooled.

When the percentage of B and C cells in various groups is compared, it is seen that Groups 1 and 2 had higher percentages than Group 3 and the control group. The difference between the combined results from the exposed groups and the control group is statistically significant. These results confirm the findings of Funes-Cravioto

Table 1

Results from analyses of chromosome abnormalities in workers employed in PVC manufacture (B and C cells classified according to Buckton & Pike 1964)

	No. of Workers	B Cells (%)	CU Cells (%)	CS Cells (%)
Group 1	18	6.4	1.72	0.44
Group 2	21	6.9	1.48	0.30
Group 3	5	6.6	1.20	0.20
Group 4	12	5.1	1.10	0.41
Controls on site	19	3.6	0.53	0.10
Controls off site	5	2.6	0.50	0.00

et al. (1975) and Ducatman *et al.* (1975) that workmen exposed to vinyl chloride have an increased percentage of chromosomal abnormalities. There is also some incomplete evidence that higher exposure results in larger increases in abnormalities. This relationship still requires to be studied in more detail.

The induction of chromosomal abnormalities is indicative of a mutagenic effect of vinyl chloride. It is important to know whether vinyl chloride is capable of inducing mutagenic effects in other test systems and particularly whether such an effect is produced on germ cells. Accordingly vinyl chloride was examined for dominant lethal effects in mice. Groups of 15 male mice were exposed to 3000, 10 000 or 30 000 parts/10⁶ of vinyl chloride for 6 hours per day for 5 consecutive days. Each male was mated with 2 virgin females per week for 8 weeks and the females were killed at 13 days and examined for dominant lethal effects. There was no significant increase in any of the parameters (early deaths per implantation, early deaths per pregnancy). Vinyl chloride, therefore, did not produce dominant lethal effects in mice, indicating that it did not produce a mutagenic effect in germ cells even at these high levels.

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DISCUSSION

Dr Sylvia D Lawler (Royal Marsden Hospital, London SW3) asked were the chromosome breaks distributed at random? Was a banding technique used? Were the people who actually had symptoms separated out? Genetic effects on human gonads were not absolutely excluded by negative results in a dominant lethal experiment in mice. Was there any evidence of lower fertility?

Dr I F H Purchase replied that the chromosome breaks were distributed randomly. No banding technique was used. The people selected to take part in the study were randomly selected and had not been separated into those with and without symptoms. The only evidence that had been produced experimentally suggested that genetic effects did not occur in the gonads and no effect on fertility was seen.

Dr L de Boer (*The Hague, Netherlands*) said that Mrs I Fleig had reported (Medichem Conference on Chromosome Aberrations, Milan, October 1974, in press) on chromosome studies in which there were not more abnormalities in the exposed group compared with a control group.

Dr I F H Purchase said that his was the third study which had described such abnormalities, the other being those by Funes-Cravioto *et al.* (1975, *Lancet* i, 459) and Ducatman *et al.* (1975, *Mutation Research* 31, 163).

Dr D G Smith (*Zerolit Ltd, Isleworth, Middlesex*) asked whether Dr Purchase's results showed a statistically significant difference between categories 1-4 of exposed workers, i.e. those working on the autoclave (1 and 2) and those away from the autoclave (3 and 4), assuming that the autoclave area was the one of maximum exposure.

Dr I F H Purchase replied that there was a statistically significant difference between the results from autoclave workers and controls, and between the results from all exposed workers and controls.

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Preliminary Results of Grey-scale Ultrasonography in the Detection of Vinyl Chloride Related Liver and Spleen Disease

A number of cases of angiosarcoma of the liver in workers exposed to vinyl chloride monomer (VCM) led to the recognition of the potential hazards of such exposure (Creech & Johnson 1974, Block 1974, Lee & Harry 1974). To date, there are only 47 such cases described in world literature, so angiosarcoma can be regarded as a rare manifestation of VCM toxicity. However, less dramatic changes including periportal fibro-

sis, portal hypertension, oesophageal varices and splenomegaly may be common results of VCM toxicity (Marsteller *et al.* 1973, Smith & Williams 1974, Makk *et al.* 1974, Thomas *et al.* 1975, Lange *et al.* 1974).

In view of these adverse reports, a survey was undertaken of 487 workers with varying exposures to VCM by two of the authors (Williams *et al.* 1975). Full blood pictures were obtained and standard liver function tests were done. Two patients identified by a thrombocytopenia of 72 000 and 45 000/mm³, and slightly raised G-glutamyl transpeptidase G-GT levels, were subsequently found to have periportal fibrosis, portal hypertension, splenomegaly and oesophageal varices on barium swallow, plain abdominal radiography, splenic venography and needle biopsy of liver.

It was clearly unacceptable to carry out these invasive investigations on all exposed workers, but the less invasive techniques seemed relatively insensitive. Thus, a pilot project was carried out to ascertain whether ultrasound offered a possible noninvasive method for visualizing the liver and spleen in workers exposed to hepatotoxic agents. Initial results proved encouraging (Taylor *et al.* 1975, Williams *et al.* 1976).

Although ultrasound has been used as a diagnostic tool in obstetrics for many years, the instrumentation was comparatively crude since the relevant echoes to be displayed were of large magnitude and did not require sophisticated instrumentation. Kossoff (1974) developed greatly improved equipment which was clinically applied to obstetrics, the eye, breast and thyroid. Using similar instrumentation, the technique was evaluated for the investigation of liver and splenic pathology (Taylor *et al.* 1973, Taylor & Milan

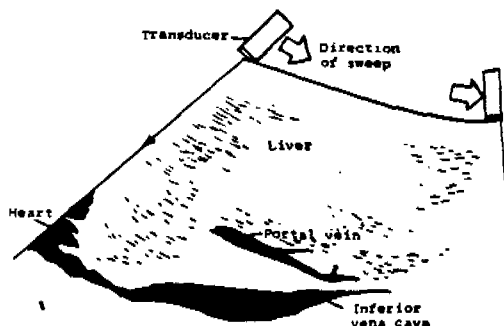


Fig 1 Schema to show movement of transducer to display the anatomical features shown in Fig 2. The portal vein is shown anterior to the inferior vena cava



Fig 2 Parasagittal midline showing no and inferior vena cava Taylor *et al.* 1975,

1976). This test grey-scale ultrasound between this ability to display. Thus, whereas to be a relatively e tour and size of the normal nology to be Small space small defects of

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Table 1

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13	41		
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15	50	Im	
16	55		
17	32		
18	43		
19	46		

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Time given in years a

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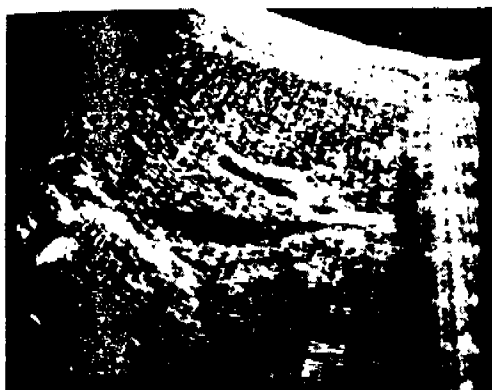


