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Section of Occupational Medicine

President Suzette Gauvain MRCP

Meeting 12 September 1975

Vinyl Chloride

Dr Suzette Gauvain
(Medical Advisory Service, Health and Safety Executive, Baynards House, 1 Chepstow Place, Westbourne Grove, London W2 4TF)

Vinyl Chloride: Introduction to the Problem

The story of vinyl chloride, when it comes to be written, will be seen as a watershed in the history of occupational medicine, forcing us to take a new attitude to occupational hazards and react quickly to first evidence of harm.

The polymerization process of vinyl chloride to polyvinyl chloride was first discovered in Germany in the mid-1930s. The fire and explosion risks and the narcotic effect were quickly appreciated. Acro-osteolysis, a condition mainly affecting the terminal phalanges of the fingers, sometimes the toes, and to a lesser extent the other bones of the body, was first recognized in autoclave cleaners in Belgium (Cordier *et al.* 1966) and subsequently confirmed in a number of investigations of autoclave workers in Canada, England and the USA. Soft tissue changes, coldness and numbness of the hands and fingertips, resembling Raynaud's phenomenon, were also described.

Lilis *et al.* (1975), summarizing the findings in the world literature in relation to the prevalence of disease among vinyl chloride and polyvinyl chloride workers, make the point that hepatitis-like liver changes were reported by Tribukh, from Russia, in 1949. However, until Viola reported (Viola *et al.* 1971) that he had failed in an attempt to produce acro-osteolysis in rats exposed to 30 000 parts/10^6 of vinyl chloride, but demonstrated carcinogenic effects, little attention was paid to this earlier finding. The level of exposure of the rats was so high that its significance to humans was not clear and further testing was necessary. Maltoni, commissioned by a consortium of European chemical interests, including Imperial Chemical Industries, to undertake further studies, confirmed cancer in animals at exposures as low as 250 parts/10^6 (Maltoni *et al.* 1973).

As a result of Maltoni's work an epidemiological study was undertaken in the USA on men who had previously worked as cleaners of autoclaves (reactors) in a polyvinyl chloride polymerization plant. Creech & Johnson published this work in 1974, but their findings of a cluster of cases of angiosarcoma of the liver in one factory were transmitted to the National Institute of Occupational Safety and Health (United States) on 22 January 1974 (United States Senate 1974), to the Department of Employment (HM Chief Inspector of Factories) on 23 January, and to the Acting Chief Employment Medical Adviser on the following day.

On 29 January 1974 Imperial Chemical Industries put out a press statement announcing that it was taking steps to inform government departments, the TUC, its own workers and its customers, of the facts available so far; and that a single suspected death in the United Kingdom was under urgent investigation. Subsequently this 70-year-old retired autoclave worker, who had died at the end of 1972 after twenty years of exposure, was confirmed to have died of angiosarcoma of the liver.

Since 1974 intensive investigations have taken place in this and many other countries. The United States government have published an account of the hearing before the Subcommittee on Environment of the Senate Committee on Commerce, on the dangers of vinyl chloride (United States Senate 1974). Senator Tunney, in

his opening statement, said: 'This hearing will be focusing on ways to mitigate the problems involved with vinyl chloride as well as ways to avoid crises of this type in the future.' Previously, on 10 and 11 May 1974, the New York Academy of Sciences, the American Cancer Society, the National Institute for Occupational Safety and Health and the Society of Occupational Environmental Health held a workshop entitled Toxicity of Vinyl Chloride – Polyvinyl Chloride (Selikoff & Hammond 1975).

The International Agency for Research on Cancer (1974, 1975) published technical reports of a working group on vinyl chloride held in June 1974 and of a succeeding meeting in January 1975. The International Chemical Workers Federation published for its members a handbook on vinyl chloride and its hazards (Levinson 1974). The Environmental Protection Agency in Washington, DC published in September 1974 a preliminary assessment of the environmental problems associated with vinyl chloride and polyvinyl chloride, in which it set forth recommendations to clarify and reduce the associated risks.

Meanwhile, the Department of Employment staff in the United Kingdom had been taking active part in consultations in Europe and in the United States. As soon as the information was communicated in January 1974, HM Inspectors of Factories and Employment Medical Advisers throughout the United Kingdom were notified, and industry on its own initiative set out to ensure that no person would be exposed to amounts of vinyl chloride vapour that were above a concentration of 50 parts/10^6.

The TUC and the CBI accepted an invitation from HM Chief Inspector of Factories to form a joint working group with representatives of government departments. The first meeting took place on 14 June 1974. An interim hygiene standard was adopted and two subgroups were set up to draft the environmental and medical sections of a code of practice; these were published in February 1975 in temporary format by the Health and Safety Executive (1975). In the introduction Mr Bryan Harvey, Deputy Director of the Health and Safety Executive, states that the code sets out to (*a*) define an interim hygiene standard that must not be exceeded; (*b*) require regular monitoring to measure the concentrations of vinyl chloride in the atmosphere; (*c*) outline methods of achieving (*a*); (*d*) provide for medical supervision; (*e*) provide for joint consultation and education and training. He further states: '... the Code as now published is based on our existing knowledge and will be improved where additional information shows this to be necessary ... The success of the Code depends primarily on the united efforts of management, supervisors and employees. This is very much a first edition of the Code in temporary format; I hope that those who have suggestions for improving it will put them forward via the joint consultative machinery required by the Code.'

Medical Subgroup

The medical subgroup defined its terms of reference as being: 'To examine the medical aspects of exposure to vinyl chloride; to decide in the light of existing clinical, pathological, toxicological and epidemiological information the examinations which should be included in the Code of Practice; and to indicate those which require further research before inclusion in the Code'.

The subgroup consulted and gratefully acknowledged the help given by experts on diseases of the liver and relevant diagnostic procedures. Because of the difficulty of determining which medical tests indicate the effects of vinyl chloride on the liver preceding the development of angiosarcoma, they 'concluded that insufficient experience with liver function tests or screening tests is as yet available to enable firm recommendations to be made regarding them in this Code of Practice. Liver function tests for this purpose are however in use in factories making PVC ...'. As a result of experience gained from these tests and from other information, 'formal recommendations may be issued as a supplement to the Code in due course'.

The medical aspects of the code are contained in parts 12, 13 and 14. Part 12 defines 'supervised workers'. Part 13 is concerned with their medical supervision. Supervised workers should undergo pre-employment medical examinations. Those already employed should be examined, if this has not been previously done, within twelve months. The examinations should be repeated annually, and should include: (1) a full medical and occupational history; (2) a clinical examination with particular reference to the abdomen, skin and extremities; (3) X-ray examination of the hands; (4) such further tests as may be indicated by the above procedures or may be recommended in supplements to the Code. The leaflet describing the early effects of vinyl chloride monomer should be given to the supervised workers at this examination unless issued previously.

The physician engaged to provide medical supervision for the workers should see a supervised worker who reports symptoms which ma[illegible]

be due to exposure; he or she should see a supervised worker who has been absent from work more than two weeks owing to illness. These absences should be reviewed on a group and individual basis. If indicated, medical examination should be undertaken at any time. Section 16 provides for the keeping of confidential medical records of all supervised workers; these must not be destroyed without the agreement of the Chief Employment Medical Adviser.

The purpose of the present symposium is to review British experience of the environmental, clinical, epidemiological and pathological effects of exposure to vinyl chloride arising in the course of polymerization of vinyl chloride monomer to polyvinyl chloride, and to exchange information.

The implications of the association of angiosarcoma of the liver with exposure of workers to vinyl chloride monomer have had such a profound effect on industry, workers and governments that these effects must be seen in the wider context of occupational carcinogenesis generally. I think it is necessary to consider what the future may hold in the way of carcinogenic risks. We can, I believe, regard the experience we have gained throughout the world with vinyl chloride as a pilot study on a newly discovered occupational carcinogen. Frank and open discussion between government departments and both sides of industry is indispensable to the achievement of success.

Postscript

The Working Group on Vinyl Chloride Code of Practice for Health Precautions met on 8 October 1975 and adopted a new hygiene standard agreed by the Working Group as 'a ceiling value of 30 ppm and a time weighted average of 10 ppm, allowing that wherever practicable exposure should be brought as near as possible to zero concentrations.' The figures of 30 parts/10^6 and 10 parts/10^6 replace the original figures of 50 parts/10^6 and 25 parts/10^6.

Other requirements of the Code, including medical supervision, are currently being reviewed.

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Mr A W Barnes
(ICI Plastics Division, Welwyn Garden City, Hertfordshire)

Vinyl Chloride and the Production of PVC

Polymerization Characteristics of Vinyl Chloride

Vinyl chloride has a boiling point of −13.5°C: under normal pressures and temperatures it is a gas. In its liquefied form under pressure, it can be readily polymerized at temperatures in the range 40–70°C to give polyvinyl chloride (PVC), a white solid material. The addition polymerization of about 500–1500 molecules of vinyl chloride produces one molecule of PVC and the polymerization reaction is strongly exothermic. The polymer itself is insoluble in the liquid monomer and so precipitates out as it is produced. The polymer is, however, capable of absorbing high proportions of monomer (40% by weight) so that as the polymerization reaction proceeds and more polymer is precipitated, so equally is more monomer absorbed by the polymer to the point at about 70% conversion where monomer as a separate liquid phase disappears and the remaining monomer must be polymerized in its dissolved state within the swollen polymer. As this phase of the polymerization proceeds, the concentration of monomer in the polymer decreases and the rate of reaction correspondingly diminishes until at about 92–95% total conversion the speed of polymerization becomes uneconomically slow. These are the fundamental characteristics of vinyl chloride and its polymerization mechanism which decide the principal features of industrial processes for the production of PVC.

