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Brief Summary

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SUMMARY:

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HEALTH EFFECTS OF VINYL CHLORIDE

LUNG

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INTRODUCTION

Vinyl Chloride-Associated Injury in Man

Vinyl chloride (CH_2 = CH-Cl monochloroethylene, a gas) has been the basic molecule or monomer of polyvinyl chloride and its co-polymers and has been one of the most important organic intermediates in the plastics industry for over a quarter of a century. During this time, evidence for both chemical toxicity and carcinogenicity has been accumulated in man and in animals. Reports from across the world have indicated the presence of thrombocytopenia, reticulocytosis, and leukopenia among the hematological disorders. Scleroderma type skin lesions, acro-osteolysis of the distal phalanges, and Raynaud's phenomenon have been well described. Abnormalities in pulmonary functional capability and cardiac arrythmias associated with its use as an anesthetic have also been noted. The most widely known disorders include hepatic fibrosis, peliosis hepatis, hepatomegaly, splenomegaly, portal hypertension, and hepatic angiosarcoma (1). There is at present some epidemiological and histological data that large clear cell carcinoma of the lung and neuroblastoma of the brain are also associated with exposure to vinyl chloride.

Vinyl Chloride-Associated Injury in Animals

Many of these lesions have also been described and shown to develop in animals exposed to vinyl chloride. In addition to the liver angiosarcomas and the brain neuroblastomas, vinyl chloride-exposed rats and mice have shown Zymbal gland (sweat gland) carcinomas, nephroblastomas, subcutaneous angiomas, skin carcinomas, and a variety of adenomas of the breast, pituitary glands, and other assorted sarcomas of the ovary, pulmonary, and uterus.

A simple summary of cancers by site in vinyl chloride workers in our cohort who had worked more than one year is shown in Table I.

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UPDATE OF NEW MEDICAL FINDINGS RELATED TO VINYL CHLORIDE

A. Histological Sequences of Injury:

The hepatic lesions in the humans and in animals related to prolonged exposure to vinyl chloride have been fairly well characterized. One of the earliest findings is "activation" or morphological changes in the sinusoidal lining cells without evidence of hepatocellular toxicity. These morphological changes in the sinusoidal lining cells are not usually associated with an inflammatory process or evidences of localized necrosis. The more advanced lesions are associated with an increase in subcapsular fibrosis with subcapsular bile duct proliferation, which causes the liver surface to appear "pitted" with small white scars when viewed at laparotomy or by peritoneoscopy. These lesions are associated with increased portal fibrosis of varying degree most often rounded in shape on the cut surface and only rarely showing short stellate radiation into the parenchyma. The lobular architecture, in general, is preserved, with the central vein areas being devoid of excessive collagen deposition, as illustrated in Figure 1. The sinusoidal lining cells tend to be helmet shaped, have triangular nuclei and appear to be associated with increased deposition of collagen in adjacent sinusoidal spaces. In addition, there is a focal sinusoidal dilatation within the lobular architecture often associated with bi-nuclear hepatocytes, suggesting active regeneration of the hepatocytes. More recently, Dr. Hans Popper has described focal areas of hepatocytic hyperplasia consisting of two or three cell thick plates, not associated with lobular fibrosis and regeneration as seen in alcoholic and viral injuries. With progressive exposure to vinyl chloride, there appears to develop increasing atypia of the sinusoidal lining cells, progressive worsening of the focal sinusoidal dilatation (Figure 2), and ultimately, the malignant transformation of the sinusoidal lining cells (Figure 3). At present, it is not clear which of the sinusoidal lining cells (macrophage/Kupffer cell, fibroblast/Ito cell, or the sinusoidal endothelial lining cell) is the malignant stem cell which develops angiosarcoma. Most present data strongly suggests that it is the endothelial lining cell which ultimately becomes malignant and forms the angiosarcoma. Further studies will be needed to verify this thesis.

B. Biochemical Detection:

Biochemical detection of these lesions has until recently, been mainly by traditional biochemical hepatocellular studies. These have included the alanine and aspartic aminotransferases (SGPT-SGOT), gamma glutamyl transpeptidase (GGTP), alkaline phosphatase, bilirubin (both direct and indirect), and other enzymatic studies, such as sorbital dehydrogenase and isocitric dehydrogenase. As illustrated in Figure 4, our preliminary evaluation indicated that the ability of these traditional biochemical tests to predict the presence of underlying histological hepatocellular damage is at best 80-85% accurate -- the most effective of which is the alanine aminotransferase (SGPT). The gamma glutamyl transpeptidase is equally as effective but has a 6-8% false positivity; that is, abnormalities of the GGTP levels persist without histological or functional evidence of hepatocellular injury. Although elevations in alkaline phophatase most often reflected the more serious abnormality, in almost

one quarter of the individuals, it was found to be normal in the presence of hepatocellular injury.

More recently, the introduction of indocyanine green (ICG), an anionic dye similar in its physiological capabilities to Bromsulphalein (BSP), has increased our ability to identify mild and latent underlying chemical hepatocellular injury. Indocyanine green can be given in various dose levels for purposes of determining hepatic clearance. At the low dose, 0.5 mg/kg, its predictability is equal to that of the aminotransferases. By increasing the clearance dose to levels of 2.5 and/or 5.0 mg/kg, one can increase the ability to identify underlying hepatocellular injury to the 98-99% range. A definitive biostatistical evaluation of both the specificity and sensitivity of indocyanine green, in comparison to the traditional biochemical studies, is now underway.