Fig 2 Parasagittal scan of liver 2 cm to right of midline showing normal liver consistency, portal vein and inferior vena cava. (Reproduced from Taylor *et al.* 1975, by kind permission)

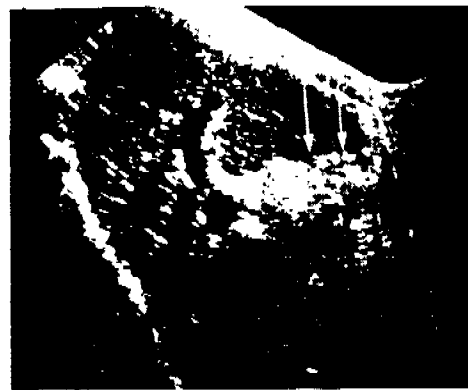


Fig 3 Parasagittal section of liver from patient with vinyl chloride-related portal hypertension. The portal vein is dilated and highly tortuous. Note that there are very large echoes from the deep surface of the liver which is consistent with capsular fibrosis (arrowed). (Reproduced from Taylor *et al.* 1975, by kind permission)

1976). This technical development was called grey-scale ultrasound, and the major difference between this and older instrumentation is the ability to display the normal tissue parenchyma. Thus, whereas the liver was previously found to be a relatively echo-free area in which only contour and size could be distinguished, the display of the normal parenchyma allowed diffuse pathology to be recognized due to an abnormal pattern. Small space-occupying lesions appear now as small defects of the normal parenchyma.

The liver is scanned in a series of paramedian sections illustrated in the schema shown in Fig 1. The resulting ultrasound scan is shown in Fig 2. Ultrasound is a fast means of acquiring data. Using this single pass technique through the liver

as shown in the diagram, good resolution is obtained without degradation by respiratory or cardiac excursions. This ultrasound technique involves no ionizing radiation nor other known hazards, no discomfort, and no need for contrast media. It does require considerable operator expertise and high quality instrumentation, which has only recently become commercially available. Machines which do not display the consistency of the liver are unsuited for examination of it.

Nineteen volunteers were selected from the factory workforce; with varying exposures to vinyl chloride monomer which are summarized in Table 1. Only 2 patients had no exposure at all, but 7 were normal on standard testing (Table 2).

Table 1

Duration and levels of VCM exposures (from Williams *et al.* 1976)

Case	Age	Constant exposure			Intermittent exposure		
		Low	Medium	High	Low	Medium	High
1	41	(No exposure)			(No exposure)		
2	40	(No exposure)			(No exposure)		
3	32				6y 4m	1y 5m	
4	45			1y 3m		15y 4m	
5	48			10m	10y 5m	3y 7m	
6	45		8y 6m		3y 4m	1y 10m	
7	36			2y 3m	8y 4m		10m
8	47				7y 5m	6y 6m	2y 4m
9	30		5y 9m	2y 3m			
10	45			2y 6m	8m	5y 3m	
11	56		15y 6m	1y 8m	1m		
12	39	1y					
13	41		3y 10m		3y 3m		
14	42		6y 8m		3y 2m		
15	50	1m	2y 8m		17y 11m	6y 3m	
16	55		12y 9m			14y 3m	
17	32		6y 6m		3y 2m		
18	43		7y 4m		3y 6m		1y 7m
19	46		7y		6y 5m	1y 4m	

Low exposure, 0-25 parts/10⁶; medium, 25-200 parts/10⁶; high, > 200 parts/10⁶
Time given in years and months

The ultrasound examinations were carried out by the same operator (KJWT), who had no knowledge of the results of the screening tests carried out at that time nor of the exposure of any particular worker. Abnormal findings included increased size and tortuosity of the portal vein associated with portal hypertension, probable capsular fibrosis (Fig 3) and splenomegaly (Fig 4).

The results of routine screening and ultrasound are shown and compared in Table 2. Routine screening consisted of clinical examination, full blood picture, urinalysis and standard liver function tests. Repeated abnormality in any investigation led to further investigation including barium swallow, plain abdominal radiography,

Table 2

Comparison of abnormalities detected by standard methods and by ultrasonography (from Williams *et al.* 1976)

Case	Standard methods	Ultrasonography
1	Normal	Normal
2	Normal	Normal
3	Normal	Normal
4	Liver 6 cm enlarged	Slightly enlarged liver but normal consistency
5	Normal	Normal
6	Normal	Technically difficult (obesity). Enlarged portal vein. 50% increase in spleen size
7	Normal	Enlarged portal vein, splenomegaly (12 cm)
8	Normal	Enlarged liver with a degree of abnormal fibrosis
9	Alkaline phosphatase 51 iu/l	Portal vein not shown. Spleen twice normal size. Liver consistency slightly abnormal
10	Wedge liver biopsy: portal tract fibrosis in places extending into parenchyma	Enlarged liver with possible fatty infiltration
11	Bilirubin 31 μ mol/l SGOT 60 iu/l	Portal vein slightly enlarged. Marked splenomegaly (18 cm). Liver technically difficult to see
12	Needle liver biopsy: slight fibrosis and fatty change	Normal
13	SGOT 60 iu/l, GGT 95 iu/l. Needle liver biopsy: moderate fatty degeneration and mild portal fibrosis	Portal vein and spleen normal. Liver difficult to see (obesity)
14	Platelets 106 000/mm ³	Large portal vein and spleen (12 cm). Liver enlarged, slight change in consistency
15	SGPT 62 iu/l. Needle liver biopsy: fatty change	Portal vein and spleen normal, but possible cirrhotic changes in liver
16	SGOT 60 iu/l γ -GT 59 iu/l	Normal
17	Bilirubin 21 μ mol/l, GGT 66 iu/l, platelets 99 000/mm ³ . Splenomegaly, oesophageal varices, periportal fibrosis	Marked enlargement of portal vein and spleen. Slight change in liver consistency
18	GGT 82 iu/l, platelets 45 000/mm ³ . BSP 19% (45 min). Splenomegaly, oesophageal varices. Fatty degeneration with minimal periportal fibrosis	Splenomegaly. Marked cirrhotic changes and fatty infiltration
19	Bilirubin 43 μ mol/l, SGOT 50 iu/l, platelets 80 000/mm ³ . BSP 21% (45 min). Splenomegaly (Portacaval shunt 1968)	Marked splenomegaly and severe cirrhosis

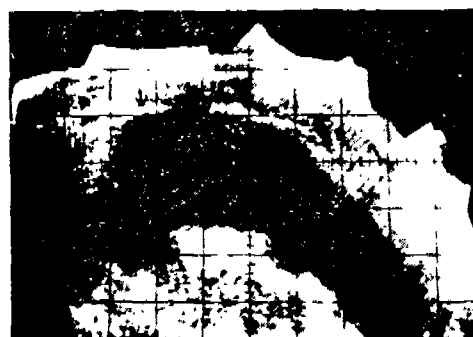


Fig 4 Ultrasonogram of spleen scanned along tenth left interspace. When the spleen is enlarged due to portal hypertension, low-level echoes are returned and so appear dark. The grid squares are 2 cm apart, and the spleen is thus 17 cm in length. This enlargement was not apparent on a plain abdominal radiograph

oesophagoscopy, splenic venography and liver biopsy.