The Production Process for PVC

Because it must be polymerized in liquefied form at temperatures above its boiling point, the industrial process must be carried out in pressure vessels (at 50°C the vapour pressure of vinyl chloride is ~7 atmospheres). Because the reaction is exothermic, means must be found for removal of the heat produced so that the temperature of reaction (and thus the pressure, and the properties of the end-product) may be kept under control. In the most widely used process, this control is achieved by dispersing the liquid monomer into tiny droplets (about 100 μm in diameter) in approximately equal quantities of water, by means of mechanical agitation together with the addition of small quantities of surface-active agents which facilitate the breakdown of the monomer into droplets and stabilize it in this form. This fine subdivision of liquid monomer enables the heat evolved from the polymerizing monomer to be rapidly transferred to the surrounding water and then removed by a cooling jacket on the reactor, the process being aided by agitation. The subdivision of the monomer into droplets has also the vital property of ensuring that the polymer, which is produced within each droplet, is presented at the end of the reaction in finely divided, powder form, and not as an intractable horny mass.

As polymerization proceeds, the two phase system of monomer dispersed in water becomes a three phase system of solid polymer precipitated within liquid monomer droplets which are in turn dispersed in a continuous water phase. A great deal of research has been devoted in the past thirty years to the control and stabilization of this rather delicate colloidal system but, even so, small quantities of polymer are still thrown out from it and form a thin continuous film of PVC on the walls of the reactor. If left, this will increase in thickness and, since PVC is a poor thermal conductor, will reduce the heat transfer characteristics of the vessel and make temperature control impossible. At the end of the reaction it is therefore essential that this film should be cleaned away. This is one of the basic reasons why a truly continuous process has never yet been developed for making PVC and why the polymer, the world over, is still made by a batch process in relatively small reactors. This, as we shall see, has a significant influence on the ease of controlling fugitive monomer in a PVC plant.

As polymerization nears 90–92% conversion, the rate of reaction slows down markedly and at about 95% conversion has become so slow as to be quite uneconomic. There is no possibility therefore of continuing polymerization to 100% conversion and solving some of the problems connected with vinyl chloride toxicity in this way. At the termination point of the reaction, therefore, the 5–6% residual monomer (still at a pressure of 4–5 atmospheres) is vented back to a gasholder and a slurry of PVC particles (100–150 μm diameter), suspended by stirring in water, is left in the reactor.

Now to a description of the process in engineering rather than chemical terms: polymerization is carried out in cylindrical, stirred, jacketed pressure vessels. To begin, water, surfactive agents and free radical catalyst are added to the reactor: the air space above this liquid phase is purged of oxygen (which inhibits polymerization) and liquid vinyl chloride is then injected into the reactor. (In the UK, reactor sizes range from 10m³ to 40m³ and the monomer charge per batch ranges up to about 15 tons.) The reactor contents are then heated to and maintained at reaction temperature. After a reaction time of the order of eight hours, excess monomer is vented to a gasholder (for recycling) and the reactor is evacuated, at elevated temperature, to strip as much monomer as possible from the polymer on which it is absorbed. The polymer slurry is then transferred to closed tanks prior to the next stage in the process.

Meanwhile the empty autoclave, which still contains vinyl chloride gas at a low partial pressure is further evacuated before opening to atmosphere, and automatic high pressure water cleaning jets are activated to remove polymer scale from the walls. At this stage, the cycle is complete.

Vinyl chloride monomer has a strong affinity for PVC and the last traces of it are difficult to remove from the polymer; the polymer in the slurry after stripping therefore still contains around 500 parts/10^6 of vinyl chloride. This slurry is centrifuged to remove the water phase and the wet powder is then dried in continuous driers; during this process further vinyl chloride is removed in the drier gases and the final dried powder currently contains about 50 parts/10^6 of monomer.

Interfaces between Vinyl Chloride and People

This description of the production process gives some indication of the relative potentials of different parts of the process for creating significant exposures of people to vinyl chloride. If we take a plant capable of making 100 000 tons per annum (tpa) of PVC then the polymerization building will, during the course of a year, have handled over 100 000 tons of vinyl chloride in

liquefied form under pressure. Into the drying section will have passed 50 tons of vinyl chloride in a form strongly absorbed on the polymer and at a concentration on polymer of about 0.05%. In the finished product, 5 tons of vinyl chloride will leave the factory, each year, still absorbed on the polymer at a concentration of 0.005%. Although strictly outside the scope of this paper it is worth proceeding further and pointing out that in further fabrication operations on the polymer, some of this small residual concentration of monomer is driven off so that in the final fabricated article only ~5 parts/10^6 of monomer remain or 0.5 tons out of the original annual total of 100 000 tons. In fabricated articles which are used for foodstuffs packaging (bottles, film and foil), and which represent about 10% of total UK production, the monomer concentration is still lower, and the pro rata amount absorbed on foodstuff containers from a 100 000 tpa plant would be 50 lb. Of this quantity 3½ lb might migrate into the foodstuff where its average concentration is unlikely to exceed 10 parts per thousand million. Since total UK production is about 400 000 tpa this means that the annual ingestion by the average UK citizen cannot exceed 0.0001 g, a figure which agrees well with calculations based on diet analysis.

A final potential interface arises because at points in the production process, vinyl chloride is exhausted to atmosphere. On a typical PVC plant and with current levels of achievement, 0.3% of the monomer is lost to atmosphere: with this performance ground level concentrations at the factory boundary are well below 0.1 parts/10^6 and even these low amounts decay very rapidly with distance. In the band ¼–1 mile (0.4–1.6 km) around one factory, for instance, the concentrations determined are in the range 0.01–0.0001 parts/10^6.

These figures should make clear that by far the biggest potential for exposure exists in the polymerization section of the plant, since here 100 000 tons per year of a liquefied gas under pressure are handled in a confined space, in contrast to other parts of the process and to the later downstream operations of the plastics industry. In these downstream operations the corresponding quantities, this time in the form of absorbed vapour at a low partial pressure and not confined to a single geographic situation, range from 5 tons down to 3 lb per year. That the polymerization section is in fact the area where hazard has existed in the past is confirmed by the fact that all the authenticated cases of vinyl chloride-related angiosarcoma of the liver throughout the world have been of workers engaged in plants where liquid vinyl chloride under pressure was used in large quantities.

The nature of the polymerization process, as described above, illustrates why exposures in the past could have been large. The plants are composed of a large number of batch reactors of small capacity per batch, relative to the total annual throughout. In each reactor, two complete cycles per day are carried out and each cycle requires vinyl chloride to be injected under pressure, heated, contained, stirred and polymerized almost completely: at the end of the cycle unpolymerized monomer has to be removed and the reactor opened and cleaned. The possibilities of small leakages from pumps, valves, stirrer glands and from the opened reactor at the end of the cycle were obviously significant: and the manual cleaning of reactors gave further opportunity for high exposures. This was particularly true during the long period in the 1940s to 1960s when vinyl chloride was thought to be harmless and when a recommended exposure limit did not exist or, late in the 1950s, was set by regulatory authorities, industrial hygienists, &c., at a level of 500 parts/10^6.

The general consensus of opinion throughout the world, today, is that average atmospheric exposure for polymerization workers between 1940 and 1970 might have been of the following orders: 1945–55, ~1000 parts/10^6; 1955–60, ~400–500; 1960–70, ~300–400; mid-1973, ~150; 1975, ~5 parts/10^6. Across the world, there will have been variations around these figures because of differences in plant design or process operation. Even the way in which jobs were organized can have caused variations. In some countries or on some plants workmen were employed specifically to clean out autoclaves (where exposures could have been very high) while in others autoclave cleaning was part only of a whole range of jobs carried out by individual work people. Some spokesmen have suggested, perhaps for full-time cleaners, exposure levels as high as 3000 parts/10^6 in the early days of the industry.

With these very high figures as background, the progress made by the PVC industry in the UK in reducing atmospheric concentrations since the carcinogenic hazard of vinyl chloride became known in early 1974 is shown in Table 1, which also shows improvements made at all the other interfaces described earlier in this paper. Although, as we have seen, the exposure levels in these other places are many orders of magnitude lower than on the polymerization plants, industry has aimed to reduce fugitive vinyl chloride levels

at every point in order to eliminate concern wherever it might exist. With work still in progress, all these figures will be reduced further though, in view of the effort already put in, it is likely that the polymerization plant atmospheres are approaching a limiting value of 2–5 parts/10^6.

Table 1

Vinyl chloride monomer levels in UK industry

	January 1974 (*parts/10^6*)	*July 1975* (*parts/10^6*)
Polymerization		
VCM in plant atmosphere (weekly average)	~150	~5
VCM emissions	0.75% of output	0.3% of output
VCM in product	200–500	< 50 for most grades
Fabrication and Use		
VCM in plant atmospheres	2–15	<2
VCM in PVC bottles	~50	~2
VCM in beverages	0.1	0.01

Finally a few rough calculations of the daily dosages at the current exposure levels and at the higher atmospheric levels which previously could have existed on PVC plants may be helpful in putting current plant performance and present downstream exposures into perspective, one with another, and in comparison with earlier figures (Table 2).