Figure 5 illustrates the correlation found during preliminary studies between liver histology and dye clearance among vinyl chloride workers with increasing degrees of total vinyl chloride exposure. This is further supported by the frequency of abnormal dye clearances at both the low 0.5 mg/kg and the high 5.0 mg/kg clearance dose among vinyl chloride exposed workers (2). Although these tests are very sensitive to identifying underlying disease, they have very poor specificity in identifying the causal agent and, because of this, are suited as screening tools rather than diagnostic ones.

C. Various Tumor Types:

Hepatic angiosarcoma, although appearing to be of a single cell origin, may be of multiple cell origins. Morphologically it occurs in a cellular, cavernous, and solid form. The cavernous and the solid tumor forms are most effectively detected by radioisotopic liver scans. In addition, diagnostic angiographic characteristics differentiate angiosarcoma from primary hepatocellular carcinomas, adenomas, cavernous hemangiomas, focal nodular hyperplasia, and macronodular regeneration of cirrhosis. Whelan et al., have described the characteristic angiography and radionuclide changes that are characteristic of hepatic angiosarcoma (3). The tumors exhibit central hypovascularity with puddling and are surrounded by a peripheral stain which persists late into the venous phase of the angiographic study. Radioisotopically this form of a tumor presents with a negative peripheral defect which, on occasion, may be missed on the anterior view of a scan but is seen on the lateral or posterior view. As demonstrated by Whelan et al., healing hepatic infarcts secondary to wedged hepatic venography can create a false positive lesion on angiography similar to that seen in angiosarcomas.

D. Non-Tumor Vascular Lesions:

A second lesion often seen in the non-tumorous portions of the liver is that of peliosis hepatis; it has been extensively described by Pliskin (4). These lesions tend to be numerous, involving the entire liver and have a diffuse stain throughout the nodules. The stain does persist into the late venous phase and may not be associated with any radioisotopic abnormalities of the liver scan. Whether these findings represent a pre-carcinogenic or pre-angiosarcomatous lesion in vinyl chloride

workers is still under study.

E. Radioisotopic Detection:

The ability of 99mTc sulfur colloid liver scan to detect anatomical lesions, based on the best medical diagnosis, is supported by the findings that, of the 19 cases with anatomical lesions, only three were radioisotopically reported as normal. In one of the three reported normal cases, subsequent radioisotopic scans done three months later revealed the underlying abnormalities. What is equally important is that in the 957 "normal" individuals, the scan was reported as abnormal in only 32 cases. These data, therefore, illustrate an 84% sensitivity (16/19) and a 97% specificity (925/976), with only a 3% false positive rate (32/957). This false positive rate was markedly reduced in subsequent years when repeated radioisotopic scans could be compared to initial baseline ones. It is our present opinion that the radioisotopic scan, either camera or rectolinear, represents the most effective means of identifying early anatomical lesions with the least degree of false positivity, thus preventing unnecessary diagnostic evaluation. The value and effectiveness of ultrasound versus the radiological isotopic scan as a screening procedure is under study.

Do we agree in UK?

F. Associated Spleen Disorders:

An enlargement of the spleen, as determined by radioisotopic scans (greater than 14 cm in longitudinal length) and verified by autopsy or laparotomy in 12 cases, has been seen in 60% of the individuals with angiosarcoma and 40% of those individuals with the peliosis hepatis lesion. As illustrated in Figure 6 the correlation between spleen size and wedged hepatic vein pressure among vinyl chloride workers illustrated some disparities. At least 10-12% of those individuals with splenomegaly had no evidence of an elevated portal pressure as reflected by wedged hepatic vein pressure. In addition, angiographic studies demonstrated circular lesions in the spleen (lienal peliosis) which had persistent staining characteristics and were associated with a shortened celiac artery to portal vein circulation time and increased spleen scan size. The use of 99mTc sulfur colloid clearance by both the liver and spleen gives further suggestive evidence that spleen macrophage cell activity might play a role in the splenomegaly and/or the vascular findings. In the individuals with lienal peliosis, there is a steep rise in the uptake of 99mTc sulfur colloid by the spleen after initial recirculation. This may be due to either increased blood flow and/or increased total number of activated macrophagic cells. Studies are now under way to further delineate these lesions.

G. Lung Findings:

The medical surveillance program has also illustrated the presence of an unusual lung finding among this cohort of vinyl chloride workers. The abnormality is characterized by a midzonal lateral pleural thickening, which, on histological examination, thus far has simply illustrated fat and fibrosis. The importance of this finding in approximately 4% of the work force may be non-occupational but regional, i.e., other environmental pollutants, infections, etc. These lesions do not appear to be

first description I have seen in print!

associated with any pulmonary functional disorders; and their significance and relationship to smoking, tuberculosis, asbestosis, fungal infection or possible geographic non-occupational environmental pollutants are under study.

There is, however, preliminary epidemiological and histological data that strongly suggests an increase in the frequency of lung cancer among vinyl chloride industrial workers. Falk and associates have been studying the incidence of large clear cell carcinoma occurring among vinyl chloride polymerization workers, which appears to be higher than one would expect to find in the general population matched for age, race, and sex. Preliminary studies using regional histologically matched lung cancer patients as controls indicate that the occurrence of this particular cell type does not appear to be a geographic phenomena. Analysis is now underway to determine if there exists a correlation between this particular histological cell type and the work exposure history of this cohort population. The correlation, if any, between our pleural findings and this cellular type of lung cancer has yet to be determined.