Comparison of the results of ultrasound and routine methods in Table 2 shows that known pathology in Cases 4, 9, 10, 11, 14, 15 and 17-19 were confirmed on ultrasound examination. Cases 1, 2, 3 and 5 were confirmed to be normal. Cases 12 and 13 were known to have liver abnormality on histological examination but this was not detected by ultrasound examination. However, additional information was obtained by ultrasound in Cases 6, 7, 9 and 11. In all these workers, the ultrasound findings led to a review of the radiological results and these are summarized in Table 3. The ultrasound results were confirmed in 3 patients and were not contradicted in Case 6, in whom obesity prevented adequate assessment of spleen size on a plain abdominal radiograph. These volunteers were taken from a workforce of 487 of whom 20.9% had abnormal biochemical or haematologic results on initial testing. Further, intensive investigation failed to reveal the early pathology which was demonstrated by grey-scale ultrasound and was confirmed retrospectively by radiological examination. The main advantage of ultrasound lies in its potential as a noninvasive technique for monitoring populations at risk. The lack of ionizing radiation is a great advantage in this respect.

These preliminary results suggest that ultrasound will result in a small incidence of false negatives (2 out of 19), so that the method is complementary rather than a replacement for current techniques. Both acquiring the ultrasound scans and interpreting them requires operator expertise, but automated scanners should become available within the next year, while experience

Table 3

Further findings subsequent to

Case	Initial assessment	Ultrasonography
6	Normal	Splenomegaly
7	Normal	Splenomegaly
9	Normal	Splenomegaly
11	Normal	Splenomegaly

can be gained if the sufficiently promising being made for a m the application of g detect any liver pat United States which air pollution with exposed during the This further study assessment of the technique.

Acknowledgment:
We would like to of the Working Par of the Chemical Inc

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Table 3

Further findings subsequent to ultrasound examination

Case	Initial assessment	Ultra-sonography	Further assessment
6	Normal	Splenomegaly	Barium swallow normal. Spleen not seen on X-ray abdomen.
7	Normal	Splenomegaly	Barium swallow normal. Spleen wide transversely but did not extend below level of 12th rib
9	Normal	Splenomegaly	Barium swallow after Buscopan. Showed possible Grade I varices. Splenomegaly confirmed on review of straight X-ray of abdomen
11	Normal	Splenomegaly	Possible Grade I varices

can be gained if the potential of the method is sufficiently promising. Preparations are currently being made for a more extensive investigation of the application of grey-scale ultrasonography to detect any liver pathology in a community in the United States which has been heavily exposed to air pollution with VCM, as well as in workmen exposed during the course of their employment. This further study should allow a more detailed assessment of the relative value of this new technique.

Acknowledgment:

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Collagen Studies in Acro-osteolysis

Collagen is a fibrous protein present in most connective tissues and it is the nature and arrangement of collagen fibres that are principally responsible for the mechanical properties of these tissues. The collagen molecule consists of three chains of amino acids formed into a triple helix, and these molecules are aligned in the fibre in a parallel and quarter-stagger arrangement giving rise to the characteristic banded appearance of collagen seen on electron microscopy. This quarter-stagger arrangement is maintained by specific lysine-derived intermolecular crosslinks and it is these crosslinks which are responsible for the strength of collagen.

When collagen is newly formed, the intermolecular crosslinks are labile aldimine bonds, and can be detected by reduction with tritiated potassium borohydride (Bailey *et al.* 1970). However, as the collagen matures these crosslinks become stable and nonreducible and are therefore no longer readily detectable. Studies of the collagen crosslink patterns in normal human skin will therefore show the highest levels in infancy and during the rapid growth period, but will fall to virtually baseline levels by adulthood. If excess labile aldimine bonds are detectable in adult human skin, then proliferation of new collagen is occurring.

Collagen Studies in Scleroderma

The skin changes of acro-osteolysis (AOL) are in many respects analogous to those of scleroderma. In both conditions there is severe rigidity and thickening of large areas of skin, suggesting qualitative or quantitative changes in the collagen.

In a study of skin biopsies from adult patients with scleroderma (Herbert *et al.* 1974) we found an increased proportion of labile aldimine crosslinks in 9 of 11 patients with active progressing disease. In contrast, in patients with longstanding nonprogressive scleroderma there was no excess of the labile bonds. Analysis of the centre and the growing edge of a plaque of morphea demonstrated the maximum level of crosslinks at the

edge of the plaque and much lower levels towards the centre where the collagen has matured. This provides a direct confirmation of increased collagen synthesis in the skin in scleroderma.

Collagen Studies in Acro-osteolysis

Case 1

A D, aged 36 years, was a plasterer until six years before we saw him. He then started as a reactor cleaner and a 'B' operator in a plant manufacturing polyvinyl chloride, scraping the inside of the reactor with a chisel, wearing gloves and overalls but no mask. Following this initial three-week period he became an 'A' operator, working outside the reactor, and was involved in charging and recovery from the reactor and controlling the flow of chemicals including vinyl chloride through various valves. There was no direct contact with the chemicals, but he frequently noticed fumes escaping from the valves.

After three years he noticed the onset of Raynaud's phenomenon which progressed with gradual shortening and instability of the tips of the fingers. There was a gradual thickening and coarsening of the skin spreading up his arms on to the face and a little on the chest wall and axilla. Two years later he gave up work with marked weakness of his hands and arms, which caused great difficulty in gripping and lifting heavy weights.

Examination confirmed the features of acro-osteolysis with gross thickening of the skin, but with the following differences from scleroderma: (1) No ulceration of the fingertips. (2) Instability of the tips of the fingers. (3) Hair follicles and hair preserved. (4) No puckering around the mouth. (5) No telangiectasia. (6) General coarsening of the features. (7) No tightening of the skin across the nose.

Investigations showed slightly raised plasma viscosity of 1.80 cP, and positive antinuclear factor (1:10). Skin histology showed distinct sclerosis of the deep layers of the skin without epidermal atrophy. On radiography there was gross lysis of the central parts of the terminal phalanges, the sacroiliac joints, certain costovertebral joints, the left condyle of the temporomandibular joint, and loss of definition of the right mandibular vertical ramus.