Table 2

Daily dosages at current and earlier exposure levels

	Daily dose (*g/kg body weight*)
Polymerization plant operator at 1000 parts/10^6	0.36
Polymerization plant operator at 500 parts/10^6	0.18
Polymerization plant operator now at ~5 parts/10^6	0.0018
Fabrication plant operator at 1 part/10^6	0.0004
Average UK citizen through ingestion in food	0.000000004

In later papers to this conference, a wide range of diseases or symptoms which have been associated with or attributed to exposure to vinyl chloride will be discussed. It is important to note that most, if not all, of these have been contracted by people who worked under conditions represented by the highest figures in the above table. Today no one is exposed to doses at this level. The exposure of workers in industry is now at least two orders of magnitude lower, while the general public in the UK absorbs, through foodstuffs, a quantity which is some fifty million times lower.

While the conference will be concentrating primarily on problems which have occurred in the past, I hope it may find some time to consider whether there remains any possibility of similar effects occurring at the markedly lower – and in some areas almost incomprehensibly lower – levels which prevail today. For it is on this, quite properly, that industry, and society generally, have focused their attention in the past eighteen months.

DISCUSSION

Dr M D Kipling (*Employment Medical Advisory Service, Birmingham*) said that it was known that workers bagging the PVC powder were sometimes covered with the dust and that this powder contained a percentage of vinyl chloride monomer. He asked whether any information was available on the particle-size of the dust produced in differing processes throughout the world and the incidence of vinyl chloride disease.

Mr A W Barnes replied that the particle sizes of PVC powder did vary very widely, depending on the application for which the PVC powder was made. However, most manufacturers produced all grades of polymer so that it was unlikely that any medical conditions peculiar to a particular manufacturing site could be explained in terms of the polymer and its particle size. Moreover, it should be remembered that all the significant medical effects under discussion at this conference (angiosarcoma, acro-osteolysis &c.) had, throughout the world, been observed exclusively in workers on polymerization plants or, in two cases, plants handling liquid vinyl chloride under pressure. Features common to all these workers were that they were exposed to vinyl chloride vapour in the atmosphere but were not exposed to PVC dust since the polymer was maintained in aqueous suspension throughout this stage of the process.

It was in the drying and bagging sections of the PVC-producing process that exposure to solid PVC particles could arise but, despite extensive medical investigation, no significant abnormalities had been found among drier operators or packers. It was perhaps worth noting, too, that the greater proportion of PVC powder was of a particle size similar to sand so it did not generally pose an airborne dust problem. For those powders which might cause true dust exposures it had been customary in industry, because of the nuisance and discomfort factors alone, to provide some form of respiratory protection.

Dr C S Darke (*Royal Infirmary, Sheffield*) said that he had investigated 14 cases of breathlessness in workers exposed to vinyl chloride monomer. The findings were: no abnormal physical signs; chest radiographs normal; routine respiratory function tests difficult to evaluate but some results slightly below predicted values, especially impaired CO diffusion in 6 individuals; perfusion and ventilation scans showed striking abnormalities as illustrated by one slide revealing marked perfusion defects of upper lobes. One patient underwent open biopsy of each of the three lobes of the right lung. Histology revealed focal alveolar wall thickening with macrophages in the alveolar spaces and increased reticulin and collagen

formation seen on electron microscopy. No obvious vascular abnormality except on fluorescent examination. It might be of importance that some of the worst affected men were concerned in a polymerization process that yielded 'plastisol', a very fine PVC powder with particle size around 0.5 μm. These particles, containing vinyl chloride monomer, could be carried to the alveolar walls where they might be retained and thus set up a reaction of the type seen on light microscopy.

Professor I J Selikoff (*Mount Sinai School of Medicine, City University of New York*) said that pulmonary abnormalities had been unexpectedly common findings among some 1200 vinyl chloride polymerization workers in his studies. Obstructive pulmonary function defects were noted in approximately 50%. Neither age nor cigarette smoking served to explain the findings. For those under age 40, obstructive findings were predominantly among cigarette smokers, as expected. After that age, however, the prevalence of changes was very much the same among smokers and nonsmokers. Of course, age correlated strongly with duration of employment. These two factors were analysed separately and it was found that the changes were generally among smokers with less than 20 years from onset of exposure, but that thereafter they were present in both smokers and nonsmokers. Radiographic changes were less common. Overall, 13.3% of 985 chest films showed linear, reticular or nodular changes characterized as 1/0 or 1/1 in the ILO U/C Classification. Dyspnœa was uncommon and signs or symptoms of chronic bronchitis were not striking (Miller *et al.* 1975, Miller 1975).

The pathogenesis of these abnormalities was not clear. It was not known, for example, whether they reflected another biological change associated with exposure to vinyl chloride monomer, or another factor. Mr A W Barnes had noted that manufactured PVC might currently contain 5 parts/10^6 of retained vinyl chloride monomer, as well as other agents added in the polymerization process. Inhalation of such PVC particles might be associated with adverse effect. Frongia and his colleagues (1974) had reported significant histopathological changes in the lungs of guinea-pigs exposed to PVC powder in a PVC plant. In the polymerization facilities investigated by Professor Selikoff, there had usually been opportunity for PVC dust exposure as well as vinyl chloride exposure, either by a period of work with the polymer during the employment span and/or as the result of incomplete separation of the various parts of the production process. PVC dust was often to be found in several parts of the plants.

It would seem of interest to study further the influence of vinyl chloride and PVC in the experimental animal, as well as the pulmonary status of workers producing vinyl chloride monomer but not exposed to PVC during or after the polymerization process.

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Dr K S Williamson
(ICI Ltd, Central Medical Group, Fulshaw Hall, Wilmslow, Cheshire, SK9 1QB)

Review of Animal Studies

Since vinyl chloride is a gas at normal temperature and pressure, inhalation is the important route of exposure in industry, and most animal studies have used this method of dosing. Many experimental studies have demonstrated the very low acute toxicity of the compound. The acute inhalation toxicity was studied by Mastromatteo *et al.* (1960), who found that the lethal concentration for mice, rats and guinea-pigs exposed for 30 minutes was between 200 and 300 000 parts/10^6. In long-term studies few toxic effects were reported, though Torkelson *et al.* (1961) found that inhalation of vinyl chloride resulted in minimal microscopic changes in the liver and kidneys of several species of experimental animals exposed seven hours a day to 500–200 parts/10^6 for six-month periods. No significant changes were found in any species exposed to 50 parts/10^6 for six months.

In 1971, however, Viola *et al.* reported that while attempting to produce acro-osteolysis in rats, they had found tumours of the ceruminous glands, lungs and bones in animals exposed for 4 hours a day, 5 days a week, for 12 months to 30 000 parts/10^6 of vinyl chloride. Viola's findings, which are the earliest to be published describing the oncogenic effect of vinyl chloride, caused considerable concern throughout the world and led to further epidemiological and animal studies, many of which are still incomplete. The most complete series of animal studies available to us are those conducted by Maltoni and his co-workers (Maltoni 1973, Maltoni & Lefemine 1974). In these experiments groups of rats were exposed to vinyl chloride vapour concentrations ranging from 10 000 to 50 parts/10^6 for 4 hours a day, 5 days a week, for 12 months. The animals were then maintained for the rest of their lives unless they became ill. Tumours of the ceruminous glands, angiosarcomata of liver and other organs, nephroblastomata and a variety of other tumours were found in animals exposed to vinyl chloride. In animals exposed to 50, 250 and 500 parts/10^6 the logarithms of the numbers of animals having angiosarcomata and the total tumour-bearing animals are linearly related to the dose of vinyl chloride, but in animals exposed to higher concentrations, this relationship is not found. Tumours have also been found in mice and hamsters by Maltoni and by Keplinger *et al.* (1975), who reported the findings of angiosarcomata and lung adenomata in mice exposed

by inhalation to 2500, 200 and 50 parts/10^6 of vinyl chloride. More recently both Maltoni *et al.* (1975) and Purchase (1975, personal communication) and his co-workers have found liver tumours in rats given high daily oral doses of vinyl chloride in oil. Neither investigation is completed yet. Maltoni *et al.* dosed Sprague Dawley rats daily by gavage at 50, 16.6 and 3.3 mg/kg for 12 months. They reported the occurrence of one angiosarcoma of the thymus in the 50 mg/kg group and one angiosarcoma of the liver in the 16.6 mg/kg group in an interim report approximately 13 months after the start of the experiment.

Purchase and his co-workers dosed Wistar rats daily by gavage at 300, 30 and 3 mg/kg for 6 months. Fourteen months from the start of the experiment, a large proportion of the animals in the 300 mg/kg group and several of those in the 30 mg/kg group have been found to have liver tumours. Preliminary histopathological work suggests that some of these tumours are hepatocellular carcinomata, though further work is necessary before this can be confirmed.

To facilitate comparison between the dosage of vinyl chloride received by the animals in these very different long-term experiments, I have made some simple calculations which are presented in Tables 1 and 2. These calculated doses make no allowances for possible differences in the amount of vinyl chloride retained in inhalation and oral dosing experiments, and because of their low inherent accuracy are no more than rough guides to the doses involved.