METABOLIC/PATHOGENESIS UPDATE ON VINYL CHLORIDE

Our present knowledge of the metabolism and pathogenic mechanism by which vinyl chloride induces hepatic lesions may best be summarized by TableII. At concentrations of less than 50 ppm, vinyl chloride appears to be metabolized by the alcohol dehydrogenase system. At levels in the range of 200 ppm, oxidation appears to occur by the peroxidase - catalase system. With higher levels, the mixed function oxidase system appears to be the major route of oxidation of vinyl chloride into its metabolic intermediates: chloroethylene oxide spontaneously rearranges to form chloroacetaldehyde, which is then further oxidized to monochloroacetic acid or converted to chloroethanol. Monochloroacetic acid is not seen in urine samples at low doses and may be only formed with higher exposures of vinyl chloride. Chloroethanol and chloroacetaldehyde are most likely detoxified via the glutathione-cysteine conjugation system. This system, however, is saturable; and at higher levels, vinyl chloride is excreted via the lungs unchanged (5). Elmore et al., utilizing a modified Ames system and pure synthesized vinyl chloride intermediates, have shown that vinyl chloride, chloroethanol and chloroacetic acid are not mutagenic in their biological systems (6). This strongly supports the hypothesis that vinyl chloride monomer is neither hepatotoxic nor carcinogenic until it has been metabolized to its intermediate forms by the liver and/or other tissues. However, chloroacetaldehyde and chloroethylene oxide were definitely found to be mutagenic, producing recombination DNA defects in bacteria.

These findings present difficulty in explaining why the hepatocyte, as the primary metabolic site for vinyl chloride, does not undergo any significant evidence of hepatotoxicity nor malignant transformation. The adjacent sinusoidal lining cells must either metabolize the vinyl chloride in a similar manner but have a less effective detoxification of the metabolite or receive from the hepatocyte the intermediate metabolites, such as chloroethanol, which it may then convert to chloroacetaldehyde without being able to detoxify or further oxidize this mutagen. Although the hepatocyte is the primary site for vinyl chloride

metabolism, its capacity to detoxify the vinyl chloride intermediate metabolites may be the major reason it does not undergo malignant transformation.

Primary hepatocellular biochemical alterations observed during prolonged exposure to vinyl chloride in the rat may add further evidence to support this concept. Subcellular enzymes and metabolites were studied in animals exposed to 10-20,000 ppm of vinyl chloride ranging from 14-137 hours. Microsomal, mitochondrial, and cytosol enzymes, including p450, NADPH cytochrome c reductase and mixed function oxidase, were studied. Glutathione and glutathione reductase as oxidative and detoxification markers were also determined, in addition to the conventional clinical biochemical studies, which included aspartate (SGOT) and alanine (SGPT) aminotransferase, alkaline phosphatase, bilirubin, lactic acid dehydrogenase, total protein, albumin, cholesterol and triglycerides. After 137 hours of exposure, no significant changes occurred in the mitochondrial or the microsomal enzymes nor in the glutathione content. There was an increase in the glutathione reductase at 30 hours and a significant decrease in glucose-6-phosphatase (G-6-P) after 71 hours of exposure, followed with an increase in glucose-6-phosphate dehydrogenase (G-6-PD). These biochemical findings occurred without evidence of histologically discernible changes in the conventional biochemical studies.

This decrease in G-6-P and increase in G-6-PD after "simulated" chronic exposure are very similar changes to those found by Weber and Lee (7) in rapidly developing primary hepatocellular tumors. Their studies demonstrated a decrease in gluconeogenesis with a reduction in G-6-P and an increase in G-6-PD and transaldolase. These biochemical changes were followed by an increase in purine biosynthesis (increased phosphoribosylpyrophosphate aminotransferase - PRPP) and eventually an increase in the production of ATP and GTP, leading to increased nucleic acid synthesis.

At the termination of our experiment (at 37 hours), there were no significant changes in PRPP; but studies are now underway exposing animals to up to 250 hours to determine if the hepatic enzyme biochemistry in vinyl chloride exposure is similar to that seen in rapidly dividing primary hepatocellular tumors. It may well be that these findings may represent an adaptation of the hepatocyte, with increasing nucleic acid synthesis for purposes of repair, and may make these cells more susceptible to malignant transformation if the carcinogenic agent is unable to be removed or detoxified with sufficient efficiency. In contrast, the sinusoidal lining cells may well be able to oxidize these metabolites but unable to detoxify them effectively and therefore be more susceptible to developing DNA injury.

Studies have begun in our laboratory to isolate hepatocytes and the various sinusoidal lining cells and determine the individual cell types' ability to both oxidize vinyl chloride, as well as detoxify its intermediate metabolites. These studies, only recently begun, have already demonstrated unusual differences between the enzyme activity of hepatocytes versus mesenchymal cells. Our preliminary studies, which require further verification, failed to demonstrate mixed function oxidase activity (based on micromoles per minute per million cells) in contrast to the hepatocytes. Further purification of the mesenchymal cells and

verification of their cellular type must be done before any definitive conclusions can be drawn from these preliminary observations. They do, however, suggest that metabolic differences of the various cell types may play an important role in the ability of cells to oxidize and/or detoxify potential carcinogens.

Pathogenesis via Human Case Studies:

The co-factor role of such agents as alcohol in the pathogenesis of vinyl chloride carcinogenesis may be suggested by a naturally paired two-case study. Case A - Employee began to work in vinyl chloride polymerization plant in 1947 as a chemical operator. He worked in the polymerization process for 18 years, and estimated exposure during this time ranges from 50-10,000 ppm of vinyl chloride. He had a history of extensive alcohol consumption and was discharged from employment because of this in 1968. In 1962 he had the first clinical abnormalities related to liver injury, and these were identified histologically as being alcohol induced in 1964. His alcohol consumption was greater than 512 cc per day. Case B - This individual was also employed in the same polymerization plant and began working at the same time and at the same jobs and from 1947 until Case A was discharged 18 years later. Case B continued to work in polymerization plant process for an additional ten years at exposure ranges of 50-10,000 ppm.

can't identify from ASI list — look at Tamburro's letter of 9/1/79

In 1974 during the medical surveillance program's initial phase, Case B was identified as having persistent biochemical abnormalities which were clinically and histologically shown to be due to vinyl chloride injury and a developing cellular type of angiosarcoma. His alcohol consumption had been less than 50 cc per day. He did, however, have a history of malaria during his military service prior to vinyl chloride exposure and was transiently HB_sAg positive in 1974.