Skin Crosslink Studies in Acro-osteolysis

A skin biopsy was obtained from this patient. Reduction with potassium borohydride revealed a high proportion of the hydroxylysine norleucine crosslink typical of new collagen formation in scleroderma. There was also a second reduceable component present in significant amounts but further studies will be required in order to identify its nature.

Quantification of Collagen Synthesis

Hydroxyproline is an amino acid that is unique to collagen and is formed from proline. By growing tissue in a culture medium containing radioactive-labelled proline and measuring the synthesis of hydroxyproline, an index of the rate of collagen formation can be obtained. We obtained

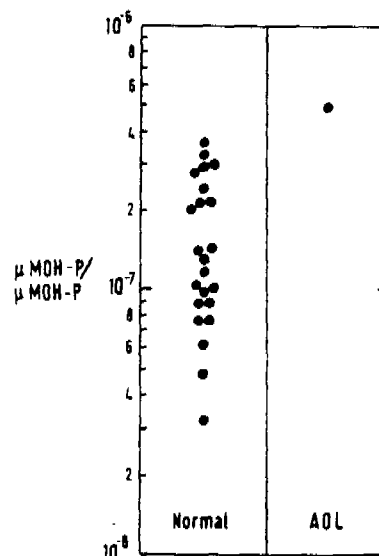


Fig 1 Rate of synthesis of hydroxyproline related to the original hydroxyproline content of normal and AOL skins (μmol)

samples of skin from the patient with AOL and also at surgery from patients with other conditions not thought to involve any abnormality of collagen metabolism. They were cultured on a stainless steel raft at the interface between a culture medium containing ^3H -proline and an atmosphere of 20% oxygen, 5% carbon dioxide, 75% nitrogen in a modified MacIntosh Fildes jar at 37°C for 24 hours. Following culture the specimen was homogenized, dialysed to remove excess ^3H -proline, hydrolysed and separated in an amino acid analyser and the quantity of synthesized ^3H -hydroxyproline was determined. This was related to the hydroxyproline content of the original biopsy. The results are presented in Fig 1 and show that the rate of collagen synthesis in the patient with AOL was considerably greater than that of the normal controls.

Discussion

By both crosslink analysis and by measurement of ^3H -proline incorporation into hydroxyproline, we have confirmed excess new collagen synthesis in the skin of a patient with AOL. These results are analogous to the findings in the skin in scleroderma (Laitinen *et al.* 1969, Herbert *et al.* 1974), and account for the thickening of the skin. It is possible that the effect is generalized, and excess collagen proliferation in the blood vessels could lead to chronic ischaemia with ulceration of the fingertips and further local collagen production. Ischaemic necrosis could similarly occur in AOL and so produce the typical bone lesions.

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However, the AOL bone lesions differ in appearance from those of systemic sclerosis.

The cause of increased collagen synthesis in scleroderma has not been elucidated. Leroy (1974) studied the rate of collagen synthesis by individual fibroblasts from scleroderma and control patients. He found that, when first cultured, scleroderma fibroblasts synthesize new collagen much more rapidly than controls. This implies that cellular factors are of greater importance in causing excess new collagen formation. In addition Johnson & Ziff (1974) reported that lymphokine from normal human donors can increase the rate of collagen synthesis.

Several chemicals are known to induce abnormal fibrosis. Practolol (Brown *et al.* 1974) can lead to peritoneal fibrosis. Methysergide can cause retroperitoneal fibrosis and ergotamine can lead to peripheral ischaemia and has been used in the rat as an experimental model for scleroderma (Harris & Robinson 1974). Epidemiological investigations strongly implicate vinyl chloride in the pathogenesis of acro-osteolysis, and therefore as a further possible chemical cause of increased collagen synthesis. D-penicillamine is a useful agent in the treatment of scleroderma, but only when the disease is active and progressive, that is whilst the crosslinks are labile and can be cleaved by the drug. When the collagen has matured, the crosslinks become stable and the drug is no longer effective (Herbert *et al.* 1974). It may be that D-penicillamine will be of value for treating AOL, but only for active disease.

It is of fundamental interest to determine the manner by which vinyl chloride leads to excess collagen proliferation. This should lead to a better understanding of the processes of collagen synthesis and could well act as a useful model for the study of scleroderma.

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Dr Robin Walker (Walton General Hospital, Liverpool, 9) spoke on the subject of
Clinical Aspects of Vinyl Chloride Disease: Liver

Epidemiological Studies

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Epidemiological Studies of PVC Manufacturers and Fabricators, and Primary Angiosarcoma of the Liver

The Joint Working Group on the Vinyl Chloride Code of Practice decided from the outset that epidemiological studies would be necessary to evaluate the extent of the risk to workers engaged in the manufacture and fabrication of PVC. The Employment Medical Advisory Service (EMAS) proposed three studies: a prospective study of PVC manufacturers, a prospective study of PVC fabricators, and a retrospective study of primary angiosarcoma of the liver. As these studies were intended to be as comprehensive as possible they could only be accomplished by drawing on the cooperation and expertise of a number of bodies: the industry, HM Factory Inspectorate, the Registrars General for England and Wales, and Scotland, the Royal College of Pathologists and experts from university departments and elsewhere.

Prospective Study of PVC Manufacturers

In the past, workers engaged in PVC manufacture were exposed to vinyl chloride as a result of working inside autoclaves or from leaks occurring at various stages of the process. The main aim of this survey is to evaluate the effects of this exposure in terms of mortality and cancer registration rates according to certified causes by including all past workers at every factory manufacturing PVC in Great Britain. Present and future workers are also to be incorporated. Identification details of the workers, including duration of employment and details of past exposure, are entered by the factory personnel departments onto individual survey cards according to instructions provided by EMAS. Past exposure had been graded into high (>200 parts/10⁶), medium (>25 parts/10⁶), and low (<25 parts/10⁶), with 'constant' and 'intermittent' categories. The cards are updated annually and sent to EMAS headquarters. Under the new Code of Practice all present and future exposures will be 'low'. Identification details of the workers are sent through EMAS to the National Health Service Central Registries in England and Wales, and Scotland. Death certificates for these persons

are coded according to the International Classification of Diseases (1967) by the Registrars General. Workers alive at the start of the survey are flagged, a procedure which results in the coded death certificates being picked out and notified to EMAS at the time of death.

This procedure should result in an almost complete follow up of workers. The total number of males and females identified as having worked in the manufacture of PVC is 7746 of whom only 84 (1%) have not been traced, 72 (1%) have missing information, and 147 (2%) have emigrated. Workers entered into the present analysis number 7410, over half of whom are current employees; 88% were exposed to 'low' or 'medium' concentrations, only 12% having worked in 'high' concentrations; 46% had constant exposures.