Table 1

Rat inhalation studies (data of Maltoni)
Ventilation = 100 ml air/min = 6 litres/hour
24 litres per 4-hour exposure period = 0.024 m^3
Weight of rats assumed to be 500 g

Parts/10^6	*mg/m^3*	*Daily dose (mg) (0.024 × mg/m^3)*	*Daily dose (mg/kg)*	*Annual dose (g/kg) (daily dose × 250)*
500	1250	30	60	15
250	625	15	30	7.5
50	125	3	6	1.5

Table 2

Rat oral dosing studies

Study	*Daily dose (mg/kg)*	*Total dose (g/kg)*
Maltoni	50	12.5●
(250 doses)	16.6	4.0●
	3.3	0.8
Purchase	300	37.5●
(125 doses)	30	3.7●
	3	0.4

● tumours found

It is of some interest to compare the dose received by animals in long-term studies with calculated theoretical doses for men exposed to various shift-average concentrations of vinyl chloride at work (Table 3). Again the calculated figures are no more than very rough indications of dose, but they do give a useful measure for assessing the animal data.

Table 3

Men at work
Ventilation = 10 m^3 air per 8-hour shift
Weight assumed to be 70 kg

Parts/10^6	*mg/m^3*	*Daily dose (mg/m^3 × 10)*	*Daily dose (mg/kg)*	*Annual dose (g/kg) (daily dose × 250)*
500	1250	12 500	180	44.6
100	250	2500	40	8.9
50	125	1250	18	4.5
10	25	250	4	0.9
1	2.5	25	0.4	0.1

Green & Hathway (1975) and Watanabe *et al.* (1975) have studied the pharmacodynamics and metabolism of vinyl chloride using ^{14}C-labelled material given by different dosing methods to rats. Both groups have shown that the proportion of the dose retained and metabolized is greater following small doses than large, though the absolute amount metabolized falls with diminishing dose (Table 4).

Table 4

Amounts of vinyl chloride metabolized after differing single doses given orally in corn oil (Green & Hathway 1975)

Dose (mg/kg)	*Percentage metabolized*	*Amount metabolized (mg/kg)*
450	8	36
300	12	36
30	46	13.8
3	69	2.1
1	86	0.86
0.25	96.3	0.24

Three principal eliminative routes have been identified by both groups: expiration of unchanged vinyl chloride by the lungs, expiration as CO_2 by the lungs, and excretion of metabolites in the urine. The proportion of vinyl chloride eliminated by these different routes varies with dose (Table 5).

Table 5

Proportion of a single oral dose of vinyl chloride eliminated by various routes (Green & Hathway 1975)

Dose (mg/kg)	*Proportion eliminated (%)*		
	Unchanged	*Co_2*	*Urine metabolites*
0.25	4	12	75
450	92	1	6

Major metabolites identified in the urine are: (1) thiodiglycolic acid; (2) S-(2-chlorethyl) cysteine and N-acetyl-S-(2-chlorethyl) cysteine; (3) urea. Thiodiglycolic acid is derived from monochloracetic acid (this can itself be detected in small amounts in the urine) which in turn might reasonably be supposed to derive from cyclic chlorethylene peroxide or epoxide, powerful unstable alkylating agents which, though likely to have a very short life within the body, must have high potential biological activity. The cysteine containing metabolites may be presumed to arise by the reaction of vinyl chloride with cysteine derived from glutathione. Since the size of the glutathione pool may well be limited, vinyl chloride could cause significant depletion, so reducing the available protective mechanisms within the liver cells. Watanabe *et al.* (1975) have reported progressive depletion of the hepatic non-protein sulphydryl content (equivalent to glutathione in this context) in rats exposed to 1000 and 250 parts/10^6 vinyl chloride by inhalation. No such depletion was found following exposure of rats to 10 parts/10^6 for 7 hours. Hathway (1975, personal communication) considers that the ethyl cysteines themselves may well be mutagens. Thus work on the metabolism of vinyl chloride has already begun to identify several interesting areas for further investigation.

Though many important animal studies are still incomplete, there is already a substantial body of evidence to show that vinyl chloride is oncogenic, and there are some intriguing indications of the possible mechanisms of this action. The further studies which will be available in the near future may well help us to define working conditions which will not present health hazards to men exposed to vinyl chloride, and may perhaps allow us some insight into the fundamental mechanisms of the oncogenic effect.

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DISCUSSION

Dr L Magos (*MRC Toxicology Unit, Carshalton*) said that the dose plotted against the log of the number of malignancies gave a straight line, making it very difficult to draw any conclusion about the threshold or no-effect level, as the zero-effect level could theoretically never be reached.

Secondly, Dr Williamson's data on the metabolism of vinyl chloride depending on dose indicated that at low exposure levels a high proportion of vinyl chloride was metabolized and less was exhaled unchanged. This might mean that increasing exposure above a certain level would exhaust the biochemical ability of the organism to convert vinyl chloride to a toxic metabolite responsible for the carcinogenic effect.

These considerations indicated that experimental data must be interpreted with the utmost care.

Dr H E Stokinger (*Toxicology Branch, National Institute for Occupational Safety and Health, Cincinatti, Ohio*) said, in amplification of Dr Williamson's remarks on metabolism of vinyl chloride, that two metabolites had been identified in the liver of rats exposed to vinyl chloride: N-acetyl-S-(2-hydroxyethyl) cysteine and thiodiglycolic acid. The importance of knowing the nature of these endogenously supplied moieties was that they represented free, available sulphydryl (SH) groups that acted as 'scavengers' of the vinyl free radical, thus removing its oncogenic potential. In a series of decreasing exposures of rats the findings were: at 1000 parts/10^6, rapid and complete saturation of available free SH groups (liver); at 200 and 100 parts/10^6, fairly rapid saturation of available free SH groups; at 50 parts/10^6, a plateau of the saturation curve; at 10 parts/10^6, no disturbance in the amounts of free SH.

Inferences and conclusions: (1) From the fact that hæmangiomas occurred in the liver, and not in the lung (the primary site of entry), it could be inferred either that little or no vinyl chloride metabolism to free radical occurred in the lung, or that there was ample free SH to scavenge the vinyl radical. (2) Most important, the liver had a built-in antagonist to the vinyl free radical that provided the basis for a threshold for the carcinogenic response, in this case a threshold for an occupational carcinogen demonstrated by a specific biochemical constituent reaction. This finding explained the fact that among the tens of thousands of workers exposed only a small handful of hæmangiomas had been found. (3) Finding an oncogenic threshold of appreciable magnitude (between 50 and 10 parts/10^6) removed concern about general exposure of the public to small amounts (*see* Barnes, p 280) of vinyl chloride in PVC plastic wrappings of foods; the United States FDA could forget it! (4) To bolster resistance to effects of vinyl chloride, vegetables of the Brassica family should be eaten. Factors reducing free SH were: certain industrial exposures that were detoxified by cysteine, e.g. brombenzene; substances or conditions, e.g. certain chronic diseases.

Clinical Aspects of Vinyl Chloride Disease

Dr B J Preston,
Dr K Lloyd Jones
and Dr R G Grainger
(Departments of Radiology and Rheumatology, Harlow Wood Orthopædic Hospital, near Mansfield, and Department of Radiology, Northern General Hospital, Sheffield)

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 (A D) 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

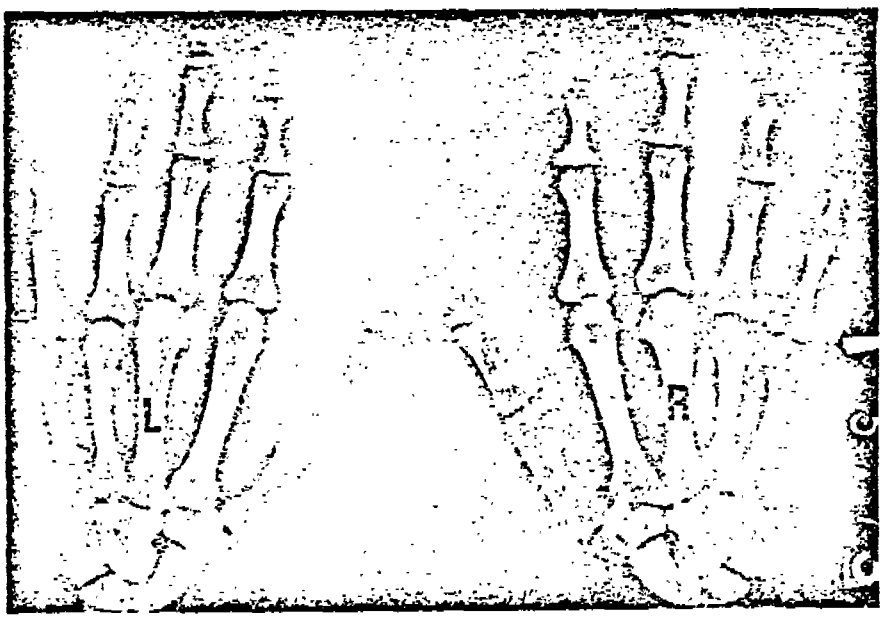

Fig 1 Case 1 *Hands (1.5.73), showing transverse defects in distal phalanges, osteolysis, erosions and soft tissue thickening*

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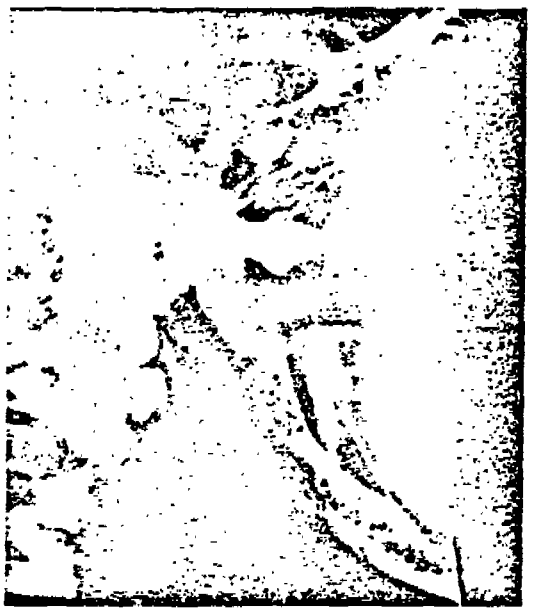

Fig 2 Case 1 *Mandible, revealing marked erosion of ascending rami*

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 radialis indicis 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 radialis indicis artery 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.