Histologically, Case B was verified as having angiosarcoma. During the same year, Case A was shown to have evidences of both alcoholic injury with cirrhosis and the characteristic lesions of vinyl chloride injury, including subcapsular fibrosis with bile duct proliferation, peliosis hepatis, sinusoidal cell activation, focal sinusoidal dilatation and areas of rounded portal fibrosis. Histologically, the hepatocytes showed atypical change consistent with hepatocellular carcinoma and the sinusoidal lining cell changes characteristic of angiosarcomatous tissue.

In these two case studies, in which the duration and degree of exposure was as identical as one could expect in human biological system, we have individuals developing tumors of two different cell types. It is suggested from these findings that alcohol played a significant role in the hepatocyte's inability to detoxify the vinyl chloride metabolites, thereby causing DNA injury and ultimately leading to the development of primary hepatocellular carcinoma.

Some recent animal studies by Dr. Martha Radike and her group (8) in Cincinnati have shown a four-fold increase in hepatic tumors among alcohol-fed rats exposed to vinyl chloride in contrast to those exposed to vinyl chloride alone. The role of secondary or co-factors in the development of chemical carcinogenesis needs much further study, both in

Does IFHP know Dr. Radike well enough to write + ask for data?

animals and in human observations.

The importance of the hepatocyte's ability to adequately metabolize vinyl chloride is further illustrated by the preliminary reports of Dr. Maltoni et al., (9), indicating that newborn rats exposed to vinyl chloride develop a four-fold increase in primary hepatocellular cancer. In contrast, the adult rat of the same species develops angiosarcomas.

Review of Prospective Medical Surveillance System:

It is highly unlikely that any singular approach to the understanding of the chemical carcinogenesis (i.e., chemical structure studies, animal experiments or human epidemiological studies) will completely succeed in characterizing the pathogenic sequence. Structural studies of chemicals can help direct attention to those agents which may be more carcinogenic. However, metabolic activation of chemicals also needs to be done and further studied in Ames-type bacterial systems to determine whether the metabolites are the potential mutagen/carcinogens. Even with this information, the methods by which these agents produce cancer must be illustrated in animals so that we may develop earlier and more effective means of prevention and screening of our industrial workers.

Although vinyl chloride has demonstrated both in animals and humans almost identical histological and morphological changes, this illustration of animal model extrapolation to humans is by far the exception rather than the rule. It is, therefore, equally important that one continue to gather accurate epidemiological data in a prospective fashion, to determine the human variation from animal studies as well as to document the effectiveness of our prevention methods and surveillance programs, which are often instituted on the basis of limited knowledge and in time of crisis. To this point, a prospective medical surveillance system has been designed and initiated by the University of Louisville in collaboration with the B. F. Goodrich Company and its unions (Distillery Workers Union, International Brotherhood of Electrical Workers, International Association of Machinist Workers, and Pipefitters Union).

This prospective prototype system is based on the classification of industrial environments into three categories (10). Type A or possible carcinogenic: This would include those industries utilizing materials not yet studied for their carcinogenic potential. Type B or probably carcinogenic: This would include those industries utilizing a material or materials suspected to be potentially carcinogenic. Type C or actually carcinogenic: This would include all industries utilizing a material known to be cancer-producing either in animals or man.

The basic epidemiological data required from the various industrial categories is based upon the possible, probable or actual presence of a carcinogen. Those Type A industrial environments would need to collect or record minimal epidemiological data, almost 90% of which is already being recorded or collected by most industries for other socio-economic reasons and would require only minimum outlay of cost and personnel time. This basic data would include an employee work history, a job exposure history, and a medical illness history composed of three parts. First, a record of previous medical illnesses based on pre-employment history

and examination. Second, a record of all medical illnesses and hospitalization during employment. In most cases, with certain modifications, this can be obtained by way of third party insurance payments. Third, a company/plant-based mortality record based on the diagnosis at time of death for each worker. Almost all of this information is presently recorded and kept in various forms by chemical industries (for business purposes), the medical care systems or as part of vital statistics.

At the second level, Type B, a periodic medical history and physical examination should be required; and, in addition, rank order monitoring should be performed for each job occupation where individual chemical monitoring is available. Where possible, area monitoring data should be utilized for these rank orderings, and preferably, when scientifically available, individual monitoring would be substituted for the rank order system.

Updating of job classifications and job exposure indices based on rank order determinations has already been done in actual industrial environments at a cost of approximately $10/person for the initial updating. The cost of maintenance of such records is estimated to be less than $3/person/year employed.

In Type C industries, those environments actually using carcinogens, regular history and physical examination will be required and performed with increasing frequency as the duration of employment increases. Individual monitoring should be used to determine the actual exposure. Where this is not yet scientifically developed, efforts should be made to design usable monitors for this purpose. In Type C industrial environments, collaborative and cooperative efforts among the industrial community, the labor force, and the scientific community are essential in order to allow an accurate, ongoing systematic collection and analysis of the epidemiological information. These data will help resolve the problems of safe exposure levels, frequency of screening needed, effectiveness of screening, and the identification and effect of co-factors upon individuals exposed to actual carcinogens.