Statistical comparisons will be made between observed and expected deaths, calculated using the England and Wales sex-age-standardized rates supplied by the Registrar General.

PVC Fabricators

Exposure to vinyl chloride during the manufacture of the finished articles from raw PVC occurs as the vinyl chloride trapped in PVC synthesis is released during the further handling and processing of the PVC. This survey aims to study the mortality and cancer registration rates for all causes in each sector of the industry and to determine whether these rates are related to vinyl chloride exposure. There are at least seventeen different types of industry and twenty types of operation, and the size of the work staff varies from a handful to hundreds of men. Records of employment and exposures are likely to be poor or nonexistent in some of the smaller factories and for this reason a sample will be taken of workers employed at, or near to, the present time, over a wide range of the industry, the names of the factories making up the sampling frame being provided by HM Factory Inspectorate and trade organizations. As many as 20 000 workers may be involved. The procedure for the follow up of workers and the analysis of the results will be similar to that described for the study of manufacturers.

Retrospective Study of Angiosarcoma

The significance of cases of angiosarcoma of the liver occurring in vinyl chloride workers relates to the rarity of the tumour in the general population. To assess its rarity and to look for any time trends, EMAS asked the Registrar General for England and Wales to collect all death certificates with a possible diagnosis of angiosarcoma of the

liver between 1963 and 1973. The results of this study have been reported elsewhere (Baxter & Fox 1975) and showed that, on average, only 3 adult cases were certified a year in England and Wales. One case reported in 1972 had previously been employed as a PVC worker. (The only other angiosarcoma death in Great Britain known to have occurred in a PVC worker was in 1974. Both workers had been engaged on the manufacturing side.)

The main aim of this study is to identify and verify all diagnosed cases of primary angiosarcoma of the liver occurring from 1974 onwards, and to evaluate their association with occupational exposure to vinyl chloride. From 1974 onwards, the Registrars' General Offices are sending all death certificates with an underlying cause of death stated as being liver cancer (including primary, secondary and unspecified categories) to EMAS headquarters, where diagnoses likely to be angiosarcoma are selected. Angiosarcomas are also notified to EMAS from cancer registries, hospital pathologists and hospital discharges (Scotland only). A sample will be taken from amongst the other liver cancers, and for both these and the angiosarcoma cases the hospitals where they were treated will be contacted in order to request the loan of available histological material. Sections will be submitted for diagnosis to a panel of expert histopathologists who will not know the history or identity of the cases. An estimate will then be made of how many angiosarcomas are misdiagnosed or misclassified as other liver cancers. With the permission and assistance of the hospital consultants and general practitioners concerned, the next of kin of the deceased angiosarcoma cases will be traced and an interview requested with one of our Employment Nursing Advisers trained in interviewing techniques. The nurse will seek to obtain a full occupational history of the deceased.

The controls, matched for age, sex and death register (locality), will be chosen from the other liver cancer deaths and also from deaths from all causes. Four liver cancer controls for each angiosarcoma case will be randomly selected by EMAS. The controls of deaths from all causes will be selected by the Registrar General's Office from the same death register as an angiosarcoma case. The next of kin of both sets of controls will be interviewed in an identical manner to the angiosarcoma cases. As far as possible the interviewers will not know the cause of death of the deceased. Finally, our Employment Medical Advisers will investigate the places where the cases and controls worked and record details of occupational exposure to vinyl chloride and other

chemicals. The copies of all records for the

The verified entered into a national historic records, and a angiosarcoma frequency of chloride will sarcoma cases

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hemicals. They will also attempt to obtain photocopied copies of all hospital and general practitioner records for the verified cases of angiosarcoma.

The verified cases of angiosarcoma will be entered into a register which will include occupational histories and the copies of the medical records, and an estimate of the true incidence of angiosarcoma will be obtained. Finally, the frequency of occupational exposure to vinyl chloride will be compared between the angiosarcoma cases and the controls.

In conclusion, prospective and retrospective studies are being carried out to provide a comprehensive assessment of the risk of occupational exposure to vinyl chloride and the development of primary angiosarcoma of the liver. The prospective mortality and cancer registration studies will also permit the testing of hypotheses concerning the carcinogenicity of vinyl chloride in other sites, such as the lung and brain. And in the absence of a satisfactory objective test for use in morbidity surveys, mortality data should enable the more serious complications of periportal fibrosis due to vinyl chloride to be assessed.

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DISCUSSION

Dr A J Fox (*Employment Medical Advisory Service, London*) said that in the prospective study of PVC manufacturers described by Dr Baxter great care had been taken to elucidate the role of (1) year of entry into the industry, (2) level of exposure as estimated by people who had worked in the individual plants, (3) length of exposure in the industry, and (4) length of follow up. These studies, coupled with those of 'healthy population effect' and 'survivor population effect' were of fundamental importance in the evaluation of the results of exposure to vinyl chloride monomer.

Dr L Magos (*MRC Toxicology Unit, Carshalton*) said that in the retrospective epidemiological study reviewed by Dr Baxter vinyl chloride workers were divided according to exposure time and level of exposure. How could data be obtained on the level of exposure of a worker who had had twenty years' exposure?

In the German literature there were many cases of splenomegaly, fibrosis of the liver, and thrombocytopenia. Dr Magos was surprised that no similar cases had been reported from the UK during the meeting.

Professor K Weinbren

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Histopathology of Liver Lesions Associated with Exposure to Vinyl Chloride Monomer

So far only 2 cases of angiosarcoma of the liver have been reported in British workers exposed to vinyl chloride monomer (Lee & Harry 1974) but more material has been studied in the United States by Bradford Block (1974) and by Thomas *et al.* (1975). The lesions encountered in this last publication included 15 angiosarcomas and the structural changes are clearly presented by these authors. At the same time, angiosarcomas have been described in other circumstances, which included prolonged exposure to arsenical medication for psoriasis (Regelson *et al.* 1968) arsenic toxicity in vineyard workers (Roth 1957) and after exposure to thorium dioxide for arteriography (Visfeldt & Poulson 1972). The lesion has been encountered also in patients with no evidence of exposure to a particular toxin (Baker *et al.* 1956). The characteristics of the tumour are for the most