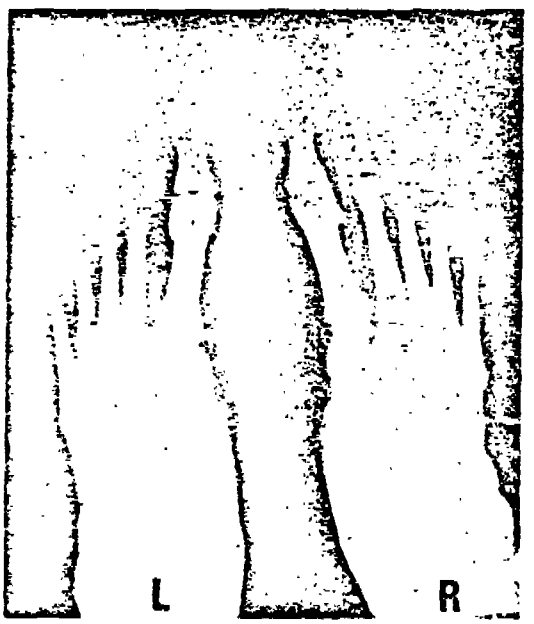

Fig 3 Case 1 *Feet, six months after presentation*

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 hyperæmia of the pulps of the fingers in a case of clubbing due to bronchial carcinoma and a similar mechanism may apply in our case, as there is a strong clinical resemblance to clubbing.

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DISCUSSION

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

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

Dr K Lloyd Jones added that Dr Preston's Case 1 al[illegible] 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 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, thrombocytopænia, 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 in the fingers but no [illegible] 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 [illegible] 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 anæsthesia. 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.

Table 1

Presenting symptoms in 37 men

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

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 [illegible] phenomenon; [illegible] 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 sclerœdema 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.

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 dyspnœa, cramp-like pains in the limbs, paræsthesia, 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 sclerœdema (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 Djerassi wondered whether this was an immedi[illegible] 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 sclerœdema-like change observed in 4 of the men varied considerably from day to day but in two men had persisted for at least eighteen months after the last exposure.

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

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

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

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

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

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

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

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

Dr A Milford Ward
(*Department of Immunology, 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 multisystem 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 hyperimmunoglobulinæmia, cryoglobulinæmia and cryofibrinogenæmia, 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 aminoacid 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 hyperimmunoglobulinæmia. 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 theoreti-

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 œsophageal 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 hæmaturia. 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 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 *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/10^6 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.

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

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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.

Dr K J W Taylor
(*Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut, USA*),
Dr J J Barrett
(*Department of Nuclear Medicine, King's College Hospital, London SE5*),
Dr D M J Williams
(*BP Chemicals International Ltd, Sully, Penarth, South Glamorgan*),
Dr P M Smith
(*Department of Medicine, Welsh National School of Medicine, Llandough Hospital, Penarth, South Glamorgan*),
and **Dr B W Duck**
(*Occupational Health Unit, BP Research Centre, Sunbury on Thames*)

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 fibrosis, portal hypertension, œsophageal 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 œsophageal 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

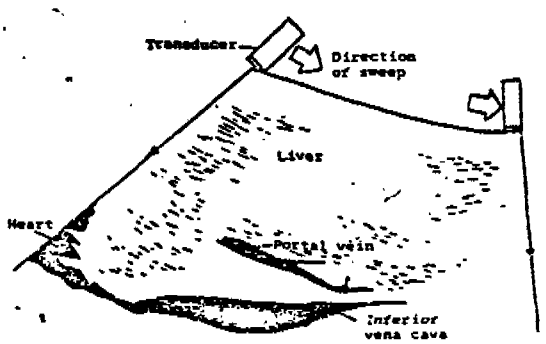

Fig 1 Schema to show movement of transducer to display the anatomical features shown in Fig 2. The portal vein is shown anterior to the inferior vena cava

Fig 2 *Parasagittal 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)

		Constant exposure			*Intermittent exposure*		
Case	*Age*	*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 9m	

Low exposure, 0–25 parts/10^6; medium, 25–200 parts/10^6; high, > 200 parts/10^6
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, œsophagoscopy, splenic venography and liver biopsy.

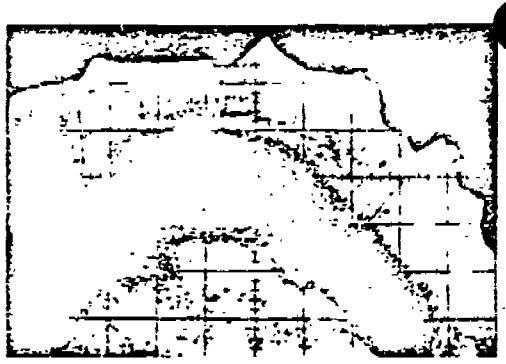

Fig 4 *Ultrasonogram of spleen scanned along tenth left interspace. When the spleen is enlarged due to portal hypertension, low-level echoes are returned and so appear dark. The grid squares are 2 cm apart, and the spleen is thus 17 cm in length. This enlargement was not apparent on a plain abdominal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

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 μmol/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/mm³	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 μmol/l, GGT 66 iu/l, platelets 99 000/mm³. Splenomegaly, œsophageal varices, periportal fibrosis	Marked enlargement of portal vein and spleen. Slight change in liver consistency
18	GGT 82 iu/l, platelets 45 000/mm³. BSP 19% (45 min). Splenomegaly, œsophageal varices. Fatty degeneration with minimal periportal fibrosis	Splenomegaly. Marked cirrhotic changes and fatty infiltration
19	Bilirubin 43 mol/l, SGOT 50 iu/l, platelets 80 000 mm³. BSP 21% (45 min). Splenomegaly. (Portacaval shunt 1968)	Marked splenomegaly and severe cirrhosis

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 on 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 hæmatologic 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 ultrasound examination

Case	Initial assessment	Ultrasonography	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.

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Dr M I V Jayson
(*Department of Medicine, University of Bristol*)
Dr A J Bailey
(*ARC Meat Research Institute, Langford, Bristol*)
Dr C Black
(*Department of Medicine, University of Bristol*)
Dr K Lloyd Jones
(*Harlow Wood Orthopædic Hospital, Mansfield*)

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 of 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 morphœa 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 hydroxylysinonorleucine 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

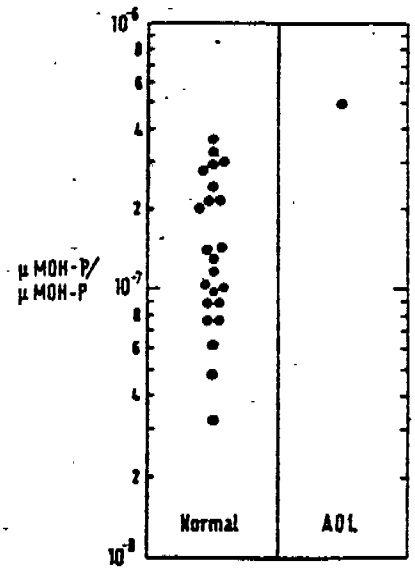

Fig 1 *Rate of synthesis of hydroxyproline related to the original hydroxyproline content of normal and AOL skins (μmol)*

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 ^{3}H-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 ^{3}H-proline, hydrolysed and separated in an amino acid analyser and the quantity of synthesized ^{3}H-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 ^{3}H-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 ischæmia with ulceration of the fingertips and further local collagen production. Ischæmic necrosis could similarly occur in AOL and so produce the typical bone lesions.