INDUSTRIAL HEALTH EDUCATION

In order to accomplish this, expansion of educational programs within these industries is needed and must be continually improved and updated. Any industry working with possible carcinogens should have educational programs directed not only at their employees, but also their families, the managerial personnel, and union representatives. In those environments where probably carcinogens are involved, educational programs are needed for industrial medical personnel and para-medical personnel. This is especially important in those industries where Federal occupational laws require or an industry desires to institute a surveillance program. Finally, in those industrial environments where an actual carcinogen is in use, educational endeavors must be expanded beyond the industrial environment. These should include the local medical community (in order to help them better understand the medical surveillance service being rendered in relationship to the private physician's role in the care of the employees), the local community (relative to its potential danger), the business community, and the industrial community

not involved in similar use of carcinogens, so that they may better understand the health and safety of these employees. The lack of understanding on the part of the non-involved business and industrial communities can lead to unnecessary socio-economic stigmatization or economic difficulties.

As evidence of the potential effectiveness of such medical surveillance systems in an actual carcinogenic environment, Table III illustrates the compliance rates for medical screening over the past three years. This high voluntary compliance on the part of the employees illustrates the concern of the employees and the cooperative effectiveness of management and labor in identifying and correcting industrial problems. It has become clear in our past four years, that industry's need for scientific expertise and assistance must be coupled with the medical and scientific communities' better understanding of the work environment and its socio-economic relationship. The conducting of medical surveillance programs on an ongoing, long-term basis requires adaptation of our present methods of medical screening so as not to cause unnecessary and excessive interference with the industrial function and at the same time deliver the best screening surveillance system at the lowest cost. Much more work is needed in adapting such systems and demonstrating their implementability and their cost effectiveness. This is not a short-term endeavor and will require well thought out planning and a marked increase in the collaborative effort among industry, the labor force, the local community, and the scientific communities (local or regional ones). Regional and geographic cancer centers can play a major role in assisting and supporting, with scientific expertise, their local industries in endeavoring to better identify potential carcinogens and develop the most effective means of preventing both acute toxicity and long-term carcinogenicity.

SUMMARY

Vinyl chloride is a basic chemical for plastics manufacturing and has been used as an anesthetic agent. Vinyl chloride's previously unknown carcinogenic capability appears to be related to the body's ability to convert it from a non-toxic or minimally toxic chemical to a toxic and, with prolonged exposure, cancer-forming agent. Early exposure in animals causes body cells to make adaptive changes which may prepare them for malignant transformation and appear to precede evidence of morphological injury. These findings appear to occur before a low-grade chemical injury occurs. Vinyl chloride chemical injury in man appears to follow the same pattern. Present clinical data in humans now demonstrate evidence of pre-cancer injury and cancer transformation of various types of cells in different organs of the body. Manifestations of pre-cancerous injury to organs other than the liver (such as the lung, heart, spleen, brain and lymphatic system) may also be occurring and require further investigation.

Early detection of these pre-cancerous chemical injuries requires a prospective ongoing system of surveillance and the development of diagnostic methods which can identify specific causal agents in the presence of non-specific injury. Such a systematic approach has been developed and is now in operation. Its initial achievements appear to be the

foundation for future success in controlling the health effects of industrial chemicals.

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TABLE I

CANCERS BY SITE IN POLYVINYL CHLORIDE PRODUCTION PLANT COHORT WORKING MORE THAN 1 YEAR WHO DIED DURING THEIR WORK PERIOD OR AFTER RETIREMENT.

SITE	NUMBER
LUNG	28
LIVER	10
BRAIN	5
COLON	4
PANCREAS	2
THYROID	1
PROSTATE	1
EYE	1
UNKNOWN	1

TABLE II

PROPOSED VINYL CHLORIDE METABOLISM PATHWAY IN THE RAT

I. $Cl\text{-}CH{=}CH_2 \longrightarrow Cl\text{-}CH_2\text{-}CH_2\text{-}OH \xrightarrow[\text{DEHYDROGENASE}]{\text{ALCOHOL}} Cl\text{-}CH_2\text{-}CHO \longrightarrow ClCH_2\text{-}COOH$

II. $Cl\text{-}CH_2\text{-}CH_2\text{-}OH \xrightarrow[\text{CATALASE}]{H_2O_2} ClCH_2\text{-}CH_2OOH \longrightarrow ClCH_2\text{-}CHO$

III. $Cl\text{-}CH{=}CH_2 \xrightarrow{\text{OXIDASE}} Cl\text{-}CH\underset{O}{\overset{\diagup\diagdown}{}}CH_2 \longrightarrow Cl\text{-}CH_2\text{-}CHO \longrightarrow ClCH_2\text{-}COOH$

TABLE III

COMPLIANCE OF 992 PEOPLE EMPLOYED CONTINUOUSLY AT TYPE C PLANT (JUNE 1, 1975 TO MAY 31, 1977)

	YEARS			NONE OF* 3 YEARS
	1ST	2ND	3RD**	
LABORATORY TESTS	89%	86%	84%	3%
LIVER-SPLEEN SCANS	73%	85%	81%	7%
HISTORY AND PHYSICALS	58%	76%	69%	12%

* THIS IS PERCENTAGE OF EMPLOYEES WHO HAVE NOT PARTICIPATED IN ANY OF THE THREE SCREENING COMPONENTS DURING ANY OF THE YEARS.