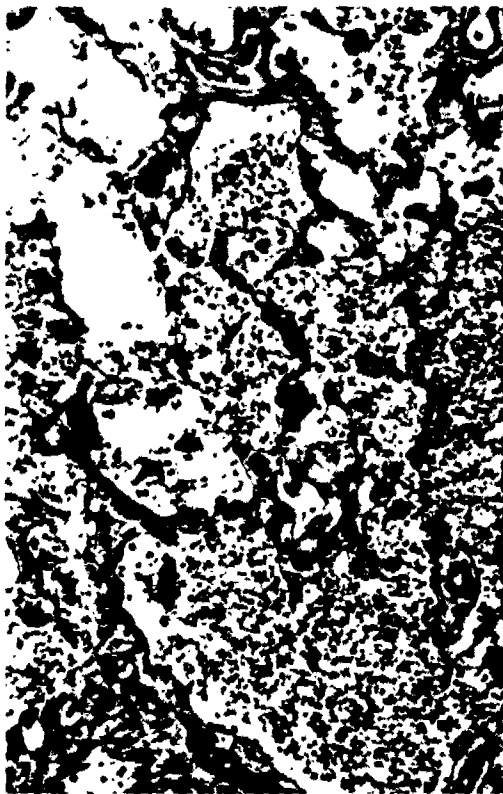


Fig 1 Angiosarcoma showing dilated sinusoidal spaces containing red blood cells and lined by tumour cells. H & E. $\times 150$



Fig 2 Papillary formations of tumour cells are borne on a core of connective tissue and hepatocytes. H & E. $\times 600$

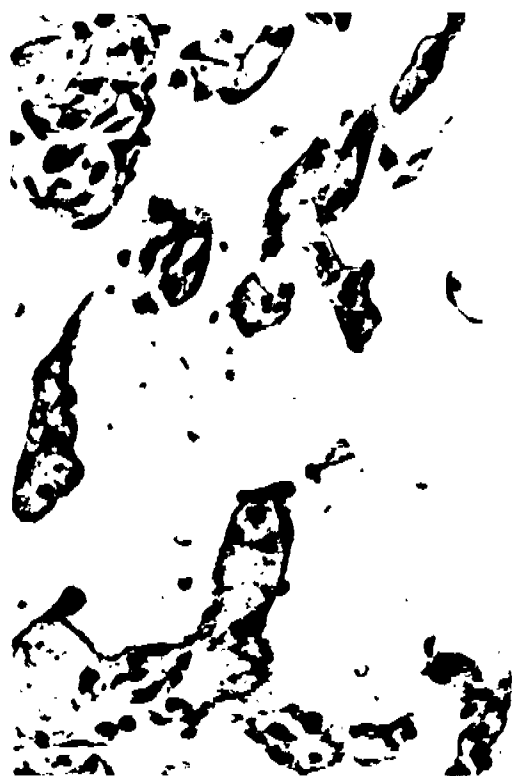


Fig 3 Well-differentiated flattened tumour cells, resembling endothelial cells on connective tissue cores and lining vascular spaces. H & E. $\times 400$

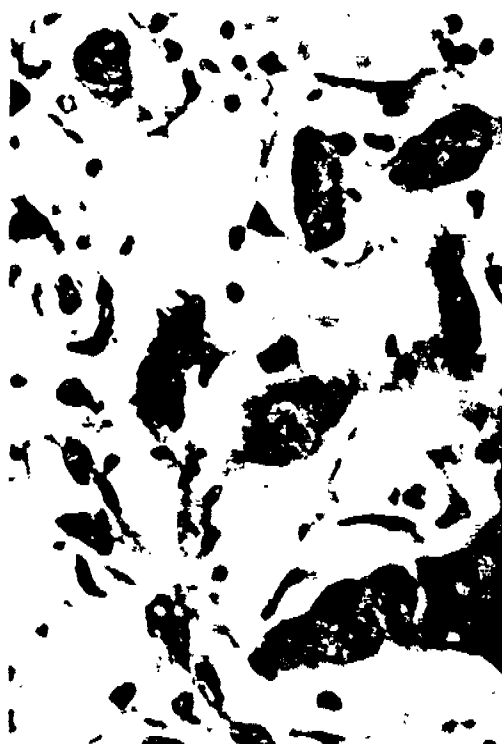


Fig 4 Bizarre giant tumour cell in papillary angiosarcoma. H & E. $\times 600$



Fig 5 Solid area of tumour cells in angiosarcoma. H & E. $\times 400$

part agreed by these various workers and I propose to outline them. I shall also briefly discuss some of the other changes which have been noted in the livers of patients suffering from angiosarcoma and those of patients who had been exposed to vinyl chloride monomer but did not show evidence of the development of tumours.

The tumour consists of cells which vary considerably in appearance but seem to have enough common features, particularly in their mode of growth, relationship to vascular spaces and stromal changes, to support the view that they are derived essentially from one cell type.

In general the tumours show a gross appearance of dark haemorrhagic nodules in the liver; there is a variable distortion and apparent fibrosis in the intervening liver tissue. Sometimes foci are macroscopically less haemorrhagic. There is often frank necrosis.

The microscopical appearances at first glance are variable, but analysis suggests a consistency. Thomas *et al.* (1975) have delineated 3 main types depending really on the relationship of the tumour cells to the vascular spaces: (1) The sinusoidal pattern, in which dilated hepatic sinusoids are lined by enlarged and proliferating tumour cells,

with hepatocyte foci between the tumour nodules found most often (1) common is termed papillary formation: on a core of connective tissue recognizable surviving canaliculi containing blood (Fig 2). (3) The canal blood-filled spaces surrounded by thick layers of tumour cells several variables. Tumour cells differentiated in the cells of liver sinusoids difficult to distinguish from hepatocyte cells, or they may appear irregularly shaped. They may also present cells, suggesting an anaplastic or epithelial diagnostic feature in relationship to hepatocyte spaces. The poor differentiation in the frequently found cells look like solid evidence in many cases. In sum, the tumour



Fig 5 Solid area of tumour resembling solid spindle-cell sarcoma. H & E. $\times 400$

with hepatocyte plates clearly recognizable between the tumour cells. This appearance is found most often (Fig 1). (2) The second most common is termed the papillary type, in which papillary formations of tumour cells are borne on a core of connective tissue, which may include recognizable surviving hepatocytes, often with canaliculi containing inspissated bile pigment (Fig 2). (3) The cavernous type, in which the blood-filled spaces appear even larger and are surrounded by thick fibrous walls which seem to be lined by the tumour cells. In addition there are several variables. The tumour cells may be well-differentiated in that they simulate endothelial cells of liver sinusoids (Fig 3) and it may be difficult to distinguish tumour cells from reactive cells, or they may be quite unusual, showing irregular bizarre and giant-cell forms (Fig 4). They may also present as solid box-like polygonal cells, suggesting an appearance similar to carcinoid or epithelial tumour cells. The helpful diagnostic feature may well be the close relationship to hepatocyte plates or obvious blood-filled spaces. The poor differentiation may be seen also in the frequently found solid areas in which the cells look like solid spindle-cell sarcoma, without evidence in many foci of vascular spaces (Fig 5). In sum, the tumour cell is distinguishable from

hepatocytes, resembles cells normally associated with vessel walls and appears to be closely related to vascular spaces with variable degrees of abnormality.