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 ischæmia 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

Dr P J Baxter
(*Employment Medical Advisory Service, Health and Safety Executive, Baynards House, 1 Chepstow Place, London W2 4TF*)

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/10^6), medium (>25 parts/10^6), and low (<25 parts/10^6), 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 miscertified 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. They will also attempt to obtain photocopies 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 ther 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
(*Department of Histopathology, Royal Postgraduate Medical School, Du Cane Road, London W12 0HS*)

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. × 150*

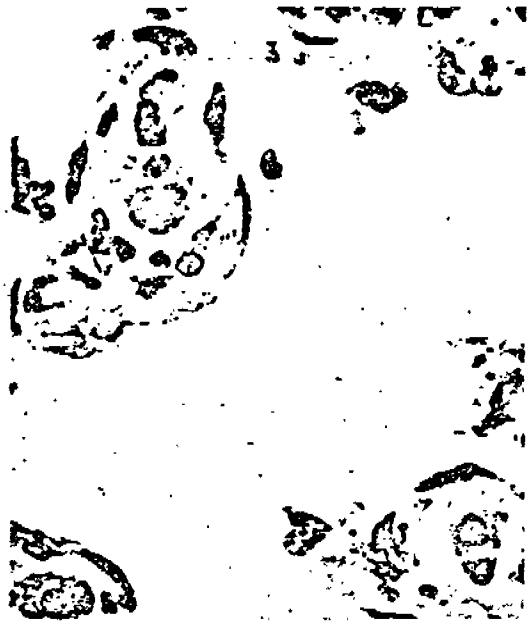

Fig 2 *Papillary formations of tumour cells are borne on a core of connective tissue and hepctocytes. H & E. ×600*

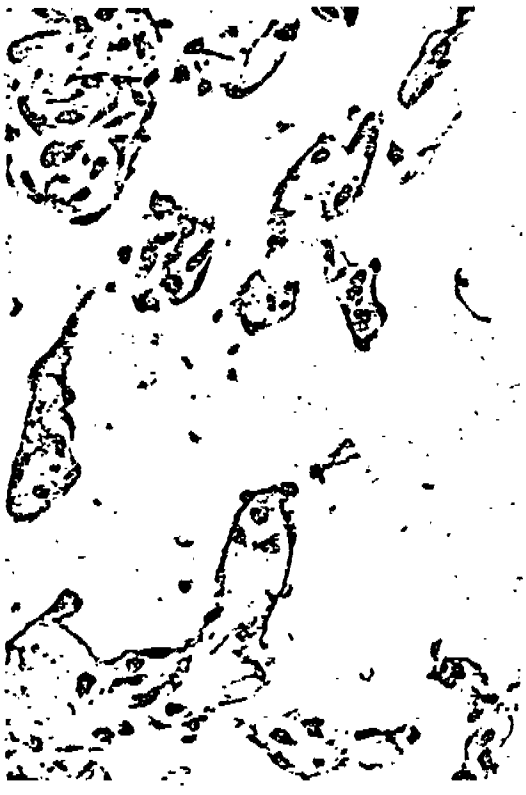

Fig 3 *Well-differentiated flattened tumour cells, resembling endothelial cells on connective tissue cores and lining vascular spaces. H & E. ×400*

Fig 4 *Bizarre giant tumour cell in papillary angiosarcoma. H & E. ×600*

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 hæmorrhagic nodules in the liver; there is a variable distortion and apparent fibrosis in the intervening liver tissue. Sometimes foci are macroscopically less hæmorrhagic. 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,

Fig 5 *Solid area of tumour resembling solid spindle-cell sarcoma. H & E. ×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 manœuvres 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. × 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

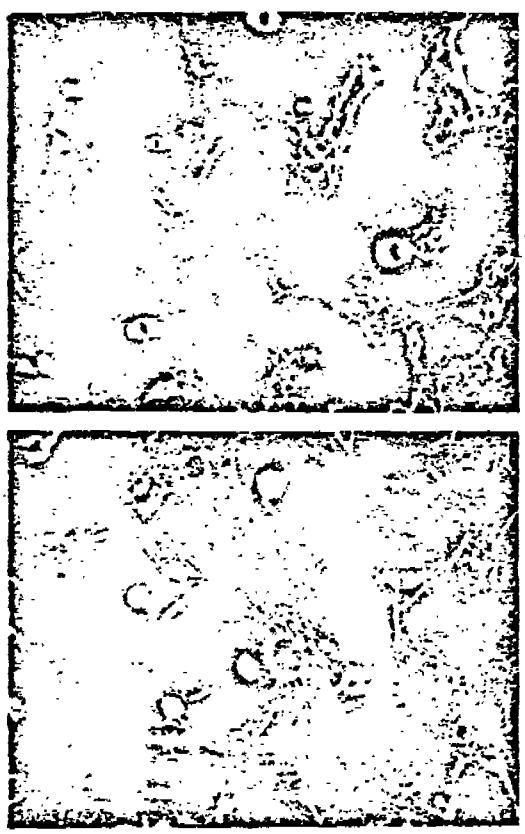

Fig 7 *Liver biopsy sections showing variations in intralobular sinusoidal reticulin. Upper, slight increase. Lower, much increase. Gordon & Sweet silver impregnation: Dark-ground illumination.* × *360*

Fig 8 *Hepatic capsular fibrosis in patient exposed to vinyl chloride monomer and presenting with portal hypertension. H & E.* × *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 nontumourous 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 and enlarged sinusoidal lining cells and hepatocyte mitotic abnormality in same patient as Fig 8. H & E. × 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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Dr Henry Falk
(*Cancer and Birth Defects Division, Bureau of Epidemiology, Center for Disease Control, United States Public Health Service, Department of Health, Education, and Welfare, Atlanta, Georgia 30333, USA*)
and Mr Richard J Waxweiler
(*Division of Field Studies and Clinical Investigations, National Institute for Occupational Safety and Health, Center for Disease Control, United States Public Health Service, Department of Health, Education, and Welfare, US Post Office Building, Cincinnati, Ohio 45202, USA*)

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, Lilis *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, parallelling 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

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 occupations, toxic exposures, and places of residence is underway.

Medical Screening of VC Workers

Together with the Occupational Health Studies Group of the University of North Carolina, NIOSH-CDC recently concluded a cross-sectional medical screening examination of 530 workers at a plant in Pennsylvania which contains both a large tyre-building facility as well as one of the oldest PVC polymerization plants in the United States. Included in the study were approximately 130 current PVC polymerization workers and a similar number of control workers from the tyre plant who had never worked in the polymerization facility. The 2 groups were comparable in age, alcoholic intake, and socioeconomic background; the controls were chosen from those areas of the tyre plant where exposure to solvents and dusts was least.

Preliminary review of the results shows no significant differences between the 2 groups for any of the 6 liver function tests performed (SGOT, bilirubin, alkaline phosphatase, LDH, GGTP, and ornithine carbamyl transferase). Additional analyses based on levels of VC exposure, duration and type of job, and other subgroupings are being done; these preliminary results however do not suggest the occurrence of liver function abnormalities on a broad scale secondary to VC exposure. One should of course be cautious about generalizing from the results at a single plant, and it will be important to compare these findings to studies at other PVC plants. It is also important to realize that since liver function tests are relatively insensitive to the early finding of VC-induced hepatic disease (i.e. fibrosis), the results of this type of testing are not a reliable estimate for the prevalence of VC-induced disease. Liver scans were also performed on all workers with more than 10 years duration of work in the PVC polymerization plant, and no cases of HAS were detected. Some increase in frequency of palpable livers on physical examination was found, however, among VC workers. A full report of findings from this comprehensive medical screening study is in preparation and will be available shortly.

Cohort Mortality Study at Four PVC Polymerization Plants

One of the results of this NIOSH-CDC study was the demonstration of an increased SMR for respiratory system cancer among members of the cohort (Waxweiler *et al.* 1976). On preliminary pathologic review, it was also noted that of the 12 lung cancer cases all 8 for which pathologic specimens were available were either large cell undifferentiated or adenocarcinoma of the lung; if confirmed, this unusual cell type distribution may support the association between VC exposure and occurrence of lung cancer.

Table 3

Lung cancer among workers at PVC polymerization plants in the United States by histologic type and extent of VC exposure

	Extent of VC exposure			
Histologic type	*None*	*Less than one year*	*More than one year*	*Total*
Epidermoid	1	1	0	2
Small cell undifferentiated	0	3	0	3
Adenocarcinoma	1	1	4	6
Large cell undifferentiated	4	0	6	10
Unclassified	1	0	0	1
	7	5	10	22

There are, however, two additional features which should be considered in evaluating this potential relationship. When all of the workers at these 4 plants are considered, including those who were not part of the defined VC-exposed cohort, a total of 22 cases of lung cancer (out of 48) were available for pathologic review. The increased incidence of large cell undifferentiated and adenocarcinoma of the lung was seen in VC workers with more than 1 year of exposure, while a distribution more closely resembling the expected small cell predominance was seen for VC workers with less than 1 year of exposure. Interestingly, however, cases of lung cancer in non-VC workers at these plants, although small in number, appeared to have a cell type distribution which was also predominantly large cell undifferentiated (Table 3). In addition, unlike the situation for HAS in these plants where all but one of the cases were long-term reactor cleaners and operators, the workers with large cell undifferentiated and adenocarcinoma of the lung were distributed in a number of different job categories. As a result, cases of lung cancer seem not to correlate as tightly with VC exposure as cases of HAS and it is conceivable therefore that some additional chemical exposure at these plants may be working together with VC (or even separately) to produce this effect. Further studies are currently underway in an effort to confirm these preliminary pathologic findings.

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DISCUSSION

Dr Mitchell R Zavon (*Baton Rouge, Louisiana*) asked whether the clinical examiners at Pottstown knew whether or not the person being examined worked in vinyl chloride.

Dr H Falk replied that none of the clinical examiners were aware of the occupational status of the workers at the time of the examination.

Dr R I McCallum (*University of Newcastle upon Tyne*) asked Dr Falk to give in more detail the way in which histological diagnosis was made in the case of lung cancer shown in his slide. Was this done by one individual or by a panel of pathologists? How were the specimens of tissue obtained: by biopsy, surgical resection or at autopsy? It was remarkable that in none of the cases was an oat cell carcinoma diagnosed, as this was the type often considered a characteristic result of exposure to a chemical carcinogen.

Dr H Falk replied that the WHO lung cancer classification scheme of Kreyberg (1967) was used. Four pathologists reviewed the slides and agreed on the interpretation (Dr Louis B Thomas and Dr T Powell, National Institutes of Health; Dr M Kuschner, State University of New York; and Dr Laszlo Makk, St Anthony Hospital, Louisville, Kentucky). All available pathological material for each case was reviewed.