** THE DECREASE IN THE 3RD YEAR OCCURRED MAINLY AMONG NON-PRODUCTION WORKERS, ESPECIALLY THOSE IN ADMINISTRATIVE JOBS.

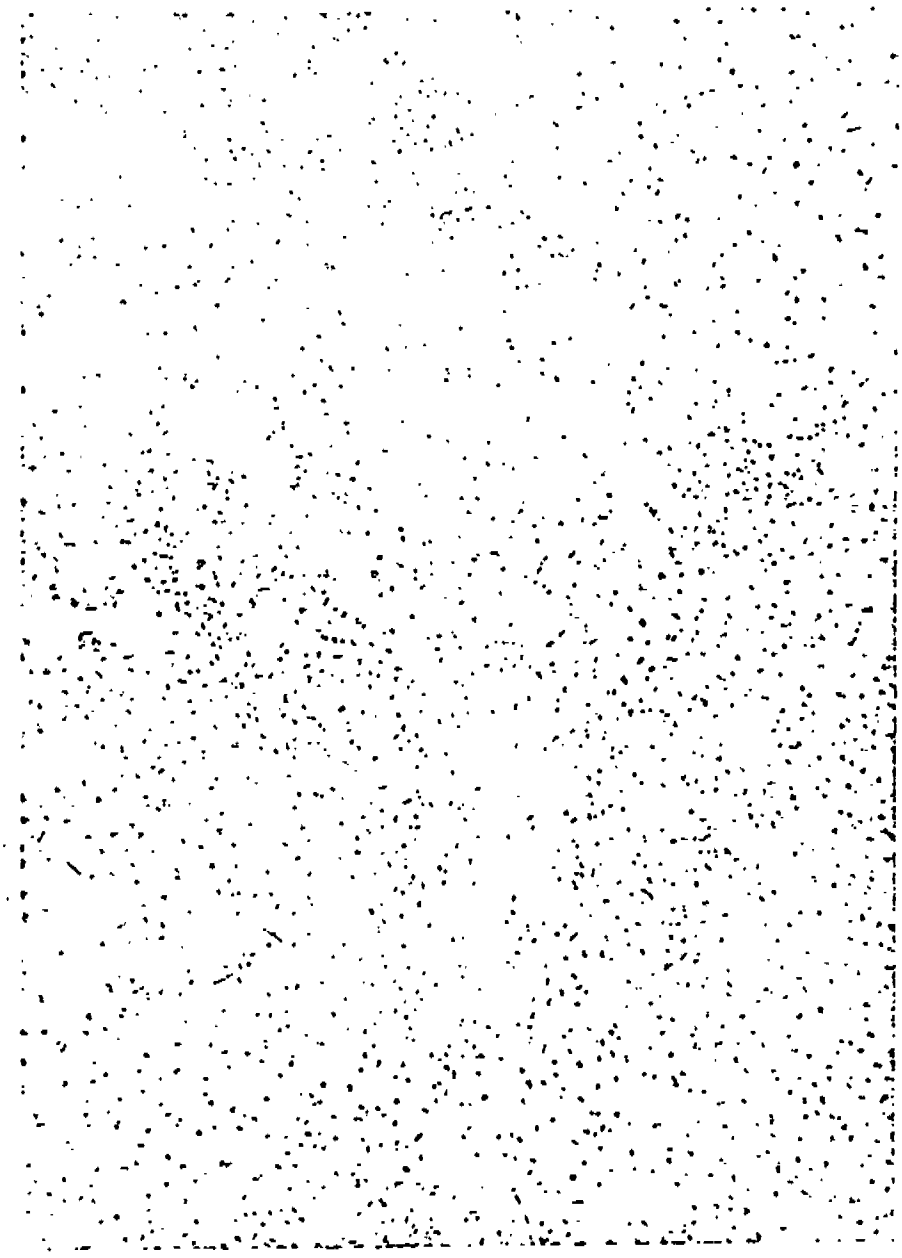

Figure 1. Typical portal area showing increased portal fibrosis with mild bile duct proliferation, with few inflammatory cells mainly mononuclear cell. (Low power x 100)