There are changes in other elements, both in tumour-bearing regions and in parts of the liver which appear to be free of tumour. These changes seem to involve mostly the supporting stroma. In the regions of the tumour, the perisinusoidal reticulin fibres are prominent, obviously increased and appear to run between the tumour-bearing sinusoid and the hepatocyte plate, apparently causing reticulin increase in the space of Disse, which exists between liver cell and normal sinusoidal wall. The alteration varies from a minor inconspicuous (as the authors abroad put it) increase in reticulin fibres which may not be seen without the use of special stains (and in fact, both special stains and special optical manoeuvres may be employed to highlight this change) to massive increase of collagen fibres which surround the hepatocyte plates, clearly obstructing the lumen, sometimes apparently en-

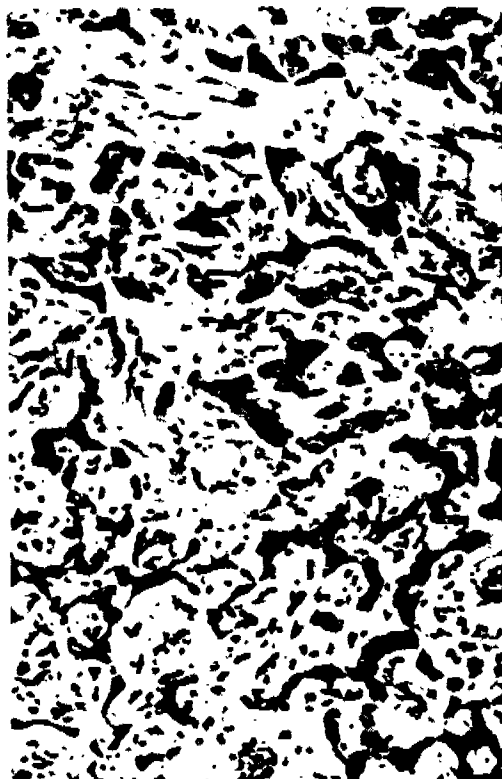


Fig 6 Fibrosis associated with obliteration of sinusoids and disappearance or atrophy of hepatocytes in angiosarcoma. H & E. $\times 150$

trapping single hepatocytes, and sometimes with no hepatocytes appearing to survive (Fig 6). It is, of course, not clear whether the fibrosis precedes hepatocyte loss or not, but appearances suggest that it does. Such hepatocyte survival occurs even in the middle of very poorly differentiated tumour, a phenomenon which is quite unusual in the case of other tumours.

Remote from the tumour-bearing areas, such perisinusoidal reticulin increase is recognized and again it varies from the minor inconspicuous form to quite striking fibrosis (Fig 7).

There is also conspicuous fibrosis in portal tracts with a patchy, sometimes marked, perivascular and periductal fibrosis. The venous lumina which are thought sometimes to be compromised in other forms of fibrosis, such as the Indian noncirrhotic portal fibrosis, are not regularly affected in this way and would be unlikely to provoke the portal hypertension sometimes described. Subcapsular fibrosis has been

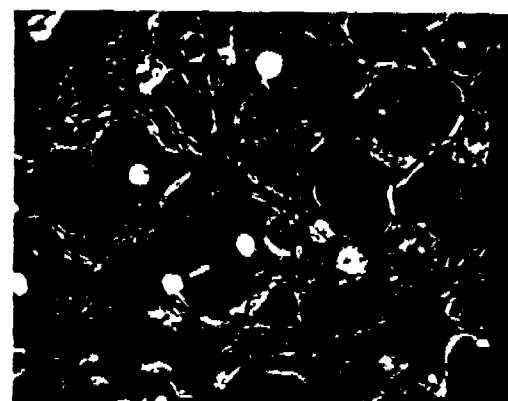
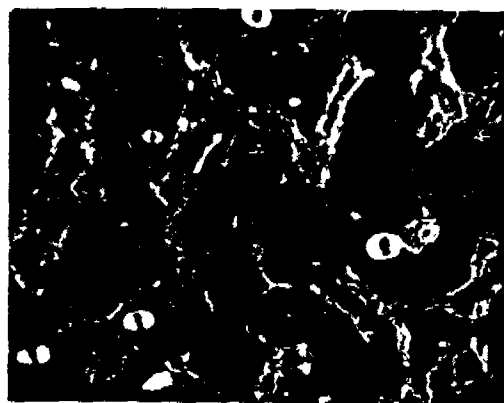


Fig 7 Liver biopsy sections showing variations in intralobular sinusoidal reticulin. Upper, slight increase. Lower, much increase. Gordon & Sweet silver impregnation: Dark-ground illumination. $\times 360$



Fig 8 Hepatic capsular fibrosis in patient exposed to vinyl chloride monomer and presenting with portal hypertension. H & E. $\times 150$

repeatedly observed in the cases from the United States and this seems sometimes to be continuous with the fibrosis in the portal tracts.

The relevance of such nontumorous changes to the subsequent development of angiosarcoma is of course one of the major practical issues at present. Such changes are sometimes found in the livers of workers exposed to vinyl chloride monomer and we have had an opportunity to see sections referred by several clinicians concerned with this problem, including Dr F Lee, Dr Robin Walker, and Dr I F H Purchase. The findings will probably be incorporated in their own reports but, in summary, several liver biopsy sections have been looked at for the nontumour changes described. It happens that both controls and exposed patients have quite a content of fat and that several of the exposed personnel do show sinusoidal thickening, difficult to make out, but easier in dark-ground preparations. One particular case, which I hope Dr Frank Lee will report, presented with portal hypertension and had quite striking capsular thickening, diffuse sinusoidal reticulin increase, hypertrophy and possibly hyperplasia of endothelial cells, and what seems



Fig 9 Bizarre anaplastic hepatocyte mitosis. H & E. $\times 400$

to be striking mitotic abnormality.

The question is as pre-malignant as many of the conditions such as endometrial hyperplasia and of hepatocellular carcinoma. The primary liver cancer is a question also the formation of the curious fibrous nodules. Under probably enigmatic circumstances of individual risk whether there

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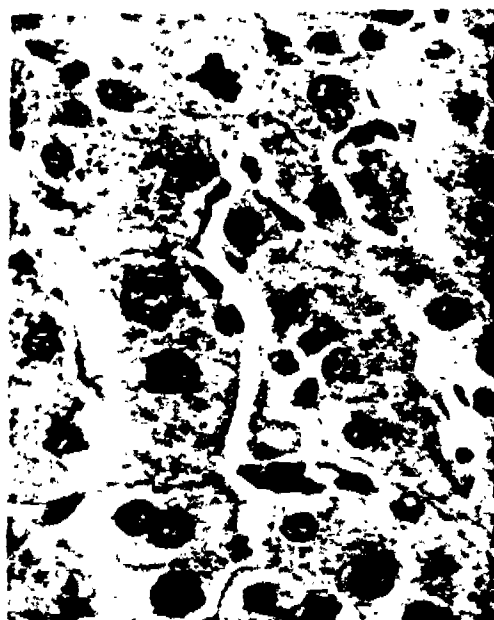


Fig 9 Bizarre and enlarged sinusoidal lining cells and hepatocyte mitotic abnormality in same patient as Fig 8. H & E. $\times 600$

to be striking hepatocyte involvement, even with mitotic abnormalities (Figs 8-9).