The expanded pathological review currently underway would include the selection of multiple control cases of lung cancer from the same hospitals (with similar age and date of diagnosis to the study cases) and a blind review by a panel of pathologists in a more detailed evaluation of available pathology material.

To Dr Falk's knowledge large cell undifferentiated carcinoma of the lung had not been related to exposure to chemical carcinogens, which made the findings in the VC cohort even more intriguing.

Dr A J Fox (*Employment Medical Advisory Service, London*) asked how many factories had been studied individually in the USA. What proportion of these had indicated vinyl-chloride-associated disease?

Dr H Falk replied that cases of hepatic angiosarcoma had been seen at 5 of the 8 PVC polymerization plants opened prior to 1950.

There was some confusion in this area in that a number of the VC worker mortality studies had been overlapping. Three separate studies, for example, (the NIOSH-CDC study, the Tabershaw study, and the Monson-Peters study) had all looked at the Louisville, Kentucky plant where the initial angiosarcoma cases occurred as well as at a varying number of additional plants. Compounding the problem was the fact that the definitions for entrance into the cohorts studied differed from study to study, so that the results even at the same plant were not identical.

Dr J A Bonnell (*Central Electricity Generating Board*) asked whether, since vinyl chloride monomer was a carcinogenic agent, there was any evidence in experimental animals or in human clinical experience that the skeletal or skin changes described might be premalignant conditions.

Dr H Falk said that cases of angiosarcoma in the USA did not have a history of acro-osteolysis or skin problems, although they did not have the multiple tests for early changes of acro-osteolysis. It would seem, therefore, that the skin changes were not premalignant conditions.

Professor I J Selikoff (*Mount Sinai School of Medicine, City University of New York*) said that a review of known details of identified cases of vinyl-chloride-associated angiosarcoma of the liver by Dr Lloyd (1975) of the National Institute for Occupational Safety and Health had demonstrated that the median duration from onset of exposure was approximately seventeen years. These cases were derived from the rather small number of polymerization workers employed during the establishment and initial growth of the vinyl chloride industry. Attempts were underway to identify and trace the initial groups of workers, employed during the years 1938–55, since analysis of their experience would allow evaluation of the risks which might be suffered by the very much larger group of vinyl chloride workers exposed more recently, in a period during which PVC production was increasing at the rate of approximately 10% per annum.

Limited data bearing on the problem had been obtained. In one polymerization process studied, 257 men had been employed for five years or more in the period between 1946, when the plant opened, and 1964. Each man had been traced to 1 July 1974, with 25 deaths from all causes: 3 of the deaths were due to angiosarcoma of the liver (Nicholson *et al.* 1975), each confirmed on review of autopsy material (Thomas & Popper 1975); in addition there was one death due to ruptured œsophageal varices. Another worker, examined during the clinical survey at this facility (Lilis *et al.* 1975) had had a successful portacaval shunt operation for the same condition. These experiences suggested that vinyl-chloride-associated disease would be an important hazard for vinyl chloride workers in the future, unless control of exposure resulted in at least some reversal of the risk.

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Dr B W Duck
(*Occupational Health Unit,*
BP Research Centre,
Sunbury on Thames, TW16 7LN)

Medical Surveillance of Vinyl Chloride Workers

Following the announcement in January 1974 of the first cases of angiosareoma of liver among workers exposed to vinyl chloride in the USA, the Chemical Industries Association in the United Kingdom set up a Vinyl Chloride Committee, with a number of specialist working groups, including one on health aspects.

The first task confronting this working group, which comprised medical representatives of the four British companies engaged in the production of vinyl chloride (VC) and polyvinyl chloride (PVC), was to review all the relevant medical and toxicological information available and decide what action should be taken to protect the health of exposed employees. This is an interim report on one aspect of the group's work.

At that time, little was known about angiosarcoma of the liver and its treatment. Due to its rarity, there was considerable doubt about both its natural history and appropriate methods of early diagnosis. Reports indicated that non-malignant forms of liver pathology, such as fibrotic changes, might be more prevalent among vinyl chloride workers than had hitherto been suspected, but the significance of such disturbances of liver function and structure in relation to the development of angiosarcoma had yet to be established. Similar considerations arose in respect of the previously recognized condition of acro-osteolysis (AOL) and its various manifestations, since it was speculated that there might be some common underlying vascular pathology.

To complicate the situation still further, long-term carcinogenicity tests on laboratory animals had not only produced many angiosarcomas, but also a considerable number of renal and other tumours.

The situation was discussed with medical colleagues in Government and Trade Union agencies, and specialists in liver disease, and much helpful advice was received from them and from various overseas sources, especially from doctors in the United States. It soon became apparent, however, that there was no established procedure for the early detection of liver angiosarcoma that could serve as a basis for a large-scale screening programme in industry. As practical screening possibilities were very limited and the early diagnostic value of suitable techniques was uncertain, vinyl chloride workers could not be asked to volunteer for medical examination on the grounds that this would detect early malignant disease of the liver; nor could they assume that such examinations would be beneficial to individuals in terms of preventive medical action. In the latter context, effort had to be concentrated on urgent measures to reduce exposure to vinyl chloride, a task which was being energetically tackled by our technical colleagues.

Nevertheless, there were many arguments in favour of inviting vinyl chloride workers to attend site medical centres to participate in a standard medical examination programme: (1) Opportunity for personal discussion. (2) Establish prevalence of disease. (3) Establish prevalence and significance of liver dysfunction. (4) Correlate positive findings. (5) Identify possibly susceptible individuals. (6) Compare findings in VC workers and controls. (7) Assess feasibility and value of medical surveillance. (8) Establish data base for further studies. For these reasons it was decided to carry out an initial clinical survey on all sites where VC and PVC were produced, based as far as possible on the application of standard procedures to both vinyl chloride workers and controls. A programme of action was discussed and agreed with medical representatives of Government and Trade Union agencies and it was accepted that one of the main objectives was to gather clinical and epidemiological data to provide a reasonable foundation for future decisions concerning regular medical surveillance.

The survey population was divided as follows: Vinyl chloride workers Group 1 – all autoclave floor workers, vinyl chloride monomer (VCM) production workers with five or more years' service; Group 2 – vinyl chloride monomer production workers with less than five years' service, all other VCM/PVC production workers. Controls – workers from same sites with no history of VC exposure.

A standard medical examination procedure was adopted: Initial examination comprising medical history (questionnaire), physical examination, biochemical tests (SGOT, SGPT, GGTP, alkaline phosphatase, bilirubin), platelet count, urinalysis. Follow up of abnormal findings, with repeat biochemical tests and platelet count, and persisting abnormalities referred to consultant for specialist investigation.

The programme was introduced simultaneously on the six production sites and the employees concerned were informed that it was not an individual screening test, but a joint investigation to provide data that would help to establish future medical policy. It was also explained that any individuals with suspicious findings, notably persistently abnormal test results, would be referred for appropriate specialist investigation by arrangement with their family doctors.

Due to a variety of reasons, not least the problem of interpreting the significance of borderline

abnormalities and workload difficulties experienced by both medical advisers on sites and consultants and laboratory staff in National Health Service hospitals, the programme has taken longer than expected and is still incomplete. Hence interim findings only can be presented at this stage and no firm conclusions can be drawn until all the facts have been elicited and the mass of data obtained has been appropriately analysed. So far, 1357 vinyl chloride workers and 429 controls have been examined. The examinations of vinyl chloride workers include 882 from Group 1 (representing an average response rate of 80%) and 475 from Group 2 (in which the proportion volunteering for examination is lower). Initial liver function test abnormalities have been found in 12.5% of the vinyl chloride workers and 16.5% of the controls. Repeat tests on vinyl chloride workers with abnormal findings have revealed persistent abnormalities in about one-third of the individuals concerned (56 men, 4.1% of the original group). No comparable data for the controls can be presented at this stage.

The 56 vinyl chloride workers with persistently abnormal liver function test results have been referred to consultants at local NHS hospitals for further investigation. These investigations have not revealed any cases of angiosarcoma and the consultants concerned have already attributed many of the persistent abnormalities to pathological conditions unrelated to vinyl chloride exposure. At present, the causes of liver dysfunction remain uncertain in about one third of these 56 cases, where precise diagnosis rests largely on the final conclusions reached by expert pathologists who are studying relevant liver biopsy specimens. To put these interim results in perspective, it should be noted that almost all the men in the latter group remain in full employment, although many of them have been transferred to work involving no further exposure to vinyl chloride in case their liver dysfunction renders them unduly susceptible to potentially hepatotoxic agents.

While this survey was in progress, previously established procedures for the detection of AOL and related conditions among vinyl chloride workers remained in force and 2 new cases of AOL have been diagnosed. The survey provided an opportunity to assess the prevalence of Raynaud's phenomenon among controls on three sites and comparisons with findings in vinyl chloride workers suggest that the condition may be equally prevalent in the two groups. However, no standard diagnostic criteria were applied and the prevalence of the condition varied widely between sites. No association has been observed between Raynaud's phenomenon and liver function abnormalities in individuals, which is of interest in view of the apparent rarity of AOL in the cases of liver angiosarcoma that have been reported in the literature. The routine urinalyses have revealed no relevant abnormalities.