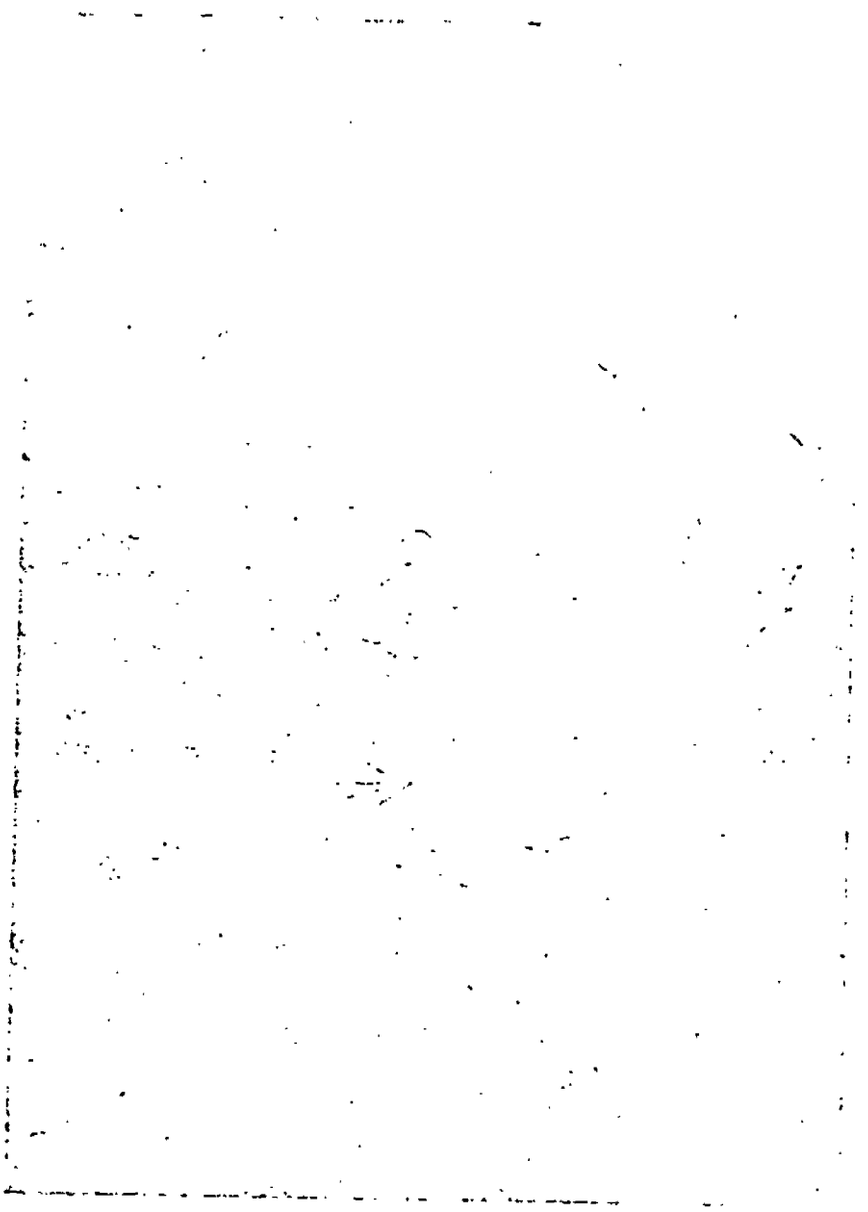

Figure 2. Focal sinusoidal dilatation is seen with activated sinusoidal cells (arrows). Lobular architecture otherwise well preserved with normal appearing hepatocyte with some increased number of bi-nuclear hepatocytes. (Low power x 100)

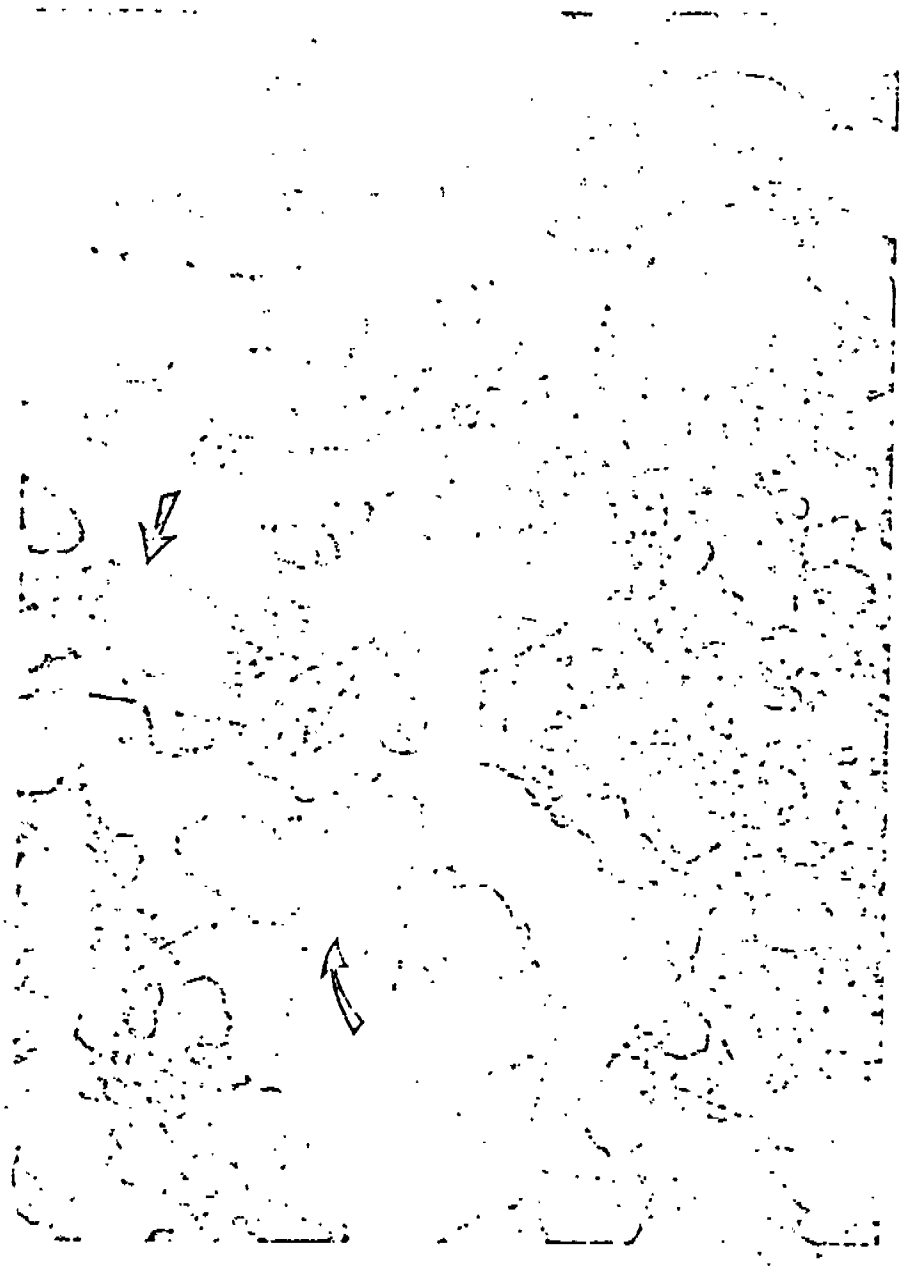

Figure 3. Markedly atypical sinusoidal cell change with malignant transformation (arrows) and piling up of sinusoidal cells into sinusoidal spaces. (High power x 400)