The question whether these lesions are significant as premalignant changes is unanswered, as many of the alterations can be found in other conditions such as congestive cardiac failure, endothelial cell hyperplasia in cases of lymphoma, and of hepatocyte and other changes in many drug toxicity situations. Other pathogenetic questions also have to be posed, such as what is the primary lesion, which cell is involved in the formation of the tumour, what is responsible for the curious fibrosis and survival of the hepatocytes. Understanding these processes would probably enable us to make a better assessment of individual risk factors and perhaps to work out whether there is a tolerable exposure.

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Epidemiological Studies of Vinyl Chloride Health Effects in the United States

The vinyl chloride (VC) problem has had a considerable impact in the United States during the past year and a half. Perhaps related to the age and conditions of the VC industry, or simply to the sheer size of it, the United States has so far had the largest share of cases of VC-induced hepatic angiosarcoma (HAS); at the present time there have been 17 known cases in polymerization workers (Lloyd 1975). The finding of the initial cases was a dramatic event, and unlike what has occurred with many other proven or suspect carcinogens, the confirmatory experimental evidence arrived almost simultaneously with the epidemiologic results (Maltoni & Lefemine 1974). The widespread industrial applications and uses by the consumer were instantly appreciated, and since the VC problem also arrived at a time of growing awareness and concern among workers and consumers about environmental and occupational hazards, it served to focus these concerns.

Within the first few months after the initial cases were described a number of worrisome reports appeared. Investigators in Louisville, Kentucky, and also at Mount Sinai Hospital in New York demonstrated a high percentage of liver function abnormalities in polymerization workers, suggesting a broad problem (Makk *et al.* 1974, Lillis *et al.* 1975), and, in addition to this, the earliest mortality studies (Monson *et al.* 1974, Tabershaw & Gaffey 1974) suggested increased rates for nonhepatic tumours, paralleling the multiplicity of tumour types seen in experimental studies (Maltoni & Lefemine 1974). Review of records at the Connecticut Tumor Registry, started in 1935, revealed 5 definite cases of HAS; 4 cases were clustered in one industrialized area and had occurred since 1967; 3 of these (and possibly a fourth case where the diagnosis was uncertain after review of slides) occurred in workers at two polyvinyl chloride (PVC) fabricating plants or in residents living nearby (Landrigan & Heath 1976). Further concern was generated by

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reports of the potential carcinogenicity of chemicals structurally related to VC, e.g. chloroprene (Lloyd *et al.* 1975) and trichloroethylene (National Cancer Institute 1975, unpublished data), and by the knowledge that VC workers in many instances have been exposed to multiple related chemicals, including vinylidene chloride and acrylonitrile (vinyl cyanide).

As part of the United States Public Health Service response to the VC problem, the National Institute of Occupational Safety and Health (NIOSH) and the Bureau of Epidemiology, Center for Disease Control (CDC), have worked on a number of VC-related epidemiologic projects during the past year and a half; in this paper we will briefly review some of the early results of three of these studies.

HAS Surveillance

A death certificate search for all cases of HAS recorded under ICD Code 197.8 (8th Revision), which encompasses various miscellaneous forms of liver tumour including most cases of HAS, was undertaken by CDC for the years 1966-73 in the United States. This search is almost completed, with only data for New York City not yet available at the time of this review.

Table 1 shows the number of cases of HAS and non-angio hepatic sarcomas by year of death for 1966-73; there is no evidence for an increase in the incidence of these malignancies during this period.

A review of the relative occurrence of hepatic sarcomas recorded under ICD Code 197.8 showed angiosarcoma to be the largest group (35% of total hepatic sarcomas), followed by sarcoma of unspecified type (31%), leiomyosarcoma (12%), fibrosarcoma (7%), and a grouping of miscellaneous sarcomas (15%).

Table 1

Hepatic sarcoma in the United States by reported histology and year of death, 1966-1973

Year of death	All sarcoma	Angiosarcoma	Non-angio sarcoma
1966	31	9	22
1967	40	13	27
1968	23	9	14
1969	14	7	7
1970	31	15	16
1971	23	5	18
1972	9	1	8
1973	25	9	16
	196	68	128

From death certificates, ICD Code 197.8 (8th Revision). Data from New York City not included

■ Half year sample

Table 2

Hepatic angiosarcoma in the United States by age at death and sex, 1966-1973

Age at death (years)	Male	Female	Total
0-9	2	2	4
10-19	1	1	2
20-29	1	1	2
30-39	5	4	9
40-49	7	2	9
50-59	13	2	15
60-69	5	5	10
70-79	11	3	14
80+	1	2	3
	46	22	68

From death certificates, ICD Code 197.8 (8th Revision). Data for New York City not included

There was approximately 1 case of HAS for every 300 death certificates reviewed.

Table 2 demonstrates a male to female ratio of 2:1 for HAS. Sixty-two percent of cases occurred in the group aged 50 or more, with 26% in the 30-49 year age group. Non-angio hepatic sarcomas differed in having a male to female ratio of only 1:1, and an altered age grouping with 78% of cases aged 50 or more and only 9% in the 30-49 year age group. These differences are consistent with a hypothesis that occupational exposure may be a more significant factor in the causation of HAS than of non-angio hepatic sarcoma.

Only 2 of the patients with HAS in the death certificate review were recorded as having worked in PVC or plastics plants (1 PVC polymerization worker and 1 accountant in a PVC fabrication plant); both were cases which had been identified prior to this study. No other occupation is recorded more than twice except for the occurrence of 5 printers. Although all were subsequently confirmed as printers, a preliminary review of pathology records and specimens suggests that 4 of the 5 cases may have been incorrectly diagnosed as HAS.

CDC has supplemented the death certificate survey with an intensive case-finding effort, including a national mailing to all pathologists, state epidemiologists, and major cancer referral centres and tumour registries, seeking information on as many cases of HAS as possible diagnosed in the US during the years 1964-74. At the present time approximately 240 cases have been identified. Pathology specimens for about two-thirds of these are currently under review at the National Cancer Institute and the Armed Forces Institute of Pathology. An epidemiologic evaluation of all cases to obtain more detailed histories regarding

past occupation residence is under

Medical Screening
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Preliminary significant data any of the 6 li bilirubin, all and ornithin analyses base and type of being done; not suggest abnormalities exposure. Or generalizing it will be im studies at o to realize th tively insen induced hep of this type for the prev scans were more than 1 polymeriza detected. S livers on p ever, amon from this c is in prepar

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