Tentative Conclusions

Abnormal liver function test findings were relatively common in both vinyl chloride workers (12.5%) and controls (16.5%) even though results had to fall well outside (2 or 3 standard deviations) the normal range in order to be classified as abnormal. Repeat testing revealed persistent abnormalities in one third of the vinyl chloride workers in whom the initial findings were abnormal and these 56 men were referred for further investigation. Comparable data for the controls are at present unavailable.

If less stringent criteria of abnormality had been adopted, the number of individuals for retesting would have been considerably greater and the effect this might have had on specialist investigation and disease detection is a matter for conjecture. The definition of abnormality is critical in this context and merits further consideration and study if the correct balance is to be achieved.

In view of the findings to date, it is not surprising that opinions of working group members about the value of periodic liver function tests in vinyl chloride workers are divided. No obvious liver disease due to vinyl chloride exposure has been identified so far, but evidence of non-cirrhotic fibrosis has been found in some cases and until the results of blind interpretation of the liver biopsy specimens become available no firm opinions can be expressed about the presence or absence of any specific pathology related to vinyl chloride in the survey population. The procedure has enabled individuals with persistent liver dysfunction to be detected and removed from exposure to vinyl chloride, and some doctors propose to continue regular liver function tests for this and other reasons, such as the need to assess sequential changes. On other sites, the yield of significant clinical findings has been so low in comparison with all the difficulties encountered that it is considered liver function tests should only be applied on a discretionary basis in future. In this connexion, it is argued that, in order to be effective, the tests used should: (*a*) yield positive findings at an early stage of disease; (*b*) produce few false positive and negative results, and (*c*) ideally, be able to differentiate between pathological conditions due to vinyl chloride and those due to other causes, such as alcohol.

It is also argued that continued application of a battery of tests to vinyl chloride workers is likely to cause considerable alarm and disquiet if the

results serve only to raise further doubt and confusion. At the present time, it appears that detection of structural rather than functional changes in the liver is likely to be more rewarding for screening purposes, and for this reason attention is now being focused on evaluation of grey-scale ultrasonography as an acceptable, noninvasive technique for the periodic examination of vinyl chloride workers.

In conclusion, although the survey is incomplete, it has already yielded information of value for planning purposes, as originally intended. From now on, it seems advisable to concentrate effort on smaller and more detailed studies that are designed especially to evaluate specific hypotheses, particularly in view of the fact that the stringent environmental standards now in force are expected to minimize, if not eliminate, any risks to health associated with exposure to vinyl chloride.

DISCUSSION

Dr A John Robertson (*Liverpool*) asked what was done for those whose tests, under the surveillance scheme, were abnormal. A man had been mentioned who was refused life insurance because of abnormal liver function tests. Taking a parallel with lead, a man could be suspended because of a raised blood lead level, and could then be refused industrial compensation because he did not have a scheduled disease, and yet the employer would not pay his wages.

Dr B W Duck replied that men with persistently abnormal liver function test results were referred to consultants for further investigation and their family doctors were kept informed throughout. In the light of the findings the consultants and other doctors concerned decided whether removal from vinyl chloride work was indicated and the men in question were advised accordingly. It was then left to the men to decide whether to accept or reject this advice. To date, only one man had rejected such medical advice and the rest had been transferred to alternative work with no loss of pay.

Dr Robert Murray (*Sudbury*) said that this was a very real problem which it was proposed to deal with in the Employment Protection Bill currently under discussion in Parliament. This would give to a man laid off for preventive reasons, because he showed early signs of absorption, the right to full wages during the period of lay-off. The more sensitive the methods of early diagnosis or the more stringent the standards of exposure, the greater would be the need to have some system to cover the no man's land between absorption which was not compensatable and disease which was. In large organizations it was usually easy to transfer the individual, without loss of money, to alternative work not involving exposure, but in smaller industries this might be difficult or impossible.

Dr L Magos (*MRC Toxicology Unit, Carshalton*) said that in Dr Duck's paper no distinction was made between data on workers from a factory where polyvinyl monomer pollution had decreased rapidly over the past few years (as in the plant described by Mr A W Barnes) and data on those employed in a factory where (as in Dr Anne Walker's cases) even in recent years acute narcotic episodes had occurred. This lack of distinction might completely distort Dr Duck's statistical evaluation of clinical data obtained during the survey.

Dr B W Duck replied that Dr Magos' point was well taken. However, as explained in the text, the paper presented interim findings from which no firm conclusions could be drawn. When all the data were complete it was envisaged that the industrial doctors and their consultant colleagues would publish the results obtained from individual factories.

Mr H F Henning
(*Health and Safety Executive, 403-405 Edgware Road, London NW2 6LN*)

Environmental Monitoring

It is a common misconception that environmental monitoring is easy, just a matter of collecting a sample, analysing it and getting a figure. Environmental monitoring is never easy and when an industry is faced with a sudden and substantial tightening of the standard to be applied there are equally suddenly many questions to be asked and answered. In addition, when industry and Government have to write a Code of Practice before the event, and therefore without the benefit of experience or hindsight, there are many more questions. Some of these are discussed in this paper.

Instrumental Techniques

When the threshold limit value (TLV) for vinyl chloride monomer (VCM) was 200 parts/10^6, that is before 1974, the instrumentation used for monitoring was relatively fairly crude and insensitive. One common instrument had a lower response at about 200 parts/10^6 so that a nil reading was taken to indicate a concentration below 200 parts/10^6, a very convenient situation. Even the chemical indicator tubes were not designed to show concentrations below 100 parts/10^6.

With the introduction in early 1974 of the new standard of 25 parts/10^6 (time weighted average) and 50 parts/10^6 (ceiling value) other existing instrumental techniques had to be adopted for use in the VCM atmospheres. Unfortunately some of the equipment which had been designed for laboratory use was not flame proof and so could not be installed directly in factory workplaces. However, many of the difficulties were overcome and all the VCM and PVC manufacturing plants have now installed what we originally called

continuous monitoring but which is more correctly termed automatic sequential fixed point sampling. This is supplemented where necessary by short-term sampling for investigations or for checks on equipment and by long-term personal sampling to show the work people's actual exposure over long periods, e.g. four or eight hours.

Presentation of Results

The Code of Practice requires the results to be available to the workforce and for summaries to be posted in work rooms. Each fixed point monitoring system takes a sample once per minute and therefore provides nearly 500 readings per shift so that trying to decide beforehand how the results should be summarized and presented was a major problem because there was little previous experience of monitoring, and recording the results of monitoring, on such a scale.

One way of presenting the results would be to take an overall average. This has recently been done and figures provided by the industry show that the average concentration in the UK factories had been reduced in a matter of months from 24 to 6 parts/10^6. Recent figures from some of the plants even show long-term averages of about 2 parts/10^6. This suggests enormous progress, as indeed it is, and compares favourably with averages published by other countries. However, an overall average such as this is influenced very considerably by selection of the sampling sites and by the frequency of sampling, two aspects which are completely lost in this method of presentation and of course it offers little of use in the protection of the worker, which is the main objective of monitoring.

Influence of Peaks

An average over any period of time is influenced very considerably by peaks. For example, in a 20 point system sampling every minute a single peak of 600 parts/10^6 due to a transient leak from nearby plant would add 25 parts/10^6 to the shift average. In the UK we feel that it is essential to record these peaks, because they indicate escapes of VCM due perhaps to defective plant or perhaps to incorrect work practice, both matters which ought to be remedied. If the monitoring points are selected to provide a balance between operator work stations and areas where leaks may occur then we must expect to obtain some high readings. These occasions will generally be investigated and will therefore play an important role in the long-term reduction of atmospheric concentration of VCM, but in the short term they make the picture look bad, both by their presence as peaks and by their contribution to the overall shift average. There is of course no suggestion that any operator is necessarily exposed to such peaks or to such a raised average, since many of the peaks may have occurred in specially selected areas where no person works regularly or the operator may have known about the situation and worn a respirator during that period.

Influence of Sampling Frequency

The frequency of sampling can also have an influence on the picture. Let us assume that some of the sampling points have been chosen to pick up leaks from the plant so that, say, 10% of the readings are above the ceiling value of 50 parts/10^6. In a multi-point monitoring system sampling every minute this means that 48 readings per shift for that system alone will be above the ceiling value. Sampling at the minimum frequency required by the Code of Practice, i.e. once per shift, would give on average one high reading in each work area every tenth shift. Sampling at the minimum frequency required by the US standard, i.e. once per month, would give on average one high reading in each work area every tenth month.

We see therefore that frequent static sampling at carefully chosen points can provide much useful information but it does not necessarily tell us exactly what concentrations the work people are actually exposed to. This can be shown best by personal monitoring which is normally done at less frequent intervals because it is time-consuming for the testing staff and somewhat restrictive for the operator wearing the equipment. Nevertheless this is an extremely useful supplement to the general workroom monitoring.

Other Problems

I have said nothing in this short paper about preservation of records, which provides many problems not previously encountered in industry, nor about atmospheric monitoring in the PVC user industry where general atmospheric concentrations are less than 5 parts/10^6 and usually less than 2 parts/10^6, with a few known and controllable problem areas.

In short, we in the UK believe that atmospheric monitoring should be used to provide the maximum amount of information. This means that the monitoring schemes incorporating extensive multi-point systems can provide (*a*) useful information on deficiencies in plant or in operating procedures, (*b*) information with which to demonstrate progressive improvements in our aim to reduce exposure to near zero, (*c*) information on personal operator exposure which can be kept for future reference. Unfortunately in the short term it also provides much ammunition for our critics. This, however, is a small price to pay for the long-term benefits which we know will accrue from our efforts.