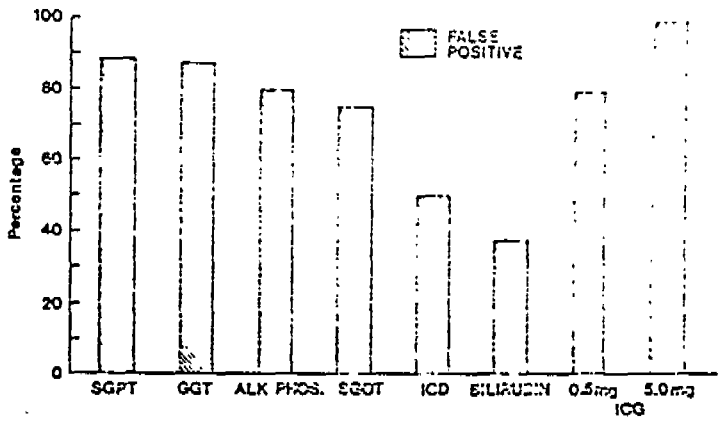

Figure 4. Frequency of biochemical abnormalities being present and correctly indicating the presence of significant histological abnormalities (SGPT = alanine aminotransferase; GGT = gamma glutamyl transpeptidase; ALK PHOS = Alkaline Phosphatase; SGOT = aspartic aminotransferase; ICD = isocitric dehydrogenase and ICG = indocyanine green clearance).

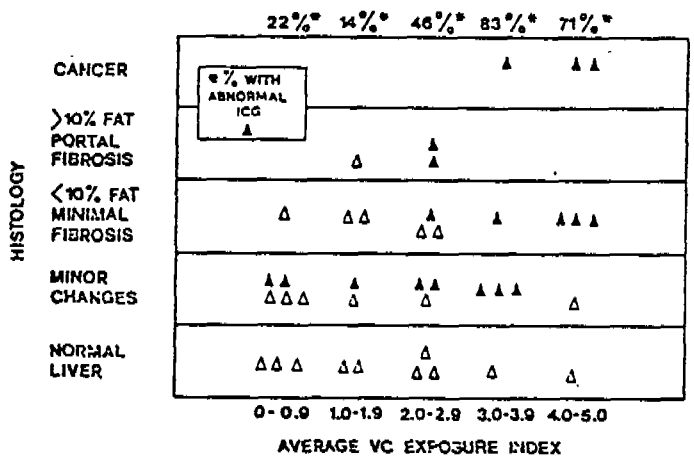

Figure 5. Correlation between liver histology and indocyanine dye clearance (0.5 mg and 5.0 mg dose) abnormalities in vinyl chloride workers with increasing vinyl chloride exposure as determined by average exposure index = $\frac{\Sigma n_1 E_i}{\Sigma n_i}$ where: Σn_i = number of months at exposure level E;
E_i = exposure rated on a rank order scale from 1 to 6 (1-lowest; 6-highest)
Σn_1 = total months service at VC plant

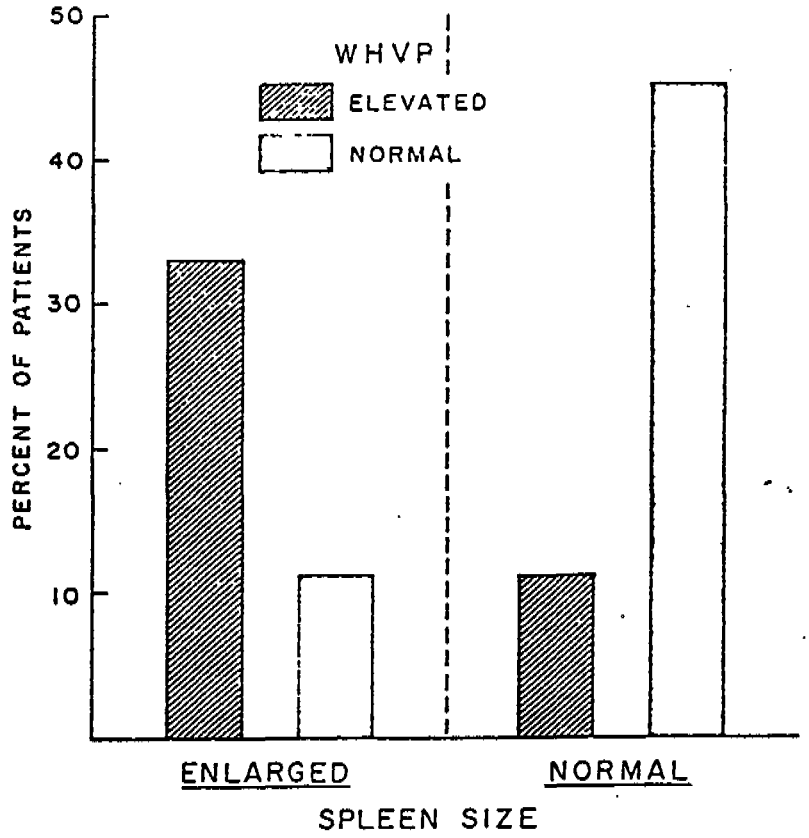

Figure 6. The correlation between spleen size and wedged hepatic vein pressure in vinyl chloride workers.

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